Synthesis of Aza-Heterocycles

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Synthesis of Aza-Heterocycles

THÈSE

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par

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de
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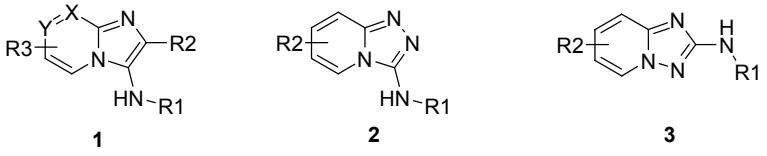
1. Introduction

Le but de ce travail a été de développer la synthèse de divers hétérocycles aminés originaux d'une façon nouvelle et robuste afin de pouvoir préparer des bibliothèques plus ou moins large de composés en un minimum d'étapes et avec un bon niveau de pureté. Plusieurs approches ont été envisagées, en particulier des synthèses utilisant des réactifs sur support solides et des conditions réactionnelles compatibles avec une large variété de groupes fonctionnels.

Dans le cadre de cette thèse, la synthèse des 3-aminoimidazo[1,2-*a*]azines (**1**), 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines (**2**) et 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**) a été investiguée (Fig. 1, ci-dessous).



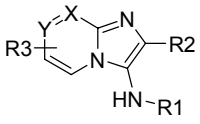
1 **2** **3**

X,Y = CH or N
R1 = alkyl, (hetero)-aryl, acyl
R2 = alkyl, (hetero)-aryl, acyl, halogen
R3 = alkyl, (hetero)-aryl

Fig. 1. Structures des hétérocycles aminés.

2. Synthèse des 3-aminoimidazo[1,2-*a*]azines (**1**)

Au début de notre travail, nous étions intéressés par la synthèse de 3-aminoimidazo[1,2-*a*]azines (**1**) (Fig. 2). Le but était de développer un protocole robuste et général, pouvant donner accès à une chimiothèque de 1000 à 3000 composés.



X	Y	
CH	CH	imidazo[1,2-*a*]pyridine
CH	N	imidazo[1,2-*a*]pyrazine
N	CH	imidazo[1,2-*a*]pyrimidine

1

R1, R2 = R, COR, Ar
R3 = R, COR, halogen

Fig. 2. 3-Aminoimidazo[1,2-*a*]azines (**1**).

La synthèse des 3-aminoimidazo[1,2-*a*]azines (**1**) a déjà été décrite par différents groupes utilisant des voies de synthèse différentes, en phase liquide ou sur phase solide. Une approche qui nous paraissait être particulièrement attrayante pour la synthèse d'une grande variété de composés, est la synthèse multi-composés illustrées dans le Schéma 1 ci-dessous. Il s'agit de la condensation entre un isocyanure (**6**), un aldéhyde (**7**) et une amidine hétérocyclique (**8**) en catalyse acide.

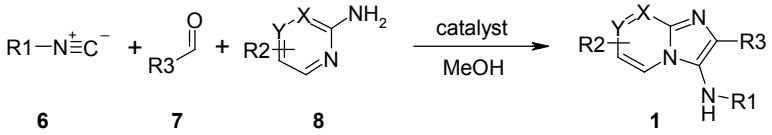


Schéma 1. Reaction multi-composés pour l'obtention de **1**.

Malheureusement, la plupart des conditions réactionnelles décrites manquent de généralité pour synthétiser une bibliothèque de plus de 1'000 composés.

Pour atteindre notre but, nous avons tout d'abord envisagé une synthèse sur phase solide. Pour cela, nous avons décidé de synthétiser l'hétérocycle (**1**) à partir de l'isocyanure (**29**) sur support solide (Schéma 2).

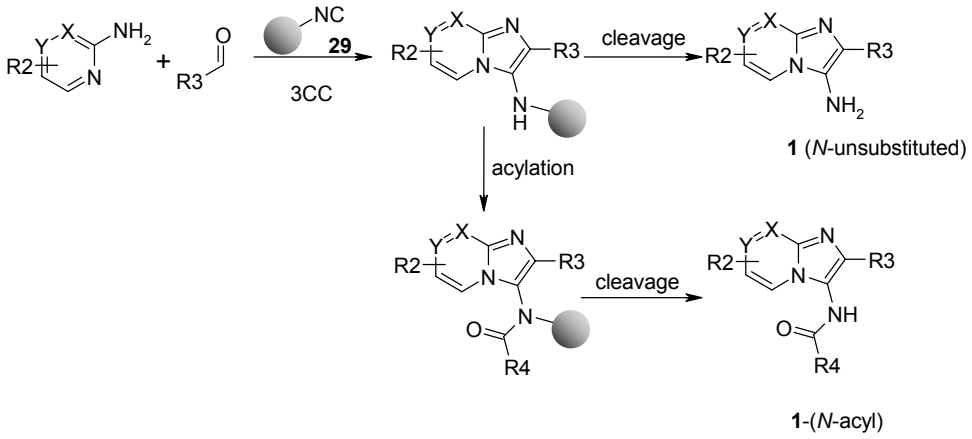


Schéma 2. Approche proposée pour la synthèse de **1** sur phase solide.

Comme la plupart des résines isocyanure ont été brevetées, le premier objectif de notre travail a été de développer notre propre résine isocyanure. Nous avons choisi un linker du type indole car il permettait de décrocher les produits de la résine dans des conditions acide très douces. La résine indole-isocyanide (**29**) a été synthétisée en cinq étapes à partir de 3-(aminomethyl)indole (**30**) selon le Schéma 3.

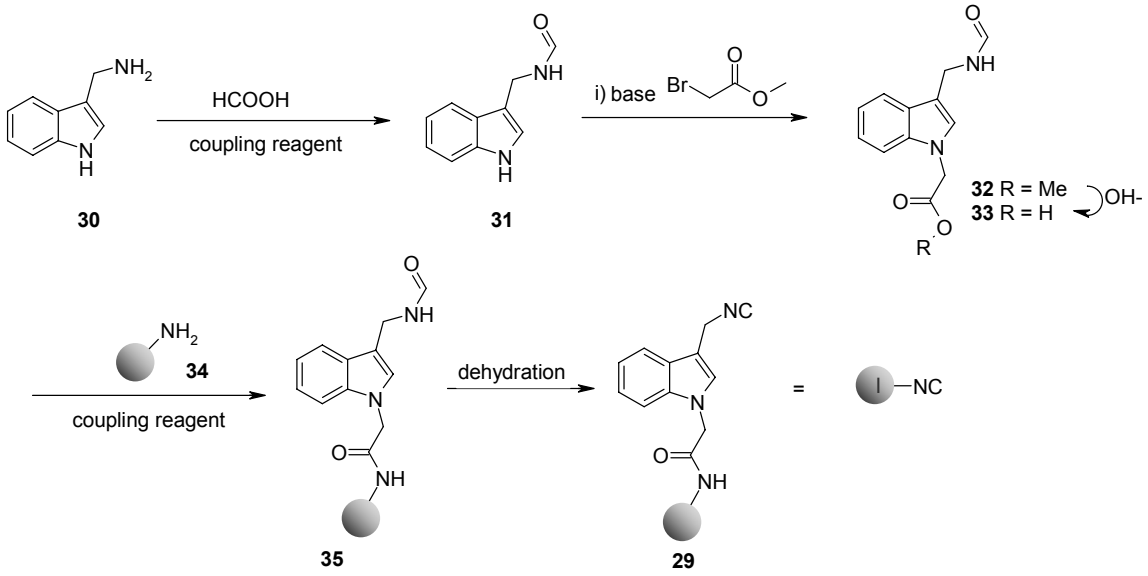


Schéma 3. Synthèse de la résine indole-isocyanure (**29**).

L'ester (**32**) a été obtenu avec un bon rendement par formylation de l'amine primaire (**30**) en présence du réactif de Mukaiyama suivi par l'alkylation du 3-(formylaminomethyl) indole (**31**) par le bromoacetate de méthyle. L'hydrolyse puis l'attachement de l'acide (**33**) à la résine aminopolystyrène (**34**) suivi d'une étape de déshydratation en présence de triphénylphosphine permet l'obtention de la résine (**29**).

La synthèse des 3-aminoimidazo[1,2-*a*]pyridines (**39**) avec la résine indole-isocyanure (**29**), différents aldéhydes (**36**) et 2-amino-5-methylpyridine (**37**) à été développée en présence de triflate de scandium comme catalyseur (Schéma 4). Le décrochage de la résine par une solution diluée d'acide chlorhydrique, a donné une variété de produits avec des bonnes puretés (>96%) et des rendements de moyens à très bons suivant les cas (55-94%), ceci même en utilisant des aldéhydes aromatiques portant des groupes électrodonneurs ou électroattracteurs ainsi qu'avec des aldéhydes alkyliques.

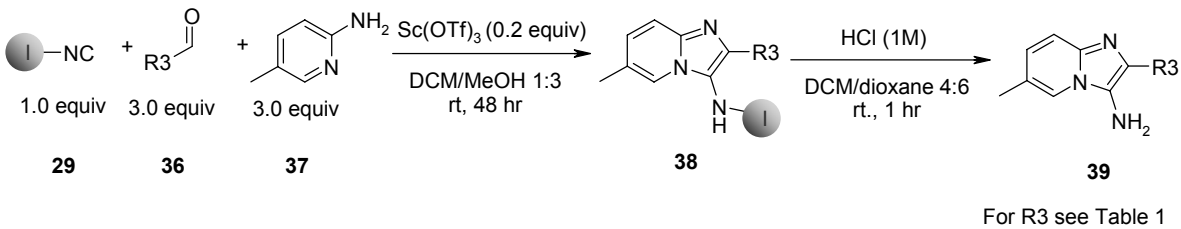


Schéma 4. Synthèse de 3-aminoimidazo[1,2-*a*]pyridines (**39**) sur phase solide.

La réaction de la 2-aminopyrazine (**41**) avec l'isocyanure supporté (**29**), différents aldéhydes (**36**) en utilisant les mêmes conditions que celles décrites précédemment a permis de générer des molécules portant le squelette 3-aminoimidazo[1,2-*a*]pyrazine (**43**) (Schéma 5).

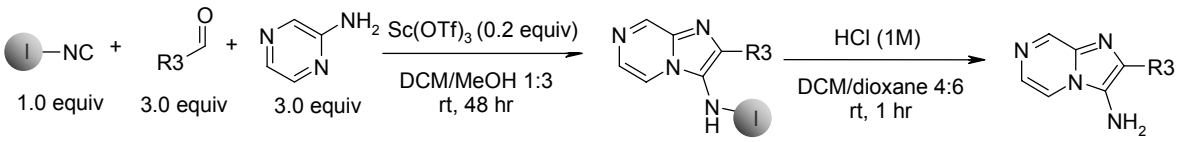


Schéma 5. Synthèse de 3-aminoimidazo[1,2-*a*]pyrazines (**43**) sur phase solide.

Le décrochage de la résine a donné des composés de structure générale (**43**) avec des puretés faibles, résultant de la présence du compose de départ (**41**) malgré un lavage intensif de la résine pour l'éliminer. La purification sur silice à permis l'obtention des composés désirés mais avec de faible rendements (17-55%).

Cette approche n'étant pas compatible avec la synthèse de 1000 à 3000 composés, une approche en phase liquide suivie d'une purification sur colonne SPE a ensuite été investiguée. Nous avons choisi cette méthode de purification car elle est plus facile à le développer d'une façon semi-automatique que les méthodes classiques de purification.

L'optimisation de condition pour la synthèse en phase liquide des hétérocycles de type (**45**) et (**46**) a montré que l'utilisation de l'acide perchlorique (0.5 équiv.) ou du triflate de scandium (0.5 équiv.) comme catalyseur permettait l'obtention des produits désirés, et cela même pour l'amidine hétérocyclique (**41**) la moins réactive (Schéma 6).

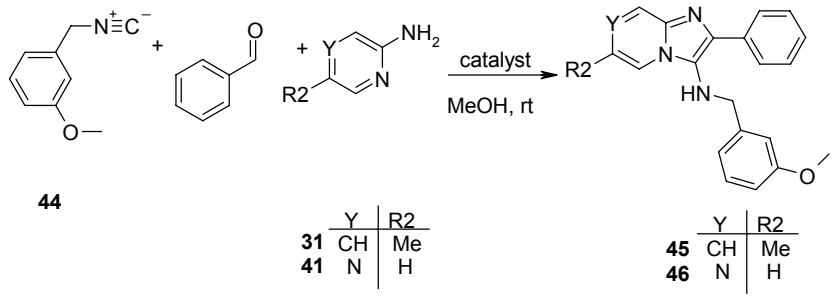


Schéma 6. Synthèse de 3-aminoimidazo[1,2-a]azines (**43**).

Ces conditions associées à une purification sur colonne SPE-SCX donne d'une manière générale les produits désirés avec de bons niveaux de puretés et de bons rendements (Schéma 7). Il est important de noter que cette procédure est compatible avec la préparation en parallèle de composés divers et présentant un grand nombre de groupes fonctionnels.

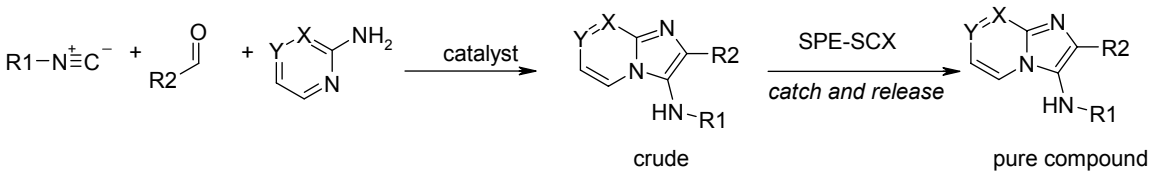


Schéma 7. Synthèse de **1** associés à une purification par SPE-SCX.

2. Synthèse de 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines (**2**).

A notre connaissance, il n'y a que peu d'études reportant la synthèse des 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines (**2**). Nous avons envisagé de les préparer par cyclo-désulfurisation de thiosemicarbazides de type **77** (Schéma 8).

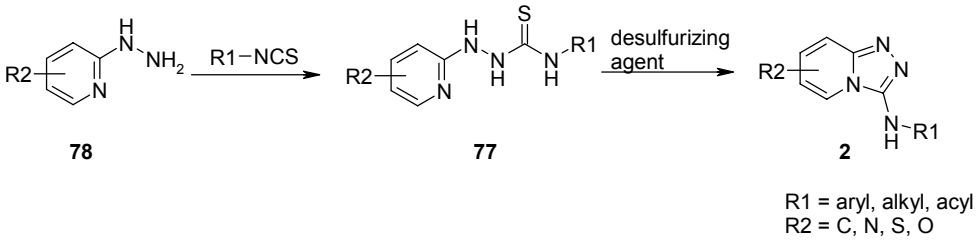


Schéma 8. Proposition de synthèse de 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines.

Nous avons commencé nos études avec la 2-hydrazinopyridine (R2 = H) comme réactif modèle. Les précurseurs de type 1-(pyridine-2-yl)thiosemicarbazide (**81**) furent obtenus avec de bon rendement par condensation 2-hydrazinopyridine (**79**) avec différents isothiocyanures (**80**) dans le THF à température ambiante (Schéma 9).

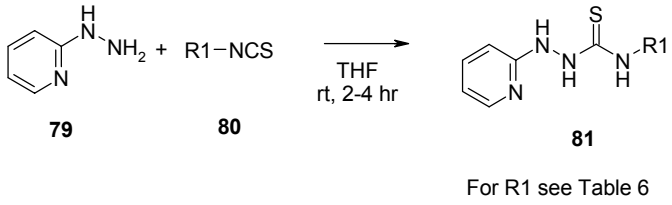


Schéma 9. Synthèse des 1-(pyridine-2-yl)thiosemicarbazides (**81**).

La cyclo-désulfurisation des intermédiaires (**81**) a été évaluée avec différents réactifs de désulfurisation. Nous avons montré que le réactif de Mukaiyama permettait efficacement de convertir les 1-(pyridine-2-yl)thiosemicarbazides (**81**) en produits désirés (**83**) avec de bons rendements (63-78%) par extraction de (**83**) en milieu aqueux acide (Schéma 10).

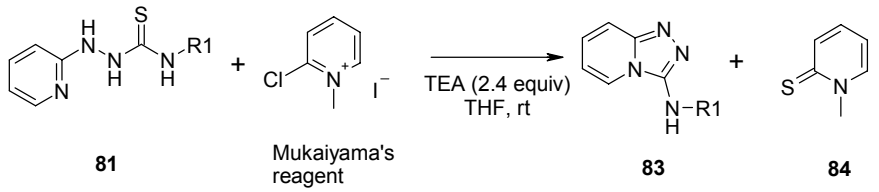


Schéma 10. Synthèse de **83** avec le réactif de Mukaiyama.

La version du réactif de Mukaiyama supporté sur phase solide (**PS-Muk1**) a été étudiée dans le but de faciliter l'isolation du produit formé et de permettre la synthèse en parallèle. La réaction du thiosemicarbazide (**81**) avec (**PS-Muk1**) permet l'obtention des heterocycles (**83**), mais dans ce cas, le produit désiré est accompagné d'une quantité importante d'un produit secondaire (Schéma 11).

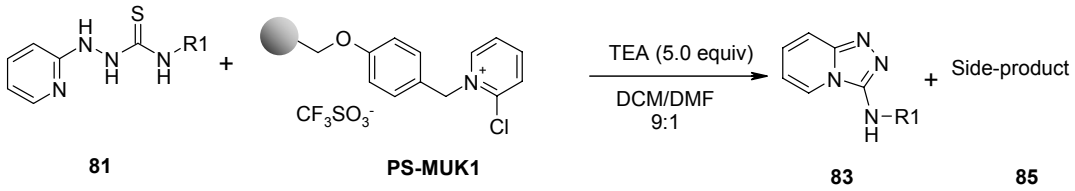


Schéma 11. Synthèse de **83** avec le réactif de Mukaiyama supporté (PS-Muk1).

Le produit secondaire (**85f-1**) a été identifié comme étant le résultat de l'incorporation du groupement pyridyle provenant de la résine (**PS-Muk1**) sur le produit désiré **83**. Une explication possible pour la formation d'un tel sous produit impliquerait la réaction du produit formé avec l'excès de résine, suivit de la rupture de la liaison benzylique du linker (Schéma 12).

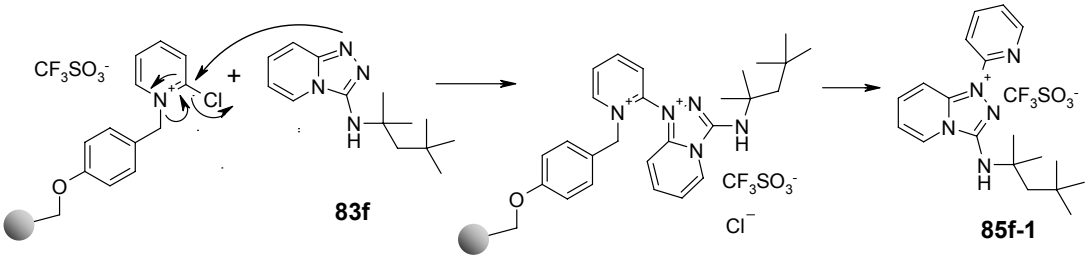
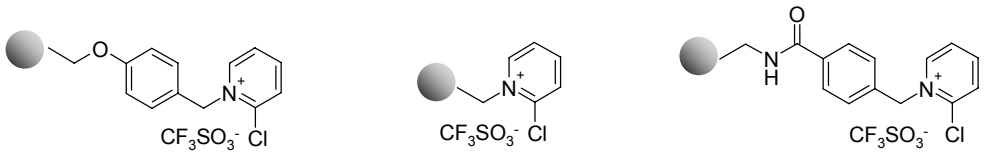


Schéma 12. Mécanisme possible pour la formation du sous-produit **85f-1**.

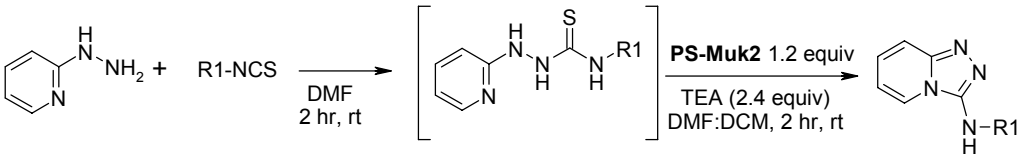
La caractérisation de ce sous-produit nous a permis d'imaginer une nouvelle version du réactif de Mukaiyama supporté, dont le linker devrait être moins labile (**PS-Muk2** and **PS-Muk3**) (Fig. 3).



PS-Muk1 **PS-Muk2** **PS-Muk3**

Fig. 3. Nouveaux réactifs de Mukaiyama supportés.

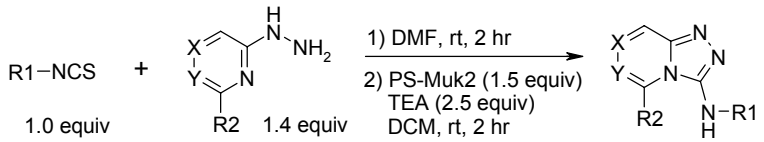
Les études de réactivité de ces résines ont montré, comme supposé, une meilleure stabilité concernant la rupture de la liaison benzylique ainsi qu'une conversion en produit (**83**) plus rapide et plus complète. Les avantages majeurs de l'utilisation de cette nouvelle version du réactif de Mukaiyama supporté sont la conversion totale, l'absence de produit secondaire ainsi que la purification des produits par simples filtrations sur SPE. La simplicité d'utilisation de ces résines a permis la mise au point d'un protocole "one pot" en 2 étapes séquentielles (Schéma 13).



79 1.1 equiv **80** 1.0 equiv **81** **83**

Schéma 13. Protocole "one-pot" pour la synthèse de **83**.

L'application de cette méthodologie à permis avantageusement la préparation de divers hétérocycles aminés par simple remplacement du dérivé hydrazine de départ (Schéma 14). Différents aminotriazoles (**87**-**89**) ont été obtenus avec un rendement moyen de 60% et de très bonnes puretés.



	X	Y	R2
79	CH	CH	H
90	CH	CH	Cl
91	N	CH	H
92	CH	N	SMe

	X	Y	R2
83	CH	CH	H
87	CH	CH	Cl
88	N	CH	H
89	CH	N	SMe

For R1 see Table 12

Schéma 14. Extension du protocole "one pot".

3. Synthèse de 2-Amino-[1,2,4]triazolo[1,5-*a*]pyridine (**3**).

Dans les paragraphes précédents, nous avons montré que l'étape clef de la synthèse de 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines (**2**) consistait en une cyclo-désulfurisation. Ici, nous avons considéré une approche similaire pour la formation de leurs régioisomères, les 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**) (Schéma 15), hétérocycles très peu documentés dans la littérature.

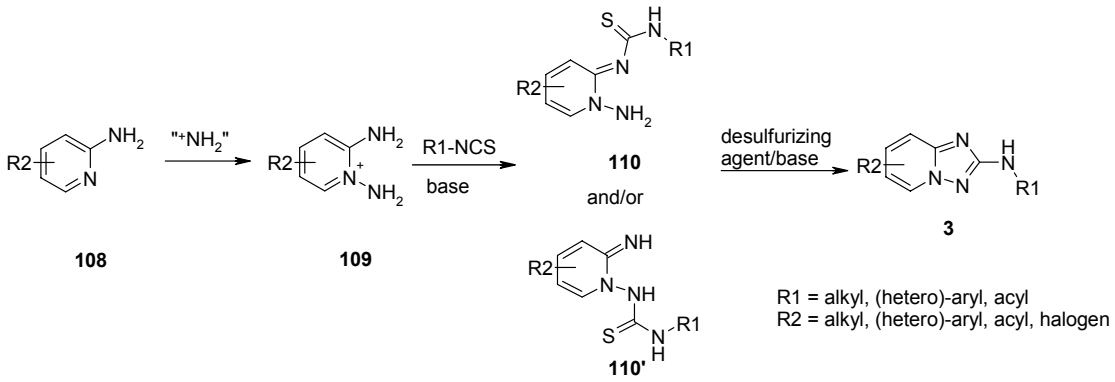


Schéma 15. Nouvelle route pour la synthèse des 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine (**3**).

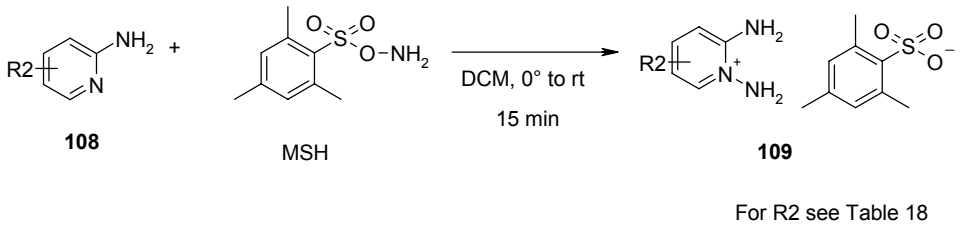
Les 2-aminopyridines (**108**) sont converties en sels de 1,2-diaminopyridinium (**109**) au moyen d'un agent d'amination électrophile (synthèse discutée dans le paragraphe suivant). Leurs condensations avec un isothiocyanate à température ambiante pendant 16 heures à permis la formation des thiourées correspondantes (**110**). La cyclo-désulfurisation de cet intermédiaire clef en présence du réactif de Mukaiyama supporté (**PS-Muk2**), en suivant le protocole « one pot » développé précédemment donne accès aux hétérocycles attendus (**3**). L'optimisation des conditions de couplage et de cyclisation combinée avec une désalification par SPE permet d'obtenir ces hétérocycles avec de très bonnes puretés (>99%) et de bons rendements (60%) indépendamment de la nature des substituants sur le noyau aromatique.

La possibilité d'effectuer des réactions en parallèle, ainsi que la robustesse de cette voie de synthèse optimisée, à été validée par la production d'une petite chimiothèque de 15 composés qui ont été, pour la plupart, obtenus avec des rendement supérieur à 70% et de très bonnes puretés.

4. Synthèse de sels de 1,2-diaminopyridinium.

Dans la voie de synthèse des 2-amino-[1,2,4]triazolo[1,5-a]pyridines (**3**) par cyclo-désulfurisation, les sels 1,2-diaminopyridiniums constituent les intermédiaires clefs. Ceux-ci peuvent être préparer par amination électrophiles d'aminopyridines (**108**).

Le mésitilène sulfonate d'hydroxylamine (**MSH**) est l'un des réactifs le plus décrit pour ce genre de réaction. Il a été obtenu avec de bon rendement en suivant le protocole décrit dans la littérature. L'amination d'une série d'aminopyridines (**108**) par le MSH a conduit aux composés désirés (**109**) ($MesSO_3^-$) avec de bons rendements (53-81%) et d'excellentes puretés (Schéma 16).

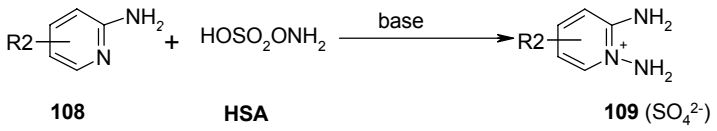


108 MSH **109**

For R2 see Table 18

Schéma 16. Synthèse de **109** ($MesSO_3^-$) avec MSH.

L'étude de la stabilité du MSH par calorimétrie différentielle à balayage (DSC) ainsi que des rapports issus de la littérature, laissent penser que ce réactif est peu stable et présente des dangers d'explosion. Le risque potentiel généré par l'utilisation de MSH en grande quantité nous a conduit à évaluer un agent d'amination plus stable et moins dangereux tel que l'acide O-hydroxylamine sulfonique (HSA) (Schéma 17).



108 **HSA** **109** (SO_4^{2-})

Schéma 17. Synthèse de **109** avec HSA.

Les conditions décrites dans la littérature ainsi que plusieurs variantes ont été tentées. Par exemple, la modification de la base utilisée, tel que le remplacement l'oxyde de barium par du bicarbonate de potassium ou la modification du pH grâce à l'utilisation de milieux tamponnés. A chaque fois, les taux de conversion observés pour la réaction d'amination électrophile ont été très faibles (<40%).

L'instabilité de l'acide *O*-hydroxylamine sulfonique (HSA) comme réactif dans les conditions réactionnelles (milieux aqueux et alcooliques), ainsi que son insolubilité dans les autres solvants organiques nous ont amenés à développer une variante de ce réactif utile à la réaction de N-amination des 2-aminopyridines. Pour cela, nous avons envisagé de remplacer le proton du HSA par un cation tetrabutylammonium.

La réaction de HSA avec le chlorure ou l'hydroxyde de tetrabutylammonium permet d'obtenir le sulfonate de l'hydroxylamine de tetrabutylammonium (TBAHS) par simple évaporation des solvants (Schéma 18).

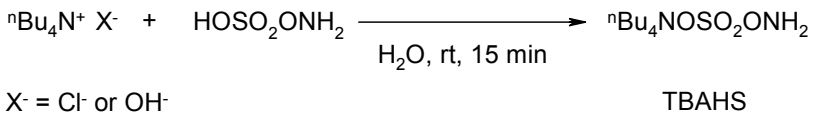


Schéma 18. Preparation de TBAHS.

Des analyses de DSC ont démontré que ce nouveau réactif (TBAHS) est bien plus stable et présente moins de risque que les réactifs précédemment décrits. La synthèse de l'intermédiaire (**109**) en présence de TBAHS présente des taux de conversion satisfaisants (~90%) après 16 heures de réaction à 65 °C (Schéma 19).

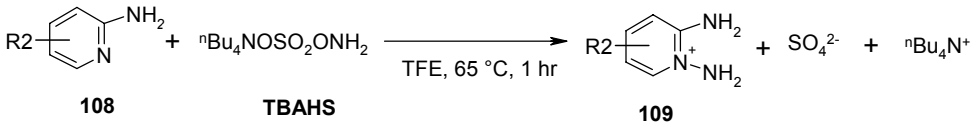


Schéma 19. Synthèse des sels de 1,2-diaminopyridinium avec TBAHS.

L'utilisation du TBAHS à plus grosse échelle (>10 mmol) a été réalisée de façon reproductible sans rencontrer de problème majeur du point de vue sécuritaire. L'isolation du produit (**109**) du milieu réactionnel a été difficile et s'est avérée dépendante du substituant (R2). Néanmoins, les produits désirés ont pu être isolés par différentes méthodes de précipitation avec de bons rendements et de bonnes puretés. En particulier, le hexafluorophosphate de potassium a été utilisé comme agent de précipitation sélectif. Par comparaison avec le réactif d'amination MSH, le TBAHS reste l'agent d'amination de choix pour la synthèse de sels de diaminopyridinium à grande échelle.

6. Synthèse des 2-amino-[1,2,4]triazolo[1,5-a]pyridines à partir de 1-(2-pyridyl)guanidines

Dans la dernière partie de notre travail, nous nous sommes concentrés sur l'élaboration d'une voie alternative conduisant aux dérivés 2-amino-[1,2,4]triazolo[1,5-a]pyridines (**3**) en évitant l'utilisation de réactifs d'amination électrophile pour des raisons de sécurité, en particulier pour des réactions sur plus grosse échelle.

La synthèse des 2-amino-[1,2,4]triazolo[1,5-a]pyridines (**3**) à partir de N-hydroxyguanidine *O*-substitué (OR = group partant) (**144**) présente une telle alternative (Schéma 20).

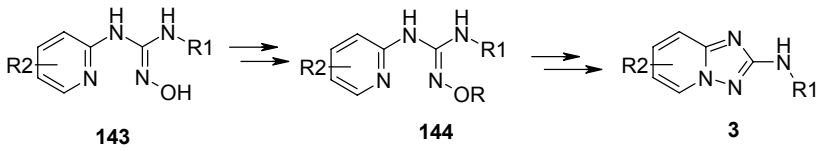
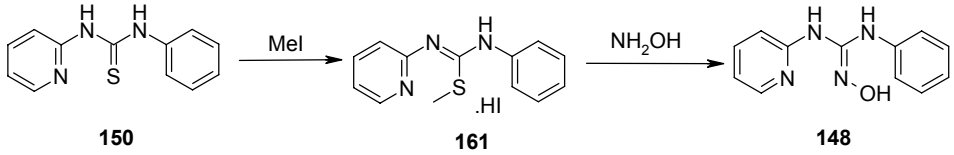


Schéma 20. Synthèse des 2-amino-[1,2,4]triazolo[1,5-a]pyridines à partir de 1-(2-pyridyl)guanidines.

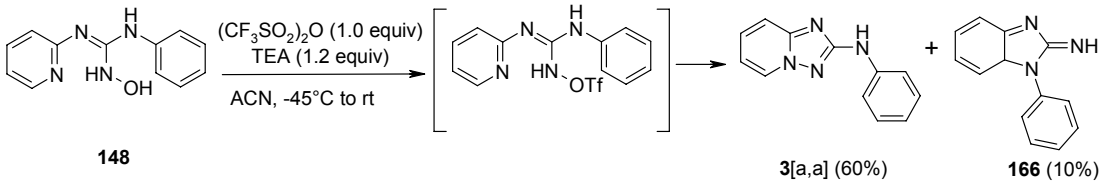
L'approche la plus efficace concernant la synthèse du composé *N*-hydroxyguanidine (**148**) comme modèle s'effectue en 3 étapes en partant d'une 2-aminopyridine. Tout d'abord, la réaction de la 2-aminopyridine avec l'isothiocyanate de phényle a donné la thiourée (**150**) correspondante. Ensuite, cette thiourée (**150**) a été convertie en *S*-methylisothiourée (**161**) par réaction avec l'iodométhane. Enfin, la réaction de **161** avec du chlorhydrate de l'hydroxylamine en présence de base a permis d'obtenir l'hydroxyguanidine (**148**) avec 64% de rendement (Schéma 21).



150 **161** **148**

Schéma 21. Synthèse de l'intermédiaire **148**.

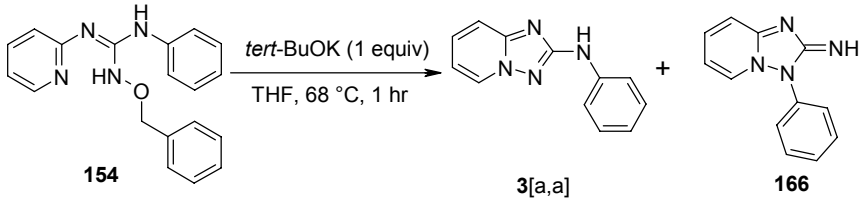
Nous avons ensuite tenté la cyclisation de l'hydroxyguanidine (**148**) par l'intermédiaire de son ester triflique comme groupe partant. La réaction de (**148**) avec l'anhydride triflique a donné directement le produit cyclisé **3**[a,a] (60%), son isomère (**166**) (10%) ainsi que d'autres impuretés (30%) (Schéma 22).



148 **3**[a,a] (60%) **166** (10%)

Schéma 22. Cyclisation de l'hydroxyguanidine (**148**) par l'intermédiaire de son ester triflique.

D'autre part, lorsque le composé benzylé (**154**) (obtenu par une autre voie de synthèse) a été traité par du *tert*-butylate de potassium, la cyclisation a conduit à un meilleur rapport isomérique **3**[a,a]/**166** de (74:20). Par ailleurs, le produit désiré **3**[a,a] a été isolé après chromatographie avec un rendement de 58% (Schéma 23). En suivant cette route, nous avons pu préparer 7 g de derivé **3**[a,a] en trois étapes avec un rendement global de 51% en partant de la 2-aminopyridine.



154 **3**[a,a] **166**

Schéma 23. Cyclisation de l'éther benzylique (**154**) par réaction avec le t-BuOK.

La dernière voie de synthèse envisagée pour la synthèse des 2-amino-[1,2,4]triazolo[1,5-a]pyridines **3**[a,a] implique la formation du carbamate (**168**) comme intermédiaire clef (Schéma 24). Nous avons montré que cet intermédiaire pouvait quantitativement être converti en **3**[a,a] par simple traitement basique (par exemple NaOH dans l'éthanol). Le mécanisme de cette transformation n'est pas complètement déterminé, mais il pourrait impliquer la formation d'un intermédiaire de type nitrène, suivi du réarrangement de ce nitrène.

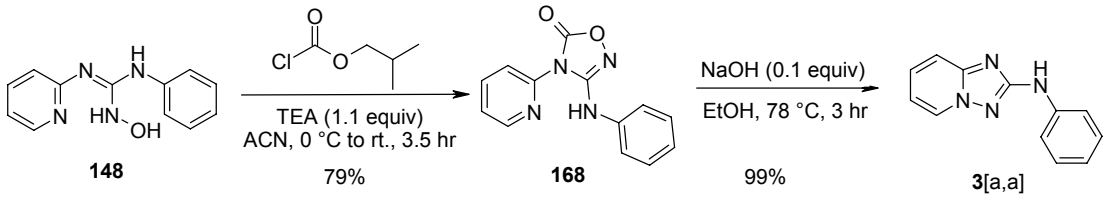


Schéma 24. Synthèse de **3**[a,a] à partir de **148**.

La chimie a été validée sur 350 mg de composé final. L'avantage principal de cette voie de synthèse est que les produits désirés sont obtenus par précipitation ou recristallisation à chaque étape. La possibilité d'appliquer cette voie de synthèse sur des quantités plus importantes reste à évaluer, de même son extension à d'autres 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines.

Abbreviations

3CC	3 component condensation
δ	chemical shift
ACN	acetonitrile
aq.	aqueous
Ar	aryl
Boc	*tert*-butoxycarbonyl
bs	broad singulet
°C	degree Celcius
calcd	calculated
COSY	correlation spectroscopy
d	doublet
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DIC	diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylfromamide
DMSO	dimethylsulfoxide
DPPH	*O*-diphenyl-phosphinyl hydroxylamine
DSC	differential scanning calorimetry
DVB	divinylbenzene
equiv.	equivalent
ESI	ElectronSpray Ionization
EtOAc	ethyl acetate
Et_2O	diethyl ether
g	gram
het	heterocycle
hr	hour
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
HSA	hydroxylamine o-sulphonic acid
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
^{i}PrOH	isopropanol
IR	infra-red
J	coupling constant
L	liter
LC	liquid chromatography
M	molar, mole per liter

m	multiplet
MAM	*N*-methyl-*N*-aminomorpholinium
MeOH	methanol
Mes	mesityl (2,4,6-trimethylphenyl)
MHz	Megahertz
min	minute
mol	mole
MSH	*O*-mesitylenesulfonyl hydroxylamine
mp	melting point
MS	mass spectroscopy
m/z	mass over charge ratio
NBH	*O*-p-nitrobenzoyl hydroxylamine
n.d.	not determined
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	nuclear magnetic resonance
ppm	parts per million
PS-Muk	polymer supported Mukaiyama's reagents
q	quadriplet
rt	room temperature
s	singulet
SPE	Solid Phase Extraction
SPOS	Solid Phase Organic Synthesis
SCX	Strong Cation exchange
t	triplet
TBAHS	tetrabutylammonium hydroxylamine *O*-sulfonate
TEA	triethylamine
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMAHS	tetramethylammonium hydroxylamine *O*-sulfonate
TMHI	trimethylhydrazinium iodide
TPPHS	tetraphenylphosphonium hydroxylamine *O*-sulfonate
UPLC	Ultra Performance Liquid Chromatography
t_R	retention time

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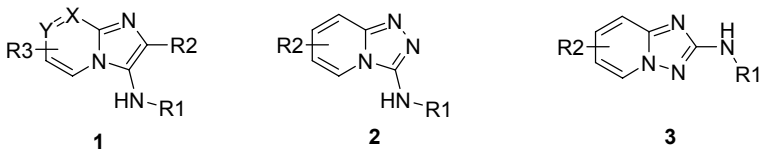
1. Introduction

1.1. Project outline

Nowadays, in many pharmaceutical companies there is a strong need to revitalize their corporate compound collection with novel proprietary molecules to enhance the likelihood of finding active compounds that could lead to new drugs. In the present work, we focused in the synthesis of novel aza-heterocycles as a potential class of biologically active compounds. In particular, we focused our work on the synthesis of 3-aminoimidazo[1,2-*a*]azines (**1**), 3-amino-[1,2,4]-triazolo[4,3-*a*]pyridines (**2**) and 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**) (Figure 1).



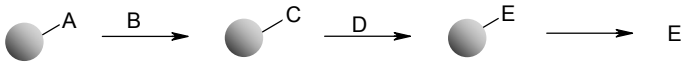
X,Y = CH or N
R1 = alkyl, (hetero)-aryl, acyl
R2 = alkyl, (hetero)-aryl, acyl, halogen
R3 = alkyl, (hetero)-aryl

Figure 1. Novel aza-heterocycles.

The aim was to generate a large number of new compounds in a clean, fast, and efficient manner. Therefore, during these investigations we privileged state-of-the-art techniques for parallel synthesis over standard methods of synthesis since an optimized and easy protocol is required in order to increase the throughput of the synthesized compounds.

1.1.1. Solid phase synthesis, supported reagents and scavengers.

The methodology introduced by Merrifield in 1963[1] for peptides synthesis has evolved and now is known as *Solid Phase Organic Synthesis* (SPOS). It consists in using a polymeric resin or other solid material to support a substrate, which can then be elaborated before it is detached from the support material and isolated following a simple filtration (Scheme 1).

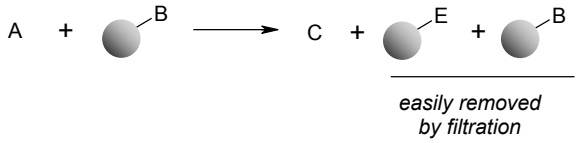


Scheme 1. Concept of SPOS

The advantages gained by this methodology are: i) Simple protocol for the synthetic step: addition of reagents, filtering, and washing the resin, thus allowing many simple automated procedures to be developed. ii) The elimination of purification steps in route. For each step of a multiple-step synthesis, the only purification needed is a resin-washing step. Only the final product of cleavage might need to be purified. iii) High concentration of the reagents can be

used to drive reactions to completion. The main drawback of SPOS might be the difficulty to monitor the reaction progress since the product is attached to the insoluble support.

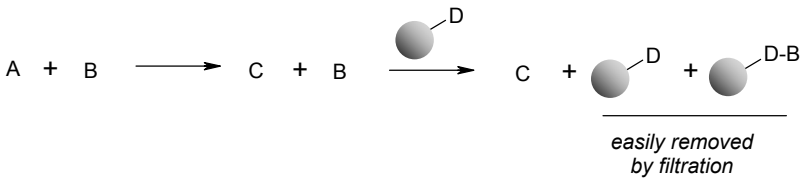
A complementary approach to SPOS is the use of *supported reagents*, which are defined as "reactive species which are associated with a support material. They transform a substrate (or substrates) to a new chemical product (or products) and the excess or spent reagent may be removed by filtration" (Scheme 2).[2]



Scheme 2. Concept of the use of supported reagents.

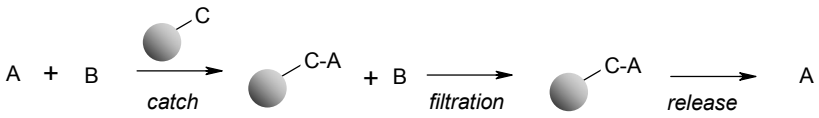
When supported reagents are used, the reactions can be optimized readily because they can be constantly monitored using conventional chromatographic methods (TLC, HPLC, LC/MS, NMR). In addition, because the chemistry in carried out in solution, they often require only minimal optimisation compared to that involved on transferring a solution phase reaction onto a polymer-bound substrate. A key advantage is that it is possible to use an excess of the supported-reagent to drive the reaction to completion since it can be easily removed by simple filtration and further purification of the desired product is often not required.

Supported scavengers are an alternative to the precedent methods or can even be used in combination with *supported reagents*. They were defined as "reactive species which are associated with a support material. They selectively quench or sequester by-products of the reaction or remove excess or unreacted starting materials and may be removed by filtration" (Scheme 3). [2]



Scheme 3. Concept of the use of supported scavengers

Another possibility to make the isolation of the product easier consists on the "*catch and release*" technique defined as "a technique used to selectively trap the desired product of a solution-phase reaction onto a functionalised support material. Following filtration (and washing) to remove solution-phase contaminants, the compound may then be released from the support " (Scheme 4).[2]



Scheme 4. Concept of "catch and release".

For instance, any basic compound can be caught with a supported-sulfonic acid (*e.g.* Dowex) and the impurities washed-off before releasing the compound with a solution of ammonia.

Typical supports used for SPOS or to support reagents/scavengers consist of polystyrene with a 1-2% DVB cross-linking. These insoluble supports have a gel-type structure, which readily allows penetration of reagents and solvents into the beads to sites where chemistry is taking place. The three dominant polystyrene supports currently in use are chloromethylpolystyrene, hydroxymethylpolystyrene and aminomethylpolystyrene. Typically, these solid supports are used with DCM, DMF or THF as solvent, since they ensure a good swelling of the beads and polar protic solvents such as methanol might be avoided. On the contrary, silica-supported reagents/scavengers can be used with polar solvents and usually have a better mechanical resistance compared with the polystyrene supports.

1.1.2. Solid phase extraction columns

Both "*catch and release*" principle and the use of *supported scavengers* can be done on a "batch" manner (*i.e.* adding the supported material to the reaction mixture and then filtered-off) or in columns which are filled with the adequate sorbent. Today, some of these columns are commercially available and known as SPE (solid phase extraction) columns. The most common sorbents are sulfonic acid, primary amine, quaternary ammonium and thiol functions anchored to a silica support (Figure 2).[3]

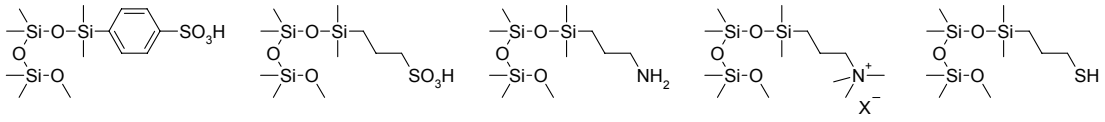


Figure 2. Most common sorbents in SPE columns.

For a successful purification, the reagents and eventual side-products must have different affinity respect to the product towards the sorbent (usually acid/base/neutral properties). When they have not, it is necessary to consume during the reaction, the reagent that has the same acid/base/neutral behaviour than the desired compound (for example using this reagent in default respect to the others). The reaction of an amine with an excess of acyl chloride in presence of triethylamine was chosen as an example to illustrate this methodology. When the reaction mixture is passed through a SPE-NH_2 column, the excess of acyl chloride and the

hydrogen chloride are scavenged and the amide eluted with the resulting triethylamine that can be removed together with the solvent (Figure 3).

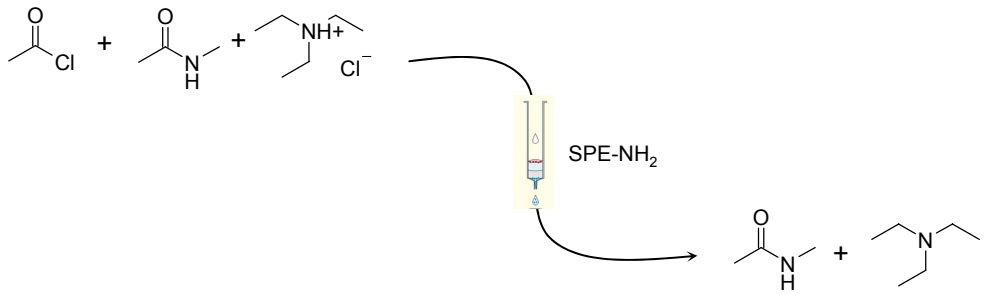


Figure 3. Concept of purification of an amide through a SPE-NH_2 column.

This technique is different from chromatography on silica since, from the practical point of view, it is usually a simple filtration.

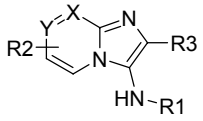
1.2. Project aims.

The main goal of this work was to develop a robust protocol for the synthesis of each aza-heterocycle **1**, **2** and **3**, under mild conditions tolerable by many functional groups that can produce in parallel many compounds in good purity, requiring a minimum of experimental steps. In addition, we also considered the tractability of the developed pathway to be transferred to a larger scale. The novelty of the concerned heterocycle will be discussed in details at the beginning of the corresponding chapter.

2. Synthesis of 3-aminoimidazo[1,2-*a*]azines

2.1. Introduction and project aims.

In the beginning of our work, we were interested in the synthesis of 3-aminoimidazo[1,2-*a*]azines (**1**) as pharmaceutically relevant class of aromatic heterocycles (Figure 4).



1

X	Y	
CH	CH	imidazo[1,2-*a*]pyridine
CH	N	imidazo[1,2-*a*]pyrazine
N	CH	imidazo[1,2-*a*]pyrimidine

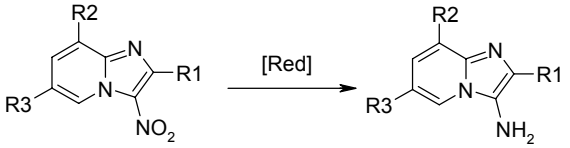
R1 = alkyl, (hetero)-aryl, acyl
R2 = alkyl, (hetero)-aryl, acyl, halogen
R3 = alkyl, (hetero)-aryl

Figure 4. 3-Aminoimidazo[1,2-*a*]azines (**1**)

The synthesis of **1** has already been described following different pathways as is shown in the next section. The aim of the present work was to develop a robust and general protocol appropriate for the synthesis of a 1000-3000 members library. Therefore, this protocol should include synthetic and purification techniques suitable for parallel synthesis. In particular, solid phase synthesis and the use for the purification of solid phase extraction columns (SPE columns) were considered in order to achieve our purpose.

2.1.1. Previous syntheses in solution phase

The first 3-aminoimidazo[1,2-*a*]azines (**1**) were synthesised *via* reduction of the corresponding nitro derivative. For instance, reduction of the 3-nitroimidazo[1,2-*a*]pyridines **4** afforded the expected heterocycles **5** in poor to moderate yields (24-57%) depending on the substitution and on the reducing agent used (Scheme 5).[4-6]

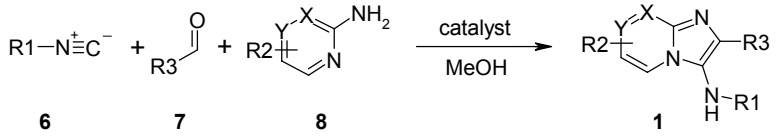


4 **5**

R1	R2	R3	[Red]	yield (%)
COOEt	H	H	NaSH	57
COOEt	H	Me	NH_2NH_2/Pd	50
Me	BnNH	H	$SnCl_2$/HCl	24

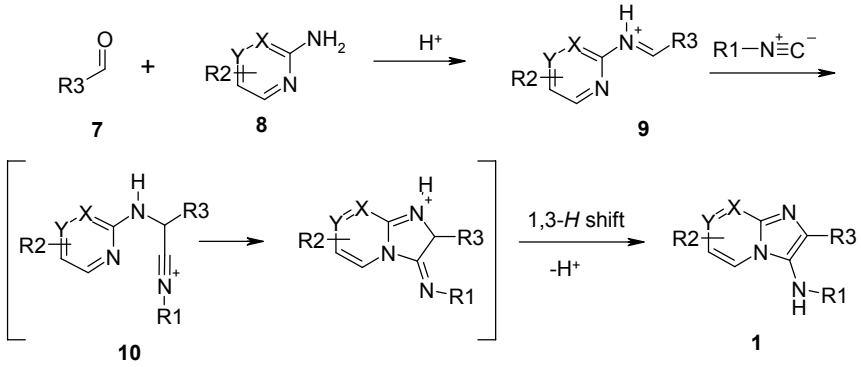
Scheme 5. Synthesis of 3-aminoimidazo[1,2-*a*]pyridines **3** from the nitro derivative.

It was in 1998 when three independent pharmaceutical research groups simultaneously reported a much more convenient and versatile synthesis of 3-aminoimidazo[1,2-*a*]azines (**1**).[7-9] This reaction consisted in a three-component condensation (3CC) between an isocyanide (**6**), an aldehyde (**7**) and a heterocyclic amidine (**8**) under acid catalysis (Scheme 6). Since then, the increase in the number of papers describing the synthesis of **1** demonstrates the interest of such compounds, especially in the pharmaceutical area.[10-14]



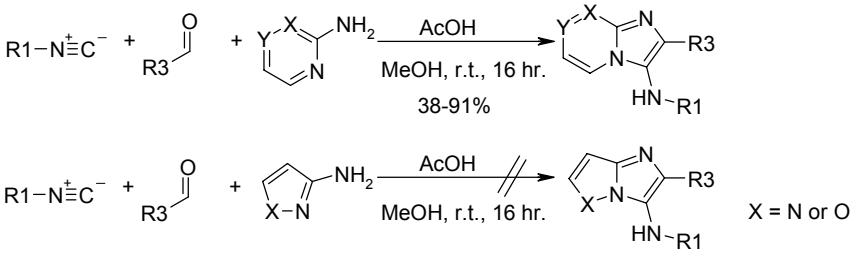
Scheme 6. Synthesis of 3-aminoimidazo[1,2-*a*]azines (**1**) through a 3CC.

The reaction proceeds presumably *via* an iminium species **9**,[7-9] which is attacked by the isocyanide with the formation of **10** (Scheme 7). Intramolecular cyclisation followed by deprotonation and 1,3-*H* shift results in the formation of the fused heterocycle **1**.



Scheme 7. Plausible mechanism for the 3CC.

In one of the first reports,[7] the reactions were carried out with equimolecular amounts of the three components in methanol in presence of acetic acid (1.0-2.0 equiv) as catalyst at ambient temperature overnight (Scheme 8). Under these conditions, six-membered heterocyclic amidines afforded the corresponding fused heterocycles in moderate to good yields (38-91%) after purification by chromatography column or crystallization. On the contrary, these conditions were completely ineffective for five-membered heterocyclic amidines like isoxazoles or pyrazoles and formation of complex products mixtures were observed.



Scheme 8. Synthesis of 1 under acetic acid catalysis

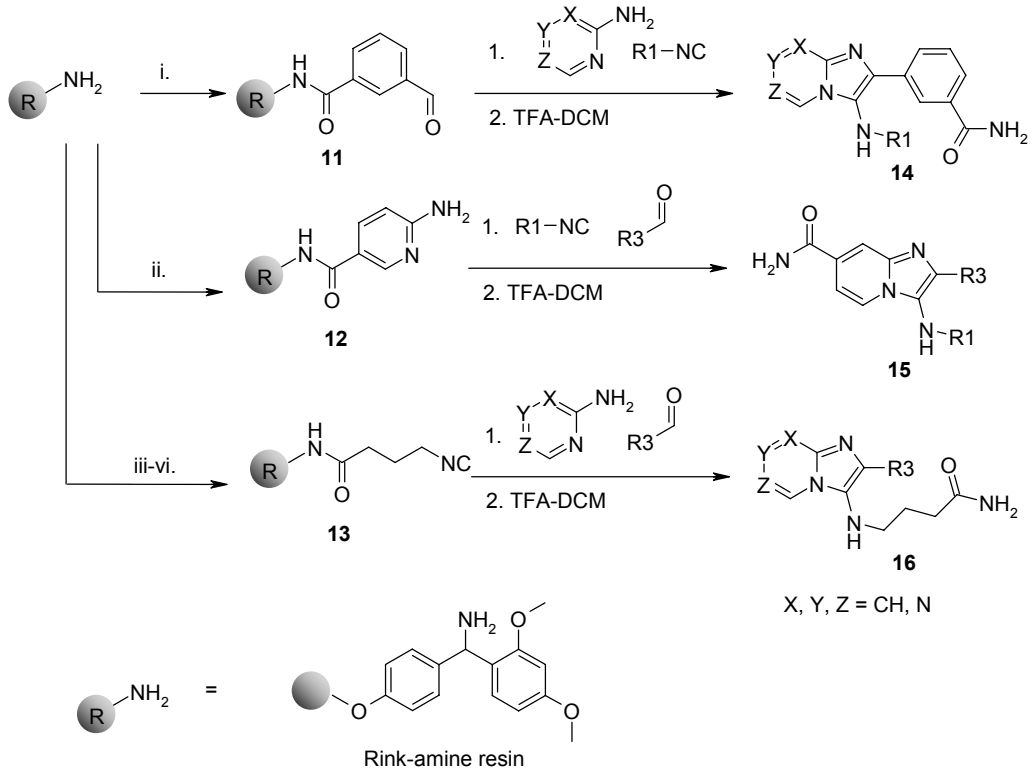
Later, the substrate scope was explored more in details.[9] During these experiments the aldehyde (1.0-3.0 equiv) and isocyanide (1.2-1.5 equiv) were used in excess respect to the

cyclic amidine. The reactions were carried out in methanol with perchloric acid (0.1 equiv) as catalyst at ambient temperature overnight. Under these conditions, five and six-membered heterocyclic amidines afforded the respective heterocycles in poor to good yields (33-95%) after an aqueous work-up followed by recrystallization. Aldehydes and isocyanides did not represent a major limitation for this reaction while the heterocyclic amidine showed to be the most problematic partner. The reaction with electron-poor amidines (*e.g.* 2-amino-3,5-dibromopyridine or 2-aminopyrimide) tended to be slow and side-products accumulated.

The first microwave-assisted synthesis of imidazo[1,2-*a*]azines (**1**) was reported under solvent-free conditions on clay.[11] The usual long reaction time required for this conversion (16 hr at ambient temperature) was reduced to 1 minute under microwaves irradiation (household microwave, potency: 900 W, temperature not specified). Fused aminopyridines and pyrazines were isolated in good yields (81-88%) by crystallization or by chromatography column. On the contrary, the pyrimidine derivatives were obtained in lower yields (56-58%) because the reaction was not complete. Another approach using microwave irradiation was reported but this time in solution and using scandium triflate as catalyst.[14] The reactions were carried out at 160 °C (200 W) for 10 min and the heterocycles were obtained in poor to good yields (33-93%) after purification by chromatography column. The lowest yields corresponded to the thiazole and pyrazine derivatives.

2.1.2. Previous syntheses in solid phase

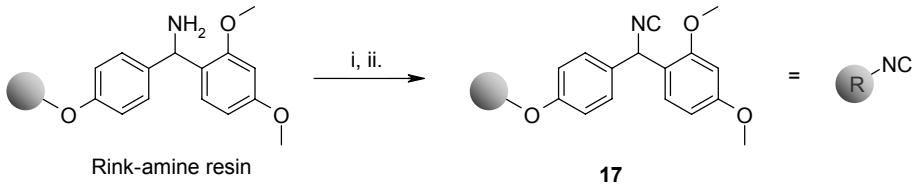
One of the three groups who discovered this reaction promptly attempted to perform it on solid phase with any of the three reacting partners tethered to a solid support.[15] The aldehyde, the isocyanide or the heterocyclic amidine were anchored to the Rink-amine resin *via* an appropriate bifunctional carboxylic acid to give the resins **11**, **12** and **13**, respectively (Scheme 9).



Scheme 9. Solid phase synthesis of **1**. i) 3-Carboxybenzaldehyde, HATU, DIPEA. ii) 6-Aminonicotinic acid, HATU, DIPEA. iii) Fmoc-GABA-OH, HATU, DIPEA. iv) Piperidine-DMF (1:4). v) 2,3,5-Trichlorophenyl-formate, DMF. vi) CCl_4, TEA, DCM.

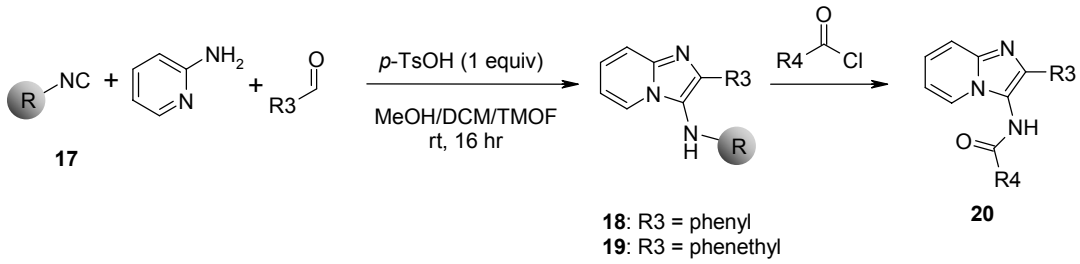
The 3CC was performed in methanol/DCM at ambient temperature in presence of scandium triflate (0.05 equiv) as catalyst. After 48 hr, the resins were washed and then cleaved using two treatments with TFA-DCM (1:1) at ambient temperature. Resin **11** afforded the products **14** in good purities (92%), except when 4-aminopyrimidine was used (X = Y = CH, Z = N) that only 3-formylbenzamide was recovered. The reaction with resin **12** proceeded well and the products **15** were recovered in good purities (>82%). With the isocyanide resin **13** lower purities (60-85%) were obtained with 2-amino -pyridine, -pyrazine and -pyrimidine and only traces (10%) of the desired product with 4-aminopyrimidine. The isolated yields were not reported. The calculated yields extracted from a calibration curve suggested that the products were obtained in poor to good yields (20-80%). Unfortunately, the applicability of this approach is limited to a specific substitution (carboxamide derivatives only), since all the products beard evidence of the resin attachment.

Rink-amine resin was later used for solid phase synthesis of **1** but in a different manner.[13] This resin was converted into an isocyanide resin **17** after formylation followed by dehydration of the resulting formamide (Scheme 10).



Scheme 10. Preparation of Rink-isocyanide resin **17**. i) Formic acid/DIC. ii) $POCl_3$/DIPEA

This Rink-isocyanide resin **17** was then used for the synthesis of polymer-bound imidazopyridines **18** and **19**, which were acylated with simultaneous cleavage to afford the amide derivatives **20** (Scheme 11). These amides were isolated by *catch and release* using DOWEX ion-exchange resin in poor to moderate crude yields (23-60%) and further purified using chromatography column (yields of pure products not reported). Through this pathway, only *N*-acyl derivatives **20** could be synthesized. Direct cleavage of **18** and **19** to give the *N*-unsubstituted derivatives was not attempted in this report.



Scheme 11. Use of Rink-isocyanide in the synthesis of *N*-acyl derivatives of **1**.

The same year, a similar patented procedure was disclosed showing that polymer-supported imidazopyridines could be directly cleaved from the Rink linker using HCl (4M) in DCM/dioxane 1:1 or TFA (20%) in DCM, affording the *N*-unsubstituted derivatives in good purities (>75%).[12]

*2.1.3. Development of a new isocyanide resin for the solid phase synthesis of **1**.*

These previous studies suggested that the 3CC between an isocyanide, an aldehyde and a heterocyclic amidine is the most convenient route for the synthesis of 3-aminoimidazo[1,2-*a*]azines (**1**). Unfortunately, most of the described reaction conditions lacked of generality to synthesize 1000-3000 members library.

We consider the synthesis on solid phase a valid option for our purpose, since it could be easily automated. The most attractive strategy would be to anchor the least readily available component, namely the isocyanide, to the solid support. The readily available isocyanide

resins that could act as a traceless linker[a] for 3-aminoimidazo[1,2-*a*]azines (**1**) are depicted in Figure 5. Most of them have been already patented (**17**, **21**-**24**),[12] as well as their use in the 3CC. Therefore, we decided to develop our own isocyanide resin to have freedom to operate.

When these resins **17**, **21**-**24** were used in the 3CC, high concentration of HCl (4 M) or the use of TFA (20% in DCM) was necessary to release the product **1** from the solid support.[12] TFA is not particularly convenient to be used with the Rink linker since it can cleave some of the Rink linker from polystyrene support and introduce colored impurities into the cleaved product.[16] In addition, the use of high concentration of TFA can lead to trifluoroacetylated side-products.

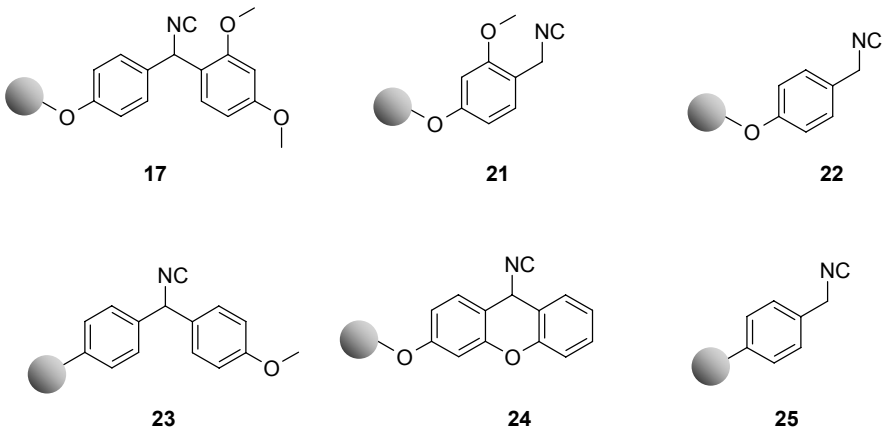


Figure 5. Possible traceless isocyanide resins for the synthesis of **1**.

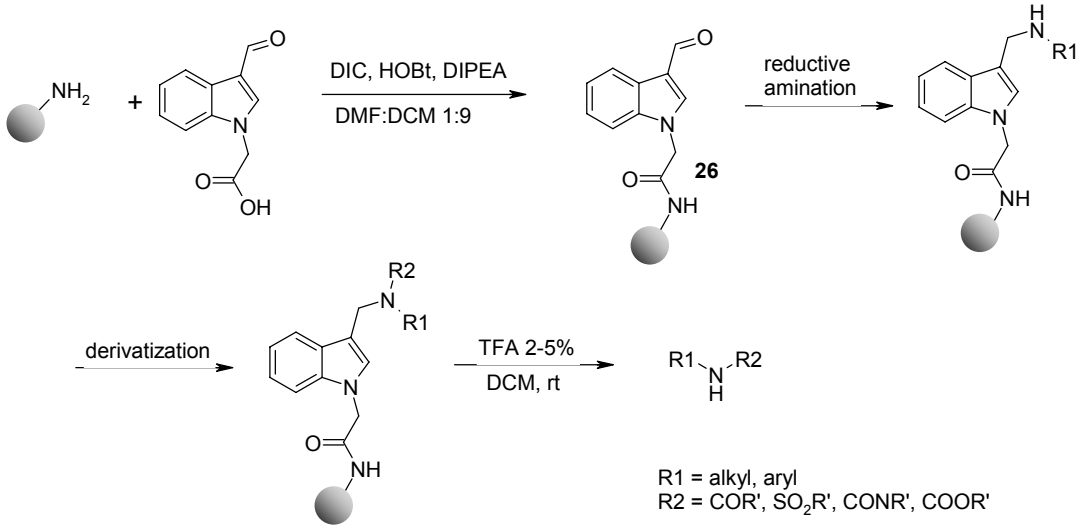
Concerning the isocyanide resins (**25**) that can be easily obtained from the commercially available aminomethylpolystyrene,[17] we could anticipate that it would require harsher conditions as compared to Rink (**17**) or Sieber (**24**) resin, since the latter are known for being one of the most acid sensitive linkers for amines. Therefore, we decided to investigate another type of linker which structure is completely different from the ones presented before that could release the product **1** under milder conditions as compared with the *N*-(alkoxybenzyl)-substituted isocyanide resins discussed above.

Looking for milder cleavage conditions, Estep *et al*. has developed a non-integral indole linker (**26**)[18] for the synthesis of amides, sulfonamides, ureas and carbamates which needs 2-5% TFA/DCM to release most of the products from the resin (Scheme 12).[18,19] Variations of this linker is now commercialized by one of the major vendors of resins.[b] It consists on an indole-carbaldehyde core linked to a solid support through an amide spacer. The amines are bound

[a] *Traceless linker*: the released compound reveals no trace of the point of attachment to the solid support.

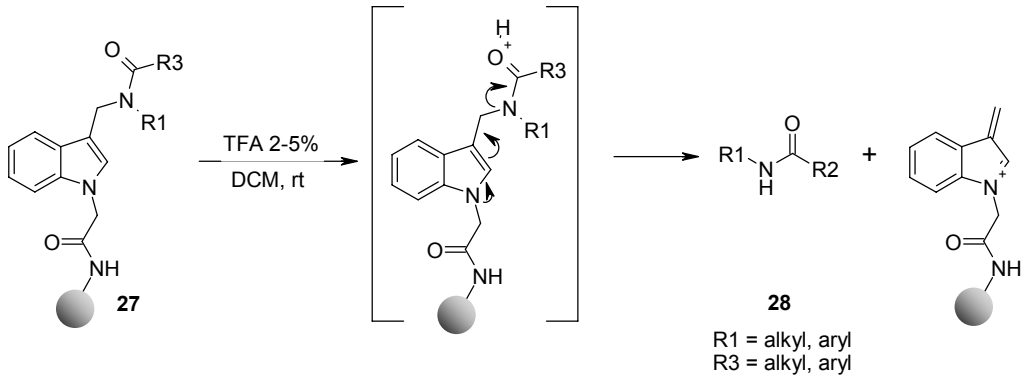
[b] Novabiochem, catalogue number 01-64-0398 and 01-64-0451

to the linker *via* reductive amination with the aldehyde group and further derivatized (acylated, sulfonylated, etc) prior cleavage.



Scheme 12. Synthesis of amides, sulfonamides, ureas and carbamates using Estep's indole linker.

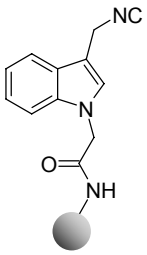
The proposed mechanism[18] for the cleavage is exemplified with the amide derivative **27** (Scheme 13). It probably proceeds *via* protonation of the amide and elimination of the product **28** from the electron-rich indole core. It is worth to highlight that under these mild cleavage conditions, the amide spacer showed to be stable and indole-containing by-products were not observed. Interestingly, an aniline derivative (R1 = 3,5-diMe-4-OTBS-phenyl) was released from the resin in excellent yield despite the absence of an activating R2 capping group (R2 = H).[18]



Scheme 13. Plausible mechanism for the cleavage from the indole linker.

We considered the isocyanide version of this linker (**29**) (Figure 6) particularly interesting since it would allow to release the products under milder conditions as compared to the use of the Rink-isocyanide (**17**) previously described. Besides, the spacer together with the indole core will distance chemistry from the solid support avoiding steric and electronic interferences

with the resin and giving more “solution-like” properties. To the best of our knowledge this indole-isocyanide resin has not been described yet.

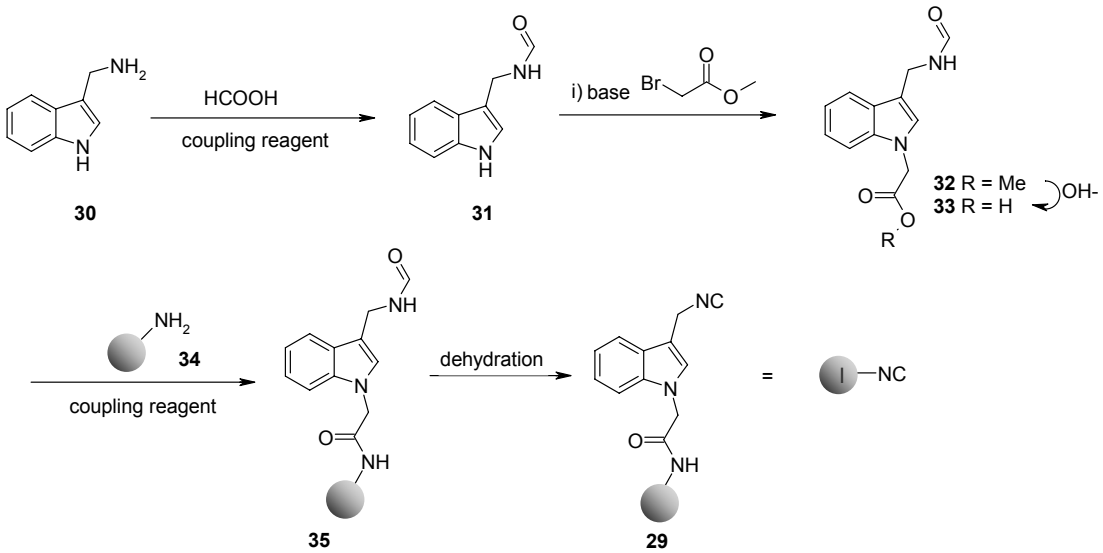


29

Figure 6. Indole-isocyanide resin **29**.

2.1.3. Objectives

The aim of the present work was to develop a robust and general protocol appropriate for the synthesis of a 1000-3000 members library of 3-aminoimidazo[1,2-*a*]azines (**1**). The first objective was to synthesize the new indole-isocyanide resin **29** from 3-(aminomethyl)indole **30**, following the pathway depicted in Scheme 14.

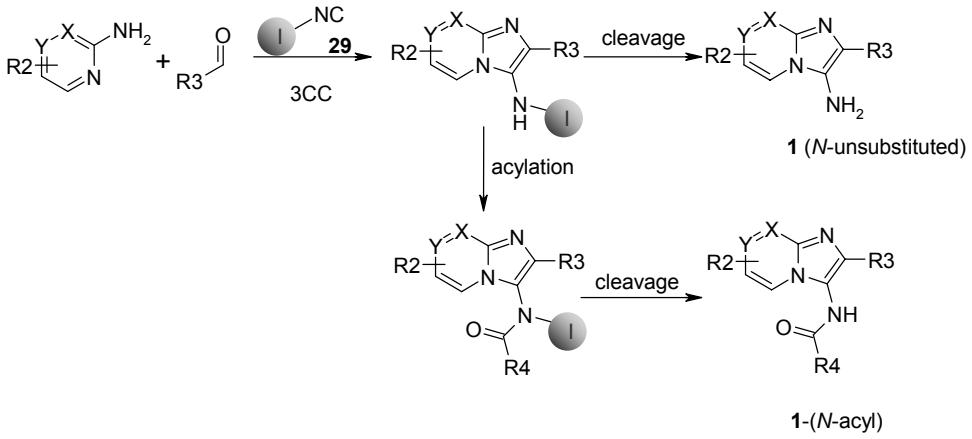


30 **31** **35** **29**

Scheme 14. Proposed synthetic pathway for the synthesis of the indole-isocyanide resin **29**.

We planned to perform the formylation of the primary amine of **30** (as a precursor of the isocyanide moiety) in the first step since it can act at the same time as the protecting group needed for the alkylation step. The spacer could be then be introduced *via* alkylation of 3-(formylaminomethyl) indole **31** with methyl bromoacetate. Further hydrolysis of the resulting ester **32** would allow the attachment of intermediate **33** into the aminomethylpolystyrene resin (**34**) through an amide bond. In the last step, dehydration of polymer-supported formylamino derivative **35** would give the indole-isocyanide resin **29**.

Once achieved the first obejctive, we planned to perform the synthesis of **1** using **29** according to Scheme 15.



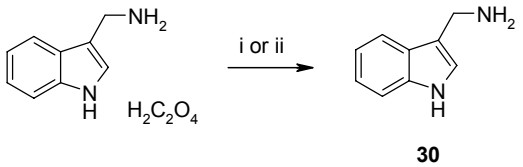
Scheme 15. Synthesis of **1** using the indole-isocyanide resin **29**.

Through this solid phase approach we expected to prepare many compounds in parallel in good purity and requiring a minimum of experimental steps in a semi-automated manner.

2.2. Discussion

*2.2.1. Synthesis of the indole-isocyanide resin **29**.*

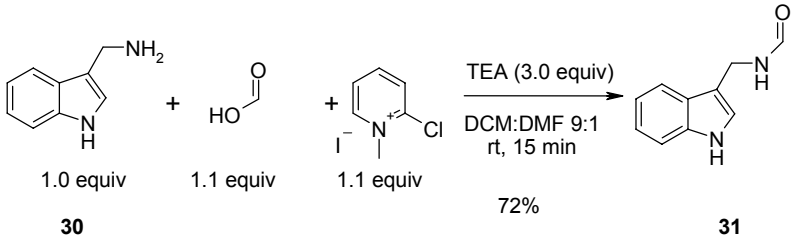
3-(Aminomethyl) indole is commercially available as its oxalate salt. It was necessary to remove the oxalate before the amide bond formation as it could compete with the formic acid during the formylation step. Performing standard liquid-liquid extractions in basic media (EtOAc/aqueous $NaHCO_3$) allowed to recover only 10% of the free base from the organic phase. Alternatively, the desalification of the oxalate salt was successfully performed using SPE-NH_2 column and MeOH as eluent and 3-(aminomethyl) indole free base was recovered in 94% yield (Scheme 16).



i: $NaHCO_3$ (aq)/EtOAc, 10% recovery
ii: SPE-NH_2/MeOH, 94% recovery

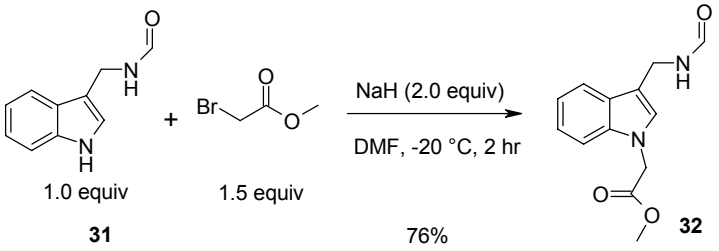
Scheme 16. Isolation of **30** as free base.

The formylation of **30** with formic acid was performed in a mixture DCM/DMF 9:1 in presence of Mukaiyama's coupling reagent and triethylamine at ambient temperature for 15 min (Scheme 17). After purification by flash chromatography, compound **31** was obtained in 72% yield.



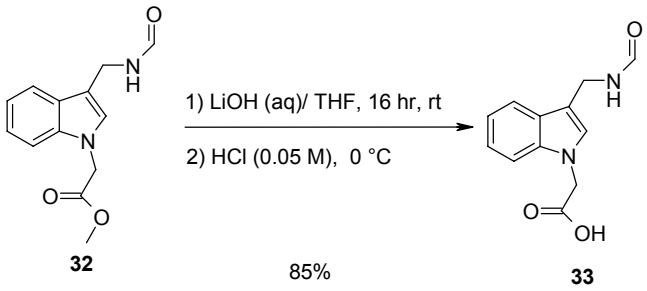
Scheme 17. Synthesis of 3-(formylaminomethyl)indole **31**.

The spacer was introduced *via* alkylation of the indole core with methyl bromoacetate (Scheme 18). The highest conversion (86%) was obtained when **31** was stirred with sodium hydride (2.0 equiv) in DMF at –20 °C for 30 min before the addition of methyl bromoacetate (1.5 equiv) and stirred at such temperature for an extra 1.5 hr. Longer reaction time or higher temperature (-20 °C to ambient temperature) was inefficient to drive the reaction to completion and also side-products were observed. After purification by flash chromatography, compound **32** was obtained in 76% yield.



Scheme 18. Alkylation of **31** with methyl bromoacetate

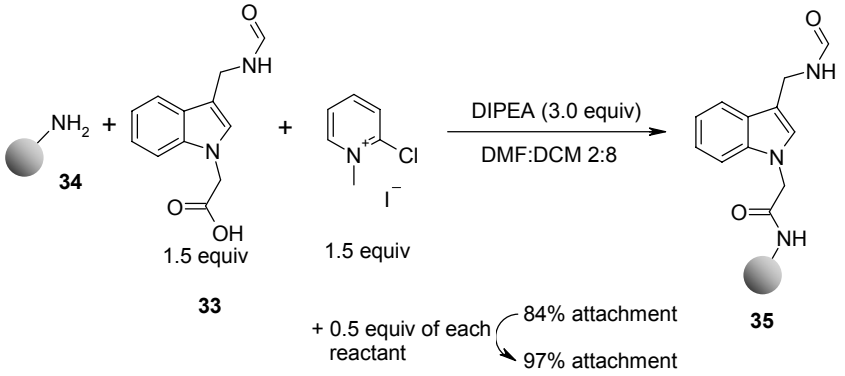
The hydrolysis of the ester **32** was performed with lithium hydroxide in a mixture THF/water at ambient temperature for 16 hr. After addition of hydrochloric acid to reach pH 3 followed by evaporation of volatiles, the expected product **33** was isolated by simple filtration in 85% yield. The acidification was done using diluted HCl (0.05 M) at low temperature (0 °C) to avoid potential cleavage of the formamide group of **33** under stronger acidic conditions (Scheme 19).



Scheme 19. Hydrolysis of **32**.

With the acid **33** in hands, we proceeded to the attachment on the aminomethyl polystyrene (**34**) as the solid support. The main disadvantage in solid phase synthesis is the difficulty to follow the reaction when the expected product is attached to the resin. IR spectroscopy, together with colorimetric tools has been used to overcome this issue but in most of the cases, they are just qualitative.[20] However, there are a few useful assays such as Kaiser test, to determine quantitatively primary amines attached to solid supports.[21,22] This technique involves the reaction of free primary amine with ninhydrin under carefully controlled conditions and the determination of the resulting chromophore in solution at 570 nm. In this way we could follow quantitatively the attachment of **33** by determination of the unreacted primary amines remaining on the solid support.[c]

The reaction of acid **33** (1.5 equiv) with aminomethyl polystyrene (1.0 equiv) was carried out in a mixture DMF/DCM 2:8 at ambient temperature in presence of using Mukaiyama's coupling reagent (1.5 equiv) and DIPEA (3.0 equiv) (Scheme 20). After 16 hr, 84% of the acid **33** was attached to the resin. It was necessary to repeat the procedure but using 0.5 equiv of each reactant to finally reach 97% of attachment as determined by Kaiser test.

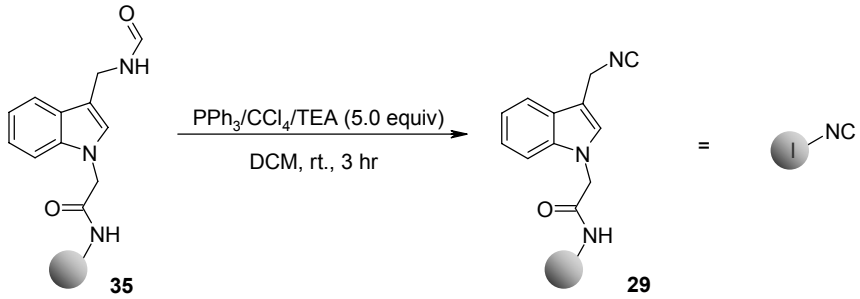


Scheme 20. Attachment of **33** into aminomethylpolystyrene.

The last step in the synthesis of the idole-isocyanide resin **29** consisted in the dehydration of the formamide moiety. The reaction of the formylamino resin **35** was carried out using

[c] It was assumed that only **33** could be loaded into the resin.

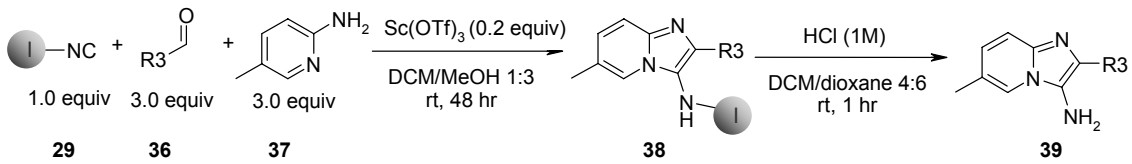
triphenylphosphine (5 equiv) and carbon tetrachloride (5 equiv) in presence of triethylamine (5 equiv) in dichloromethane at ambient temperature for 3 hours. The IR spectrum of the resin **29** showed the isocyanide stretching band at 2145 cm^{-1}.



Scheme 21. Dehydration of **35** to obtain indole-isocyanide resin **29**.

2.2.2. Solid phase synthesis of 3-aminoimidazo[1,2-a]pyridines

We first examined the application of idole-isocyanide resin **29** in the synthesis of 3-aminoimidazo[1,2-*a*]pyridines **39**. The reaction of **29** with 2-amino-5-methylpyridine **37** (3 equiv) and the corresponding aldehyde **36** (3 equiv) was performed in DCM:MeOH 1:3 in presence of scandium triflate (0.2 equiv) at ambient temperature for 48 hr (Scheme 22).



Scheme 22. Solid phase synthesis of **39** using indole-isocyanide resin **29**.

The resin **38** was thoroughly washed to remove the excess of reagents and catalyst and then treated with different acid solutions to promote the cleavage of the products from the solid support. It turned out that 1 M solution of hydrogen chloride in DCM:dioxane was enough to release the expected heterocycles **39** (Table 1). More diluted HCl solutions gave lower recovery.

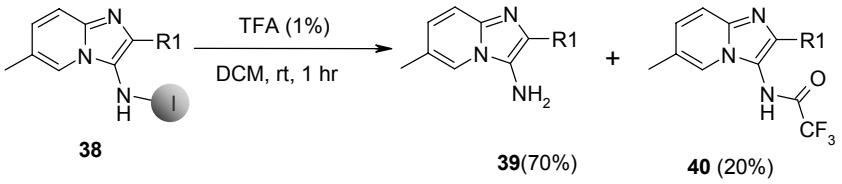
entry	R3	39	yield (%)†
1	Ph	**39a**	76
2	3-(PhO)-Ph	**39b**	53
3	4-(AcN)-Ph	**39c**	55
4	4-Cl-Ph	**39d**	66
5	cyclohexyl	**39e**	94

† Isolated yield of pure compound after cleavage as hydrochloride salt.

Table 1. Cleavage of resin-bound aminoimidazopyidines **38**.

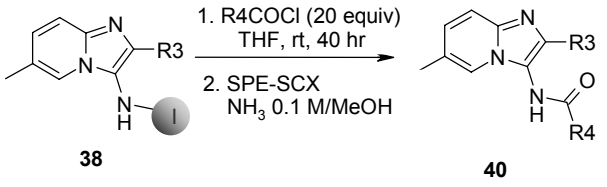
We were pleased to observe that the indole linker released the heterocycles **39** under relatively milder conditions and in better purities (>96%) as compared with the Rink-isocyanide resin (see page 9). The expected heterocycles **39** were obtained in moderate to good yields (55-94%) as the hydrochloride salt. Aryl aldehydes bearing electron donating or withdrawing groups were tolerated (entries 1-4) as well as alkyl aldehydes (entry 5).

In the course of our studies on the cleavage step, we observed that TFA was not appropriate since the product were recovered contaminated with the trifluoroacetamide analogues **40** (Scheme 23).



Scheme 23. TFA induced cleavage of **38**.

With regards to these results, our interest was focused on the potential ability of **38** to allow concomitant acylation and spontaneous cleavage in presence of acyl chloride, since HCl is generated upon acylation. The reaction of **38** with the corresponding acyl chloride (20 equiv) was performed in THF at ambient temperature for 40 hr. The *N*-acylated derivatives **40** were isolated from the excess of acyl chloride using *catch and release* in a SPE-SCX column (Scheme 24).



For R3 and R4 see Table 2

Scheme 24. Acylation and expontaneous cleavage of **38**.

Similar results were obtained with **38a** and **38e** (R3 = phenyl and cyclohexyl respectively) and the corresponding acylated products were obtained in high purity but poor yields (12-34%) with diverse acyl chlorides (Table 2). The exception was the reaction with benzoyl chloride, which gave a mixture acylated/deacylated product (61:37) with **38a** (entry 4).

entry	R3	R4	40	yield (%)†
1	Ph	benzyl	**40a**	12‡
2	Ph	cyclohexyl	**40b**	21
3	Ph	isobutyl	**40c**	23
4	Ph	phenyl	**40d**	n.d.§
5	cyclohexyl	benzyl	**40e**	15
6	cyclohexyl	cyclohexyl	**40f**	22
7	cyclohexyl	isobutyl	**40g**	34
8	cyclohexyl	phenyl	**40h**	41

† Isolated yield of the pure compound **40** after SPE-SCX column except if other is indicated.

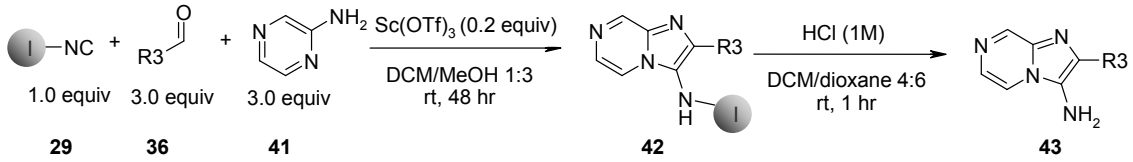
‡ Mixture of **40**/**38** 85:9. § Mixture of **40**/**38** 61:37 was obtained

Table 2. Acylation and expontaneous cleavage of **38**.

The first results were particularly encouraging since, when the Rink-isocyanide resin was used in a similar approach, the products had to be purified by chromatography column after the *catch and release* process.[13]

2.2.3. Solid phase synthesis of 3-aminoimidazo[1,2-a]pyrazines.

The next goal was the above protocol with less reactive heterocyclic amidines, in particularly with 2-aminopyrazine **41**. The reaction of **29** with **41** (3 equiv) and the corresponding aldehyde **36** (3 equiv) was performed in DCM:MeOH 1:3 in presence of scandium triflate (0.2 equiv) at ambient temperature for 48 hr (Scheme 25). The resin **42** was thoroughly washed to remove the excess of reagents and catalyst and then treated with a 1 M solution of hydrogen chloride in DCM:dioxane to release the expected products from the solid support.



For R3 see Table 3

Scheme 25. Solid phase synthesis of **43** using indole-isocyanide resin **29**.

Unfortunately, the cleavage of the polymer-bound imidazopyrazines **42** released the corresponding products **43** in lower purity as compared to **39**. The main impurity was the

starting 2-aminopyrazine (**41**) that remained in the solid-support despite of the extensive washings. The difference in polarity between **43** and 2-aminopyrazine **41** allowed the purification by a short plug of silica affording the pure **43** but in low yields (Table 3).

entry	R3	43	yield (%)[†]
1	Ph	**43**a	27
2	3-(PhO)-Ph	**43**b	17
3	4-(AcN)-Ph	**43**c	23
4	4-Cl-Ph	**43**d	55
5	cyclohexyl	**43**e	32

[†] Isolated yield of pure compound after short plug of silica.

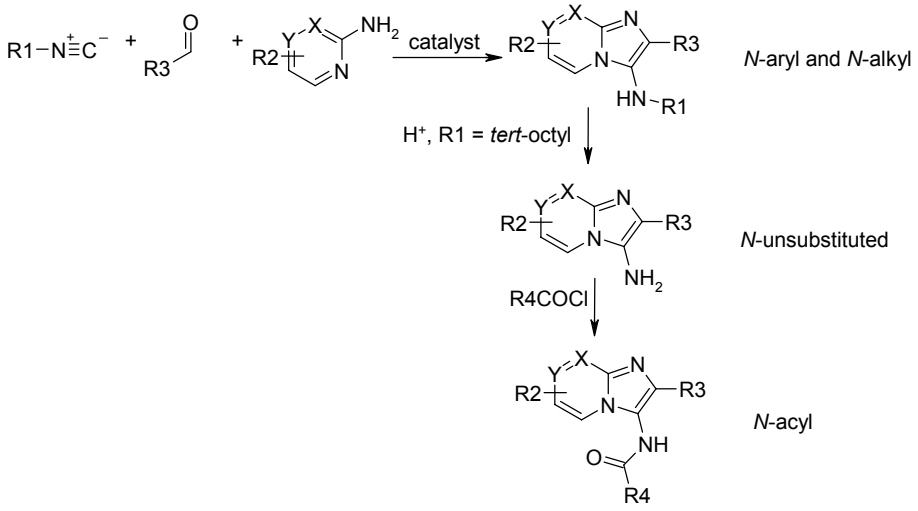
Table 3. Cleavage of resin-bound aminoimidazopyridazines **42**.

Similar results were obtained with other heterocyclic amidines (*e.g.* 2-amino-5-chloropyridine, 2-aminopyrazine and 2-amino-5-trifluoromethylpyridine among others). After the cleavage, the expected product was obtained in low purity and therefore, a further purification step was required. This fact prompted us to investigate a solution phase approach coupled to a purification by solid phase extraction (SPE) columns.

2.2.4. Solution phase synthesis of 3-aminoimidazo[1,2-a]azines

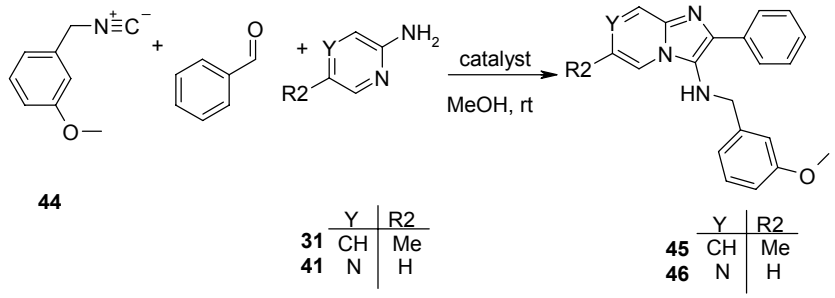
The potential disadvantage in terms of throughput respect to the previous solid phase approach could be circumvented with an appropriate the use of SPE columns. Generally, it is not the synthesis but the purification the most time consuming task in the whole process and the use of SPE columns can be easily carried out in parallel. The basic nature of the final heterocycle prompted us to consider the catch and release technique on a SPE-SCX column. Hence, for an efficient synthesis/SPE-SCX purification process the heterocyclic amidine has to be consumed during the reaction. Therefore, an excess of aldehyde and isocyanide could be use to help to drive the reaction to completion since they could be removed by washings during the SPE-SCX purification.

Furthermore, the solution phase approach has the advantage to broad the scope in terms of substituents at the exocyclic amino group (Scheme 26). It would allow the synthesis of *N*-aryl and *N*-alkyl derivatives from *N*-aryl and *N*-alkyl isocyanides, respectively. *N*-unsubstituted derivatives could be synthesized via acidic cleavage of the *N*-*tert*-octyl residue[10] and finally, the *N*-acyl derivatives could be obtained through acylation of the *N*-unsubstituted compound.



Scheme 26. Diversity at R1 through a solution phase approach.

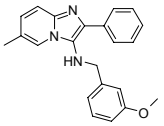
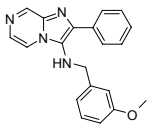
The reaction of 2-amino-5-methylpyridine **37** and 2-aminopyrazine **41** with benzaldehyde and 3-methoxybenzylisocyanide **44** were chosen to evaluate the best catalyst and optimal reaction time (Scheme 27). The 3CC was performed in methanol at ambient temperature in presence of scandium triflate or perchloric acid (0.1 and 0.5 equiv) as catalyst during 16 or 40 hr.



Scheme 27. Model reactions for the chose of catalyst and optimal reaction time.

The highest conversions were obtained after 16 hr with perchloric acid (0.5 equiv) or scandium triflate (0.5 equiv) as catalyst[d] (Table 4). Longer reaction time led to partial decomposition. Under these conditions, even the less reactive 2-aminopyrazine gave the corresponding product **46** in high conversion (>90%). Moreover, **45** and **46** could be isolated from the excess of isocyanide and aldehyde in excellent purity and moderate yield by a *catch and release* on a SPE-SCX column. While we were optimizing the reaction conditions (*e.g.* catalyst, reaction time, temperature) we discovered that the reaction was favored at relatively high concentration (0.32 M).

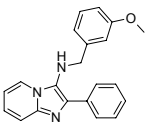
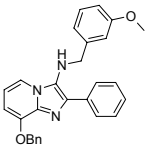
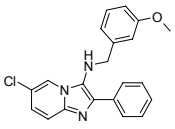
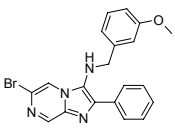
[d] Lower amount of catalyst did not totally consume the heterocyclic amidine.

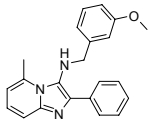
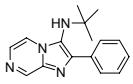
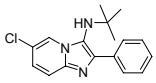
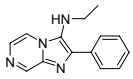
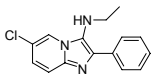
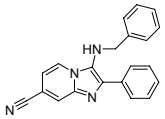
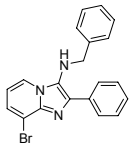
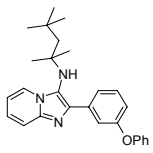
		$Sc(OTf)_3$ (0.5 equiv), 16 hr, rt			$HClO_4$ (0.5 equiv), 16 hr, rt		
	compound	**product (%)†**	**SM (%)†§**	**yield (%)‡**	**product (%)†**	**SM (%)†§**	**yield (%)‡**
45		94	6	82	93	-	76
46		95	2	57	91	-	61

† Determined by HPLC (254 nm) after *catch and release* on a SPE-SCX column. ‡ Isolated yield.§ SM: starting material (heterocyclic amidine)

Table 4. Use of scandium triflate and perchloric acid in the synthesis of **45** and **46**.

The solution phase approach seemed to be more efficient for the parallel synthesis of **1** since even the less reactive amidine gave the corresponding product in good yield and purity. It prompted us to extend these conditions first, to other heterocyclic amidines and later, to other isocyanides. A selection of the synthesized compounds are included in Table 5.

		$Sc(OTf)_3$ (0.5 equiv)			$HClO_4$ (0.5 equiv)		
	compound	**product (%)†**	**SM (%)†§**	**yield (%)‡**	**product (%)†**	**SM (%)†§**	**yield (%)‡**
47		96	0	46	77	0	n.d.
48		54	46	n.d.	100	0	60
49		44	48	n.d.	90	1	50
50		93	-	41	75	-	n.d.

		$Sc(OTf)_3$ (0.5 equiv)			$HClO_4$ (0.5 equiv)		
	compound	product (%)[†]	SM (%)[†§]	yield (%)[‡]	product (%)[†]	SM (%)[†§]	yield (%)[‡]
51		93	7	45	100	0	65
52		94	-	62	99	-	66
53		96	-	67	99	-	63
54		96	-	72	90	2	59
55		93	2	48	97	-	64
56		67	17	n.d.	93	-	74
57		94	-	68	84	-	n.d.
58		94	-	68	96	-	83

[†] Determined by HPLC (254 nm). [‡] Isolated yield. .[§] SM: starting material (heterocyclic amidine)

Table 5. Extension to other heterocyclic amidines.

In many cases, no significant differences were observed between both catalysts and the expected heterocycles were isolated in good purity (>90%), although in few cases the results were completely different. For instance, **48** and **49** were obtained in high purity (>90%) with perchloric acid whereas low conversion (ca. 50%) was observed with scandium triflate. It was difficult to correlate the reactivity of the heterocyclic amidine with the structure since **48** and **49** bear an electrondonating and electronwithdrawing groups, respectively.

In general, the less reactive heterocyclic amidines did not complete the reaction in presence of scandium triflate but the reaction could be driven to completion with perchloric acid (compounds **48**, **49** and **51**). With the most reactive heterocyclic amidines scandium triflate is the catalyst of choice because with perchloric acid, although the reaction was complete, a side reaction was observed affording a mixture of uncharacterized products (compounds **47** and **50**).

When the reaction was extended to other isocyanides or aldehydes (compounds **52**-**58**) no significant differences were observed and the corresponding products were isolated in high purities.

This solution phase approach combined to a purification by SPE columns allowed to broad the substrates scope. Furthermore, it is particularly convenient for parallel synthesis since it is easy to automate.

2.3. Conclusions

Two different approaches were investigated for the synthesis of 3-aminoimidazo[1,2-a]azines (**1**). The first approach concerned a 3CC on solid phase using a new indole isocyanide resin, which was synthesized in five steps from commercially available reagents. The success of this approach depended on the target heterocycle. It was observed that the purity of the product after cleavage depended on the reactivity of the other two partners, especially on the heterocyclic amidine. For instance, 3-aminoimidazo[1,2-a]pyridines were obtained in high purities after the cleavage, whereas 3-aminoimidazo[1,2-a]pyrazines required a further purification step. Therefore, we considered this method not particularly attractive for the synthesis of 1000-3000 members library and prompted us to investigate a solution phase approach.

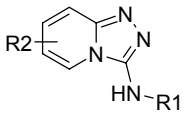
This time, the 3CC was performed in solution and showed to be more general in terms of substrate scope, particularly with the most problematic reactant, namely the heterocyclic amidine. High conversions were achieved while using an excess of the other two partners (aldehyde and isocyanide) in presence of scandium triflate or perchloric acid as catalyst. The accomplishment of this method was based on the purification by *catch and release* on a SPE-

SCX column. The products could be released in high purity after removal of the excess of reactants by simple washings. The solution phase approach coupled with the SPE purification allowed to adapt the protocol for a parallel mode and 3031 compounds were easily synthesized in our laboratories. SPE remains one of the most convenient alternatives to the standard aqueous work-up since it can be carried out in parallel in an automated manner.

3. Synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines

3.1. Introduction and project aims

In our continuous effort to access interesting nitrogen-containing heterocycles, we focused in the synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridine derivatives (**2**). They are particularly interesting as potential biological active compounds and also as synthetic targets, as the synthesis of this heterocycle has not been very well described in the literature and is limited to a few examples with specific substitutions.



2

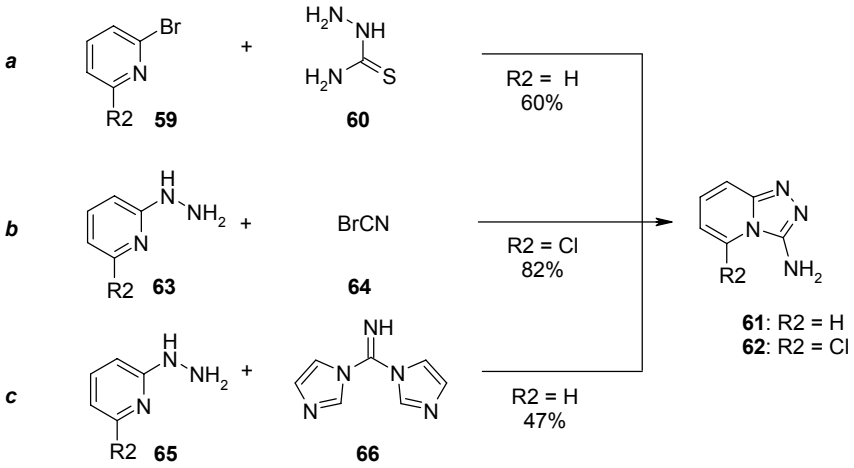
R1 = alkyl, (hetero)-aryl, acyl
R2 = alkyl, (hetero)-aryl, acyl, halogen

Figure 7. 3-amino-[1,2,4]triazolo[4,3-*a*]pyridine.

The aim of the present work was to develop a *robust and general* protocol for the synthesis of **2** under *mild conditions* tolerable by many functional groups that can produce in parallel many compounds in good purity, requiring a minimum of experimental steps.

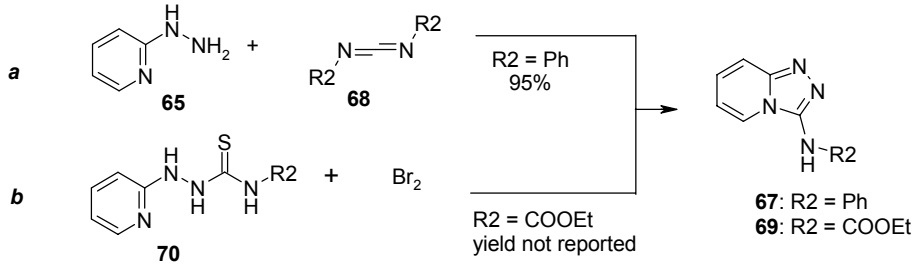
3.1.1. Previous syntheses

To the best of our knowledge, only three approaches described the synthesis of *N*-unstubstituted 3-amino[1,2,4]triazolo[1,5-*a*]pyridines (R1 = H) (Scheme 28, pathways *a*, *b* and *c*). The first synthesis (*a*) used the reaction of 2-bromopyridine (**59**) with thiosemicarbazide (**60**), *via* an oxidative cyclization of the corresponding adduct under heating conditions, affording the product **61** after purification in moderate yield.[23] In the second approach (*b*), the expected product **62** was obtained in good yield from 6-chloro-2-hydrazinopyridine (**63**) and cyanogen bromide (**64**).[24] Later, product **61** was synthesized from 2-hydrazinopyridine (**65**) and di(imidazol-1-yl)methanimine (**66**) (*c*).[25]



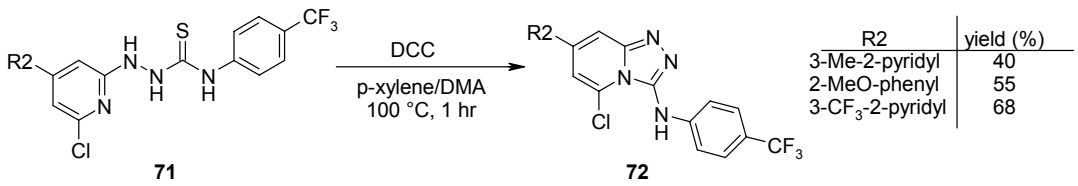
Scheme 28. Synthesis of *N*-unsubstituted 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines previously described.

Concerning the *N*-substituted 3-amino-[1,2,4]triazolo[4,3-a]pyridines **2** (R1 ≠ H), their syntheses have not been extensively explored. The synthesis of the *N*-phenyl derivative (**67**) was reported in good yield starting from 2-hydrazinopyridine (**65**) and diphenylcarbodiimide (**68**) (Scheme 29, pathway *a*).[26] This approach is not general and is limited to specific symmetric carbodiimides. The *N*-ethoxycarbonyl derivative (**69**) was obtained from the corresponding thiosemicarbazide (**70**) (Scheme 29, pathway b).[27] The limitation is the use of bromine to promote the cyclization that might be not compatible with all heterocycles.



Scheme 29. Synthesis of *N*-substituted 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines previously described.

Finally, the most attractive route described to date to synthesize *N*-aryl 3-amino derivatives consisted in cyclodesulfurization of thiosemicarbazides **71** with dicyclohexylcarbodiimide (DCC).[28] The desired heterocylces **72** were obtained in moderate yields after an aqueous work-up and chromatography column on silica. In this patent, few details are provided and the substrate scope has not been investigated (only 3 examples).



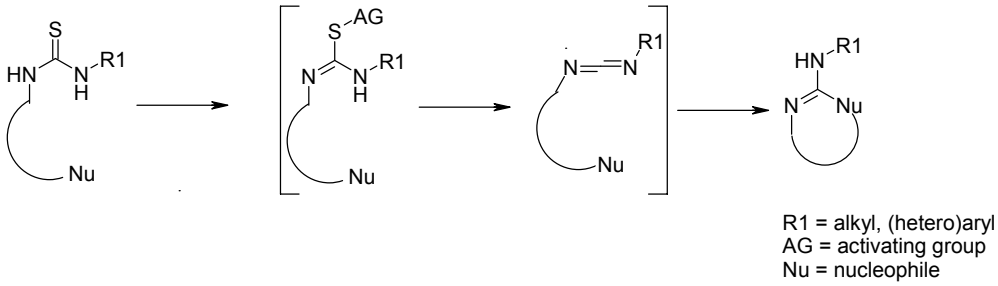
R2	yield (%)
3-Me-2-pyridyl	40
2-MeO-phenyl	55
3-CF_3-2-pyridyl	68

Scheme 30. Synthesis of *N*-aryl 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines previously described.

The latter approach is not the only example of cyclodesulfurization in heterocyclic chemistry. This methodology is known to get access to cyclic amidines as it is shown in the next section.

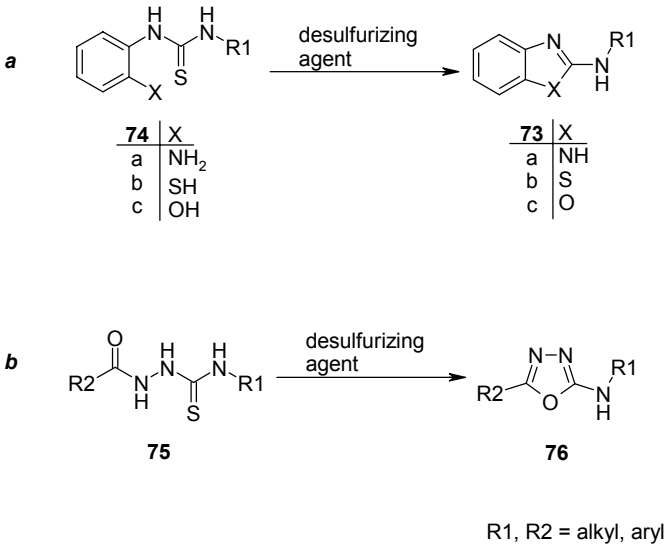
3.1.2. Cyclodesulfurization: Carbodiimides as useful intermediates in heterocyclic chemistry.

The intramolecular ring closure of carbodiimides is a strategy that has precedents in the synthesis of heterocycles.[29,30] The appropriate substituted carbodiimide can be obtained via desulfurization of the corresponding thiourea. Generally, it cannot be isolated but further reacts to give the cyclised product (Scheme 31).



Scheme 31. Proposed pathway for cyclodesulfurization.

The synthesis of 2-aminobenzimidazoles **73a** is a good example to illustrate the mentioned strategy (Scheme 32, pathway a, X = N). This reaction was first described by Kiffer *et al.* in 1968 who used mercury oxide as desulfurizing agent of *N*-arylthioureas of type **74a**.[31] Later, many other conditions were reported including dimethyl sulfate,[32] methyl iodide[32-34] and even carbodiimides[35-37] to promote the cyclisation. Recently, a straightforward method was developed using polymer supported carbodiimide with the advantage that the product was easily isolated after filtration of the resin.[38] 2-Aminobenzothiazoles[38,39] **73b** and 2-aminobenzooxazoles[38,40-43] **73c** have been synthesized in an analogueous manner (Scheme 32, pathway a, X = O, S). Similarly, desulfurization of 1-acyl-3-thiosemicarbazides **75** afforded 2-amino-1,3,4-oxadiazoles[44,45] **76** (Scheme 32).



Scheme 32. Cyclodesulfurization in synthesis of heterocycles

Nowadays, there are several desulfurizing agents described[29,46] including heavy metal salts and oxides, copper (I) chloride, dimethyl sulfate, methyl iodide, tosyl chloride/pyridine, carbodiimides and 2-halopyridinium salts (Mukaiyama's reagent). Some among them allow to perform cyclodesulfurizations under mild conditions tolerable by many functional groups.

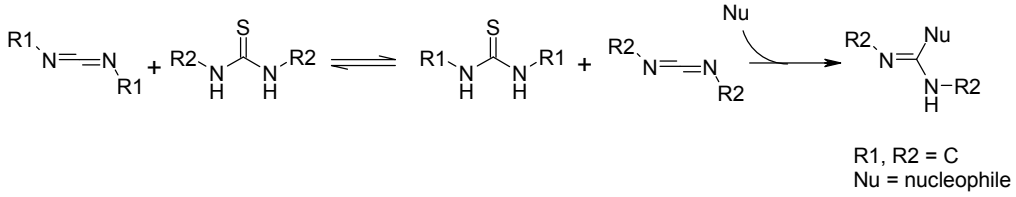
3.1.3. Desulfurizing agents for thioureas

Heavy metals salts and oxides.

Heavy metal salts and oxides ($HgCl_2$, $Hg(OAc)_2$, HgO, Pb_2O_4) have been the most used desulfurizing agents over the time. They required a full equivalent of heavy metal (*e.g.* Hg^{2+}) and produce undesirable by-products that must then be removed and properly disposed. There has been an increasing interest to replace the use of heavy metals by more convenient desulfurizing reagents. Some of them are discussed hereafter.

Carbodiimides

The use of carbodiimides as amide coupling agents is of particular significance[29,46] but they have also been employed as desulfurizing agents of thioureas. In the latter case, the newly formed carbodiimide usually reacts with a nucleophile in a second step (Scheme 33).



Scheme 33. Carbodiimides as desulfurizing agents of thioureas.

There are many commercially available carbodiimides (DCC, EDC, DIC, etc.) or readily accessible by various methods.[29,46] Among these methods, dehydration of isocyanates in presence of catalytic phosphine oxides has shown to be an efficient approach for the industrial scale production of symmetric carbodiimides to be later used in many manufacturing processes.

Probably the main disadvantage of the use of carbodiimides as a coupling or desulfurizing agent is the necessity to remove the corresponding urea (or thiourea) that is formed as by-product. This fact prompted Weinshenker *et al.* to develop a polymer supported version which allowed the by-product removal by simple filtration while it is bound to the insoluble support.[47] Commonly used carbodiimides and their polymer-supported analogues are depicted in Figure 8.

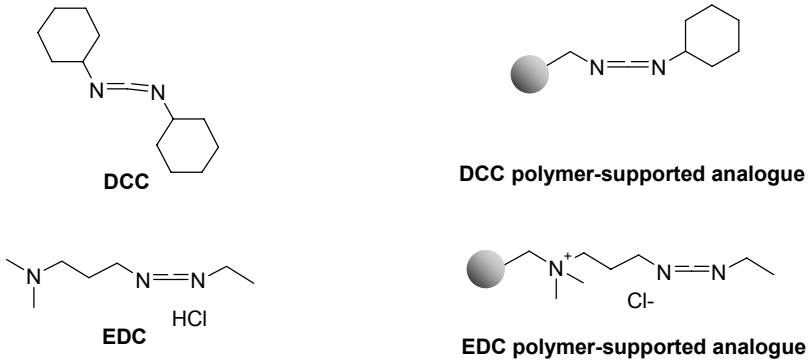
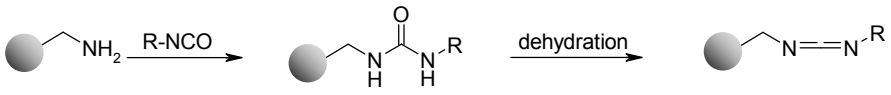


Figure 8. Common carbodiimides and their polymer-supported analogues.

While there are some polymer-supported carbodiimides commercially available, they can be prepared from aminomethylpolystyrene resin and the corresponding isocyanate upon a dehydration step (Scheme 34).[47] On an industrial scale, the dehydration reaction is executed by using *p*-toluenesulfonyl chloride and triethylamine. However, some authors claimed that better results are obtained when the dehydration is promoted by carbon tetrabromide/triphenylphosphine mixture[48] or by Burgess reagent.[49]

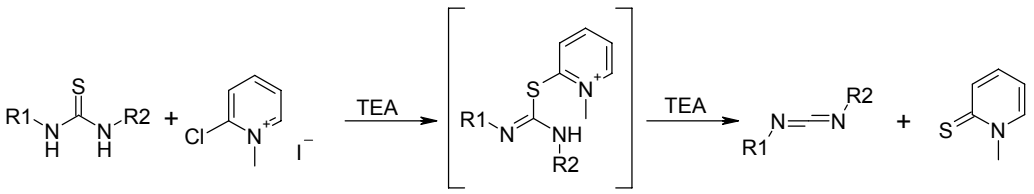


Scheme 34. Preparation of polymer-supported carbodiimdes.

Although the disadvantage of the by-product removal was circumvented, the polymer-supported version showed in many cases low reactivity and the use of a large excess (2,[38] 3,[50] and 5[44,51] equiv) and/or high temperature (above 70 [38,44]) was necessary to reach good conversions, especially while acting as desulfurizing agent.

Mukaiyama's reagent.

2-Chloro-1-methylpyridinium iodide (Mukaiyama's reagent) have been extensively used to activate under mild conditions carboxylic acids to then be transformed in various common functional groups such as esters, amides and thiol esters.[52] Furthermore, this reagent can effectively transform thioureas into carbodiimides in presence of a weak base like triethyamine (Scheme 35).[53] This process is based on the ability of the sulfidopyridinium function to act as an effective leaving group affording the carbodiimide in good yields. This method is of quite general utility; aromatic and aliphatic carbodiimides can be obtained by a simple procedure. 2-Chloro-1-methylpyridinium iodide is commercially available but it can easily be prepared via *N*-methylation of 2-chloropyridine with methyl iodide.



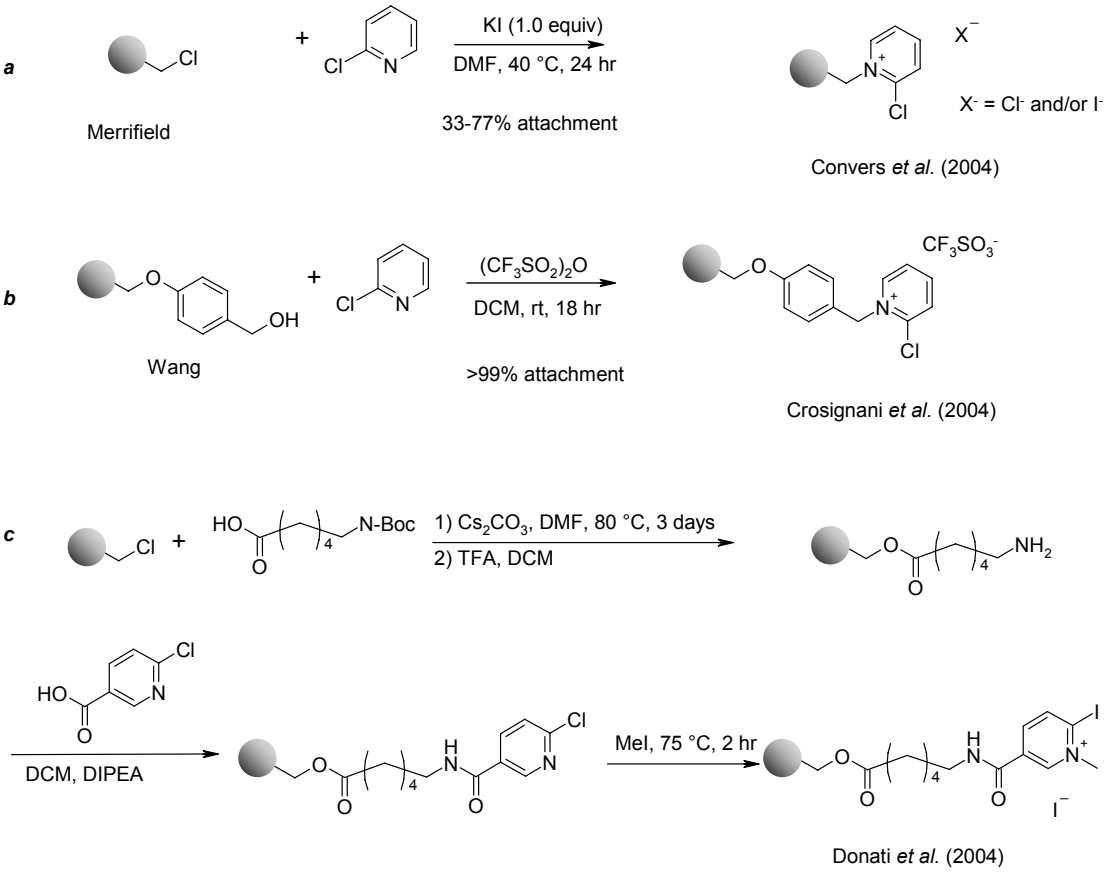
R1, R2 = aryl, alkyl

Scheme 35. Mukaiyama's reagent as desulfurizing agent of thioureas.

The use of Mukaiyama's reagent has two main drawbacks: i) the low solubility in the most common organic solvents and ii) the chromatographic purification of the desired product is generally needed to completely remove 1-methylpyridin-2-(thio)one that is formed as a by-product. Once again, different polymer-supported versions of the Mukaiyama's reagent were developed to overcome these issues.

In 2004 Convers *et al.* described the first synthesis of polymer-supported Mukaiyama's reagent from Merrifield's resin and 2-chloropyridine in presence of potassium iodide (Scheme 36, pathway *a*).[54] The loading obtained with this protocol[e] showed low reproducibility and the attachment varied between 33-72% depending on the scale, mode of stirring and loading of the starting Merrifield resin. [54]

[e] *Active loading*: determined by "end-use" assay, *i.e.* assuming 100% conversion in a known reaction.



Scheme 36. Polymer-supported Mukaiyama's reagent analogues described in the literature.

In our group, Crosignani *et al.* decided to use a better and non-nucleophilic leaving group like the triflate ester (Scheme 36, pathway b).[55] In this one-pot synthesis, Wang resin was activated *in situ* with trifluoromethansulfonic anhydride forming the triflate ester, which was immediately substituted by the 2-chloropyridine present in the reaction mixture. The excess of the 2-chloropyridine also acted as the base necessary for the formation of the triflate ester, so that the addition of another base was not necessary. Through this protocol, complete conversion of the Wang resin to the chloropyridinium salt was obtained, as judged by elemental analysis (based on nitrogen and sulfur) and mass increase of the resin. This resin is now commercialized by two of the major vendors of polymer-supported reagents[f] proving the simplicity and efficiency of this one-pot method.

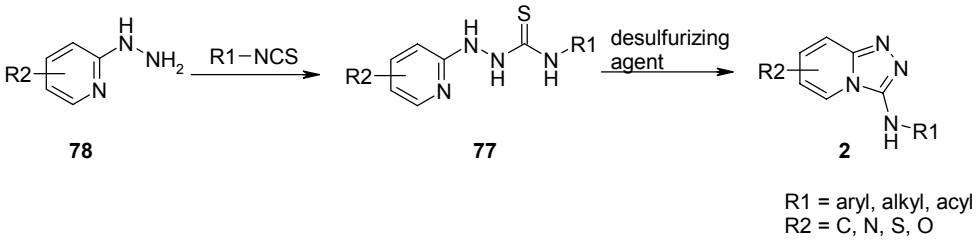
Almost simultaneously, Donati *et al.* descibed a longer and tedious synthesis[56] as compared to Crosignani's, to obtain a derivative bearing a longer linker between the solid support and the pyridinium salt (Scheme 36, pathway c). They claimed that this linker would decrease the interactions between the reactants and the solid-support matrix.

[f] PolymerLabs (catalogue number 3495-1689) and Sigma-Aldrich (catalogue number 657182-5G)

The polymer-supported Mukaiyama reagents presented before have been used in the synthesis of guanidines,[54] esters,[55,57] amides,[55,58] and lactames.[56]

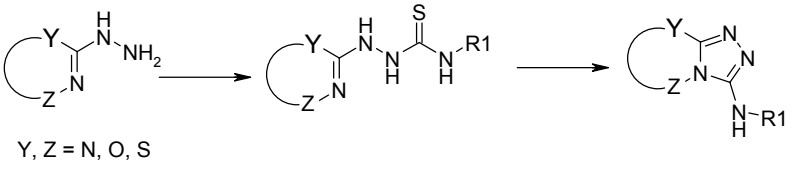
3.1.4. Objectives

The synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines (**2**) via cyclodesulfurization of the corresponding thiosemicarbazide (**77**) was chosen for further investigations (Scheme 37).



Scheme 37. Proposed pathway for the synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines

Despite the previously reported route described the synthesis of *N*-aryl derivatives, the substrate scope has not been explored (only three examples).[28] We considered this route attractive for many reasons: i) simple starting materials: thiosemicarbazides **77** can be prepared from hydrazines **78** and isothiocyanates, both reagents commercially or readily accessible; ii) it could be a general approach to *N*-alkyl, *N*-aryl and *N*-acyl derivatives; iii) *N*-unsubstituted derivatives (R1 = H) could be obtained in two steps: synthesis of the *N*-*tert*-octyl derivative followed by acidic cleavage.[10] iv) It could be extended to other related fused heterocycles (Scheme 38).



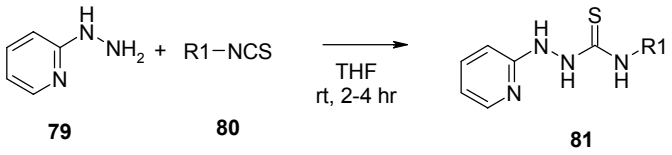
Scheme 38. Extension to other related fused 3-aminotriazoles

The objective in the present work was to find an adequate desulfurizing agent that could allow the a straightforward synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines.

3.2. Discussion

3.2.1 Synthesis of 1-(pyridine-2-yl)thiosemicarbazides

The synthesis of 1-(pyridine-2-yl)thiosemicarbazide **81** involved the reaction of 2-hydrazinopyridine (**79**) with the corresponding isothiocyanate (**80**) (Scheme 39). In order to determine the scope of the current approach, five aryl isothiocyanates were selected taking into account diversity in terms of electron distribution and steric hindrance. *Tert*-octyl isothiocyanate was also included in these studies as an example of alkyl derivative and also because it gives the possibility of further derivation after acidic cleavage.[10]



79 **80** **81**

For R1 see Table 6

Scheme 39. Synthesis of 1-(pyridine-2-yl)thiosemicarbazides **3**.

The thiosemicarbazide formation proceeded in THF as solvent at ambient temperature and was complete after 4 hr. Although the crude purity was above 96% by HPLC (254 nm), **81** was simply purified by recrystallization from acetonitrile to give analytical pure compound (Table 6).

entry	R1	compound	yield (%)[†]
1	phenyl	**81a**	71
2	3-F-phenyl	**81b**	69
3	4-MeO-phenyl	**81c**	85
4	2-Me-phenyl	**81d**	88
5	4-CF_3-phenyl	**81e**	58
6	*tert*-octyl	**81f**	77

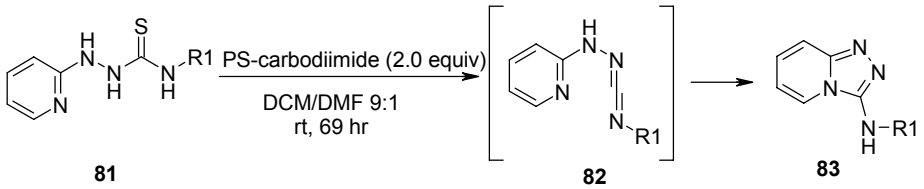
[†] Isolated yield of pure compound.

Table 6. Synthesis of 1-(pyridine-2-yl)thiosemicarbazides **81**.

3.2.2. Cyclodesulfurization using PS-carbodiimides

With the thiosemicarbazides **81** in hands, we first perform the cyclodesulfurization using a polymer-supported carbodiimide since it would allow the isolation of the desired product **83** by

simple filtration of the resin (Scheme 40). The reactions were carried out with an excess of this reactant (2.0 equiv) in a mixture DCM/DMF 9:1 to ensure the solubility of **81**.[g]



Scheme 40. Use of PS-carbodiimide in the synthesis of **83**.

The reactions with aryl isothiocyanates bearing electron-donating substituents were slow and high conversions were achieved only after 69 hr (entries 3 and 4). Electron-withdrawing substitution on the aryl favoured the reaction and the product showed to be stable under the reaction conditions over 69 hr (entry 2). The *tert*-octyl analogue showed low conversion (7%) after 45 hr at ambient temperature but it dramatically increased (64%) in the last 24 hr at 50 °C. Unfortunately, many other non identified impurities were also observed (entry 5).

entry	R1	ratio 81/83 (%)[†]		
		21 hr	45 hr	69 hr
1	phenyl	16 / 84	5 / 95	0 / 100
2	3-F-phenyl	0 / 100	0 / 100	0 / 100
3	4-MeO-phenyl	40 / 60	7 / 93	0 / 100
4	2-Me-phenyl	52 / 48	27 / 73	12 / 88
5	*tert*-octyl[‡]	99 / 0[‡]	93 / 7[‡]	22 / 64[‡]

[†] Determined by HPLC (254 nm). [‡] 45 hr at rt. + 24 hr at 50 °C

Table 7. Use of PS-carbodiimide in the synthesis of **83**.

When complete conversion was achieved (entries 1-3 Table 7), the desired pure heterocycles were isolated in excellent yields after simple filtration of the resin followed by solvent evaporation (Table 8).[h]

[g] Typically, DCM is the solvent of choice when polystyrene-supported reagents are used since it ensures a good swelling of the beads and consequently, a better access inside the matrix where the chemistry takes place. Due to the low solubility of **81** in DCM, the use DMF (10%) as co-solvent was needed.

[h] A first quick experiment was done to confirm that the isolated compound was the desired heterocycle **83** and not the intermediate **82** (^{1}H NMR or MS could not unambiguously distinguish both). The isolated compound was heated in presence of acetic acid and no reaction was observed as expected if it was the carbodiimide intermediate **82**. Moreover, it did not show the characteristic C=N stretching band of

entry	R1	compound	yield (%)†
1	phenyl	**83a**	93
2	3-F-phenyl	**83b**	90
3	4-MeO-phenyl	**83c**	87

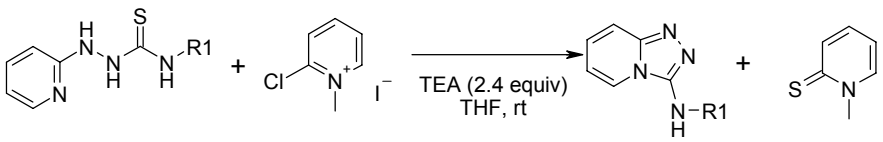
† Isolated yield of pure compound.

Table 8. Isolation of **83**.

The substituents on the phenyl ring showed to have an important impact on the rates of this transformation. A general protocol independent of the substrate is often desirable in parallel synthesis and therefore, we considered another alternative for the cyclodesulfurization step that is presented in the next section.

3.2.3. Cyclodesulfurization using Mukaiyama's reagent

The ability of Mukaiyama's reagent to promote the cyclodesulfurization to obtain the target heterocycles was investigated (Scheme 41). Although this reagent has been previously used to obtain carbodiimides from thioureas,[53] to the best of our knowledge it was the first time that was used in a cyclodesulfurization process.



81 **83** **84**

Scheme 41. Use of Mukaiyama's reagent in the synthesis of **83**.

The reaction of the thiosemicarbazide **81** with Mukaiyama's reagent (1.2 equiv) was performed in THF at ambient temperature in presence of triethylamine (2.4 equiv) during 1 hr. Under these mild conditions, complete conversion into the desired product **83** was observed for the six derivatives. Moreover, the difference in basicity between **83** (pKa ≅ 3.8)[59] and the by-product **84** (pKa = -1.2)[60] allowed the isolation of the pure product in moderate to good yields (63-78%) with an acidic aqueous extraction followed by precipitation at pH = 6 (Table

this moiety in the IR spectrum. These two experiments suggested the formation of 3-arylamino-[1,2,4]triazolo[4,3-*a*]pyridines that was finally confirmed by 2D-NOESY spectroscopy. A NOE effect between the exchangeable proton and the phenyl ring was observed)

9). The difference in yield among the six derivatives was due to the isolation process that was not optimized for each particular case.

entry	R1	compound	yield (%)†
1	phenyl	**83a**	78
2	3-F-phenyl	**83b**	63
3	4-MeO-phenyl	**83c**	69
4	2-Me-phenyl	**83d**	75
5	4-CF_3-phenyl	**83e**	72
6	*tert*-octyl	**83f**	68

† Isolated yield of pure compound

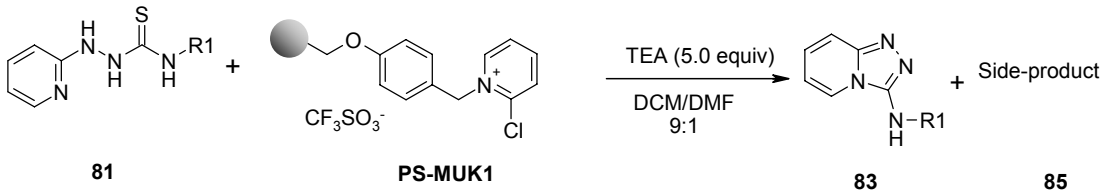
Table 9. Use of Mukaiyama's reagent in the synthesis of **83**.

Mukaiyama's reagent proved to be particularly convenient for the synthesis of **83** since the reactions proceeded smoothly under mild conditions and independently from the substrate **81**. In order to adapt this process to a parallel mode, the isolation of the desired products should be improved since the liquid-liquid extractions are not easy to automate. We considered that the use of polymer-supported Mukaiyama's reagent could help to overcome this issue.

3.2.4. Cyclodesulfurization using PS-Mukaiyama's reagent

Encouraged by the results obtained with Mukaiyama's reagent, we envisaged to perform the reaction using one of its polymer-supported versions. We chose Crosignani's resin (**PS-Muk1**), since it is easy to prepare from readily available starting materials and is stable under standard storage conditions. Using **PS-Muk1**, we expected to improve the isolation of the desired product to then develop a straightforward protocol for parallel synthesis.

The reaction of thiosemicarbazides **81** with **PS-Muk1** (2.0 equiv) was performed in DCM:DMF 9:1 at ambient temperature in presence of triethylamine (5.0 equiv). Under these conditions, the desired heterocycle **83** was formed but in contrary to the use of Mukaiyama's reagent, a major side-product was observed in each reaction (Scheme 42). This side-product could not be identified at first glance and required a deeper analysis as it will be discussed later (section 3.2.5).



Scheme 42. Use of **PS-Muk1** (2.0 equiv) in the synthesis of **83**.

While we were trying to figure out the structure of the side-product **85**, it was decided to investigate in parallel whether the side-reaction could be avoided by decreasing the amount of **PS-Muk1** (from 2.0 to 1.25 equiv) and TEA (from 5.0 to 2.5 equiv). Unfortunately, it did not suppress the side-reaction at ambient temperature but there was a big improvement when the reaction was performed at lower temperature (5 °C) for 21 hours (Table 10). The *N*-aryl 3-amino-[1,2,4]triazolo[4,3-a]pyridine **83** were obtained as the main product (>82 %) (Table 10, entries 1-5). On the contrary, in the case of the *tert*-octyl derivative the side-reaction was still important (37%) (Table 10, entry 6).

entry	R1	ratio 81 / 83 / 85 (%)†			
		1 hr at rt	1 hr at 5 °C	4 hr at 5 °C	21 hr at 5 °C
1	phenyl	8 / 55 / 37	21 / 76 / 0	4 / 87 / 8	0 / 82 / 13
2	3-F-phenyl	11 / 50 / 34	37 / 60 / 0	3 / 92 / 1	0 / 93 / 2
3	4-MeO-phenyl	12 / 67 / 21	17 / 82 / 0	2 / 87 / 8	0 / 85 / 12
4	2-Me-phenyl	23 / 57 / 20	32 / 67 / 0	2 / 87 / 8	0 / 85 / 12
5	4-CF_3-phenyl	0 / 77 / 23	0 / 97 / 0	0 / 94 / 2	0 / 92 / 2
6	*tert*-octyl	15 / 64 / 18	57 / 29 / 0	27 / 45 / 23	19 / 41 / 37

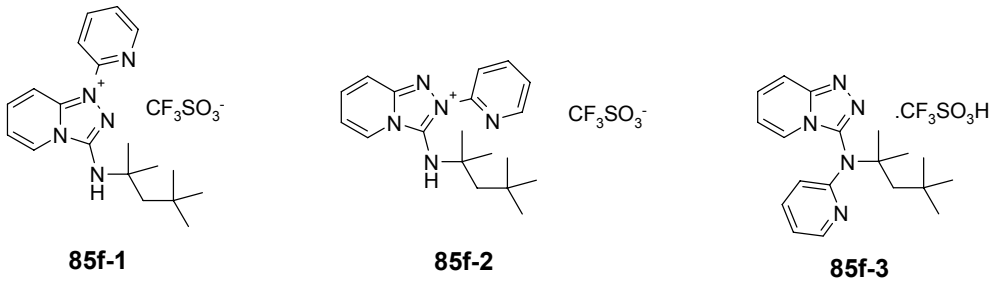
† Determined by HPLC (254 nm).

Table 10. Use of **PS-Muk1** in the synthesis of **83**: ambient temperature *versus* 5 °C.

3.2.5. Side-product characterization. Development of a new PS-Mukaiyama's reagent analogue.

We focused our attention on the side-product characterization. Mass spectra analyses of the side-products showed a *m/z* ratio to be equal to the *m/z* of the desired heterocycle **83** plus a mass of 77, which suggested that a pyridyl moiety was incorporated to the molecule. Hence, to further characterize the side product **85**, we chose to study the reaction implying the thiosemicarbazide **81f** (R1 = *tert*-octyl) to simplify the NMR analysis in the aromatic region. The side-reaction was driven to completion after 20 hr, in presence of a large excess of **PS-Muk1** (3.0 equiv) and TEA (5.0 equiv). The crude was passed through a SPE-NH_2 column and the eluted compound was subjected to a series of analyses (^{1}H and ^{13}C NMR, COSY, NOESY, HMQC, HSQC, MS, elemental analysis). Unfortunately, based on these analyses, we could not unambiguously discriminate between the three regioisomers listed in Figure 9.[i]

[i] ^{1}H NMR (DMSO-d_6) clearly showed the signals corresponding to the *tert*-octyl, 2-pyridyl and triazolopyridinyl moieties and one exchangeable proton (confirmed by adding MeOD-d_4) at 7.63 ppm. Moreover, ^{19}F NMR (DMSO-d_6, singlet at -78.2 ppm) and ^{13}C NMR (DMSO-d_6, quadruplet with $^1J_{C\text{-}F}$ = 322.4 Hz at 120 ppm) suggested the presence of trifluoromethanesulfonate group.



85f-1 **85f-2** **85f-3**

Figure 9. Proposed structures for **85f**.

Finally, while these studies were in progress, the structural formula was determined by X-ray crystallography that gave the definitive answer (Figure 10).[j]

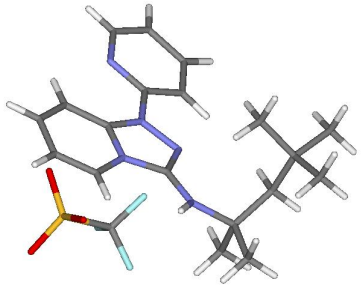
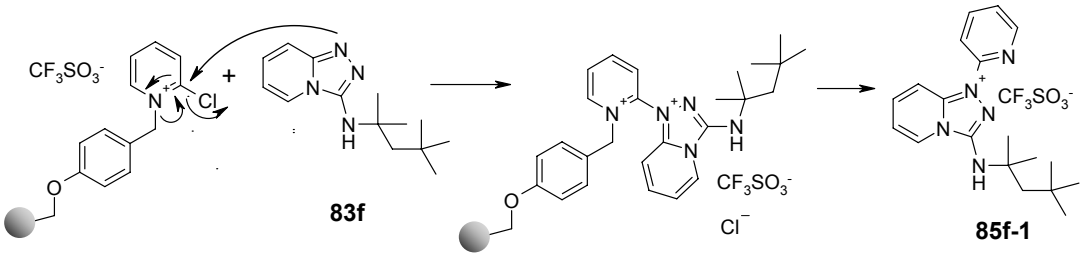


Figure 10. Side-product **85f-1** structure determined by X-ray crystallography.

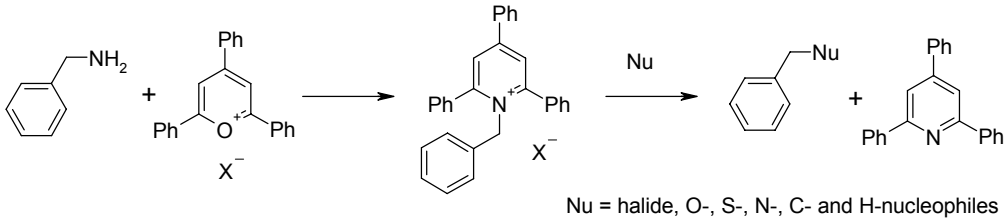
A plausible mechanism for the formation of **85f-1** is depicted in Scheme 43. Compound **83** could further react with the excess of **PS-Muk1** (with loss of chloride) and a benzylic cleavage released the compound **85f-1** from the polymer support. This cleavage could be promoted by a nucleophilic addition (chloride or TEA) at the benzylic position (S_N2), or by a S_N1 mechanism involving the stabilized benzylic carbocation.



Scheme 43. Proposed mechanism for the formation of side-product **85f-1**

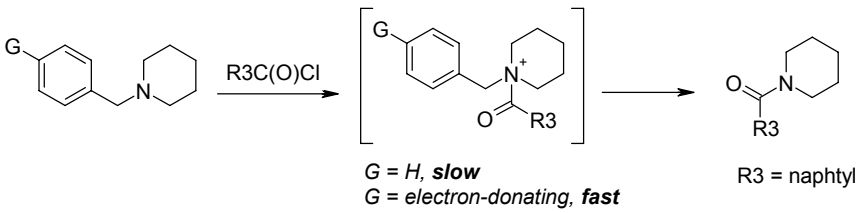
[j] In **85f-1** the pyridine-2-yl moiety is bonded directly to the triazole ring giving a cationic compound. Hence, in the mass spectrometry (positive mode), the observed *m/z* = 323 corresponds to the MW and not to MW+1. Elemental analysis was in agreement to the proposed structures with 4% of chloride as co-anion.

There are precedents in the literature concerning benzylic cleavages of *N*-benzyl pyridinium salts. For instance, this reaction forms the second step in the pyrylium mediated strategy developed by Katritzky to convert benzyl amines (or any other primary amine in a less extend) into other functionalities by nucleophilic displacement of *N*-benzyl group of the pyridinium cation (Scheme 44).[61-65] Although the pyridinium salt can be obtained under mild conditions, the second step is usually performed at high temperatures to be synthetically useful. Specific substitution on the pyridine ring is also required for both steps being 2,4,6-triphenylpyridinium salts the most frequently used. Electron-donating *p*-substituted benzylamines generally afford higher yields when halides are used as nucleophiles.



Scheme 44. Precedents of benzylic cleavage in *N*-benzyl pyridinium salts

In the same way, benzylic cleavage of quaternary ammonium salts has also been reported. During the development of a traceless linker for the synthesis of tertiary amides, Miller *et al.* studied the amide-forming cleavage step using various *N*-(para-substituted benzyl) piperidines to mimic the different polymer supports (Scheme 45).[66] Through the reaction with 1-naphtoyl chloride as model, they proved that substrates bearing electron-donating groups underwent clean conversion to the naphtamide at room temperature in less than one hour whereas *N*-benzyl piperidine (G = H) gave no significant cleavage over 24 hours under identical conditions. Therefore, to facilitate both easy and selectivity of cleavage, they developed the linker starting from Wang resin. This linker was later reviewed and more general cleavage conditions were established.[67]



Scheme 45. Precedents of benzylic cleavages of *N*-benzyl piperidinium salts

At this point it was strongly believed that a new polymer-supported Mukaiyama's reagent analogue with different reactivity and *stability* of the linker could be developed. For this purpose, hydroxymethyl polystyrene and 4-hydroxymethylbenzoic acid aminomethyl polystyrene were used for the synthesis of **PS-Muk2** and **PS-Muk3** respectively (Figure 11), which would be more stable towards the benzylic cleavage than **PS-Muk1**. Their preparation

was carried out following the same protocol as for **PS-Muk1** achieving a quantitative attachment for both versions.

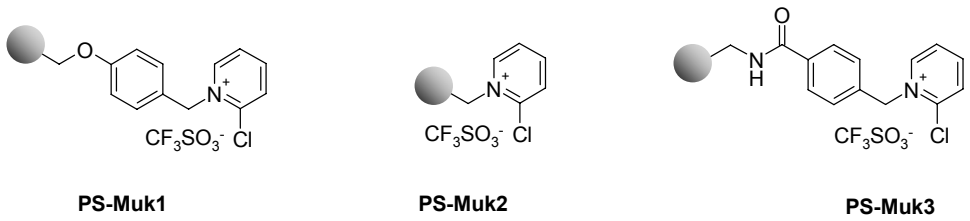
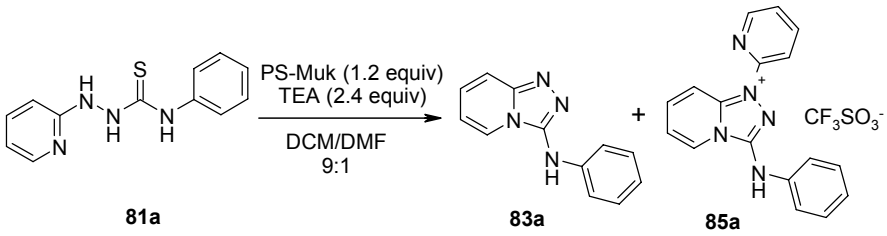


Figure 11. New polymer-supported Mukaiyama's reagent analogues.

In order to compare the relative reactivity of the new supported reagents, the reaction from **81a** was selected as model (Scheme 46) and the results are summarized in Table 11.



Scheme 46. Synthesis of **83a** using **PS-Muk2** and **PS-Muk3**.

entry	R1	ratio 81a / 83a / 85a (%)†	
		1 hr at rt	21 hr at rt
1	PS-Muk1	8 / 55 / 37	7 / 56 / 37
2	PS-Muk2	0 / 99 / 0	0 / 98 / 2
3	PS-Muk3	0 / 99 / 0	0 / 95 / 3

† Determined by HPLC (254 nm).

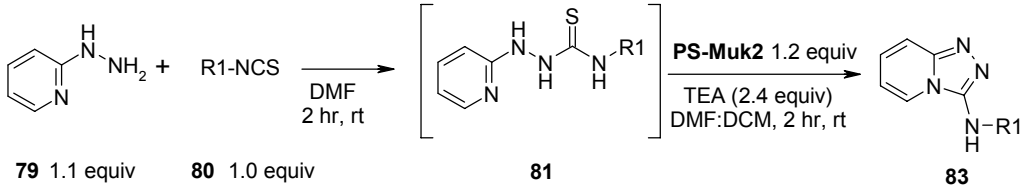
Table 11. Comparison of **PS-Muk1**, **PS-Muk2** and **PS-Muk3** in the synthesis of **83a**.

Gratifyingly, the new two linkers showed a better stability towards the benzylic cleavage and allowed to achieve 99% conversion into the desired heterocycle after 1 hr (entries 2 and 3 *vs* 1). Only after 21 hr, traces of the side-product **85a** were detected. It is important to notice that, with the new linkers, it was the first time that the starting thiosemicarbazide **81a** was totally consumed before the side-reaction took place. The resin-bound pyridine-2-thione by-product was removed by simple filtration and the triethylammonium salts were removed using a SPE-NH_2 column followed by evaporation of the resulting TEA at the solvent removal stage. Using **PS-Muk2** and **PS-Muk3**, **83a** was isolated in good yield (79 and 76% respectively) without any chromatographic separation.

PS-Muk2 was chosen as the best reagent candidate for further studies because its preparation is less expensive and it is easier to handle as compared to **PS-Muk3**. The reactions of **81** with **PS-Muk2** (1.2 equiv) in DCM/DMF 9:1 at ambient temperature in presence of TEA (2.4 equiv) gave complete conversion for the six derivatives was obtained after 1 hr. Even the most problematic *tert*-octyl thiosemicarbazide **81f** gave the product in excellent purity. The final heterocycles were easily isolated in good yields (66-98%) and excellent purities (>99%) without any chromatographic separation or any further purification, as shown by elemental analysis of the final heterocylces **83**.

3.2.6. One-pot protocol and extension to other related heterocycles

Our next goal was to develop a one-pot protocol that was easily adapted from the previous results. It consisted in reacting hydrazinopyridine **79** with the isothiocyanates **80** in DMF during 2 hours at ambient temperature before adding the TEA (2.4 equiv) and **PS-Muk2** (1.2 equiv) (Scheme 47).

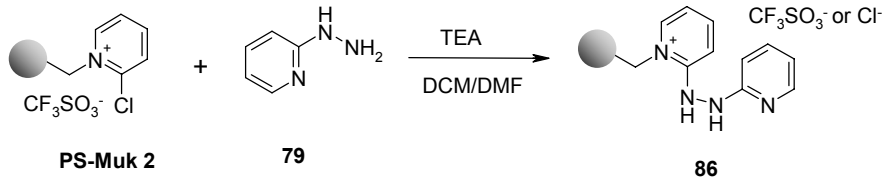


Scheme 47. One-pot protocol for the synthesis of **83**.

The two steps were sequentially performed in a single pot and the compounds **83** were isolated in good yields (45-70%) and excellent purities (>99%). No significant differences were observed in terms of purities and overall yields when the syntheses were performed in two separated steps or following the one-pot protocol.

While attempting to simplify the one-pot protocol mixing all the reagents at once, we serendipitously discovered that 2-hydrazinopyridine **79** was scavenged by **PS-Muk2** most probably to give an adduct of type **86** (Scheme 48).[k]

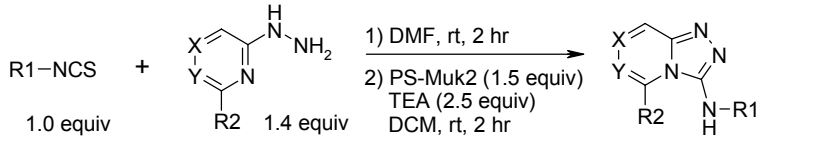
[k] It was confirmed later mixing 1 equiv of each reagent under the same conditions of solvent, concentration and temperature for 2 hr, where only 25% of the hydrazinopyridine was recovered after washing the resin and solvent removal



Scheme 48. **PS-Muk2** as scavenger of 2-hydrazinopyridine.

Consequently, the stepwise one-pot protocol was required to get the final compounds in good purities and yields but the new role of **PS-Muk2** as scavenger gave the opportunity to use the hydrazine in excess to drive the first step to completion when needed. The fact of having one reagent in excess is often desirable in parallel synthesis.

Encouraged by these results, we prompted to extend this methodology to the synthesis of other related fused 3-aminotriazoles (**87**-**89**) (Scheme 49). *A priori*, any other hydrazine derivative bearing a nitrogen atom in alpha position of an aromatic ring can replace the 2-hydrazinopyridine (**79**), leading to novel and interesting heterocycles. As examples we chose 6-chloro-2-hydrazinopyridine **(90**), 2-hydrazinopyrazine (**91**) and 2-methylsulfanyl-4-hydrazinopyridazine (**92**). We also extended the approach to acylisothiocyanates that afford the *N*-acyl 3-amino[1,2,4]triazolo[1,5-*a*]pyridines.

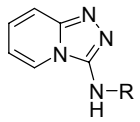
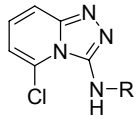
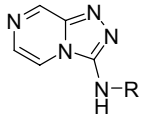
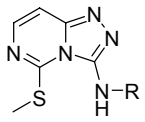


	X	Y	R2
79	CH	CH	H
90	CH	CH	Cl
91	N	CH	H
92	CH	N	SMe

	X	Y	R2
83	CH	CH	H
87	CH	CH	Cl
88	N	CH	H
89	CH	N	SMe

Scheme 49. General protocol for the synthesis of fused 3-aminotriyzoles

The reactions of hydrazines **79**, **90**, **91** and **92** with different isothiocyanates were carried out in a parallel, using an excess of hydrazine derivative (1.4 equiv) for the first step and **PS-Muk2** (1.5 equiv)/TEA (2.5 equiv) for the cyclodesulfurization. They proceeded with high conversions and no further optimization was required to get the fused 3-aminotriazoles (**87**-**89**). The isolation was performed using a SPE-NH_2 column affording the compounds in good yields (Table 12). The volume of elution for the SPE-NH_2 was not optimized for each particular case, which might explain the differences in the recovery of the desired compounds. As evidence of the very high purities obtained, the NMR spectra of compound **87d** as a typical example is shown in Figure 12.

entry	scaffold	R1	compound	yield (%)†
1	 **83**	phenyl	**83a**	67
		3-F-phenyl	**83b**	48
		4-MeO-phenyl	**83c**	56
		2-Me-phenyl	**83d**	69
		4-CF_3-phenyl	**83e**	43
		tert-octyl	**83f**	54
		benzoyl	**83g**	72
2	 **87**	phenyl	**87a**	78
		3-F-phenyl	**87b**	63
		4-MeO-phenyl	**87c**	69
		2-Me-phenyl	**87d**	75
		4-CF_3-phenyl	**87e**	72
3	 **88**	phenyl	**88a**	78
		3-F-phenyl	**88b**	79
		4-MeO-phenyl	**88c**	69
		2-Me-phenyl	**88d**	77
		4-CF_3-phenyl	**88e**	70
4	 **89**	phenyl	**89a**	60
		3-F-phenyl	**89b**	51
		4-MeO-phenyl	**89c**	56
		2-Me-phenyl	**89d**	66
		4-CF_3-phenyl	**89e**	45

† Isolated yield of pure compound

Table 12. Synthesis of fused 3-aminotriazoles using a one-pot protocol.

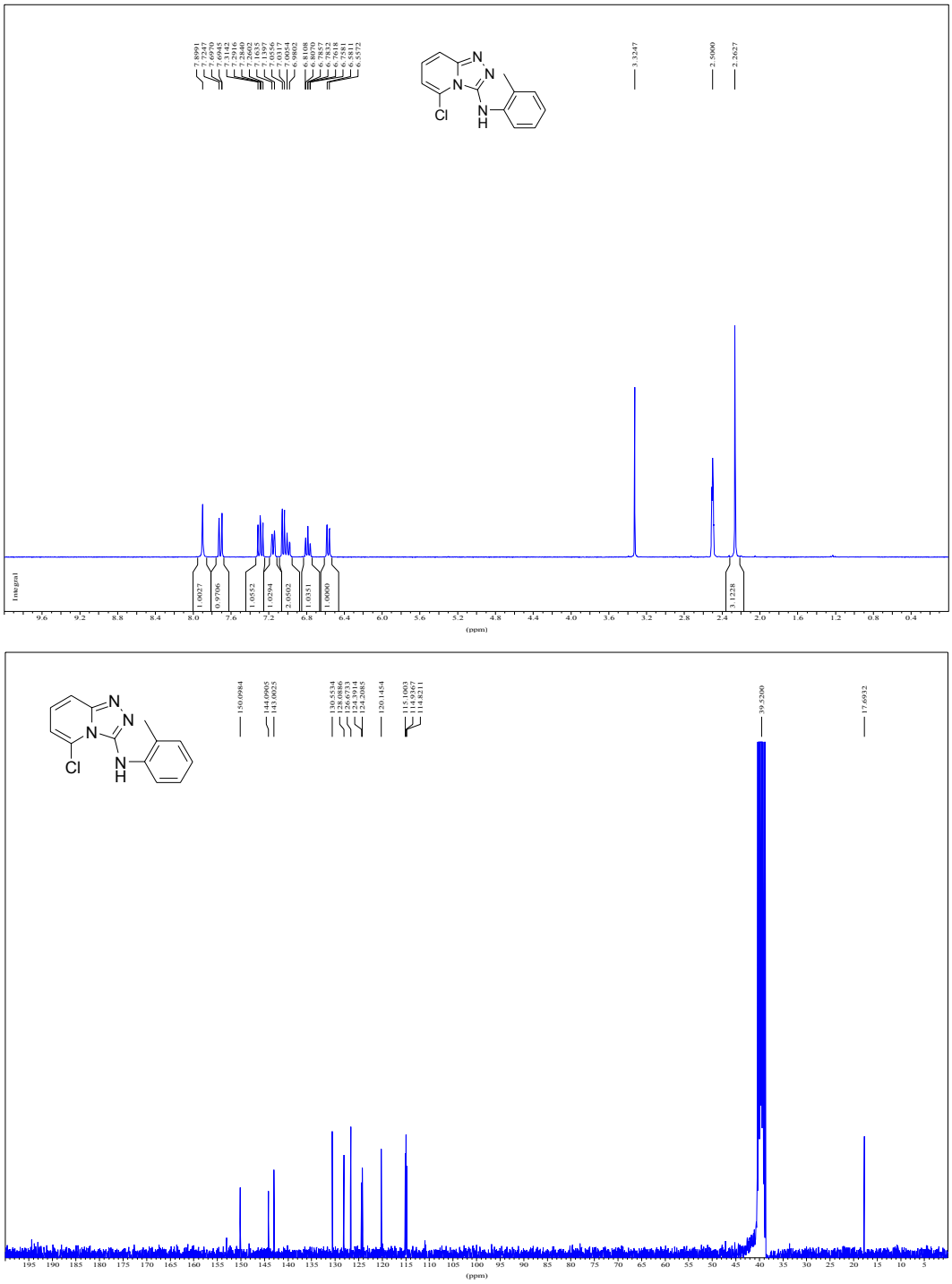


Figure 12. NMR analyses of **87d** prepared using the developed one-pot protocol

3.3. Conclusions

We have developed two convenient protocols for the synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridine derivatives under mild conditions.

The first protocol, particularly useful for medium to large scale, used Mukaiyama's reagent to promote the cyclodesulfurization of the corresponding thiosemicarbazides. The desired pure heterocycles were isolated with a simple aqueous work-up, in contrary to the previously reported use of DCC that required a chromatographic separation.

Furthermore, we demonstrated that a polymer-supported Mukaiyama's reagent can be an efficient alternative to promote this transformation. But for the success of the new process, an appropriate PS-Mukaiyama's reagent (**PS-Muk2**) had to be developed to overcome the instability issues observed with the previously reported analogue. The alternative use of PS-carbodiimides as desulfurizing agent showed some drawbacks in the synthesis of the desired heterocycles, namely slow reactions and substrate scope limited. Using **PS-Muk2**, the cyclodesulfurization showed to be fast and substrate independent and a one-pot protocol from hydrazinopyridine and isothiocyanates was easily adapted. The isolation of the final heterocycles was done by simple filtration through a SPE-NH_2 column followed by a solvent evaporation stage. The simplicity of the reaction and the purification step make of this one-protocol an excellent choice for parallel synthesis.

The one-pot protocol developed for 3-amino-[1,2,4]triazolo[4,3-*a*]pyridine derivatives showed to be robust in the extension to the synthesis of related fused 3-aminotriazoles and a small library (22 compounds) could be synthesized in a short period of time. Based on this protocol, a group at Merck Serono synthesized a 300-members library.

While these studies were in progress, new syntheses of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines were developed in the pharmaceutical[68] and agrochemical[69] industry and very recently disclosed, showing the interest of such heterocycles in these fields. The approach was similar to ours, but using isocyanates instead of isothiocyanates. The cyclisation was promoted by phosphorous oxychloride and the products were isolated after chromatography column (yields not reported). In our opinion, none of these recent approaches has the generality and the simplicity of our protocol.

4. Synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (pathway 1)

4.1. Introduction and project aims

The previous chapter described the synthesis of 3-amino-[1,2,4]triazolo[4,3-*a*]pyridine derivatives (**2**) through a cyclodesulfurization process. We then considered that a similar approach could be proposed for its regioisomer 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine (**3**). Here again, the synthesis of such compounds has not been extensively explored, particularly the *N*-substituted derivatives (R1 ≠ H) and therefore, **3** was our next target heterocycle.

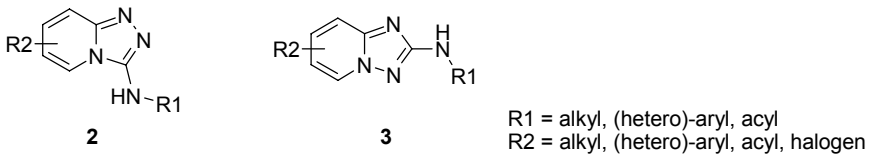
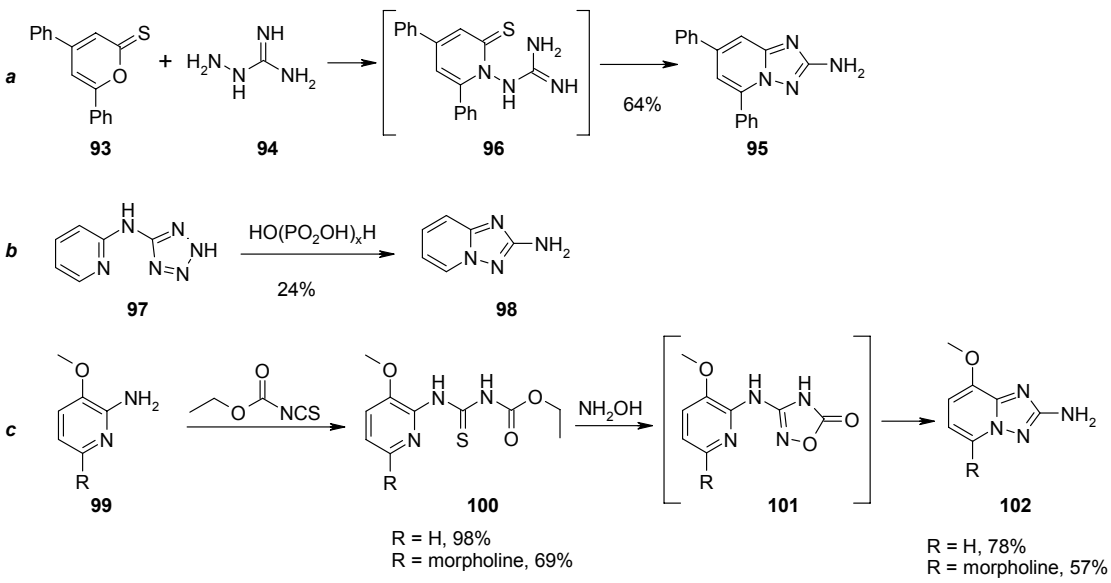


Figure 13. 3-amino-[1,2,4]triazolo[4,3-*a*]pyridine (**2**) and 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine (**3**)

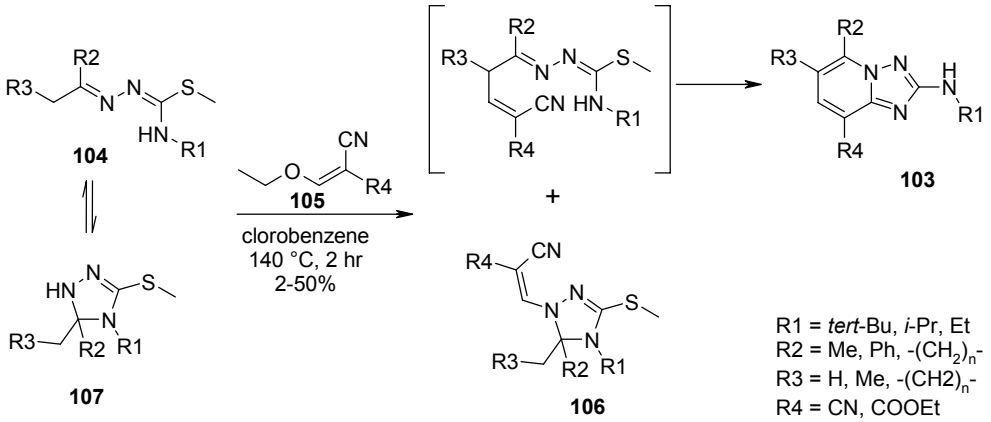
4.1.1. Previous syntheses

To the best of our knowledge, three syntheses have been described in the literature to obtain the *N*-unsubstituted derivatives (Scheme 50, pathways *a*, *b* and *c*). The first report (*a*) described the reaction of 4,6-diphenylpyran-2-thione **93** with aminoguanidine **94** to give the expected heterocycle **95** in 64% yield *via* formation of 1-guanidyl-pyridine-2-thione **96** as intermediate.[70] The synthesis of pyridine-2-thiones from pyran-2-thiones has only been described for **93**, which might be a limitation for the reaction. In the second approach (*b*), *N*-(pyridin-2-yl)-5-amino-2H-tetrazole **97** was converted in the desired heterocycle **98** in presence of polyphosphoric acid at 200 °C in 24% yield.[71] The extension of this approach to other derivatives might be restricted due to the harsh conditions that could not be compatible with many functional groups. Finally, in our opinion the best route described to date to synthesize the *N*-unsubstituted derivatives consists in a two-steps synthesis starting from 2-aminopyridines **99** and ethoxycarbonyl isothiocyanate. In the second step, the resulting thiourea **100** was subjected to cyclisation employing hydroxylamine, *via* formation of the 4*H*-[1,2,4]oxadiazol-5-one **101** intermediate. The desired heterocycles **102** were obtained in good yields (57-78%) after purification by chromatographic separation.[72]



Scheme 50. Synthesis of *N*-unsubstituted 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines previously described.

The *N*-substituted derivatives have been even more neglected. Most of them are *N*-acyl derivatives coming from acylation of the heterocycles described above.[72] Apart from them, to the best of our knowledge there is only a single report describing the formation of *N*-alkyl 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (10 examples), but in this case a different route was used for their synthesis (Scheme 51).[73]



Scheme 51. Synthesis of *N*-substituted 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines previously described.

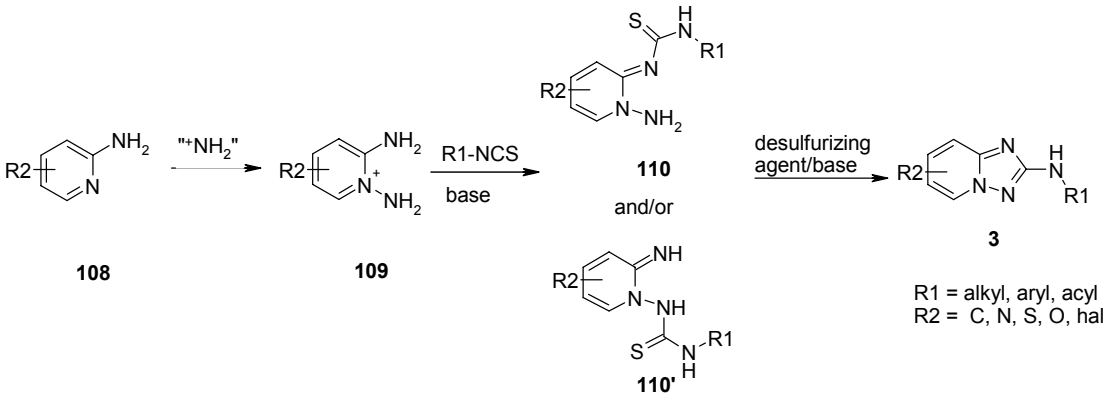
The *N*-alkyl derivatives **103** were obtained by reaction of the ketone isothiosemicarbazone **104**, carrying a bulky group on the terminal nitrogen (R1 =*tert*-butyl, *iso*-propyl) and at least one α-methylene group, with an active ethoxymethylene compound **105** (R4 = CN or COOEt), under heating conditions. When the substituent on the terminal nitrogen in less bulky (R4 = ethyl), the reaction gave a mixture of **103** and the triazoline **106** (ca. 3:2), since **104** was in equilibrium with the cyclised from **107**.

This approach is limited to specific substitution since an activated Michael acceptor (R4 = CN, COOEt) and a bulky R1 group were required. Moreover, the products were obtained in poor to moderate yields after chromatographic separation and therefore, we considered this route was not attractive for our propose.

In addition to the lack of general access to *N*-alkyl derivatives, to the best of our knowledge the *N*-aryl (or heteroaryl) analogues have not been described yet.

4.1.2. Cyclodesulfurization in the synthesis of 2-amino-[1,2,4]triazolo[1,5-a]pyridines

In chapter 3 we described the synthesis of 3-amino-[1,2,4]triazolo[4,3-a]pyridines via a cyclodesulfurization process. We discovered that such process could be efficiently carried out on many different substrates without significant differences and under very mild reaction conditions. This fact prompted us to propose a completely novel synthetic pathway for **3** where the synthesis and subsequent cyclodesulfurization of 1,2-diaminopyridine intermediates **110** are the key steps (Scheme 52).



Scheme 52. Proposed pathway for the synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**).

The proposed route consisted in a three steps synthesis starting from 2-aminopyridine **108**, which could be converted in the 1,2-diaminopyridinium cation **109** with an electrophilic aminating reagent. Further reaction of **109** with an isothiocyanate in presence of a base could lead the corresponding thiourea **110** that could be desulfurized in the last step to give the desired heterocycle **3**. Two different intermediates can be proposed for the reaction of **109** with an isothiocyanate (**110** and **110'**). Both would lead to the expected heterocycle through the formation of the corresponding carbodiimides and therefore, it would not be an issue for this approach.

4.1.3. Objectives

Many reasons prompted us to propose the route depicted in Scheme 52 for the synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines **3**: i) simple starting materials: 2-aminopyridines and isothiocyanates are commercially or readily available; ii) it could be a general approach to *N*-alkyl, *N*-acyl and *N*-aryl derivatives; iii) the formation and use of 1,2-diaminopyridinium salts in heterocyclic chemistry has not been widely investigated; iv) the opportunity to further explore the acquired experience in cyclodesulfurization processes.

The aim of the present work was to develop a *robust and general* protocol for the synthesis of *N*-aryl 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines under mild conditions tolerable by many functional groups. The synthesis of such compounds has not been described yet and consequently it could lead to completely novel and undisclosed heterocycles.

4.2. Discussion

4.2.1. 1,2-Diaminopyridinium salts

The first step of the proposed route consisted in an electrophilic amination of 2-aminopyridines. Several aminating agents have been described in the literature and their synthesis, reactivity, stability and ability to convert 2-aminopyridines into the corresponding 1,2-diaminopyridinium salts will be deeply discussed in the Chapter 5. The 1,2-diaminopyridinium salts discussed in the present chapter are depicted in Figure 13. In the text, the counterion will be precised between brackets.

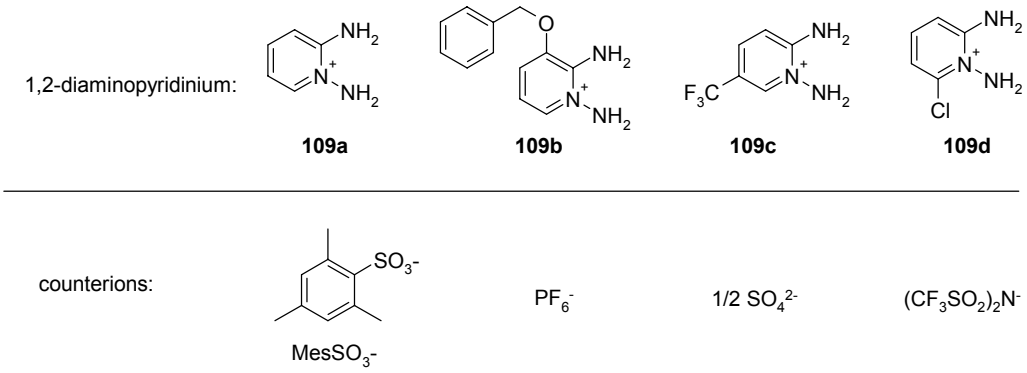
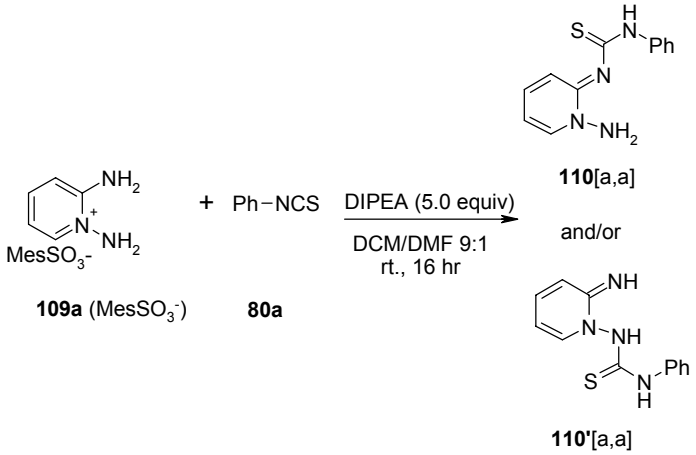


Figure 14. Structure of 1,2-diaminopyridinium and counterions.

4.2.2. Reaction of 1,2-diaminopyridinium salts with isothiocyanates.

To the best of our knowledge, the reaction of 1,2-diaminopyridinium salts with isothiocyanates has not been described yet. The reaction of 1,2-diaminopyridinium salt **109a** ($MesSO_3^-$) with phenylisothiocyanate (**80a**) was taken as model. It was carried out in DCM/DMF 9:1 at ambient temperature and in presence of DIPEA (5.0 equiv) (Scheme 53).



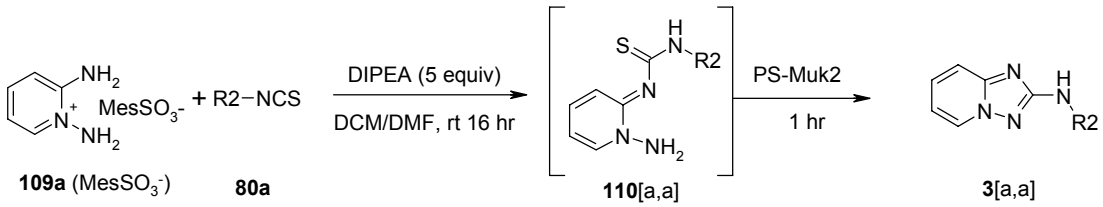
Scheme 53. Reaction of 1,2-diaminopyridinium salt **109a** ($MesSO_3^-$) with phenylisothiocyanate.

After 16 hr, both starting materials were totally consumed and only one compound was observed. Based on the mass spectrometry data it was not possible to determine whether compound **110**[a,a] or its regioisomer **110'**[a,a] was formed.[I] Unfortunately, all efforts undertaken to isolate the product were unsuccessful and the regiochemistry remains unknown. It most probably decomposed during the chromatography separation (standard or reverse phase) since no material could be recovered. For simplicity, from now on, only compound **110**[a,a] will be depicted in the schemes and considered for discussion, knowing that it could be **110'**[a,a] or even a mixture of both.

4.2.3. Cyclodesulfurization in presence of PS-Muk2

The fact that the intermediate **110**[a,a] could not be isolated prompted us to proceed to the cyclodesulfurization step in a one-pot protocol (Scheme 54).

[I] When the same reaction was performed in absence of base, only traces of **110**[a,a] or **110'**[a,a] was observed after 16 hr.



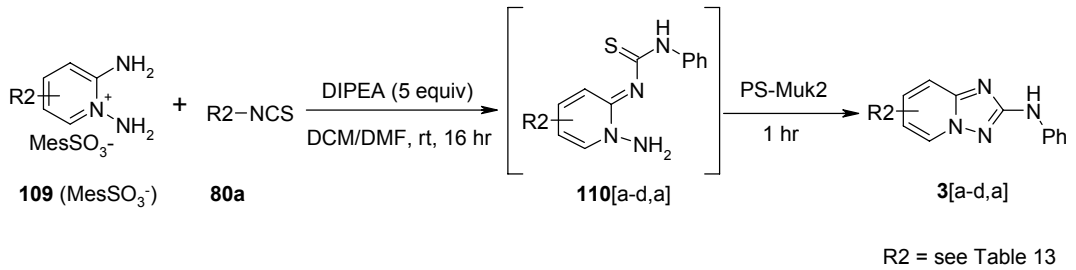
Scheme 54. One-pot protocol for the synthesis of **3**[a,a]

When the reaction of 1,2-diaminopyridinium salt **109a** ($MesSO_3^-$) with phenylisothiocyanate (**80a**) was complete, **PS-Muk2** was added as desulfurizing agent without isolation of the intermediate **110**[a,a]. Since a large excess of DIPEA was used for the first step, no further base was needed for the cyclodesulfurization and after 1 hr of reaction, the intermediate **110**[a,a] had been totally consumed to give the desired product **3**[a,a]. The diisopropylethylammonium salts were removed using a SPE-NH_2 column affording **3**[a,a] in excellent purity (>99%) and good yield (60%, elution volume not optimized).

With these experiments we confirmed the feasibility of synthesizing 2-amino-[1,2,4]triazolo[1,5-a]pyridines following the route shown in Scheme 52.

4.2.4. Cyclodesulfurization: diversity in the pyridine ring

The scope of the reaction in terms of substituents on the pyridine ring was further investigated. With this purpose, the one-pot protocol was extended to the 1,2-diaminopyridinium mesitylensulfonates **109** ($MesSO_3^-$), keeping phenylisothiocyanate (**80a**) as second partner (Scheme 55).



R2 = see Table 13

Scheme 55. Extension of the one-pot protocol to the synthesis of **3**[a-d,a]

The substituents on the pyridine ring did not have a strong influence in the reactivity of the 1,2-diaminopyridinium salts with phenylisothiocyanate and no further optimization was required for the synthesis of **3**[b,a] and **3**[c,a] (R2 = 3-benzyloxy and 5-trifluoromethyl respectively). Electrondonating and withdrawing groups were well tolerated and both compounds were isolated in good yields following the same procedure as for **3**[a,a] (entries 2 and 3, Table 13).

entry	R2	compound	yield (%)[†]
1	H	**3**[a,a]	60
2	3-BnO	**3**[b,a]	71
3	5-CF_3	**3**[c,a]	66
4	6-Cl	**3**[d,a]	-

[†] Isolated yield of pure product

Table 13. Extension of the one-pot protocol to the synthesis of **3**[a-d,a]

Interestingly, in contrary to the formation of the intermediate **110**[a,a] (R1 = H) where only one compound was detected by UPLC/MS, the reaction of **109b** ($MesSO_3^-$) (R2 = 3-BnO) and **109c** ($MesSO_3^-$) (R2 = 5-CF_3) with phenylisothiocyanate showed two intermediates in ca. 1:1 ratio, that afforded the desired heterocycles upon desulfurization. It means that depending on the substituents, one or two intermediates (**110** and **110'** in Scheme 52) can then be formed.

We could identify one restriction in terms of substituents on the pyridine ring. When **109d** ($MesSO_3^-$) (R2 = 6-chloro) was allowed to react with **80a**, the desired intermediate **110**[d,a] was not observed. Instead, the thiadiazole derivative **111** was formed (Scheme 56).[m] It was interesting since this reaction could be used in the preparation of other novel heterocycles.

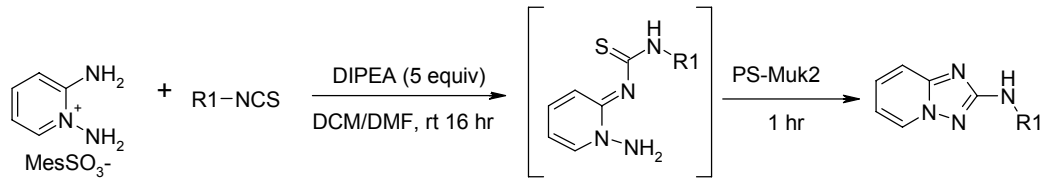
109d ($MesSO_3^-$) **80a** **111**

Scheme 56. Formation of **111** from **109d** and **80a**

4.2.4. Cyclodesulfurization: diversity in the isothiocyanate

The reaction of **109a** ($MesSO_3^-$) as the simplest 1,2-diaminopyridinium salt with different isothiocyanates was then investigated. Diversity in terms of electron distribution and steric hindrance for the phenylisothiocyanate derivatives was considered to determine the scope of the reaction (Scheme 57). The reactions were carried out under the same conditions as for **3**[a-d,a] and the results are summarized in Table 14.

[m] ^{1}H NMR of **111** was not conclusive whether the nitrogen or the sulfur atom was the nucleophile. Hence, the reaction was performed using benzylisothiocyanate instead of phenylisothiocyanate to give **112**. ^{1}H NMR (DMSO-d_6) analysis of **112** suggested the formation of thiadiazole derivative (the doublet at 4.68 ppm could be assigned to the benzylic protons which became a singlet after addition of D_2O). We assumed that the same happened to the phenyl derivative.



Scheme 57. Extension of the one-pot protocol to the synthesis of **3**[a,a-e].

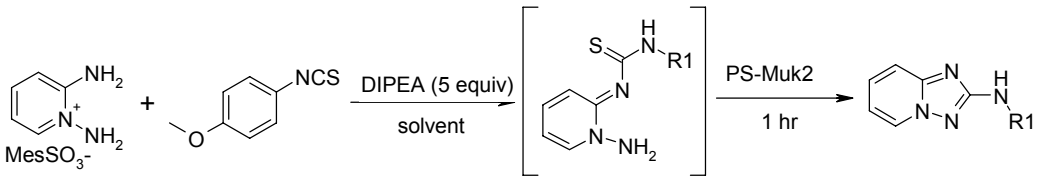
entry	R1	compounds	ratio 80 / 3 (%)†
1	phenyl	**80a / 3**[a,a]	0 / 99
2	4-MeO-phenyl	**80b / 3**[a,c]	41 / 59
3	2-Me-phenyl	**80c / 3**[a,d]	38 / 62
4	4-CF_3-phenyl	**80d / 3**[a,e]	2 / 98

† Determined by UPLC (254 nm) after SPE-NH_2.

Table 14. Extension to other isothiocyanates

In contrary to the results with phenylisothiocyanate, **80a** (R1 = Ph), the outcome of the one-pot procedure appeared to be dependent on the substituents. When the isothiocyanate **80** beard electrondonating groups, unreacted isothiocyanate (38-41%) was present after the SPE-NH_2 column (entries 2-3); with electonwithdrawing group, the reaction was almost complete (entry 4). It is important to notice that the second step was complete and clean and therefore, it was the first step that required further investigations to develop an efficient one-pot, two steps protocol suitable for diverse substrates.

In an effort to increase the conversion of the first step, different solvents and temperatures were attempted for the reaction of **109a** ($MesSO_3^-$) with 4-methoxy-phenylisothiocyanate (**80c**), the less reactive partner used until now (Scheme 58).



Scheme 58. Optimization of the one-pot protocol with the synthesis of **3**[a,c]

In the previous experiments, even if both reagents were added in solution (**80c** in DCM and **109** ($MesSO_3^-$) in DMF), **109a** ($MesSO_3^-$) precipitated out after few seconds of reaction, as it is

poorly soluble in DCM. This fact has not been an issue for the synthesis of **3**[a-c,a] as the reactions were complete and the final compounds were isolated with excellent purity. Nevertheless, ensuring a homogeneous mixture might help the reaction to proceed and for this reason, this step was carried out in DCM at higher temperatures (sealed tube), as well as in THF, DMF and DMSO. These solvents are compatible with the polymer-bound reagent used in the second step. The reaction was monitored after each step and the results are summarized in Table 15.

entry	conditions				step 1 ratio **80c** / **110**[a,c] ‡	step 2 ratio **80c** / **3**[a,c]§
	solvent	temp. (°C)†	time (hr) step 1	**109a** ($MesSO_3^-$) (equiv)		
1	DCM	rt	16	1.0	44 / 45	n.d
2	DCM	rt	16	1.5	40 / 52	n.d.
3	DCM	50	16	1.0	12 / 81	13 / 83
4	DCM	50	16	1.2	6 / 84	6 / 92
5	DCM	50	16	1.5	6 / 86	5 / 92
6	DCM	80	2	1.0	12 / 73	9 / 90
7	DCM	80	2	1.5	3 / 77	3 / 93
8	THF	rt	16	1.0	78 / 11	n.d.
9	THF	rt	16	1.5	77 / 11	n.d.
10	THF	80	16	1.0	0 / 31	n.d.
11	THF	80	16	1.5	0 / 44	n.d.
12	DMF	rt	16	1.0	14 / 80	3 / 97
13	DMF	rt	16	1.5	0 / 62	n.d.
14	DMF	50	16	1.0	0 / 83	0 / 95
15	DMF	80	16	1.0	0 / 25	n.d.
16	DMF	80	16	1.5	0 / 51	n.d
17	DMSO	rt	16	1.0	17 / 66	4 / 96
18	DMSO	rt	16	1.2	12 / 68	4 / 97
19	DMSO	rt	16	1.5	5 / 72	1 / 99
20	DMSO	50	16	1.0	0 / 86	5 / 95
21	DMSO	50	16	1.2	0 / 81	0 / 94
22	DMSO	50	16	1.5	0 / 82	0 / 91

† Sealed vials were used for temperatures above solvent bp. ‡ Determined by UPLC (254 nm) before addition of PS-Muk2. **110**[a,c] = sum of both intermediate regioisomers. § Determined after addition of PS-Muk2 followed by SPE-NH_2 column.

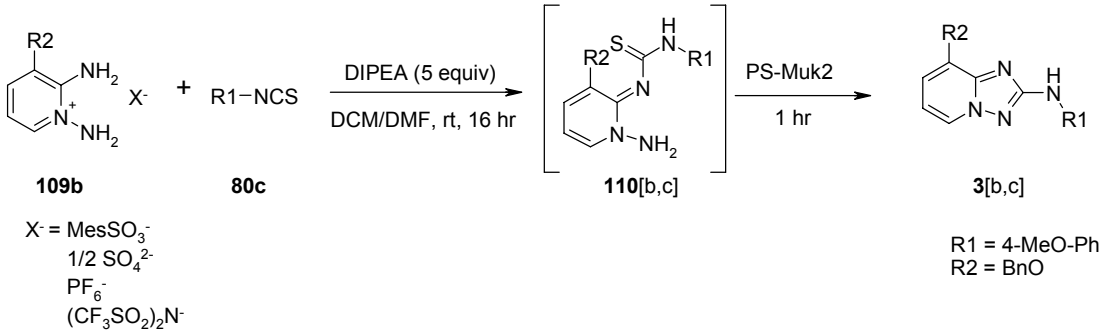
Table 15. Solvent and temperature effect in the synthesis of **3**[a,c]

In general, the reaction proceeded better in homogeneous mixtures given that the lowest conversions were obtained in DCM and THF at ambient temperature where the 1,2-diaminopyridinium salt **109a** ($MesSO_3^-$) was not soluble (entries 1, 2, 8 and 9). Higher temperatures in the case of DCM improved the conversion for the first step at such rate that the final heterocycle was obtained in good purity although a small amount of unreacted

isothiocyanate was still observed (5-13%, entries 3-7). Increasing **109a** ($MesSO_3^-$) from 1.0 to 1.5 equiv slightly improved the results (entry 3 *vs* 4-5; entry 6 *vs* 7). Contrarily to DCM, the increase of temperature in THF led to lower conversion and to the degradation of the starting materials (entries 10-11). When the reaction was performed in DMF while using 1.0 equiv of **109a** ($MesSO_3^-$), good, but not complete conversion was obtained over 16 hr. Unfortunately, with the use of a slight excess of **109a** ($MesSO_3^-$) (1.2 and 1.5 equiv) and/or increasing the temperature (from rt. to 50 or 80 °C), a side reaction took place with the consequential loss in purity. Finally, DMSO showed to be appropriate for this transformation since the reaction achieved high conversion under mild conditions and the final compound could be isolated with excellent purity (entries 17-19). In this case, 1.5 equiv of **109a** ($MesSO_3^-$) gave the best result. It is important to notice that the excess of this reactant could be removed by simple filtration through SPE-NH_2 column.

4.2.5. Counterion effect

The previous experiments prompted us to investigate the influence of the counterion of the pyridinium derivative in this transformation, since it has an effect on the solubility. For this, the reaction of 1,2-diamino-3-benzyloxypyridinium **109b** ($MesSO_3^-$) was compared with the reaction of **109b** (½ SO_4^{-2}), **109b** (PF_6^-) and **109b** [$(CF_3SO_2)_2N^-$)] with 4-methoxy phenylisothiocyanate (**80c**) in DMSO in presence of DIPEA (Scheme 59). Since we failed to isolate the intermediate **110**[b,c], we proceeded to the cyclodesulfurization and the results of the whole transformation were compared.



Scheme 59. Counterion effect in the synthesis of **3**[b,c]

entry	counterion	solvent	time (hr) step 1	reaction mixture	step 1 **80c** / **110**[b,c] ‡	step 2 **80c** / **3**[b,c]§
1	$MesSO_3^-$	DMSO	16	solution	8 / 72	1 / 99
2	PF_6^-	DMSO	16	solution	0 / 75	0 / 98
3	$(CF_3SO_2)_2N^-$	DMSO	16	solution	2 / 78	0 / 96
4	½ SO_4^{-2}	DMSO	72	suspension	3 / 83	0 / 90
5	½ SO_4^{-2}	MeOH	16	solution	3 / 75	42 / 33
6	½ SO_4^{-2}	DMSO/H_2O	16	bi-phasic solution	7 / 89	0 / 99

† Determined by UPLC (254 nm) before addition of PS-Muk2. **110**[b,c] = sum of both intermediates. § Determined after addition of PS-Muk2 followed by SPE-NH_2 column.

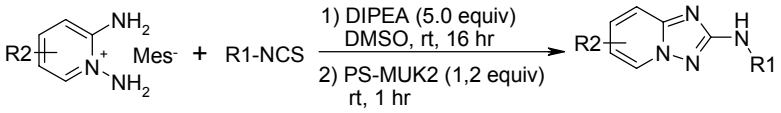
Table 16. Counterion effect

The organic counterions ($MesSO_3^-$, PF_6^- and $(CF_3SO_2)_2N^-$) provided a good solubility to **109b** in DMSO and high conversions were obtained for the first step after 16 hr. In these cases, after cyclodesulfurization, the expected product was obtained in high purities (>96%) and good yields (72-84%) (Table 16, entries 1-3). On the contrary, due to the low solubility of **109b** (½ SO_4^{-2}) in DMSO (suspension obtained), 72 hr were necessary to achieve high conversions for the first step and some impurities accumulated. In this case, **3**[b,c] was isolated with slightly lower purity (entry 4). Then, the reaction with **109b** (½ SO_4^{-2}) was performed in methanol to ensure the solubility and a good conversion was obtained after 16 hr but unfortunately, the second step did not proceed well since this solvent is not compatible with polystyrene-supported reagents (**PS-Muk2**) (entry 5). Finally, a mixture DMSO:water 1:1 seemed to be a good compromise for **109b** (½ SO_4^{-2}) and the final heterocycle was obtained in high purity but lower yield (45%) (entry 6).

From the counterions that gave better results ($MesSO_3^-$, PF_6^- and $(CF_3SO_2)_2N^-$), we chose to pursue our studies ($MesSO_3^-$) since they are easier to obtain as it will be discussed later.

4.2.6. Application of the optimized protocol. Synthesis of a small library.

A small library of compounds was synthesized in parallel fashion following the optimized protocol. The first step was carried out using 1,2-diaminopyridinium mesitylensulfonates **109** (1.5 equiv) and isothiocyanates **80** (1.0 equiv) in DMSO at ambient temperature for 16 hr. **PS-Muk2** (1.2 equiv) was then added as desulfurizing agent for the second step (Scheme 60).

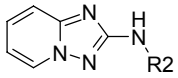
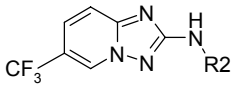
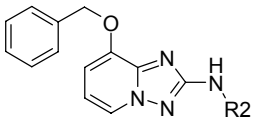


109 **80** **3**

For R1 and R2 see Table 17

Scheme 60. Optimized protocol for the parallel synthesis of **3**.

The reactions proceeded as expected and the final compounds were isolated with excellent purities after a simple filtration on SPE-NH_2 column. Electron donating and withdrawing groups in both phenyl and pyridne ring were well tolerated. The results are summarized in Table 17.

entry	scaffold	R1	compound	yield (%)†
1		phenyl	**3**[a,a]	62
		4-MeO-phenyl	**3**[a,c]	86
		2-Me-phenyl	**3**[a,d]	66
		4-CF_3-phenyl	**3**[a,e]	91
		3-Cl-phenyl	**3**[a,g]	39
2		phenyl	**3**[b,a]	68
		4-MeO-phenyl	**3**[b,c]	87
		2-Me-phenyl	**3**[b,d]	68
		4-CF_3-phenyl	**3**[b,e]	83
		3-Cl-phenyl	**3**[b,g]	74
3		phenyl	**3**[c,a]	76
		4-MeO-phenyl	**3**[c,c]	84
		2-Me-phenyl	**3**[c,d]	79
		4-CF_3-phenyl	**3**[c,e]	78
		3-Cl-phenyl	**3**[c,g]	69

† Isolated yield through filtration on SPE-NH_2 column, elution volume not optimized.

Table 17. Parallel synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**)

As evidence of the very high purities obtained, the NMR spectra of compound **3**[a,c] as a typical example is shown in Figure 15.

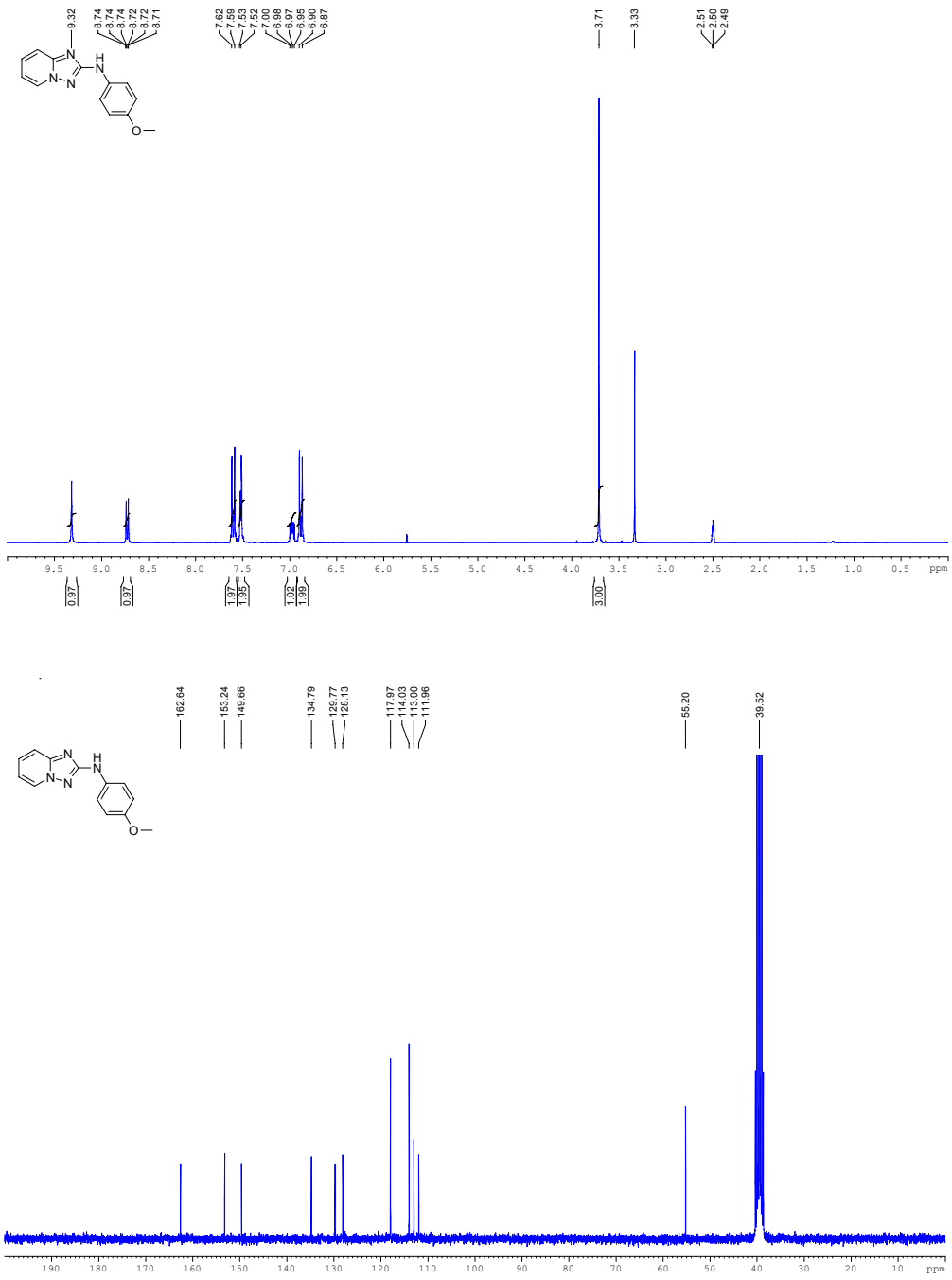


Figure 15. NMR spectra of **3**[a,c] prepared using the developed one-pot protocol.

4.3. Conclusions

We have developed a new synthetic route for the synthesis of *N*-aryl 2-amino-[1,2,4]triazolo[1,5-a]pyridines under mild conditions. To the best of our knowledge, it was the first report of the synthesis of such compounds.

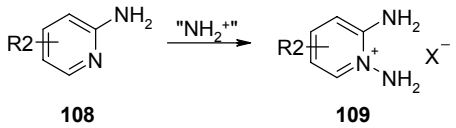
The synthetic route consisted in three steps where the last two could be combined in a one-pot. The success of the one-pot protocol lies on the conversion for the second step, since the cyclodesulfurization proceeded smoothly under the conditions developed in the previous chapter. In order to reach high conversions in the second step, a homogeneous reaction mixture was required, especially for phenylisothiocyanates bearing electrondonating groups. The isolation of the final heterocycles was done by simple filtration through a SPE-NH_2 column followed by a solvent evaporation stage.

The simplicity of the reactions and the purification step makes this route particularly convenient for parallel synthesis. To validate this, a small library was easily synthesized during this work. Following this protocol, a group at Merck Serono synthesized a 250-members library.

5. Synthesis of 1,2-diaminopyridinium salts

5.1 Introduction and project aims

In the previous chapter we showed how 1,2-diaminopyridinium salts **109** could be employed as a key reagent in the synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**). The preparation of these salts *via* an electrophilic amination of the corresponding 2-aminopyridine (**108**) (Scheme 61) was not discussed and it will be the object of this chapter.



108 **109**

Scheme 61. *N*-amination of 2-aminopyridines

Several aminating agents have been described in the literature that could be used in the synthesis of 1,2-diaminopyridinum salts. Some of them have been reported as hazardous materials as it will be discussed later but to the best of our knowledge, no comparative study has been done on this topic. Therefore, we decided to evaluate different aminating agents in terms of *reactivity and thermal stability* in order to find the best for our purpose.

5.1.1. Aminating agents

Amines represented by the general structure NH_2-X, where X is a leaving group, have both nuclephilic and electrophilic properties in one molecule and can be considered as a source of nitrenium ions (NH_2^+).

An exhaustive literature search revealed that chloramine, *O*-sulfonyl, *O*-acyl, *O*-aryl and *O*-phosphinyl hydroxylamines, hydroxylamine *O*-sulfonic acid, *N*,*N*,*N*-trialkylhydrazonium salts and oxaziridines have been used as aminating agent of different nucleophiles. The most representative example of each series is represented in Figure 16.

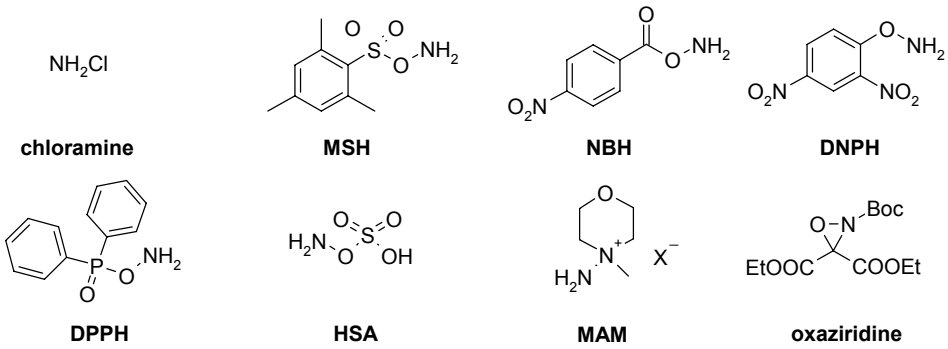
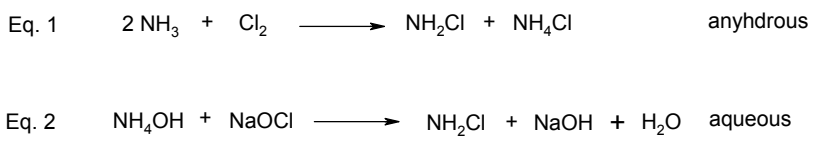


Figure 16. Most common aminating agents. Chloramine. *O*-Mestitylenesulfonyl hydroxylamine (MSH). *O*-*p*-Nitrobenzoyl hydroxylamine (NBH). *O*-Dinitrophenyl hydroxylamine (DNPH). *O*-Diphenyl-phosphinyl hydroxylamine (DPPH). Hydroxylamine *O*-sulfonic acid (HSA). *N*-Methyl-*N*-aminomorpholinium (MAM) salts. Oxaziridine.

A summary of the literature concerning each main aminating agent is presented hereafter. The aim is to illustrate their physical and chemical properties and the type of nucleophiles that have been used with.

Chloramine

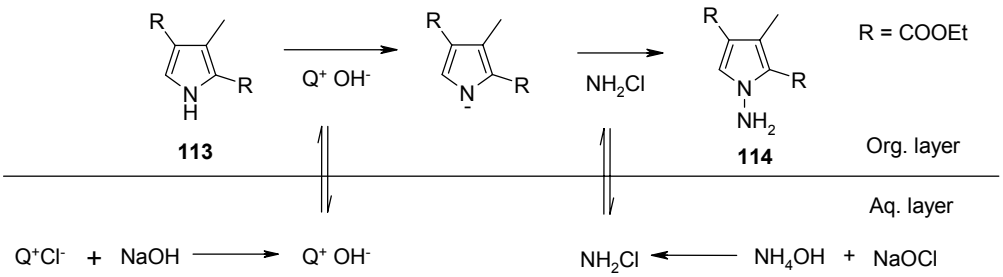
Chloramine is the oldest aminating agent described, being the first reports from the late 1920's.[74] Anhydrous chloramine can be prepared by the gas phase reaction of chlorine with excess of ammonia (Eq. 1, Scheme 62)[75] but this appears to be almost useless as it decomposes at -50 °C with formation of nitrogen, chlorine and the highly unstable and shock-sensitive nitrogen trichloride.[76] Aqueous solutions can be prepared *in situ* by the reaction of aqueous ammonia and sodium hypochlorite (Eq. 2, Scheme 62)[77,78] and only diluted solutions are recommended. Chloramine is generally prepared immediately before use as on standing, it decomposes to dichloramine and nitrogen trichloride constituting a potential hazard concern.[79]



Scheme 62. Preparation of chloramine

Despite the potential hazard, many reactions have been developed using chloramine as an aminating agent.[80] More recently, an etheral solution of chloramine was used to *N*-aminate pyrrole and indole derivatives at ambient temperature in presence of sodium hydride. The products were obtained in moderate to high yields (44-95%) after chromatographic separation.[81] Soon later, a smart and safer protocol was developed for large-scale

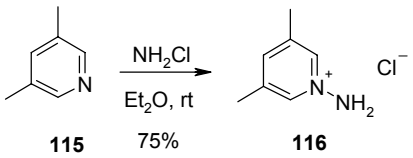
electrophilic amination of pyrroles using *in situ* generated chloramine and Aliquat-336 (methyltrioctylammonium chloride) as phase transfer catalyst (PTC) (Scheme 63).[82]



Scheme 63. One-pot, phase transfer N-amination of pyrrole with chloroamine. Q+Cl- : quaternary ammonium salt Aliquat 336 (PTC)

In the optimal procedure, chloramine is generated in the aqueous layer through oxidation of ammonia by sodium hypochlorite. At the same time, the substrate **113** is deprotonated in the organic phase and promptly reacts with the small portion of chloramine present in the organic layer affording the desired *N*-aminopyrrole derivative **114** in high yield. This process avoids any undesirable accumulation of chloramine. These conditions were also successfully applied to prepare a series of *N*-amino heterocycles (pyrroles and indoles) in consistently high yields (91-96%).

In contrary to the amination of pyrroles and indoles, heteroaromatic tertiary amines gave less satisfactory results when reacted with an ethereal solution of chloramine.[83] It was observed that only 3,5-lutidine (**115**) afforded the expected compound **116** (Scheme 64) whereas the very close analogues 2,3-lutidine, 2,4-lutidine, 2,6-lutidine and 2,4,6-collidine gave the corresponding hydrochloride salts and ammonium chloride. The same behavior was previously reported for the reaction of pyridine and 2-methylpyridine with chloramine.[84]

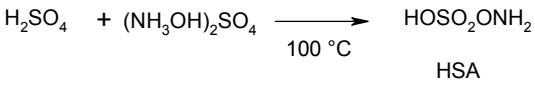


Scheme 64. *N*-amination of 3,5-lutidine with chloramine.

To the best of our knowledge, the synthesis of **116** remains the only application of chloramine in *N*-amination of heteroaromatic tertiary amines.

Hydroxylamine O-sulfonic acid (HSA)

HSA is a readily available reagent that can be purchased from different common suppliers or synthesized by reaction of bis hydroxylammonium sulfate with 30% fuming sulfuric acid.[85]



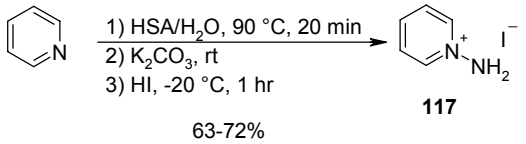
Scheme 65. Synthesis of HSA.

In the pure form is a white microcristalline solid, melting with decomposition at 210-211 °C. It is hygroscopic in nature but it is stable for long periods of time if stored in moisture-free atmosphere.[85] However, aqueous solutions are unstable, decomposing slowly below 25 °C but rapidly above this temperature. In solution HSA exists in equilibrium between the zwitterionic and the neutral from (pKa in water is 1.48). In addition to be soluble in water, it dissolves in methanol but is only slightly soluble in ethanol. It is insoluble in chloroform, diethylether, dichlorsomethane and tetrahydrofurane.[85]

The use of HSA in organic chemistry started in the late 1950's. Since then, many reactions have been reported and reviewed,[86] resulting from the ability of the nitrogen center to act both as a nucleophile and as an electrophile, according to the circumstances. Most of the uses of HSA is for amination on nitrogen, although amination at carbon and sulfur have also been described.[86]

There are several examples of *N-N* bond formation with HSA including formation of hydrazines[87] and amination of heteroaromatic secondary and tertiary amines (indole, pyrazine, pyridazine, pyridine, pyrimidine). Since we were particularly interested in electrophilic amination of 2-aminopyridines, we focused on the use of HSA with heteroaromatic tertiary amines.

The first report was the amination of pyridine, where the resulting 1-aminopyridinium sulfate formed upon reaction with HSA, was converted to its iodide salt **117** to facilitate the isolation (Scheme 66).[87]

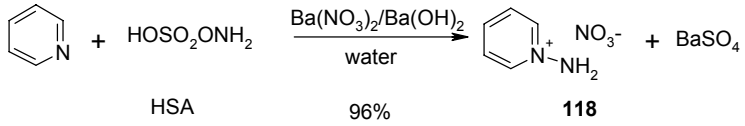


Scheme 66. Amination of pyridine with HSA

The same protocol was later applied by another group to 2-aminopyridine but in this case the yield dropped to only 30% due to isolation issues.[88] May be for the same reason, in a later report the 1,2-diaminopyridinium salt was not isolated but further reacted with benzoyl chloride to afford the expected *N*-benzoyl derivative in poor to medium yield (18-60%)

depending on the substitution on the pyridine ring.[89] The same authors got better yields (64-97%) for these reactions when HSA was replaced by MSH.[89]

An alternative procedure to prepare such compounds consisted in using a mixture of barium nitrate and barium oxide together with HSA.[90] The resulting barium sulfate could be removed by filtration and the 1-aminopyridinium nitrate (**118**) was isolated sufficiently pure by evaporation of the filtrate under reduce pressure. Using this protocol, Dabco, pyrazine and pyridazine were *N*-aminated in 63, 38 and 34% yield respectively.[90]

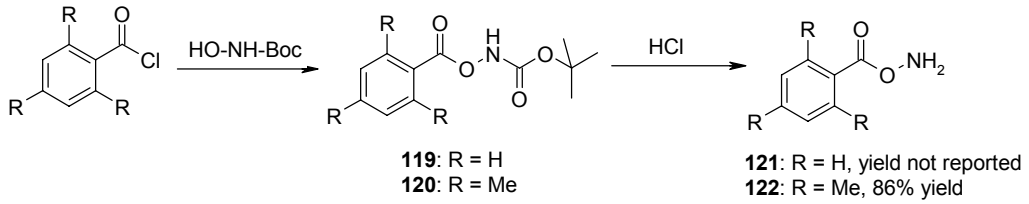


Scheme 67. Amination of pyridine using HSA and $Ba(NO_3)_2/Ba(OH)_2$.

As you can see for the previous reports describing the electrophilic amination of pyridines, the isolation of the resulting salt appears to be a critical issue, since they are highly soluble in the solvents in which the reactions are usually performed (water, methanol).

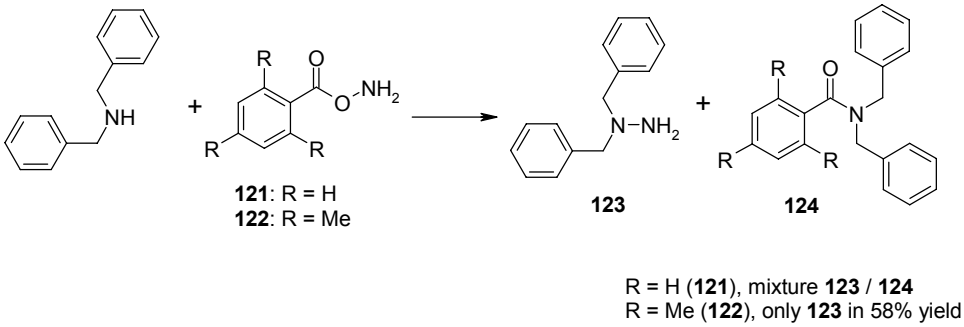
O-Acyl hydroxylamines

The use of *O*-acyl hydroxylamines as aminating agents was first described by Carpino in the early sixties, in particular *O*-benzoyl derivatives.[91] They were synthesized from the *N*-Boc protected analogue (**119**-**120**) with HCl in good yields (Scheme 68). He first studied the relative stability and reactivity of *O*-benzoyl hydroxylamine (**121**) and the *O*-mesitoyl analogue (**122**), identifying the latter as the most stable.[91]



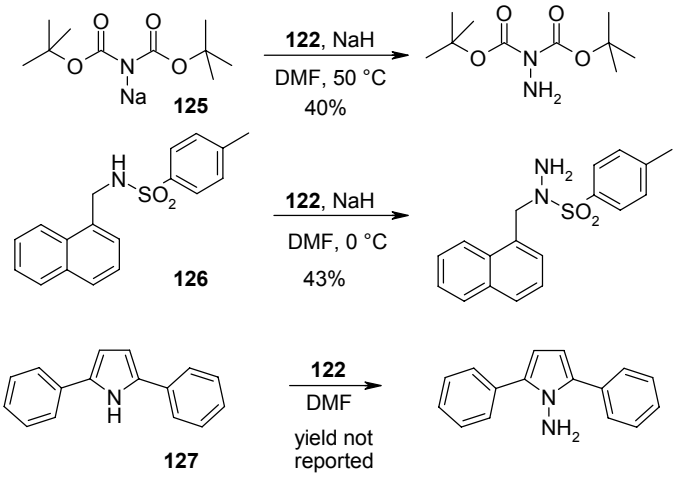
Scheme 68. Synthesis of *O*-acylhydroxylamines **121** and **122**.

In addition, the steric effect of the mesitoyl group of **122** allowed nucleophilic displacements on nitrogen to occur without complications due to attack of the nucleophile at the carbonyl group. As an example, reaction of **121** with dibenzylamine gave a mixture of 1,1-dibenzylhydrazine (**123**) and *N,N*-dibenzylbenzamide (**124**) whereas with **122**, no evidence for the amide formation was noticed and the hydrazine was obtained in good yield (58%) (Scheme 69).[91]



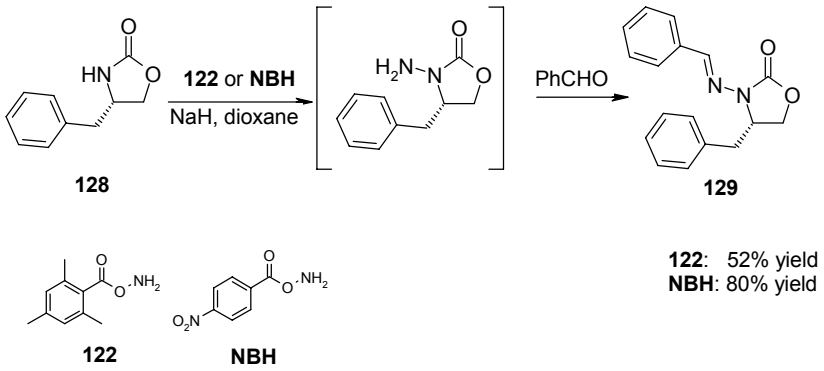
Scheme 69. Reaction of dibenzylamine with **121** and **122**.

Soon after, **122** was used in the *N*-amination of *tert*-butyl iminodicarboxylate sodium salt (**125**),[92] *N*-α-menaphtyl-*p*-toluensulfonamide (**126**)[93] and 2,5-diphenylpyrrole (**127**)[94] with relative success as the corresponding *N*-aminated products were obtained in poor yields (Scheme 70).



Scheme 70. Examples of electrophilic amination using **122**.

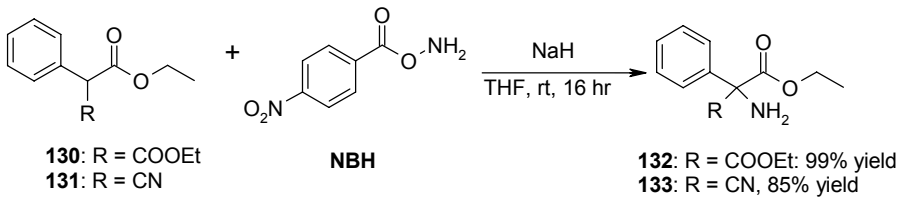
More recently, 2-oxazolidinone **128** was *N*-aminated using **122** and the resulting *N*-amino compound was converted in the corresponding phenyl hydrazone **129** using benzaldehyde in 52% overall yield (Scheme 71).[95] It was found that *O*-*p*-nitrobenzoyl hydroxylamine (NBH) improved the results affording **129** in 80% overall yield.[95] The use of NBH was successfully extended to other 2-oxazolidinones and the final hydrazones were obtained in good yields (76-99%).[95,96]



Scheme 71. Amination of 2-oxazolidinone **128** with **122** and NBH.

NBH was also used in the *N*-amination of heteroaromatic secondary amines, in particular pyrroles and indoles[97] as an alternative to the method with chloramine described above.[81,82]

But NBH has not been used for *N*-*N* bond formation exclusively. Indeed, it has been effectively employed in electrophilic amination of carbanions, in particular in the reaction with highly stabilized enolates. For example, NBH was used for the amination of the enolate of the esters **130**-**131** and the products **132**-**133** were obtained in very good yields (Scheme 72).[98]

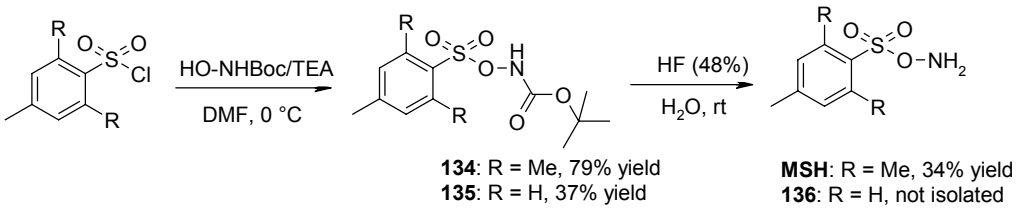


Scheme 72. Electrophilic amination of carbanions with NBH.

Although *O*-acyl hydroxylamines have been used with a wide rage of substrates, to the best of our knowledge *N*-amination of heteroaromatic tertiary amines has not been described yet.

O-Mestitylenesulfonyl-hydroxylamine (MSH)

When Carpino reported the use of *O*-acylhydroxylamines in 1960, he also mentioned *O*-sulfonyl hydroxylamines as an alternative aminating agent, especially *O*-mesitylenesulfonyl-hydroxylamine (MSH).[91] It was prepared by deprotection of the *N*-Boc derivative **134** with HF in 34% yield (Scheme 73). MSH showed to be more stable than its analogue *O*-*p*-toluenesulfonylhydroxylamine (**136**) under the cleavage conditions, since all attempts to isolate **136** were unsuccessful.[91] The effect of the substituents in the stability goes in the same direction than for the *O*-acyl series. Later, **136** could be synthesized using a different protecting group.[99]



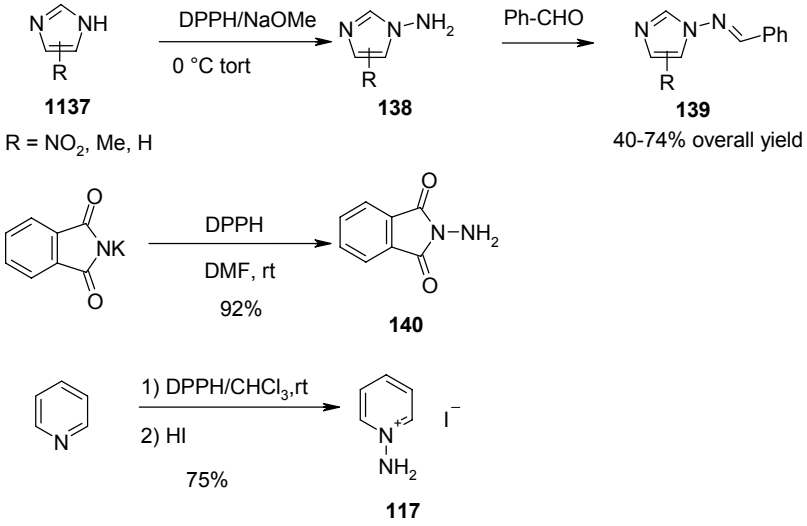
Scheme 73. Synthesis of *O*-sulfonyl hydroxylamines.

The crude reaction of MSH showed to be unstable and spontaneously decomposed on standing overnight at ambient temperature.[91] On the contrary, once recrystallized it decomposed in air at ambient temperature within 2-3 days, but could be kept for at least two weeks upon storage in a freezer. MSH is freely soluble in commonly used organic solvents such as ether, chloroform, dichloromethane, ethanol, tetrahydrofurane but is insoluble in water and hexane.

Although MSH has been use in many different transformations,[100] it is best known for *N*-amination of heteroaromatic tertiary amines (pyridines,[101-124] pyrazines,[125-128] pyridazines,[125] pyrimidines,[125,129] quinolines,[130-133] imidazopyridines,[134] thienopyridines).[135,136] In particular, MSH has been used in the synthesis of 1,2-diaminopyridinium salts from 2-aminopyridines.[125] Usually the reaction proceeds under mild conditions and the mesitylenesulfonate salts can be easily isolated by filtration in good yields.

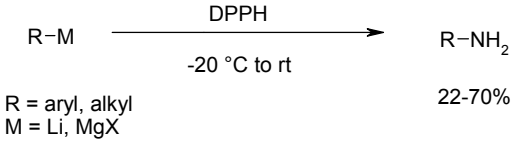
O-(Diphenylphosphinyl)hydroxylamine (DPPH)

Klotzer first described the use of *O*-(diphenylphosphinyl) hydroxylamine (DPPH) as aminating agent in 1982 (Scheme 74).[137] A series of imidazoles **137** were *N*-aminated at ambient temperature in presence of DPPH and sodium metoxide. The resulting *N*-aminoimidazoles **138** were isolated as phenylhydrazones **139** in 40-74% yield by reaction with benzaldehyde. DPPH showed to be even more efficient in the *N*-amination of potassium phtalimide and pyridine (92 and 75% yield respectively). In the latter case, hydroiodic acid was added to facilitate the isolation of the product **117**. The same strategy for the isolation was previously described when HSA was used as aminating agent.



Scheme 74. First reactions of DPPH as aminating agent.

Boche *et al*. described the synthesis of primary amines *via* electrophilic amination of organometallic compounds, in particular organomagnesium and organolithium reagents (Scheme 75).[138] Yields were poor to moderate most probably because of the protonation of these basic carbons by the amino group occurs. When the amino does not have any acidic proton (*e.g. N*-*N*-dimethyl derivative of DPPH), generally better yields are obtained.[138]



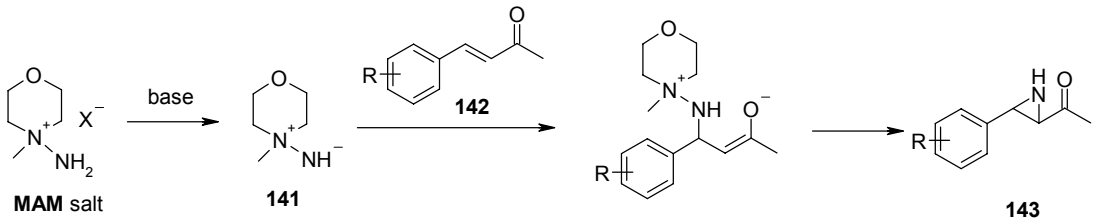
Scheme 75. Synthesis of primary amines with DPPH

More recently, DPPH has been used mainly for *N*-amination of heteroaromatic secondary amines (imidazoles,[139,140] indoles,[141] pyrroles).[142,143] and in the *N*-amination of 2-oxazolindiones.[144-146]

To the best of our knowledge, the synthesis of *N*-aminopyridinium iodide (**117**) remains the only example of *N*-amination of heteroaromatic tertiary amine with DPPH.

N-amino-N-methylmorpholinium salts

N-amino-*N*-methylmorpholinium (MAM) salts have been recently described as highly active aziridination reagents for chalcones (Scheme 76).[147,148] The reaction most probably proceeds *via* a nucleophilic conjugate addition of the aminimide **141** to the chalcone **142** followed by cyclization to form the aziridine **143** with the loss of *N*-methylmorpholine. The *in situ* generated version of MAM from *N*-methylmorpholine and DPPH was also developed.[149]



Scheme 76. Synthesis of aziridines with MAM salts

MAM (NO_2^-) has been synthesized via electrophilic amination of *N*-methylmorpholine with HSA and barium nitrate at high temperature.[147] As an alternative route, the same substrate was *N*-aminated under milder conditions using MSH affording MAM ($MesSO_3^-$).[148] A more convenient approach was developed for MAM (I^-) synthesis, via *N*-methylation of *N*-aminomorpholine with iodomethane.[147]

As the previous described aminating agents, MAM salts have an amino group bearing a leaving group, which in this specific reaction of aziridination of chalcones; it was activated in presence of a base *via* formation of the aminimide **141**. Hence, without any activation, this compound could be envisaged for electrophilic amination processes.

5.1.2. Objectives

Several safety issues have been reported for electrophilic aminating reagents such as chloramine,[n] MSH,[o] DNPH,[p] MAM iodide [q] and oxaziridine.[r] For that reason, the aim of this work was to search a *safe and convenient reagent* to perform the amination of 2-aminopyridines, in order to have access to 1,2-diaminopyridinium salts.

To the best of our knowledge, there are no studies that compare the thermal stability and potential hazard of the aminating agents in a quantitative manner. Hence, the main concerns of this work were: i) to investigate the formation of 1,2-diaminopyridinium salts with the selected aminating agent. ii) to study the thermal behavior of these reagents by Differential Scanning Calorimetry (DSC) in order to figure out its potential danger.

[n] "It is important for anyone working in the *N*-halamine area to be cognizant of the real and potential hazards, namely toxicity and explosiveness"[80]

[o] "A dried sample decomposed after putting into an amber bottle for storage, the screw cap being shattered"[150] "MSH was exploded on several occasions in our laboratory (....) it should be stored in a plastic container sealed with plastic or wax film"[151] "We experienced a mild explosion in attempting to dry 4.5 g of MSH at rt under vacuum"[152] "Since we have also experienced an explosion of this material upon storage below 0 °C, we strongly recommend that it be prepared immediately prior use, and that it not be stored"[153]

[p] "An experiment with DNPH and KH was proceeding (rt, stirring, nitrogen entrainment) when a detonation occurred which demolished the ceramic top of the magnetic stirrer and the glassware associated with the experiment"[154] "DNPH was initially subjected to DSC analysis; this resulted in the over-pressurization of the medium-pressure stainless steel cell with enough force to shatter the ceramic sensor and damage the surrounding oven (....) Onset temperature 110 °C, energy 2308 J/g)"[155] "Our laboratory confirmed these results although a lower energy was observed: 1269 J/g, onset 100 °C (...) It has the potential for detonation"[156]

[q] "DSC exotherm at 170 °C"[147]

[r] "DSC showed a broad exotherm at 100 °C. We therefore recommend that this reagent is not heated above rt"[157]

5.2 Discussion

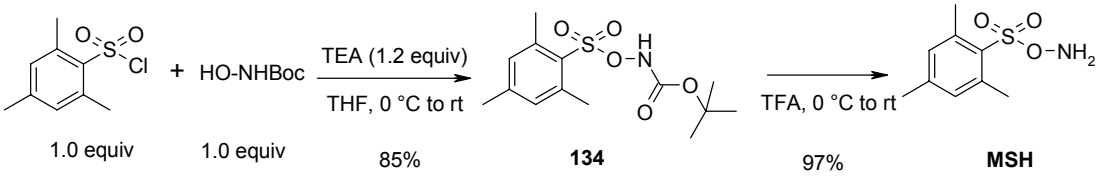
Each aminating agent used during the current studies was synthesized with extreme precautions (protective shield, low temperature, cold rotatory-evaporator bath, sash closed) and in a maximum scale of 5 mmoles. All the electrophilic amination reactions were first carried out in small scale (0.25 mmol) in order to minimize the potential danger. After this initial evaluation, the reactions were scaled-up to 10 mmoles depending on the thermal stability.

5.2.1. O-Mestitylenesulfonylhydroxylamine (MSH)

As it was previously discussed, MSH seems to be one of the best options to *N*-aminate tertiary amines and thus, it was our first choice for this investigation.

- Synthesis and thermal stability.

Two syntheses have been reported for MSH, both starting from mesitylensulfonyl chloride and *N*-protected hydroxylamine to avoid *N*-sulfonylation. Zinner *et al*. used ethyl acetohydroxamate and in this case, perchloric acid is required to cleave the protecting group. On the contrary, Carpino *et al*. preferred *N*-Boc protected hydroxylamine that could be cleaved with HF to afford MSH. Interestingly, most of the authors who experienced explosions with MSH had used Zinner's method to prepare it. The presence of traces of perchloric acid might have a synergy effect in the explosive properties. For this reason, MSH was synthesized following Carpino's report with some modifications (Scheme 77). In our hands, the replacement of DMF by THF in the first step and the use of TFA instead of HF for the cleavage, afforded MSH as a pure crystalline solid in a better overall yield (82%). This is strongly desirable since the pure form presented a better stability as observed by Carpino.[91]



Scheme 77. Synthesis of MSH

Based on the DSC analysis,[s] MSH and its precursor **134** can be considered as dangerous compounds since: i) they showed an important exothermic event (-717 and -628 J/g) with a

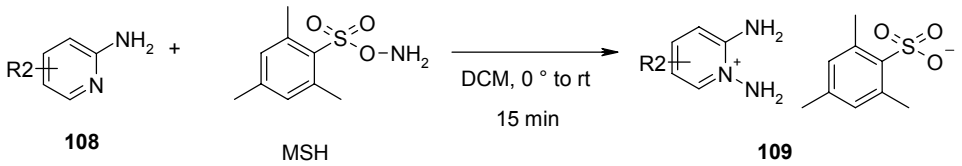
[s] A brief introduction to DSC including the definition of the different parameters used for discussion can be found in Appendix toghether with the thermograms.

relatively low T_{onset} (66 and 118 °C respectively); ii) they showed steep peaks (T_f-T_i = 14 and 18 °C respectively) that are associated to compounds that decompose violently.

MSH and **134** present a ΔT_{ad} above 200 K/g and therefore, for a safe and successful large scale synthesis, effective management of the heat released in case of decomposition is critical. As a safety guidance, highly energetic materials should not be heated above their T_{onset} -100 °C to minimize the risk of decomposition.[158] In the case of MSH this temperature is -34 °C which is unavoidable during the synthesis and handling. In other words, there is always a potential danger while using MSH.

- Use of MSH in the synthesis of 1,2-diaminopyridine salts.

The reaction of aminopyridines **108** with MSH (1.0 equiv) were carried out in DCM for 15 min from 0 °C to ambient temperature in a 2 mmol scale[t] (Scheme 78).



For R2 see Table 18

Scheme 78. Synthesis of 1,2-diaminopyridinium mesitylensulfonattes **109** ($MesSO_3^-$).

The desired compounds **109** ($MesSO_3^-$) were simply isolated by precipitation induced by adding diethylether with moderate to good yields (53-81%) and excellent purity (Table 18). These salts showed to be insoluble in diehtylether, partially soluble in DCM or THF and very soluble in DMF or DMSO. They could be stored at -20 °C for 1 month without decomposition.

entry	R1	compound	yield (%)[†]
1	H	**109a** ($MesSO_3^-$)	81
2	3-BnO	**109b** ($MesSO_3^-$)	85
3	5-CF_3	**109c** ($MesSO_3^-$)	68
4	6-Cl	**109d** ($MesSO_3^-$)	53

[†] Isolated yield of the pure compound.

Table 18. Synthesis of 1,2-diaminopyridinium mesitylenesulfonates **109** ($MesSO_3^-$).

[t] It was first performed on a 0.25 mmol scale. The products **109** ($MesSO_3^-$) did not show any important exothermic event by DSC and therefore, the reaction could be scaled up to 2 mmol.

MSH showed to be a good aminating agent for 2-aminopyridines. It seems to be general in terms of substrates and it has the advantage of the easy isolation of the products by precipitation.

All the mentioned advantages of MSH were partially disvalued by its potential risk. It could be particularly convenient for a small scale, since the hazard associated would be lower. Unfortunately, it is not compatible with grams scale of 1,2-diaminopyridines since it would require to synthesize and handling larger quantities of MSH. This fact prompted us to investigate other aminating agents suitable for large scale synthesis.

5.2.2. Hydroxylamine O-sulfonic acid (HSA)

It was then decided to evaluate HSA since it is readily available and, to the best of our knowledge, it has not presented hazard issues. Nevertheless, it was subjected to DSC analysis to study the thermal stability.

- Thermal stability of HSA

Based on the DSC analysis, HSA could be considered safer than MSH. Although the exothermic event released higher energy (-920 J/g), the T_{onset} was much higher (209 °C) and the peak was broader (T_f-T_i = 74). It means that the risk of decomposition is lower and in case it happens, the energy would be gradually released as compared to MSH. Hence, in a large scale process it would be easier to control the heat load with heat exchangers or condensers.

- Use of HSA in the synthesis of 1,2-diaminopyridine salts.

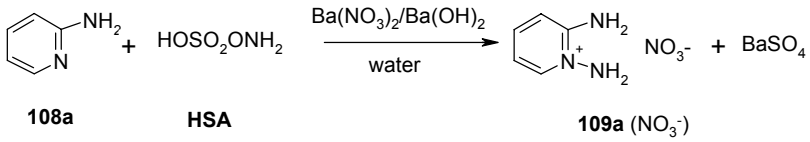
The isolation of 1-aminopyridinium salts showed not to be a trivial matter when HSA was used since they are highly soluble in the solvents in which the reactions are usually performed (water, methanol). Usually they have been isolated by precipitation or solvent evaporation. In the latter case, high conversions are needed; otherwise the expected product would be contaminated with the remaining starting material. Considering the cationic nature of the product, some limitations with the common chromatographic methods might be encounter for the purification. Based on the literature, we could anticipate that the isolation of the desired 1,2-diaminopyridinium salts would be the most difficult task of these investigations.

The *N*-amination of 2-aminopyridine with HSA was previously described with only 30% yield after precipitation of 1,2-diaminopyridinum iodide. It was then decided to investigate the use of different bases to carry out this transformation in order to improve the conversion and consequently facilitate the isolation of the products.

- Barium hydroxide as base

As it was previously discussed, the combination of HSA with barium nitrate and barium hydroxide showed to be efficient for the amination of tertiary amines, both aliphatic and heteroaromatic. The advantage of this method is the formation of the highly insoluble barium sulfate, which would facilitate the isolation of the desired compound.

Following the reported conditions for pyridine,[90] the reaction of 2-aminopyridine (**108a**, 1.0 equiv) with HSA (1.0 equiv) in presence of barium nitrate (0.5 equiv) and barium hydroxide (0.5 equiv) was performed in water at ambient temperature for 2 hr (Scheme 79).



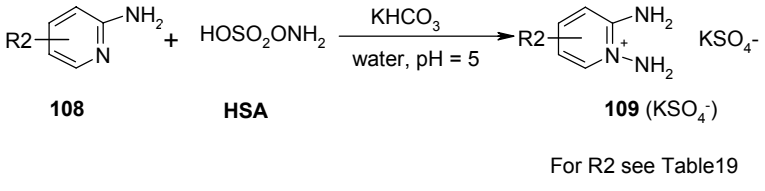
Scheme 79. Use of HSA in presence of $Ba(NO_3)_2/Ba(OH)_2$.

Under these conditions only 30% conversion into the product **109a** was obtained and it did not increase with time. The expected product **109a** (NO_3^-) could not be isolated from the unreacted starting material **108a**. Unfortunately, higher temperature (100 °C) or the use of methanol as co-solvent did not improve the results.

As control experiment, the reaction of pyridine gave 100% conversion under the same conditions.

- Potassium bicarbonate as base

HSA has been used in presence of potassium bicarbonate for *N*-amination of pyridazine.[20] The reaction of 2-aminopyridines **108** (1.0 equiv) with HSA (1.0 equiv) were carried out in water during 3.5 hr and using potassium bicarbonate to adjust the pH to 5 (Scheme 80). The results are summarized in Table 19.



Scheme 80. Use of HSA in presence of potassium bicarbonate

entry	R2	compounds	ratio 108/109	
			rt	70 °C
1	H	**108a/109a**	100 / 0[†]	67 / 33[†]
2	3-BnO	**108b/109b**	100 / 0[‡]	60 / 40[‡]

[†] Determined by ^{1}H NMR. [‡] Determined by UPLC (254 nm).

Table 19. Use of HSA with potassium bicarbonate at rt and 70 °C

The reactions did not proceed at ambient temperature and the starting material was recovered unreacted. When the reactions were carried out at 70 °C for 3.5 hr, the expected products **109** could be observed but in low conversion (<40%).

The fact that the conversion did not increase with time could be related to the instability of HSA in water at high temperatures. In order to confirm this hypothesis, HSA was dissolved in water and heated at 70 °C for 30 min. Iodometric titration revealed that only 15% of HSA remained in the resulting solution.

It was then decided to evaluate the effect of the use of methanol as co-solvent, [u] since it could help to i) solubilize the reactants and thus favor the desired conversion; ii) overcome the instability issues of HSA.

To the homogeneous mixture of **108b** and HSA in water/methanol 1:1, potassium bicarbonate was added to reach pH 5 and then the mixture was heated at 70 °C for 3 hr. To evaluate the potential decomposition of HSA under the new conditions, a second equivalent of this reagent was added after 3 hr and the pH adjusted again. The results are summarized in Table 20.

entry	HSA (equiv)	solvent	ratio **108b** / **109b** (%)[†]
1	1	water	60 / 40
2	1	water/MeOH (1:1)	55 / 45
3	1 + 1	water/MeOH (1:1)	40 / 60

[†] Determined by UPLC (254 nm).

Table 20. Use of methanol as co-solvent at 70 °C

[u] No significant differences were observed between the 2-aminopyridines **108a** and **108b**. For simplicity, **108b** was chosen as model compound for further experiments since both, **108b** and the respective product **109b** could be easily detected by standard chromatographic methods, as compared to **109a**.

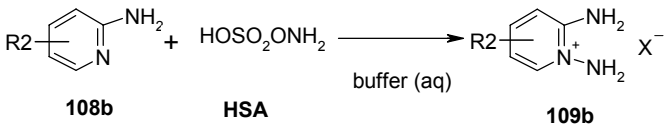
We observed that the use of methanol as a co-solvent slightly improved the results obtained in water (entries 1 and 2) and the second addition of an extra equivalent of HSA allowed to increase the conversion to 60% (entries 2 and 3). These experiments suggested that the instability of HSA was responsible for the low conversion, being the decomposition of HSA faster than the desired reaction.

It was also noticed that during the reaction the pH dropped from 5 to 1. It was suspected to be related to the low conversion and therefore, we decided to investigate the influence of the pH in the reaction. We expected to find an optimal pH where the desired conversion was faster than the decomposition of HSA.

- pH effect

The reaction of **108b** with HSA was performed at different pH, from 1 to 12 (Scheme 81). The experiment at pH 1 was done without addition of any base, it means at the pH obtained by dissolution of both reactants in water. Then, the range pH 4-6 was covered by the different buffers solutions listed below.[v] Two different buffers for pH 5 were included to determine whether the buffer itself had an influence in the reaction. Unfortunately, the range 7-11 was not investigated since the most common buffer solutions for such range are formed by amines and their conjugated acid that could interfere in the *N*-amination. Finally, pH 12 was reached by adding LiOH, NaOH, and KOH to the reaction mixture. The results are summarized in Table 21.

- Buffer 1: 2 M AcONa/AcOH pH = 4
- Buffer 2: 2 M AcONa/AcOH pH = 5
- Buffer 3: 2 M Na_2HPO_4/NaH_2PO_4 pH = 5
- Buffer 4: 2 M Na_2HPO_4/NaH_2PO_4 pH = 6



108b **HSA** **109b**

R2 = 3-BnO

Scheme 81. Use of HSA in buffered solutions.

[v] In these experiments, 10 mL of a 2M buffer solution were used in order to maintain the pH constant for the reaction of 1.0 mmol of **108b** with 1.0 mmol of HSA.

entry	pH	buffer or base	HSA (equiv)	temp (°C) ‡	109b (%)†
1	1	--	1	70	-
2	4	AcONa/AcOH	1	70	14
3	5	AcONa/AcOH	1	70	33
4	5	Na_2HPO_4/NaH_2PO_4	1	70	34
5	6	Na_2HPO_4/NaH_2PO_4	1	70	19
6	5	AcONa/AcOH	2	70	37
7	5	AcONa/AcOH	2	120	57
8	5	AcONa/AcOH	10	120	55
9	12	LiOH/water	1	120	33
10	12	NaOH/water	1	120	34
11	12	KOH/water	1	120	30

† Determined by UPLC (254 nm). ‡ Reactions performed in sealed tubes

Table 21. pH effect in the reaction of **108b** with HSA

When the reaction was performed at 70 °C (entries 1-6), the expected product **109b** was not observed at pH 1 (entry 1) and pH 4 and 6 gave the lowest conversions (14-18%, entries 2 and 5). pH 5, independent from the buffer used, gave the highest conversion (33-34%, entries 3 and 4) and a slight improvement (37%) was observed when 2.0 equivalents of HSA were used (entry 6). [w] The increase in temperature had bigger impact in the conversion and 57% was reached at 120 °C using 2.0 equivalents of HSA (entry 7) but it did not improve when the reaction was performed with 10 equivalents of this reagent (entry 8). When the reaction was performed at pH = 12, independent from the base used, lower conversion was obtained (30-33%, entries 9-11).

In the previous experiments, the pH could be maintained during the reaction. Although small differences were observed at the different pH, in general the *N*-amination of **109b** with HSA proceeded with low conversions. It was most probably related to the instability of HSA in aqueous solutions and not to the changes in pH. This fact prompted us to develop a new version of HSA, *soluble in organic solvents* and *without the acidic character* of this reagent. In this manner, it could be possible to find a solvent in which such reagent has a better stability. This novel reagent is presented herafter.

5.2.3. Tetrabutylammonium hydroxylamine O-sulfonate (TBAHS)

We anticipated that **TBAHS** could be a new reagent that could help to overcome the issues faced with HSA in the amination of 2-aminopyridines, namely insolubility in common organic solvents and the acidic character that makes the use of base a need. The replacement of the

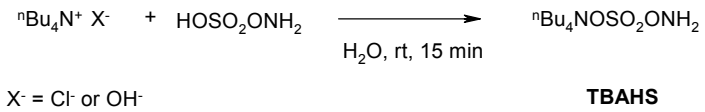
[w] It has to be considered the fact that, to be able to increase the number of equivalents of HSA keeping the buffer capacity of the solution, there was a dilution effect respect to **108b**.

proton in HSA by tetrabutylammonium made **TBAHS** freely soluble in most commonly used organic solvents and the use of base for the *N*-amination would not be necessary anymore.

This reagent has not been described in the literature and therefore, apart from the preparation method, an accurate and confident purity assay had to be developed.

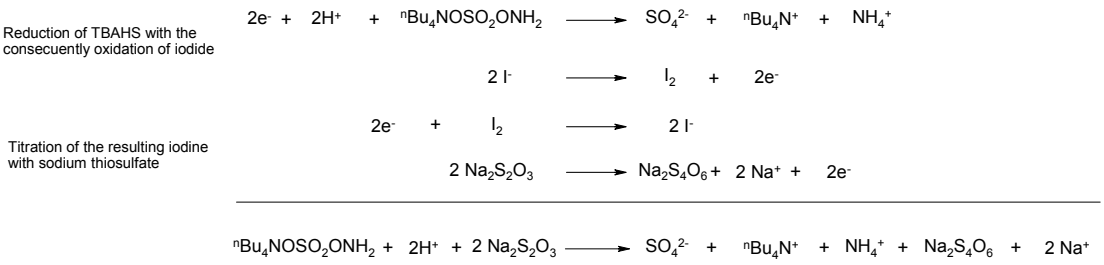
- Synthesis and thermal stability

TBAHS was prepared from HSA with tetrabutylammonium hydroxide or chloride with the same results. The reagents were mixed in water and then **TBAHS** was extracted in DCM. When tetrabutylamonium chloride was used, the solution was neutralized with sodium bicarbonate before proceeding to the extractions (Scheme 82).



Scheme 82. Synthesis of **TBAHS** from HSA

Simple evaporation of the solvent followed by an extensive drying (at 40 °C under vacuum over calcium chloride) afforded **TBAHS** as a white solid in 94% yield. To determine the purity of **TBAHS,** [d] the titration method described for HSA was followed considering that both could have similar oxidant character (Scheme 83).



Scheme 83. Iodometric titration of **TBAHS**

The method described for iodometric titration of HSA in water using sulfuric acid as source of protons was not reproducible for **TBAHS.** Therefore, the technique described to titrate the tetrabutylammonium version of Oxone® developed by Trost was assayed.[23] Sulfuric acid was replaced by acetic acid and THF was used as co-solvent. In this case, iodine was formed and could be titrated with sodium thiosulfate. This method showed to be reproducible and could also be applied to HSA giving the same purity than the first method.

[d] ^{1}H NMR showed the signals corresponding to the tetrabutylammonium and two exchageables protons at 5.86 ppm. In this case, NMR spectroscopy could not be used as criteria of purity.

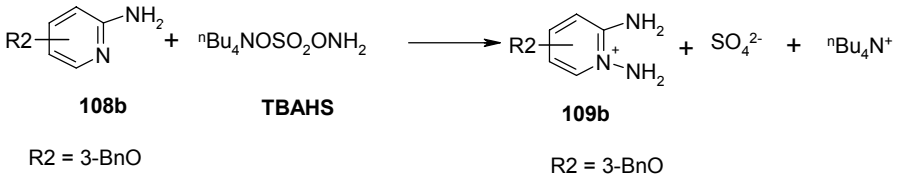
TBAHS prepared following the procedure described above was >95% pure and showed to be stable in a tightly closed bottle at -20 °C during at least two months period. Although it is slightly hygroscopic, it can be handled without major problems. It is freely soluble in water, methanol, ethanol, DCM, THF, dioxane, ACN, DMF and DMSO.

DSC analysis of **TBAHS** showed an exothermic event but with lower energy (-410 J/g) compared with MSH. The T_{onset} was much higher (171 °C) and the peak was broader (T_f-T_i = 51 °C). In other words, TBHAS could be considered safer than MSH since the risk of decomposition is lower and the energy would be gradually released in case it happens.

- Use of **TBAHS** in the synthesis of 1,2-diaminopyridinium salts.

- Solvent and temperature effect

The reaction of 2-aminopyridine **108b** with **TBAHS** (1.0 equiv) was performed in water and in methanol in order to compare results obtained with HSA (Scheme 84). The results are summarized in Table 22.



108b **TBAHS** **109b**

R2 = 3-BnO R2 = 3-BnO

Scheme 84. N-amination of 2-aminoypridines with **TBAHS**

entry	solvent	temp. (°C) ‡	time (hr)	108b/109b †
1	water	rt	24	18
2	water	120	1	81
3	methanol	rt	24	23
4	methanol	120	1	79

† Conversion determined by UPLC (254 nm). ‡ Reactions performed in sealed tubes

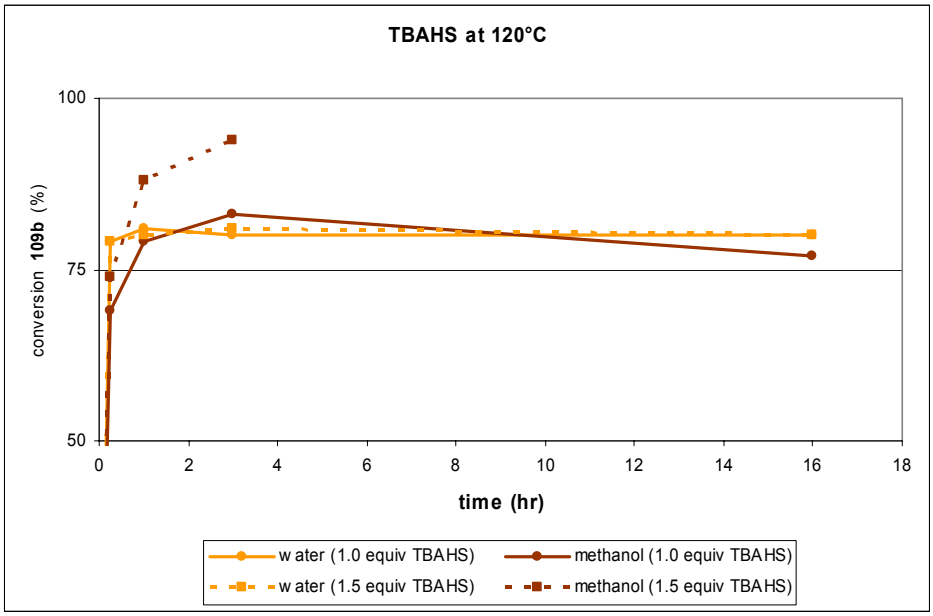
Table 22. Solvent and temperature effect

Low conversion was obtained at ambient temperature after 24 hr (entries 1 and 3). However, it dramatically increased when the reactions were performed at higher temperatures (entries 2 and 4). When both water and methanol were used as solvent, high conversion (81% and 79% respectively) into **109b** was observed after 1 hr. It was a great improvement compared to HSA since the best conversion obtained with 1.0 equiv of this reagent was only 45%.

Since **TBAHS** is not an acid, in the reaction mixture **108b** remained as free base and therefore, the use of a base was not needed. Indeed, the reaction of **108b** with **TBAHS** in presence of acetic acid (1.0 equiv) was performed as a control experiment and in this case, only 32% conversion was obtained.

- Conversion over the time

In the previous experiments was noticed that the reaction was fast at 120 °C and the conversion did not increase with time. Hence, the conversion over the time was studied for methanol and water as solvents using **TBAHS** (1.0 and 1.5 equiv). The reactions were monitored at 15 min, 1, 3, and 16 hr (Graph 1).



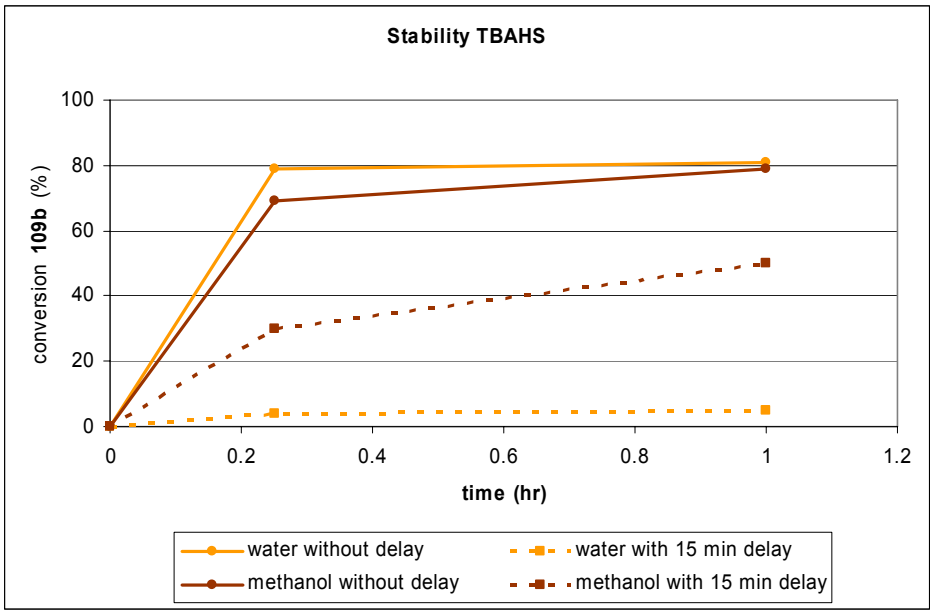
Graph 1. Conversion into **109b** over time with **TBAHS** (1.0 and 1.5 equiv).

The reactions in water were faster than in methanol but the conversion did not increase with time. Besides, no significant differences were observed while using 1.0 or 1.5 equiv of **TBAHS.** On the other hand, when methanol was used as solvent, higher conversion was obtained with 1.5 equiv **TBAHS** (94%) than with 1.0 equiv (84%). The fact that the conversion increased with time suggested that **TBAHS** was more stable in methanol than in water. It was then decided to study the stability of **TBAHS** in these two solvents.

- Stability of **TBAHS** in water and methanol

To determine the stability in water and methanol of **TBAHS**, the reactions were carried out as before but the addition of the aminopyridine **108b** was delayed in time *i.e.* **TBAHS** (1.0 equiv)

was dissolved in methanol or water and the mixture was heated in the sealed vial for 15 min before adding **108b** (1.0 equiv). The results are summarized in Graph 2.



Graph 2. Stability of **TBAHS** in water and methanol

The experiments clearly showed that in water, a significant portion of **TBAHS** was degraded after 15 min at 120 °C. In contrary, **TBAHS** had a better stability in methanol and although the conversion was much lower when the addition of **108b** was delayed, it increased with time. We could observe that the solvent had an influence in the stability of **TBAHS** and consequently, in the final conversion. Therefore, it was then decided to try other solvents to perform this transformation looking for a better stability of **TBAHS.**

- Solvent effect

The *N*-amination of **108b** with **TBAHS** (1.0 equiv) was carried out in different solvents and at 65 °C to avoid overpressure (Table 23).

entry	solvent	**109b** (%)[†]		
		1 hr	3 hr	16 hr
1	water	64	69	71
2	methanol	25	47	76
3	ethanol	17	37	73
4	isopropanol	4.4	17	42
5	*n*-butanol	33	50	8
6	trifluoroethanol	74	83	89
7	THF	-	-	-
8	dioxane	-	-	-
9	ACN	-	-	-
10	DMF	-	-	-

[†] Conversion determined by UPLC (254 nm).

Table 23. Solvent effect in the use of **TBAHS**

The reaction only proceeded with protic polar solvents (entries 1-6). Among them, trifluoroethanol gave the best conversion (89%) after 16 hr. TFE was selected as the best solvent for further experiments.

- Scale-up and isolation of the 1,2-diaminopyridinium salts

The reaction of **108b** with **TBAHS** (1.0 equiv) in TFE at 65 °C could be gradually scaled up from 0.25 to 10 mmoles without experience any safety issue and with reproducible results (ca. 90% conversion). The use of an excess of **TBAHS** (1.5 equiv) did not increase the conversion.

We then focused in the isolation of **109b**. Since **109b** and tetrabutylammonium (TBA) are both cationic organic compounds, we first tried to induce a selective precipitation. Following the described procedure for 1-aminopyridinium,[87] hydroiodic acid (HI) was added to the reaction mixture, since it could induce the precipitation of **109b** (I^-) while TBAI remains in solution. Unfortunately, the desired product did not precipitate at ambient temperature or at -20 °C and when Et_2O was added, a mixture of **109b**/TBA 6:4 was obtained[x] (entry 1, Table 24).

Then, the selective precipitation was attempted by adding different solvents or mixture of solvents, to the reaction mixture. It turned out that ACN afforded **109b** (½ SO_4^{-2}) in good purity (**109b**/TBA 98:2) and moderate yield (64%) (entry 2, Table 24)

[x] The counterion was iodide and/or sulfate.

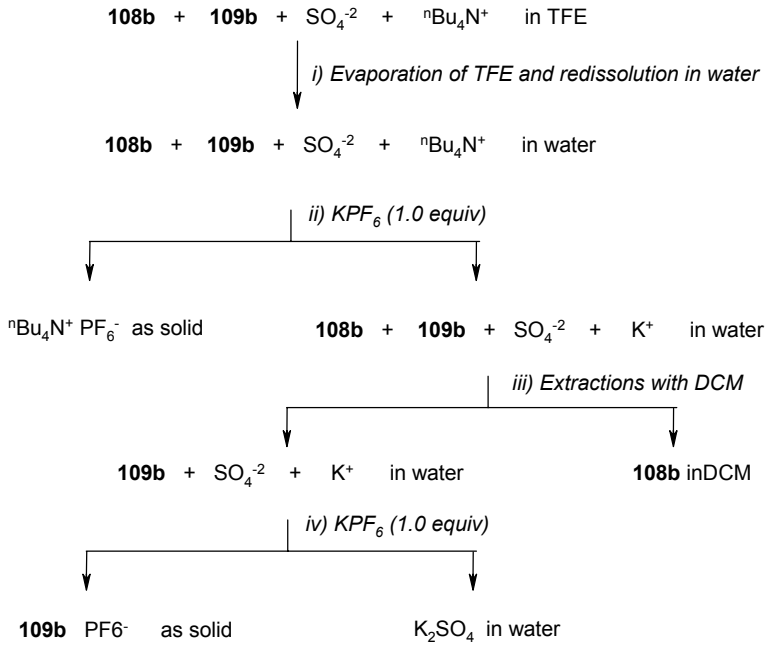
entry	R1	compound	Isolation method	**109b** / TBA	yield (%)[†]
1	3-BnO	**109b** (I^-)	HI/Et_2O	60 / 4	n.d.
2	3-BnO	**109b** (½ SO_4^{-2})	ACN	98 / 2	64
3	3-BnO	**109b** (PF_6^-)	KPF_6	100 / 0	67
4	3-BnO	**109b** [$(CF_3SO_2)_2N^-$]	$(CF_3SO_2)_2NLi$	99 / 1	72

[†] Isolated yield.

Table 24. Isolation of **109b**.

Finally, we decided to use KPF_6 in water since the exchange of sulfate by a more lipophilic counterion (PF_6^-) could decrease the solubility of the pyridinium salt in such polar solvent facilitating the isolation. Indeed, an appropriated protocol was developed (Scheme 85) which allowed the isolation of **109b** (PF_6^-) in excellent purity (entry 3, Table 24)

This protocol consisted in: i) Evaporation of TFE (otherwise selective precipitation was not achieved) and redissolution of the residue in water. ii) Addition of KPF_6 (1.0 equiv) to induce the precipitation of tetrabutylammonium hexafluorophosphate (TBA PF_6), which was removed by filtration. iii) Removal of the unreacted **108b** by extractions with DCM. iv) Addition of KPF_6 (1.0 equiv) to induce the precipitation of **109b** (PF_6^-), which was isolated by filtration in 67% yield.



Scheme 85. Isolation of **109b** using KPF_6.

Similar results were obtained when NH_4PF_6 was used instead of KPF_6. On the other hand, when bis-trifluoromethanesulfonimidate [$(CF_3SO_2)_2N^-$] was used as lipophilic counterion, **109b** [$(CF_3SO_2)_2N^-$] did not precipitate at the final step and had to be extracted with DCM (entry 4, Table 24).

We promptly extended the optimal reaction conditions developed with **108b** to the other two members of the series, **108a** (R = H) and **108c** (R = 3-BnO). The syntheses proceeded well and high conversion into **109a** and **109a** were achieved (86 and 80% respectively). On the contrary, the isolation showed to be more complicated and substituent dependent.

Following the first isolation protocol (precipitation with ACN), the sulfate salts of **109a** and **109c** were obtained in good purities since only traces of TBA co-precipitate with the pyridinium salts (entries 1 and 3, Table 25).

However, the isolation protocol using KPF_6 was only efficient for **109c** (entry 4, Table 25). The precipitation of TBA (PF_6^-) with the first equivalent of KPF_6 was completely selective and the unreacted **108c** could be removed by extractions with DCM. Finally, the addition of a second equivalent of KPF_6 induced the precipitation of **109c** (PF_6^-) in 46% yield. Unfortunately, this protocol was inefficient for the most polar compound of the series **109a**. Although the precipitation of TBA (PF_6^-) was selective, the unreacted starting material **108a** could not be extracted in organic solvents (highly soluble in water). Moreover, **109a** did not precipitate at the final step and could not be extracted with DCM or EtOAc.

entry	R1	compound	Isolation method	ratio pyridinium / Bu_4N^+	yield (%)[†]
1	H	**109a** (½ SO_4^{-2})	ACN	99.8 / 0.2	79
2	H	**109a** (PF_6^-)	KPF_6	-	-
3	5-CF_3	**109c** (½ SO_4^{-2})	ACN	95 / 5	43
4	5-CF_3	**109c** (PF_6^-)	KPF_6	100 / 0	46

[†] Isolated yield.

Table 25. Isolation of **109a** and **109c**.

The *N*-amination of 2-aminopyridines with **TBAHS** seemed to be general since high conversions were obtained with 2-aminopyridines bearing electronwithdrawing and donating groups. However, the isolation showed to be substituent dependent. It was then decided to evaluate the synthesis and isolation of 1,2-diaminopyridiniums when other organic cations replaced the tetrabutylammonium in **TBAHS**.

5.2.4. Tetramethylammonium hydroxylamine O-sulfonate (TMAHS)

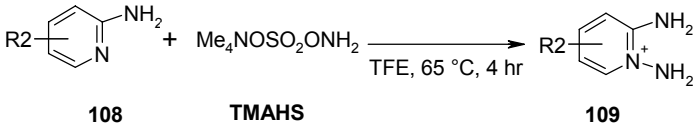
- Synthesis and thermal stability

TMAHS was prepared from HSA and tetramethylammonium hydroxide in water. In contrary to **TBAHS** (more lipophilic counterion), **TMAHS** could not be extracted in organic solvents and therefore, the aqueous solution was lyophilized. Iodometric titration of the resulting solid gave 70% purity.

Based on DSC analysis, **TMAHS** seemed to be more dangerous than **TBAHS** since it showed an important exothermic event (-812 J/g) with a relatively low T_{onset} (99 °C) similarly to MSH. However, it could be considered safer than MSH since it presented a broader peak (T_f-T_i = 66 °C).

- Use of **TMAHS** in the synthesis of 1,2-diaminopyridinium salts.

The reaction of 2-aminopyridines **108** with **TMAHS** (1.0 equiv) were performed in TFE at 65 °C for 4 hr (Scheme 86). Slightly lower conversions (68-79%) were observed compared to the use of **TBAHS**.



108 **TMAHS** **109**

For R2 see Table 26

Scheme 86. *N*-amination of 2-aminoypridines with **TMAHS**

Besides, the isolation of the desired compounds was problematic. Only **109a** (½ SO_4^{-2}) could be isolated in good purity *via* selective precipitation induced with ACN (entry 1, Table 26). **109b-c** did not precipitate with such solvent and when Et_2O was used, co-precipitation of the tetramethylammonium was obtained (entries 2 and 3, Table 26). The isolation of the iodide or hexafluorophosphate salts as previously described while using **TBAHS** were unsuccessful.

entry	R2	compound	Isolation method	ratio 109 / Me_4N^+	yield (%)†
1	H	**109a** (½ SO_4^{-2})	ACN	97 / 3	57
2	3-BnO	**109b** (½ SO_4^{-2})	Et_2O	54 / 46	n.d
3	5-CF_3	**109c** (½ SO_4^{-2})	Et_2O	36 / 64	n.d.

† Isolated yield.

Table 26. Use of **TMAHS** in the synthesis of **109**.

The potential safety issues of **TMAHS** and the issues faced to isolate the final compounds made **TMAHS** not particularly attractive for our purposes.

5.2.5. Tetraphenylphosphonium hydroxylamine O-sulfonate (TPPHS)

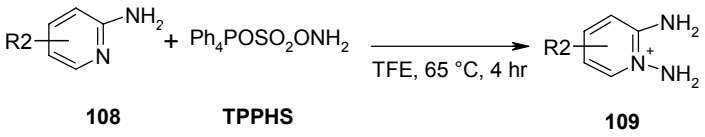
- Synthesis and thermal stability

TPPHS was prepared from HSA and tetraphenylphosphonium chloride in water. After addition of KOH until reach pH 7, **TPPHS** could be extracted with DCM. The recovery was lower (53%) compared to **TBAHS** but **TPPHS** showed high purity (98%) by iodometric titration.

Based on DSC analysis, **TPPHS** could be considered safer than **TBAHS** since it showed a relatively low exothermic event (-197 J/g) with a high T_{onset} (256 °C) and a broad peak (T_f-T_i = 52).

- Use of **TPPHS** in the synthesis of 1,2-diaminopyridinium salts.

The reaction of 2-aminopyridines **108** with **TPPHS** (1.0 equiv) were performed in TFE at 65 °C (Scheme 87). No significant differences in terms of conversion were noticed compared to **TBAHS** .



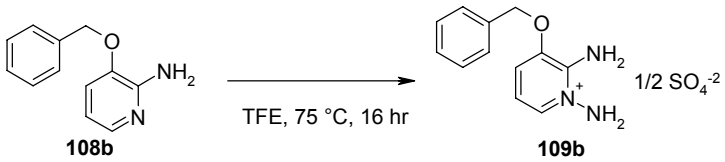
108 **TPPHS** **109**

Scheme 87. *N*-amination of 2-aminoypridines with **TPPHS**

On the other hand, none of the mentioned isolation methods presented before afforded the desired compounds with good purities (always co-precipitation with tetraphenylphosphonium was observed). As the last option, the unreacted 2-aminopyridine **108b** could be removed by chromatography column on silica but the final compound **109b** was recovered as a mixture 1:3 with tetraphenylphosphonium sulfate.

5.2.6. HSA in presence of KOH and 18-crown-6

When we attempted to generate *in situ* the aminating agent **TPPHS** from TPPCl, HSA and KOH, we notice that the amination of **108b** (Scheme 88) was partially suppressed by the presence of potassium ions, achieving only 15% of conversion compared to 90% obtained with pure **TPPHS** (Table 27)



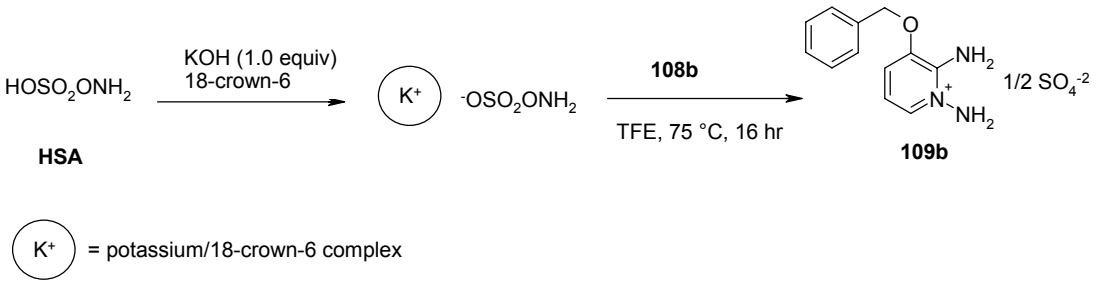
Scheme 88. Amination of **108b** with **TPPHS**: isolated *versus* prepared *in situ.*
(for conditions see Table 27)

entry	conditions	109b (%)†
1	Ph_4P^+ $^-OSO_2$-ONH_2 (**TPPHS**) (1 equiv)	90
2	Ph_4P^+ Cl^- (1 equiv) + $HOSO_2$-ONH_2 (1 equiv) + KOH (1 equiv)	15

† Determined by UPLC (254 nm)

Table 27. Use of **TPPHS**: isolated *versus* prepared *in situ*.

This fact prompted us to use 18-crown-6 ether to coordinate the potassium ions in its central cavity to somehow mimic the organic cations previously discussed ($^nBu_4N^+$, Me_4N^+, Ph_4P^+) (Scheme 89).



Scheme 89. Use of HSA in presence of potassium/18-crown-6 complex

The reaction of **108b** with HSA (1.0 equiv) in presence of KOH (1.0 equiv) and 18-crown-6 (0, 0.1, 0.5 and 1.0 equiv) were carried out in different solvents at 65 °C and the results are summarized in Table 28.

entry	solvent	18-crown-6 (equiv)	109b (%)†
1	TFE	-	32
2	TFE	1	81
3	TFE	0.1	44
4	TFE	0.5	80
5	MeOH	1	48
6	water	1	31

† Determined by UPLC (254 nm)

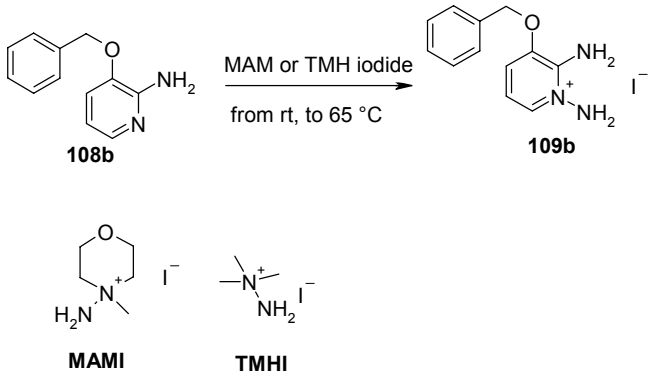
Table 28. Use of HSA in presence of KOH and 18-crown-6

Gratifyingly, when 1.0 equiv of 18-crown-6 ether was used in TFE, high conversion was obtained (entry 2). On the contrary, without using 18-crown-6, only 32% conversion was achieved (entry 1). The amount of 18-crown-6 could be decreased to 0.5 equiv without major impact on the conversion (entry 4) but 0.1 equiv was not enough (entry 3). Methanol and water gave lowest conversions (entries 5-6) most probably due to the instability of potassium/18-crown-6 hydroxylamine *O*-sulfonate in such solvents.

Unfortunately, once again it was the isolation of the product that was unsuccessful. Extractions of the reaction mixture (after evaporation of TFE and redissolution of the residue in water) allowed the removal of the unreacted 2-aminopyridine **108b**, but all attempts to precipitate the product afforded mixtures with 18-crown-6 ether.

5.2.7. MAM iodide and TMH iodide

In parallel to the previous investigations, the *N*-amination of **108b** with *N*-methyl-*N*-aminomorpholinium (MAM) iodide[147] was attempted in three different solvents (TFE, DMSO, ACN) and different temperatures (from rt to 65 °C) (Scheme 90) but the expected product could not be observed and the starting material was recovered unreacted. The same results were obtained with trimethylhydrazinium iodide (TMHI). Moreover, the DSC analyses of these reagents discourage us to continue the investigations.



Scheme 90. Use of MAM or TMH iodide in the amination of **108b**.

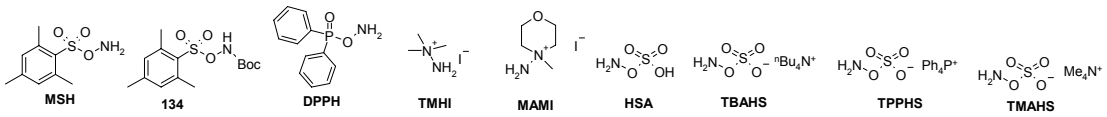
5.2.8. O-(Diphenylphosphinyl)hydroxylamine (DPPH)

DPPH was synthesized following the described procedure[149] and was subjected to DSC analysis. It presented similar characteristics compared to MSH except that the T_{onset} was lower (130 °C). It means that the risk of decomposition is a bit lower but in case it happens, the hazard would be similar. For this reason we decided to perform only one reaction with 2-

aminopyridine **108b** in order to evaluate its reactivity. The reaction was performed in DCM at 0 °C and the product **109b** ($Ph_2PO_2^-$) was isolated in 70% yield after precipitation.

5.2.9. Summary of the thermal properties of the aminating agents.

Table 29 summarizes the different parameters from the thermograms obtained by DSC analysis of the aminating agents used in this chapter. The color code *is only for relative comparison*. The minimum and maximum value of each parameter was used to calculate the ranges.



	MSH	134	DPPH	TMHI	MAMI	HSA	TBAHS	TPPHS	TMAHS
T_{onset} (°C)	66	118	130	238	176	209	171	256	99
ΔH (J/g)	-717	-628	-864	-470	-409	-920	-410	-197	-812
T_f-T_i (°C)	14	18	14	13	55	74	51	52	66

Table 29. Parameters obtained by DSC analysis of the aminating agents.

T_{onset}	66	129	192	256
ΔH (J/g)	920	679	438	197
T_f-T_i (°C)	13	33	53	74

5.3. Conclusions

Different aminating agents were evaluated for the *N*-amination of 2-aminopyridines. Among them, *O*-sulfonyl and *O*-phosphinyl hydroxylamine derivatives showed to be the most reactive, in particular *O*-mesitylensulfonyl hydroxylamine (MSH). The reactions with MSH proceeded under mild conditions and the expected 1,2-diaminopyridinium mesitylensulfonates were isolated by precipitation in good yields and high purities. But these advantages while using MSH were partially eclipsed by its latent hazard. Based on the reported hazard and DSC analysis, MSH should be considered dangerous since it presented high risk of decomposition and the high energy associated with this event would be suddenly released. It is therefore not compatible with large scale synthesis because it would require to synthesize and handling larger quantities of MSH.

We developed tetrabutylammonium hydroxylamine *O*-sulfonate (**TBAHS**) as a safer alternative to MSH. The risk of decomposition is lower and in case it happens, the energy would be gradually released. Hence, in a large scale process, it would be easier to control the heat load with heat exchangers or condensers. In contrary to the use of MSH, higher

temperatures were needed to achieve high conversions with **TBAHS**. The synthesis of 1,2-diaminopyridinium salts was progressively scaled up to 10 mmoles with consistent results and without experience any safety issues. Unfortunately, the isolation of the 1,2-diaminopyridinium salts showed to be a difficult task and substituent dependent. Nevertheless, it was always possible to find the appropriate way to isolate the desired product in high purity and good yield. From our experience, **TBAHS** remains the best choice for large scale *N*-amination of 2-aminopyridines.

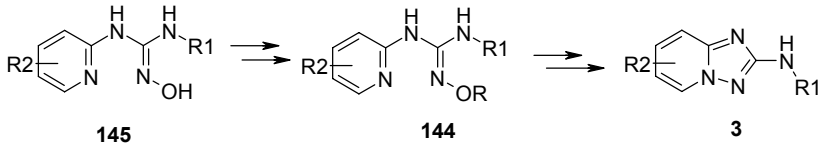
6. Synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (Pathway 2)

6.1. Introduction and project aims

In Chapter 4, we developed the synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**) using 1,2-diaminopyridiniums salts as key reagents. The availability of large quantities of these salts might be limited because of the use of potential hazardous aminating reagents. Therefore, we decided to explore an alternative pathway for large scale synthesis of our target heterocycle, without the need of an electrophilic amination step.

6.1.1. Synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines from 1-(2-pyridyl)guanidines

We decided to explore the pathway depicted in Scheme 91. We considered that an appropriated *O*-substituted *N*-hydroxyguanidine **144** (OR = leaving group) could give the desired heterocycle **3** *via* cyclisation and formation of the triazole ring.



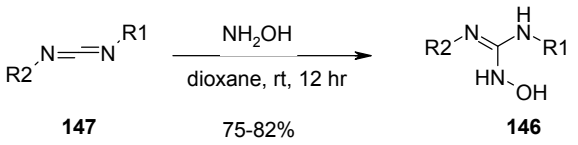
Scheme 91. Proposed pathway for the synthesis of 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines from 1(2-pyridyl)hydroxyguanidines

To assess this proposed route, the first goal was to synthesize the *N*-hydroxyguanidine **145** from simple starting materials to then convert the hydroxyl in a better leaving group to perform the cyclisation. This pathway would avoid the use of electrophilic amination reagents and therefore, it would allow a safer large scale synthesis of the target heterocycle. For these studies, **3**[a,a] (R1 = phenyl and R2 = H) was chosen as a model compound.

6.2. Discussion

6.2.1. Synthesis of N,N′-disubstituted-N″-hydroxyguanidines from carbodiimides or thioureas

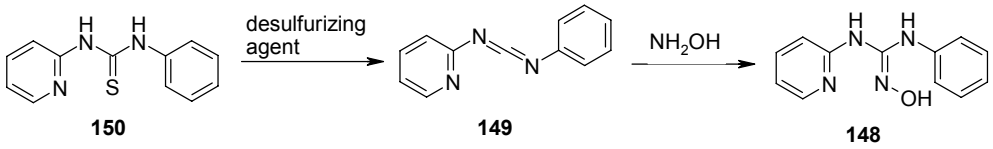
The synthesis of *N,N′*-disubstituted-*N″*-hydroxyguanidines **146** has been described from the corresponding carbodiimide **147** and hydroxylamine in moderate to good yields (Scheme 92).[159]



R1 = cyclohexyl, *p*-tolyl
R2 = cyclohexyl, *p*-tolyl, *tert*-butyl

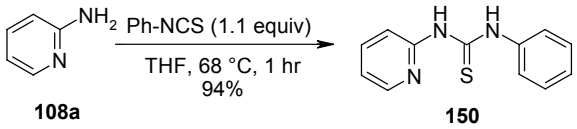
Scheme 92. Synthesis of *N,N'*-disubstituted *N'''*-hydroxyguanidines from carbodiimides

During those studies, simple carbodiimides were used and the substrate scope was not explored. We planned to synthesize the target *N*-hydroxy-*N'*-(pyrid-2-yl)guanidine **148** from the corresponding carbodiimide **149** (Scheme 93). To the best of our knowledge the synthesis and isolation of 1-(pyrid-2-yl)carbodiimides have not been described yet but we proposed to achieve the synthesis of **149** *via* desulfurization of the corresponding 1-(pyrid-2-yl)thiourea **150**.



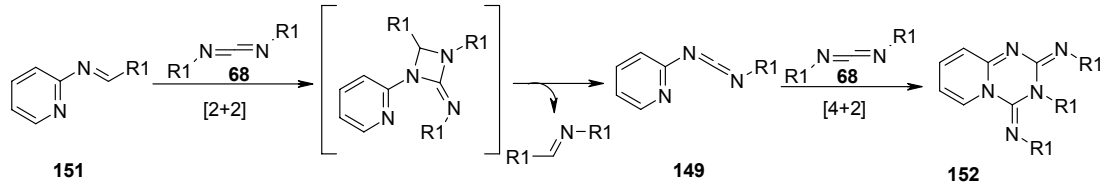
Scheme 93. Proposed synthesis of hydroxyguanidine **148** from thiourea **150**.

The reaction of 2-aminopyridine **108a** with phenylisothiocyanate in THF at 68 °C during 1 hr afforded **150** in 94% yield after removal of the solvent followed by washings of the desired products with heptane (Scheme 94).



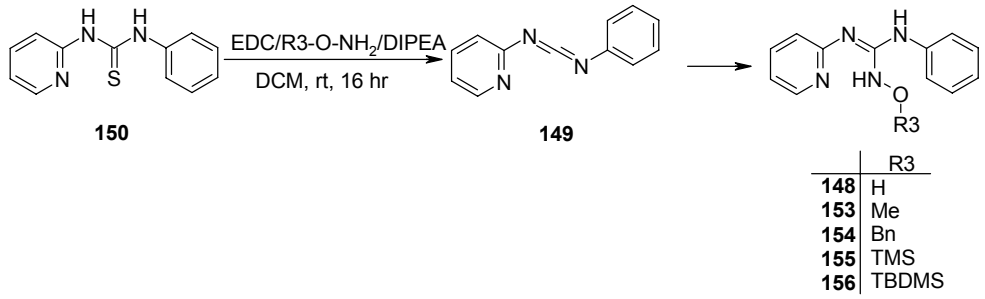
Scheme 94. Synthesis of thiourea **150**.

Thioruea **150** was then subjected to desulfurization under different standard conditions (EDC, Mukaiyama's reagent and PS-Muk2 as desulfurizing agents) but the expected 1-(pyrid-2-yl)carbodiimide **149** was not observed. Instead, a complex mixture of unidentified compounds was obtained. **149** has been reported as reactive intermediate in [4+2] cycloadditions[160] but to our knowledge, it has been never isolated. Indeed, the reaction of azomethine (**151**) with diphenylcarbodiimide (**68**) afforded directly compound **152** as a result of the reaction of **149** with a second molecule of **68** (Scheme 95)



Scheme 95. Precedents of **149** in cycloaddition reactions.

Therefore, we decided to perform the reaction in presence of hydroxylamine (R3 = H) in order to trap *in situ* the carbodiimide once is formed (Scheme 96).



Scheme 96. Synthesis of **148** and *O*-substituted derivatives from **150**.

Unfortunately, the reaction of **150** with hydroxylamine chlorhydrate in DCM in presence of EDC and DIPEA at ambient temperature for 16 hr gave only 9% conversion into the desired product **148** (entry 1, Table 30). There are precedents that *O*-protected hydroxylamine gave better conversions in this type of reactions.[161,162] In fact, when hydroxylamine was replaced by *O*-methyl or *O*-benzyl hydroxylamine, the corresponding products **153** and **154** were obtained in high yields (entries 2-3). On the other hand, when *O*-silyl hydroxylamines were used, the desired compounds **155** and **156** were not observed and partial degradation of the starting materials was obtained (entries 4-5).

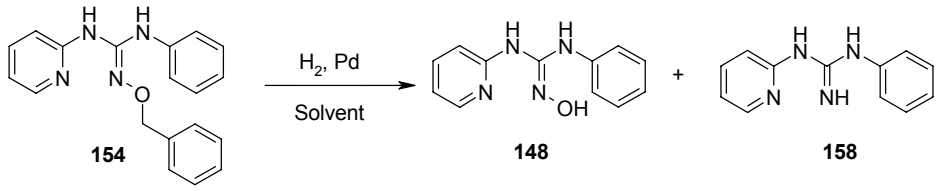
entry	R3	compound	conversion (%)†	yield (%)‡
1	H	**148**	9	n.d.
2	Me	**153**	100	69
3	Bn	**154**	100	94
4	TMS	**155**	0	n.d.
5	TBDMS	**156**	0	n.d.

†Determined by UPLC/MS (254 nm). ‡Isolated yield of pure compound.

Table 30. Synthesis of *N*-hydroxyguanidines from thiourea **150**.

An alternative way to synthesize *N*-hydroxyguanidine **148** was *via* hydrogenolysis of compound **154** (Scheme 97). To the best of our knowledge, only few reports described this

reaction but on different substrates.[163,164] The reaction of **154** with hydrogen in presence of palladium catalyst was performed in different solvents at ambient temperature and atmosphere pressure (Table 31). In all cases, the desired product **148** was formed and partial *N-O* cleavage was observed giving the side-product **158** (Scheme 97).[y]



Scheme 97. Synthesis of **148** *via* hydrogenolysis of **154**.

entry	solvent	catalyst (equiv)	time (hr)	154 (%)†	148 (%)†	158 (%)†
1	ACN	Pd/C (0.1)	1	39	56	6
			2	11	80	8
			3	6	82	12
			4	3	78	19
			16	-	59	41
2	MeOH	Pd/C (0.1)	1	26	74	-
			2	19	81	-
			3	13	81	5
			16	-	53	47
3	MeOH	Pd/C (0.2)	1	15	79	6
4	EtOH	Pd/C (0.1)	1	52	37	11
5	THF	Pd/C (0.1)	1	65	25	7
6	MeOH	Pd/$CaCO_3$ (0.1)	1	85	14	1
			2	72	23	5
			3	50	39	12

† Determined by UPLC/MS (254 nm).

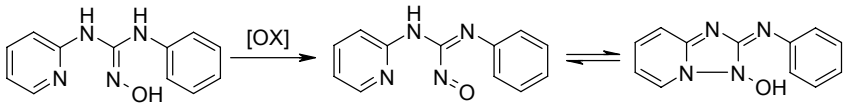
Table 31. Synthesis of **148** *via* hydrogenolysis of **154**.

The highest conversion (ca. 80%) and selectivity into the desired compound **148** was achieved using Pd/C (0.1 equiv) in methanol during 2hr (entry 2). If the reaction was let stand for longer to totally consume **148**, side-product **158** was formed and accumulated with time, suggesting that the *N-O* bond cleavage occurred preferentially on compound **148**. With acetonitrile as solvent, similar results were obtained with the difference that **158** was already present (6%) after 1 h (entry 1). The use of tetrahydrofurane or ethanol as solvents (entries 4-5) or the increment in Pd/C to 0.2 equiv in methanol (entry 3) did not improve the results.

[y] Compound **158** was also observed in the reaction of **150** with ammonia in presence of Mukaiyama's reagent and TEA.

Using $Pd/CaCO_3$ (0.1 equiv) in methanol the reaction was much slower and the formation of **158** was not avoided (entry 6).

The isolation and purification of **148** was problematic since it appeared to be unstable in solution in the presence of oxygen. Based on mass spectroscopy analysis, it was most probably oxidized to the corresponding nitrosoamidine **159** (*m/z* **159** = *m/z* **148** – 2) that could exist in equilibrium with the cyclised form **160** (Scheme 98). There are precedents in the literature of this type of oxidation[165] and indeed, when **148** was treated with sodium hypochlorite, the ratio **159**/**148** increased.

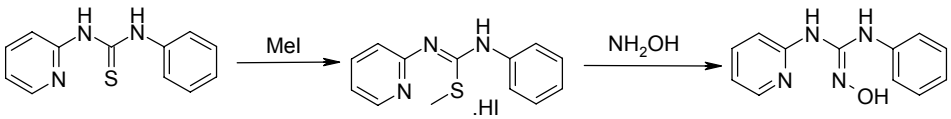


148 **159** **160**

Scheme 98. Plausible oxidation of **148** into **159**.

6.2.2. N,N'-disubstituted-N''-hydroxyguanidines from S-methylisothiourea

Due to the difficulty to isolate the product **148** after reduction of **154**, we decided to investigate the substitution of the *S*-methyl isothiourea **161** with hydroxylamine (Scheme 99). This reaction has been described with *O*-substituted hydroxylamines.[163,166]



150 **161** **148**

Scheme 99. Synthesis of **148** through the S-methyl isothiourea **161**.

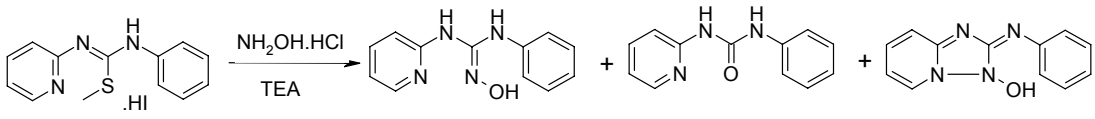
Isothiourea **161** was synthesized via *S*-methylation of the thiourea **150** with methyl iodide (Table 32). When the reaction was performed in methanol/acetone (entry 1), formation of the corresponding urea was observed that had to be removed by recrystallization from acetonitrile. When this mixture of solvents was replaced by anhydrous solvents (dichloromethane or tetrahydrofurane) at ambient temperature, this side reaction could be avoided but low conversion was obtained (entries 2 and 3). A sharp improvement was observed while performing the reaction at 40 °C using 2.0 equiv of methyl iodide to finally get almost quantitative yield when an excess of this reagent was used (entries 4 and 5). The final product was isolated pure as its hydroiodide salt after simple washings with pentane.

entry	solvent	MeI (equiv)	temp (°C)	time (hr)	161 (%)†	yield (%)‡
1	MeOH/acetone (1:1)	2.0	20	20	79	69
2	DCM	2.0	20	20	15	n.d.
3	THF	2.0	20	20	17	n.d.
4	THF	2.0	40	6	89	82
5	THF	4.0	40	6	100	98

† Conversion determined by UPLC-MS (254 nm). ‡ Isolated yield of pure compound as hydroiodide salt.

Table 32. Synthesis of *S*-methylisothiourea **161**.

With the isothiourea **161** in hands, we performed the reaction with hydroxylamine chlorhydrate (2.0 equiv) in ethanol in presence of triethylamine (4.0 equiv) (Scheme 100).



161 **148** **162** **160**

Scheme 100. Reaction of **161** with hydroxylamine chlorhydrate.

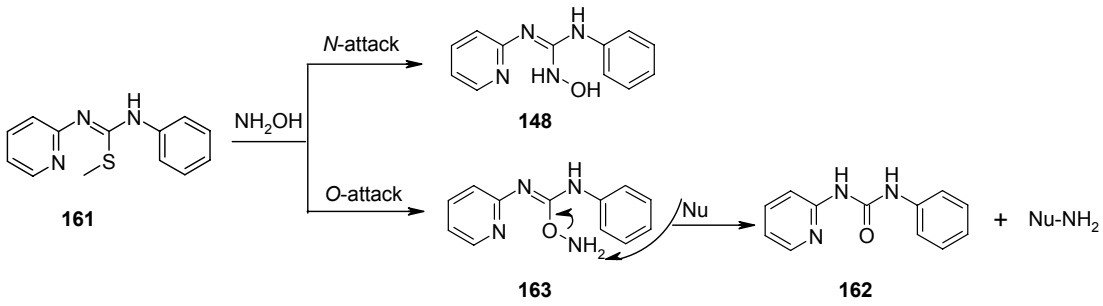
After 16 hr at ambient temperature, low conversion (34%) into *N*-hydroxyguanidine **148** was obtained (entry 1, Table 33). Increasing the amount of hydroxylamine to 4.0 equiv, the starting **161** was totally consumed but the urea **162** (15%) and **160** (2%) were observed as side-products (entry 2). We decided to perform the reaction in anhydrous solvents (methanol, dimethylformamide, tetrahydrofurane) and under argon atmosphere to avoid the formation of the urea **162** but without success (entries 3-7). Higher temperatures decreased the reaction time but with similar results in terms of urea formation (entries 4 and 7).

entry	solvent	$NH_2OH.HCl$ (equiv)	temp (°C)	time (hr)	161 (%)†	148 (%)†	162 (%)†	160 (%)†
1	EtOH	2.0	20	16	60	34	4	2
2	EtOH	4.0	20	16	-	74	15	2
3	MeOH‡	4.0	20	16	-	78	12	4
4	MeOH‡	4.0	65	0.5	-	82	10	-
5	MeOH‡, §	4.0	20	16	-	74	9	7
6	DMF‡	4.0	20	0.1	-	59	4	23
7	THF‡	4.0	66	1.5	-	82	14	-

†Determined by UPLC-MS (254 nm). ‡ Anhydrous solvent. § In presence of molecular sieves (4 Å).

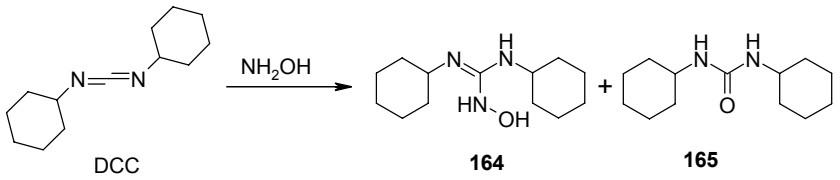
Table 33. Reaction of **161** with hydroxylamine hydrochloride.

The previous experiments suggested that the formation of the urea **162** involved a different pathway that a simple addition of water to **161** as initially thought (Scheme 101). Hydroxylamine can behave as an ambident nucleophile. Indeed, the *O*-attack would give the intermediate **163** that can be seen as an electrophilic aminating reagent. The *N*-amination of a nucleophile present in the reaction mixture (*e.g*. hydroxylamine, methanethiol) would release the urea **162**.



Scheme 101. Proposed pathway for the urea **162** formation.

A similar phenomenon was already observed in the reaction of carbodiimides with hydroxylamine.[159,167] The ratio hydroxyguanidine/urea depended on the solvent used. For instance, the main product of the reaction of DCC with hydroxylamine in ethanol was the corresponding hydroxyguanidine **164** whereas in DMF was dicyclohexylurea **165** (Scheme 102).



solvent	164/165
EtOH	74:23
DMF	8:87

Scheme 102. Solvent effect in the addition of hydroxylamine in DCC.

We chose methanol to continue our studies since it gave the lowest amount of urea **162**. We then focus on the side-product **160**. Although the amount formed during the reactions in methanol was not important (0-7%), it increased during the work-up and purification stages, achieving 17% when the recrystallization was performed in an open vessel (entries 1-3, Table 34). On the contrary, a better purity was obtained while performing the recrystallization under argon atmosphere but the recovery of **148** was low (46%) (entry 4, Table 34)

entry	Isolation/purification step	148 (%)†	162 (%)†	160 (%)†
1	End of the reaction	78	12	4
2	After aqueous work-up	68	14	8
3	After recrystallization from DCM (open vessel)	82	1	17
4	After recrystallization from DCM under argon atmosphere	98	1	1

†Determined by UPLC-MS (254 nm). ‡ Isolated yield

Table 34. Composition of the crude during the isolation and purification of **148**.

It was then decided to perform the reaction and work-up under reducing conditions in order to avoid the formation of **160**. For this, sodium thiosulfate was added to the reaction mixture and the final *N*-hydroxyguanidine **148** could be isolated with a better yield (64%) since the oxidation was totally suppressed (Table 35). The recovery of the recrystallization in DCM was low but it was the best solvent found to remove the urea **162**.

entry	Isolation/purification step	148 (%)†	162 (%)†	160 (%)†
1	End of the reaction	84	7	-
2	After aqueous work-up	80	8	-
4	After recrystallization from DCM under argon atmosphere	98	1	-

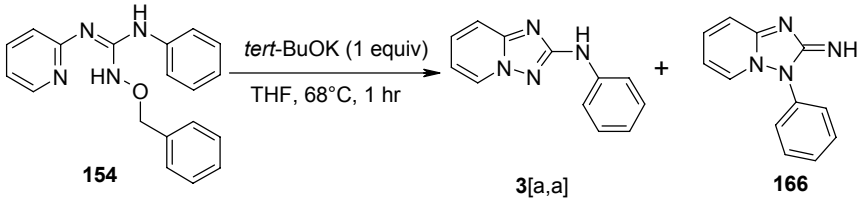
†Determined by UPLC-MS (254 nm).

Table 35. Composition of the crude during the isolation and purification of **148** in presence of sodium thiosulfate.

Hydroxyguanidine **148** showed to be more stable as solid than in solution and could be stored at -20 °C without decomposition for at least one week.

6.2.3. Cyclisation of O-substituted N-hydroxyguanidines

The next step was to convert the hydroxyl group of the hydroxyguanidine **148** in a better leaving group in order to promote the cyclisation. Nevertheless, we first attempted the cyclisation of compound **154** in presence of a base since the benzyloxy group could act as the required leaving group (Scheme 103). Among the different bases and solvents tested, potassium *tert*-butoxide in tetrahydrofurane gave the highest conversion into **3**[a,a] (74%) but the regioisomer **166** (20%) was also detected (Scheme 103). After separation by chromatography column **3**[a,a] was obtained in 58% yield. Spectroscopic data of **3**[a,a] was in compliance with the data obtained with the previous route.

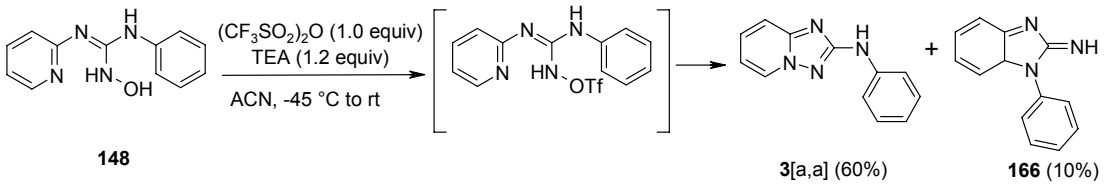


Scheme 103. Cyclisation of the *O*-benzyl hydroxyguanidine **154**.

In order to validate this route in a larger scale (35 mmol, 11 g), we first studied the thermal stability of **154** by DSC. Although the thermogram showed an exothermic event, it released a relatively low energy (-416 J/g). The high T_{onset} (191 °C) and the broad peak (T_f-T_i = 47 °C) made us comfortable to perform the reaction in such scale. In fact, following this route **3**[a,a] could be synthesized in 7 g scale from 2-aminopyridine in three steps with 51% overall yield.

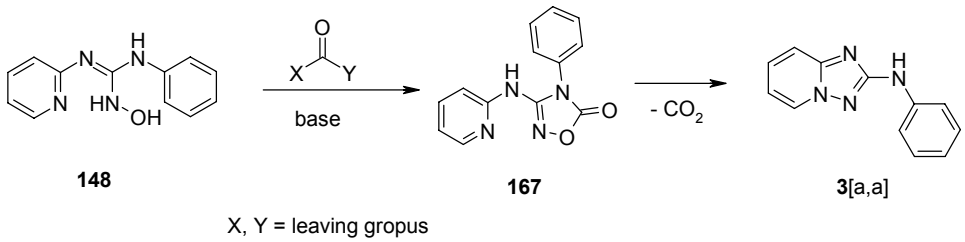
As a second approach, we decided to attempt the cyclisation with a better leaving group than benzyloxy, in particular with a triflate ester. Hence, the reaction of **148** with triflic anhydride

(1.0 equiv) was performed in acetonitrile in presence of triehtylamine (1.2 equiv) from –45 °C to ambient temperature. Over 16 hr, **148** was totally consumed to give the desired product **3**[a,a] together with **166** (10%) and many other impurities (Scheme 104)



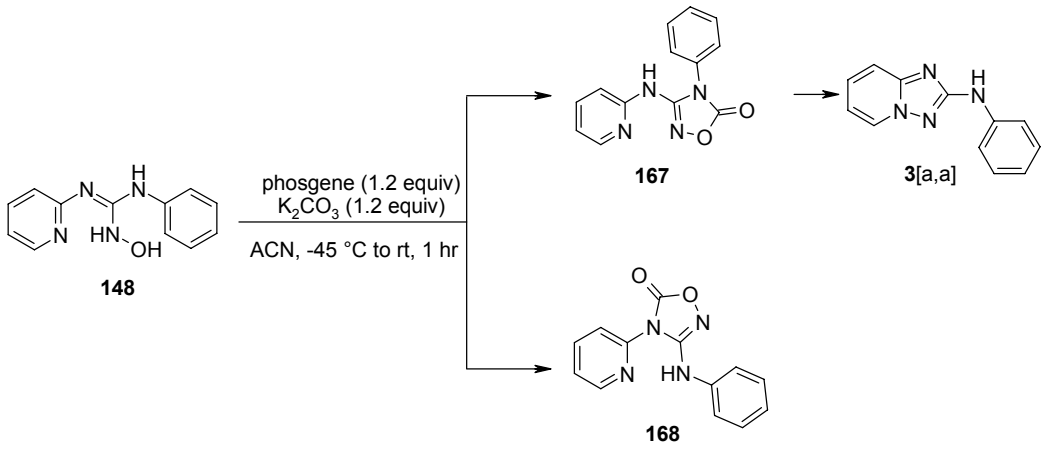
Scheme 104. Cyclisation of the *O*-trifluoromethanesulfonyl hydroxyguanidine.

In a last approach to improve the route to the target heterocycle **3**[a,a], we proposed that the desired product **3**[a,a] could be synthesized *via* decarboxylation of the oxadiazolone **167** (Scheme 105).



Scheme 105. Synthesis of **3**[a,a] *via* cyclisation of the oxadiazolone **167**.

The reaction of **148** with phosgene (1.2 equiv) in ACN in presence if potassium carbonate (1.2 equiv) from –45 °C to ambient temperature afforded the product **3**[a,a] in low conversion (28%) since another compound (ca.60%) was also formed (Scheme 106). Similar results were obtained when THF replaced ACN.



Scheme 106. Reaction of **148** with phosgene.

Based on the NMR and MS analysis, we could not distinguish if the isolated compound was the intermediate **167** or its regioisomer **168** but it could be later characterized by X-ray crystal structure analysis to be **168** (Figure 17).[z]

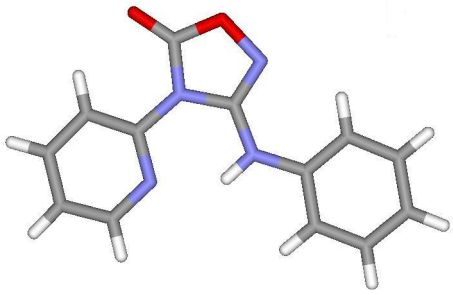
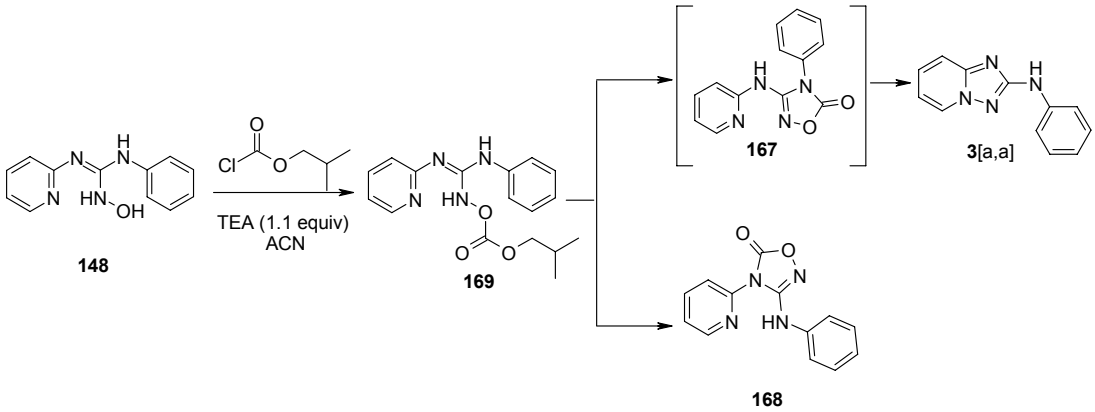


Figure 17. X-ray crystal structure of **168**.

We then tried to preferentially form the intermediate **167** over **168** proceeding stepwise through the compound **169** (Scheme 107)



Scheme 107. Stepwise formation of oxadiazolone **167**.

The reaction of **148** with isobutylchloroformiate in presence of triethylamine was carried out at 0 °C for 30 min and then allowed to reach ambient temperature. The ratio **169** /**168**/**3**[a,a] showed to be dependent on the solvent and reaction time (Table 36).

[z] The fact that **3**[a,a] was already present at –45 °C and the ratio **3**[a,a]/**168** did not change upon heating, already suggested that the isolated product was **168** and not **167**.

entry	solvent	time	169 (%)[†]	168 (%)[†]	3[a,a] (%)[†]
1	ACN	0.1	89	6	5
2	ACN	0.1	89	2	-
		0.5	83	3	-
		3.5	-	93	-
3	THF	0.1	81	8	6
		0.5	73	11	8
		3.5	61	17	11

[†]Determined by UPLC-MS (254 nm).

Table 36. Reaction of **148** with isobutylchloroformiate.

After 5 min of reaction in acetonitrile, the main compound **169** could be isolated pure by precipitation in water in moderate yield (64%) (entry 1). If the reaction was allowed to stand longer to reach ambient temperature, **169** was converted in **168**, which was isolated in very good yield (79%) (entry 2). Similar results were obtained in tetrahydrofurane, although the conversion into **168** showed to be slower and **3**[a,a] was also present in the reaction mixture (entry 3).

When the isolated **169** was heated in ethanol at 78 °C for 2.5 hr, **168** was formed preferentially since the major product in the reaction mixture was **3**[a,a].[aa] However, the low selectivity towards **3**[a,a] (**3**[a,a]/**168** 6:4) rendered this route not particularly attractive since a purification step would be further required.

At this stage, the main goal was to find an easy way to transform **168** into **3**[a,a]. One possibility was to recycle **168** into the hydroxyguanidine **148** to then proceed to the same sequence of reactions. This option was far to be the best since **148** showed to be difficult to handle and purify due to the oxidation issues.

We serendipitously discovered that compound **168**, in presence of catalytic amounts of sodium hydroxyde (0.1 equiv) in ethanol at 78 °C converted into **3**[a,a] (Table 37).

[aa] **167** was never detected since it most probably gave **3**[a,a] as soon as it was formed.

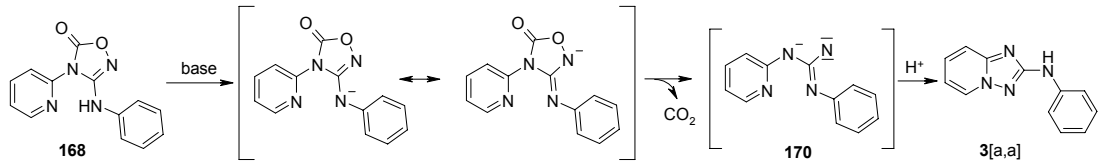
entry	time (hr)	168 (%)†	3[a,a] (%)†
1	0	39	60
2	0.5	25	73
3	16	-	98

†Determined by UPLC-MS (254 nm).

Table 37. Conversion of **168** into **3**[a,a] in presence of sodium hydroxide (0.1 equiv).

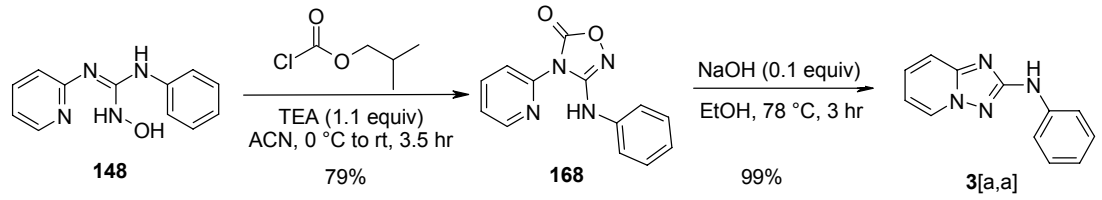
The same results were obtained when sodium hydroxyde was replaced by other less nucleophilic bases such was TEA or pyridine and when the reaction was carried out in aprotic solvents like ACN of THF.

A pausible mechanism for this transformation could involve the formation of a nitrene (**170**) as intermediate generated upon deprotonation of **168** followed by decarboxylation. This reactive intermediate could rearrange into the desired product **3**[a,a] (Scheme 108).



Scheme 108. Pausible mechanism for the conversion of **168** into **3**[a,a].

Based on the previous results, we proposed **168** as key intermediate in the synthesis of **3**[a,a] since it could be easily synthesized from **148** and isolated in good yield after simple precipitation in water (entry 2, Table 36). In the presence of sodium hydroxide (0.1 equiv) in ethanol at 78 °C, the intermediate **168** gave **3**[a,a] in quantitative yield (Scheme 109).



Scheme 109. Synthesis of **3**[a,a] through intermediate **168**.

With this pathway, **3**[a,a] was synthesized in five steps from 2-aminopyridine 350 mg scale with 46% overall yield. The main advantage of this route was that each synthetic intermediate

was isolated and purified by precipitation or recrystallization, which is highly desirable on large scale synthesis. The applicability of this new route in a larger scale and in the extension to other 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines need to be addressed.

6.3. Conclusions

Two different new routes were developed for the synthesis of *N*-phenyl 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine 3[a,a] without the need of an electrophilic amination step.

The first route consisted in a three steps synthesis involving the cyclisation of benzyloxyguanidine **154** under basic conditions to give **3**[a,a]. Through this pathway, **3**[a,a] could be synthesized in 7 g scale with 51% overall yield and only the last step required a chromatographic separation.

The second approach was longer in number of steps (5) and the final compound was synthesized in 350 mg scale with 46% overall yield. The main advantage of this approach was that **3**[a,a] and all the intermediates were isolated and purified by precipitation of recrystallization. The applicability of this new route in a larger scale and in the extension to other 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines needs to be addressed.

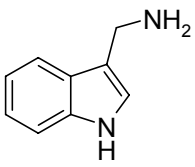
7. Experimental part

7.1. General

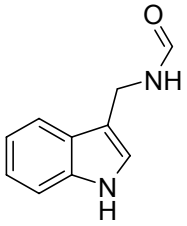
The commercially available starting materials used in the following experimental description were purchased from Aldrich, Fluka or Acros unless otherwise reported.

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded with a BRUKER DPX-300 spectrometer. HPLC analyses were performed on a Waters 2695 instrument, equipped with a Waters 996 Photodiode Array Detector and an X-Bridge column C8 50 x 4.6 mm 3.5 μm. Chromatographic conditions consisted in a gradient from 95% H_2O (0.1% TFA): 5% ACN (0.1% TFA) to 5% H_2O (0.1% TFA): 95% CH_3CN (0.1% TFA) over 8 minutes with a flow of 2 mL/min. LC/MS spectra were determined on a Waters Alliance 2795 coupled with ZMD (ES) equipped with Waters X-Bridge column C8 30 x 2.1 mm 3.5 μm. UPLC/MS were performed on a Waters Acquity coupled with Waters Acquity SQD (ES) equipped with Waters Acquity BEH column C18 50 x 2.1 mm 1.7 μm, using the following conditions: MeCN /H_2O (NH_4OAc 10mM), 5 to 100% (2-3 min), max plot 230-400 nm. Elemental analyses were performed on an Erba Science 11108 CHN analyzer. Melting points were determined on Buchi Melting Point B-545 apparatus and were uncorrected. All reagents were purchased and used without further purification. Wang resin (4-hydroxymethylphenoxymethyl polystyrene, cross-linked with 1% divinylbenzene, 150-300 μm, loading 1.7 mmol/g, Part no. 1463-4689), hydroxymethyl resin (hydroxymethyl polystyrene cross-linked with 1% divinylbenzene, 150-300 μm, loading 2.0 mmol/g, Part no. 3468-4689) were purchased from Polymer Laboratories. Aminomethyl resin (Aminomethylpolystyrene cross-linked with 1% divinylbenzene, 150-300 μm, loading 0.96 mmol/g, Part no. 01-64-0447) was purchased from Novabiochem. All SPE columns were purchased from Separtis.

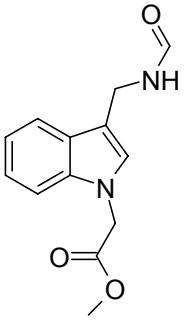
7.2. Chapter 2



3-(Aminomethyl)indole (**30**). 3-(Aminomethyl)indole oxalate salt (750 mg, 3.17 mmol of salt, 6.35 mmol of H^+) was dissolved in MeOH (10 mL) and the resulting solution was passed through a preconditioned SPE-NH_2 column (10g, 0.67 mmol/g) and eluted with MeOH (40 mL). After evaporating the solvent, aminomethylindole free base (**30**) was obtained as a pale yellow solid (438 mg, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (bs, 1H), 7.58 (d, 1H, J = 9 Hz), 7.31 (d, 1H, J = 6 Hz), 7.20 (s, 1H), 7.06 (dt, 1H, J = 7.14 and 1.14 Hz), 6.96 (dt, 1H, J = 7.14 and 1.14 Hz), 3.87 (s, 2H). Note: 3-(aminomethyl)indole is very soluble in water and with a liquid-liquid extraction only 10% of the free base was recovered in the organic phase.

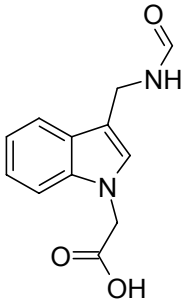


3-(Formylaminomethyl)indole (**31**). 3-(Aminomethyl)indole (**30**) (6.66 g, 45.58 mmol, 1.00 equiv) was dissolved under nitrogen in DMF (80 mL) and DCM (700 mL) was added followed by formic acid (1.89 mL, 50.10 mmol, 1.1 equiv) and TEA (19.0 mL, 136.70 mmol, 3.0 equiv) to give a cloudy solution. Then, 2-chloro-1-methylpyridinium iodide (12.81 g, 50.14 mmol, 1.1 equiv) suspended in DCM (100 mL) was added slowly. The clear solution was stirred at rt for 30 min. Solvents were removed under reduced pressure and the residue was taken up in EtOAc (800 mL) and washed with NH_4Cl sat (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ anhyd, filtered and concentrated under reduced pressure. The resulting brown oil was purified by flash chromatography over silica gel (c-hexane/EtOAc from 9:1 to 4:6) to afford the title compound as a pale yellow solid (5.72 g, 72% yield) ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (bs, 1H), 8.23 (m, 1H), 8.05 (s, 1H), 7.54 (d, 1H, J = 7.9 Hz), 7.36 (d, 1H, J = 7.92 Hz), 7.26 (d, 1H, J = 2.28 Hz), 7.08 (dt, 1H, J = 7.1 and 1.1 Hz), 6.98 (dt, 1H, J = 7.14 and 1.1 Hz), 4.42 (d, 2H, J = 6.0 Hz); MS (ESI) *m/z* 130.18 $(M+H)^+$; HPLC t_R = 1.65 min.

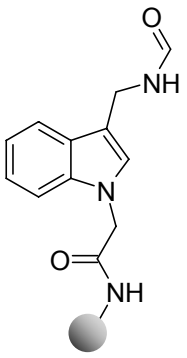


(3-Formylaminomethyl-indol-1-yl)-acetic acid methyl ester (**32**). In a oven-dried round bottom flask and under nitrogen, 3-(formylaminomethyl)indole (**31**) (3.10 g, 17.8 mmol, 1.0 equiv) was dissolved in anyhd DMF (60 mL) and the solution was cooled down to -20 °C before adding sodium hydride (0.84 g, 35.59 mmol, 2.0 equiv) in 3 portions over a period of 10 min and the mixture was stirred at such temp for 30 min. Then, a solution of methyl bromoacetate (2. 45 mL, 26.69 mmol, 1.5 equiv) in anhyd DMF (30 mL) was added and the mixture was stirred for 1.5 hr. DMF was evaporated under reduce pressure and the residue was taken up in EtOAc (600 mL) and water (20 mL). The organic phase was washed with NH_4Cl saturated (1 x 90 mL), dried over $MgSO_4$ anhy, filtered and concentrated under reduced pressure. The crude purified by flash chormatography on silica gel (EtOAc/cyclohexane from 1:9 to 6:4) to

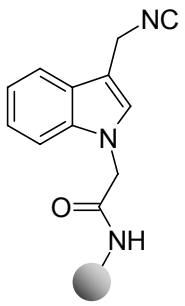
afford the title compound as a white solid (3.33 g, 76 %). mp 122.7-125.6° C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (bs, 1H), 8.06 (s, 1H), 7.56-7.58 (d, J =7.8 Hz, 1H), 7.34-7.36 (d, J = 7.5 Hz, 1H), 7.26 (s, 1H), 7.16-7.11 (m ,1H), 7.06 (m, 1H), 5.10 (s, 2H), 4.41 (d, J = 4.8 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9, 161.1, 137.2, 128.4, 127.2, 122.0, 119.5, 119.3, 112.6, 110.2, 52.5, 47.1, 32.6; MS (ESI) *m/z* 247.02 $(M+H)^+$; HPLC t_R = 2.18 min.



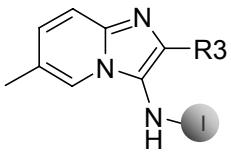
(3-Formylaminomethyl-indol-1-yl)-acetic acid (**33**). To a solution of **32** (10.0 g, 40 mmol, 1.0 equiv) in THF (75 mL) and water (25 mL) was added LiOH (1.4 g, 60 mmol, 1.5 equiv) and the mixture was stirred at rt for 16 hr. The mixture was cooled down (ice bath) and acidified with 0.05 N HCl to pH = 3 and the solvent was evaporated under reduced pressure. The solid obtained was suspended in water, filtered and dried under suction to afford the titled compound as an off-white solid (8.0 g, 85%). mp 200.0-204.6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (bs, 1H), 8.34 (bs, 1H), 8.06 (s, 1H), 7.55-7.57 (d, J = 7.8 Hz, 1H), 7.33-7.35 (d, J = 7.5 Hz, 1H), 7.25 (s, 1H), 7.10-7.15 (m, 1H), 7.00-7.05 (m, 1H), 4.97 (s, 2H), 4.40-4.42 (d, J = 5.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.9, 161.1, 137.2, 128.5, 127.1, 121.9, 119.4, 119.3, 112.2, 110.2, 47.3, 32.7; MS (ESI) *m/z* 233.1 $(M+H)^+$; HPLC t_R = 1.66 min; Anal. Calcd. for $C_{12}H_{12}N_zO_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.25; N, 11.78.



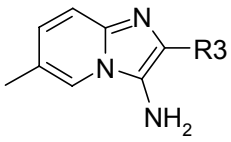
(3-Formylaminomethyl-indol-1-yl)-acetamide polymer-supported (**35**). In round-bottom flask and under nitrogen **33** (2.0 g, 8.64 mmol, 1.5 equiv) was dissolved in anhyd DMF (12 mL) and anhyd DCM (15 mL) was added followed by DIPEA (3.0 mL, 17.2 mmol, 3.0 equiv) and 2-chloro-1-methylpyridinium iodide (2.4 g, 9.22 mmol, 1.5 equiv) and after few seconds a clear solution was obtained. This solution was poured onto the pre-swollen (DCM) aminomethylpolystyrene (6.0 g, 5.76 mmol, 1.0 equiv) and the mixture was shaken at rt for 20 hr. The resin was filtered, washed with DCM, DMF, MeOH, DCM, MeOH, DCM (twice with each solvent) and dried under vacuum at 30 °C (84% attachment by Kaiser test). The same procedure was followed but using 0.5 equiv of each reactant. After the same sequence of washings, the resin was dried under vacuum at 30 °C (97% attachment by Kaiser test). IR (cm^{-1}) 1663.5 (broad, amide), 1492.3, 1451.6, 740.3. Elemental analysis gave N 3.36%, which corresponds to a loading of 0.80 mmol/g.



Indole-isocyanide resin (**29**). Resin **35** (3.5 g, 2.79 mmol, 1.0 equiv) was swollen in anhyd DCM (40 mL) and a solution of triphenylphopsphine (3.7 g, 14.00 mmol, 5.0 equiv), carbone tetrachloride (1.35 mL, 14.00 mmol, 5.0 equiv) and TEA (1.95 ml, 14.0 mmol, 5.0 equiv) in anhyd DCM (15 mL) was added and the mixture was shaken at rt for 3 hr. Then, the resin was filtered and washed with anhyd DCM, MeOH, DCM, MeOH, DCM (twice with each solvent) and dried under vacuum at rt. IR (cm^{-1}) 2144.7 (isocyanide), 1674.2 (broad, amide), 1492.5, 1451.8, 736.3. Elemental analysis gave N 3.40%, which corresponds to a loading of 0.81 mmol/g.



General procedure for resin bound 3-aminoimidazo[1,2-a]pyridines (**38**). In a screw-cap vial, to a solution of the 2-amino-5-methlypyridine (**37**) (52 mg, 0.48 mmol, 3.0 equiv) in MeOH:DCM 1:3 (1.0 mL) the corresponding aldehyde **36** (0.48 mmol, 3.0 equiv) was added followed by a solution of scandium trifluoromethanesulfonate (0.03 mmol, 15 mg, 0.2 equiv) in MeOH:DCM 1:3 (0.5 mL) and the indole-isocyanide resin (**29**) (0.16 mmol, 200 mg, 1.0 equiv). The mixture was shaked at rt for 48 hr and the resin was filtered, washed with DCM, MeOH, DMF, MeOH, DMF, MeOH, DCM (twice with 1.0 mL) and dried under vacuum.



General procedure for 3-aminoimidazo[1,2-a]pyridines (**39**)

Cleavage solution: HCl 1M in DCM:dioxane (4:6) + 1% water.

Cleavage: the resin **38** (0.08 mmol) was swollen in DCM and the cleavage solution (1.5 mL) was added. After shaking at rt for 1 hr, the resin was filtered and washed with DCM (0.2 mL) and MeOH (shake vigorously to dissolve the product in case it has precipitated out during the cleavage). The combined filtrated and washings were evaporated and dried under vacuum to give the product as hydrochloride salt (**39a**, 76%; **39b**, 53%; **39c**, 55%; **39d**, 66%; **39e**, 94%).

Compound **39a** (R3 = Ph) (hydrochloride salt)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.33 (d, J = 1.1 Hz, 1H), 7.83 (d, J = 7.4 Hz, 2H), 7.74 (dd, J = 9.3, 1.5 Hz, 1H), 7.69 (d, J = 9.1 Hz, 1H), 7.57 (t, J = 7.5 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, MeOD-d_4) δ 136.1, 135.8, 130.4, 130.2, 128.7, 128.4, 128.0, 123.2, 119.8, 111.7, 18.2; MS (ESI) *m/z* 224.2 $(M+H)^+$; HPLC t_R = 4.09 min.

Compound **39b** (R3 = 3-(PhO)-Ph) (hydrochloride salt)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.44 (d, J = 1.1 Hz, 1H), 7.73 (dd, J = 9.2, 1.5 Hz, 1H), 7.67 (d, J = 9.4 Hz, 1H), 7.65-7.50 (m, 3H), 7.39 (m, 2H), 7.16 (m, 1H), 7.10-7.00 (m, 3H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, MeOD-d_4) δ 159.7, 158.0, 136.2, 136.0, 132.0, 131.1, 130.5, 128.8, 128.4, 125.0, 123.3, 122.6, 120.3, 120.0, 119.1, 117.9, 111.8, 18.2; MS (ESI) *m/z* 316.2 $(M+H)^+$; HPLC t_R = 5.56 min.

Compound **39c** (R3 = 4-(AcN)-Ph) (hydrochloride salt)

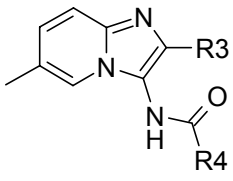
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.55 (s, 2H), 8.00-7.5 (m, 7H), 2.43 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.7, 139.5, 133.9, 132.0, 131.6, 128.9, 127.0, 125.9, 121.9, 119.2, 116.0, 110.9, 24.1, 17.8; MS (ESI) *m/z* 281.1 $(M+H)^+$; HPLC t_R = 3.30 min.

Compound **39d** (R3 = 4-Cl-Ph) (hydrochloride salt)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.45 (d, *J* = 1.1 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.75 (dd, *J* = 9.2, 1.1 Hz, 1H), 7.75-7.62 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, MeOD-d_4) δ 136.7, 136.4, 131.0, 129.9, 129.2, 128.8, 127.9, 123.7, 119.0, 112.3,18.2; MS (ESI) *m/z* 258.1 $(M+H)^+$; HPLC t_R = 4.80 min.

Compound **39e** (R3= cyclohexyl) (hydrochloride salt)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.32 (d, *J* = 1.1 Hz, 1H), 7.67 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.62 (dd, *J* = 9.0, 0.8 Hz, 1H), 3.2-3.0 (m, 1H), 2.48 (s, 3H), 2.00-1.85 (m, 4H), 1.85-1.75 (m, 1H), 1.70-1.30 (m, 5H). ^{13}C NMR (75 MHz, MeOD-d_4) δ 135.8, 135.0, 128.1, 127.6, 126.7, 123.1, 111.6, 34.9, 32.8, 27.3, 26.7, 18.1; MS (ESI) *m/z* 230.2 $(M+H)^+$; HPLC t_R = 4.33 min.



General procedure for *N*-acyl 3-aminoimidazo[1,2-*a*]pyridines (**40**)

In a screw-capped vial, resin **38** (0.04 mmol, 1.0 equiv) was swollen in anhyd THF (0.4 mL) and a solution of acylchloride (20.0 equiv) in THF (0.4 mL) was added. The mixture was shaken at rt for 40 hrs and the resin was filtered and washed with THF (MeOH was used to dissolve the product when there was a solid). The combined filtrated and washings were purified by SPE-SCX (400 mg) as following:

1. Column conditioning (1.0 mL MeOH)
2. Column equilibration (1.0 mL DCM:MeOH 1:1)
3. Sample application
4. Washing (2 x 0.6 mL MeOH:DCM)
5. Washing (2 x 0.6 mL DCM)
6. Elution of the product (4.5 mL NH_3 0.1 M in MeOH) and evaporation under vacuum to give the compound as the free base.

Compound **40a** (R3 = Ph, R4 = benzyl)

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.80 (dd, *J* = 7.9, 2.0 Hz, 2H), 7.72 (s, 1H), 7.55-7.25 (m, 9H), 7.17 (dd, *J* = 9.1, 1.5 Hz, 1H), 3.82 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (75

MHz, DMSO-d_6) δ 171.1, 135.4, 129.2, 128.5, 128.3, 126.9, 126.4, 42.6, 17.7; MS (ESI) *m/z* 342.2 $(M+H)^+$; HPLC t_R = 4.73 min.

Compound **40b** (R3 = Ph, R4 = cyclohexyl)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.91 (d, *J* = 7.92 Hz, 2H), 7.71 (s, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.45-7.40 (m, 2H), 7.35-7.28 (m, 1H), 7.17 (dd, *J* = 9.0, 1.5 Hz, 1H), 2.62-2.53 (m, 1H), 2.32 (s, 3H), 2.08-1.96 (m, 2H), 1.87-1.75 (m, 2H), 1.74-1.62 (m, 1H), 1.57-1.15 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.1, 140.9, 137.2, 133.6, 128.4. 128.1, 127.5, 126.6, 121.5, 120.7, 116.3, 115.3, 43.8, 29.0, 25.4, 25.2, 17.7; MS (ESI) *m/z* 334.3 $(M+H)^+$; HPLC t_R = 4.95 min.

Compound **40c** (R3 = Ph, R4 = isobutyl)

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.94 (d, *J* = 7.1 Hz, 2H), 7.77 (s, 1H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36-7.28 (m, 1H), 7.18 (dd, *J* = 9.0, 1.6 Hz, 1H), 2.40 (d, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.22-2.12 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 140.9, 137.1, 133.6, 128.4, 128.1, 127.6, 126.6, 121.5, 120.8, 116.4, 115.3, 44.4, 25.4, 22.42, 17.7; MS (ESI) *m/z* 308.3 $(M+H)^+$; HPLC t_R = 4.57 min.

Compound **40e** (R3 = cyclohexyl, R4 = benzyl)

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.60 (s, 1H), 7.45-7.25 (m, 6H), 7.08 (dd, *J* = 9.4, 1.5 Hz, 1H), 3.75 (s, 2H), 2.60-2.52 (m, 1H), 2.23 (s, 3H), 1.80-1.60 (m, 5H), 1.58-1.40 (m, 2H), 1.30-1.10 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.2, 144.5, 140.1, 135.9, 129.1, 128.4, 126.9, 126.7, 120.9, 120.5, 115.8, 114.1, 42.3, 36.0, 31.8, 26.1, 25.7, 17.6; MS (ESI) *m/z* 348.3 $(M+H)^+$; HPLC t_R = 5.06 min.

Compound **40f** (R3 = cyclohexyl, R4 = cyclohexyl)

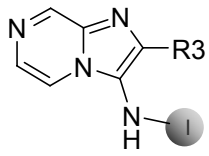
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.55 (s, 1H), 7.62 (s, 1H), 7.39 (d, *J* = 9.1 Hz, 1H), 7.08 (dd, *J* = 9.1, 1.6 Hz, 1H), 2.65-2.53 (m, 1H), 2.50-2.40 (m, 1H, underneath residual DMSO peak), 2.27 (s, 3H), 2.00-1.10 (m, 20H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.1, 140.0, 120.9, 120.4, 115.7, 114.3, 43.7, 36.0, 31.8, 29.1, 26.1, 25.8, 25.4, 25.2, 17.7; MS (ESI) *m/z* 340.3 $(M+H)^+$; HPLC t_R = 5.31 min.

Compound **40g** (R3 = cyclohexyl, R4 = isobutyl)

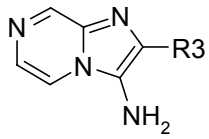
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.64 (s, 1H), 7.67 (s, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.08 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.68-54 (m, 1H), 2.31 (d, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 2.20-2.05 (m, 1H), 1.85-1.40 (m, 8H), 1.40-1.15 (m, 2H), 0.89 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 140.2, 126.7, 120.8, 120.5, 115.8, 114.3, 44.4, 36.0, 32.0, 26.1, 25.7, 25.6, 22.3, 17.7; MS (ESI) *m/z* 314.3 $(M+H)^+$; HPLC t_R = 4.92 min.

Compound **40h** (R3 = cyclohexyl, R4 = Ph)

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.08 (d, J = 7.0 Hz, 2H), 7.82 (s, 1H), 7.70-7.55 (m, 3H), 7.43 (d, J = 8.8 Hz, 1H), 7.11 (dd, J = 9.1, 1.0 Hz, 1H), 2.68-2.55 (m, 1H), 2.27 (s, 3H), 1.80-1.40 (m, 7H), 1.35-1.05 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 145.0, 140.4, 133.2, 132.2, 128.6, 128.0, 126.9, 120.9, 120.8, 115.8, 114.1, 36.0, 32.0, 26.0, 25.8, 17; MS (ESI) *m/z* 334.3 $(M+H)^+$; HPLC t_R = 5.04 min.



General procedure for resin bound 3-aminoimidazo[1,2-a]pyrazines (**42**). In a screw-capped vial, to a solution of 2-amino-pyrazine (**41**) (46 mg, 0.48 mmol, 3.0 equiv) in MeOH:DCM 1:3 (1.0 mL) the corresponding aldehyde **36** (0.48 mmol, 3.0 equiv) was added followed by a solution of scandium trifluoromethanesulfonate (0.03 mmol, 15 mg, 0.2 equiv) in MeOH:DCM 1:3 (0.5 mL) and the indole-isocyanide resin (**29**) (0.16 mmol, 200 mg, 1.0 equiv). The mixture was shaked at rt for 48 hr and the resin was filtered, washed with DCM, MeOH, DMF, MeOH, DMF, MeOH, DCM (twice with 1.0 mL) and dried under vacuum.



General procedure for 3-aminoimidazo[1,2-a]pyridines (**43**)

Cleavage solution: HCl 1M in DCM:dioxane (4:6) + 1% water.

Cleavage: the resin **42** (0.08 mmol) was swollen in DCM and the cleavage solution (1.5 mL) was added. After shaking at rt for 1 hr, the resin was filtered and washed with DCM (0.2 mL) and MeOH (shake vigorously to dissolve the product in case it has precipitated out during the cleavage). The combined filtrated and washings were evaporated. The residue was redissolved in (cyclohexane/EtOAc/4 M NH_3 in MeOH 1:1:0.02) and passed through silica plug to afford the title compounds as free base (**43a**, 27%; **43b**, 17%; **49c**, 23%; **43d**, 55%; **43e**, 32%).

Compound **43a** (R3 = Ph)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.76 (d, J = 1.1 Hz, 1H), 8.17 (dd, J = 4.9, 1.4 Hz, 1H), 7.93 (m, 2H), 7.76 (d, J = 4.8 Hz, 1H), 7.55-7.45 (m, 2H), 7.40-7.32 (m, 1H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 141.9, 129.9, 128.9, 128.5, 238.3, 116.5; MS (ESI) *m/z* 211.2 $(M+H)^+$; HPLC t_R = 2.90 min.

Compound **43b** (R3 = 3-(PhO)-Ph)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.79 (s, 1H), 8.21 (dd, J = 5.3, 0.9 Hz, 1H), 7.75-7.65 (m, 2H), 7.65-7.60 (m, 1H), 7.52 (t, J = 8.0 Hz, 1), 7.42-7.35 (m, 2H), 7.20-7.10 (m, 1H9, 7.10-7.02 (m, 3H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 159.6, 158.3, 137.4, 136.4, 135.4, 134.6, 131.6, 131.0, 124.8, 123.1, 120.3, 120.1, 118.6, 116.3; MS (ESI) *m/z* 303.2 $(M+H)^+$; HPLC t_R = 4.79 min.

Compound **43c** (R3 = 4-NH_2-Ph)

This compound was synthesized from 4-acetamidobenzaldehyde and hydrolysis of the acetyl group was observed during the acidic cleavage. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.69 (d, J = 1.1 Hz, 1H), 8.12 (dd, J = 4.8, 1.3 Hz, 1H), 7.73 (d, J = 4.8 Hz, 1H), 7.68 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 141.4, 129.4, 128.9, 123.8, 116.4, 116.2; MS (ESI) *m/z* 226.2 $(M+H)^+$; HPLC t_R = 2.22 min.

Compound **43d** (R3 = 4-Cl-Ph)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.77 (d, J = 1.5 Hz, 1H), 8.18 (dd, J = 4.8, 1.5 Hz, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 4.8 Hz, 1H), 7.49 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 142.2, 130.0, 129.7, 128.5, 116.6; MS (ESI) *m/z* 245.1 $(M+H)^+$; HPLC t_R = 3.95 min.

Compound **43e** (R3 = cyclohexyl)

^{1}H NMR (300 MHz, MeOD-d_4) δ 8.64 (d. J = 1.5 Hz, 1H), 8.04 (dd, J = 4.5, 1.1 Hz, 1H), 7.70 (d, J = 4.9, 1H), 3.00-2.85 (m, 1H), 1.95-1.30 (m, 10H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 141.2, 128.7, 116.2, 37.1, 33.3, 27.7, 27.1; MS (ESI) *m/z* 217.2 $(M+H)^+$; HPLC t_R = 3.50 min.

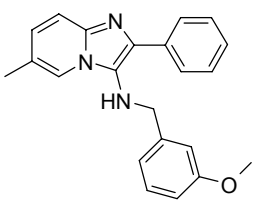
General procedure for 3-aminoimidazo[1,2-a]azines (**45**-**58**)

Solution **A**: heterocyclic amidine 0.8 M
Solution **B**: aldehyde 4.8 M
Solution **C**: isocyanide 2.4 M
Solution **D**: perchloric acid or scandium triflate 0.8 M

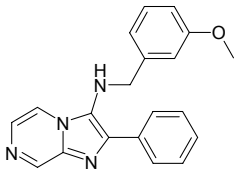
The reactions were performed in screw-cap vials of in 96-well analytical plates. To solution **A** (50 μL, 40 μmol, 1.0 eq) was added solution **B** (25 μL, 120 μmol, 3.0 eq), **C** (15 μL, 60 μmol, 1.5 eq) and **D** (10 μL, 20 μmol, 0.5 eq). The vial/plate was capped and shaked at for 16 hr at rt. The reaction mixture was diluted with DCM (0.15 mL) and purified by SPE-SCX column (400 mg, 0.29 mmol/g, 2.9 eq)

Catch and release on SPE-SCX column:
1. Column conditioning (1.0 mL MeOH)
2. Column equilibration (1.0 mL DCM:MeOH 1:1)
3. Sample aplication (eluted discarded)
4. Washing (2 x 0.6 mL MeOH:DCM, eluted discarded)
5. Washing (2 x 0.6 mL DCM, eluted discarded)
6. Elution using NH_3 0.1 M in MeOH
    Fraction 1: 1.5 mL (discarded)
    Fraction 2: 2.0 mL (collected in vial)

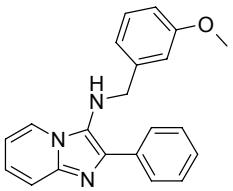
Spectroscopy data:



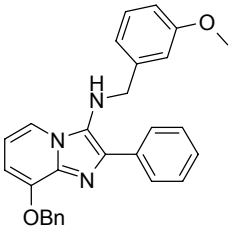
Compound **45**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 3H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.40-7.30 (m, 1H), 7.30-7.20 (m, 1H), 7.20-7.10 (m, 1H), 7.00-6.70 (m, 4H), 4.20 (s, 2H), 3.77 (s, 3H), 2.41 (s, 3H); MS (ESI) *m/z* 344.3 $(M+H)^+$; HPLC t_R = 2.81 min.



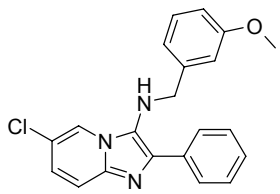
Compound **46.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.01 (d, *J* = 6 Hz, 2H), 7.87 (m, 2H), 7.60-7.40 (m, 3H), 7.30 (m, 1H), 6.90 (m, 3H), 4.27 (d, *J* = 6 Hz, 2H), 3.81 (s, 3H). MS (ESI) *m/z* 331.3 $(M+H)^+$; HPLC t_R = 3.90.



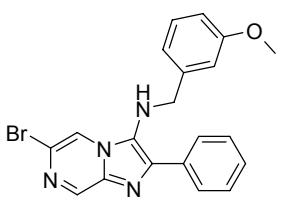
Compound **47**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 3H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.46 (m, 2H), 7.40-7.30 (m, 1H), 7.30-7.20 (m, 1H), 7.20-7.10 (m, 1H), 7.00-6.70 (m, 4H), 4.20 (s, 2H), 3.77 (s, 3H); MS (ESI) *m/z* 330.3 $(M+H)^+$; HPLC t_R = 2.76 min.



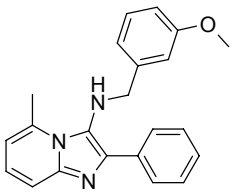
Compound **48**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.86 (m, 2H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.40-7.05 (m, 8H), 6.82-6.76 (m, 2H), 6.75-6.65 (m, 2H), 6.44 (t, *J* = 7.2 Hz, 1H), 6.28 (d, *J* = 7.5 Hz), 5.28 (, s, 2H), 4.04 (d *J* = 6.3 Hz, 2H), 3.60((s, 3H); MS (ESI) *m/z* 436.6.3 $(M+H)^+$; HPLC t_R = 4.97 min.



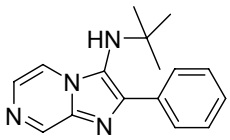
Compound **49**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.90 (m, 2H), 7.52-7.40 (m, 3H), 7.40-7.30 (m, 1H), 7.30-7.15 (m, 2H), 7.09 (dd, *J* = 9.4, 2.1 Hz, 1H), 6.95-6.80 (m, 3H), 4.17 (s, 2H), 3.77 (s, 3H); MS (ESI) *m/z* 436.51 $(M+H)^+$; HPLC t_R = 4.97 min.



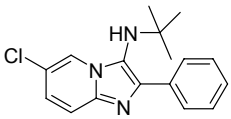
Compound **50**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.92 (m, 3H), 7.55-7.40 (m, 3H), 7.25 (m, 1H), 6.85 (m, 3H), 4.19 (d, *J* = 6 Hz, 2H), 3.77 (s, 3H); MS (ESI) *m/z* 409.3 $(M+H)^+$.



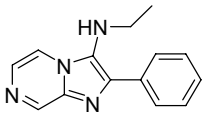
Compound **51**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.45-7.36 (m, 3H), 7.33-7.26 (m, 1H), 6.98 (dd, *J* = 9.04, 6.8 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.82-6.75 (m, 2H), 6.40 (d, *J* = 6.8 Hz, 1H), 4.03 (d, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 2.92 (s, 3H); MS (ESI) *m/z* 343.4 $(M+H)^+$.



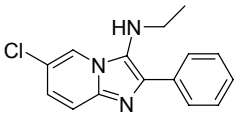
Compound **52**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.15 (d, *J* = 3 Hz, 1H), 7.88 (m, 3H), 7.47 (m, 2H), 7.38 (m, 1H), 1.05 (s, 9H). MS (ESI) *m/z* 267.3 $(M+H)^+$.



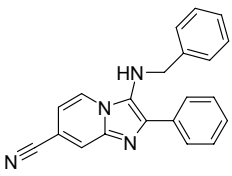
Compound **53**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 3 Hz, 1H), 7.87 (d, *J* = 9 Hz, 2H), 7.53 (d, *J* = 9 Hz, 1H), 7.44 (m, 2H), 7.34 (m, 1H), 7.12 (dd, *J* = 9, 3 Hz, 1H), 1.04 (s, 9H); MS (ESI) *m/z* 300.9 $(M+H)^+$.



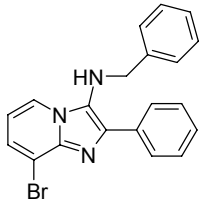
Compound **54**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.05 (m, 4H), 7.87 (d, *J* = 6 Hz, 1H), 7.50 (t, *J* = 7Hz, 2H), 7.38 (m, 1H), 3.17 (m, 2H), 1.24 (t, *J* = 7 Hz, 3H); MS (ESI) *m/z* 238.4 $(M+H)^+$.



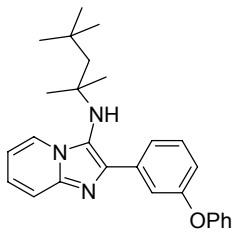
Compound **55**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2 Hz, 1H), 7.97 (m, 2H), 7.58 (d, *J* = 9 Hz, 1H), 7.47 (d, *J* = 9 Hz, 1H), 7.45 (d, *J* = 9 Hz, 1H), 7.35 (m, 1H), 7.13 (dd, *J* = 12, 3 Hz, 1H), 3.11 (q, *J* = 7 Hz, 2H), 1.23 (t, *J* = 7 Hz, 3H); MS (ESI) *m/z* 272.8 $(M+H)^+$.



Compound **56**. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.17 (d, *J* = 6 Hz, 1H), 7.95 (d, *J* = 6 Hz, 2H), 7.86 (s, 1H), 7.45 (dd, *J* = 9, 6 Hz, 2H), 7.37 (m, 1H), 7.15 (m, 5H), 6.94 (m, 1H), 4.14 (s, 2H); MS (ESI) *m/z* 325.5 $(M+H)^+$.

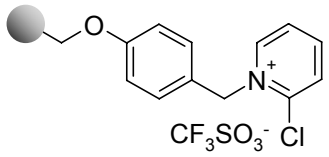


Compound **57.** ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.13 (d, *J* = 6 Hz, 1H), 7.95 (d, *J* = 6 Hz, 2H), 7.46 (m, 3H), 7.42 (m, 1H), 7.16 (m, 5 H), 6.70 (t, *J* = 9 Hz, 1H), 4.11 (s, 2H); MS (ESI) *m/z* 379.3 $(M+H)^+$.

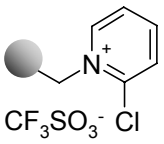


Compound **58**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9 Hz, 1H), 7.63 (dt, *J* = 8, 1 Hz, 2H), 7.41 (t, *J* = 9 Hz, 1H), 7.33 (m, 2H), 7.15-6.95 (m, 5H), 6.77 (td, *J* = 7, 1 Hz, 1H), 1.55 (s, 2H), 1.02 (s, 9H), 0.96 (s, 6H); MS (ESI) *m/z* 314.6 $(M+H)^+$.

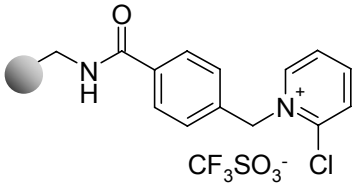
7.3. Chapter 3



Polymer-supported Mukaiyama's Reagent **- PS-Muk1.** In a 500 mL 3 necked round botton flask and under argon, Wang resin (50 g, 1.77 mmol/g, 85 mmol, 1.0 equiv) was swollen in anhyd DCM (500 mL) and 2-chloropyridine (40.21 mL, 425 mmol, 5.0 equiv) was added under stirring. The mixture was cooled down in an ice-water bath before adding neat trifluoromethanesulfonic anhydride (20.14 mL, 119 mmol, 1.4 equiv) at such rate that the temperature did not rise above 20 °C (internal temp). The mixture was stirred gently overnight. The resin was filtered, washed with DCM, DMF, DCM (several times) and Et_2O and dried under high vacuum at rt to obtain 65 g of the title reagent as a pale yellow solid. Elemental analysis gave 3.47% Cl and 5.78% F, which represents a loading of 1.0 mmol/g.



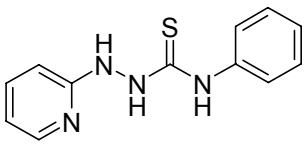
Polymer-supported Mukaiyama's Reagent **- PS-Muk2.** The same procedure as for PS-Muk1 but using hydroxymethylpolystyrene (40 g, 2.0 mmol/g, 80 mmol, 1.0 equiv), DCM (300 mL), 2-chloropyridine (37.8 mL, 400 mmol, 5.0 equiv) and trifluoromethanesulfonic anhydride (18.9 mL, 112 mmol, 1.4 equiv), afforded 55 g of the title reagent as a pale yellow solid. Elemental analysis gave 4.15% Cl, 6.85% F and 3.95% S, which represents a loading of 1.2 mmol/g.



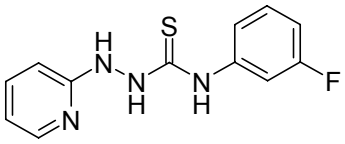
Polymer-supported Mukaiyama's Reagent **- PS-Muk3**. The same procedure as for PS-Muk1 but using 4-hydroxymethylbenzoic acid aminomethylpolystyrene (2 g, 0.83 mmol/g, 1.66 mmol, 1.0 equiv), DCM (20 mL), 2-chloropyridine (0.79 mL, 8.3 mmol, 5.0 equiv) and trifluoromethanesulfonic anhydride (0.39 mL, 2.32 mmol, 1.4 equiv), afforded 1.98 g of the title reagent as a pale yellow solid. Elemental analysis gave 2.52% Cl, 4.46% F, which represents a loading of 0.75 mmol/g.

- **General protocol for 1-(pyridine-2-yl)thiosemicarbazides** (**81**).

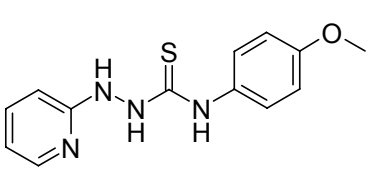
2-Hydrazinopyridine (2.73 g, 25 mmol, 1.0 equiv) was dissolved in THF (100 mL) and a solution of the corresponding isothiocyanate (25 mmol, 1.0 equiv) in THF (25 mL) was added over a period of 5 min using a dropping funnel. The reaction was stirred until completion (2-4 hr, monitored by HPLC) and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from ACN and dried under vacuum at 40 °C.



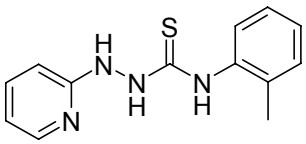
***N*-phenyl-2-pyridin-2-ylhydrazinecarbothioamide** (**81a**). Yield = 71%. mp 180.1-180.6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.73 (s, 1H), 8.55 (s, 1H), 8.14 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.68-7.58 (m, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 6.87-6.77 (m, 1H), 6.66 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.2, 159.2, 147.6, 139.2, 137.8, 127.9, 125.2, 124.7, 115.7, 107.2; IR 3149.3, 1545.7, 1434.8 cm^{-1}; MS (ESI) *m/z* 245 (M+H)$^+$; HPLC t_R = 1.62 min; Anal. calcd. for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93. Found: C, 59.03; H, 4.95; N, 23.00.



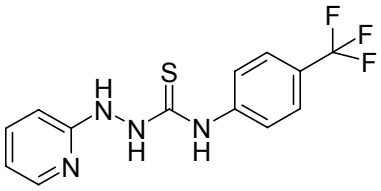
***N*-(3-fluorophenyl)-2-pyridin-2-ylhydrazinecarbothioamide** (**81b**). Yield = 69%. mp 164.7-165.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.96 (s, 1H), 9.87 (s, 1H), 8.57 (s, 1H), 8.14 (d, *J* = 4.1 Hz, 1H), 7.72-7.56 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.31 (dd, *J* = 14.9 8.1 Hz, 1H), 6.94 (dt, *J* = 8.4 2.3 Hz, 1H), 6.82 (t, *J* = 5.8 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.03, 161.4 (d, J_{FC} = 240.8 Hz), 159.1, 147.64, 141.1 (d, J_{FC} = 10.9 Hz), 137.8, 129.3 (d, J_{FC} = 10.9 Hz), 120.6, 115.9, 111.5 (d, J_{FC} = 25.3 Hz), 111.1 (d, J_{FC} = 22.4 Hz); IR 3114.6, 1435.7, 1230.1 cm^{-1}; MS (ESI) *m/z* = 263 (M+H)$^+$; HPLC t_R = 1.67 min; Anal. calcd. for $C_{12}H_{11}N_4SF$: C, 54.95; H, 4.23; N, 21.36. Found: C, 54.77; H, 4.14; N, 21.33.



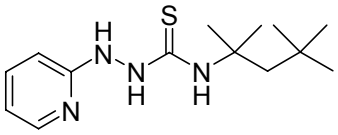
***N*-(4-methoxyphenyl)-2-pyridin-2-ylhydrazinecarbothioamide** (**81c**). Yield = 85%; mp 181.4-181.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.60 (s, 1H), 8.49 (s, 1H), 8.13 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.62 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 6.90-6.77 (m, 3H), 6.63 (d, *J* = 8.5 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.5, 159.3, 156.6, 147.6, 137.8, 132.1, 127.0, 115.6, 113.1, 107.1, 55.2; IR 1602.9, 1510.7, 1242.7 cm^{-}1; MS (ESI) *m/z* = 275 (M+H)$^+$; HPLC t_R = 1.47 min; Anal. calcd. for $C_{13}H_{14}N_4OS$: C, 56.91; H, 5.14; N, 20.42. Found: C, 56.81; H, 4.99; N, 20.44.



***N*-(2-methylphenyl)-2-pyridin-2-ylhydrazinecarbothioamide** (**81d**). Yield = 88%; mp 185.0-185.3 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.57 (s, 1H), 8.59 (s, 1H), 8.15 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.26-7.10 (m, 4H), 6.82 (dd, *J* = 6.8, 5.3 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 2.15 (s, 3H);^{13}C NMR (75 MHz, DMSO-d_6) δ 182.1, 159.3, 147.7, 138.1, 137.8, 135.2, 129.9, 128.7, 126.4, 125.7, 115.6, 106.9, 17.7; IR 3156.7, 1452.6, 1433.5, 1256.1 cm^{-1}; MS (ESI) *m/z* = 259 (M+H)$^+$; HPLC t_R = 1.44 min; Anal. calcd. for $C_{13}H_{14}N_4S$: C, 60.44; H, 5.46; N, 21.69. Found: C, 60.50; H, 5.39; N, 21.74.



***N*-(4-trifluoromethylphenyl)-2-pyridin-2-ylhydrazine-carbothioamide** (**81e**). Yield = 58%. mp 171.4-171.9 °C;^{1}H NMR (300 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.95 (s, 1H), 8.61 (s, 1H), 8.15 (d, *J* = 3.8 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.71-7.74 (m, 3H), 6.83 (t, *J* = 5.7 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H);^{13}C NMR (75 MHz, DMSO-d_6) δ 181.2, 159.0, 147.7, 143.1, 137.8, 126.2, 125.0, 124.9, 122.6, 115.9, 107.4; IR 3126.6, 1450.9, 1432.2, 1321.9 cm^{-1}; MS (ESI) *m/z* = 313 (M+H)$^{+}$; HPLC t_R = 2.79 min; Anal. Calcd. for $C_{13}H_{11}N_4SF_3$: C, 49.99; H, 3.55; N, 17.94. Found: C, 49.91; H, 3.36; N, 17.83;



***N-tert*-octyl-2-pyridin-2-ylhydrazinecarbothioamide** (**81f**). Yield = 77%. mp 131.4-131.8 °C;^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.38 (s, 1H), 8.10 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.61 (td, *J* = 7.8, 1.5 Hz, 1H), 7.07 (s, 1H), 6.80 (dd, *J* = 6.8, 5.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 1.93 (s, 2H), 1.48 (s, 6H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.2, 159.3, 147.7, 137.8, 115.9, 106.7, 56.1, 50.7, 31.17, 31.15, 29.1; IR 3185.7, 1541.8, 1391.0, 1257.4 cm^{-1}; (ESI) *m/z* =281 (M+H)$^{+}$; HPLC t_R = 2.96 min; Anal. calcd. for $C_{14}H_{24}N_4S$: C, 59.96; H, 8.63; N, 19.98. Found: C, 60.18; H, 8.54; N, 20.12;

- **General protocol for 3-amino-[1,2,4]triazolo[4,3-*a*]pyridines** (**83**)

The reactions were performed in screw-cap vials or in the GreenHouse parallel synthesizer (Radleys)

Condition 1: from thiosemicarbazides **81** and using PS-carbodiimide. Thiosemicarbazide **81** (0.05 mmol, 1.0 equiv) was dissolved in DMF (0.1 mL) and DCM (0.9 mL) was added followed by PS-carbidiimide (95 mg, 0.10 mmol, 2.0 equiv). The capped vial was shaked at rt and the reaction monitored by HPLC. After 69 hr MeOH (1.0 mL) was added, the resin was filtered and washed with DCM (1.0 mL). Evaporation of the solvent under reduced pressure afforded **83** (**83a**, 93%; **83b**, 90%; **83c**, 87%).

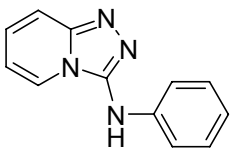
Condition 2: from thiosemicarbazides **81** and using Mukaiyama's reagent. In a round bottom flask, thiosemicarbazides **81** (2.0 mmol, 1.0 equiv) was dissolved in THF (10 mL) and a solution of triethylamine (0.66 mL, 4.8 mmol, 2.4 equiv) in THF (2 mL) was added followed by 2-chloro-1-methylpyridinium iodide (0.62 g, 2.4 mmol 1.2 equiv). The mixture was stirred at rt until completion (1-2 hr, monitored by HPLC) and the solvent was evaporated under vacuum. The residue was taken up in EtOAc (50 mL) and washed with HCl 0.1 N (2 x 10 mL). The aqueous layers were combined and NaOH (1 N) was added until pH 6. The resulting solid

was filtered, washed with water and dried under vacuum at 40 °C. (**83a**, 78%; **83b**, 63%; **83c**, 69%; **83d**, 75%; **83e**, 72%; **83f**, 68%)

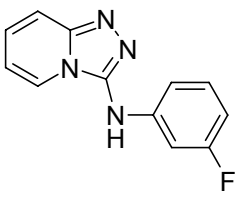
Condition 3: from thiosemicarbazides **81** and using **PS-Muk2**: Thiosemicarbazide **81** (0.05 mmol, 1.0 equiv) was dissolved in DMF (0.1 mL) and a solution of TEA (2.4 equiv) in DCM (0.9 mL) was added followed by PS-Muk2 (1.2 equiv). The capped vial was shaked at rt for 1 hr and MeOH (1 mL) was added. The crude was passed through a SPE-NH_2 column (500 mg, 0.56 mmol/g) and eluted with DCM (4.0 mL). Evaporation of the solvent under reduced pressure afforded the title compound. (**83a**, 79%; **83b**, 77%; **83c**, 85%; **83d**, 74%; **83e**, 71%; **83f**, 81%).

Condition 4: one-pot protocol from 2-hydrazinopyridine and using **PS-MUk2**. 2-Hydrazinopyridine (23 mg, 0.21 mmol, 1.4 equiv) was dissolved in DMF (0.3 mL) and a solution of the corresponding isothiocyanate (0.15 mmol, 1.0 equiv) in DCM (1.0 mL) was added and the mixture was shaked at rt for 2hr. Then, TEA (52 uL, 0.38 mmol, 2.5 equiv) was added followed by PS-Muk2 (1.5 equiv) and the mixture was shaked at rt for 2 hr. MeOH (1 mL) was added and the crude was passed through a SPE-NH_2 column (500 mg, 0.56 mmol/g) and eluted with DCM (4.0 mL). Evaporation of the solvent under reduced pressure afforded the title compound. (**83a**, 67%; **83b**, 48%; **83c**, 56%; **83d**, 69%; **83e**, 43%; **83f**, 54%; **83g**, 72%).

Spectroscopy data:

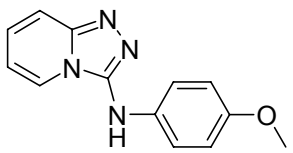


N-phenyl-3-amino-[1,2,4]triazolo[4,3-*a*]pyridine **83a**. mp 232.5-233.3 °C;^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.34 (dt, J = 6.9, 1.0 Hz, 1H), 7.61 (dt, J = 9.4, 1.0 Hz, 1H), 7.56 (dd, J = 8.6, 1.0 Hz, 2H), 7.35-7.27 (m, 2H), 7.24 (ddd, J = 9.3, 6.4, 1.0 Hz, 1H), 6.95-6.86 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.3, 144.3, 141.4, 129.0, 126.5, 122.6, 120.4, 116.2, 115.5, 112.3; IR 1606.2, 1556.7, 1498.4 cm$^-$1; MS (ESI) *m/z* = 211 $(M+H)^+$; HPLC t_R = 1.77 min; Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.21; H, 4.81; N, 26.45.

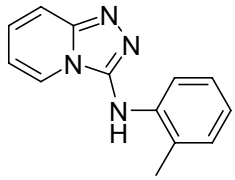


***N*-(3-fluorophenyl)-3-amino-[1,2,4]triazolo[4,3-*a*]pyridine 83b**. mp 258.5-259.3 °C;^{1}H NMR (300 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.36 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 9.4 Hz, 1H), 7.56 (dt, J = 12.2, 202 Hz, 1H), 7.39-7.21 (m, 3H), 6.92 (t, J = 6.2 Hz, 1H), 6.77-6.68 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.8 (d, J_{FC} = 240.5 Hz), 146.3, 143.9, 143.2 (d, J_{FC} = 11.6), 130.5 (d, J_{FC} = 9.4 Hz), 126.7, 122.6, 115.5, 112.5, 112.2 (J_{FC} = 2.9 Hz), 106.7 (d, J_{FC} = 21.1 Hz), 102.9 (d, J_{FC} = 26.9 Hz); IR 1614.4, 1556.8, 1495.0, 1139.0 cm^{-1};

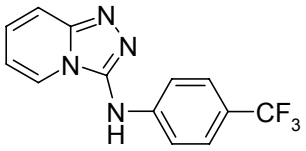
MS (ESI) *m/z* = 229 $(M+H)^+$; HPLC t_R = 2.01 min; Anal. Calcd. for $C_{12}H_9FN_4$: C, 63.15; H, 3.97; N, 24.55. Found: C, 62.82; H, 4.07; N, 24.30.



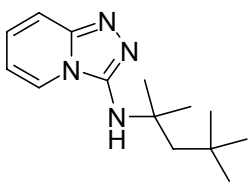
***N*-(4-methoxyphenyl)-3-amino-[1,2,4]triazolo[4,3-*a*]pyridine 83c**. mp 240 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.32 (d, *J* = 7.2 Hz, 1H), 7.61-7.49 (m, 3H), 7.20 (ddd, *J* = 9.4, 6.4, 1.1 Hz, 1H), 6.96-6.82 (m, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.6, 146.0, 144.9, 134.6, 126.2, 122.5, 117.9, 115.5, 114.2, 112.0, 55.2; IR 1572.6, 1496.0, 1233.6 cm^{-1}; MS (ESI) *m/z* = 241 $(M+H)^+$; HPLC t_R = 1.86 min; Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.79; H, 5.08; N, 23.03.



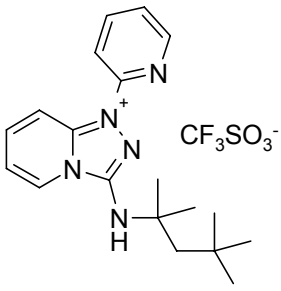
***N*-(2-methylphenyl)-3-amino-[1,2,4]triazolo[4,3-*a*]pyridine 83d**. mp 189.0-189.5 °C; ^{1}H NMR (DMSO-d_6) δ 8.19 (s, 1H), 8.11 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.65 (dt, *J* = 9.13. 1.0 Hz, 1H), 7.27 (ddd, *J* = 9.4, 6.5, 1.0 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.12-6.97 (m, 2H), 6.93-6.83 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 147.3, 144.7, 140.4, 130.7, 126.8, 126.6, 126.5, 123.0, 121.4, 117.1, 115.5, 112.5, 17.9; IR 1476.3, 1379.4, 1247.1 cm^{-1}; MS (ESI) *m/z* = 225 $(M+H)^+$; HPLC t_R = 1.77 min; Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98. Found: C, 69.37; H, 5.45; N, 24.76.



***N*-(4-trifluoromethylphenyl)-3-amino-[1,2,4]triazolo[4,3-*a*]-pyridine 83e**. mp 270 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.51 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.69-7.60 (m, 3H), 7.27 (ddd, *J* = 9.4, 6.5, 1.1 Hz, 1H), 6.92 (td, *J* = 6.7, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.5, 145.0, 143.6, 126.9, 126.3 (q, J_{FC} = 3.8 Hz), 124.8 (q, J_{FC} = 270.9 Hz), 122.9, 120.3 (q, J_{FC} = 32.0 Hz), 115.9, 155.5, 112.6; IR MS (ESI) *m/z* = 279 $(M+H)^+$; HPLC t_R = 2.76 min; Anal. Calcd. for $C_{13}H_9N_4F_3$ + (0.2% DMF) C_3H_7NO:C, 55.78; H, 3.58; N, 20.09. Found: C, 55.43; H, 3.29: N, 19.93.



***N-tert*-octyl-3-amino-[1,2,4]triazolo[4,3-*a*]pyridine 83f**, 68%. mp 168 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (d, *J* = 6.8 Hz, 1H), 7.43 (d, *J* = 9.4 Hz, 1H), 7.06 (ddd, *J* = 9.4, 6.8, 1.0 Hz, 1H), 6.70 (dd, *J* = 6.8, 1.0 Hz, 1H), 6.00 (s, 1H), 1.91 (s, 2H), 1.49 (s, 6H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.0, 145.2, 125.2, 122.5, 115.2, 111.0, 55.1, 49.9, 31.4, 31.16, 29.5; IR 1572.7, 1387.1, 1226.4 cm^{-1}; MS (ESI) *m/z* = 247 $(M+H)^+$; HPLC t_R = 2.94 min; Anal. Calcd. for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 67.92; H, 8.92; N, 21.74.

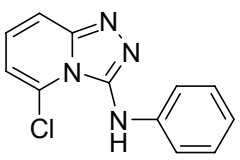


1-pyridin-2-yl-3-tert-octylamino-[1,2,4]triazolo[4,3-a]pyridin-1-ium tri-fluoromethanesulfonate (**85f-1)**. In a screw-cap vial, **81f** (140 mg, 0.5 mmol, 1.0 equiv) was dissolved in DMF (1 mL) and a solution of TEA (0.35 mL. 2.5 mmol, 5.0 equiv) in DCM (9 mL) was added followed by **PS-Muk1** (1200 mg, 1.5 mmol, 3.0 equiv). The mixture was shaked at rt for 20 hr and passed through a SPE-NH_2 column (10g, 0.56 mmol/g). Elution with MeOH followed by evaporation of the solvent, afforded the title compound (186 mg, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (d, J = 7.2 Hz, 1H), 9.00 (d, J = 9.4 Hz, 1H), 8.68 (dd, J = 4.7, 1.3 Hz, 1H), 8.29 (dd, J = 8.9, 7.3 Hz, 1H), 8.20 (dd, J = 7.9, 1.8 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.63 (s, 1H), 7.56 (dd, J = 6.8, 4.9 Hz, 1H), 1.98 (s, 2H), 1.61 (s, 6H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.1, 148.5, 144.9, 140.5, 139.8, 139.7, 126.1, 123.1, 120.0 (q, J = 322.4 Hz), 118.2, 114.6, 113.7, 56.7, 49.4, 31.4, 31.1, 28.5; ^{19}F NMR (282 MHz, DMSO-d_6) δ -78.2; MS (ESI+) *m/z* = 324; HPLC t_R = 3.86 min; Anal. Calcd. for $C_{19}H_{26}N_5.CF_3O_3S$ (96%) + $C_{19}H_{26}N_5.Cl$ (4%): C, 51.10; H, 5.59; N, 14.93; Cl, 0.29 Found: C, 50.72; H, 5.31; N, 14.71; Cl, 0.29.

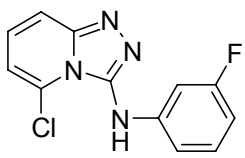
- **General protocol for 3-amino-5-chloro[1,2,4]triazolo[4,3-a]pyridines** (**87**).

The reactions were performed in screw-cap vials or in the GreenHouse parallel synthesizer (Radleys). The same protocol as for **83** (condition 4) but using 6-chloro-2-hydrazinopyridine (30 mg, 0.21 mmol, 1.4 equiv) instead of 2-hydrazinopyridine. (**83a**, 78%; **83b**, 63%; **83c**, 69%; **83d**, 75%; **83e**, 72%)

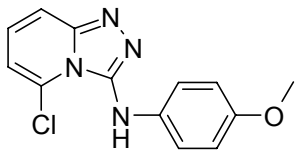
Spectroscopy data:



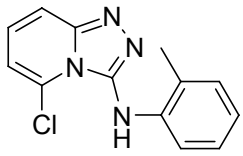
***N*-phenyl-3-amino-5-chloro[1,2,4]triazolo[4,3-a]pyridine** (**87a**). mp 200 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.29 (dd, J = 9.4, 7.2 Hz, 1H), 7.20 (t, J = 7.9 Hz, 2H), 7.06 (d, J = 6.8 Hz, 1H), 6.86-6.77 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.1, 144.9, 143.6, 129.1, 128.1, 124.2, 119.6, 115.1, 115.0, 114.9; IR 1624.8, 1534.8, 1480.7, 788.0 cm^{-1}; MS (ESI) *m/z* = 247 $(M+H)^+$; HPLC t_R = 2.57 min; Anal. Calcd. for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90. Found: C, 58.53; H, 3.65; N, 22.77.



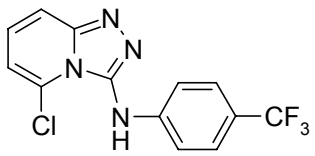
***N*-(3-fluorophenyl)-3-amino-5-chloro[1,2,4]triazolo[4,3-a]pyridine** (**87b**), 76%. mp 180.0-180.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.81 (s, 1H), 7.73 (d, J = 9.3 Hz, 1H), 7.32 (dd, J = 9.3, 7.0 Hz, 1H), 7.21 (dd, J = 14.9, 8.1 Hz, 1H), 7.08 (d, J = 6.4 Hz, 1H), 6.72-6.56 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0 (d, J_{FC} = 241.2 Hz), 150.3, 147.0 (d, J_{FC} = 10.9 Hz), 142.9, 130.7 (d, J_{FC} = 10.2 Hz), 128.3, 124.2, 115.2, 115.1, 110.8 (d, J_{FC} = 2.2 Hz), 105.9 (d, J_{FC} = 21.1 Hz), 101.6 (d, J_{FC} = 26.2 Hz); IR 1627.1, 1531.3, 1485.1, 769.6 cm^{-1}; MS (ESI) *m/z* = 265 (M+H)$^+$; HPLC t_R = 2.91 min; Anal. Calcd. for $C_{12}H_8ClFN_4$ + (0.08% DMF) C_3H_7NO: C, 54.75; H, 3.21; N, 21.38. Found: C, 54.35; H, 3.13; N, 21.02.



***N*-(4-methoxyphenyl)-3-amino-5-chloro[1,2,4]triazolo[4,3-a]-pyridine** (**87c**). mp 180.7-182.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.24 (dd, J = 9.0, 6.9 Hz, 1H), 7.01 (d, J = 6.9 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.3, 149.7, 144.8, 137.7, 127.8, 124.2, 117.0, 115.1, 114.7, 114.4, 55.2; IR 1538.9, 1508.0, 1242.5, 766.3 cm^{-1}; MS (ESI) *m/z* = 277 (M+H)$^+$; HPLC t_R = 2.40 min; Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.39. Found: C, 56.49; H, 4.00; N, 20.36.



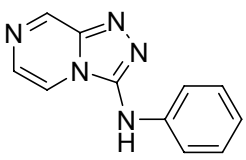
***N*-(2-methylphenyl)-3-amino-5-chloro[1,2,4]triazolo[4,3-a]pyridine** (**87d**). mp 169.9-170.7 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (s, 1H), 7.71 (dd, J = 9.1, 0.9 Hz, 1H), 7.29 (dd, J = 9.1, 7.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.78 (td, J = 7.4, 0.9 Hz, 1H), 6.57 (d, J = 7.2 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.1, 144.1, 143.0, 130.6, 128.1, 126.7, 124.4, 124.2, 120.1, 115.1, 114.9. 114.8, 17.7; IR 1628.4, 1537.4, 1448.4, 779.2 cm^{-1}; MS (ESI) *m/z* = 261 (M+H)$^+$; HPLC t_R = 2.78 min; Anal. Calcd. for $C_{13}H_{11}ClN_4$: C, 60.35; H, 4.29; N, 21.66. Found: C, 60.07; H, 4.21; N, 21.48.



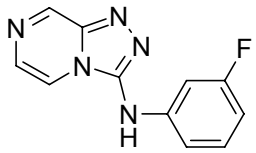
***N*-(4-trifluoromethylphenyl)-3-amino-5-chloro[1,2,4]triazolo-[4,3-a]pyridine** (**87e**). mp 234.1-234.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.77 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.35 (dd, J = 9.0, 7.0 Hz, 1H), 7.11 (d, J = 7.0 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.57, 148.7, 142.3, 128.6, 126.9 (q, J_{FC} = 3.9 Hz), 124.2, 120.0 (q, J_{FC} = 31.6 Hz), 115.4, 115.2, 114.4; IR 1631.2, 1537.0, 1319.9, 1104.2, 777.6 cm^{-1}; MS (ESI) *m/z* = 315 (M+H)$^+$; HPLC t_R = 3.70 min; Anal. Calcd. for $C_{13}H_8ClF_3N_4$: C, 49.94; H, 2.58; N, 17.92. Found: C, 49.69; H, 2.65; N, 17.79.

❑ **General protocol for 3-amino-[1,2,4]triazolo[4,3-a]pyrazines** (**88**).

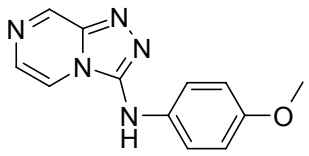
The reactions were performed in screw-cap vials or in the GreenHouse parallel synthesizer (Radleys). The same protocol as for **83** (condition 4) but using 2-hydrazinopyrazine (23 mg, 0.21 mmol, 1.4 equiv) instead of 2-hydrazinopyridine (**88a**, 78%; **88b**, 79%; **88c**, 69%; **88d**, 77%; **88e**, 70%).



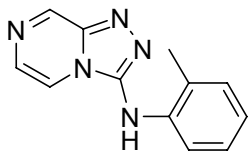
***N*-phenyl-3-amino-[1,2,4]triazolo[4,3-a]pyrazine** (**88a**). mp 262 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.21 (d, J = 1.6 Hz, 1H), 8.39 (dd, J = 5.1, 1.6 Hz, 1H), 7.81 (d, J = 4.9 Hz, 1H), 7.68 (dd, J = 8.7, 0.8 Hz, 2H), 7.35 (dd, J = 8.6, 7.3 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.2, 144.1, 142.0, 140.5, 129.0, 127.6, 121.1, 116.7, 115.5; IR 1614.0, 1564.7, 1377.8 cm^{-1}; MS (ESI) *m/z* = 212 (M+H)$^+$; HPLC t_R 1.83 min; Anal. Calcd. for $C_{11}H_9N_5$ + (0.06% DMF) C_3H_7NO: C, 62.28; H, 4.40; N, 32.87. Found: C, 62.01; H, 5.00; N, 33.15.



***N*-(3-fluorophenyl)-3-amino-[1,2,4]triazolo[4,3-a]pyrazine** (**88b**). mp 255 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (bs, 1H), 9.24 (d, J = 1.7 Hz, 1H), 8.39 (dd, J = 4.9, 1.7 Hz, 1H), 7.84 (d, J = 4.9 Hz, 1H), 7.67 (dd, J = 12.4, 1.8 Hz, 1H), 7.42-7.35 (m, 2H), 6.84-6.74 (m, 1H); IR 1619.1, 1567.4, 1153.3 cm^{-1}; MS (ESI) *m/z* = 230 (M+H)$^+$; HPLC t_R = 2.42 min; Anal. Calcd. for $C_{11}H_8FN_5$ + (0.1% H_2O): C, 57.19; H, 3.58; N, 30.32. Found: C, 57.02; H, 3.88; N, 30.78.

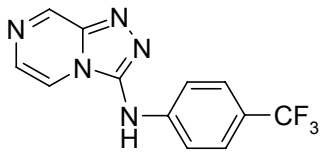


***N*-(4-methoxyphenyl)-3-amino-[1,2,4]triazolo[4,3-a]pyrazine** (**88c**). mp 256 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (d, J = 1.5 Hz, 1H), 8.35 (dd, J = 4.9, 1.5 Hz, 1H), 7.78 (d, J = 4.9 Hz, 1H), 7.62 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.0, 145.8, 144.1, 141.9, 133.7, 127.4, 118.4, 115.4, 114.3, 55.2; IR 1574.1, 1511.0, 1381.8, 1234.4 cm^{-1}; MS (ESI) *m/z* = 242 (M+H)$^+$; HPLC t_R = 1.74 min; Anal. Calcd. for $C_{12}H_{11}N_5O$ + (0.1% H_2O): C, 59.30; H, 4.64; N, 28.81. Found: C, 58.94; H, 4.94; N, 29.09.



***N*-(2-methylphenyl)-3-amino-[1,2,4]triazolo[4,3-a]pyrazine** (**88d**). mp 193.1-194.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.22 (d, J = 1.5 Hz, 1H), 8.50 (s, 1H), 8.22 (dd, J = 4.9, 1.5 Hz, 1H), 7.80 (d, J = 4.9 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.98 (td, J = 7.3, 1.1 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 137.3, 106.5 226.4, 224.4 227.4, 224.4; IR 1564.9, 1484.0, 1379.7, 1251.3 cm^{-1}; MS (ESI)

m/z = 226 $(M+H)^+$; HPLC t_R = 1.94 min; Anal. Calcd. for $C_{12}H_{11}N_5$ + (0.07% H_2O): C, 63.63; H, 4.96; N, 30.92. Found: C, 62.24; H, 4.36; N, 31.01.

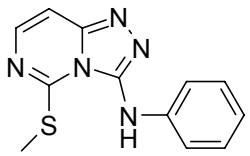


***N*-(4-trifluoromethylphenyl)-3-amino-[1,2,4]triazolo[4,3-a]-pyrazine** (**88**). mp 225 °C (dec); ^{1}H NMR (300 MHZ, DMSO-d_6) δ 10.03 (s, 1H), 9.26 (d, *J* = 1.9 Hz, 1H), 8.42 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.90-7.82 (m, 3H), 7.71 (d, *J* = 8.7 Hz, 2H) ; IR 1615.8, 1517.8, 1326.2, 1107.7 cm^{-1}; MS (ESI) *m/z* = 280 $(M+H)^+$; HPLC t_R = 3.00 min; Anal. Calcd. for $C_{12}H_8F_3N5$: C, 51.62; H, 2.89; N, 25.08. Found: C, 51.33; H, 3.20; N, 25.11.

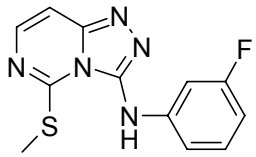
- **General protocol for 3-amino-5-methylsulfanyl[1,2,4]triazolo[4,3-a]pyrazines** (**89**).

The reactions were performed in screw-cap vials or in the GreenHouse parallel synthesizer (Radleys). The same protocol as for **83** (condition 4) but using 4-hydrazino-2-(methylthio)pyrimidine (33 mg, 0.21 mmol, 1.40 equiv) instead of 2-hydrazinopyridine (**89a**, 60%; **89b**, 51%; **89c**, 56%; **89d**, 66%; **89e**, 45%).

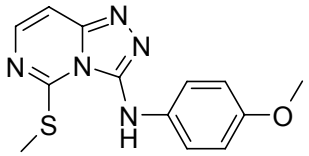
Spectroscopy data:



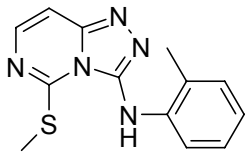
***N*-phenyl-3-amino-5-methylsulfanyl[1,2,4]triazolo[4,3-a]pyrazine** (**89a**). mp 197.6-198.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (s, 1H), 7.83 (d, *J* = 6.6 Hz, 1H), 7.43 (d, *J* = 6.6 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (75 MHZ, -d_6) δ 151.1, 148.3, 145.1, 143.0, 140.4, 129.1, 119.8, 115.1, 105.9, 13.5; IR 1536.9, 1645.5, 1307.6 cm^{-1}; MS (ESI) *m/z* =258 $(M+H)^+$; HPLC t_R = 2.62 min; Anal. Calcd. for $C_{12}H_{11}N_5S$: C, 56.1; H, 4.31; N, 27.22; S, 12.46. Found: C, 56.12; H, 4.46; N, 27.26; S, 12.32.



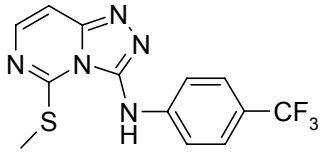
***N*-(3-fluorophenyl)-3-amino-5-methylsulfanyl[1,2,4]triazolo[4,3-a]-pyrazine** (**89b**). mp 192.5-194.1 °C; ^{1}H NMR (300 MHZ, DMSO-d_6) δ 8.92 (s, 1H), 7.84 (d, *J* = 6.6 Hz, 1H), 7.45 (d, *J* = 6.6 Hz, 1H), 7.22 (dd, *J* = 15.3, 8.1 Hz, 1H), 6.71-6.52 (m, 3H), 2.57 (s, 3H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 164.6, 150.9, 148.6 (d, *J* = 11.0 Hz), 142.2, 140.5, 130.7 (d, *J* = 10.3 Hz), 111.0 (d *J* = 2.1 Hz), 106.2 (d, *J* = 21.8 Hz), 106.0, 101.9 (d *J* = 25.8 Hz), 13.5; IR 1600.9, 1487.7, 1468.9 cm^{-1}; MS (ESI) *m/z* = 276 $(M+H)^+$; HPLC t_R = 2.83 min; Anal. Calcd. for $C_{12}H_{10}FN_5S$: C, 52.35; H, 3.66; N, 25.44; S, 11.65. Found: C, 52.38; H, 3.75; N, 25.43; S, 11.68.



***N*-(4-methoxyphenyl)-3-amino-5-methylsulfanyl[1,2,4]-triazolo[4,3-a]pyrazine** (**89c**). mp 175.9-176.7 °C; ^{1}H NMR (300 MHZ, DMSO-d_6) δ 8.38 (s, 1H), 7.79 (d, J = 6.4 Hz, 1H), 7.39 (d, J = 6.4 Hz, 1H), 6.85-6.74 (m, 4H), 3.68 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 153.4, 151.1, 147.9, 144.1, 140.2, 138.2, 116.8, 114.4, 105.9, 55.2, 13.6; IR 1509.9, 1461.5, 1309.2, 1232.8 cm^{-1}; MS (ESI) *m/z* = 288 (M+H)$^{+}$; HPLC t_R = 2.52 min; Anal. Calcd. for $C_{13}H_{13}N_5OS$: C, 54.34; H, 4.56; N, 24.37; S, 11.16. Found: C, 54.45; H, 4.59; N, 24.58; S, 11.13.



***N*-(2-methylphenyl)-3-amino-5-methylsulfanyl[1,2,4]triazolo[4,3-a]pyrazine** (**89d**). mp 183.0-183.6 °C; ^{1}H NMR (300 MHZ, DMSO-d_6) δ 8.01 (s, 1H), 7.82 (d, J = 6.6 Hz, 1H), 7.43 (d, J = 6.6 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.80 (td, J = 7.30, 1.0 Hz, 1H), 6.50 (d, J = 7.5 Hz, 1H), 2.54 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 151.2, 148.2, 143.5, 143.0, 140.3, 130.6, 126.7, 124.5, 120.45, 115.1, 105.9, 17.8, 13.6; IR 1555.7, 1465.9, 1302.6 cm^{-1}; MS (ESI) *m/z* = 272 (M+H)$^{+}$; HPLC t_R = 2.90 min; Anal. Calcd. for $C_{13}H_{13}N_5S$: C, 57.54; H, 4.83; N, 25.81; S, 11.82. Found: C, 57.42; H, 4.89; N, 25.76; S, 11.68.



***N*-(4-trifluoromethylphenyl)-3-amino-5-methylsulfanyl-[1,2,4]triazolo-[4,3-a]pyrazine** (**89e**). mp 188.6-189.3 °C; ^{1}H NMR (300 MHZ, DMSO-d_6) δ 9.23 (s, 1H), 7.87 (d, J = 6.8 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 6.8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 150.9, 148.9, 141.7, 140.7, 126.5 (q, J = 3.7 Hz), 119.8 (q, J = 32.0 Hz), 114.8, 106.0, 13.5; IR 1601.9, 1538.0, 1468.0, 1313.3 cm^{-1}; MS (ESI) *m/z* =326 (M+H)$^{+}$; HPLC t_R = 3.63 min; Anal. Calcd. for $C_{13}H_{10}F_3N_5S$: C, 48.00; H, 3.10; N, 21.53; S, 9.89. Found: C, 48.18; H, 3.25; N, 21.59; S, 9.78.

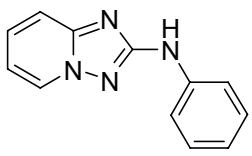
7.4. Chapter 4

General procedure for 2-amino-[1,2,4]triazolo[1,5-*a*]pyridines (**3**).

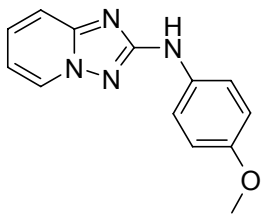
The reactions were performed in screw-cap vials or in the GreenHouse parallel synthesizer (Radleys).

Condition 1: from **109** ($MesSO_3^-$) in DCM/DMF. Compound **109** ($MesSO_3^-$) (0.16 mmol, 1.0 eq) was dissolved in DMF (0.2 mL) and a solution of the corresponding isothiocyanate (0.16 mmol, 1.0 eq) in DCM (0.8 mL) was added followed by DIPEA (141 µL. 0.81 mmol, 5.0 eq). The mixture was stirred at rt for 16 hr and DCM (1.5 mL) was added followed by PS-Muk2 (289 mg, 0.19 mmol, 1.2 eq). After 1 hr the crude was passed through a SPE-NH_2 column (2g, 0.55 mmol/g) and eluted with DCM. Evaporation of the solvent under reduced pressure afforded the title compound as a solid. (**3**[a,a], 60%; **3**[b,a], 71%; **3**[c,a], 66%)

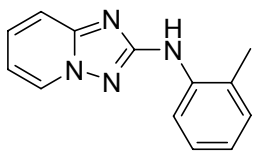
Condition 2: from **109** ($MesSO_3^-$) in DMSO. Compound **109** ($MesSO_3^-$) (0.45 mmol, 1.5 eq) was dissolved in DMSO (0.5 mL) and a solution of the corresponding isothiocyanate (0.30 mmol, 1.0 eq) in DMSO (0.5 mL) was added followed by DIPEA (1.5 mmol, 5.0 eq). The mixture was stirred at rt for 16 hr and DCM (1.5 mL) was added followed by PS-Muk2 (0.36 mmol, 1.2 eq). After 1hr the crude was passed through a SPE-NH_2 column (4g, 0.55 mmol/g) and eluted with DCM. Evaporation of the solvent under vacuum afforded the title compound as a solid. (**3**[a,a], 62%; **3**[a,c], 86%; **3**[a,d], 66%; **3**[a,e], 91%; **3**[a,g], 39%;**3**[b,a], 68%; **3**[b,c], 87%; **3**[b,d], 68%; **3**[b,e], 83%; **3**[b,g], 74%;**3**[c,a], 76%; **3**[c,c], 84%; **3**[c,d], 79%; **3**[c,e], 78%; **3**[c,g], 69%)



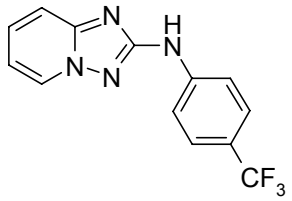
***N*-phenyl 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine** **3**[a,a] ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (bs, 1H), 8.77 (dt, J = 6.7, 1.1 Hz, 1H), 7.71 (dd, J = 8.7, 1.0 Hz, 2H), 7.57-7.54 (m, 2H), 7.28 (dd, J = 8.7, 7.4 Hz, 2H), 7.05-6.98 (m, 1H), 6.88 (tt, J = 7.3, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.3, 149.6, 141.3, 129.9, 128.7, 128.2, 120.0, 116.5, 113.2, 112.2; IR 1602.1, 1512.6, 1444.1, 1238.6, 745.9 cm^{-1}; MS (ESI) *m/z* 211.1 $(M+H)^+$; HPLC t_R = 2.49 min; Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.31; H, 4.92 ; N, 26.83.



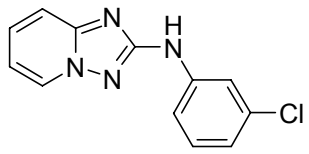
***N*-(4-methoxyphenyl)-2-amino-[1,2,4]triazolo[1,5-*a*]pyridine** **3**[a,c]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.73 (dt. J = 6.7, 1.1 Hz, 1H), 7.60 (d, J = 9.1 Hz, 2H), 7.54-7.51 (m, 2H), 7.00-6.95 (m, 1H), 6.88 (d, J = 9.1 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.6, 153.2, 149.7, 134.8, 129.8, 128.1, 118.0, 114.0, 113.0, 112.0, 55.2; IR 1605.9, 1504.7, 1230.5, 1030.8, 817.8 cm^{-1}; MS (ESI) *m/z* 241.1 $(M+H)^+$.



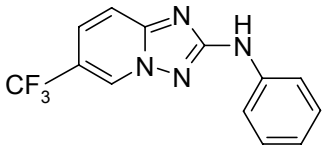
***N*-(2-methylphenyl)-2-amino-[1,2,4]triazolo[1,5-*a*]pyridine 3**[a,d] ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (d, J = 6.7 Hz, 1H), 8.42 (s, 1H), 7.92-7.86 (m, 1H), 7.55-7.49 (m, 2H), 7.20-7.12 (m, 2H), 7.03-6.88 (m, 2H), 2.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3, 149.9, 139.2, 130.4, 129.9, 128.22, 128.20, 126.3, 122.2, 120.4, 113.2, 112.2, 18.4; IR 1555.5, 1513.4, 1458.2, 1329.4, 756.1, 737.7 cm^{-1}; MS (ESI) *m/z* 225 (M+H)$^+$.



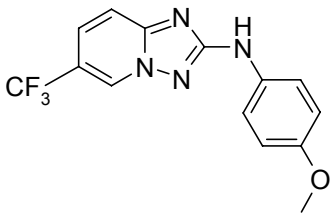
***N*-(4-trifluoromethylphenyl)-2-amino-[1,2,4]triazolo[1,5-*a*]pyridine 3**[a,e]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.82 (dt, J = 6.6, 1.1 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.66-7.57 (m, 4H), 7.10-7.05 (m, 1H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 161.6, 149.6, 144.8, 130.3, 128.4, 126.1 (q,J = 3.8 Hz), 124.9 (q, J = 271.3 Hz), 119.9 (q, J = 32.2 Hz), 116.2, 113.6, 112.8; IR 1610.1, 1517.9, 1320.3, 1099.0, 1070.0, 832.9 cm^{-1}; MS (ESI) *m/z* 279.1 (M+H)$^+$.



***N*-(3-chlorophenyl)-2-amino-[1,2,4]triazolo[1,5-*a*]pyridine 3** [a,g]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (bs, 1H), 8.82 (dt, J = 6.6, 1.1 Hz, 1H), 7.89 (t, J = 2.1 Hz, 1H), 7.63-7.55 (m, 3H), 7.30 (t, J = 8.1 Hz, 1H, 7.07-7.02 (m, 1H), 6.91 (ddd, J = 7.9, 2.0, 0.9 Hz, 1H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 161.8, 149.6, 142.8, 133.3, 130.4, 130.2, 128.4, 119.6, 115.7, 115.1, 113.5, 112.6; IR 1598.3, 1514.3, 1477.6, 1243.9, 850.2, 755.7 cm^{-1}; MS (ESI) *m/z* 245.1 (M+H)$^+$.

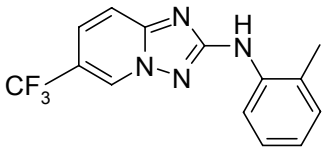


***N*-phenyl-2-amino-6-trifluoromethyl-[1,2,4]triazolo[1,5-*a*]-pyridine 3** [b,a]. ^{1}H NMR (300 MHZ, DMSO-d_6) δ 9.85 (s, 1H), 9.45 (s, 1H), 7.82 (dd, J = 9.4, 1.9 Hz, 1H), 7.75-7.70 (m, 3H), 7.31 (dd, J = 8.5, 7.4 Hz, 2H), 6.92 (tt, J = 7.3, 1.1 Hz, 1H); ^{13}C NMR (75 MHZ, DMSO-d_6) δ 163.6, 150.6, 140.8, 128.8, 127.6 (q, J = 5.1 Hz), 126.0 (q, J = 2.6 Hz), 123.5 (q, J = 270.9 Hz), 120.6, 116.9, 114.5, (q, J = 31.9 Hz), 113.8; IR 1606.9, 1570.2, 1334.3, 1313.4, 1111.6, 744.7 cm^{-1}; MS (ESI) *m/z* 279.1 (M+H)$^+$.

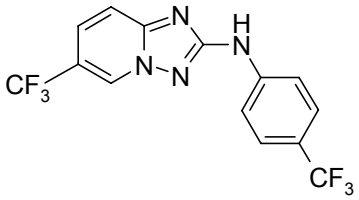


***N*-(4-methoxyphenyl)-2-amino-6-trifluoromethyl-[1,2,4]-triazolo[1,5-*a*]pyridine 3** [b,c]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (S, 1H), 9.41 (s, 1H), 7.80 (dd, J = 9.1, 1.9 Hz, 1H), 7.68 (d, 9.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.9,

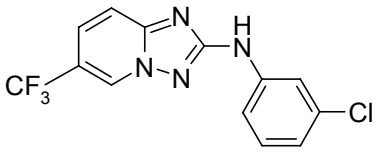
153.7, 150.7, 134.1, 127.5 (q, *J* = 5.3), 125.9 (q, *J* = 2.8 Hz), 123.7 (q, *J* = 271.7), 118.5, 114.2 (q, *J* = 34.1 Hz), 114.1, 113.5, 55.2; IR 1610.0, 1512.5, 1330.7, 1228.0, 1030.4, 822.2 cm^{-1}; MS (ESI) *m/z* 309.2 $(M+H)^+$.



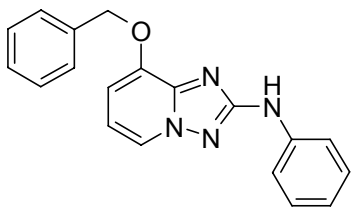
***N*-(2-methylphenyl)-2-amino-6-trifluoromethyl-[1,2,4]triazolo-[1,5-*a*]pyridine 3**[b,d]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (m, 1H), 8.78 (s, 1H), 7.81-7.78 (m, 2H), 7.68 (d, *J* = 9.3 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.01-6.96 (m, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.9, 150.9, 138.6, 130.4, 129.3, 127.4 (q, *J* = 5.1 Hz), 126.2, 125.7 (q, *J* = 2.9 Hz), 123.6 (q, *J* = 270.8), 123.3, 121.5, 114.3 (q, *J* = 33.2 Hz), 113.6, 18.1; IR 1536.7, 1326.3, 1121.3, 1038.8, 820.4, 753.9 cm^{-1}; MS (ESI) *m/z* 293.2 $(M+H)^+$.



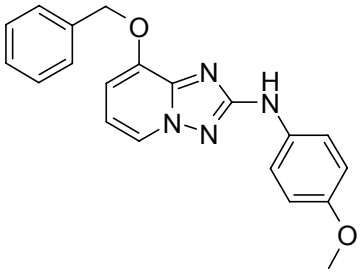
***N*-(4-trifluoromethylphenyl)-2-amino-6-trifluoromethyl-[1,2,4]triazolo[1,5-*a*]pyridine 3** [b,e]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (S, 1H), 9.51 (m, 1H), 7.92-7.85 (m, 3H), 7.80 (d, *J* = 9.3 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0, 150.6, 144.3, 127.9 (q, *J* = 5.3 Hz), 126.3 (q, *J* = 3.7 Hz), 126.2 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 262.4 Hz), 123.6 (q, *J* = 267.1 Hz), 120.5 (q, *J* = 31.1 Hz), 116.5, 114.9 (q, *J* = 35.0 Hz), 114.3; IR 1613.3, 1570.9, 1544.4, 1319.3, 1107.5, 1065.1, 840.0 cm^{-1}; MS (ESI) *m/z* 347.2 $(M+H)^+$.



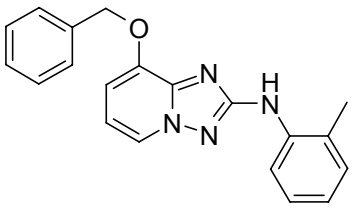
***N*-(3-chlorophenyl)-2-amino-6-trifluoromethyl-[1,2,4]-triazolo[1,5-*a*]pyridine 3** [b,g]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.51 (sept, *J* = 0.9 Hz, 1H), 7.90 (t, *J* = 2.1 Hz, 1H), 7.86 (dd, *J* = 9.2, 1.8 HZ, 1H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.58 (ddd, *J* = 8.2, 2.1, 1.0 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 6.96 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 150.6, 142.3, 133.4, 130.4, 127.9 (q, *J* = 5.1 Hz), 126.2 (q, *J* = 2.1 Hz), 123.3 (q, *J* = 283.4 Hz), 120.2, 116.0, 115.5, 114.8 (q, *J* = 34.8 Hz), 114.1; IR 1596.7, 1538.3, 1315.5, 116.5, 1039.5, 859.1, 675.8 cm^{-1}; MS (ESI) *m/z* 313.1 $(M+H)^+$.



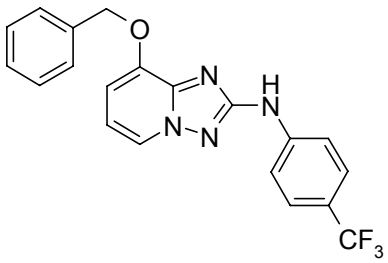
***N*-phenyl-2-amino-8-benzyloxy-[1,2,4]triazolo[1,5-*a*]pyridine 3** [c,a]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.65 (bs, 1H), 8.40 (dd, *J* = 6.8, 0.9 Hz, 1H), 7.68-7.63 (m, 2H), 7.54-7.49 (m, 2H), 7.47-7.36 (m, 3H), 7.32-7.24 (m, 2H), 7.13 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.95-6.83 (m, 2H), 5.34 (s, 2H).^{13}C NMR (75 MHz, DMSO-d_6) δ 161.5, 145.2, 143.9, 141.36, 136.4, 128.9, 128.8, 128.6, 128.5, 128.2, 127.8, 121.4,116.4, 111.9, 70.3; IR 1599.7, 1563.1, 1518.6, 1495.1, 1278.0 cm^{-1}; MS (ESI) *m/z* 317.2 $(M+H)^+$.



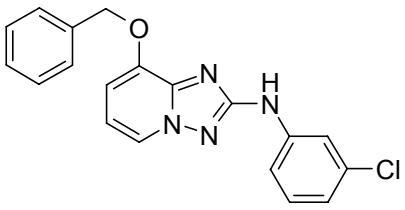
***N*-(4-methoxyphenyl)-2-amino-8-benzyloxy-[1,2,4]-triazolo[1,5-*a*]-pyridine 3**[c,c]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.36 (dd, J = 6.6, 0.9 Hz, 4H), 7.46-7.36 (m, 3), 7.10 (d, J = 7.7 Hz, 1H), 6.93-6.85 (m, 3H), 5.53 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.8, 153.2, 145.0, 144.0, 136.4, 134.9, 128.6, 128.2, 127.8, 121.3, 117.8, 114.2, 111.6, 109.4, 70.3, 55.3; IR 1601.5, 1561.9, 1506.5, 1276.9, 1226.8 cm^{-1}; MS (ESI) *m/z* 347.2 $(M+H)^+$.



***N*-(2-methylphenyl)-2-amino-8-benzyloxy-[1,2,4]triazolo-[1,5-*a*]pyridine 3**[c,d]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.34 (dd, J = 6.0, 0.8 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.55-7.46 (m, 2H), 7.45-7.35 (m, 3H), 7.20-7.05 (m, 3H), 6.94-6.84 (m, 3H), 5.31 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.2, 145.1, 144.0, 139.2, 136.2, 130.3, 128.5, 128.2, 128.0, 127.4, 126.2, 121.7, 121.2, 119.4, 111.6, 108.8, 70.3, 18.1; IR 1589.2, 1560.8, 1519.5, 1452.3, 1279.3, 1093.3 cm^{-1}; MS (ESI) *m/z* 331.2 $(M+H)^+$.

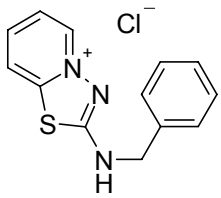


***N*-(4-trifluoromethylphenyl)-2-amino-8-benzyloxy-[1,2,4]triazolo[1,5-*a*]pyridine 3**[c,e]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.44 (dd, J = 6.7, 0.8 Hz, 1H), 7.83 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.67-7.60 (m, 2H), 7.48-7.30 (m, 3H), 7.16 (d, J = 7.9 Hz, 1H), 6.96 (dd, 7.9, 6.7 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.8, 145.3, 144.8, 143.8, 136.3, 128.5, 128.1, 127.7, 126.2 (q, J = 3.8 Hz), 124.9 (q, J = 266.9 Hz), 121.4, 119.9 (q, J = 30.6 Hz), 116.0, 112.3, 109.6, 70.3; IR 1615.4, 1563.1, 1531.7, 1427.1, 1319.8, 1257.0, 1110.5 cm^{-1}; MS (ESI) *m/z* 385.2 $(M+H)^+$.



***N*-(3-chlorophenyl)-2-amino-8-benzyloxy-[1,2,4]-triazolo[1,5-*a*]pyridine 3**[c,g]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.45 (dd. J = 6.7, 0.9 Hz, 1H), 7.82 (t, J = 2.0 Hz, 1H), 7.60-7.56 (m, 3H), 7.45-7.35 (m, 3H), 7.30 (t, J = 8.1 Hz, 1H), 7.50 (dd, J = 8.0, 0.8 Hz, 1H), 6.98-6.88 (m, 2H), 5.35 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ

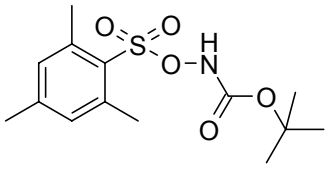
160.9, 145.2, 143.8, 142.8, 136.3, 133.3, 130.4, 128.5, 128.1, 127.7, 121.5, 119.5, 115.5, 114.9, 112.1, 109.6; IR 1596.7, 1556.9, 1519.8, 1485.3, 1275.7 cm^{-1}; MS (ESI) *m/z* 351.2 $(M+H)^+$.



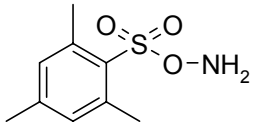
2-Benzylamino-[1,3,4]thiadiazolo[3,2-*a*]pyridin-4-ylium chloride (**112**) Plausible structure, not fully characterized. In a screw cap vial, **109d** ($MesSO_3^-$) (0.16 mmol, 1.0 eq) was dissolved in DMF (0.2 mL) and a solution of benzylisothiocyanate (0.16 mmol, 1.0 eq) in DCM (0.8 mL) was added followed by DIPEA (141 µL. 0.81 mmol, 5.0 eq). The mixture was stirred at rt for 16 hr. The solvent was removed under reduced pressure and the crude was subjected to NMR analysis. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (t, *J* = 5.7 Hz, 1H), 8.15 (bs, 2H), 7.75 (t, *J* = 8.2 Hz, 1H), 7.50-7.20 (m, 6H), 6.90 (dd, *J* = 8.7, 1.2 Hz, 1H), 4.68 (d, *J* = 5.7 Hz, 2H). After D2O exchange ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (t, *J* = 8.2 Hz, 1H), 7.50-7.20 (m, 6H), 6.90 (dd, *J* = 8.7, 1.2 Hz, 1H), 4.66 (s, 2H).

7.5. Chapter 5

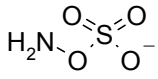
- Aminating reagents



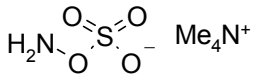
***Tert*-butyl *N*-(mesitylsulfonoxy)carbamate** (**134**) In a 3 neck round-bottom flask and under nitrogen, 2-mesitylenesulfonyl chloride (2.0 g, 9.14 mmol, 1.0 equiv) was dissolved in anhyd THF (10 mL) and *tert*-butyl *N*-hydroxycarbamate (1.2 g, 9.14 mmol, 1.0 equiv) was added. The solution was chilled to 0 °C before adding a solution of triethylamine (1.53 mL, 11.0 mmol, 1.2 equiv) in THF (10 mL). Triethylammonium chloride precipitated out and the mixture was stirred at 0 °C for 30 min and then it was allowed to reach rt After 2 hr, Solvent was evaporated under reduced pressure and the residue was taken up in water and extracted with DCM (3 x 50 mL). The organic phase was washed with $NaHCO_3$ sat, brine and dried over MgSO4 anhy. After solvent removal 2.46 g of a white solid was obtained (85%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.13 (s, 2H), 2.57 (s, 6H), 2.29 (s, 3H), 1.24 (s, 9H); MS (ESI) *m/z* = 215.8 $(M\text{-}Boc)^+$; HPLC t_R = 4.68 min.



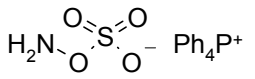
***O*-(Mesitylensulfonylhydroxylamine** (**MSH**) In round-bottom flask, **134** (1.5 g, 4.76 mmol, 1.0 equiv) was placed and cooled to 0 °C. Neat TFA (5.0 mL) was added and the reaction was stirred at 0 °C for 1hr. Water (50 mL) was added and the resulting white solid was filtered and washed with water several times until pH of the eluent was 7. The solid was dried under reduced pressure at rt to afford 1.0 g of the title compound (97%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (bs, 2H), 6.76 (s, 2H), 2.50 (s, 6H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 142.4, 136.4, 135.9, 129.9, 26.3, 22.7, 20.2: MS (ESI) *m/z* = 198.8; HPLC t_R = 3.57 min.



Tetrabutylammonium hydroxylamine *O*-sulfonate (**TBAHS**). Hydroxylamine-*O*-sulfonic acid (HSA) (3.0 g, 23.9 mmol; 1.0 equiv) was dissolved in water (5 mL) and a solution of tetrabutylammonium hydroxide 40% (15.6 mL; 23.9 mmol; 1.0 equiv) in water was added. The mixture was extracted with DCM, the combined extracts were dried over MgSO4 anhy, filtered and the solvent was evaporated under reduced pressure to give a white semi-solid which was dried for 3 days under reduced pressure at 40 °C over $CaCl_2$ to afford 8.0 g (94%) of the title compound as a white solid. Purity based on iodometric titration: >95%



Tetramethylammonium hydroxylamine *O*-sulfonate (**TMAHS)**. In a round bottom flask, hydroxylamine-*O*-sulfonic acid (2.26 g, 20.0 mmol, 1.0 equiv) was dissolved in water (30 mL) and tetramethylammonium hydroxide (7.14 mL, 2.80 M, 20.0 mmol, 1.0 equiv) was added to give pH 9. Water was added (150 mL) (otherwise it could not be lyophilized since it melted) and the mixture was frozen and then lyophilized to afford 3.7 g (94%) of the title compound as a white solid. Purity based on iodometric titration: 70%.

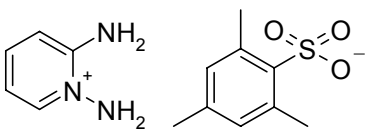


Tetraphenylphosphonium hydroxylamine *O*-sulfonate (**TPPHS)**. In a round bottom flask, tetraphenylphosphonium chloride (3.75 g, 10.0 mmol, 1.0 equiv) was dissolved in water (30 mL) and a solution of hydroxylamine-*O*-sulfonic acid (1.36 g, 0.01 mol, 1.2 equiv) in water (10 mL) was added (pH = 1) followed by potassium hydroxide (1.0 M) to reach pH 7. The cloudy solution was extracted with DCM (3 x 70 mL) and the combined extracts were dried over MgSO4 anhyd, filtered and evaporated under reduced pressure to give a white solid (53%). Iodometric titration gave 98% purity.

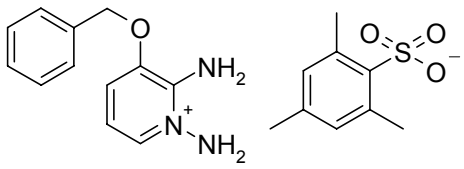
- **<u>Iodometric titration</u>** of hydroxylamine *O*-sulfonate salts.

Hydroxylamine *O*-sulfonate salt was dissolved in acetic acid (2 mL) and a solution of KI (10%, 3 mL) was added followed by THF (5 mL). The resulting iodine was titrated using a solution of $Na_2S_2O_3$ (0.15 M)

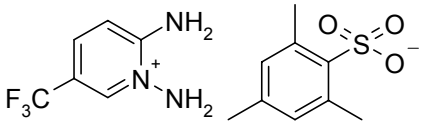
- **General procedure for 1,2-diaminopyridinium mesitilensulfonates** (**109** ($MesSO_3^-$)). 2-aminopyridine derivative (**108**) (2.0 mmol, 1.0 equiv) was dissolved in DCM (2mL) and the solution was chilled to 0 °C before adding dropwise a solution of **MSH** (430 mg, 2.0 mmol, 1.0 equiv) in DCM (6 mL). The mixture was allowed to reach rt and stirred 15 min. Et_2O was added to precipitate the product (if needed) and the resulting solid was filtered, washed with Et_2O and dried under vaccum at rt. (**109a** ($MesSO_3^-$), 81%; **109b** ($MesSO_3^-$), 85%; **109c** ($MesSO_3^-$), 68%; **109d** ($MesSO_3^-$), 53%)



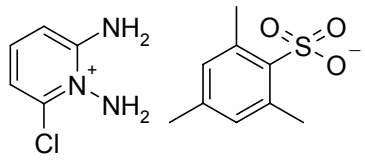
1,2-Diaminopyridinium mesitylensulfonate (**109a** ($MesSO_3^-$)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (bs, 2H), 8.02 (dd, J = 6.8, 1.0 Hz, 1H), 7.80 (ddd, J = 8.8, 7.2, 1.6 Hz, 1H), 7.05 (dd, J = 8.9, 1.1 Hz, 1H), 6.83, (td, J = 6.9, 1.5 Hz, 1H), 6.77 (s, 2H), 6.75 (s, 2H), 2.49 (s, 6H), 2.17 (s, 3H).



3-Benzyloxy-1,2-diaminopyridinium mesitylensulfonate (**109b** ($MesSO_3^-$)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (bs, 2H), 7.65 (d, J = 6.1 Hz, 1H), 7.55-7.49 (m, 2H), 7.48-7.35 (m, 4H), 6.81 (s, 2H), 6.80-6.72 (m, 3H), 5.32 (s, 2H), 2.49 (s, 6H), 2.16 (s, 3H).



5-Trifluoromethyl-1,2-diaminopyridinium mesitylensulfonate (**109c** ($MesSO_3^-$)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.22 (bs, 2H), 8.84 (s, 1H), 8.08 (dd, J = 9.3, 2.1 Hz, 1H), 7.21 (d, J = 9.4 Hz, 1H), 6.84 (s, 2H), 6.74 (s, 2H), 2.49 (s, 6H), 2.17 (s, 3H).



6-Chloro-1,2-diaminopyridinium mesitylensulfonate (**109d** ($MesSO_3^-$)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (bs, 2H), 7.75 (dd, J = 9.0, 7.6 Hz, 1H), 7.11 (dd, 7.5, 1.4 Hz, 1H), 7.03 (dd, 8.9, 1.4 Hz, 1H), 6.74 (s, 2H), 6.50 (s, 2H), 2.49 (s, 6H), 2.17 (s, 3H).

❑ **General procedure for N-amination of 2-aminopyridines** (**109**) **with TBAHS** . In a 50 mL round bottom flask and under nitrogen, 2-aminopyridine derivative (10.0 mmol, 1.0 equiv) was dissolved in TFE (20 mL) and **TBAHS** (3.7 g, 10.0 mmol, 1.0 equiv) was added. The mixture was heated at reflux for 16 hr. Conversion: **109a**, 84%; **109b**, 91%; **109c**, 80%.

Isolation method 1 (as ½ SO_4^{2-}). ACN was added to induce the precipitation and the mixture was kept at 5 °C for 16 hr. The resulting solid was filtered, washed with ACN and dried under reduced pressure at rt (**109a** (½ SO_4^{2-}), 79%; **109b** (½ SO_4^{2-}), 64%; **109c** (½ SO_4^{2-}), 43%).

109a (½ SO_4^{2-}). ^{1}H NMR (300 MHz, D_2O) δ 7.83 (ddd, J = 6.9, 1.5, 0.7 Hz, 1H), 7.72-7.64 (m, 1H), 6.97 (ddd, J = 9.0, 1.5, 0.7 Hz, 1H), 6.73 (td, J = 7.0, 1.5 Hz, 1H).

109b (½ SO_4^{2-}). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.30 (bs, 2H), 7.70-7.45 (m, 3H), 7.45-7.30 (m, 3H), 7.19 (d J = 7.9 Hz, 1H), 7.05 (bs, 2H), 6.47 (t, J = 7.3 Hz, 1H), 5.24 (S, 2H).

109c (½ SO_4^{2-}). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (bs, 2H), 8.28 (s, 1H), 7.57 (dd, J = 9.5, 2.1 Hz, 1H), 6.91 (d, J = 9.5 Hz, 1H), 6.47 (bs, 2H).

Isolation method 2 (as PF_6^-). i) TFE was evaporated and the residue was taken up in water (50 mL) ii) A solution of KPF_6 (1.84 g, 10.0 mmol, 1.0 equiv) in water (50 mL) was added. The

resulting solid (tetrabutylammonium hexafluorophosphate) was removed by filtration. iii) The mother liquor was extracted with DCM and the organic extracts were discarded (contained unreacted **108**) iv) A solution of KPF_6 (1.84 g, 10.0 mmol,1.0 equiv) in water (10 mL) was added and the mixture was kept at 5 °C for 16 hr. v) The resulting needles were filtered and dried under reduced pressure to give the title compound as a solid. **109a** (PF_6^-), did not precipitate; **109b** (PF_6^-), 67%; **109c** (PF_6^-), 46%.

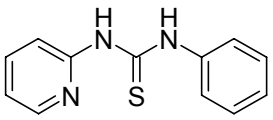
109b (PF_6^-). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (s, 2H), 7.64 (dd, *J* = 6.9, 0.9 Hz, 1H), 7.58-7.48 (m, 2H), 7.46-7.32 (m, 4H), 6.84-6.72 (m, 3H), 5.33 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.4, 143.0, 135.3, 132.1, 128.5, 128.4, 127.9, 117.4, 110.4, 70.8; ^{31}P NMR (121 MHz, DMSO-d_6) δ 144.19 (sept, *J* = 711.3 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ 70.12 (d, *J* = 711.0 Hz); MS (ESI) *m/z* 216.1 $(M)^+$

109c (PF_6^-). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (bs, 2H), 8.63 (s, 1H), 8.07 (dd, *J* = 9.4, 2.1 hz, 1H), 7.19 (d, *J* = 9.4 Hz, 1H), 6.79 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.5, 140.4 (q, *J* = 5.4 Hz), 136.1 (q, *J* = 2.7 Hz), 122.4 (q, *J* = 270.1 Hz), 115.4, 113.3 (q, *J* = 35.3 Hz); ^{31}P NMR (121 MHz, DMSO-d_6) δ 144.2 (sept, *J* = 711.1 Hz); ^{19}F NMR (282 MHz, DMSO-d_6) δ -61.1, -70.2 (d, *J* = 709.4 Hz). MS (ESI) *m/z* 178.1 $(M)^+$.

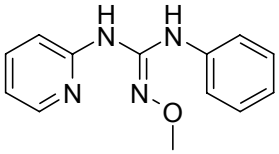
Isolation method 3 (as $(CF_3SO_2)_2N^-$). The same procedure as method 2 but using $(CF_3SO_2)_2NLi$ instead of KPF_6. At stage v), the product did not precipitated so it was extracted with DCM. The combined extracts were evaporated under reduced pressure and the resulting solid was dried under reduced pressure at rt to give the title compound. **109b** $(CF_3SO_2)_2N^-$, 72%.

109b $(CF_3SO_2)_2N^-$). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (s, 2H), 7.64 (dd, *J* = 6.9, 0.9 Hz, 1H), 7.58-7.48 (m, 2H), 7.46-7.32 (m, 4H), 6.84-6.72 (m, 3H), 5.33 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.4, 143.0, 135.3, 132.1, 128.5, 128.4, 127.9, 117.4, 110.4, 70.8; ^{19}F NMR (282 MHz, DMSO-d_6) δ -78.72.

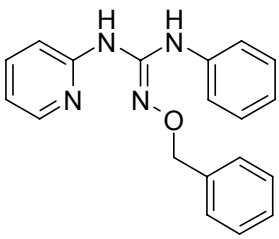
7.6. Chapter 6



1-(Pyridin-2-y)l-3-phenyl thiourea (**150**). In a 250 mL round bottom flask and under nitrogen, 2-aminopyridine (9.41 g, 100 mmol, 1.0 eq) was dissolved in THF (50 mL) and phenyl isothiocyanate (14.19 g, 105 mmol, 1.05 eq) was added. The mixture was heated at reflux for 1 hr. Solvent was evaporated under reduced pressure and the resulting solid was triturated with heptane, filtered and dried to afford the title compound as a white solid (21.52 g , 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.85 (s, 1H), 10.90 (s, 1H), 8.32 (dd, J = 5.1, 1.6 Hz, 1H), 7.88-7.78 (m, 1H), 7.71 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.27 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.10 (dd, J = 6.6, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.3, 153.6, 145.6, 139.4, 138.8, 128.5, 125.5, 124.2, 118.2, 112.9; MS (ESI) *m/z* = 230 $(M+H)^+$; HPLC t_R = 4.03 min.

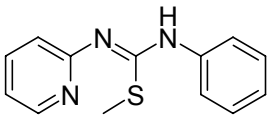


***N*''-Methoxy-*N*-phenyl-*N*'-pyridin-2-ylguanidine** (**153**). In a 50 mL round bottom flask, N-pyridin-2-yl-N'-phenylthiourea (**150**) (500.0 mg, 2.18 mmol, 1.0 equiv) was dissolved in DCM (40.0 mL) and EDC hydrochloride (1.04 g, 5.45 mmol, 2.5 equiv) was added followed by triethylamine (0.76 mL; 5.45 mmol, 2.5 equiv) and *O*-methylhydroxylamine hydrochloride (0.45 g, 5.45 mmol, 2.50 equiv) The mixture was stirred at rt for 16 hr and water (20 mL) was added and an emulsion was formed. Brine (10 mL) was added to help the layer separation, the organic phase was separated, dried over MgSO4 anhyd, filtered and concentrated. The residue was triturated with heptane, filtered and dried under reduced pressure to afford the title compound as a white solid (637 mg, 69%).Mixture of two tautomers (1:0.1) Major: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.94 (s, 1H), 8.29 (dd, J = 55, 1.2 Hz, 1H), 7.71 (ddd, J = 8.8, 6.9, 1.6 Hz, 1H), 7.55-7.49 (m, 2H), 7.58-7.49 (m, 3H), 7.00-6.80 (m, 2H), 3.74 (s, 3H). Minor: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.28 (s, 1H), 8.00 (ddd, J = 4.9, 1.9, 0.8 Hz, 1H), 7.55-7.49 (m, 2H), 7.20-7.05 (m, 2H), 7.05-7.00 (m, 3H), 3.70 (s, 3H); MS (ESI) *m/z* 243.1 $(M+H)^+$;



***N*''-(benzyloxy)-*N*-phenyl-*N*'-pyridin-2-ylguanidine** (**154**). In a 1 L round bottom flask, N-pyridin-2-yl-N'-phenylthiourea (**150**) (14.42 g, 62.89 mmol, 1.0 equiv) was dissolved in DCM (700.00 mL) and n-(3-dimethylaminopropyl)-n'-ethylcarbodiimide (EDC) hydrochloride (18.08 g, 94.33 mmol, 1.5 equiv) was added followed by triethylamine (21.79 mL; 157.21 mmol, 2.5 equiv) and o-benzylhydroxylamine (8.52 g, 69.17 mmol, 1.10 equiv) The mixture was stirred at rt for 16

hr. The reaction mixture was washed with HCl 0.25 M (3 x 200 mL) to reach pH = 5, then neutralized with brine, dried over MgSO4 anhy, filtered and concentrated under reduced pressure. The resulting yellow oil was triturated with heptane to give a white solid that was filtered and dried under reduced pressure to afford the title compound as a white solid (19.0 g, 94%). Mixture of two tautomers (1:0.13) Major: ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.14 (s, 1H), 8.98 (s, 1H), 8.25 (d, J = 4.0 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 7.55-7.10 (m, 10H), 7.00-7.80 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.9, 147.2, 145.8, 140.2, 138.9, 138.7, 128.6, 128.13, 128.09, 127.4, 120.5, 118.1, 116.6, 112.8, 74.8; Minor ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.35 (s, 1H), 8.05-8.95 (m, 1H), 7.55-7.10 (m, 8H), 7.10-7.00 (m, 2H), 7.00-6.8 (m, 2H), 6.70-6.60 (m, 1H); MS (ESI) *m/z* 319.2 $(M+H)^+$; HPLC t_R = 3.08 min.



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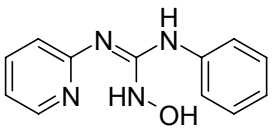
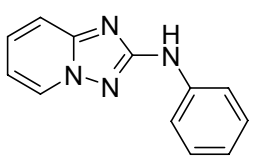
***N*-pyridin-2-yl-*N*'-phenyl-*N*''-methylisothiourea hydroiodide salt** (**161**). In a dry round bottom flask fitted with a condenser and under nitrogen, N-pyridin-2-yl-N'-phenylthiourea (**150**) (5.0 g, 21.8 mmol, 1.0 eq) was dissolved in THF (25 mL), methyliodide (2.7 mL, 2.0 eq) was added and the mixture was heated at 40 °C for 3 hr. Then, methyliodide (2.7 mL, 2.0 eq) was added and the mixture was heated for 3 hr more. The mixture was allowed to reach r.t and the resulting solid was filtered, washed with THF (4 mL) and dried under reduced pressure overnight to give the product as a white solid (7.91g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (d, J = 5.5 Hz, 1H), 8.24 (t, J = 7.7 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.6 Hz, 3H), 7.19 (t, J = 7.4 Hz, 1H) ;^{13}C NMR (75 MHz, DMSO-d_6) δ 161.8, 155.0, 145.3, 139.4, 138.2, 128.9, 125.7, 123.0, 119.5, 118.2, 15.1; MS (ESI) *m/z* = 244 $(M+H)^+$; HPLC t_R = 2.68 min.

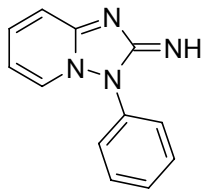


***N*''-(Hydroxy)-*N*-phenyl-*N'*-pyridin-2-ylguanidine** (**148**). In a dry round bottom flask and under nitrogen, N-pyridin-2-yl-N'-phenyl-N''-methylisothiourea hydroiodide salt (**161**). (1.0g, 2.70 mmol, 1.0 equiv), sodium thiosulfate (0.43 g, 2.70 mmol, 1.0 equiv) and hydroxylamine hydrochloride (0.75 g, 10.78 mmol, 4.0 equiv) were suspended in anhyd MeOH (20.00 mL) and n-ethyldiisopropylamine (1.9 mL; 10.78 mmol, 4.0 equiv) was slowly added. The mixture was stirred at rt for 40 min (0% **161**, 84% **148**, 7% **162**). Solvent was evaporated under reduced pressure and the residue was taken up in EtOAc (150 mL). The organic phase was washed with $NaHCO_3$ sat (30 mL), brine, dried over MgSO4 anhyd and filtered (80% **161**, 8% **162**). After evaporation of solvent a yellow solid was obtained (79% **161**, 9% **162**) that was placed in a round bottom flask fitted with a condenser. The system was flushed with argon and the solid was recrystallized from DCM. The mixture wa allowed to reach rt and the resulting solid was filtered and dried under reduced pressure to afford the title compound as a pale yellow

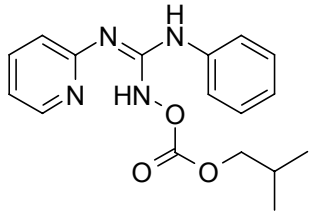
solid (98% **161**, 1% **162**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.26 (s, 1H), 8.92 (s, 1H), 8.23 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.72-7.64 (m, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.1, 147.1, 145.8, 140.7, 138.7, 128.6, 120.2, 117.9, 116.2, 112.6;MS (ESI) *m/z* 229.1(M+H)$^+$.



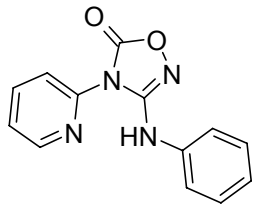
***N*-phenyl 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine 3**[a,a] (from compound **154**) In a 500 mL round bottom flask and under nitrogen, potassium *tert*-butoxide (4.26 g, 38.01 mmol, 1.1 equiv) was suspended in anhyd THF (200 mL) and a solution of N''-(benzyloxy)-N-phenyl-N'-pyridin-2-ylguanidine (**154**) (11.00 g, 34.55 mmol, 1.00 equiv) in THF (100 mL) was added. The greenish mixture was heated at reflux for 1 hr and the mixture was allowed to reach r.t (74% **3**[a,a], 20% **166**). Water (50 mL) was added to give pH 14 and HCl (1M) was added to reach pH 6-7. THF was evaporated and the resulting aqueous phase was extracted with EtOAc (3 x 200 mL). The combined extracts were washed with brine, dried over MgSO4 anhyd, filtered and concentrated under reduced pressure. Both compounds were separated by chromatography column on silica gel (4.2 g, 78%). Compound **3**[a,a]: NMR data was identical to the data obtained with the prevuous route. HPLC t_R = 2.49 min; UPLC t_R = 1.01 min; MS (ESI) *m/z* 211.1 (M+H)$^+$.



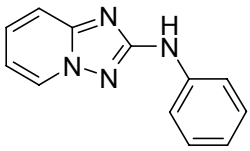
3-Phenyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-ylideneamine (**166**). Isolated as a side-product from the previous reaction. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.26 (s. 1H), 9.26 (s, 1H), 8.36 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.62 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.59-7.53 (m, 2H), 7.35-7.27 (m, 2H), 7.24 (ddd, *J* = 9.4, 6.5, 1.1, 1H), 6.95-6.86 (m, 2H); HPLC t_R = 1.86 min; UPLC t_R = 0.77 min; MS (ESI) *m/z* 211.1 (M+H)$^+$.



***N*-[(isobutoxycarbonyl)oxy]-*N*'-phenyl-*N*''-pyridin-2-yl-guanidine** (**169**). In a dry round bottom flask and under nitrogen, N''-(Hydroxy)-N-phenyl-N'-pyridin-2-ylguanidine **148** (150 mg, 0.66 mmol, 1.0 equiv) was suspended in ACN (4.5 mL) and isobutylchloroformate (128 uL, 0.99 mmol, 1.5 equiv) was added to give a solution followed by TEA (137 µL, 0.99 mmol, 1.5 eq). After 5 min, water was added to induce the precipitation and the slurry was stirred for 10 min. The resulting solid was filtered, washed with water dried under reduced pressure to give the title compound as a white solid (138 mg, 64% yield, 89% pure). MS (ESI) *m/z* 329.2 (M+H)$^+$. It was used in the next step without further purification since the impurities were 6% **168** and 5% **3**[a,a].



3-Phenylamino-4-pyridin-2-yl-4*H*-[1,2,4]oxadiazol-5-one (**168**). In a dry round bottom flask and under nitrogen, N-hydroxy-N'-phenyl-N''-pyridin-2-ylguanidine **148** (328.0 mg, 1.44 mmol, 1.0 equiv) was suspended in ACN (6 mL) and the mixture was cooled down to 0 °C before adding dropwise a solution of isobutyl chloroformate (224.30 µl; 1.72 mmol, 1.20 equiv) in ACN (2 mL) followed by a solution of triethylamine (235.80 µl; 1.72 mmol, 1.20 equiv) in ACN (2 mL). After 30 min at such temperature, the ice bath was romoved and the mixture was allowed to reach rt After 3 hr at rt, water (15 mL) was added and the mixture was stirred for 15 min. The resulting solid was filtered, washed with water (1 mL) and dried under reduced pressure to give the title compound as a white solid (365 mg, 79%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.67 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 8.14 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 8.02 (dt, *J* = 8.3, 0.8 Hz, 1H), 7.57 (ddd, *J* = 7.3, 4.9, 0.8 Hz, 1H), 7.51 (dd, *J* = 8.8, 1.1 Hz, 2H), 7.40-7.32 (m, 2H), 7.06 (tt, *J* = 7.3, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.1. 152.9, 148.3, 146.7, 140.1, 137.8, 129.1, 123.7, 122.8, 119.0, 117.8; MS (ESI) *m/z* 255.1 $(M+H)^+$.



***N*-phenyl 2-amino-[1,2,4]triazolo[1,5-*a*]pyridine** (from compound **168**). In a round bottom flask and under nitrogen, 3-phenylamino-4-pyridin-2-yl-4*H*-[1,2,4]oxadiazol-5-one (**168**) (365 mg, 1.44 mmol, 1.0 equiv) was dissolved in EtOH (4 mL) and sodium hydroxyde (aq, 0.1 M, uL, 0.14 mmol, 0.1 equiv) was added. The mixture was heated at reflux for 3 hr. The solvent was evaporated under reduced pressure and the resulting solid was dissolved in EtOAc (20 mL). The organic solution was washed with water, brine, dried over MgSO4 anhyd, filtered and concentrated under reduced pressure to give the title compound (298 mg, 99%) as a pale yellow solid. NMR data was identical to the data obtained with the previous routes.

8. References

(1) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-54.

(2) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815-4195.

(3) *ARGONAUT catalogue.*

(4) Teulade, J. C.; Grassy, G.; Escale, R.; Chapat, J. P. *J. Org. Chem.* **1981**, *46*, 1026-1030.

(5) Rees, C. W.; Smith, D. I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1159-63.

(6) Kaminski, J. J.; Hilbert, J. M.; Pramanik, B. N.; Solomon, D. M.; Conn, D. J.; Rizvi, R. K.; Elliott, A. J.; Guzik, H.; Lovey, R. G.; et al. *J. Med. Chem.* **1987**, *30*, 2031-46.

(7) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661-663.

(8) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635-3638.

(9) Bienayme, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234-2237.

(10) Blackburn, C.; Guan, B. *Tetrahedron Lett.* **2000**, *41*, 1495-1500.

(11) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665-7669.

(12) Page, P. WO patent 2001037983, 2001.

(13) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269-2271.

(14) Ireland, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2003**, *44*, 4369-4371.

(15) Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469-5472.

(16) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091-2158.

(17) Habashita, H.; Kokubo, M.; Hamano, S.-I.; Hamanaka, N.; Toda, M.; Shibayama, S.; Tada, H.; Sagawa, K.; Fukushima, D.; Maeda, K.; Mitsuya, H. *J. Med. Chem.* **2006**, *49*, 4140-4152.

(18) Estep, K. G.; Neipp, C. E.; Stephens Stramiello, L. M.; Adam, M. D.; Allen, M. P.; Robinson, S.; Roskamp, E. J. *J. Org. Chem.* **1998**, *63*, 5300-5301.

(19) Bhattacharyya, S.; Gooding, O. W.; Labadie, J. *Tetrahedron Lett.* **2003**, *44*, 6099-6102.

(20) Gaggini, F.; Porcheddu, A.; Reginato, G.; Rodriquez, M.; Taddei, M. *J. Comb. Chem* **2004**, *6*, 805-810.

(21) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595-8.

(22) Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147-57.

(23) Heinisch, L. *Zeitschrift fuer Chemie* (Leipzig) **1970**, *10*, 188.

(24) Schneller, S. W.; Bartholomew, D. G. *J. Heterocycl. Chem.* **1978**, *15*, 439-44.

(25) Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Hamilton, G. S. *J. Heterocycl. Chem.* **2003**, *40*, 191-193.

(26) Reimlinger, H.; Lingier, W. R. F.; Vandewalle, J. J. M.; Goes, E. *Synthesis* **1970**, *2*, 433.

(27) Koren, B.; Stanovnik, B.; Tisler, M. *Monatsh. Chem.* **1988**, *119*, 83-90.

(28) Brown, R. E.; Burkamp, F.; Doughty, V. A.; Fletcher, S. R.; Hollingworth, G. J.; Jones, B. A.; Sparey, T. J. WO patent 2004074290, 2004.

(29) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589-636.

(30) Molina, P.; Alajarin, M.; Ferao, A. *Heterocycles* **1986**, *24*, 3363-8.

(31) Kiffer, D.; Levy, R. *C. r. séances Acad. Sci., Ser C, Sci. chim.* **1968**, *267*, 1730-2.

(32) Omar, A. M. M. E.; El-Dine, S. A. S.; Hazzaa, A. A. B. *Pharmazie* **1975**, *30*, 85-6.

(33) Hamley, P.; Tinker, A. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1573-6.

(34) Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1925-33.

(35) Sasikumar, T. K.; Li, Q.; Burnett, D. A.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'Neill, K.; Spar, B. D.; Weig, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5427-5431.

(36) Carpenter, R. D.; DeBerdt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006**, *8*, 907-914.

(37) AboulWafa, O. M.; Omar, A. M. M. E. *Sulfur Lett.* **1992**, *14*, 181-8.

(38) Cee, V. J.; Downing, N. S. *Tetrahedron Lett.* **2006**, *47*, 3747-3750.

(39) Garin, J.; Melendez, E.; Merchan, F. L.; Merino, P.; Orduna, J.; Tejero, T. *J. Heterocycl. Chem.* **1991**, *28*, 359-63.

(40) Dai, Y.; Guo, Y.; Frey, R. R.; Ji, Z.; Curtin, M. L.; Ahmed, A. A.; Albert, D. H.; Arnold, L.; Arries, S. S.; Barlozzari, T.; Bauch, J. L.; Bouska, J. J.; Bousquet, P. F.; Cunha, G. A.; Glaser, K. B.; Guo, J.; Li, J.; Marcotte, P. A.; Marsh, K. C.; Moskey, M. D.; Pease, L. J.; Stewart, K. D.; Stoll, V. S.; Tapang, P.; Wishart, N.; Davidsen, S. K.; Michaelides, M. R. *J. Med. Chem.* **2005**, *48*, 6066-6083.

(41) Heinelt, U.; Schultheis, D.; Jaeger, S.; Lindenmaier, M.; Pollex, A.; Beckmann, H. S. G. *Tetrahedron* **2004**, *60*, 9883-9888.

(42) Hwang, J. Y.; Gong, Y.-D. *J. Comb. Chem.* **2006**, *8*, 297-303.

(43) Qian, X.; Xu, X.; Li, Z.; Li, Z.; Song, G. *J. Fluorine Chem.* **2004**, *125*, 1609-1620.

(44) Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257-3260.

(45) Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2006**, *71*, 9548-9551.

(46) Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, *67*, 107-152.

(47) Weinshenker, N. M.; Shen, C. M. *Tetrahedron Lett.* **1972**, *13*, 3281-3284.

(48) Crosignani, S.; White, P. D.; Linclau, B. *J. Org. Chem.* **2004**, *69*, 5897-5905.

(49) Lange, U. E. W. *Tetrahedron Lett.* **2002**, *43*, 6857-6860.

(50) Guisado, O.; MartInez, S.; Pastor, J. *Tetrahedron Lett.* **2002**, *43*, 7105-7109.

(51) Buckman, B. O.; Morrissey, M. M.; Mohan, R. *Tetrahedron Lett.* **1998**, *39*, 1487-1488.

(52) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707-721.

(53) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 575-6.

(54) Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 3401-3404.

(55) Crosignani, S.; Gonzalez, J.; Swinnen, D. *Org. Lett.* **2004**, *6*, 4579-4582.

(56) Donati, D.; Morelli, C.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **2004**, *69*, 9316-9318.

(57) Donati, D.; Morelli, C.; Taddei, M. *Tetrahedron Lett.* **2005**, *46*, 2817-2819.

(58) Crosignani, S.; Swinnen, D. *J. Comb. Chem* **2005**, *7*, 688-696.

(59) Measured in the analytical laboratory of Merck Serono to the 4-methoxy derivative.

(60) Albert, A.; Barlin, G. B. *J. Chem. Soc.* **1959**, 2384-96.

(61) Katritzky, A. R. *Tetrahedron* **1980**, *36*, 679-699.

(62) Katritzky, A. R.; Musumarra, G.; Sakizadeh, K. *Tetrahedron Lett.* **1980**, *21*, 2701-2703.

(63) Katritzky, A. R.; Musumarra, G.; Sakizadeh, K.; Misic-Vukovic, M. *J. Org. Chem.* **1981**, *46*, 3820-3823.

(64) Katritzky, A. R.; El-Mowafy, A. M.; Musumarra, G.; Sakizadeh, K.; Sana-Ullah, C.; El-Shafie, S. M. M.; Thind, S. S. *J. Org. Chem.* **1981**, *46*, 3823-3830.

(65) Katritzky, A. R.; Musumarra, G.; Sakizadeh, K. *J. Org. Chem.* **1981**, *46*, 3831-3835.

(66) Miller, M. W.; Vice, S. F.; McCombie, S. W. *Tetrahedron Lett.* **1998**, *39*, 3429-3432.

(67) Lee, H. B.; Balasubramanian, S. *Org. Lett.* **2000**, *2*, 323-326.

(68) Zhang, D.; Tasker, A.; Sham, K. K. C.; Chakrabarti, P. P.; Falsey, R. J.; Herberich, B. J.; Pettus, L. H.; Rzasa, R. M. WO patent 2008045393, 2008.

(69) Luethy, C.; Hall, R. G.; Edmunds, A.; Riley, S.; Diggelmann, M. WO patent 2008006540, 2008.

(70) Alajarin, M.; Molina, P.; Soler, A. *An. Quim.* **1980**, *76*, 207-10.

(71) Vercek, B.; Ogorevc, B.; Stanovnik, B.; Tisler, M. *Monatsh. Chem.* **1983**, *114*, 789-98.

(72) Nettekoven, M.; Puellmann, B.; Schmitt, S. *Synthesis* **2003**, 1649-1652.

(73) Yamazaki, C.; Miyamoto, Y.; Sakima, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 825-8.

(74) Coleman, G. H.; Hauser, C. R. *J. Am. Chem. Soc.* **1928**, *50*, 1193-1196.

(75) Sisler, H. H.; Neth, F. T.; Drago, R. S.; Yaney, D. *J. Am. Chem. Soc.* **1954**, *76*, 3906-3909.

(76) Marckwald, W.; Wille, M. *Ber. Dtsch. Chem. Ges. B* **1923**, *56B*, 1319-25.

(77) Raschig, F. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 4580-4588.

(78) Coleman, G. H.; Johnson, H. L. *Inorganic Syntheses (McGraw-Hill Book Co., Inc., New York, N.Y.)* **1939**, 59-62.

(79) Goehring, R. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. ed.; Wiley: New York, 1995; Vol. 2, p 1052-1053.

(80) Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970**, *70*, 639-665.

(81) Hynes, J., Jr.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D., Jr.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368-1371.

(82) Bhattacharya, A.; Patel, N. C.; Plata, R. E.; Peddicord, M.; Ye, Q.; Parlanti, L.; Palaniswamy, V. A.; Grosso, J. A. *Tetrahedron Lett.* **2006**, *47*, 5341-5343.

(83) Palenik, G. J.; Qian, K.; Koziol, A. E.; Sisler, H. H. *Inorg. Chem.* **1990**, *29*, 4016-4018.

(84) Omietanski, G. M.; Sisler, H. H. *J. Am. Chem. Soc.* **1956**, *78*, 1211-1213.

(85) Matsuguma, H. J.; Audrieth, L. F. *Inorganic Syntheses (McGraw-Hill Book Co., Inc., New York, N.Y.)* **1957**, *5*, 122-5.

(86) Wallace, R. G. *Org. Prep. Proced. Int.* **1982**, *14*, 265-7, 269-307.

(87) Goesl, R.; Meuwsen, A. *Org. Synth.* **1963**, *43*, 1-3.

(88) Potts, K. T.; Burton, H. R.; Bhattacharyya, J. *J. Org. Chem.* **1966**, *31*, 260-265.

(89) Yeung, J. M.; Knaus, E. E. *J. Med. Chem.* **1987**, *30*, 104-108.

(90) Olah, G. A.; Sassaman, M. B.; Zuanic, M.; Rao, C. B.; Prakash, G. K. S.; Gilardi, R.; Flippen-Anderson, J.; George, C. *J. Org. Chem.* **1992**, *57*, 1585-1588.

(91) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133-5.

(92) Carpino, L. A. *J. Org. Chem.* **1964**, *29*, 2820-4.

(93) Carpino, L. A. *J. Org. Chem.* **1965**, *30*, 321-3.

(94) Carpino, L. A. *J. Org. Chem.* **1965**, *30*, 736-9.

(95) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236-6239.

(96) Friestad, G. K.; Draghici, C.; Soukri, M.; Qin, J. *J. Org. Chem.* **2005**, *70*, 6330-6338.

(97) Parlanti, L.; Discordia, R. P.; Hynes, J., Jr.; Miller, M. M.; O'Grady, H. R.; Shi, Z. *Org. Lett.* **2007**, *9*, 3821-3824.

(98) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187-4190.

(99) Glover, E. E.; Rowbottom, K. T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 367-71.

(100) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1-17.

(101) Tamura, Y.; Minamikawa, J.; Miki, Y.; Matsugashita, S.; Ikeda, M. *Tetrahedron Lett.* **1972**, 4133-5.

(102) Katritzky, A. R.; Banerji, J.; Boonyarakvanich, A.; Cutler, A. T.; Dennis, N.; Rizvi, S. Q. A.; Sabongi, G. J.; Wilde, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 399-407.

(103) Tsuchiya, T.; Sashida, H. *J. Chem. Soc., Chem. Commun.* **1980**, 1109-10.

(104) Kurita, J.; Kojima, H.; Enkaku, M.; Tsuchiya, T. *Chem. Pharm. Bull*. **1981**, *29*, 3696-705.

(105) Kurita, J.; Kojima, H.; Tsuchiya, T. *Chem. Pharm. Bull.* **1981**, *29*, 3688-95.

(106) Tomazic, A.; Tisler, M.; Stanovnik, B. *Tetrahedron* **1981**, *37*, 1787-93.

(107) Tsuchiya, T.; Sashida, H.; Konoshita, A. *Chem. Pharm. Bull.* **1983**, *31*, 4568-72.

(108) Kang, H. C.; Boekelheide, V. *J. Am. Chem. Soc.* **1984**, *106*, 2672-80.

(109) Miki, Y.; Uragi, M.; Takemura, S.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 379-82.

(110) Chen, L. C.; Yang, S. C. *Heterocycles* **1986**, *24*, 3411-15.

(111) Eichenberger, T.; Balli, H. *Helv. Chim. Acta* **1986**, *69*, 1521-30.

(112) Miki, Y.; Tomii, O.; Utsunomiya, M.; Takemura, S.; Ikeda, M. *Chem. Pharm. Bull* **.1986**, *34*, 3588-94.

(113) Yeung, J. M.; Knaus, E. E. *J. Med. Chem.* **1987**, *30*, 104-8.

(114) Miki, Y.; Tomii, O.; Nakao, H.; Kubo, M.; Hachiken, H.; Takemura, S.; Ikeda, M. *J. Heterocycl. Chem.* **1988**, *25*, 327-31.

(115) Vlaovic, D.; Milic, B. L.; Mackenzie, K. *J. Chem. Res. Synopses* **1989**, 156-7.

(116) Paz Matia, M.; Garcia Navio, J. L.; Vaquero, J. J.; Alvarez-Builla, J. *J. Heterocycl. Chem.* **1990**, *27*, 661-5.

(117) Gawinecki, R.; Kanner, B. *Monatsh. Chem.* **1994**, *125*, 35-41.

(118) Miki, Y.; Tasaka, J.; Uemura, K.; Miyazeki, K.; Yamada, J. *Heterocycles* **1996**, *43*, 2249-2256.

(119) Pelle, C. J.; Okoro, C. O.; Wilson, T. L.; Onubogu, U. C.; Yoon, K.-J.; Redda, K. K. *Synth. Commun.* **1996**, *26*, 2703-2714.

(120) Yoon, K. J. P.; Kode, B.; Bowen, L.; Redda, K. K. *J. Heterocycl. Chem.* **2001**, *38*, 69-76.

(121) Okoro, C. O.; Wilson, T. L.; Redda, K. K. *Curr. Med. Chem.* **2003**, *10*, 313-320.

(122) Wilson, T. L.; Redda, K. K. *Med. Chem. Res.* **2003**, *12*, 69-86.

(123) Martinez, V.; Burgos, C.; Alvarez-Builla, J.; Fernandez, G.; Domingo, A.; Garcia-Nieto, R.; Gago, F.; Manzanares, I.; Cuevas, C.; Vaquero, J. J. *J. Med. Chem.* **2004**, *47*, 1136-1148.

(124) Powell, D.; Gopalsamy, A.; Wang, Y. D.; Zhang, N.; Miranda, M.; McGinnis, J. P.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1641-1645.

(125) Tamura, Y.; Kim, J.-H.; Ikeda, M. *J. Heterocycl. Chem.* **1975**, *12*, 107-10.

(126) Tsuchiya, T.; Kurita, J.; Takayama, K. *Chem. Pharm. Bull* . **1980**, *28*, 2676-81.

(127) Yao, G.; Haque, S.; Sha, L.; Kumaravel, G.; Wang, J.; Engber, T. M.; Whalley, E. T.; Conlon, P. R.; Chang, H.; Kiesman, W. F.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 511-515.

(128) Kowalchick, J. E.; Leiting, B.; Pryor, K. D.; Marsilio, F.; Wu, J. K.; He, H.; Lyons, K. A.; Eiermann, G. J.; Petrov, A.; Scapin, G.; Patel, R. A.; Thornberry, N. A.; Weber, A. E.; Kim, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5934-5939.

(129) Lempert, K.; Fetter, J.; Nyitrai, J.; Bertha, F.; Moller, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 269-75.

(130) Tsuchiya, T.; Enkaku, M.; Okajima, S. *Chem. Pharm. Bull* . **1980**, *28*, 2602-8.

(131) Kurita, J.; Enkaku, M.; Tsuchiya, T. *Chem. Pharm. Bull* . **1982**, *30*, 3764-9.

(132) Tsuchiya, T.; Okajima, S.; Enkaku, M.; Kurita, J. *Chem. Pharm. Bull* . **1982**, *30*, 3757-63.

(133) Andreev, R. V.; Borodkin, G. I.; Shakirov, M. M.; Shubin, V. G. Russ. *J. Org. Chem.* **2004**, *40*, 1379-1381.

(134) Frankowski, A. *Tetrahedron* **1986**, *42*, 1511-28.

(135) Tsuchiya, T.; Enkaku, M.; Sawanishi, H. *Heterocycles* **1978**, *9*, 621-4.

(136) Tsuchiya, T.; Sawanishi, H.; Enkaku, M.; Hirai, T *Chem. Pharm. Bull*. **1981**, *29*, 1539-47.

(137) Kloetzer, W.; Baldinger, H.; Karpitschka, E. M.; Knoflach, J. *Synthesis* **1982**, 592-5.

(138) Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982**, *23*, 5399-402.

(139) Link, H.; Kloetzer, W.; Karpitschka, E. M.; Montavon, M.; Muessner, R.; Singewald, N. *Angew. Chem.* **1990**, *102*, 559-60.

(140) Heim-Riether, A.; Healy, J. *J. Org. Chem.* **2005**, *70*, 7331-7337.

(141) Belley, M.; Scheigetz, J.; Dube, P.; Dolman, S. *Synlett* **2001**, 222-225.

(142) Borzilleri, R. M.; Zheng, X.; Qian, L.; Ellis, C.; Cai, Z.-W.; Wautlet, B. S.; Mortillo, S.; Jeyaseelan, R.; Kukral, D. W.; Fura, A.; Kamath, A.; Vyas, V.; Tokarski, J. S.; Barrish, J. C.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Bhide, R. S. *J. Med. Chem.* **2005**, *48*, 3991-4008.

(143) Borzilleri, R. M.; Cai, Z.-W.; Ellis, C.; Fargnoli, J.; Fura, A.; Gerhardt, T.; Goyal, B.; Hunt, J. T.; Mortillo, S.; Qian, L.; Tokarski, J.; Vyas, V.; Wautlet, B.; Zheng, X.; Bhide, R. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1429-1433.

(144) Fernandez, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461-2464.

(145) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741-1743.

(146) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767-2770.

(147) Armstrong, A.; Carbery, D. R.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Synlett* **2006**, 2504-2506.

(148) Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 8005-8008.

(149) Armstrong, A.; Baxter, C. A.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Org. Lett.* **2007**, *9*, 351-353.

(150) Ning, R. Y. *Chem. Eng. News* **1973**, *51*, 36-37.

(151) Johnson, C. R. K., R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458-2459.

(152) Scopes, D. I. C.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 376-377.

(153) Taylor, E. C.; Sun, J. H. *Synthesis* **1980**, 801-802.

(154) Rao, R. S.; Lowdon, G. M.; Miller, M. J. *J. Org. Chem.* **1979**, *44*, 4836-3841.

(155) Beylin, V.; Boyles, D. C.; Curran, T. T.; Macikenas, D.; Parlett, R. V.; Vrieze, D. *Org. Process Res. Dev.* **2007**, *11*, 441-449.

(156) Reddy, P. S. N.; Reddy, P. P. *Synth. Commun.* **1988**, *18*, 2179-2182.

(157) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713-716.

(158) Personal communication with Prof. Francis Stoessel, Schweizerisches Institut zür Forderung der Sicherheit, Basel.

(159) Belzecki, C.; Piotrowska, K.; Hintze, B. *Bull. Acad. Pol. Sci., Sér. Sci. Chim.* **1971**, *19*, 367-70.

(160) Boedeker, J.; Courault, K. *Tetrahedron* **1978**, *34*, 101-4.

(161) Le, V.-D.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2399-2409.

(162) Martin, N. I.; Woodward, J. J.; Marletta, M. A. *Org. Lett.* **2006**, *8*, 4035-4038.

(163) Feldman, P. L. *Tetrahedron Letters* **1991**, *32*, 875-8.

(164) Le, V.-D.; Wong, C.-H. *Journal of Organic Chemistry* **2000**, *65*, 2399-2409.

(165) Miller, C. A.; Batey, R. A. *Org. Lett.* **2004**, *6*, 699-702.

(166) Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300-2309.

(167) Belzecki, C.; Piotrowska, K. *Bull. Acad. Pol. Sci., Sér. Sci. Chim.* **1972**, *20*, 499-503.

9. Appendix

Differential Scanning Calorimetry (DSC)

DSC is a helpful measurement for solid-state characterization and scale-up processes. It is as well used for safety assessment when potential unsafe compounds have to be handled and used in organic reactions. It consists on determining any endo/exothermic event when the sample is heated in a pan in its pure form, solution or in a reaction mixture. Figure 18 represents thermogram obtained by DSC. Four main parameters can be retrieved form the thermograms which can be used to described the thermal behaviour of the sample: a) *Onset temperature (T_{onset})*: is the temperature at which the event starts, b) *Energy (enthalpy)* consumed/liberated in the event (area under the peak that is proportional to the mass, *i.e.* ΔH/g), c) Intensity of the peak, d) *Shape* of the peak: T_f-T_i can be used as a parameter to describe the shape (the smaller, the steeper).

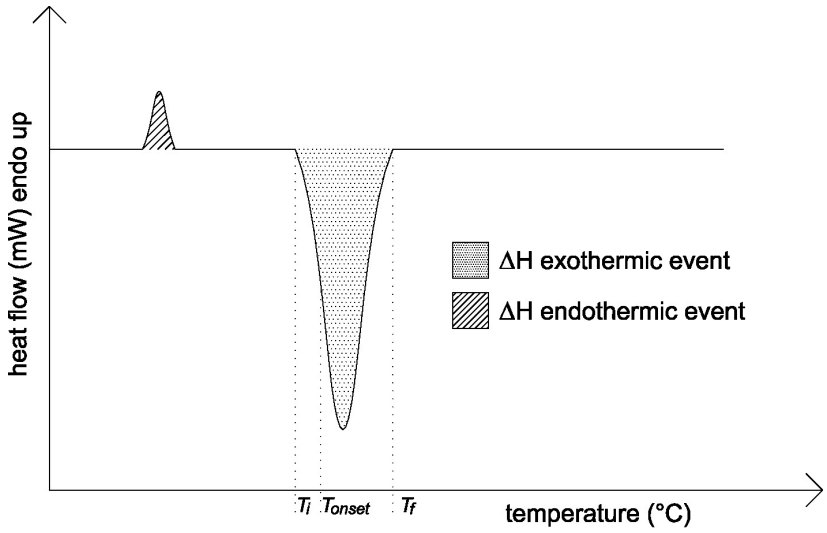


Figure 18. Thermogram obtained by DSC

When the thermal decomposition of an organic compound is an exothermic event, the hazard can be evaluated in terms of *severity* and *probability*

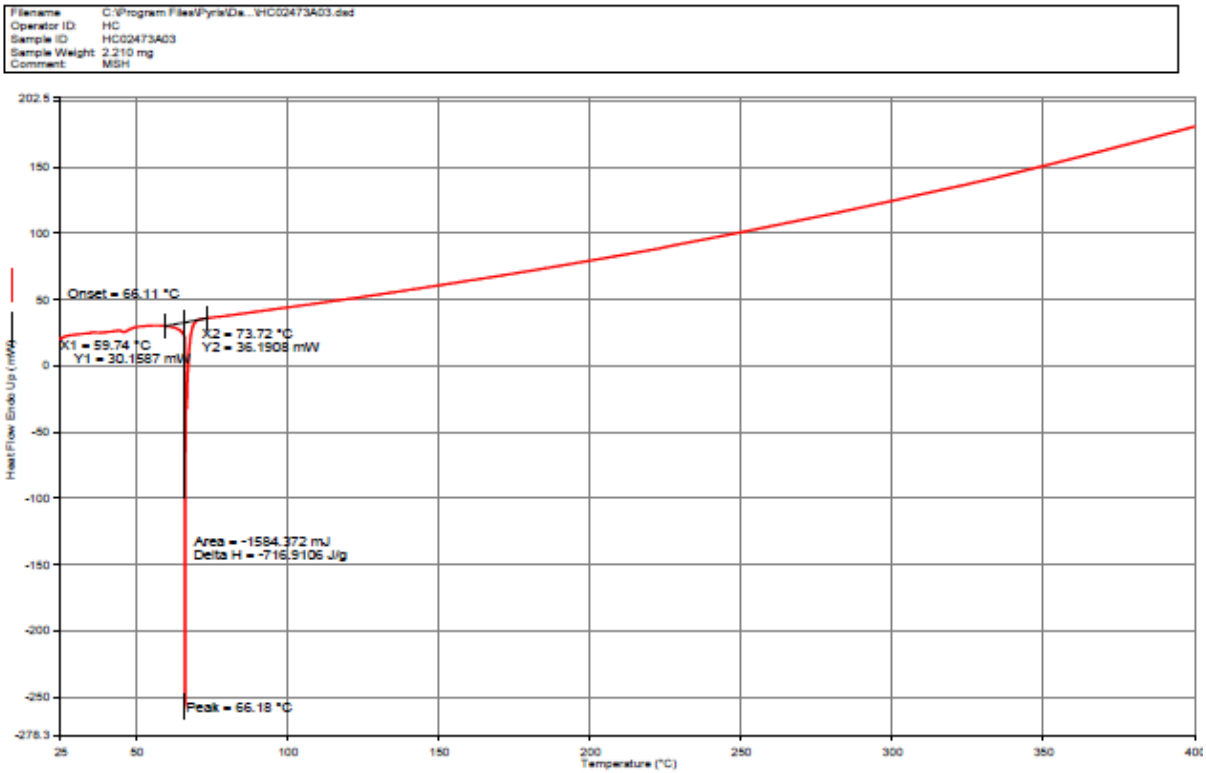
- *Severity* is related to *energy* (ΔH/g) and *shape* of the peak. Adiabatic temperature (ΔT_{ad}) is a parameter derived from the enthalpy of the process (Eq 1) that is often used to classify the samples as: self-heating materials when ΔT_{ad} <50 K and highly energetic material if ΔT_{ad} > 200 K. Sharp/steep peaks are usually associated to violent events.

Eq.1 $$\Delta T_{ad}\ (K/g) = \frac{-\Delta H/g\ (J\ g^{-1})}{Cp\ (J\ K^{-1})}$$

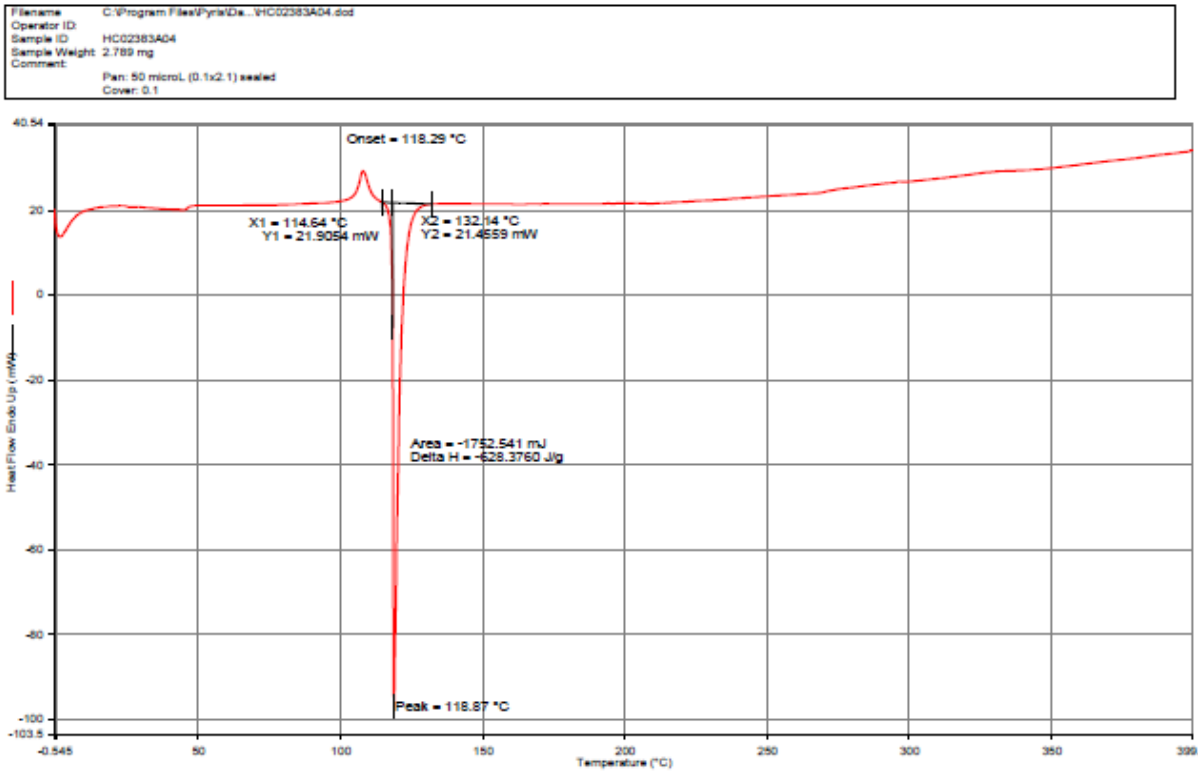
T_{ad}: adiabatic temperature
ΔH: enthylpy
Cp: specific heat capacity

- *Probability* is related to *onset temperature.* The lower the onset temperature is, the higher tendency to happen. It is function of the amount of sample, the sensitivity of the instrument, the pan and the heating rate. The usual heating rate is 5-10 °C/min from 25 to 400 °C and less than 5 mg of sample is recommended.

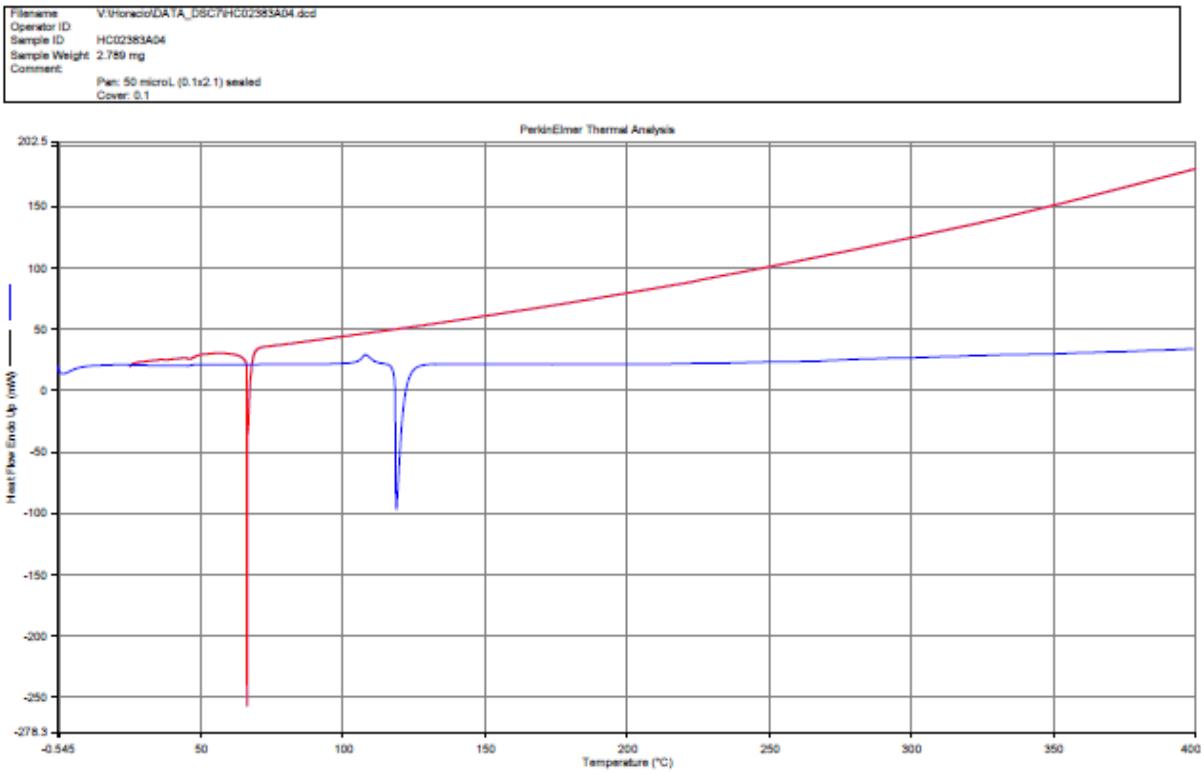
Recorded thermograms



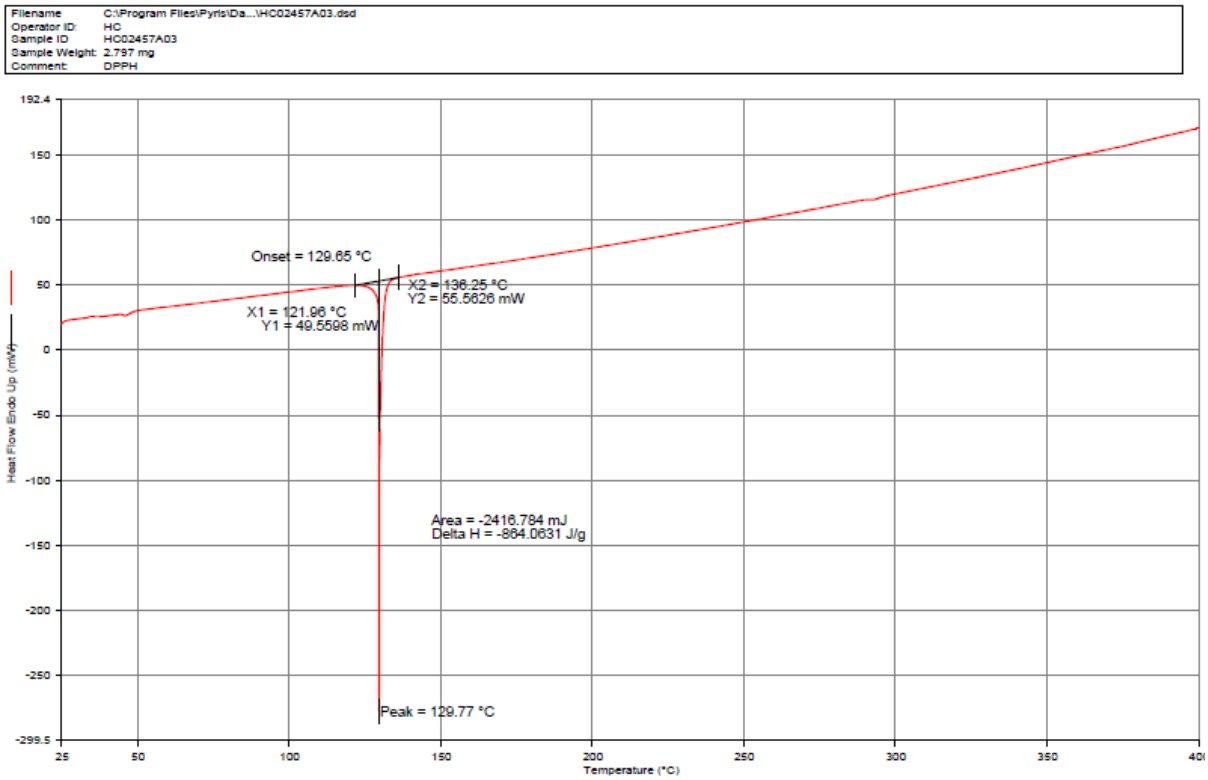
Thermogram 1. MSH



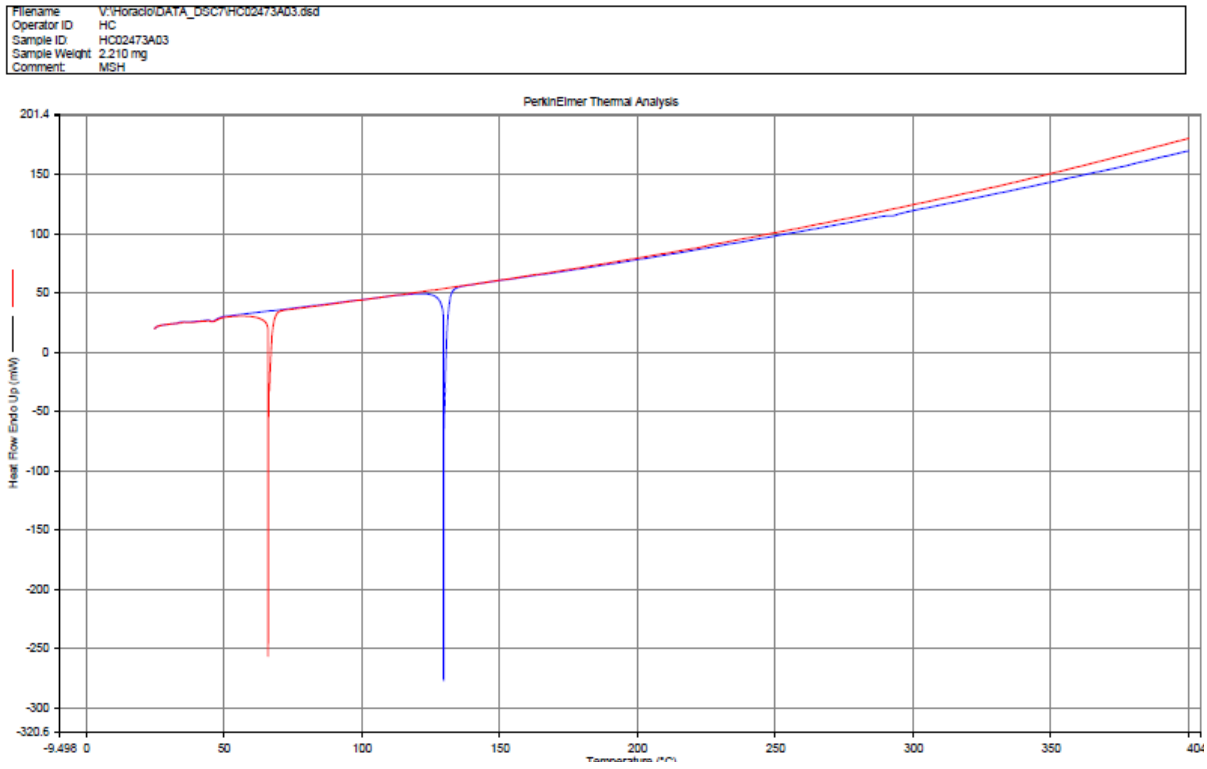
Thermogram 2. (134) MSH-Boc



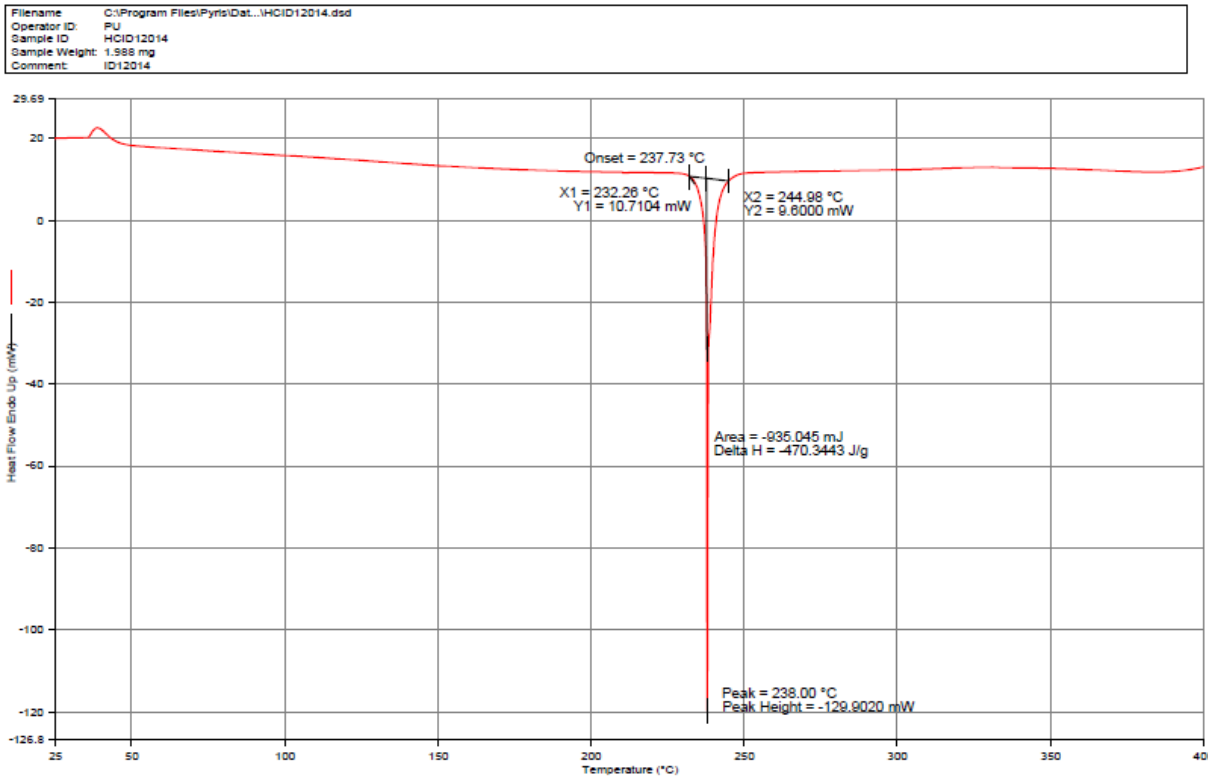
Thermogram 3. MSH (red) - MSH - Boc (blue)



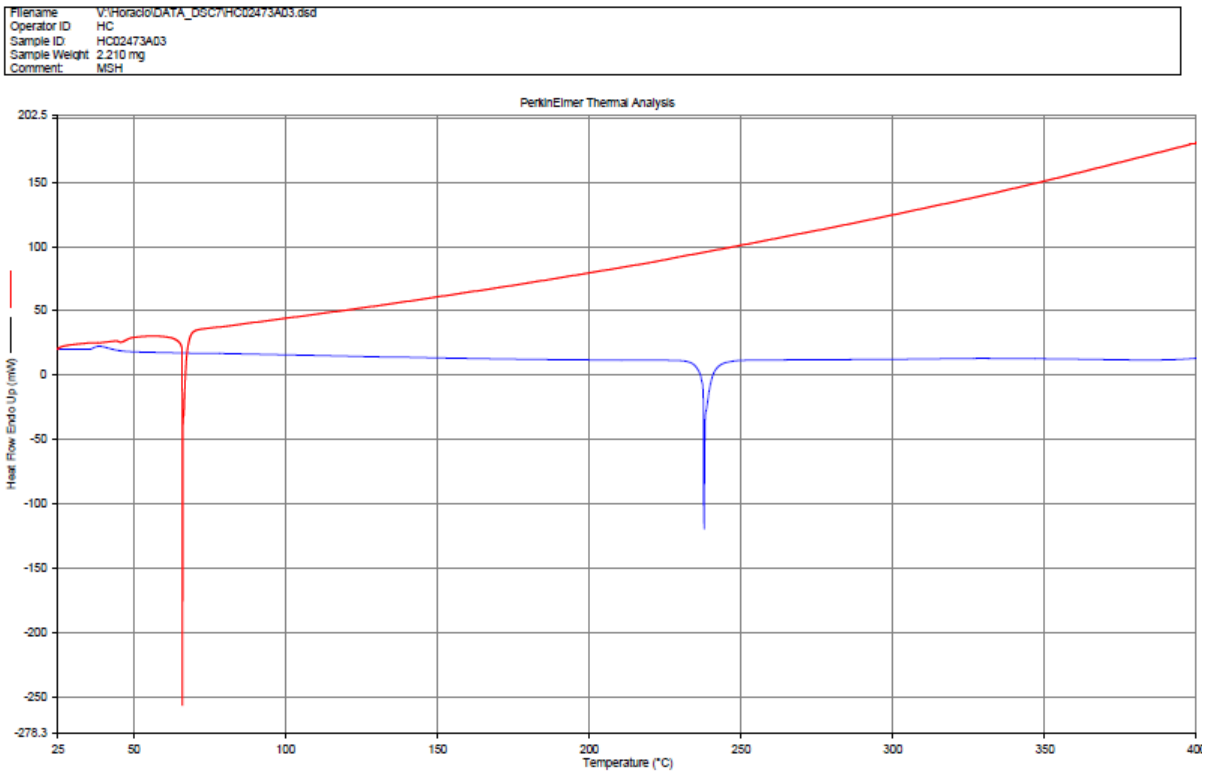
Thermogram 4. DPPH



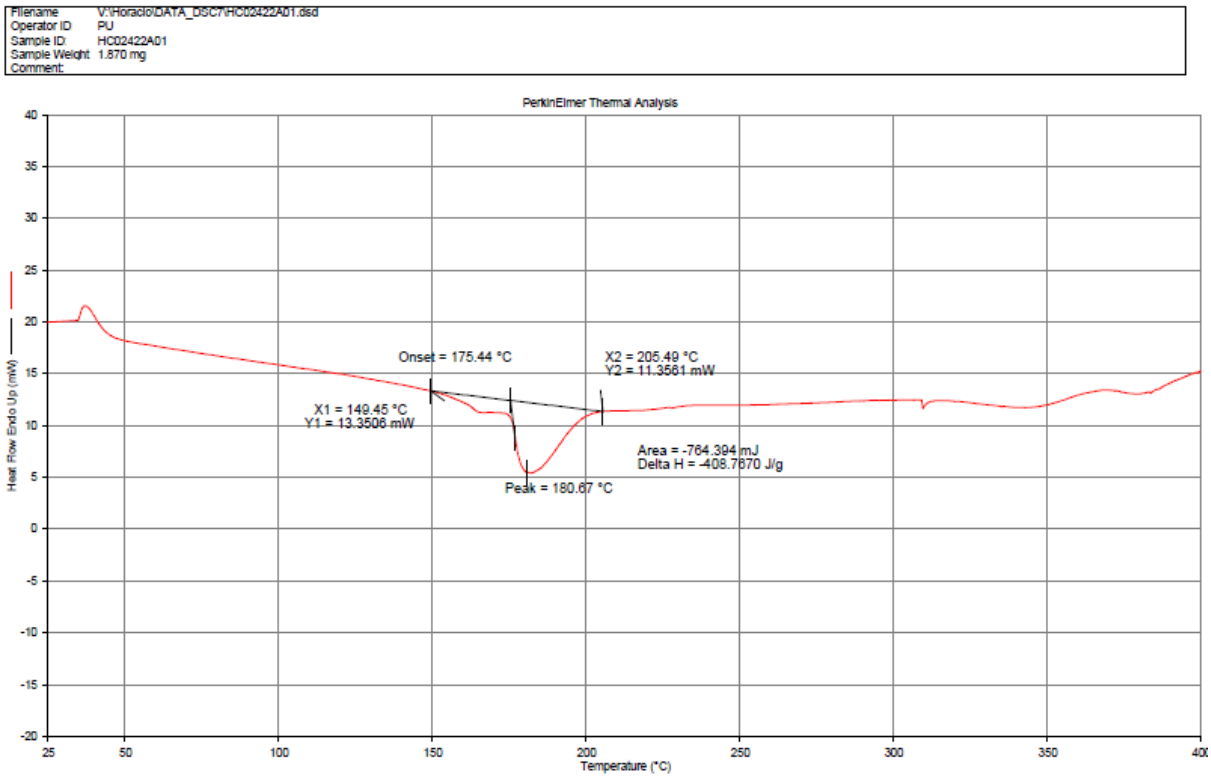
Thermogram 5. MSH (red) - DPPH (blue)



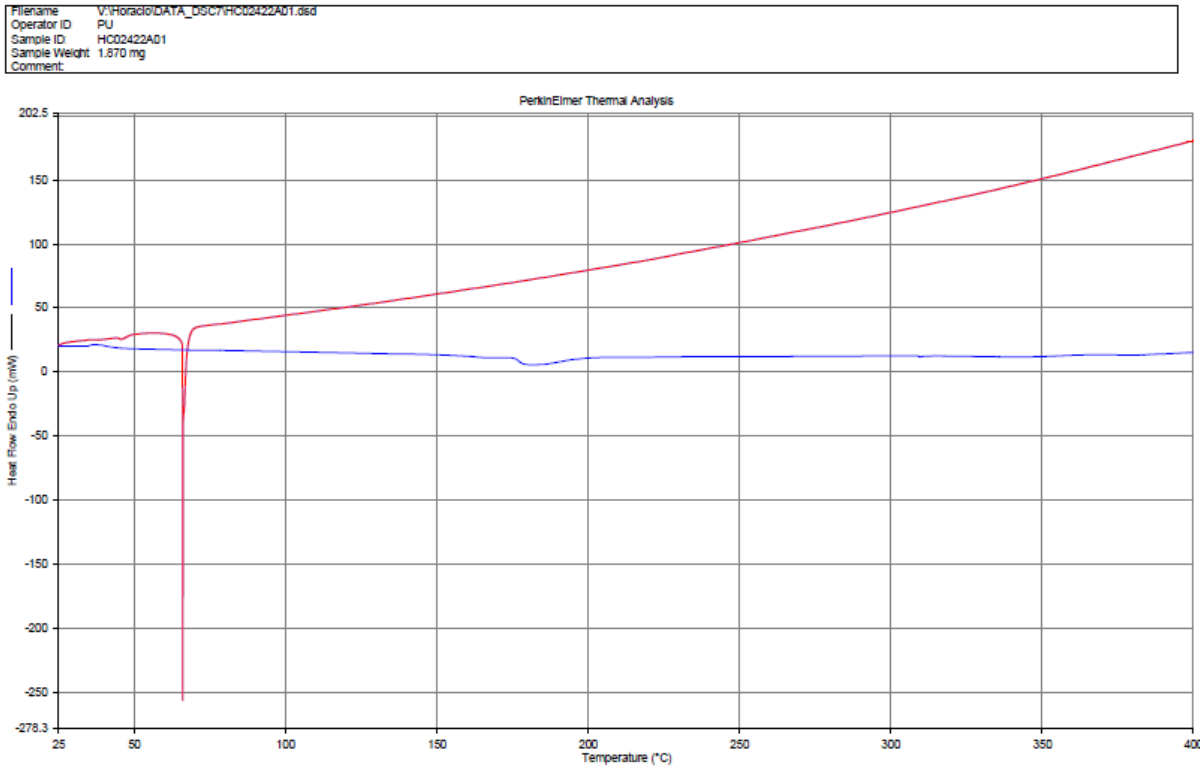
Thermogram 6. TMHI



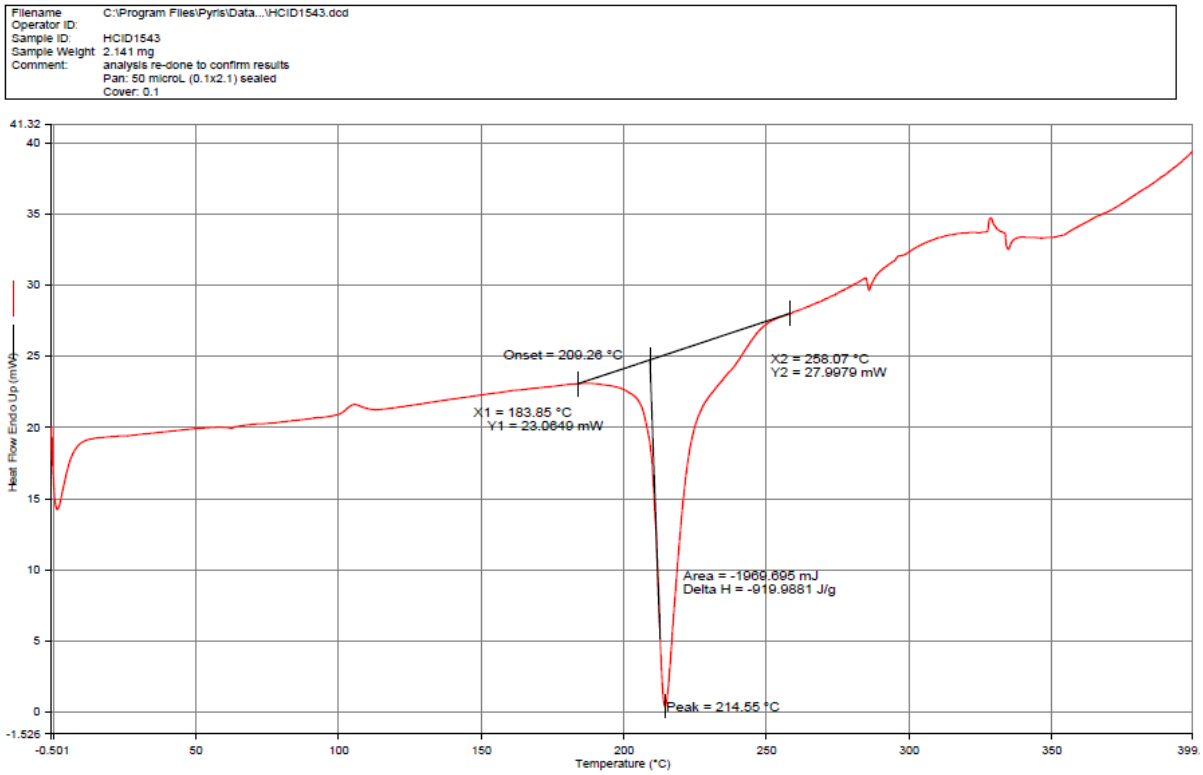
Thermogram 7. MSH (red) - TMHI (blue)



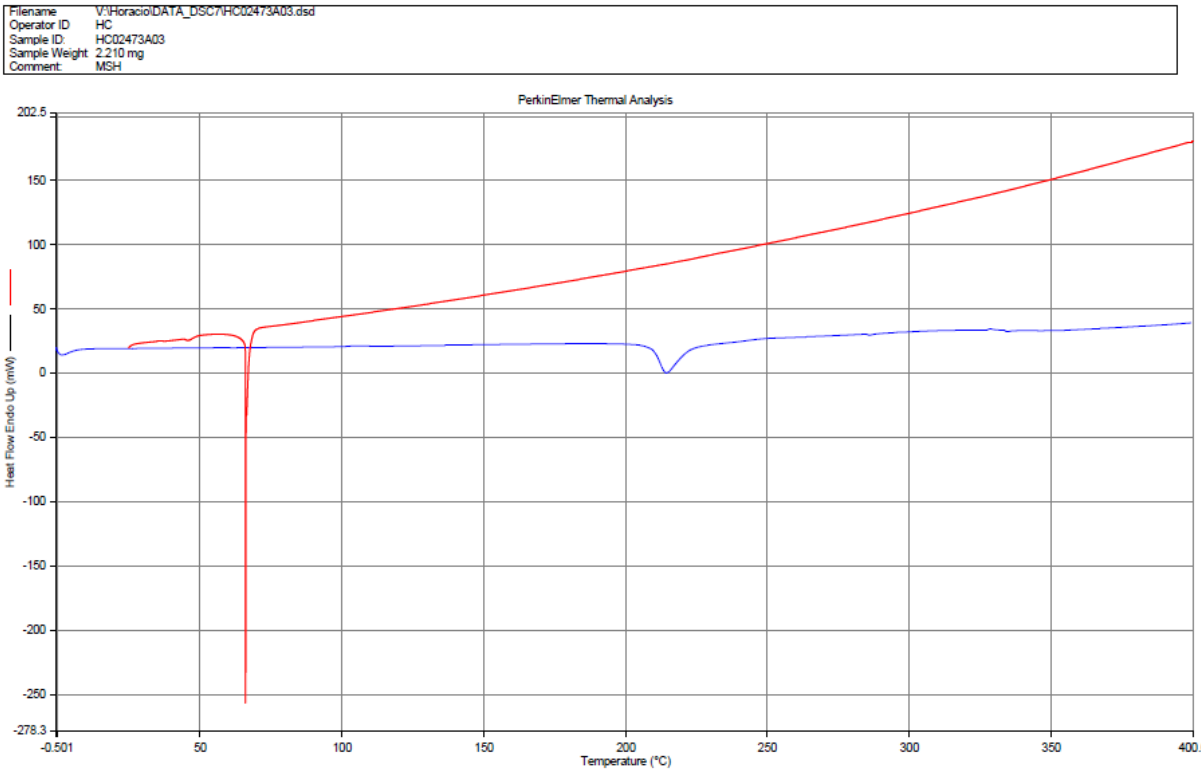
Thermogram 8. MAMI



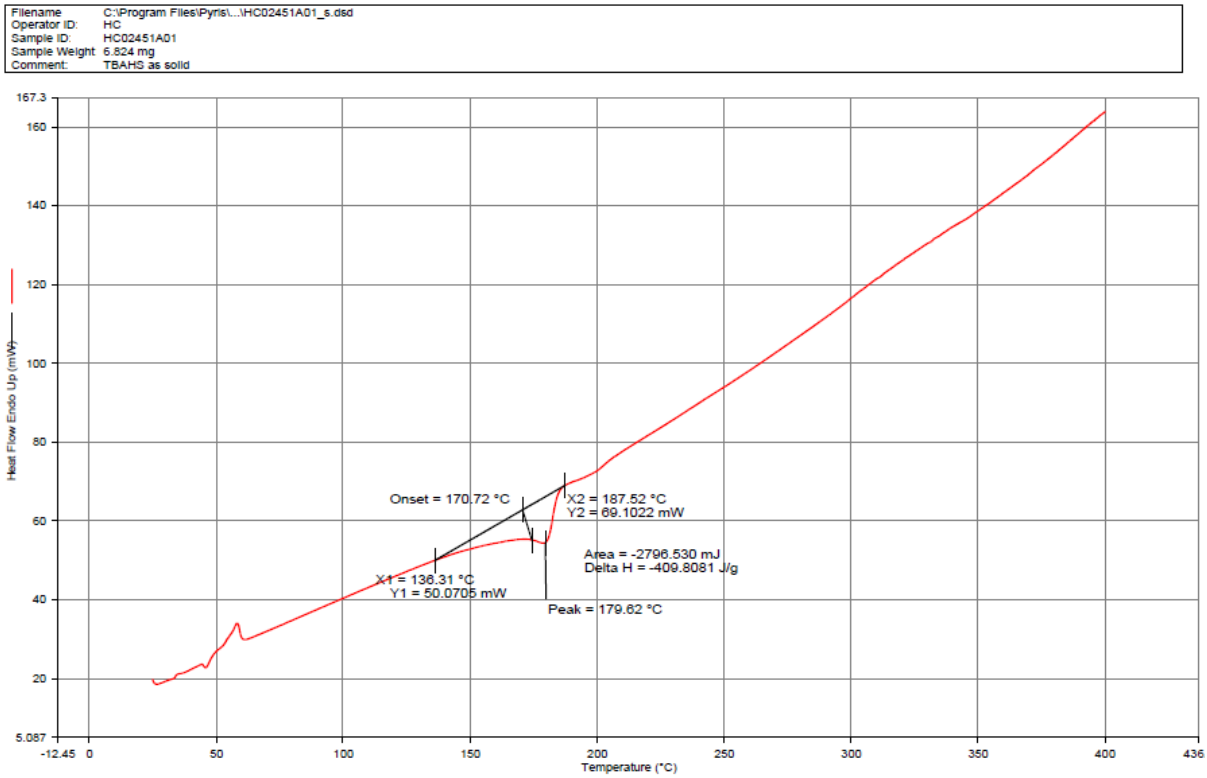
Thermogram 9. MSH (red) - MAMI (blue)



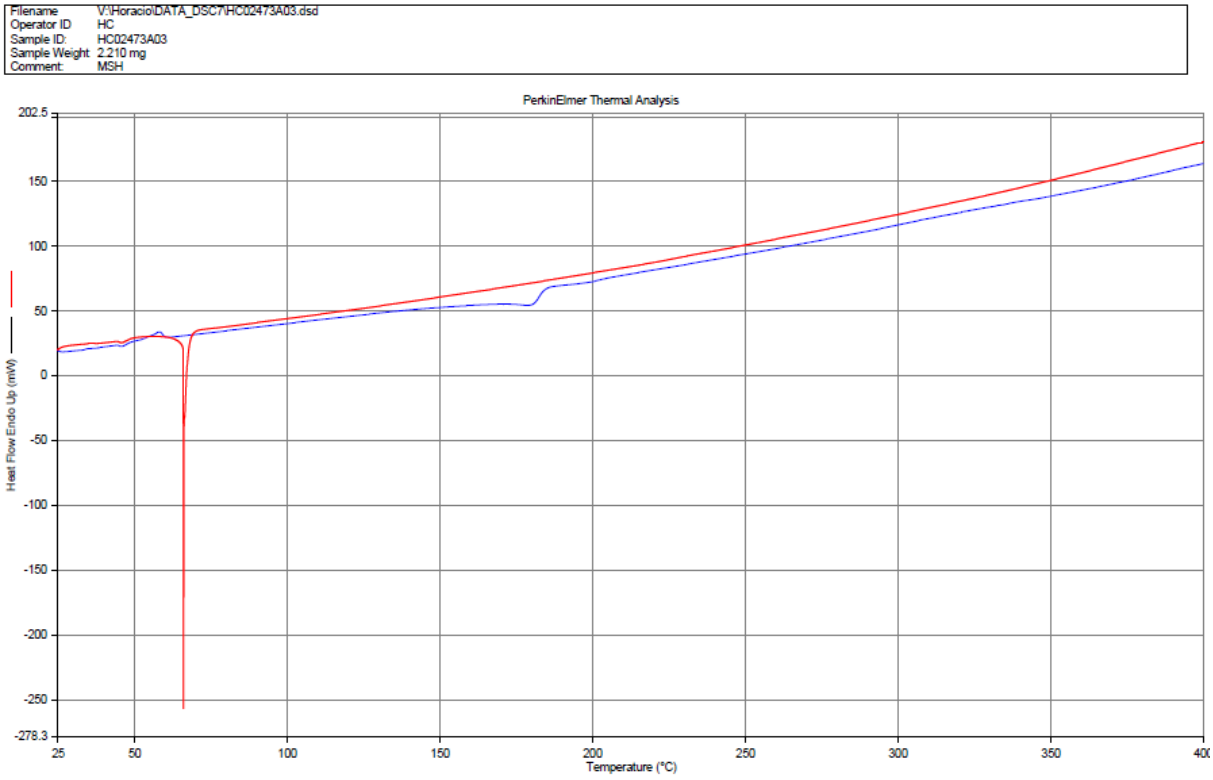
Thermogram 10. HSA



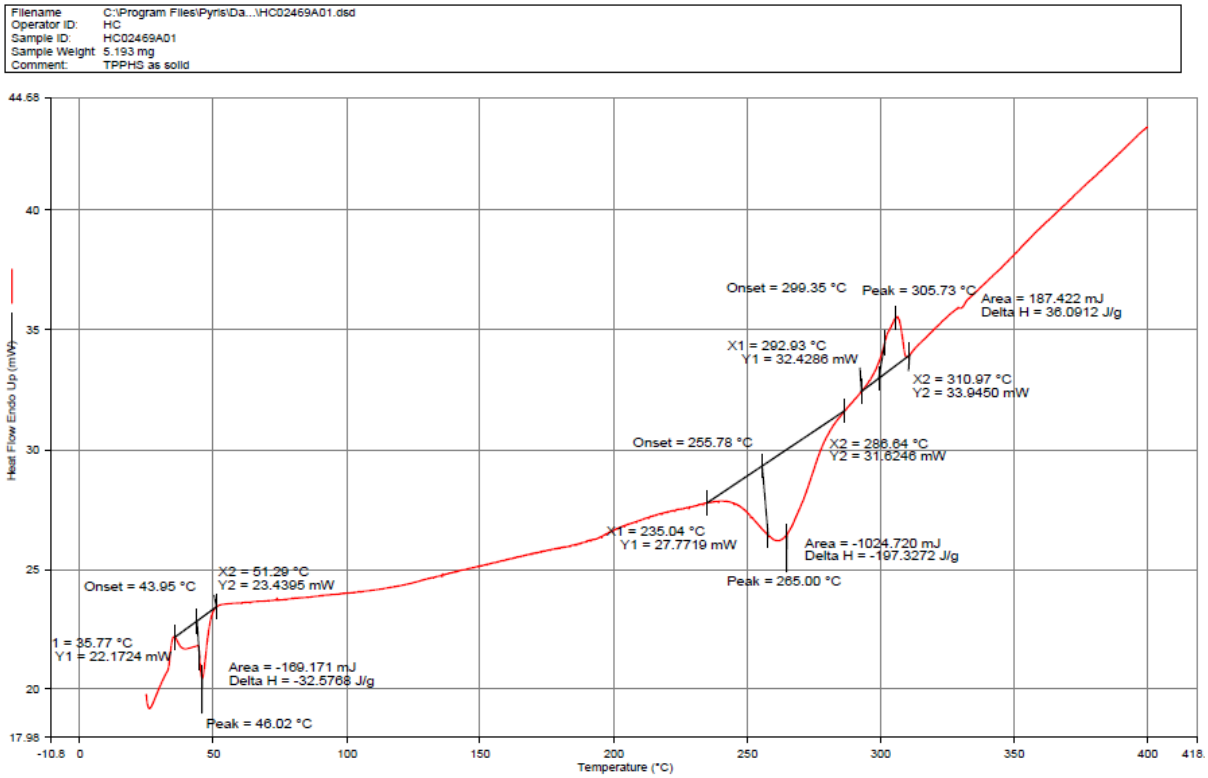
Thermogram 11. MSH (red) - HSA (blue)



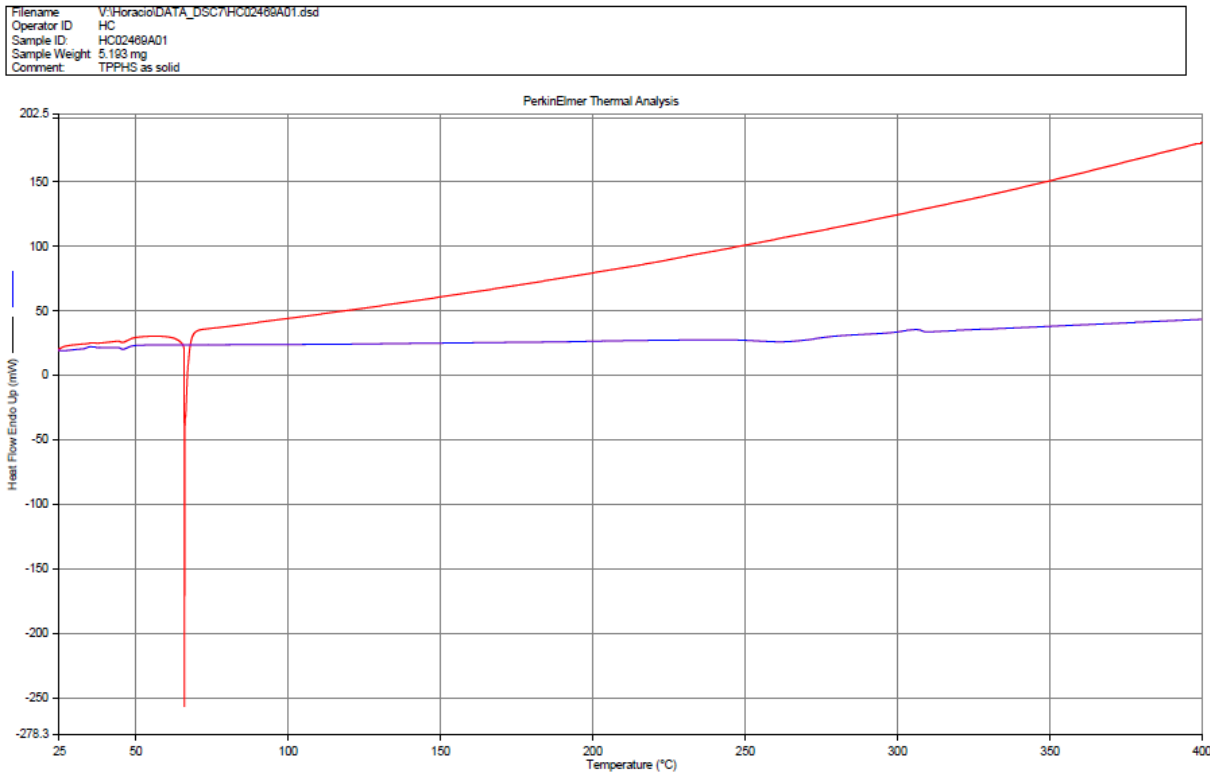
Thermogram 12. TBAHS



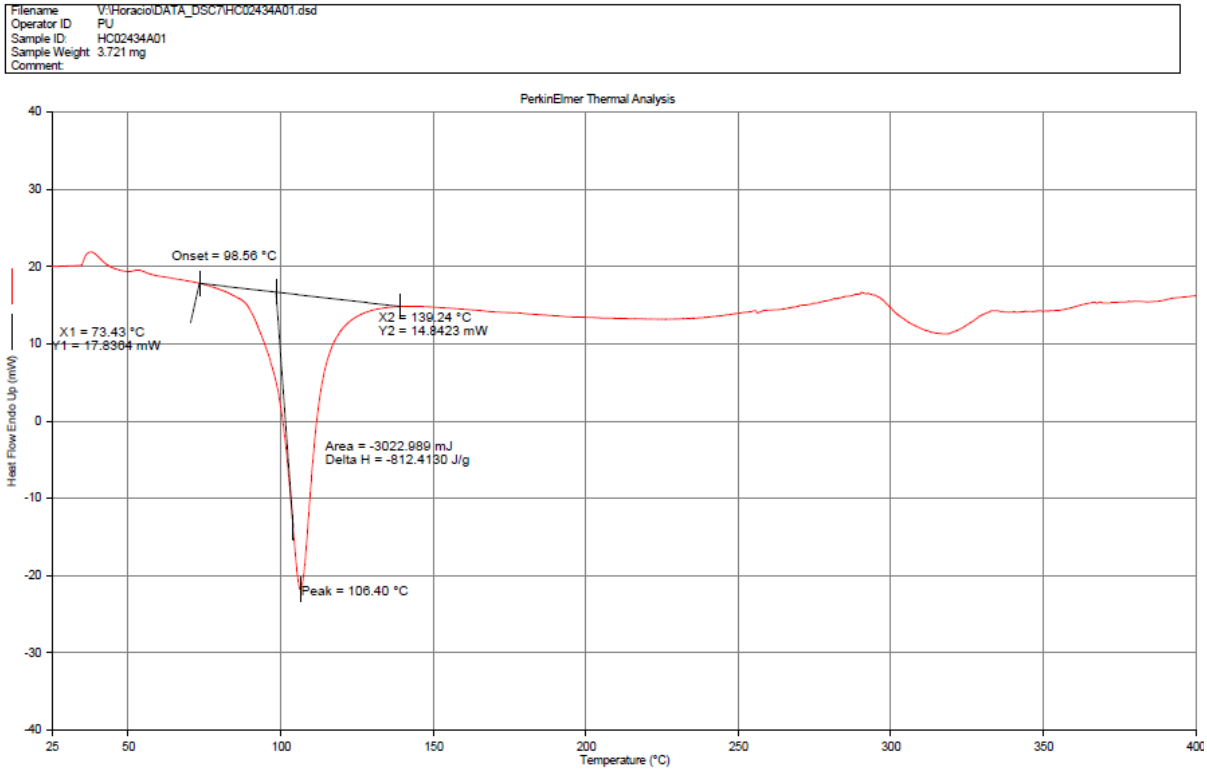
Thermogram 13. MSH (red) - TBAHS (blue)



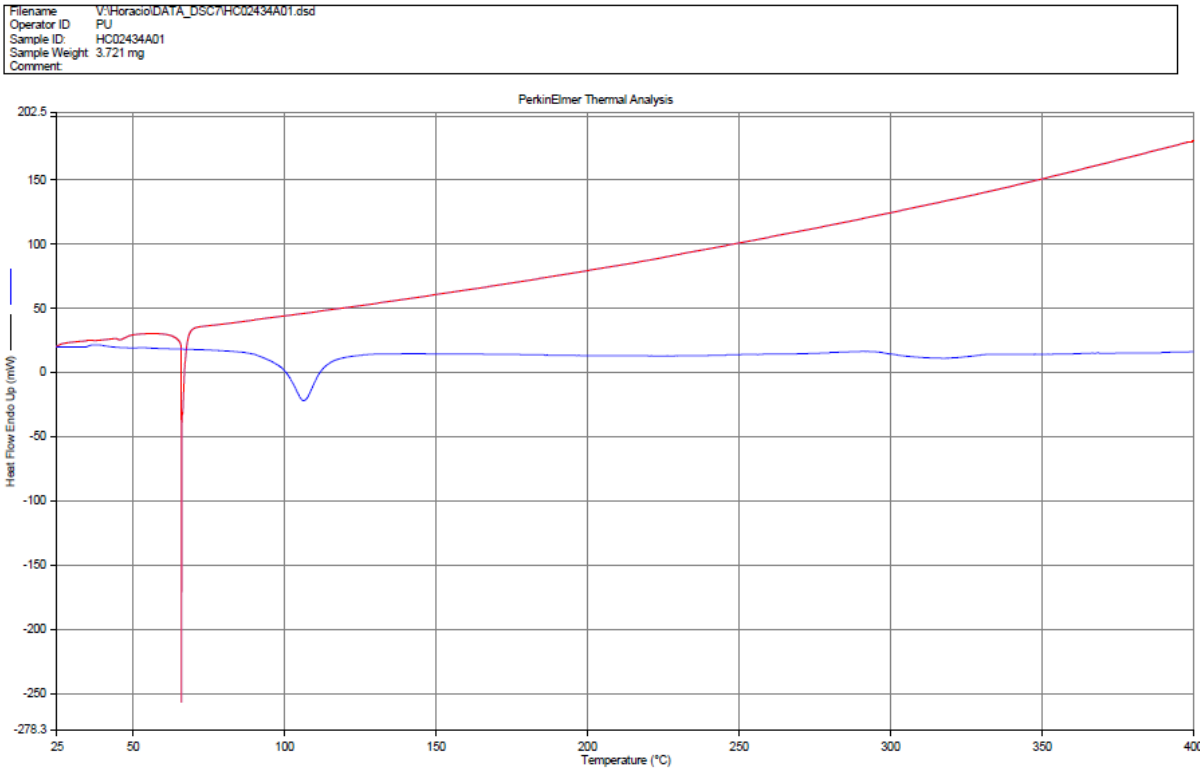
Thermogram 14. TPPHS



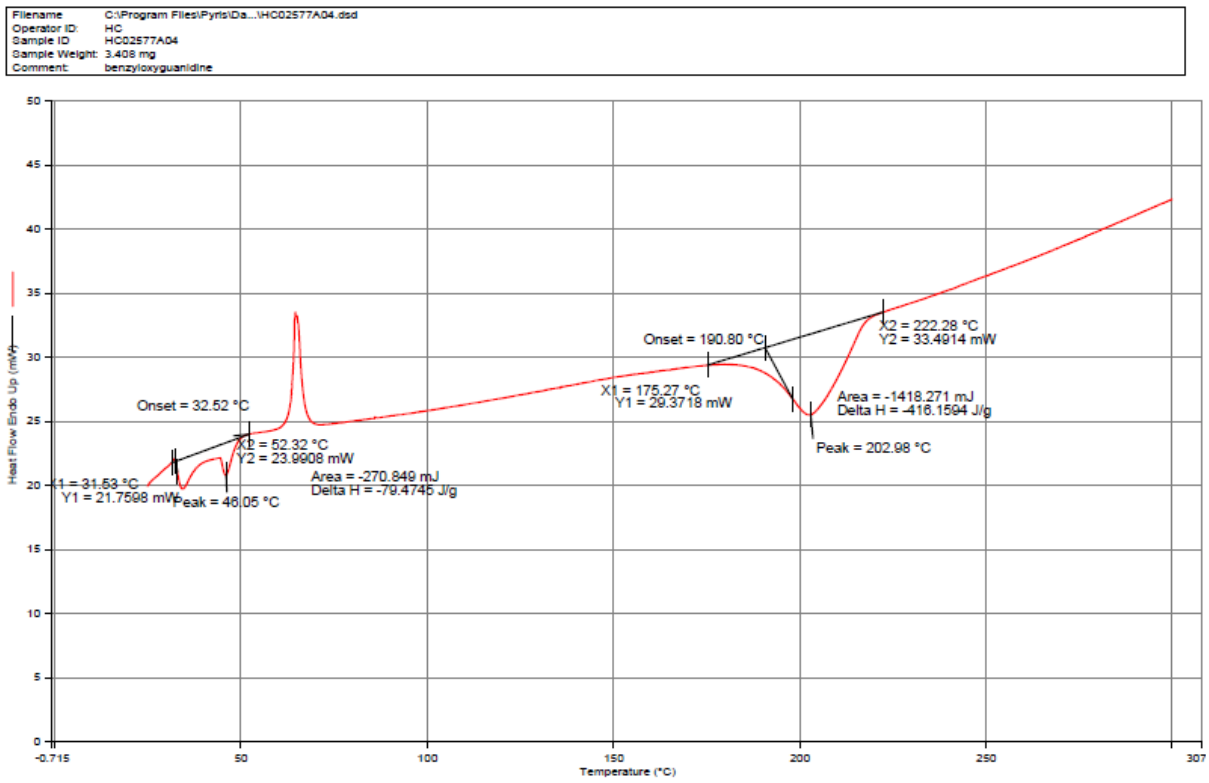
Thermogram 15. MSH (red) - TPPHS (blue)



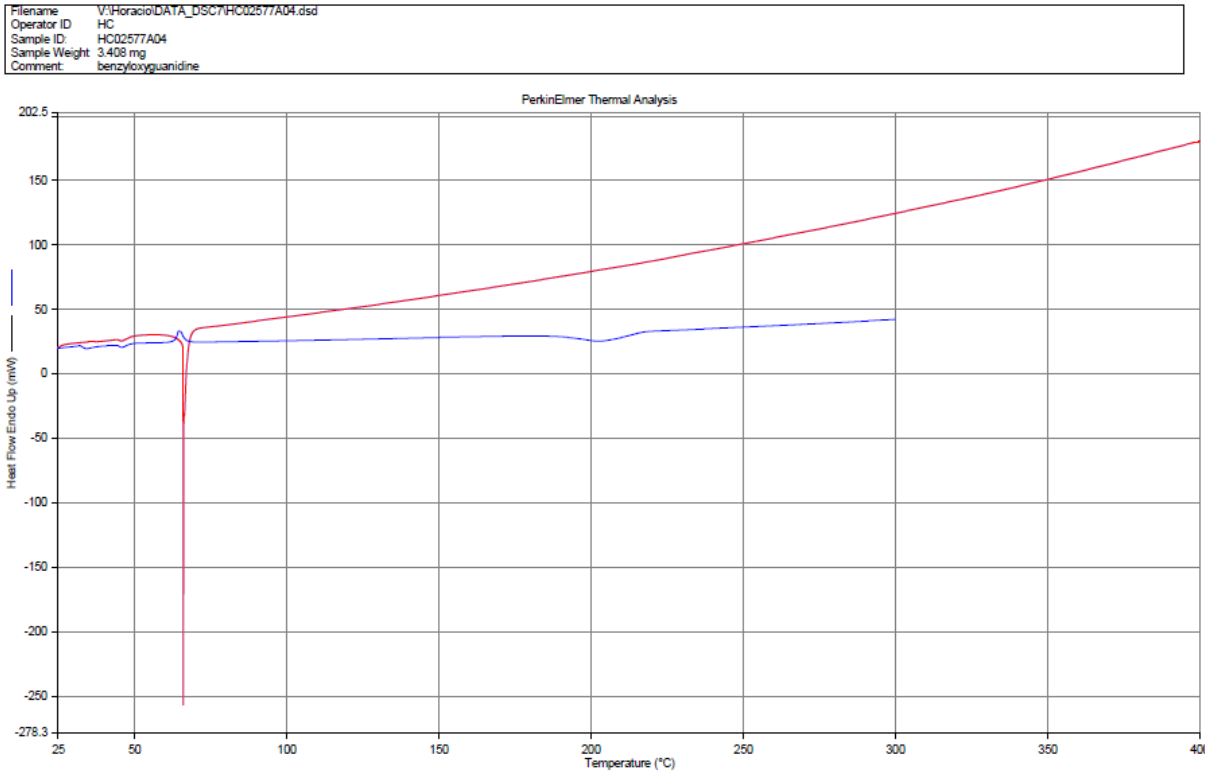
Thermogram 16. TMAHS



Thermogram 17. MSH (red) - TMAHS (blue)



Thermogram 18. Compound **154**.



Thermogram 19. MSH (red) - Compound **154** (blue).

2. Crytallographic Data

1-Pyridin-2-yl-3-tert-octylamino-[1,2,4]triazolo[4,3-a]pyridin-1-ium tri-fluoromethane-sulfonate (**85f-1**).

Formule brute:	$(C_{19}H_{26}N_5)^+ (CF_3SO_3)^-$
Poids moléculaire:	473.6
Coefficient d'absorption linéaire	μ = 0.20 mm^{-1} (Mo (Kα))
Solvant de recristallisation	?
Densité Do = ?	Dx = 1.364 ($gr.cm^{-3}$)
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Orthorhombique	Groupe d'espace: *Pbca*
a = 11.7327 (5) (Å)	α = 90°
b = 13.6679 (6)(Å)	β = 90°
c = 28.7611 (20)(Å)	γ = 90°
V = 4612.2 (4)($Å^3$)	Z = 8
Nombre de réflexions pour l'affinement des paramètres:	8000 (6.9° < 2θ < 51.5°)

Forme et dimensions du cristal

Forme: plaque (très fine); Couleur: transparent
Dimensions: 0.026 x 0.42 x 0.42 mm
Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température:	200 K	Longueur d'onde	0.7107(Å)
Mode de balayage	φ-scan	$\Delta\varphi$ / image	1.0 (°)
T Irradiation / image	3 (min)	φ min, max =	0 - 222 (°)
Distance cristal / IP	70 (mm)	Nombre d'images	222
EMS	0.012	Moyenne (I/σ(I))	3.7
Limites angulaires	4.5° < 2θ < 51.5°		
Limites d'indices	-14 < h < 14 ; -16 < k < 16 ; -35 < ℓ < 35		

Nombre de réflexions mesurées: 40'968

Réduction des données

Corrections :	LP	☒	
	Disp. anomale	☒	
	Absorption	☒	T min. , max. = 0.9260 , 0.9949

Nombre de réflexions observables	1688	|Fo|> 4σ(Fo)
Nombre de réflexions non-observables	2817	
Nombre de réflexions uniques	4505	R_{int} pour 34'032 réfl. équivalentes = 0.092

Statistique des réflexions

Facteur de température global	2.82 ($Å^2$)
Distribution des $<E^2>$: centrique	$<E^2-1> = 0.911$

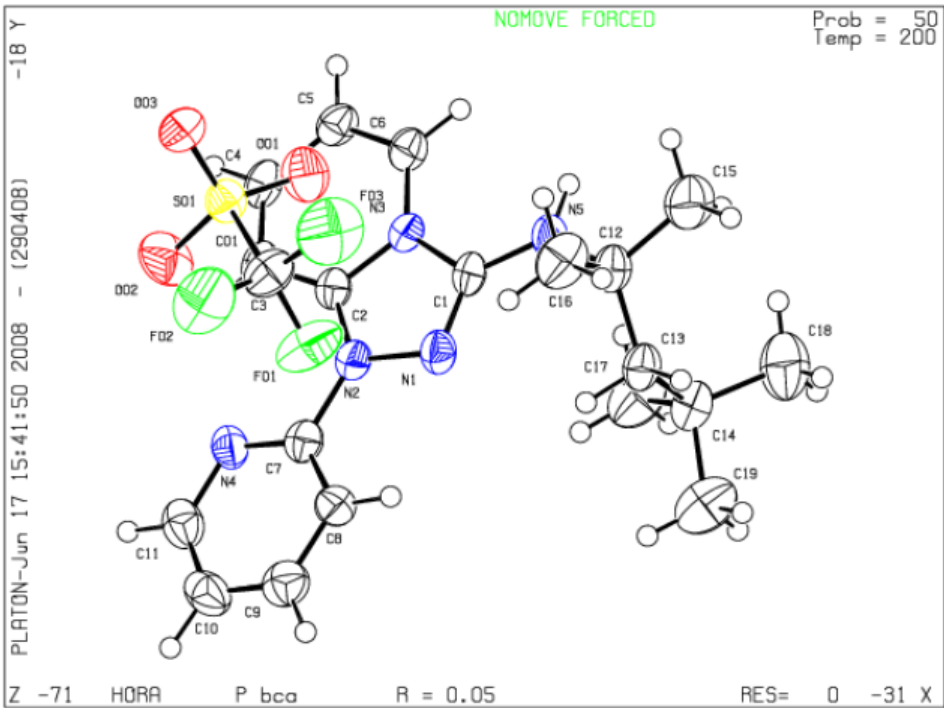
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	$\Sigma\ (\omega\ (Fo-Fc)^2)$
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.0002\ (Fo^2)]$
Nombre d'atomes affinés "iso" :	-
Nombre d'atomes affinés "aniso":	32
Coordonnées des atomes d'hydrogène:	calculées
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	289
Nombre de réflexions :	1966
Nbe reflexions / Nbe de variables	6.8
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.38 10^{-4} , Maximum : 0.36 10^{-3}
Résidus (delta F) ($eÅ^{-3}$):	-0.71 , 0.47
"Goodness of fit": S =	1.38(2)

Facteur résiduel final	**R = 0.046**
Facteur résiduel pondéré	**ωR = 0.042**



$(C_{19}H_{26}N_5)^+ (CF_3SO_3)^-$ EX/88 *Pbca* 200K IPDS

Bond Distances (Angstroms)

N1-N2	1.394(5)	N1-C1	1.312(5)
N2-C2	1.345(5)	N2-C7	1.425(5)
N3-C1	1.400(5)	N3-C2	1.370(5)
N3-C6	1.372(5)	N4-C7	1.325(6)
N4-C11	1.343(6)	N5-C1	1.342(5)
N5-C12	1.495(5)	C2-C3	1.399(6)
C3-C4	1.360(6)	C4-C5	1.411(6)
C5-C6	1.350(6)	C7-C8	1.382(6)
C8-C9	1.375(6)	C9-C10	1.389(7)
C10-C11	1.373(7)	C12-C13	1.536(6)
C12-C15	1.511(7)	C12-C16	1.527(7)
C13-C14	1.527(6)	C14-C17	1.530(7)
C14-C18	1.515(8)	C14-C19	1.528(8)
C01-S01	1.814(5)	C01-F01	1.327(6)
C01-F02	1.321(6)	C01-F03	1.320(5)
S01-O01	1.424(3)	S01-O02	1.427(3)
S01-O03	1.441(3)		

Bond Angles (degrees)

N2-N1-C1	105.1(3)	N1-N2-C2	111.9(3)
N1-N2-C7	118.6(3)	C2-N2-C7	129.3(3)
C1-N3-C2	107.8(3)	C1-N3-C6	130.4(3)
C2-N3-C6	121.8(3)	C7-N4-C11	114.9(4)
C1-N5-C12	124.1(3)	N1-C1-N3	110.1(4)
N1-C1-N5	127.9(4)	N3-C1-N5	121.9(4)
N2-C2-N3	105.1(3)	N2-C2-C3	134.6(4)
N3-C2-C3	120.3(4)	C2-C3-C4	117.5(4)
C3-C4-C5	121.4(4)	C4-C5-C6	120.3(4)

N3-C6-C5	118.6(4)	N2-C7-N4	113.8(4)
N2-C7-C8	120.0(4)	N4-C7-C8	126.2(4)
C7-C8-C9	117.0(4)	C8-C9-C10	119.2(4)
C9-C10-C11	118.3(4)	N4-C11-C10	124.4(4)
N5-C12-C13	113.5(3)	N5-C12-C15	104.8(3)
N5-C12-C16	107.3(4)	C13-C12-C15	114.0(4)
C13-C12-C16	108.2(4)	C15-C12-C16	108.7(4)
C12-C13-C14	126.1(4)	C13-C14-C17	112.8(4)
C13-C14-C18	114.9(4)	C13-C14-C19	105.8(4)
C17-C14-C18	108.6(4)	C17-C14-C19	107.9(4)
C18-C14-C19	106.5(4)		

S01-C01-F01	111.9(3)	S01-C01-F02	112.1(3)
S01-C01-F03	111.1(4)	F01-C01-F02	107.7(4)
F01-C01-F03	106.2(4)	F02-C01-F03	107.5(4)
C01-S01-O01	103.7(2)	C01-S01-O02	102.8(2)
C01-S01-O03	102.9(2)	O01-S01-O02	115.6(2)
O01-S01-O03	114.8(2)	O02-S01-O03	114.6(2)

Dihedral Angles (degrees)

C1-N1-N2-C2	.7(4)	C1-N1-N2-C7	176.2(4)
N2-N1-C1-N3	-.3(4)	N2-N1-C1-N5	-178.7(4)
N1-N2-C2-N3	-.9(4)	N1-N2-C2-C3	178.4(4)
C7-N2-C2-N3	-175.8(4)	C7-N2-C2-C3	3.6(8)
N1-N2-C7-N4	-171.5(3)	N1-N2-C7-C8	7.5(6)
C2-N2-C7-N4	3.1(6)	C2-N2-C7-C8	-177.9(4)
C2-N3-C1-N1	-.3(5)	C2-N3-C1-N5	178.3(4)
C6-N3-C1-N1	176.5(4)	C6-N3-C1-N5	-4.9(7)
C1-N3-C2-N2	.7(4)	C1-N3-C2-C3	-178.7(4)
C6-N3-C2-N2	-176.4(4)	C6-N3-C2-C3	4.1(6)
C1-N3-C6-C5	-179.4(4)	C2-N3-C6-C5	-3.0(6)
C11-N4-C7-N2	178.7(4)	C11-N4-C7-C8	-.3(6)
C7-N4-C11-C10	-.2(7)	C12-N5-C1-N1	-13.2(7)
C12-N5-C1-N3	168.5(4)	C1-N5-C12-C13	58.8(5)
C1-N5-C12-C15	-176.1(4)	C1-N5-C12-C16	-60.7(5)
N2-C2-C3-C4	179.1(4)	N3-C2-C3-C4	-1.6(6)
C2-C3-C4-C5	-1.9(6)	C3-C4-C5-C6	3.0(7)
C4-C5-C6-N3	-.6(7)	N2-C7-C8-C9	-178.1(4)
N4-C7-C8-C9	.8(7)	C7-C8-C9-C10	-.7(7)
C8-C9-C10-C11	.3(7)	C9-C10-C11-N4	.2(7)
N5-C12-C13-C14	59.0(5)	C15-C12-C13-C14	-60.9(5)
C16-C12-C13-C14	178.0(4)	C12-C13-C14-C17	-62.6(6)
C12-C13-C14-C18	62.6(6)	C12-C13-C14-C19	179.8(4)

F01-C01-S01-O01	-62.4(4)	F01-C01-S01-O02	58.3(4)
F01-C01-S01-O03	177.6(3)	F02-C01-S01-O01	176.4(3)
F02-C01-S01-O02	-62.8(4)	F02-C01-S01-O03	56.5(4)
F03-C01-S01-O01	56.1(4)	F03-C01-S01-O02	176.9(4)
F03-C01-S01-O03	-63.8(4)		

3-Phenylamino-4-pyridin-2-yl-4*H*-[1,2,4]oxadiazol-5-one (**168**).

Forrmule brute:	$C_{13}H_{10}N_4O_2$
Poids moléculaire:	254.3
Coefficient d'absorption linéaire	μ = 0.103 mm^{-1} (Mo (K□))
Solvant de recristallisation	acétonitrile
Densité Do = ?	Dx = 1.448 ($gr.cm^{-3}$)
Diffractomètre	STOE IPDS

Géométrie de la maille

Système cristallin: Monoclinique	Groupe d'espace: *I 2/a*
a = 22.5991 (14) (Å)	α = 90°
b = 8.0415 (4)(Å)	β = 105.085 (7)°
c = 26.5828 (18)(Å)	γ = 90°
V = 4664.4 (5)($Å^3$)	Z = 16 (Z' = 2)
Nombre de réflexions pour l'affinement des paramètres:	8000 (6.8° < 2θ < 51.8°)

Forme et dimensions du cristal

Forme: prisme; Couleur: trtansparent
Dimensions: 0.104 x 0.177 x 0.28 mm
Mode de fixation: RS3000

Conditions expérimentales pour la collection des intensités

Température:	150 K	Longueur d'onde	0.7107(Å)
Mode de balayage	φ-scan	$\Delta\varphi$ / image	1.2 (°)
T Irradiation / image	3 (min)	φ min, max =	0 - 235.2 (°)
Distance cristal / IP	70 (mm)	Nombre d'images	197
EMS	0.006	Moyenne (I/□(I))	6.4
Limites angulaires	5.3° < 2□ < 51.8°		
Limites d'indices	-27 < h < 27 ; -9 < k < 9 ; -32 < l < 32		

Nombre de réflexions mesurées: 22'056

Réduction des données

Corrections :	LP	☒	
	Disp. anomale	☒	
	Absorption	☒	T min. , max. = 0.9814 , 0.9904

Nombre de réflexions observables	2132	|Fo|> 4□(Fo)
Nombre de réflexions non-observables	2425	
Nombre de réflexions uniques	4557	R_{int} pour 16'608 réfl. équivalentes = 0.068

Statistique des réflexions

Facteur de température global	2.32 ($Å^2$)
Distribution des $<E^2>$: centrique	$<E^2-1> = 1.011$

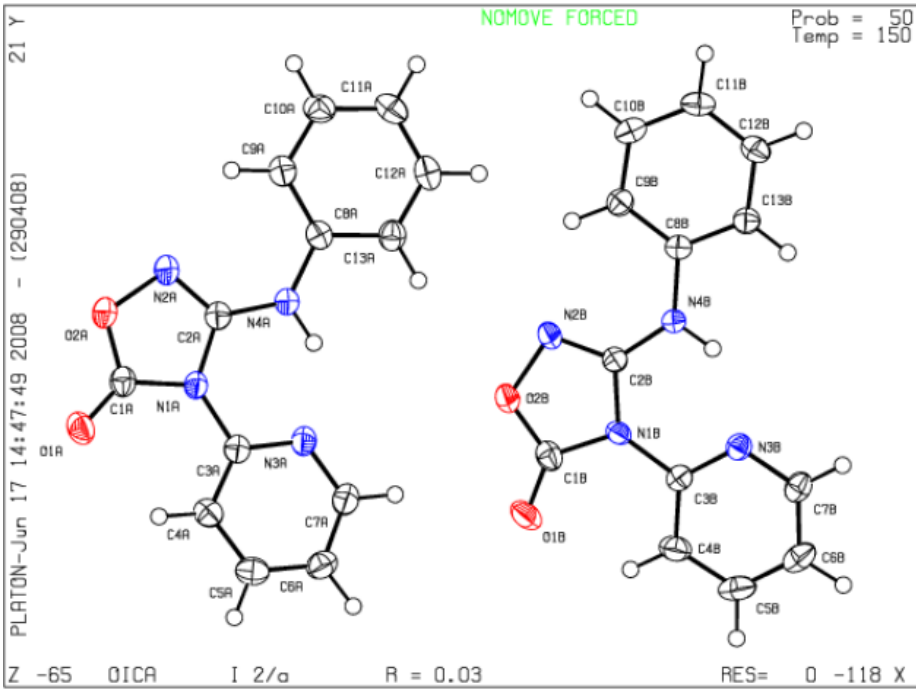
Résolution et affinement de la structure

Résolution:	Méthodes directes (SIR97)
Fonction minimisée :	$\Sigma\ (\omega\ (Fo-Fc)^2)$
Fonction de poids :	$\omega = 1/[\sigma^2(Fo) + 0.0003\ (Fo^2)]$
Nombre d'atomes affinés "iso" :	2 (H de NH)
Nombre d'atomes affinés "aniso":	38
Coordonnées des atomes d'hydrogène:	mixtes
Programme	XTAL 3.2

Valeurs obtenues en fin d'affinement

Nombre de variables:	349
Nombre de réflexions :	2541 ($\|Fo\| > 3\sigma(Fo)$)
Nbe reflexions / Nbe de variables	7.3
Affinement par moindres carrés:	Full matrix
"shift/error":	moyen : 0.39 10^{-4} , Maximum : 0.54 10^{-3}
Résidus (delta F) ($eÅ^{-3}$):	-1.28 , 0.51
"Goodness of fit": S =	1.01(1)

Facteur résiduel final	**R = 0.030**
Facteur résiduel pondéré	**ωR = 0.026**



$C_{13}H_{10}N_4O_2$ EX/97 *I* 2/*a* (Z ' = 2) 150K IPDS

Bond Distances (Angstroms)

		b
O1a-C1a	1.211(2)	1.213(2)
O2a-N2a	1.454(2)	1.456(2)
O2a-C1a	1.349(3)	1.341(3)
N1a-C1a	1.394(2)	1.390(2)
N1a-C2a	1.403(2)	1.403(2)
N1a-C3a	1.436(3)	1.430(3)
N2a-C2a	1.301(3)	1.306(2)
N3a-C3a	1.331(2)	1.334(2)
N3a-C7a	1.355(3)	1.350(3)
N4a-C2a	1.353(2)	1.351(2)
N4a-C8a	1.415(2)	1.417(2)
N4a-H04a	0.93(2)	0.90(2)
C3a-C4a	1.386(3)	1.387(3)
C4a-C5a	1.380(3)	1.388(3)
C5a-C6a	1.386(3)	1.373(3)
C6a-C7a	1.372(3)	1.376(3)
C8a-C9a	1.393(3)	1.391(3)
C8a-C13a	1.399(2)	1.392(2)
C9a-C10a	1.388(3)	1.396(3)
C10a-C11a	1.384(3)	1.383(2)
C11a-C12a	1.391(3)	1.383(3)
C12a-C13a	1.380(3)	1.388(3)

Bond Angles (degrees)

		b
N2a-O2a-C1a	110.3(1)	110.3(1)
C1a-N1a-C2a	106.2(2)	106.2(2)

C1a-N1a-C3a	125.1(1)	125.0(2)
C2a-N1a-C3a	128.7(1)	128.7(1)
O2a-N2a-C2a	104.0(1)	103.8(1)
C3a-N3a-C7a	117.6(2)	117.3(2)
C2a-N4a-C8a	128.0(2)	127.7(2)
C2a-N4a-H04a	111(1)	112(1)
C8a-N4a-H04a	121(1)	120(1)
O1a-C1a-O2a	123.2(2)	123.2(2)
O1a-C1a-N1a	130.1(2)	129.8(2)
O2a-C1a-N1a	106.6(1)	107.0(2)
N1a-C2a-N2a	112.9(1)	112.7(1)
N1a-C2a-N4a	120.7(2)	121.0(2)
N2a-C2a-N4a	126.5(2)	126.3(2)
N1a-C3a-N3a	114.5(2)	115.1(2)
N1a-C3a-C4a	121.4(1)	121.0(2)
N3a-C3a-C4a	124.1(2)	123.9(2)
C3a-C4a-C5a	117.0(2)	117.2(2)
C4a-C5a-C6a	120.4(2)	120.0(2)
C5a-C6a-C7a	118.4(2)	118.6(2)
N3a-C7a-C6a	122.6(2)	122.9(2)
N4a-C8a-C9a	124.0(2)	123.7(1)
N4a-C8a-C13a	116.1(2)	116.1(2)
C9a-C8a-C13a	119.9(2)	120.2(2)
C8a-C9a-C10a	119.0(2)	118.9(2)
C9a-C10a-C11a	121.5(2)	121.2(2)
C10a-C11a-C12a	119.0(2)	119.2(2)
C11a-C12a-C13a	120.6(2)	120.7(2)
C8a-C13a-C12a	120.0(2)	119.8(2)

Dihedral Angles (degrees)

		b
C1a-O2a-N2a-C2a	-.1(2)	1.5(2)
N2a-O2a-C1a-O1a	-179.0(2)	176.5(2)
N2a-O2a-C1a-N1a	.7(2)	-2.4(2)
C2a-N1a-C1a-O1a	178.7(2)	-176.5(2)
C2a-N1a-C1a-O2a	-1.0(2)	2.4(2)
C3a-N1a-C1a-O1a	-.5(4)	-.2(3)
C3a-N1a-C1a-O2a	179.8(2)	178.6(2)
C1a-N1a-C2a-N2a	1.0(2)	-1.6(2)
C1a-N1a-C2a-N4a	-179.3(2)	179.0(2)
C3a-N1a-C2a-N2a	-179.9(2)	-177.6(2)
C3a-N1a-C2a-N4a	-.1(3)	2.9(3)
C1a-N1a-C3a-N3a	172.5(2)	-168.7(2)
C1a-N1a-C3a-C4a	-7.9(3)	12.4(3)
C2a-N1a-C3a-N3a	-6.5(3)	6.6(3)
C2a-N1a-C3a-C4a	173.1(2)	-172.3(2)
O2a-N2a-C2a-N1a	-.5(2)	.1(2)
O2a-N2a-C2a-N4a	179.7(2)	179.6(2)
C7a-N3a-C3a-N1a	-179.4(2)	-179.1(2)
C7a-N3a-C3a-C4a	.9(3)	-.3(3)
C3a-N3a-C7a-C6a	-.3(3)	.2(3)
C8a-N4a-C2a-N1a	-174.9(2)	-179.4(2)
C8a-N4a-C2a-N2a	4.8(3)	1.2(3)
H04a-N4a-C2a-N1a	0(2)	-7(2)
H04a-N4a-C2a-N2a	-180(2)	174(2)
C2a-N4a-C8a-C9a	-2.7(3)	.7(3)
C2a-N4a-C8a-C13a	178.2(2)	179.5(2)
H04a-N4a-C8a-C9a	-178(2)	-171(2)

H04a-N4a-C8a-C13a	3(2)	7(2)
N1a-C3a-C4a-C5a	179.8(2)	179.2(2)
N3a-C3a-C4a-C5a	-.6(3)	.4(3)
C3a-C4a-C5a-C6a	-.4(3)	-.5(3)
C4a-C5a-C6a-C7a	1.0(3)	.5(3)
C5a-C6a-C7a-N3a	-.6(3)	-.3(3)
N4a-C8a-C9a-C10a	-178.4(2)	178.9(2)
C13a-C8a-C9a-C10a	.6(3)	.1(3)
N4a-C8a-C13a-C12a	177.8(2)	-178.9(2)
C9a-C8a-C13a-C12a	-1.3(3)	-.1(3)
C8a-C9a-C10a-C11a	.7(3)	-.1(3)
C9a-C10a-C11a-C12a	-1.3(3	.1(3)
C10a-C11a-C12a-C13a	.6(3)	-.0(3)
C11a-C12a-C13a-C8a	.7(3)	-.0(3)

Hydrogen bonds

N4a-H04a	0.93(2)	N4b-H04b	0.90(2)
H04a..N3a	1.87(2)	H04b..N3b	1.92(2)
N4a..N3a	2.660(2)	N4b..N3b	2.677(2)
N4a-H04a..N3a	141(2)	N4b-H04b..N3b	140(2)