Synthesis and properties of pyridine containing drugs and heterocycles

A thesis submitted to University of Sussex

By

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DECLARATION

I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another University for the award of any other degree.

Signed …… Alnomsy, Ayed khalaf

Date ……

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ABSTRACT

Chapter 1 provides an overview on the chemistry of pyridines and aminopyridines, their biological activities and their synthesis using Bohlmann-Rahtz, Hantzsch and Chichibabin methodology. It discusses the application of modern alternative reaction platforms, such as microwave-assisted synthesis and flow chemistry, of relevance to the synthesis and reactions of pyridine derivatrives.

Chapter 2 discusses Lewis acid catalysis in the Bohlmann-Rahtz pyridine synthesis and describes new one-pot, two- and three-component methodologies that have been developed for the synthesis of natural products containing the pyridine motif. These methods have been compared and contrasted and applied to the use of tetranuclear coordination clusters as Lewis acid mixed metal catalysts for Bohlmann-Rahtz cyclodehydration and pyridine synthesis.

Chapter 3 discusses the use of the Bohlman–Rahtz pyridine synthesis for the preparation of a range of fused heterocycles containing the pyridine moiety in high yield, including 1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione, 1,3-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione, 1,7-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)dione and 1-methyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

Chapter 4 describes new substrate scope for the Bohlmann-Rahtz pyridine synthesis by incorporating an amino group at the 2-position of the products. The synthesis of a range of 2,3,6-trisubstituted and 2,3,4,6-tetrasubstituted pyridines was accomplished with total regiocontrol using this new method under microwave-assisted conditions.

Chapter 5 describes a new microwave-assisted method for the synthesis of poly-deuterated pyridines. The microwave mediated deuteration of aminopyridine derivatives both with and without the presence of DCl has been studied. The regioselectivity and yields for these processes were compared. Following discovery of a new method for single cycle H/D exchange at multiple positions, high yield and high levels of deuterium incorporation have been found for a range of substrates.

ABBREVIATIONS

app	Apparent
Ac	Acetyl
Ar	Unspecified aryl substituent
BtH	Benzotriazole
Bu	Butyl
c	Concentration
CAN	Cerric ammonium nitrate
Column chromatography	Flash column chromatography
d	Doublet
DCM	Dichloromethane
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DHP	Dihydropyridine
EI	Electron impact
equiv.	Equivalent(s)
ES	Electrospray
Et	Ethyl
EWG	Electron-withdrawing group
g	Gram(s)
GHz	Gigahertz
h	Hour(s)
HRMS	High resolution mass spectrometry

Hz	Hertz
IR	Infra red
i-Pr	Isopropyl
J	Coupling constant (in Hz)
LRMS	Low resolution mass spectrometry
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
light petroleum	Petroleum ether 40–60 °C
m	Multiplet
m	*meta*
MAOS	Microwave–assisted organic synthesis
Me	Methyl
MHz	Megahertz
Mr	Molecular weight
Mr′	Average molecular weight
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry
MW	Microwave irradiation
N.A.	Not applicable
nM	Nanomolar
NMR	Nuclear magnetic resonance
p	*para*

Ph	Phenyl
PSI	pounds per square inch
q	quartet
R	Unspecified alkyl or aryl substituent
R_f	Retardation factor
R.T.	Room temperature
s	Singlet
SCX	Strong cation exchange chromatography
SM	Starting material
t	Triplet
tert	Tertiary
Tf	Triflate (trifluoromethanesulfonate)
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TsOH	*p*-Toluenesulfonic acid
W	Watt
μM	Micromolar

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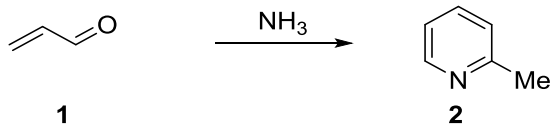
CHAPTER ONE

Introduction

1. Introduction.

1.1. Pyridines and their biological activity.

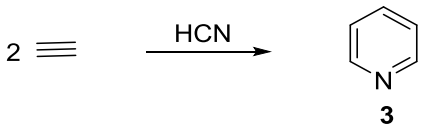
The chemistry of pyridine, as we understand it today, could be attributed in part to a number of discoveries made in the latter half of the 19th century. Thomas Anderson isolated the first pyridine base, picoline, in 1846 from bone oil.[1] In 1869 the chemistry of pyridine started to be rationalized when Wilhelm Körner and James Dewar (1871) independently formulated a mono-aza-analogue of benzene.[2] Following structural understanding a number of synthetic processes were developed, starting with Baeyer who reported the synthesis of 2-picoline (**2**), albeit in low yield,[3,4] from the reaction of acrolein (**1**) with aqueous ammonia (**Scheme 1**).



1 **2**

Scheme 1: Synthesis of 2-picoline (**2**) from acrolein (**1**) and ammonia.

In 1876 Ramsey discovered the original laboratory synthesis of pyridine (**3**).[5] Reacting a mixture of acetylene and hydrogen cyanide in a red-hot tube gave the parent heterocycle (**3**) (**Scheme 2**),[5] although large quantities of pyridine were more reliably obtained from natural sources *via* coal tar distillation.



3

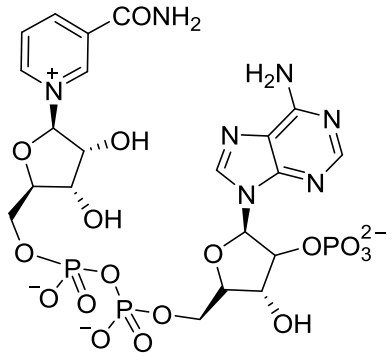
Scheme 2: Synthesis of pyridine (**3**) from acetylene and HCN.

Koehn and Elvehjem were able to isolate nicotinamide (**4**) and nicotinic acid (**5**) from vitamin B2 in the 1930s (**Figure 1**).[6] Their discovery provided a new treatment for human pellagra, a vitamin deficiency causing dermatitis and dementia. From that date, researchers started to pay closer attention to the synthesis and properties of pyridine derivatives.

4 **5**

Figure 1: Structures of nicotinamide (**4**) and nicotinic acid (**5**).

The chemistry of pyridine provided fundamental understanding of the chemistry and properties of biological systems, since this heterocycle plays an important role in both biological and chemical coordination. The pyridine ring system is one of the most common heterocyclic motifs that is found to modulate the enzymes of living organisms. For example, nicotinamide adenine dinucleotide phosphate, $NADP^+$ (**6**) (**Figure 2**), is intimately involved in various oxidation–reduction processes in biology.[7]



$NADP^+$ (**6**)

Figure 2: Structure of nicotinamide adenine dinucleotide phosphate, $NADP^+$ (**6**).

The pyridine moiety can be found in over 7000 pharmaceutical drugs such as the anti-tuberculosis drug (**7**), the HIV inhibitor L-754,394 (**8**), agrochemicals (**9–11**) (**Figure 3**)[8] and a large number of natural products.[9–11]

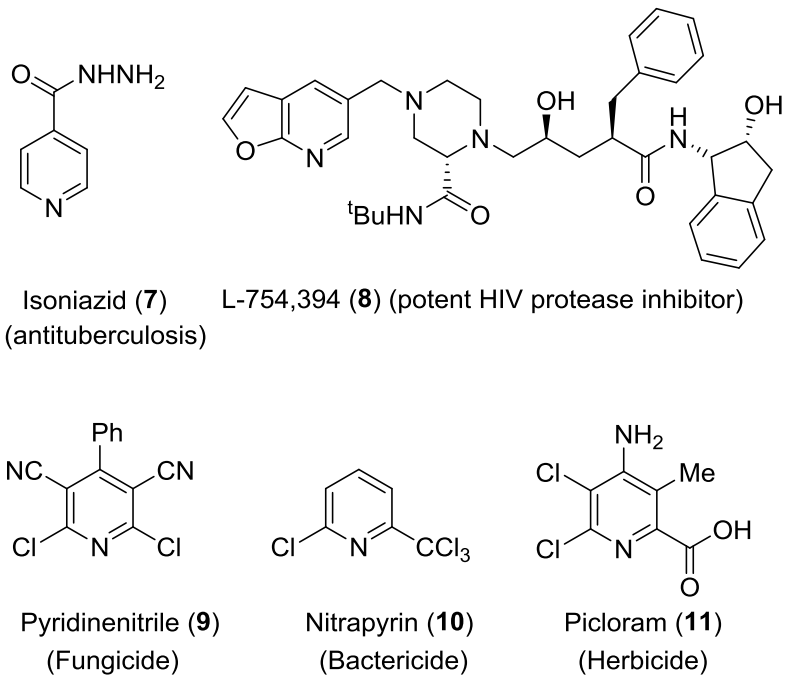
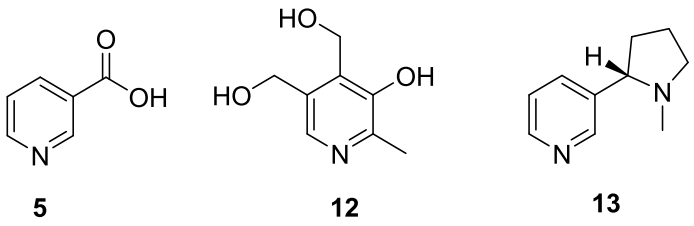


Figure 3: Structures of some pyridine containing pharmaceutical drugs and agrochemicals.

The presence of the pyridine motif in a wide range of molecules make it a very important heterocyclic class in chemistry. In modern pharmaceuticals the motif is very common, with over one hundred currently marketed drugs containing this vital unit.[12]

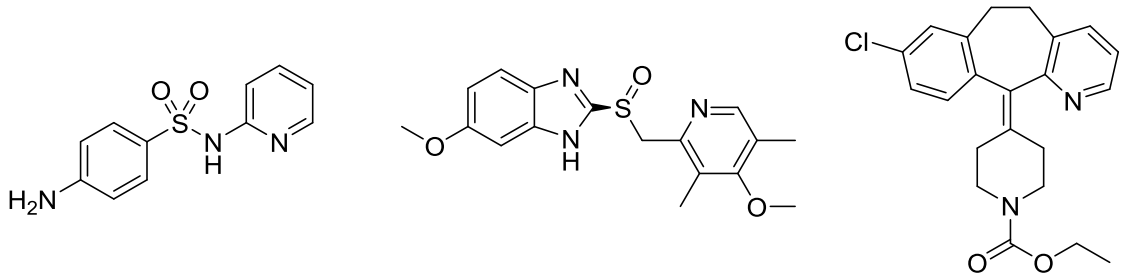
The pyridine motif is common in nature and is present in a number of biologically active natural products. In biological systems the potency of pyridines is well demonstrated by the essential vitamins niacin (**5**) (vitamin B_3) and pyridoxine (**12**) (vitamin B_6) as well as the toxic alkaloid nicotine (**13**) (**Figure 4**).[13]



5 **12** **13**

Figure 4: The pyridine motif is present in a number of biologically active molecules.

As well as natural products, the pyridine structure is commonly found in pharmaceutical agents. Sulfapyridine (**14**) was one of the first antibiotics, used to treat Winston Churchill's bacterial pneumonia in 1942. Currently marketed drugs containing the pyridine unit include the blockbuster drugs Omeprazole (**15**) (Nexium)® and loratadine (**16**) (Claritin)® (**Figure 5**).[12]



14 **15** **16**

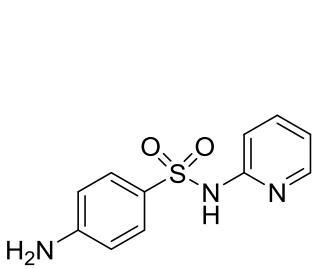
Figure 5: The pyridine structure is found in pharmaceutical agents.

Pyridines have also found applications as ligands in organic and inorganic chemistry. 2,2'-Bipyridine (bipy) is a bidentate chelating ligand that is used in the rhenium catalyzed reduction of carbon dioxide.[14] Additionally, bipy has been incorporated into metal organic frameworks as a heterogenous catalyst for the epoxidation of alkenes.[15] In synthetic organic chemistry, with potential for biological applications, pyridines have found use as nucleophilic catalysts in organic transformations. For example, 4-dimethylaminopyridine (DMAP) (**17**) has been widely used in a range of transformations including acylation and esterification reactions.[16,17]

With this wide range of applications, methods for pyridine synthesis are an ever-present focus of new research, with reviews even focusing on the most recent advances in the synthesis of pyridine derivatives.[18]

1.2. Aminopyridines and their biological activity.

There is a wide array of different substituents and possible substitution patterns of pyridine derivatives and of these, 2-aminopyridines have featured prominently in recent times as they have been incorporated into new cancer treatments.[19] Amongst many other applications, 2-aminopyridines are important as nitric oxide synthase inhibitors,[20] intermediates in the industrial synthesis of zolpidem (Ambien)®,[21] and also as ligands in organic and inorganic chemistry.[22] Aminopyridines are important compounds biologically, able to elicit a wide range of biological responses in a number of different organisms. Sulfapyridine (**14**) was one of the first effective antibiotics but their therapeutic application is just as relevant today.[23] 4-Aminopyridine (Fampridine) has been used for the symptomatic treatment of multiple sclerosis.[24] Furthermore, a 2-aminopyridine has recently been approved as a new anaplastic lymphoma kinase (ALK) inhibitor (**18**) for treatment of non-small cell lung cancer (**Figure 6**).[19]



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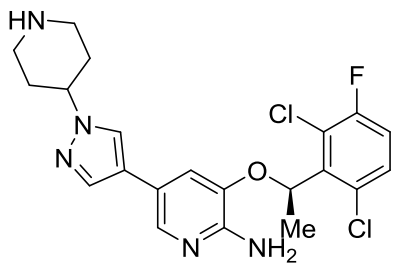

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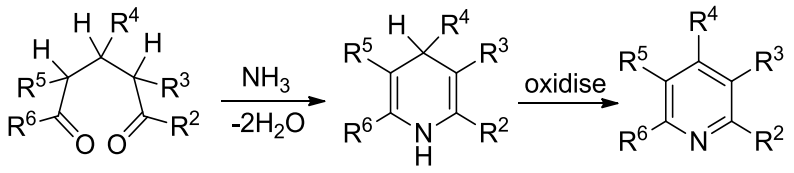
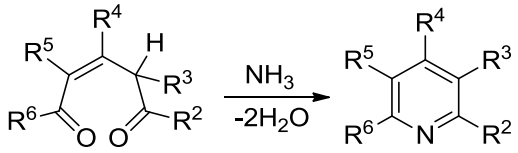
Figure 6: 2-Aminopyridines are important in the pharmaceutical industry**.**

1.3. Pyridines and their synthesis.

Synthetic approaches towards pyridine derivatives generally adopt one of two strategies: the functionalization of a pre-formed pyridine unit bearing appropriate substituents or the synthesis of the pyridine ring. The latter of these two approaches is often the more challenging, although there are many ways of achieving the synthesis of a pyridine ring. Perhaps one of the most predictable is the reaction of ammonia with a 1,5-dicarbonyl compound to give 1,4-dihydropyridines, which are easily dehydrogenated to give the corresponding pyridines (**Scheme 3**).[25] With unsaturated 1,5-dicarbonyl compounds, or their equivalents for example pyrylium ions, ammonia reacts to give the pyridine product directly (**Scheme 4**).[25]



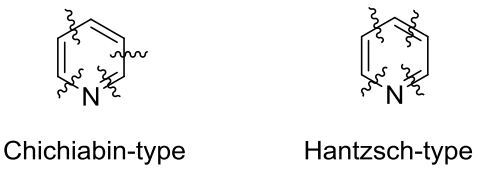
Scheme 3: Synthesis of 1,4-dihydropyridines from 1,5-dicarbonyl compounds.



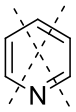
Scheme 4: Synthesis of pyridines directly from 1,5-dicarbonyl compounds, or their equivalents.

These are examples of [5+1] approaches to pyridine synthesis. Although often high yielding and able to tolerate a wide range of substituents, these methods require efficient access to the 1,5-dicarbonyl component, which is usually not readily accessible. As a result many more direct approaches have been explored using multiple component reactions.

There are two well-known [2+2+1+1]-routes for pyridine synthesis using 4-component processes, as potentially more convergent and direct approaches: the Hantzsch-type and Chichiabin-type cyclocondensation reactions.



1.3.1. The Hantzsch Dihydropyridine Synthesis [2+2+1+1].



The Hantzsch dihydropyridine (DHP) synthesis is one of the most popular methods for the synthesis of pyridines. This classical method was first published by Hantzsch in 1882 but it still remains highly relevant today.[26] In the 1980s the 1,4-DHP products were found to be useful biologically active molecules, mainly as calcium channel antagonists.[27,28] There are at lest ten currently marketed pharmaceutical agents containing the 1,4-DHP motif, including felodipine (**19**) and amlodipine (**20**) (**Figure 7**), demonstrating the importance of these compounds for the treatment of hypertension.[29, 30]

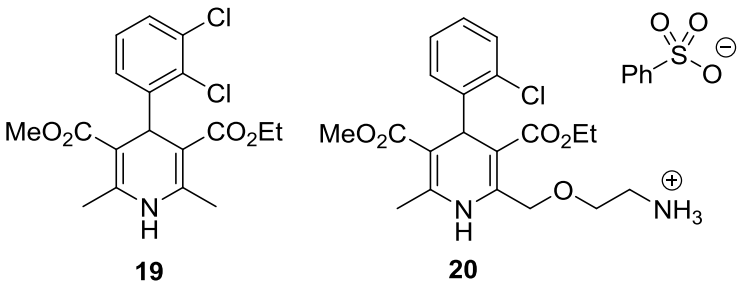
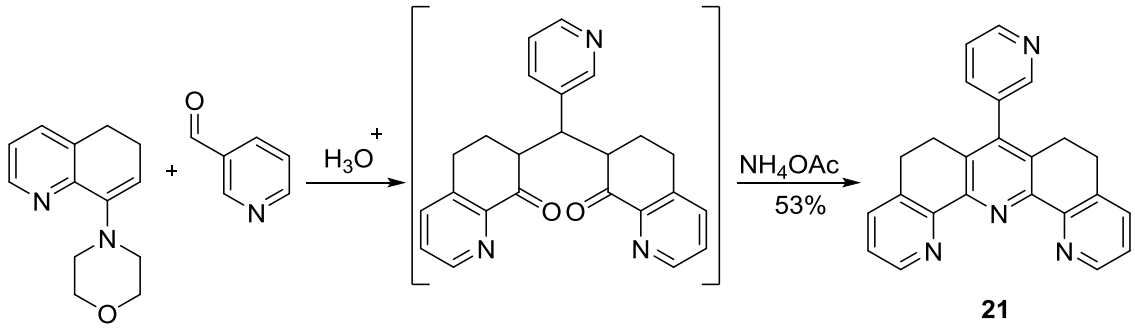


Figure 7: Two DHPs used clinically for the treatment of high blood pressure (hypertension).

The classical Hantzsch dihydropyridine synthesis is a well-known multi-component reaction that involves the cyclocondensation of an aldehyde, ketone (two molar equivalents) and ammonia or ammonium acetate.[31] Since the original report, there have been many developments and applications in the literature.

One such example of a Hantzsch-inspired strategy was reported by Hegde and co-workers in 1987 (**Scheme 5**), which required an aryl substituent at the pyridine 4-position for the synthesis of a tetrapyridine (**21**).[32]



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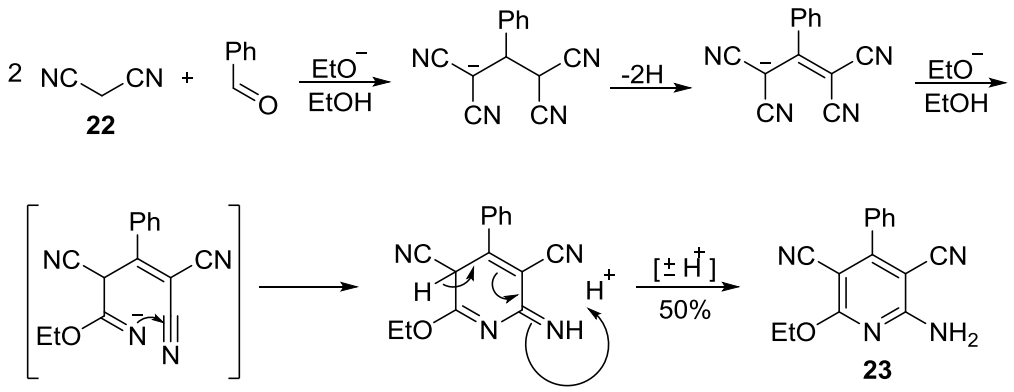
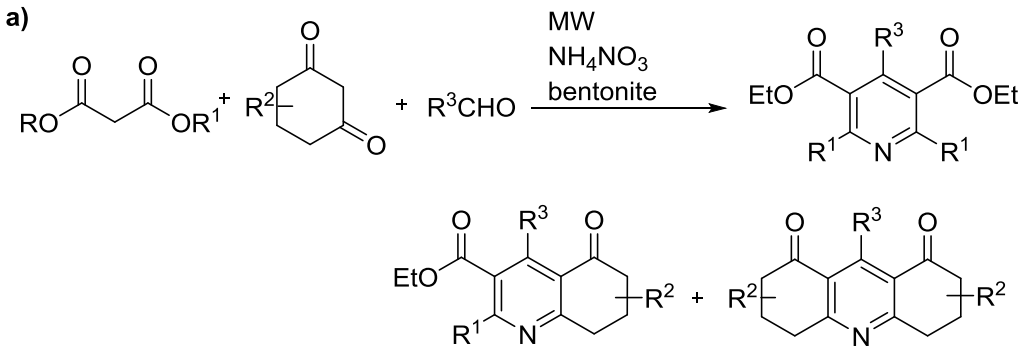
Scheme 5: An example of a [2+2+1+1] Hantzsch-strategy for the synthesis of a tetrapyridine (**21**).

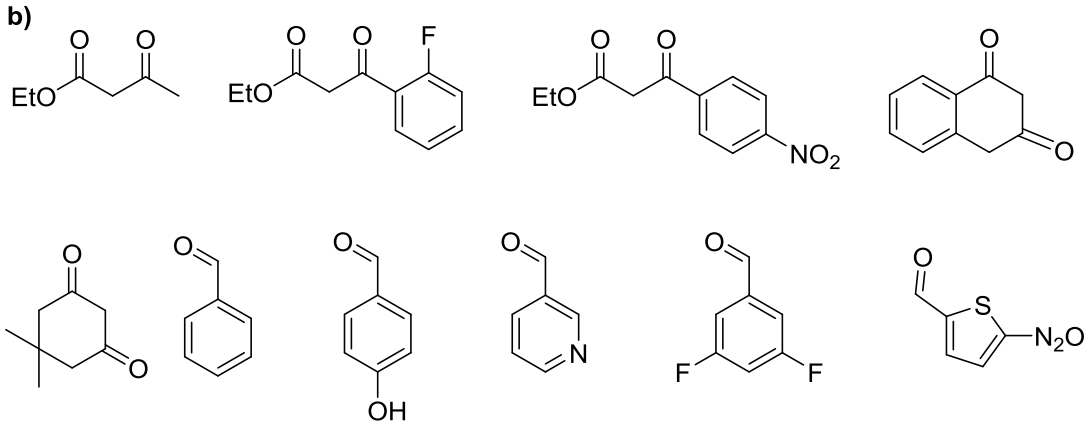
Another example, reported in 1970 by Alvarez-Insua and co-workers, used malononitrile **22** as the reactive methylene component to create the pyridine **23** functionalized with electron-donating groups at C-2 and C-6 (**Scheme 6**).[33]



Scheme 6: An example of a [2+2+1+1] Hantzsch-strategy for the synthesis of pyridines bearing electron-donating groups.

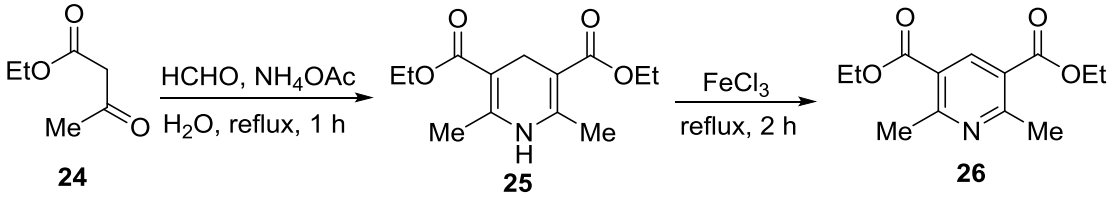
In 1998 Khmelnitsky and co-workers demonstrated the first practical application of microwave-assisted combinatorial synthesis (MICROCOS) in a Hantzsch pyridine synthesis (**Scheme 7**). Microwave-assisted organic synthesis (MAOS) can offer some interesting advantages over standard techniques, such as greatly reduced reaction times and solvent-free synthesis. A solution of the reactants (**Scheme 7a**) in a volatile solvent was impregnated into bentonite clay, the solvent was evaporated and the clay was irradiated by microwaves. Ammonium nitrate was also present as the source of ammonia and oxidant (nitric acid). The reactions were described as solution-phase as the reactants were non-covalently bound to a solid. This method was applicable to a range of ketones and aldehydes (**Scheme 7b**).[34]





Scheme 7: (a) Solution-phase combinatorial strategies for the synthesis of substituted pyridines. (b) Selection of ketones and aldehydes used in a combinatorial approach.

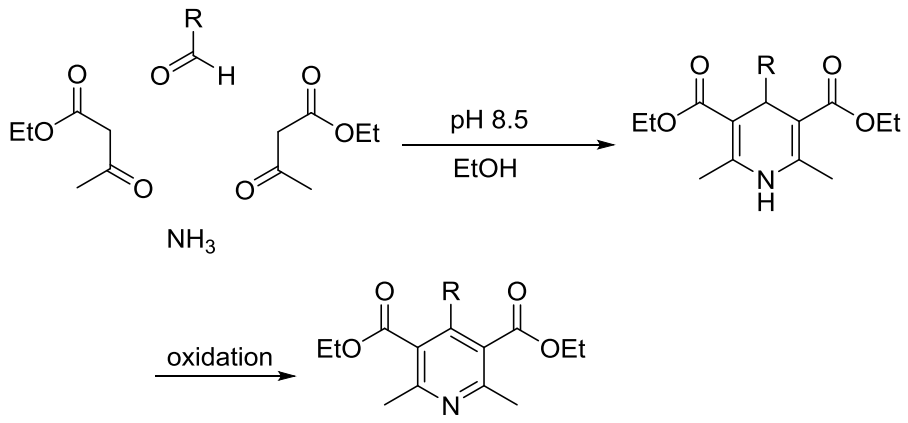
A number of different reagents have been reported for the efficient oxidation of Hantzsch DHP, including, but not limited to, nitric acid,[36] ferric chloride,[36] potassium permanganate[36] and calcium hypochlorite.[37] Even today, more than a century after the discovery of the Hantzsch DHP synthesis, research is on-going with regards to discovering greener alternatives as reagents to facilitate aromatization of the 1,4-DHP to provide the pyridine products.[38] For example, in the Hantzsch DHP synthesis, formaldehyde, ethyl acetoacetate (**24**) and ammonium acetate were reacted in aqueous medium under reflux conditions to give dihydropyridine **25**. Aromatization of **25** with $FeCl_3$ gave the corresponding pyridine derivative **26** in 93% yield (**Scheme 8**).[31]



24 **25** **26**

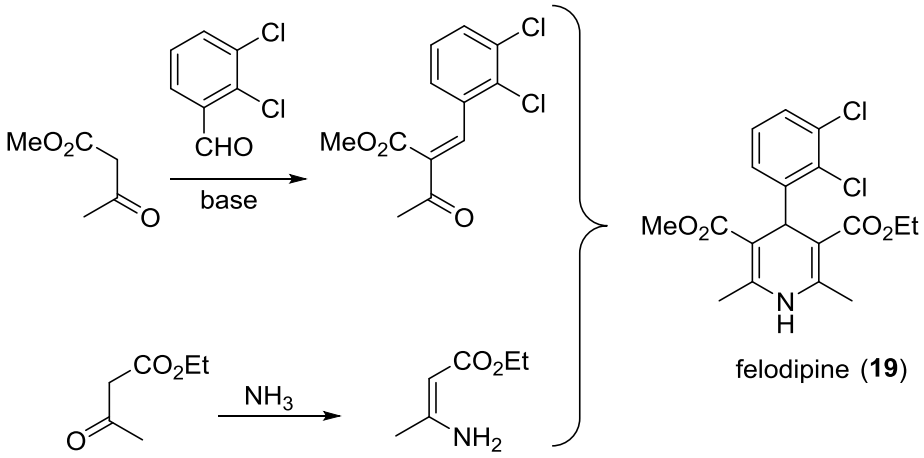
Scheme 8. Hantzsch dihydropyridine synthesis and subsequent aromatization.

The classical reaction is a three-component reaction between two equivalents of a 1,3-dicarbonyl compound, ammonia and an aldehyde to generate the DHP, followed by an oxidation (or aromatization) step to yield the corresponding pyridine (**Scheme 9**).[23]



Scheme 9: The classic Hantzsch dihydropyridine synthesis (R = aryl, alkyl).

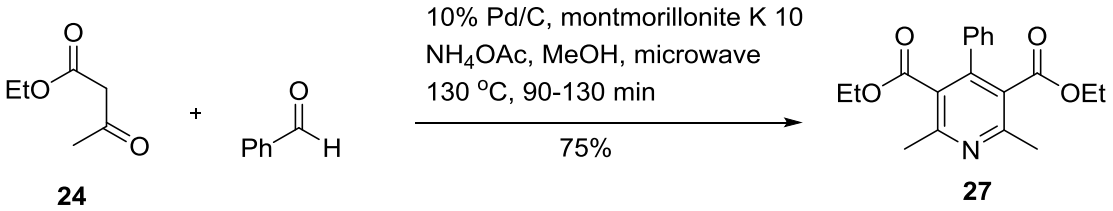
This method allows the synthesis of highly substituted pyridines on oxidation, however it is limited to symmetrical products. The synthesis of unsymmetrical 1,4-DHPs is an important modification of the classic Hantzsch method. Generating an enone separately in an aldol condensation, then reaction with an enamine can generate unsymmetrical DHPs, as demonstrated by the synthesis of felodipine (**19**) (**Scheme 10**).[23]



Scheme 10: The synthesis of unsymmetrical DHPs.

Although a valuable way to access pyridines, there are some drawbacks in the use of this methodology. The Hantzsch method is reasonably limited to carboxyl groups at the 3- and 5-positions, or other suitable electron-withdrawing groups, and aryl or alkyl groups, or other similar substituents at the 4-position.[39] In order to access different substitution patterns and incorporate alternative substituents, different synthetic approaches are required.

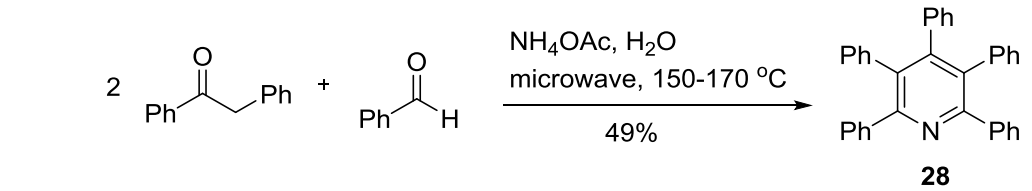
The optimum temperature seems to be 130 ^{o}C; the aromatization does not occur efficiently at lower temperatures and higher temperatures result in significant product decomposition (**Scheme 11**).[40]

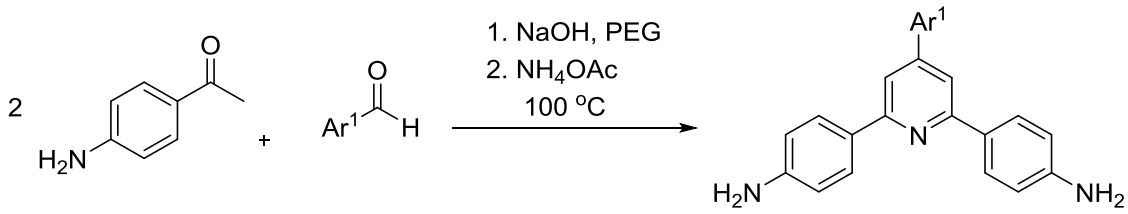


24 **27**

Scheme 11: Microwave-assisted Hantzsch pyridine synthesis.

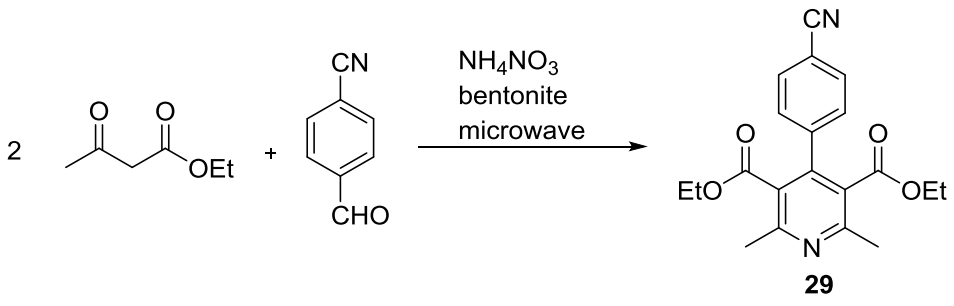
Highly substituted polyaryl pyridines (**28**), can also be obtained by Hantzsch-type methods using the combination of an aromatic ketone, an aldehyde and an ammonium salt under microwave irradiation at 150-170 ^{o}C in water.[41] A similar reaction can be carried out in one pot using poly(ethylene glycol) (PEG) as medium (**Scheme 12**).[42]





Scheme 12: Synthesis of polyarylpyridines **28**.

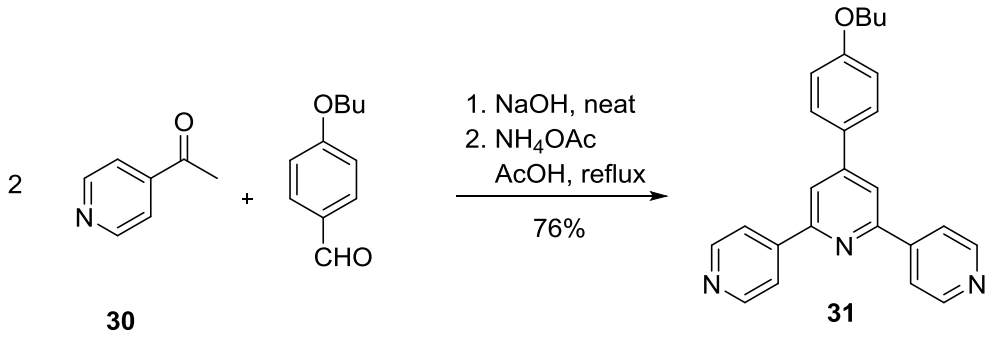
Spontaneous oxidation in situ with DHP synthesis has also been achieved under microwave irradiation. Condensation of the keto and aldehyde components using ammonium nitrate/bentonite as both the nitrogen source and oxidant in the presence of a small quantity of dimethylformamide (for heat transfer) under microwave irradiation gave pyridines directly within 5 minutes. This procedure was used in microwave-assisted combinatorial chemistry for the generation of Hantzsch esters such as **29**, in a solvent-free medium (**Scheme 13**).[43]



Scheme 13: Direct synthesis of a Hantzsch pyridine ester (**29**).

Solvent-free conditions have also been utizized in a base-catalyzed Hantzsch-type cyclocondensation using 4-acetylpyridine (**30**). Both symmetrical (*e.g.* **31**) and

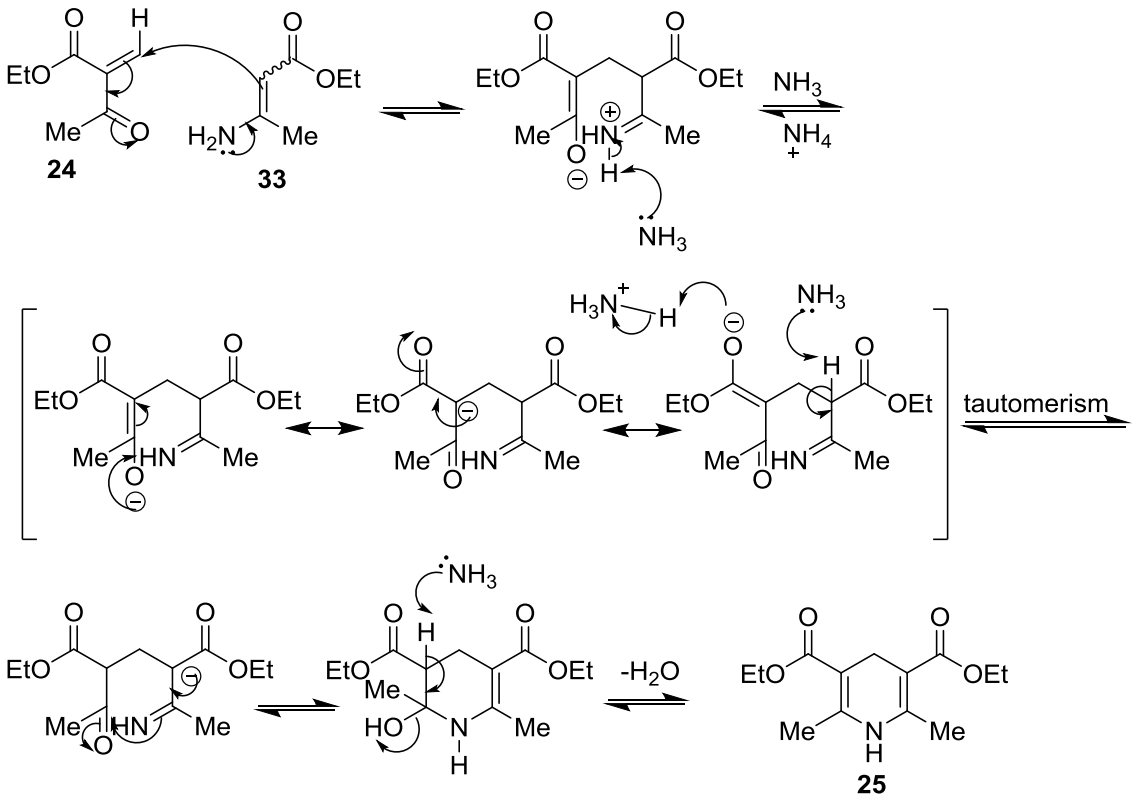
unsymmetrical 2,6-diaryl-substituted pyridines were readily accessible via sequential solvent-free aldol condensation and Michael addition using solid sodium hydroxide, followed by treatment with ammonium acetate in acetic acid, as a one-pot reaction (**Scheme 14**).[44,45]



Scheme 14: Synthesis of Hantzsch-type pyridines using solvent-free conditions.

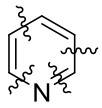
The mechanism for Hantzsch reaction involves initial Michael addition of an enamine (**33**) to an α,β-unsaturaturated ketone **24**, which is generated by an aldol aondensation, followed by cyclodehydration to give the DHP **25** product (**Scheme 15**).

Evidence for this mechanism has been found by Katrizky in a closely related transformation by ^{13}C NMR spectroscopy in which the rate-determining step was proposed to by the Michael addition on the basis of the species observed in the course of the reaction.[46]



Scheme 15. Suggested mechanism for Hantzsch dihydropyridine **25** synthesis.

1.3.2. Chichibabin Pyridine Synthesis [2+2+1+1].

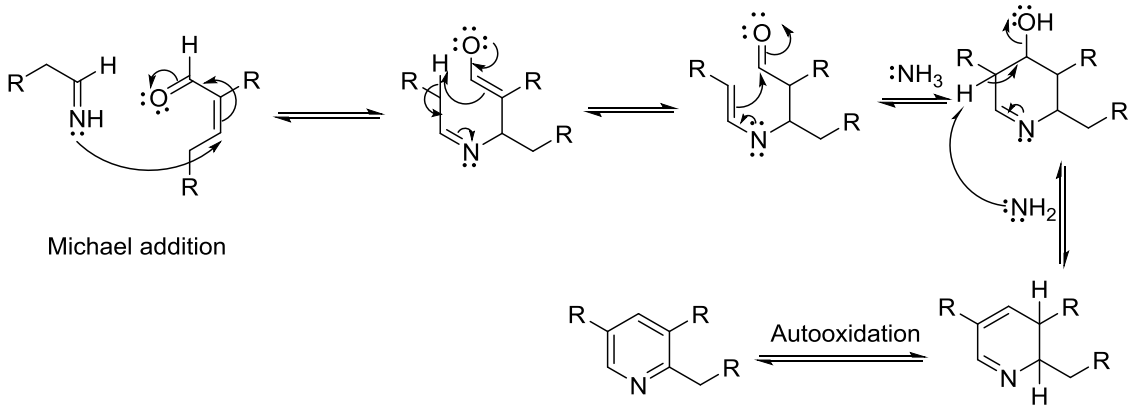


Chichibabin-type

In 1905, Chichibabin reported the thermal cyclocondensation between aldehydes, ketones, α,β-unsaturated carbonyl compounds or various derivatives of such compounds with ammonia or its derivatives to form substituted pyridines. This is one of the oldest studied organic reactions.[47]

The mechanism for Chichibabin reaction involves initial aldol condensation, followed by condensation of a third component to form an imine by the reaction of aldehyde with ammonia Michael addition of this imine with the aldol condensation product

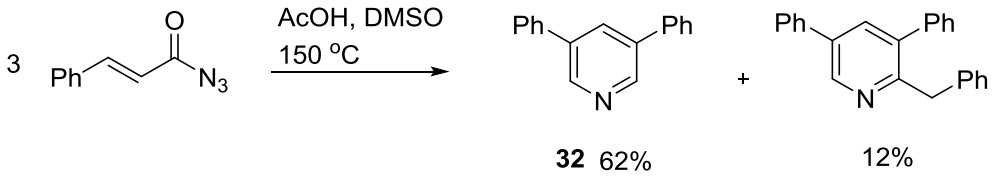
followed by cyclodehydration forms a dihydropyridine which, in turn, is dehydrogenated to the pyridine product (**Scheme 16**).[48]



Scheme 16. Suggested mechanism for Chichibabin pyridine synthesis.

Synthesis from Acryloyl Azides by Curtius Rearrangement.

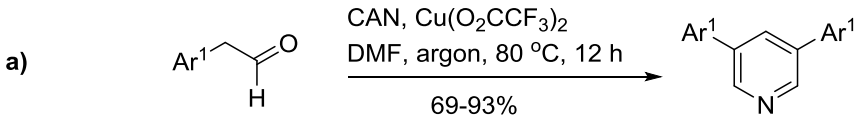
A number of modifications of the Chichibabin process have been described. A series of disubstituted pyridine derivatives (*e.g.* **32**), have been synthesized from the corresponding acryloyl azides by acid promoted cycloaddition (**Scheme 17**).[49] This represents a novel and convenient synthetic approach to symmetrical 3,5-disubstituted pyridines. The nature of the substituent on the double bond and the solvent used are crucial to give a reasonable yield of the pyridine product. The reactivity of the acid-promoted cycloaddition increases with the presence of aryl groups, such as phenyl and pyridyl moieties. The reaction is a Chichibabin-type condensation, the mechanism of which was proposed on the basis of careful examination of the crude products and involves Curtius rearrangement followed by an addition-cycloaddition sequence.[50]



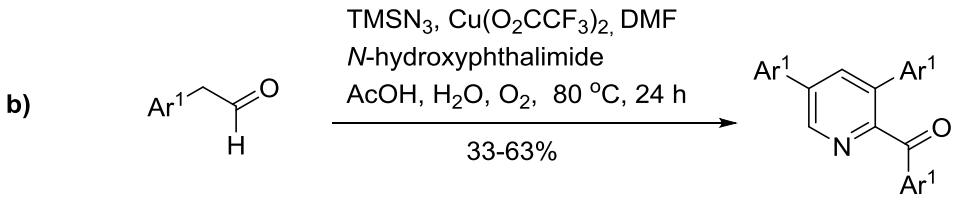
Scheme 17: Condensation of acryloyl azides in a Chichibabin-type condensation.

Synthesis from Acetaldehydes and a Nitrogen Donor.

3,5-Diarylpyridines can also be formed though a cascade Chichibabin-type cyclization using different nitrogen sources. Ammonium cerium (IV) nitrate (**Scheme 18a**) and trimethylsilyl-azide (**Scheme 18b**) are efficient nitrogen donors in this copper-catalyzed reaction which provides complementary products depending upon the conditions. Water and molecular oxygen act as the oxygen source for benzylic oxidation of the C2 substituent.[51]



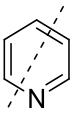
Ar^1 = Ph, 2-Tol, 3-Tol, 4-Tol, 3,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-BrC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 2-FC_6H_4, 1-naphthyl



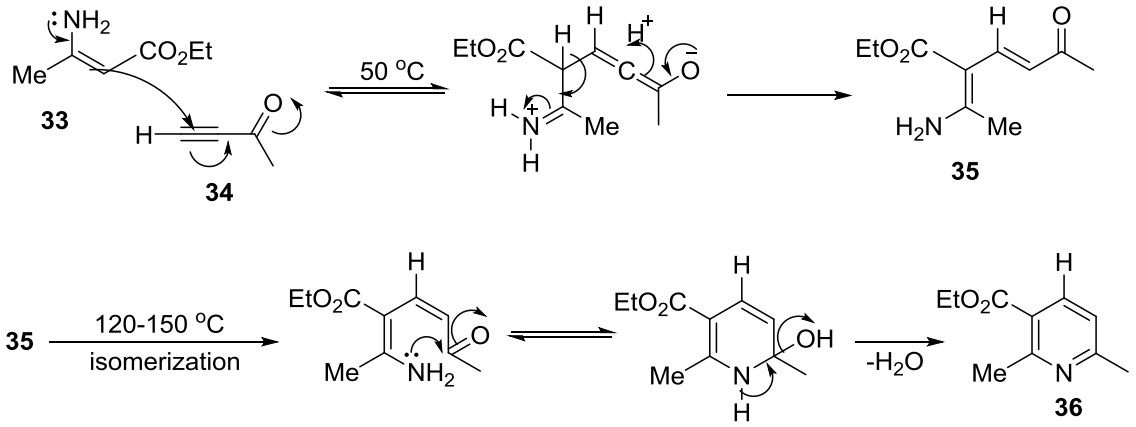
Ar^1 = Ph, 3-Tol, 4-Tol, 3,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 3-FC_6H_4

Scheme 18: Synthesis of pyridine derivatives from acetaldehydes and a nitrogen donor.

1.3.3. The Bohlmann-Rahtz Pyridine Synthesis [3+3].



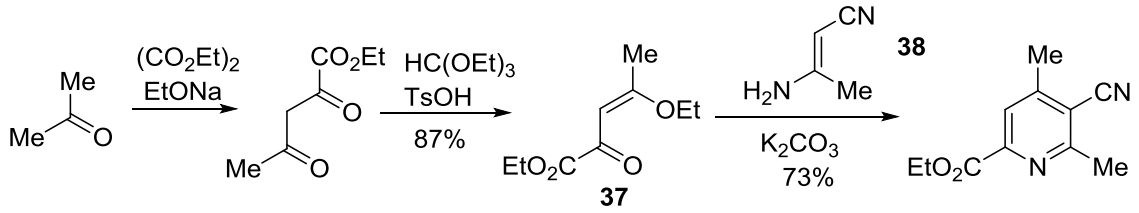
One of the most popular recent methods for the synthesis of pyridines is the Bohlmann-Rahtz pyridine synthesis. This method bears a number of similarities mechanistically to the Hantzsch DHP synthesis but accesses the pyridines directly without the need for a separate oxidation step. First outlined by Bohlmann and Rahtz in 1957, the method is efficient, totally regioselective and a two-component process that can generate 2,3,6-trisubstituted or 2,3,4,6-tetrasubstituted pyridines directly.[52] The original method reported the reaction of an enamine (**33**) and ethynyl ketone (**34**) and required two steps in order to access the target heterocycle. Firstly, Michael addition of the two components proceeded to provide an aminodiene intermediate (**35**), which was isolated and then heated at high temperature to facilitate *E*/*Z* isomerization and spontaneous cyclodehydration to yield the pyridine (**36**) (**Scheme 19**).[53]



Scheme 19: The mechanism of the two-step Bohlmann-Rahtz pyridine synthesis.

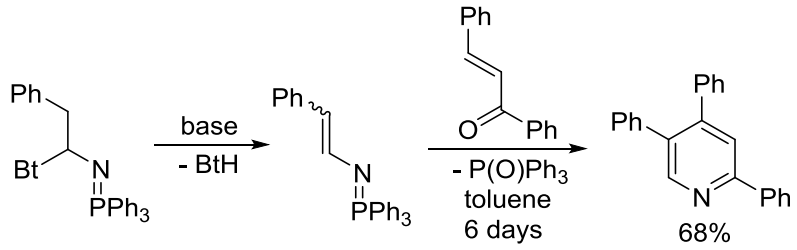
There are a number of other closely related [3+3]-based routes to pyridines, including variants of the Guareschi synthesis, in which a ketoester reacts with triethyl orthoformate

to give an ester enol ether (**37**), before Michael addition of a 3-aminoacrylonitrile (**38**), as reported by Henecke in 1949 (**Scheme 20**).[54]



Scheme 20: Alternative [3+3]-route to highly-substituted pyridines.

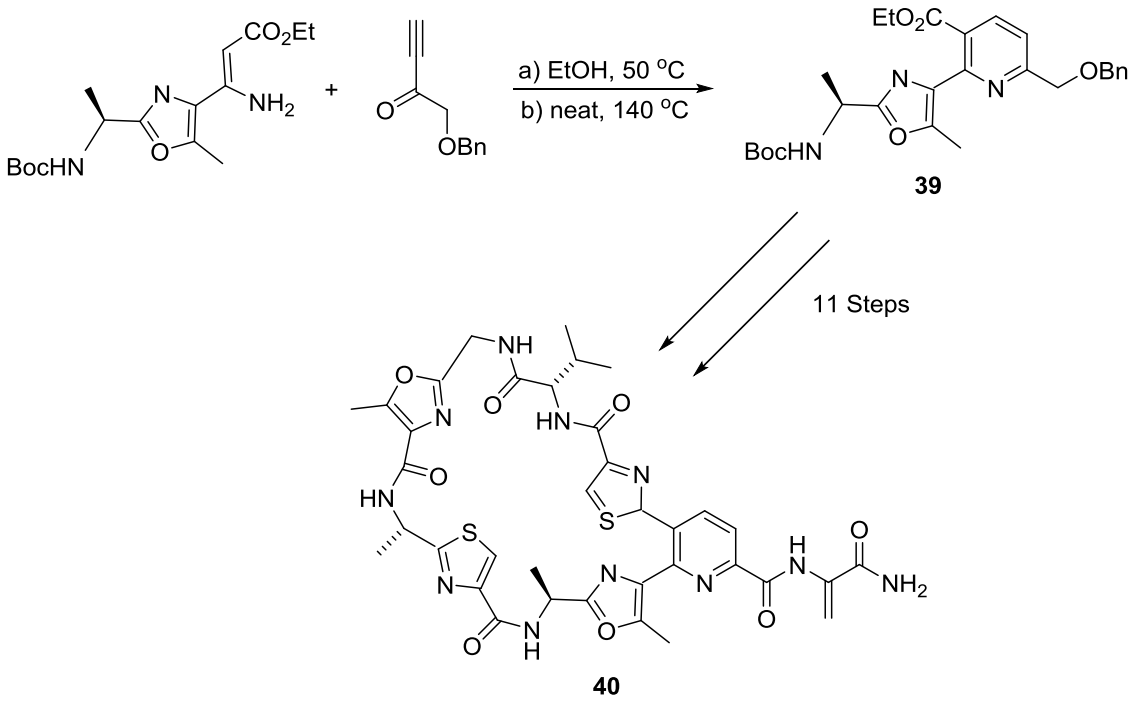
More unusual still in a related [3+3]-approach is the cyclization of an enone and iminophosphorane, prepared from the corresponding benzotriazole-substituted precursor developed by Katritzky and co-workers (**Scheme 21**).[39,55] The reaction course depends upon substrate and in this case seems to involve Michael addition followed by proton transfer and then aza-wittig reaction to give a dihydropyridine, which is readily oxidized to the product.[55]



Scheme 21: [3+3]-synthesis of pyridines using a (vinylimino)phosphorane.

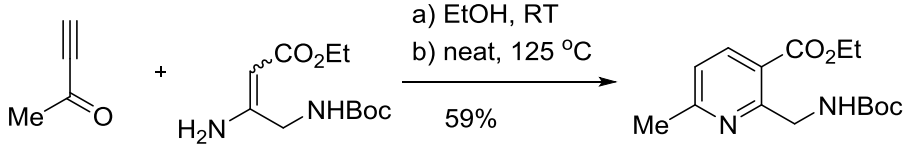
Since the discovery of the Bohlmann-Rahtz reaction, this highly regioselective and reasonably versatile pyridine synthesis was largely neglected for a number of years save for a few isolated reports by Baldwin *et al*. on the synthesis of heterocyclic amino acids,[56, 57] until its use in the first total synthesis of the thiopeptide antibiotic promothiocin A (**40**).[58] The 2,3,6-trisubstituted pyridine core (**39**) of this antibiotic was synthesized by

the Bohlmann-Rahtz method by Bagley and Moody, followed by 11 steps to reach the final product **40** (**Scheme 22**).



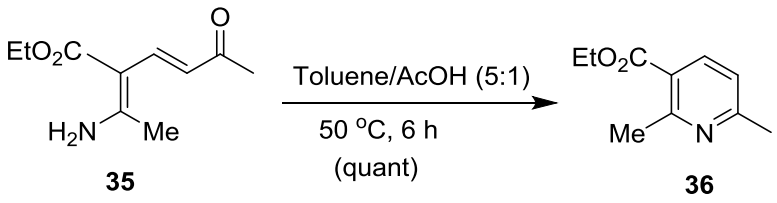
Scheme 22: The total synthesis of promothiocin A using the Bohlmann-Rahtz pyridine synthesis.

Although very efficient and providing access to highly-substituted products, a Bohlman-Rahtz approach does involve a number of distinct steps. This versatile, but little used, route to pyridines, forms a fully unsaturated pyridine directly and was demonstrated by Moody and co-workers in 2003 in the synthesis of pyridine libraries (**Scheme 23**) using the original conditions.[59]



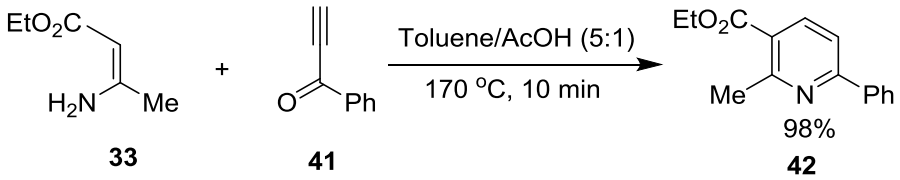
Scheme 23: An example of [3+3] pyridine synthesis using the Bohlman-Rahtz method.

The application of this method in the total synthesis of thiopeptide antibiotics resulted in research into how this neglected synthesis could be improved. A report by Bagley in 2001 described efforts to lower the reaction temperature, and incorporate the use of acid catalysts into the process.[60] The aminodiene intermediate **35** was prepared according to the initially reported conditions[52] and then stirred in a toluene/acetic acid mixture at 50 °C for 6 hours forming pyridine **36** in quantitative yield, without the need for further purification (**Scheme 24**). This example demonstrated a dramatic reduction in the temperature necessary for *E/Z*-isomerization, compared with the high temperatures (120-150 °C) that were previously required for the same transformation.



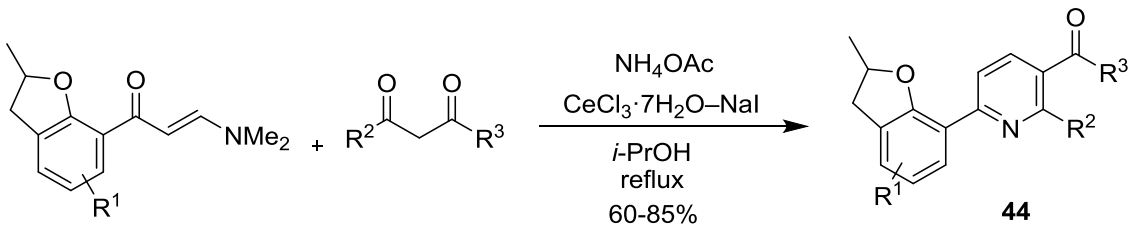
Scheme 24: Heating in a toluene/acetic acid mixture dramatically reduced the reaction temperature required to facilitate pyridine formation.

Microwave-assisted conditions can reduce the reaction times of organic transformations, compared to conventional heating methods, particularly when using laboratory-designed closed vessel reactors. In 2002, the Bagley group attempted to improve the methodology of the Bohlmann-Rahtz pyridine synthesis by employing microwave-assisted conditions.[61] In doing so they discovered that the Bohlmann-Rahtz pyridine synthesis could take place in one-step with total regiocontrol. Reaction between ethynyl ketone **41** and enamine **33** proceeded in 10 min in toluene/acetic acid (5:1) at a temperature of 170 °C, to form pyridine **42** in 98% yield (**Scheme 25**). This was the first report of the Bohlmann-Rahtz pyridine synthesis proceeding in one-step under microwave irradiation and indicated the huge potential of this method of pyridine synthesis.



Scheme 25: Microwave-assisted heating reduced the reaction time of the Bohlmann-Rahtz pyridine synthesis and proceeded in a single step.

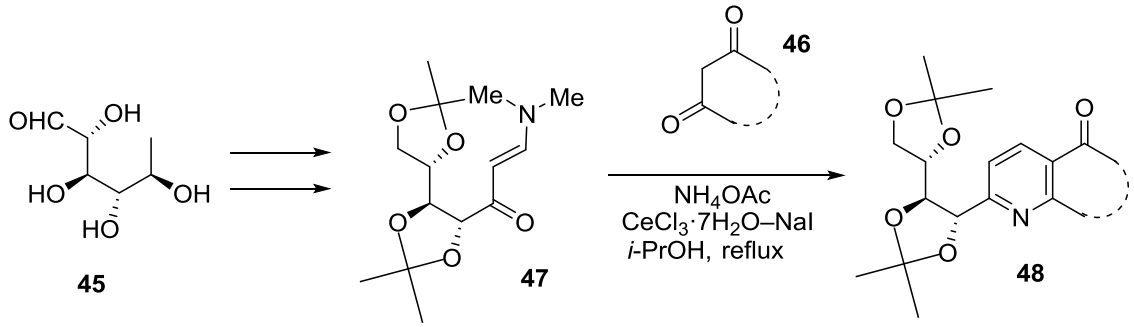
In 2010, Kantevari et al. reported the cerium(III)-catalyzed facile synthesis of dihydrobenzofuran-tethered pyridines and dihydroquinolin-5(6*H*)-ones from β-enaminones in a variant of the Bohlmann–Rahtz reaction. Inspired by the Bagley multi-component process,[62] they hypothesized that β-enaminones could serve as Bohlmann–Rahtz variants of ethynyl ketones in the synthesis of 2,3,6-trisubstituted pyridines. Given that cerium(III) chloride had emerged as an inexpensive, efficient, and green reagent for this transformation, they reported that $CeCl_3 \cdot 7H_2O$–NaI catalyzed the regioselective conversion of dihydrobenzofuranyl-substituted enaminones **43a,b** into novel substituted pyridines **44** and dihydroquinolin-5(6*H*)-ones tethered with a dihydrobenzofuran group through a Michael addition / cyclodehydration sequence in a one-pot process (**Scheme 26**).[62]



43a: R^1 = 4-Me
43b: R^1 = 5-F

Scheme 26: One-pot synthesis of pyridine **44**.

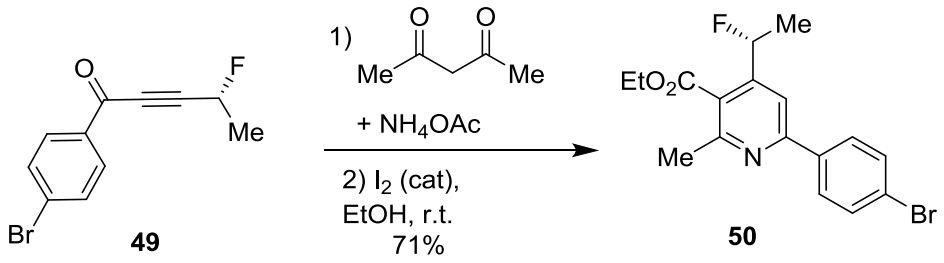
Kantevari also utilized this variant of the Bohlmann-Rahtz reaction in a facile synthesis of novel acyclo-*C*-nucleoside analogues from *L*-rhamnose. Analogues bearing substituted pyridines **48**, dihydro-6*H*-quinolin-5-ones, dihydro-*5H*-cyclopentapyridin-5-one, tetrahydrocyclohepta[*b*] pyridine-5-one, and azafluorinone were generated in very good yields, using the $CeCl_3 \cdot 7H_2O$-NaI-catalyzed one-pot cyclocondensation of the corresponding β-enaminones **47** derived from *L*-rhamnose (**45**), 1,3-dicarbonyl compound **46**, and ammonium acetate (**Scheme 27**).[63]



Scheme 27: Synthesis of pyridine **48**.

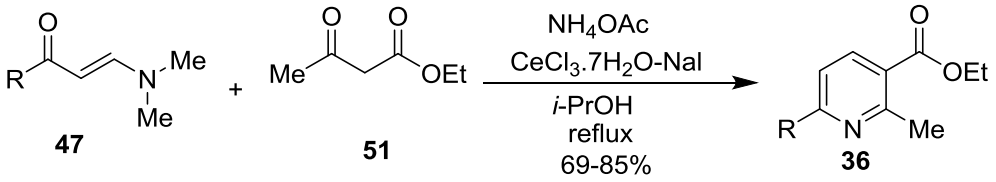
In 2007 Danielle reported a new enantioselective synthesis of monofluorinated pyridines; he found that pyridines with a fluorine atom in the benzylic position were easily accessible from optically active propargylic fluorides by using the Bohlmann–Rahtz reaction. Such pyridines, possessing four points of molecular diversity, could be useful scaffolds for the preparation of chemical libraries and the design of new strategies for the enantioselective synthesis of monofluorinated molecules.[64] Using the Bohlman–Rahtz reaction,[52] under the conditions described by Bagley,[65] and the key intermediates, optically active propargylic fluorides such as **49** as shown (**Scheme 28**), gave the desired pyridine **50** in 71% yield. This study confirmed the versatility of propargylic fluorides in

the synthesis of useful building blocks for further applications in organic and medicinal chemistry. These fluorides were easily accessible in high enantiomeric purity and the Bohlmann–Rahtz reaction afforded, under the conditions proposed by Bagley, interesting pyridines with several points of molecular diversity.[66]



Scheme 28: Synthesis of pyridine **50**.

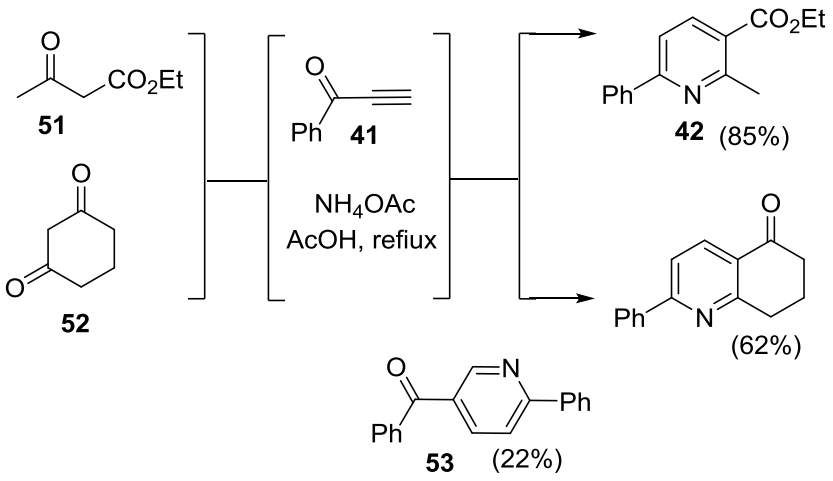
In 2011 Srinivas Kantevari used related reaction conditions to synthesize pyridine derivatives using a Bohlmann-Rahtz variant as a novel one-pot reaction, by reacting *β*-enaminones **47** with ethyl acetoacetate (**51**), and ammonium acetate in the presence of $CeCl_3.7H_2O$-NaI in 2-propanol at reflux temperature which in 4 h, gave the product **36** in 85% yield (**Scheme 29**).[67]



Scheme 29: Synthesis of pyridine **36** in a one-pot reaction.

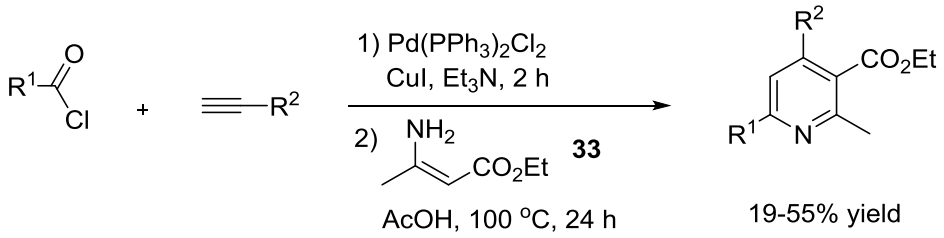
Aulakh and Ciufolini in 2009 reported Bohlmann-Rahtz reactions using modified conditions based on the use of a 5:1 mixture of toluene and acetic acid as the solvent. The

reaction of ammonium acetate and 1,3-cylohexanedione (**52**) or acetoacetate **51** with ketone **41** and NH_4OAc in progressively more acidic conditions indicated that the reaction was best carried out in refluxing acetic acid (**Scheme 30**).[68] The reaction of 1,3-cyclohexanedione (**52**) also gave rise to 5-benzoyl-2-phenylpyridine (**53**) as a side product from Bohlmann-Rahtz dimerization of ketone **41**.



Scheme 30: Synthesis of pyridines in one-pot Bohlmann-Rahtz reactions.

Recently, the one-pot 3-component cyclocondensation of a ketone, ethynyl ketone and ammonia has been named by Müller and Dohe as the Bagley-Bohlmann-Rahtz (BBR) pyridine synthesis,[69] and has been extended to a three-component or four-component coupling by incorporating a modified Sonogashira alkynone synthesis into a sequential one-pot process. Although the yields for this transformation were modest at best, it was successful for the preparation of 15 differently substituted 3-ethoxycarbonyl-2-methyl pyridines by sequential 3-component Bagley-Bohlmann-Rahtz reaction, revealing the potential of this methodology in heterocycle synthesis (**Scheme 31**).

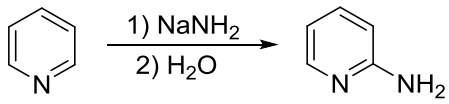


Scheme 31: 3-Component Bagley-Bohlmann-Rahtz synthesis with modified Sonogashira ethynyl ketone preparation.

These examples expanded the available substrate scope of the Bohlmann-Rahtz pyridine synthesis and provided new simpler and faster methodology for carrying out this process, that could be used to access pyridine-containing natural products such as the thiopeptide antibiotics. The temperature and reaction times required for this transformation have been reduced by these modified methods, all the while maintaining total regiocontrol. It is clear from these examples and from reviews on this process,[70] however, that the substrate scope remains limited to date at the 3-position to carboxylate derivatives or electron poor heterocycles, and at the 2-position of the pyridine targets to alkyl, aryl or heteroaryl groups and this restricts its application. If this scope could be expanded to incorporate amino groups, this would provide an alternative to the Chichibabin process (see 1.4. below) and thus access frameworks that may be more applicable to drug discovery programmes.

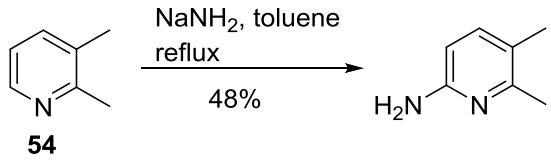
1.4. Aminopyridines and their Synthesis.

The Chichibabin reaction as it is known, distinct from the [2+2+1+2] Chichibabin pyridine synthesis, involves reaction of pyridine with sodium amide to form 2-aminopyridines (**Scheme 32**).[23] It is an unusual reaction in that hydride acts as a leaving group during the course of the reaction.



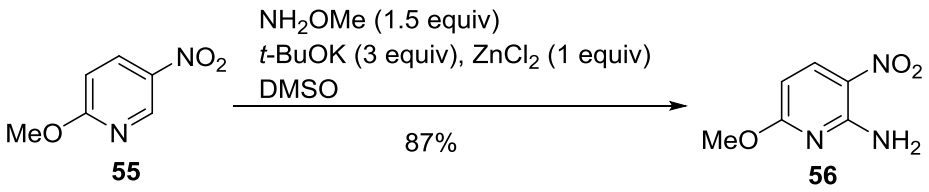
Scheme 32: The Chichibabin amination.

The classical Chichibabin (or Tschitschibabin) amination is the 2-amination of pyridine and has been extended to simple derivatives, for example the amination of 2,3-dimethylpyridine (**54**) (**Scheme 33**).[71,72] Generally, the amination of pyridines substituted with electron-withdrawing groups may give products which stem from a ring-opening reaction.[73]



Scheme 33: Tschitschibabin reaction of 2,3-dimethylpyridine.

In a related process nitropyridine **55** can be directly aminated with *O*-methylhydroxylamine in the presence of zinc(II) chloride under basic conditions to give **56** in high yield (**Scheme 34)**.[74] This zinc-promoted amination is a "vicarious nucleophilic substitution" process and high *ortho* selectivity with respect to the nitro group is observed.



Scheme 34: Amination of nitropyridine.

Thus although there are methods available for the direct 2-amination of pyridines they require forcing conditions and suffer from limited substrate scope and so new methods for the synthesis of these targets are required.

1.5. Application of alternative reaction platforms.

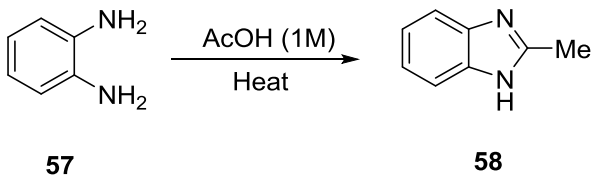
1.5.1. Microwave-Assisted Synthesis.

Over the past two and a half decades, microwave-assisted synthesis has been recognized within mainstream organic chemistry as a clean and efficient way of achieving fast, high-yielding transformations.[75] The initial adoption of microwave-assisted methods in organic synthesis was perturbed due to issues with safety, controllability and poor understanding of the mechanics of dielectric heating. However, since the development of new instruments offering a greater degree of control, microwave-assisted synthesis has emerged as one of the most convenient and practical methods of expanding reaction ranges in industry and academia.[76] Microwave heating in sealed vessels can dramatically increase the temperature of the solvent above its boiling point and therefore increase the rate of reaction in line with the Arrhenius law (Equation 1).[77]

$$k = A \exp\left(\frac{-E_a}{RT}\right)$$

[Equation 1]

An example of a reaction that demonstrates the Arrhenius relationship is the cyclocondensation of 1,2-diaminobenzene (**57**) and acetic acid to form benzimidazole (**58**) (**Scheme 35**).[78] This reaction takes 9 weeks to reach completion at room temperature, 5 hours at 100 °C under conventional heating and 1 second under microwave-conditions in a sealed vessel at 270 °C. The ability of the solvent to become 'super-heated' above its boiling temperature is a huge advantage to the organic chemist as a means to reduce reaction times and thus increase productivity.



57 **58**

Scheme 35: Temperature of the reaction mixture has a dramatic effect on reaction times for the cyclocondensation of diamine **57** and acetic acid.

Dielectric heating using microwave synthesizers takes advantage of two heating mechanisms endowed by the electric field element of electromagnetic radiation. When a polar molecule is subjected to an oscillating external electric field, dipolar polarization occurs and the molecule rotates as it attempts to align with the undulating field.

The frequency of radiation determines how quickly the molecule rotates; however, if the frequency is too high then the molecule does not have enough time to adjust and rotate, and will remain stationary. The energy window of microwave irradiation lies at a frequency that is low enough to allow the polar molecules to rotate and try to align with the field, but not too high for them to align fully before the phase of the wave has changed, creating a phase difference. This phase difference results in friction and collisions between molecules in solution, and loss of energy from the molecules as heat.

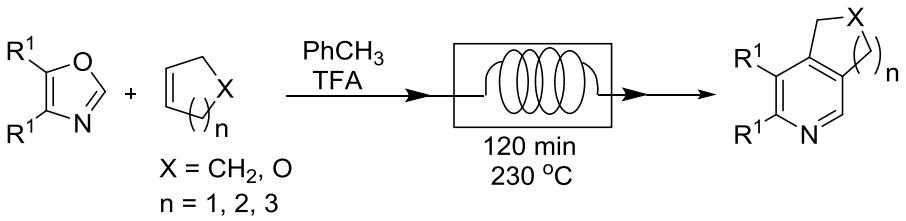
The addition of ions to solution can greatly increase the rapidity of heating through an alternative conduction mechanism. Ions will rapidly align with the oscillating electric field and travel swiftly through the solution to collide with other molecules and convert kinetic energy into heat energy. As collisions between molecules are essential, microwave dielectric heating is not possible in the gas phase.[79,80] Through a combination of these mechanisms, rapid temperature gradients can be achieved, and, through the use of sealed vessels, solvents can be heated above their atmospheric boiling point, creating energy profiles which are challenging to achieve by conventional means. These gradients can even create new selectivity profiles for reactions. For instance, reaction conditions can be tailored to favour the thermodynamic product of a regioselective reaction over the kinetic; by increasing the power of the microwaves the rate of heating is vastly increased, favouring a thermodynamic transformation.[77,78] This technology has been applied in a wide range of different fields in synthetic chemistry, including drug discovery,[81] polymer chemistry,[82] and the synthesis of colloidal inorganic nanocrystals,[83] amongst others.

1.5.2. Flow chemistry platforms.

In recent years some of the advantages, in terms of sealed vessel technology and rapid reaction kinetics, associated with microwave-assisted synthesis have been delivered by flow chemistry platforms. Given the limited penetration depth of microwave irradiation through an organic medium, continuous flow processing offers a means to scale up microwave-assisted reactions using conductive heating carried out in a flow cell at high temperature and pressure under the action of a back-pressure regulator. Flow chemistry platforms offer a number of advantages over batch processing methods, including small chemical inventories of reaction species, excellent temperature control and heat-to-mass transfer, predictable mixing, ready automation and in-line monitoring. Furthermore, a

number of different commercial instruments are available, minimizing the difficulties in transferring processes to continuous production.

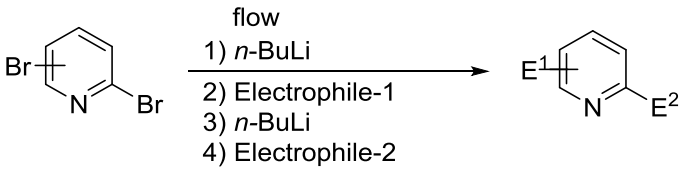
A number of methods for pyridine synthesis have been transferred to continuous processing platforms. In 2013 Rainer and Robert reported the kondrat'eva reaction in flow to provide direct access to annulated pyridines. A continuous flow inverse-electron-demand Kondrat'eva reaction was developed that provided direct access to cycloalka[*c*]pyridines from unactivated oxazoles and cycloalkenes in a one-step process under harsh conditions, as valuable scaffolds for medicinal chemistry (**Scheme 36**).[84] The flow synthesis of annulated 5-aryl-substituted pyridines by a similar process, a tandem intramolecular inverse-electron-demand hetero-/retro-Diels–Alder reaction, has been reported using continuous flow processing in good to excellent yields.[85]



Scheme 36: Flow synthesis of pyridines.

A flow microreactor method for the synthesis of disubstituted pyridines by generation of pyridyllithiums followed by reactions with electrophiles has been reported by Yoshida *et al*. By using a short residence time and efficient temperature control, the cryogenic conditions required for conventional batch macro processes were avoided and sequential

reaction of two different electrophiles with dibromopyridines was possible using an integrated flow microreactor system (**Scheme 37**).[86]



Scheme 37: An integrated flow microreactor system for sequential introduction of two electrophiles into dibromopyridines.

In a related process the flow synthesis of a series of 2-methylpyridines via α-methylation has been reported using a simplified bench-top continuous flow setup and a column packed with Raney® nickel using a low boiling point alcohol (1-propanol) at high temperature (>180 ^{o}C) to give 2-methylpyridines with high selectivity and excellent yield.[87]

An assortment of processes for the synthesis and reaction of pyridine derivatives have been described under flow conditions. Recently a continuous-flow microfluidic reactor for C-O bond formation in electron-deficient pyridines has been reported giving a cleaner reaction profile, high yield, quick scalability, and without the need for a transition metal catalyst.[88] A two step micro continuous flow assembly has been used to form polypyridine derivatives in excellent purity and yield by reaction of propargylamine with bis-α-H-methylketones over montmorillonite K-10 and gold nanoparticle impregnated alumina in a packed bed capillary reactor at reaction temperatures of 120–140 °C and residence times of 10 min.[89] In 2011 Martin reported the synthesis of annulated pyridines by intramolecular inverse-electron-demand hetero-Diels–Alder reaction under superheated continuous flow conditions. The superheating of organic solvents far beyond

their boiling point enables toxic and difficult to workup solvents such as nitrobenzene or chlorobenzene, which are usually employed for these reactions, to be replaced by less harmful ones like toluene. The relative rate of reactivity for a series of structurally close starting materials was investigated and a scalable flow process was developed, providing facile access to a series of novel annulated pyridine building blocks.[90]

1.6. Goals of this Project.

Given the value of pyridine derivatives in biology, agrochemistry synthesis and drug discovery, and the huge potential of the Bohlmann-Rahtz method, as an efficient, predicable and totally regioselective [3+3] method, this project aimed to expand the utility, application and scope of this synthetic method and apply it to a new arena. Aminopyridines are valuable targets in medicinal chemistry, hitherto inaccessible by Bohlmann-Rahtz methods. To that end, the goals of this project were:-

1- Develop more efficient catalytic methods for carrying out the Bohlmann-Rahtz process that could proceed with lower catalyst loadings.
2- Apply these methods to the hitherto-unreported Bohlmann-Rahtz synthesis of aminopyridines.
3- Explore the H/D exchange reaction of aminopyridines as a means to study the pharmacokinetic properties of aminopyridine containing drugs.

The outcome of these studies would then be new technology for the synthesis of pyridine derivatives, new diversity in the compounds that could be accessed by such methods and new understanding of methods used to elucidate their biological properties.

CHAPTER TWO

New methods for acid-catalyzed Bohlmann-Rahtz reaction

2. New methods for acid-catalyzed Bohlmann-Rahtz reaction.

Acid catalysis features in many processes in organic chemistry. Many acids can act as a proton donor to accelerate chemical reactions, changing the energy of intermediate species and the transition states involved or promoting the capability of leaving groups to convert one species into other compound classes.[91] The Bohlmann–Rahtz reaction requires a Michael donor (enamine) and a Michael acceptor (ethynyl ketone). It has been shown that the use of a Brønsted (acetic acid) or Lewis acid promotes the conjugate addition and subsequent double bond isomerization necessary for spontaneous cyclodehydration to the pyridine product, to provide a one-pot method for the synthesis of pyridines. Furthermore the presence of an acid enables the reaction to proceed at a lower temperature than the original Bohlmann–Rahtz conditions, by formation of a protonated intermediate, and avoids the need to isolate the conjugate addition product.

In recent years, the use of microwave dielectric heating in synthetic chemistry has seen widespread application.[92] Microwave–assisted organic synthesis (MAOS) benefits from no direct contact between the chemical reactants and the energy source. It can provide very fast heating rates and is readily automated using commercial instruments, leading to singnificant improvements in efficiency. Most of the available systems for organic synthesis focus microwaves in a monomodal cavity, leading to enhanced temperature control, safer operation, reproducible methodology and widespread uptake by academia and industry.[93]

Modern monomodal instruments dedicated for MAOS are very successful in small scale batch operations, but efforts to process this technology on a larger scale, for example in continuous flow (CF) reactors, are frustrated by the physical limitations of microwave heating, The Bohlmann–Rahtz pyridine synthesis has been used as a model

transformation for exploring the capability of a microwave flow reactor as well as to compare related conductive heating platforms and the transfer of reaction parameters between different technologies.[94] The development of a microwave-assisted CF process **(Figure 8**) for the synthesis of pyridines based upon the Bohlmann-Rahtz reaction has been examined in a bespoke microwave flow cell.[95] Aminodienone **35** was subjected to cyclodehydration in a CF process under homogeneous conditions in a mixture of toluene-acetic acid (5:1 by volume) over sand as a medium. The results were compared with batch experiments that were carried out in a sealed tube under microwave irradiation and a homogeneous CF process using a commercially available Teflon heating coil (**Scheme 38**).[95] Under these conditions, acetic acid acted as a homogenous acid catalyst, accelerating the process to provide an excellent yield of the pyridine product. Furthermore, the short reaction times enabled the ready transfer of this process to a CF reactor that could operate under relatively fast flow rates for continuous production.

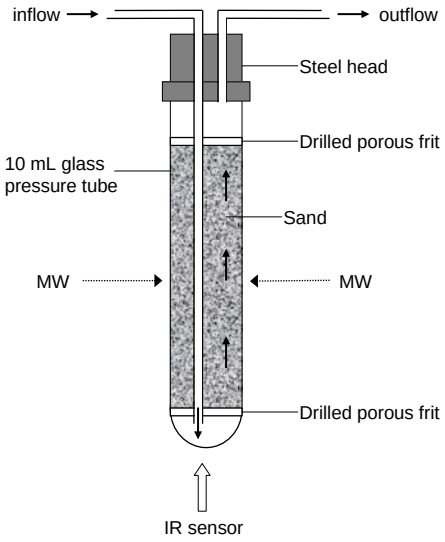
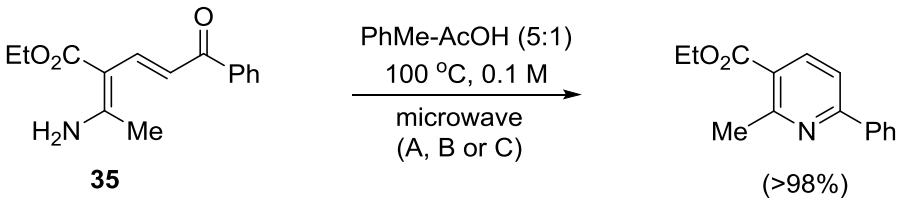


Figure 8: Schematic diagram of the CF microwave reactor.[53]



Reagents and conditions:
A: 150 W, sealed tube, 2 min.
B: 300 W, CF in Teflon heating coil, 1 mL/min.
C: 300 W, with simultaneous cooling, CF in a glass tube charged with sand, 1 or 1.5 mL/min.

Scheme 38: Microwave-assisted Bohlmann-Rahtz synthesis of a pyridine derivative.

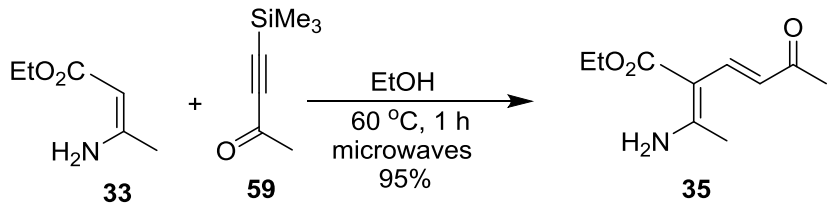
Although these observations demonstrated the potential of the Bohlmann-Rahtz reaction, in synthesis and manufacturing processes, and established the use of acid catalysis for this transformation, a substantial quantity of the acid mediator was required. Although no examples of successful catalysis have been reported using sub-stoichiometric quantities of a Brønsted acid in this transformation, the use of Lewis acid catalysts in this fashion have been described.

2.1. Lewis acid catalysis in the Bohlmann-Rahtz cyclodehydration.

Lewis acids such as $ZnBr_2$ and $Sc(OTf)_3$ have been reported to accelerate the Bohlmann-Rahtz reaction in 20-30 mol% quantities, but a systematic study to optimize this process in particular under microwave-assisted conditions has not been carried out. Thus in order to investigate this further, the Bohlmann-Rahtz cyclodehydration was chosen as the first system of study. A range of Lewis acids were to be studied in sub-stoichiometric quantities to establish which might have potential in a one-pot process.

2.1.1. Synthesis of the Bohlmann-Rahtz substrate 35.

Synthesis of the substrate aminodienone **35** was achieved in high yield by the reaction of ethyl 3-aminocrotonate (**33**) and 4-(trimethylsilyl)but-3-yn-2-one (**59**) in ethanol under microwave irradiation at 60 °C (**Scheme 39**). Under these conditions protodesilylation occurred spontaneously in the course of the reaction to give 2-amino-3-ethoxycarbonylhepta-2,4-dien-6-one (**35**) after purification by recrystallization from hexane-acetone (7:1 *v*/*v*).

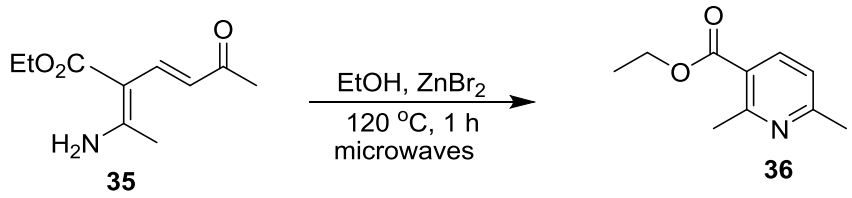


Scheme 39: Synthesis of substrate **35** under microwave-assisted conditions.

2.1.2. Investigating Lewis acids in the Bohlmann-Rahtz cyclodehydration.

The effect of Lewis acids in the Bohlmann-Rahtz reaction was first studied using substrate **35** and $ZnBr_2$ in varying quantities under microwave irradiation at 120 °C to give trisusbtituted pyridine **36** (**Table 2.1**).

Table 2.1. Bohlmann-Rahtz cyclodehydration using $ZnBr_2$ catalysis



Entry	Catalyst /mol%	Conditions	Outcome	Yield%[a]
1	150	As shown		84
2	1	RT, 24 h	**36**/**35** (6:1)[b]	n.d.
3	1	MeCN	**36**/**35** (7:1)[b]	n.d.
4	1	MeCN, 2 h		85
5	1	As shown	**36**/**35** (7:1)[b]	n.d.
6	3	As shown		99
7	0	As shown	**36**/**35** (1:1)[b]	n.d.

[a] Isolated yield of pyridine **36** after column chromatography on silica.

[b] Ratio of pyridine **36**/substrate **35** as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

n.d. Indicates not determined as multiple products and an impure sample were obtained.

The cyclodehydration was investigated in EtOH in the presence of a large excess of Lewis acid (150 mol%). In all cases the product was formed but some loss of material was observed when an excess of catalyst was present (84% yield) (Table 2.1, entry 1). When the cyclodehydration was carried out in EtOH at room temperature for 1 day with a catalytic quantity (1 mol%) of Lewis acid, the product was formed but some starting material remained (entry 2). Clearly the Lewis acid had a dramatic catalytic role even under these mild conditions. Changing the solvent and carrying out the cyclodehydration in MeCN under microwave heating with the same excess of Lewis acid (1 mol%) gave

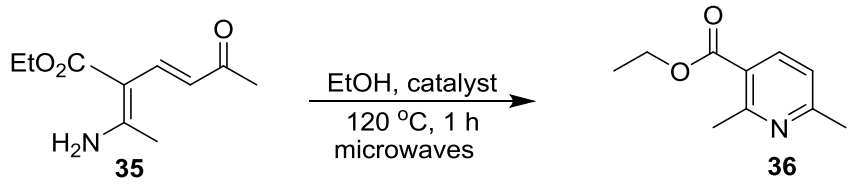
the product but with little difference in outcome (entry 3). Repeating the same reaction for entry 3, but with increased reaction time (2 h) cyclodehydration occurred, giving pyridine **36** in reasonable yield (85% yield) (entry 4). When the cyclodehydration was carried out in EtOH at 120 °C under microwave heating with a catalytic quantity (1 mol%) of Lewis acid, the outcome was multiple products were formed and an impure sample was obtained (entry 5). Increasing the quantity of Lewis acid (3 mol%) and repeating the same conditions for entry 5, gave the product in high yield (99% yield) and without any starting material present (entry 6). For comparison when the cyclodehydration was carried out in the absence of an added Lewis acid catalyst the crude material contained a substantial quantity of unreacted starting material (**35**/**36** =1:1) (entry 7).

The structure of **36** was confirmed by spectral data from NMR, MS and IR. The mass spectrum of **36** showed the presence of a pseudo molecular ion peak (MH) at *m/z* = 180 and the HRMS confirmed its formula as $C_{10}H_{14}NO_2$. The IR spectrum of **36** showed a strong absorption band at ν 1720 cm^{-1} due to the carboxylate group. The ^{1}H NMR spectrum of **36** showed two characteristic doublets (J = 8 Hz) that resonated at δ = 7.99 and 6.95 ppm which were attributed to H-4 and H-5 of the pyridine ring, respectively. The ^{13}C NMR spectrum showed a singlet signal at δ = 166.5 ppm due to the carbonyl carbon. Also, it showed resonances for all pyridine carbons and the two methyl and ethyl groups.

These studies confirmed that $ZnBr_2$ catalysis offered great potential in the Bohlmann-Rahtz reaction as a high yielding method for pyridine synthesis and EtOH would appear to be the optimum solvent, giving a single regioisomer. Given these findings, the use of alternative Lewis acid catalysts for Bohlmann-Rahtz cyclodehydration was deemed worthy of further study.

Given that $ZnBr_2$ had been shown to be a highly effective Lewis acid catalyst in the challenging step (*E/Z* isomerization) of the Bohlmann-Rahtz pyridine synthesis, even when present in very small quantities (3 mol%), a study was made of alternative Lewis acids to see how well they compared in the same transformation (**Table 2.2**). The use of $ZnCl_2$ (entry 2) or ZnI_2 (entry 3) in ethanol at 120 °C under microwave irradiation in 1 mol% quantity gave a similar outcome to the use of $ZnBr_2$ (entry 1) and provided pyridine **36** in excellent isolated yield. This was considerably more efficient than the use of a catalytic quantity of HCl as a Brønsted acid catalyst (entry 4) which gave pyridine **36** in only 58% yield. The use of $Zn(OTf)_2$ (1 mol%) (entry 5) was also high yielding, indicating that the ligands to the metal had a small influence but Zn^{II} catalysts in general were effective in the Bohlmann-Rahtz reaction. Changing the catalyst and the use of alternative metal ion catalysts, such as Ni^{II} (entry 6), Dy^{III} (entry 7) or Fe^{III} (entry 8), all promoted the formation of pyridine **36** but gave a notable reduction in efficiency.

Table 2.2. Bohlmann-Rahtz cyclodehydration using different Lewis acid catalysts



Entry	Catalyst (mol%)	Outcome	Yield%[a]
1	$ZnBr_2$ (3)		99
2	$ZnCl_2$ (1)		92
3	ZnI_2 (1)		99
4	HCl (1)		58
5	$Zn(OTf)_2$ (1)		91
6	$NiCl_2.6H_2O$ (1)	**36** / **35** (6:1)[b]	84
7	$Dy(OTf)_3$ (1)	**36** / **35** (6:1)[b]	83
8	$FeCl_3$ (5)		77

[a] Isolated yield of pyridine **36** after column chromatography on silica.

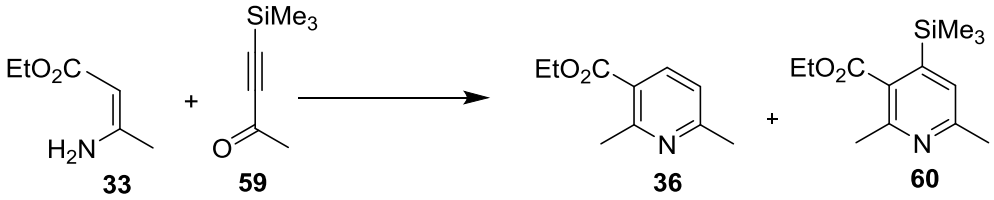
[b] Ratio of pyridine **36** / substrate **35** as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

These studies confirmed that, in sub-stoichiometric quantities, Lewis acid catalysis offered great potential in the Bohlmann-Rahtz reaction. Zn^{II} catalysts appeared to be highly efficient and effective even when used in small quantities, but other metal ion catalysts did also have promising activity. Given these findings, the role of different Lewis acid catalysts in a one-pot microwave-mediated method appeared worthy of further study.

2.1.3. Lewis acid mediated 2-in-1 Bohlmann-Rahtz pyridine synthesis.

The use of $ZnBr_2$ was investigated in the Bohlmann-Rahtz reaction using 4-(trimethylsilyl)-3-butyn-2-one (**59**) and ethyl 3-aminocrotonate (**33**). Both the Michael addition and cyclodehydration had been found to proceed in ethanol under microwave irradiation, the second step of which was promoted efficiently using Zn^{II} catalysts. However, when a one-pot process was investigated using these substrates (**Table 2.3**) it was found that protodesilylation did not proceed to completion in the presence of the Lewis acid catalyst (5 mol%) at 120 °C (entry 1) and a mixture of substrate **36**, unreacted starting material **33**, pyridine **36** and (trimethylsilyl)pyridine **60** was obtained. Under slightly more forcing conditions, at a higher temperature, longer reaction time and increased ethynyl ketone stoichiometry but reduced Lewis acid loading (entry 2), the outcome was a higher proportion of pyridine products **60** over unreacted starting material **33** or intermediates **36** was obtained, with substrate **35** also present. Under harsher conditions, at 160 °C with a longer reaction time (2 h) increased ethynyl ketone stoichiometry (3 equivalents) and increased Lewis acid loading (entry 3), a similar outcome was obtained, giving a mixture of unreacted starting material **33**, pyridines **60** and **36** and intermediate **35** in slightly altered ratio. Changing the solvent (entry 4) from EtOH to toluene, to avoid any solvent chelation to the metal, that might reduce catalyst activity, under similar conditions now gave pyridine **60** in good yield.

Table 2.3. Bohlmann-Rahtz pyridine synthesis and Lewis acid mediated 2-in-1 process.



Entry	Catalyst (mol%)	Conditions	Outcome [a]
1	$ZnBr_2$ (5)	120 °C, 1 h, 2 equiv, EtOH	**33**/**35**/**36**/**60** (8:3:2:2)[b]
2	$ZnBr_2$ (2)	130 °C, 1.5 h, 2.5 equiv, EtOH	**33**/**35**/**36**/**60** (3:1:3:2)[b]
3	$ZnBr_2$ (15)	160 °C, 2 h, 3 equiv, EtOH	**33**/**35**/**36**/**60** (4:3:4:4)[b]
4	$ZnBr_2$ (15)	160 °C, 2 h, 3 equiv, PhMe	**60** (69%)

[a] Outcome describes ratio of species in parentheses or isolated yield after purification by column chromatography on silica (entry 4).

[b] Ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

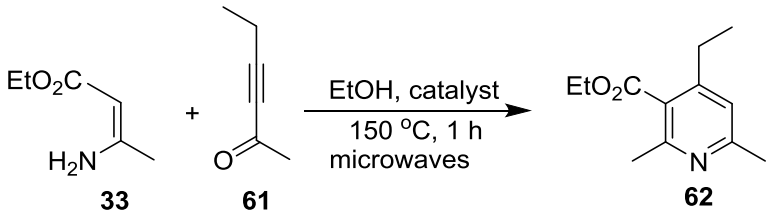
The structure of **60** was confirmed by spectral data from NMR, MS and IR spectroscopy. The mass spectrum of **60** showed the presence of a pseudo molecular ion peak (MH) at *m/z* = 252 and the HRMS confirmed its formula as $C_{13}H_{21}NO_2Si$. The IR spectrum of **60** showed a strong absorption band at ν 1730 cm^{-1} due to the carboxylate group. The ^{1}H NMR spectrum of **60** showed a characteristic singlet resonance at δ = 7.12 ppm which was attributed to H-5 of the pyridine ring. The ^{13}C NMR spectrum showed a signal at δ = 166.8 ppm due to the carbonyl carbon. Also, it showed resonances for all pyridine carbons and the six methyl groups.

These studies did demonstrate the potential for the Lewis acid mediated microwave-assisted Bohlmann-Rahtz reaction and showed that whilst ethanol was a useful solvent in terms of species solvation it was probably retarding the rate, through interacting with the

catalyst or solvating the nudeophile. It also served a role in protodesilyation but this was incomplete under these conditions. Thus in order to remove this ambiguity and in an effort to reduce the ethynyl ketone stoichiometry, an alternative, less volatile ethynyl ketone was used in place of 4-(trimethylsilyl)-3-butyn-2-one (**59**). Thus an alternative series of experiments was conducted using 3-hexyn-2-one (**61**) which would be expected to undergo slower Michael addition, but should be more facile in *E/Z*-isomerization.

Bohlmann-Rahtz pyridine synthesis and Lewis acid mediated 2-in-1 Michael addition-cyclodehydration using a different ethynyl ketone was investigated in the first instance using $ZnBr_2$ as catalyst, replacing butynone **59** with 3-hexyn-2-one (**61**) (Table 2-4, entry 1). The reaction was effective, even in EtOH, giving a good yield and thus showing the process was feasible and efficient. When the ethynyl ketone **61** stoichiometry was reduced to 1.2 equivalents (entry 2) the yield was lower and the presence of ethyl acetoacetate (**51**) was observed in the crude product. Presumably this was formed through hydrolysis of enamine **33** using H_2O produced in the cyclodehydration. This may have occurred as a result of slower Michael addition when less ethynyl ketone **61** was present. Alternatively when the Lewis acid $FeCl_3$ (entry 3) was investigated under identical conditions, the process worked better than $ZnBr_2$; the Bohlmann-Rahtz cyclodehydration proceeded in high yield and gave a single isolated product. However the presence of acetoacetate **51** was again observed in the crude product.

Table 2.4. Lewis acid mediated 2-in-1 Bohlmann-Rahtz pyridine synthesis using a different ethynyl ketone.



Entry	**33**/**61**	Lewis acid	Yield %[a]	Outcome
1	1:2	$ZnBr_2$ (20 mol%)	75	
2	1:1.2	$ZnBr_2$ (20 mol%)	67	**51** present in crude
3	1:1.2	$FeCl_3$ (20 mol%)	86	**51** present in crude
4	1:1.2	$FeCl_3$ (20 mol%), NH_4OAc (20 mol%)	[b]	
5	1:1	$FeCl_3$ (20 mol%)	84	
6	1:1	No catalyst	55	

[a] Isolated yield after column chromatography on silica.

[b] Pure product was not obtained.

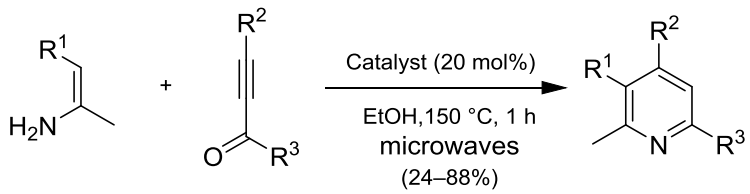
In case the hydrolysis of enamine **33** had been responsible for lowering the yield, the process was repeated in the presence of NH_4OAc (entry 4) to convert back any acetoacetate **51** formed to enamine **33**; however, this seemed to lower the activity of the catalyst and gave a mixture of products. Reducing the stoichiometry to a 1:1 ratio of enamine **33** / ethynyl ketone **61** (entry 5) gave an excellent yield of product after purification by column chromatography. Finally, to confirm the Lewis acid was serving a catalytic role, the reaction was repeated in the absence of the catalyst (entry 6); under these conditions in fact a reasonable yield of pyridine **62** was obtained (55% yield) showing that these high temperature conditions did facilitate Michael addition and

subsequent cyclodehydration. However, both Lewis acids appeared to provide some improvement over this uncatalyzed process.

The structure of **62** was confirmed by spectral data from NMR, MS and IR spectroscopy. The mass spectrum of **62** showed the presence of a pseudo molecular ion peak (MH) at *m/z* = 207 and the HRMS confirmed its formula as $C_{12}H_{17}NO_2$. The IR spectrum of **62** showed a strong absorption band at ν 1723 cm^{-1} due to the carboxylate group. The ^1H NMR spectrum of **62** showed a characteristic singlet at δ = 6.86 ppm which was attributed to H-5 and a quartet (J = 7 Hz) that resonated at δ = 4.39 ppm which was attributed to the CH_2 of the ethyl ester. The ^{13}C NMR spectrum showed a signal at δ = 168.9 ppm due to the carbonyl carbon. Also, it showed resonances for all pyridine carbons and the three methyl and ethyl groups.

Given that an effective method for rapid pyridine formation had been found under microwave irradiation using either $ZnBr_2$ or $FeCl_3$ as catalyst, the scope of these new processes was investigated using 1:1 stoichiometry, unless stated otherwise (**Table 2.5**). It was found that the synthesis of pyridine **62** using $FeCl_3$ as a Lewis acid catalyst gave improved yield in the one-pot process when compared with $ZnBr_2$ (enties 1 and 2), but for the synthesis of pyridine **36** using $FeCl_3$ as a Lewis acid catalyst gave a comparable yield in the one-pot process to the use of $ZnBr_2$ (enties 3 and 4) $FeCl_3$ gave good yields of the pyridine products using ethyl β-aminocrotonate with a range of ethynyl ketones (enties 5 and 6), but using crotononitrile gave very variable yields as shown (enties 7, 8 and 9) and much lower reaction efficiencies were observed. Pyridine **68** (entry 10) was obtained in excellent yield but with less reactive ethynyl ketones much lower reaction efficiencies were observed.

Table 2.5: Synthesis of pyridines using a Lewis acids catalyst.



Entry	Lewis acid	R^1	R^2	R^3	Product	Yield (%)[a]
1	$ZnBr_2$	EtO_2C	Et	CH_3	**62**	67
2	$FeCl_3$	EtO_2C	Et	CH_3	**62**	84
3	$ZnBr_2$	EtO_2C	H	CH_3	**36**	88
4	$FeCl_3$	EtO_2C	H	CH_3	**36**	86
5	$FeCl_3$	EtO_2C	Ph	CH_3	**63**	83
6	$FeCl_3$	EtO_2C	H	Ph	**64**	83
7	$FeCl_3$	NC	H	CH_3	**65**	57
8	$FeCl_3$	NC	Et	CH_3	**66**	24
9	$FeCl_3$	NC	Ph	CH_3	**67**	33
10	$FeCl_3$	NC	H	Ph	**68**	80

[a] Isolated yield after purification by column chromatography on silica.

The pyridine products were identified in the case of **62**, **63**, **66** and **67** by a singlet resonance at δ = 6.86, 6.93, 6.88 and 6.78 ppm, respectively, which was attributed to H-5 of the pyridine ring, or in the case of **36**, **64**, **65** and **68** by series of doublet resonance at δ = 7.99 and 6.95 ppm, δ = 8.05 and 7.58 ppm, δ = 7.87 and 6.49 ppm and δ = 8.04 and 7.48 ppm (J = 8 Hz), respectively, which were attributed to H-4 and H-5 of the pyridine ring in the ^{1}H NMR spectrum. The IR spectra of **65**, **66**, **67** and **68** showed an absorption band at ν 2195, 2190, 2290 and 2195 cm^{-1} due to the C≡N group. The IR spectrum of **36**,

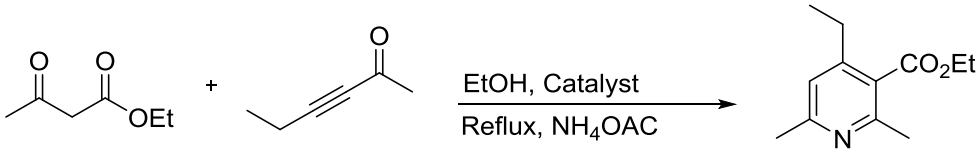
62, **63** and **64** showed a strong absorption band at *v* 1720, 1723, 1721, or 1716 cm^{-1} due to the carboxylate group. The ^{13}C NMR spectrum for C≡N containing **65**, **67** and **68** showed a quaternary carbon at δ 24.7, 23.2 and 23.9 ppm due to the nitrile group. The mass spectrum of **65** showed a pseudo molecular ion peak at *m/z* = 133 (MH) and the EI-mass spectrum showed a molecular ion peak at *m/z* = 132 ($M^{\bullet+}$). The HRMS confirmed the formula of the molecular ion as $C_8H_8N_2$. The EI–mass spectrum of **67** showed a pseudo molecular ion peak at *m/z* = 208 and the HRMS of the pseudo molecular ion confirmed its formula as $C_{14}H_{12}N_2$. The mass spectrum of **68** showed a pseudo molecular ion peak at *m/z* = 195 (MH) and the EI-mass spectrum showed a molecular ion peak at *m/z* = 194 ($M^{\bullet+}$). The HRMS confirmed the formula of the molecular ion as $C_{13}H_{11}N_2$.

2.1.4. Bagley-Bohlmann-Rahtz 3-component pyridine synthesis.

Given that an efficient process had been discovered for carrying out Bohlmann-Rahtz pyridine synthesis, with Michael addition-cyclodyhydration proceeding in one-pot, using either $ZnBr_2$ or $FeCl_3$ as a Lewis acid catalyst, this technology was next applied to a 3-component reaction. This process had been described before but, in ethanol, relatively low yields had been obtained. The studies were initiated using the potentially problematic-3-hexyn-2-one (**61**) to investigate the role of each Lewis acid under conductive heating in the presence of ammonium acetate and ethyl acetoacetate (**51**) (**Table 2.6**). The first conditions investigated in the Bagley-Bohlmann-Rahtz pyridine synthesis were carried out at reflux, with $ZnBr_2$ as Lewis acid catalyst in EtOH and in the presence of NH_4OAc to convert the acetoacetate **51** to enamine **33**. In all cases the product was formed but with an excess of ethynyl ketone (entry 1) multiple products were formed. Using equimolar quantities of **61** and **51** (entry 2) did give the product but in very low

yield. The yield was improved with a small excess of hexyone **61** providing pyridine **62** in 50% yield (entry 3) but other products were formed. Using $FeCl_3$ as Lewis acid (entry 4), which was highly effective in the Bohlmann-Rahtz reaction, was less effective in the presence of NH_4OAc, in ethanol, perhaps because Lewis acidity was attenuated by solvent or reagent acting as a Lewis base, or because the presence of the Lewis acid was interfering with enamine formation.

Table 2.6. Bagley-Bohlmann-Rahtz reaction using Lewis acid catalyst.



51 **61** **62**

Entry	Lewis acid (20 mol%)	Stoichiometry[a]	Yield %[b]
1	$ZnBr_2$	1 : 2	n.d.
2	$ZnBr_2$	1 : 1	20
3	$ZnBr_2$	1 : 1.2	50
4	$FeCl_3$	1 : 1.2	24
5	$FeCl_3$ in PhMe	1 : 2	93

[a] Molar ratio of **51** : **61**.

[b] Isolated yield after purification by column chromatography on silica.

n.d. Indicates not determined as multiple products and an impure sample were obtained.

Although a new method had been established, given the lower efficiency of reactions conducted in ethanol in comparison with toluene for the 2-in-1 method using toluene (**Table 2.3**), the 3-component reaction was investigated in toluene. Avoiding the polar protic solvent ethanol would remove any unwanted interaction between solvent and Lewis acid and prevent hydrogen bonding from attenuating nucleophile reactivity and so could promote reaction. This was found to be the case. Changing to toluene as a solvent

(Table 2.6, entry 5) gave the pyridine product **62** in excellent yield when an excess of hexynone **61** was used. This compared directly to the use of $ZnBr_2$ in this multi-component process (96% yield)[96] demonstrating that $FeCl_3$ was an effective Lewis acid in both Bohlmann-Rahtz pyridine synthesis and Bagley-Bohlmann-Rahtz cyclocondensation.

2.2. Tetranuclear coordination clusters as Lewis acid catalysts.

These studies had established the effectiveness of a range of Lewis acid catalysts containing different metal centres in the Bohlmann-Rahtz reaction and related processes. Given the different reactivity profile they exhibited, this model reaction looked ideal for probing the role of different metal centres in mixed metal catalytic systems.

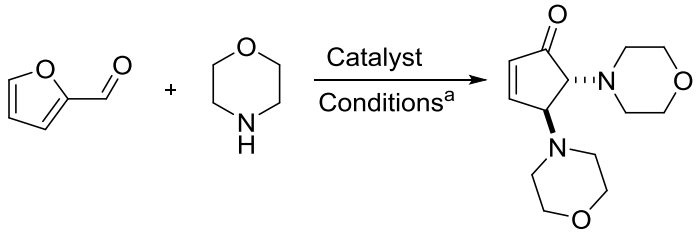
2.2.1. Previous applications of tetranuclear coordination clusters.

Polynuclear coordination clusters (CCs),[97,98] assembled from organic ligands, transition-metal elements (3*d*), and/or lanthanide (4*f*) elements, are a burgeoning class of functional materials with fascinating structures.[99–104] These materials are already used in areas ranging from molecular magnetism,[105–113] biology,[114–116] molecular imaging,[117] magnetic resonance,[118] and luminescence.[119–123] However, one of the most common applications for coordination compounds, catalysis, is much less studied for polynuclear 3d/4f heterometallic CCs with classical N,O-donor ligands[124–130] than for organometallic compounds.[131,132]

A series of heterometallic coordination clusters (CCs) $[Ni^{II}_2Ln^{III}_2(L1)_4Cl_2(CH_3CN)_2]$ $2CH_3CN$ [Ln = Y (**1Y**), Sm (**1Sm**), Eu (**1Eu**), Gd (**1Gd**), or Tb (**1Tb**)] can be readily prepared by the reaction of (*E*)-2-(2-hydroxy-3-methoxybenzylidene-amino)phenol) (H_2L1) with $NiCl_2{\cdot}6(H_2O)$ and $LnCl_3{\cdot}x(H_2O)$ in the presence of Et_3N at room

temperature. They are synthesized in quantitative yield in two steps, on up to multigram scale, and are air stable for a few months. It has been shown that these bimetallic species remain intact in organic and aqueous solutions, by ESI-MS studies, EPR studies for **1Gd** and NMR studies for **1Y** analogues. Structurally it has been shown that the Zn and the Ln centres are very close (approximately 3.3 Å), permitting both metals to coordinate to substrates and promote a series of reactions.

Dysprosium triflate, due to its mild nature, has proven to be an excellent catalyst for reactions where both nitrogen and oxygen functionalities are present.[133] Similarly these air-stable CCs containing Dy or Y demonstate efficient catalytic behaviour in the room-temperature domino ring-opening electrocyclization synthesis of *trans*-4,5-diaminocyclopent-2-enones from 2-furaldehyde (**Scheme 40**).



Scheme 40: Comparison of **1Ln** catalytic activity as CCS.[a]

Entry	Ln	Temperature	Loading[b] (mol%)	Time (h)	Yield (%)
1	Dy	r. t	1	2	quantitative
2	Y	r. t	1	24	98

[a]Reaction conditions: 1 mmol amine, 0.5 mmol 2-furaldehyde, 100 mg of 4 Å molecular sieve (MS), 4 mL of anhydrous MeCN catalyst, room temperature (r.t.). [b]Catalyst loading calculated per equivalent of Dy.

Tetranuclear $Zn^{II}_2Ln^{III}_2$ coordination clusters (CCs) have also been formd to act as catalysts for a range of other processes such as the Friedel–Crafts (FC) alkylation of indoles with trans-β-nitrostyrenes. Good to excellent yields (76–99%) were obtained at

room temperature with catalyst loadings as low as 1.0 mol%. The Dy^{III} and Y^{III} coordination clusters have also been used to catalyze the addition of aldehydes or ketones to indoles, in a facile route for the synthesis of bisindolylmethane derivatives in up to quantitative yield at 2.5-10 mol% loadings. These indole products have recently been shown to be useful in the treatment of fibromyalgia,[134] as antibacterial agents[135] and even in the prevention of cancer.[135]

The polynuclear clusters were prepared from $Ln(NO_3)_3.xH_2O$ and $Zn(NO_3)_2.6H_2O$ under aerobic conditions of H_2L in the presence of Et_3N in EtOH to give a precipitate which subsequently crystallized by vapour diffusion of Et_2O in *N*,*N*'-DMF solution, to give the air-stable tetranuclear compounds of general formula $[Zn_2^{II}Ln_2^{III}\ L_4(NO_3)_2(DMF)_2]$ where Ln was Dy (**Figure 9**).

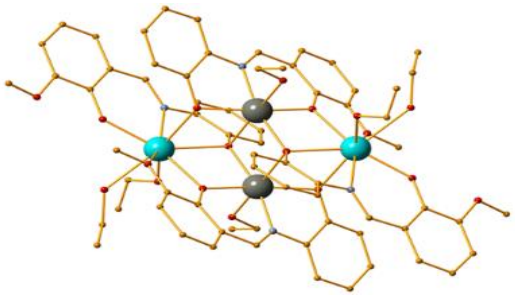


Figure 9: Molecular structure of $[Zn_2^{II}Ln_2^{III}L_4(NO_3)_2(DMF)_2]$.

Finally these heteronuclear Zn/Ln coordination clusters (CCs) have been used as catalysts for the multicomponent Mannich-type condensation of amines, aldehydes and boronic acids, known as the Petasis borono-Mannich reaction. The reaction proceeds in very good to excellent yields (84–98%, 17 products) at room temperature with catalyst loadings as low as 1.0 mol%. The cluster $[Zn_2^{II}Ln_2^{III}L_4(NO_3)_2(DMF)_2]$ (**Figure 9**)

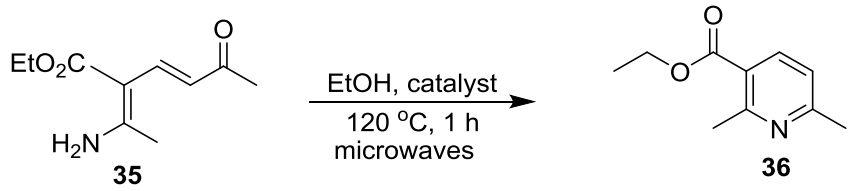
exhibited excellent efficacy in the Petasis borono-Mannich MCR at room temperature, with 1% loading giving excellent yields in a very short time.

Given this precedent that a number of Lewis acid catalyzed procedures had been observed to be promoted by these readily-available heterometallic coordination clusters, often with very low catalyst loadings, it was proposed to use clusters incorporating a range of metals in Bohlmann-Rahtz processes. These could provide new insights into the role of mixed metals in these systems and further expand the synthetic utitily of this pyridine forming reaction.

2.2.2. Bohlmann-Rahtz cyclodehydration using mixed metal catalysts.

Starting with the Bohlmann-Rahtz cyclodehydration as a model process a range of tetranuclear clusters was prepared using previously reported methods,[136] incorporating a range of different metals, and heated with aminodienone **35**. The Bohlmann-Rahtz cyclodelydration was investigated using these species at low catalyst loadings (1-11 mol%) under microwave irradiation (**Table 2.7)**.

Table 2.7. Bohlmann-Rahtz cyclodehydration using mixed metal catalysts.



Entry	Catalyst	mol%	Conditions	Outcome	Yield%[a]
1	$[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$	11	As shown		97
2	$[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$	1	As shown		98
3	$[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$	1	RT, 24h	**36**/**35** (6:1)[b]	n.d.
4	$[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$	1	MeCN	**36**/**35** (7:1)[b]	n.d.
5	$[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(MeCN)_2]$	1	As shown	**36**/**35** (5:1)[b]	76
6	$[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(MeCN)_2]$	3	As shown		98
7	$[Zn_2^{II}Y_2^{III}L_4(NO_3)_2(EtOH)_2]$	1	As shown	**36**/**35** (5:1)[b]	78
8	$[Zn_2^{II}Y_2^{III}L_4(NO_3)_2(MeCN)_2]$	1	As shown	**36**/**35** (6:1)[b]	67
9	$[Ni_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$	1	As shown	**36**/**35** (4:1)[b]	62
10	$[Ni_2^{II}Dy_2^{III}L_4(NO_3)_2(MeCN)_2]$	1	As shown	**36**/**35** (4:1)[b]	59

[a] Isolated yield after column chromatography on silica.

[b] Ratio determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

n.d. Indicates not determined as multiple products and an impure sample were obtained.

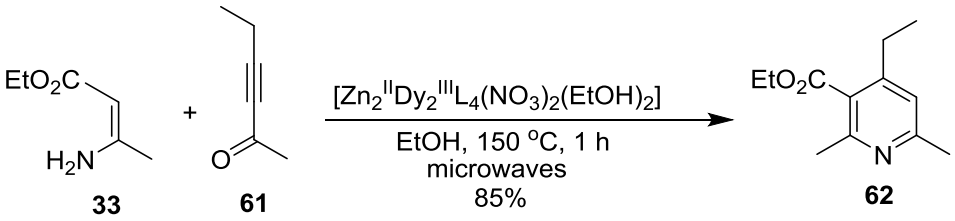
In all cases studied the pyridine product **36** was formed. The first polynuclear CC investigated was $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ which was found to act as an effective Lewis acid for Bohlmann-Rahtz cyclodehydration at 11 mol% (entry 1) or 1 mol% (entry 2) loading. Both of these experiments gave pyridine **36** in excellent yield. It was postulated that either metal centre could in principle be acting as the catalytic centre for this reaction. Using the same catalyst, $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$, but at room temperature for 1 day (entry 3) did give the product **36** predominantly but some starting material remained. It was considered that elevated temperature could promote the process by facilitating ligand exchange at the metal centre. Investigating a different reaction

solvent MeCN (entry 4) at elevated temperature was less effective and gave unreacted starting material. The role of different ligands on the metal was investigated by changing the ancillary ligand, $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(MeCN)_2]$; interestingly, the outcome was that unreacted stating material was present and only a 76% yield of product **36** was obtained after column chromatography. The reduced efficiency in comparison to $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ could be as a consequence of altered ligand exchange. The quality of catalyst was increased to 3 mol% (entry 6) and efficient conversion was obtained using this mixed metal catalyst bearing the MeCN ancillary ligand. In order to probe the role of the different metals, alternative catalysts were investigated, systematically changing one metal for alternatives. The most active catalyst $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ was replaced with $[Zn_2^{II}Y_2^{III}L_4(NO_3)_2(EtOH)_2]$ (entry 7) which caused a significant reduction in activity. Also, when $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(MeCN)_2]$ was replaced with $[Zn_2^{II}Y_2^{III}L_4(NO_3)_2(MeCN)_2]$ (entry 8) similar reductions in yield were observed in line with previous observations. Little catalyst activity was found when $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ was replaced with $[Ni_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ in either case (enties 9 and 10).

These studies confirmed that these species at low catalyst loadings were effective Lewis acids for Bohlmann-Rahtz cyclodehydration and thus offered great potential as catalysts in the Bohlmann-Rahtz reaction. The $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ catalyst appeared to be highly efficient and effective even when used in small quantities, but other mixed metal catalysts did also have promising activity. Given these findings, the role of mixed metal catalysts in a one-pot microwave-mediated method was investigated.

2.2.3. Bohlmann-Rahtz pyridine synthesis using a mixed metal catalyst.

Given the effectiveness of these mixed metal catalysts in cyclodehydration, studies were made of Bohlmann-Rahtz pyridine synthesis using the most active Lewis acid from this class $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$. Initial studies using 4-(trimethylsilyl)but-3-yn-2-one (**59**) were frustrated by incomplete protodesilylation which occurred under the reaction conditions. Thus the reaction of enamine **33** with an alternative ethynyl ketone 3-hexyn-2-one (**61**), with $[Zn_2^{II}Dy_2^{III}L_4(NO_3)_2(EtOH)_2]$ was investigated under microwave irradiation, by heating at 150 ^oC for 1 h, to give pyridine **62** in 85% yield as a single regioisomer (**Seheme 41**).



Seheme 41: pyridine **62** synthesis using a mixed metal catalyst.

Given that in the absence of a Lewis acid, this process gave a 1:1 ratio of pyridine **62** : unreacted enamine (**33**) (**Table 2.4**), the mixed metal catalyst clearly was promoting the Michael addition/cyclodehydration process. For reaction in ethanolic solvent this outcome compared very favourably with other Zn^{II} catalysts and established this process as a optional new method in Bohlmann-Rahtz chemistry under microwave irradiation.

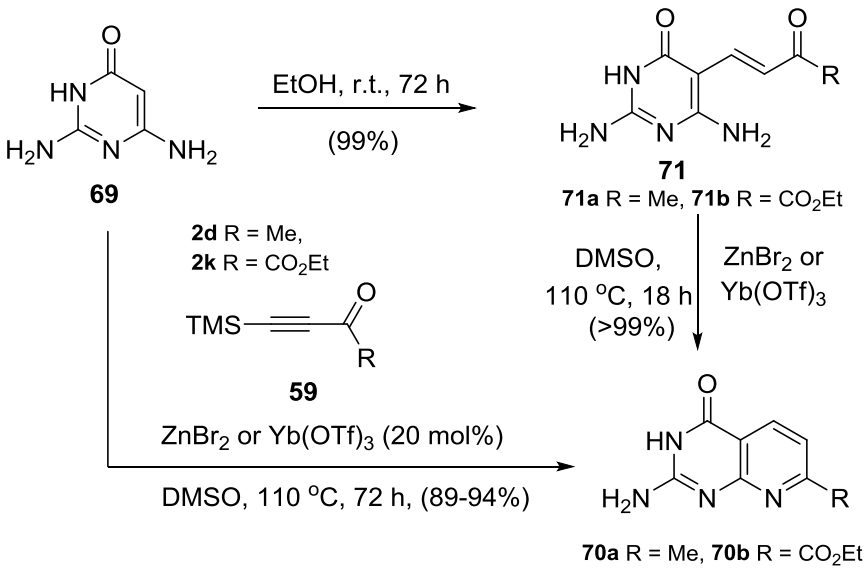
CHAPTER THREE

Bohlmann-Rahtz synthesis of pyridine [2,3-*d*]pyrimidines

3. Bohlmann-Rahtz synthesis of pyridine [2,3-*d*]pyrimidines.

3.1. Introduction.

In recent years pyrido[2,3–*d*]pyrimidine derivatives have received considerable interest as a consequence of their structural relationship to both pyridines and pteridines,[137] and the biological potential of anti-folates to elicit responses as antitumour,[138] antibacterial,[139] anti–inflammatory[140] and insecticidal agents.[141] The Bohlmann-Rahtz reaction has been applied to pyridine-fused heterocycles, notably pyrido[2,3-*d*]pyridines, as a route to the core motif of deazapterins and folates of interest. One of the first studies of this kind investigated the synthesis of pyrido[2,3-*d*]pyrimidines using ethynyl ketones under Lewis acid catalyzed conditions.[142] For example, the synthesis of 2-substituted pyrido[2,3-*d*]pyrimidines **70** from the corresponding (diaminopyrimidinyl)propanone **71** or in one pot from the reaction of diaminopyrimidinone **69** and butynone **59** was reported using the Bohlmann-Rahtz reaction (**Scheme 42**). When a solution of the pyrimidine derived Bohlmann-Rahtz intermediate **71** and zinc(II) bromide (20 mol%) in dimethylsulfoxide was heated overnight at 110 °C the heteroannelated product **70** was produced in >99% yield (**Scheme 42**).[142] Furthermore, when a solution of diaminopyrimidinone **69** and butynone **59** in dimethylsulfoxide was heated at 110 °C for 72 hours in the presence of either zinc(II) bromide (20 mol%) or ytterbium(III) triflate (20 mol%), the zinc(II) catalyzed reactions gave pure pyrido[2,3–*d*]pyrimidine **70a**,**b** in 92 and 89% yield, respectively, whereas the ytterbium(III) catalyzed process gave a slightly impure product **70a**,**b** in 94 and 91% respective yield (**Scheme 42**).[142]

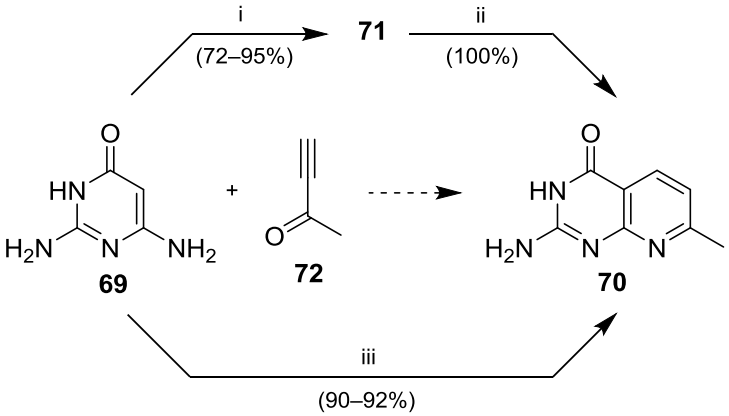


Scheme 42: Bohlmann–Rahtz synthesis of pyrido[2,3–*d*]pyrimidinones **70** using a Lewis acid as catalyst.

However, for these highly unreactive enamine precursors very forcing reaction conditions were required over extended periods of time. Furthermore, the products of Bohlmann-Rahtz processes for these substrates, the pyridopyrimidinones and their derivatives, share many physical properties with the related pteridines and suffer from poor solubility in most solvents, complicating synthetic approaches; thus fast, simple and efficient methods for the preparation of these targets are needed.

The structural identity of pyrido[2,3-*d*]pyrimidine **70** prepared by Bohlmann-Rahtz processes and the regiochemistry of the reactions conducted in acetic acid and *N*,*N*-dimethylformamide has been confirmed by further experimentation.[143] (3-Oxobut-1-enyl)pyrimidine **71** has been heated to 180 °C to facilitate Bohlmann-Rahtz cyclodehydration and the product obtained was identical to pyrido[2,3-*d*]pyrimidine **70** prepared by a one-pot Bohlmann-Rahtz cyclocndesation reaction in every respect.[142] This was also an indication that both the one and two-step methods for pyrido[2,3-

d]pyrimidine synthesis based upon a Bohlmann-Rahtz pyridine annelation, were effected with total regiocontrol (**Scheme 43**) in 72–95% yield depending on the solvent used, and proceeded by *C*-alkylation and subsequent cyclodehydration of the Michael addition product (**71**).[142]



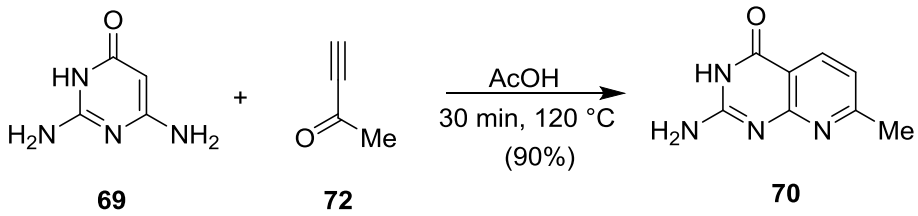
Reagents and conditions:
i: EtOH, MeOH or DMSO, 50 ^{o}C, 72 h (72–95%).
ii: 180 ^{o}C (100%)
iii: AcOH or DMF, 50 ^{o}C, 72 h (90–92%).

Scheme 43: Summary of solvent effects in the synthesis of pyridopyrimidine **70**.

3.2. Rapid method for the synthesis of pyrido[2,3-*d*]pyrimidines.

In an effort to elaborate a much simpler approach to pyridopyrimidines, the use of microwave irradiation and a Brønsted acid was investigated. Ciufolini had reported the use of neat acetic acid to mediate the Bagley-Bohlmann-Rahtz process in his synthesis of the core domain of the thiopeptide antibiotic micrococcin.[68] The application of this solvent to pyridopyrimidine targets could serve two roles: firstly, it might circumvent the need for extended reaction times and an additional Lewis acid in this process; secondly, it could overcome the poor solubility associated with this heterocyclic framework.

Preliminary studies carried out in the group,[144] verified that this approach seemed feasible: when a mixture of 2,4-diamino-6-hydroxypyimidine (**69**) and 3-butyn-2-one (**72**) was irradiated in neat acetic acid at 120 °C for 30 min, 2-amino-7-methylpyrido[2,3-*d*]pyrimidin-4-one (**70**) was obtained in 90% yield after simple precipitation of the product on addition of water (**Scheme 44**).

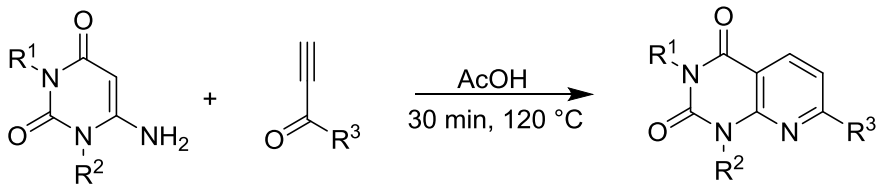


69 **72** **70**

Scheme 44: Synthesis of 2-amino-7-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**70**).

Although this demonstrated that this system was highly effective for diaminopyrimidinone **70**, less reactive aminouracil derivatives had not been screened in this promising process. Thus a series of uracil derivatives (**73**-**74**) was reacted with a range of ethynylketones in acetic acid under these conditions. The ethynyl ketone **41** was made from the oxidation of 1-phenylprop-2yn-1-ol (**79**) using a solution of Dess-Martin periodinane in dichloromethane, in a 20 min reaction to give propynone **41** as a yellow powder in 81% yield. With the ethynyl ketone **41** to hand it was found to undergo successful Bohlmann-Rahtz reaction with 6-amino-1,3-dimethyluracil (**73**) in one-pot in only 30 min in acetic acid, giving the product **75** in excellent yield (entry 1) after a simple precipitation. Use of an alternative ethynyl ketone that had a relatively low boiling point, the product was formed successfully, but in slightly lower efficiency (entry 2). Using alternative uracil derivative **74** with phenyl propynone **41** or butynone **72** was also successful giving pyridopyrimidine **77** (entry 3) and **78** (entry 4) in 80 and 99% yield, respectively.

Table 2.8. Synthesis of pyridopyrimidine derivatives using the Bohlmann-Rahtz reaction in acetic acid.



Entry	SM	R^1	R^2	R^3	Product	Yield %
1	**73**	Me	Me	Ph	**75**	>98
2	**73**	Me	Me	Me	**76**	76
3	**74**	H	Me	Ph	**77**	80
4	**74**	H	Me	Me	**78**	99

(**73**) 6-Amino-1,3-dimethyluracil.

(**74**) 6-Amino-1-methyluracil.

(**75**) 1,3-Dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

(**76**) 1,3,7-Trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

(**77**) 1-Methyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

(**78**) 1,7-Dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.

Unfortunately reactions involving 6-aminouracil **81** and the reaction of certain aminouracil derivatives **73** and **74** with 3-hexyn-2-one (**61**), 4-phenyl-3-butyn-2-one (**80**) or 4-(trimethylsilyl)-3-butyn-2-one (**59**) all resulted in complex mixtures of products that could not be easily purified. Despite this limit in substrate scope, which has been catalogued for these less-reactive uracil derivatives under related conditions,[145] it would appear that the Bohlmann-Rahtz reaction in acetic acid is effective in some cases to provide rapid access to pyridopyrimidinone derivatives.

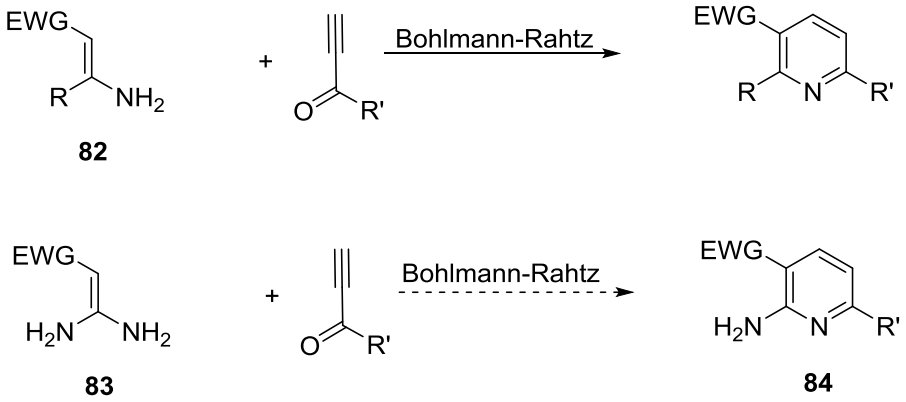
These studies expanded the scope the acid catalysed Bohlmann-Rahtz reaction and applied this to the use of challenging substrates to deliver heterocyclic frameworks of potential biological interest.

CHAPTER FOUR

Synthesis of aminopyridines using Bohlmann-Rahtz reaction

4. Synthesis of Aminopyridines using the Bohlmann-Rahtz reaction.

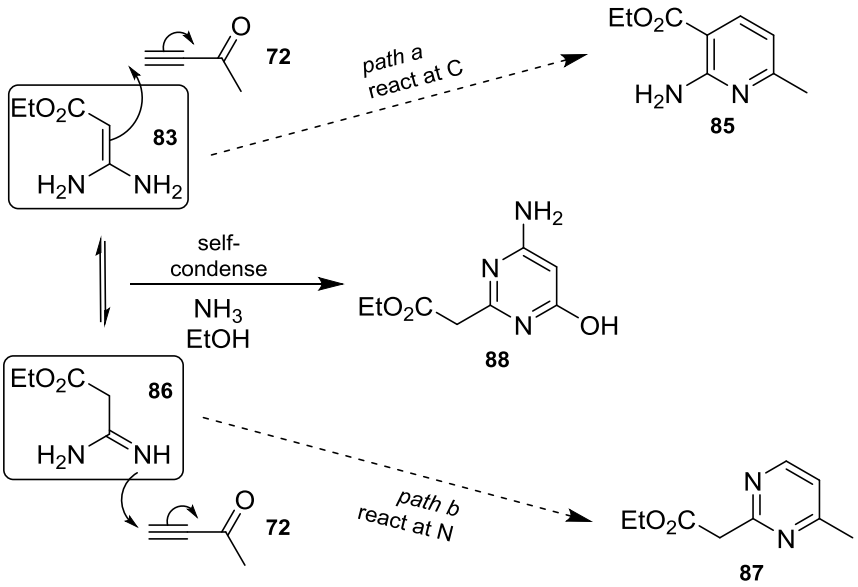
These studies have established new methods to carry out the Bohlmann-Rahtz reaction in one pot for the synthesis of pyridines and pyrido[2,3-*d*]pyrimidines using Brønsted and Lewis acid catalysts. However, the substrate scope of the Bohlmann-Rahtz reaction has changed little since the original discovery. Given the biological value of aminopyridines, it was considered that the use of an alternative enamine would enable 2-aminopyridine derivatives **84** to be generated in this reaction. This could require replacing the stable enamine **82** of the traditional Bohlmann-Rahtz reaction with a methylenediamine **83** and investigating if this changed the mechanistic couse and synthetic outcome (**Scheme 45**).



Scheme 45: The traditional Bohlmann-Rahtz reaction and the proposed new process for the synthesis of 2-aminopyridines **84**.

Diaminoacrylate derivative **85** (EWG = CO_2Et) was chosen as a suitable methylenediamine **83** for study. It has been shown[146] that methylenediamines derived from phenyl cyanomethanesulfonate do react to give 2-aminopyridines in Guareschi-Thorpe reactions. The Bohlmann-Rahtz reaction does have similarities to this process and so the methylenediamine could display a similar reactivity profile. However, pyrimidine products have been formed under acidic or basic conditions from reaction of ethynyl

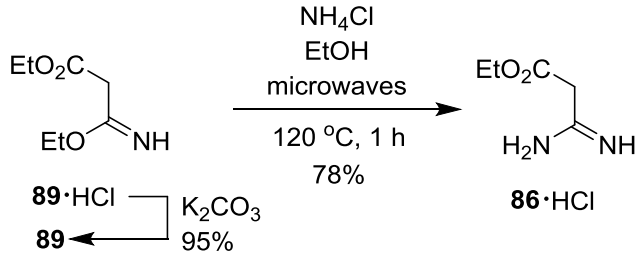
ketones with amidines and the diaminopropenoate should be in dynamic equilibrium with the carbethoxyacetamidine tautomer (**86**) (**Scheme 46**).[147-149] The reaction course could give aminopyridine **85** if it proceeded through enamine *C*-functionalization (*path a*) or alternatively could provide the corresponding pyrimidine derivative **87** if it proceeded through *N*-functionalization (*e.g. path b*); if both processes operated a mixture of products could be obtained. There have been a number of reports which indicate that these bis-nucleophiles give pyrimidine cyclocondensation products. It has been shown that carbethoxyacetamidine **86** undergoes self-condensation under basic conditions to give a pyrimidine derivative **88**[150] and the cyclocondensation of benzoylacetamidine provides 2-phenacylpyrimidine derivatives.[151] Furthermore, acetamidine **86** when reacted with a prop-2-enylidine bis-electrophile gave a mixture of pyridine and pyrimidine cyclocondensation products, in a 2:3 ratio respectively.[152] Nonetheless there was some encouraging precedent: the hydroacetate salts of iminopropanoates react by *C*-alkylation in a Michael addition for the synthesis of Hantzsch dihydropyridines.[153] Thus the Bohlmann-Rahtz reaction of these derivatives was worthy of investigation.



Scheme 46: Alternative reaction pathways due to methylenediamine **83** -acetamidine **86** tautomerization.

4.1. Synthesis of 2-aminopyridines using the Bohlmann-Rahtz reaction.

Iminopropanoate hydrochloride **86**·HCl was prepared by a modification of a known route,[153] but carried out under microwave-assisted conditions and without the use of anhydrous HCl gas, to dramatically shorten reaction times and simplify the experimental procedure. Ethyl imidate hydrochloride **89**·HCl was transformed to the free base **89** (observed, spectroscopically, as predominantly the enamine tautomer in $CHCl_3$) and reacted with ammonium chloride in EtOH under microwave irradiation at 120 °C for 1 h (**Scheme 47**) to give acetamidine hydrochloride **86**·HCl after a simple trituration.



Scheme 47: The preparation of iminopropanoate hydrochloride **86**·HCl.

The preferred tautomer in solution (NMR solvent DMSO-d_6) was inferred from the ^{1}H NMR spectroscopic data. The appearance of two separate peaks at $\delta = 9.16$ and 8.88 ppm, both with an integral of 2 and assigned to NHH and the peak at 3.63 ppm (integral of 2), assigned to CH_2, suggested the amidine tautomer and were consistent with ^{1}H and ^{13}C NMR data in the literature.[154]

With acetamidine **86** to hand, attention was given to the Bohlmann-Rahtz pyridine synthesis. An alternative purification method to column chromatography was considered as purification on silca had been found to give very low isolated yields of the 2-aminopyridine product,[155] It was suspected that the basicity of the compounds was responsible, thus making these derivatives difficult to isolate on acidic silica. The use of an ion-exchange SCX-2 SPE (Biotage) column, optimum for basic compound extraction,

comprising propylsulfonic acid functionalized silica (**Figure 10**) was used as an alternative purification method for isolating the 2-aminopyridine products. The functionalized silica 'traps' basic components (amino groups for example as the conjugate acid salt), allowing any non-basic components to be eluted and separated. The free base can then be regained from its conjugate acid by eluting with a stronger base, in this case ammonia in ethanol. The acetamidine hydrochloride salt **86**·HCl and ethynyl ketone **41** was irradiated at 150 °C in ethanol, immobilized on SCX-2 SPE column and eluted with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) or ethanolic ammonia (2 M) to give 2-aminopyridine **90** in 73% isolated yield (**Scheme 48**).

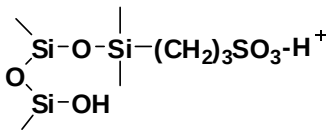
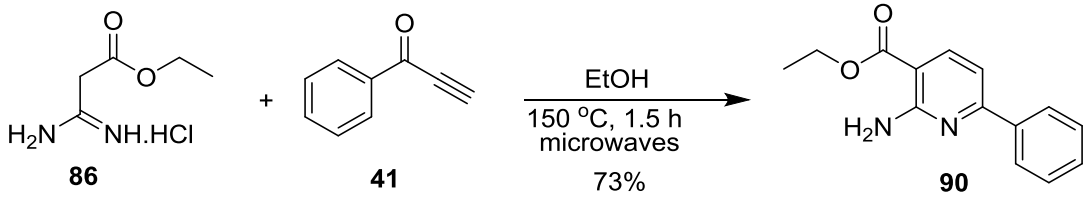
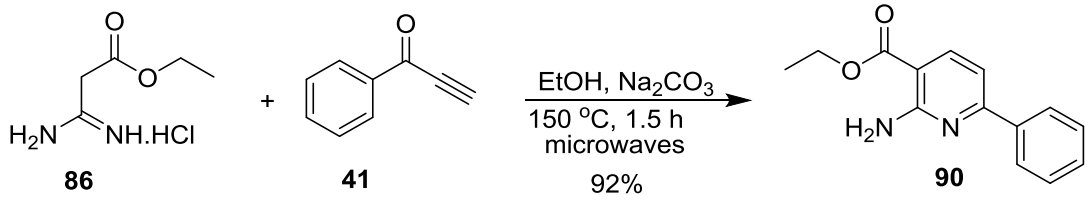


Figure 10: Propylsulfonic acid functionalised silica.



Scheme 48: Synthesis of 2-aminopyridine **90**.

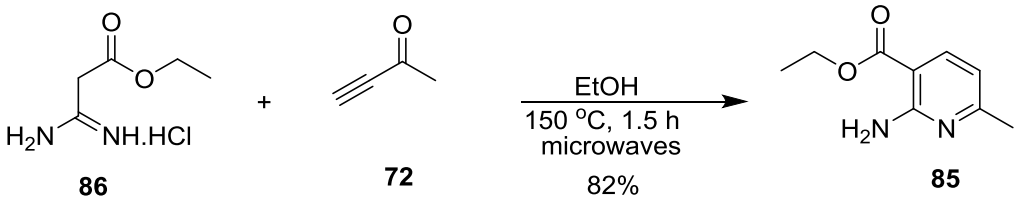
Acid catalysis has previously been reported as a method of facilitating the Bohlmann-Rahtz pyridine synthesis.[58,61] The reaction between the amidine hydrochloride salt (**86**·HCl) and ethynyl ketone **41** was repeated, this time with Na_2CO_3 present as base to explore if HCl that was present was catalyzing the reaction. However, surprisingly, in the presence of base 2-aminopyridine **90** was again formed but this time in 92% yield after purification by immobilization on a SCX-2 SPE column (**Scheme 49**).



Scheme 49: Synthesis of 2-aminopyridines **90** under basic conditions.

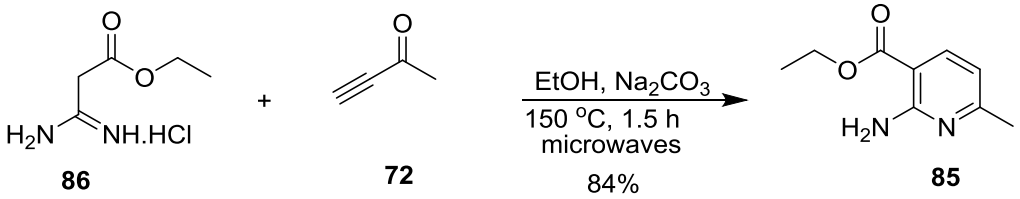
In this example, the yield was higher compared to the products obtained when ethanol only was used as a solvent without pre-treatment (- HCl) using Na_2CO_3 as base. Even more promising was that there was no evidence of pyrimidine formation by ^{1}H NMR spectroscopic analysis of the crude reaction product, where doublets with coupling constants (*J*) of approximately 4 Hz would be expected.[149] This reaction produced the 2-aminopyridine derivative **90**, as a single regioisomer and in very good yield in a highly selective process.

The use of a different ethynyl ketone 3-butyn-2-one (**72**) was explored in both the acid and base mediated reactions and was found to give the 2-aminopyridine products with a slight increase in yield. When 3-butyn-2-one (**72**) was heated with amidine (**86**) at 150 °C in the presence or absence of Na_2CO_3 base, the corresponding pyridine (**84**) was formed in 82% or 84% yield, respectively (**Scheme 50** and **51**). Overall there was little difference in the yields of these reactions which gave 2-aminopyridine **85** under microwave-asssisted conditions. It is interesting to note here again that the yield under ethanol only conditions was marginally less than that obtained using Na_2CO_3 as base. This could imply that the Na_2CO_3 was acting in some catalytic role in this process, but it is more likely that the presence of acid led to some degradation, reduced the efficiency of the isolation procedure or retarded the reaction rate probably as a consequence of amidine **86** protonation.



86 72 85

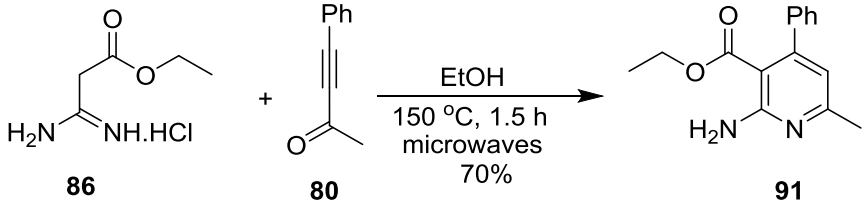
Scheme 50: Synthesis of 2-aminopyridines **85**.



86 72 85

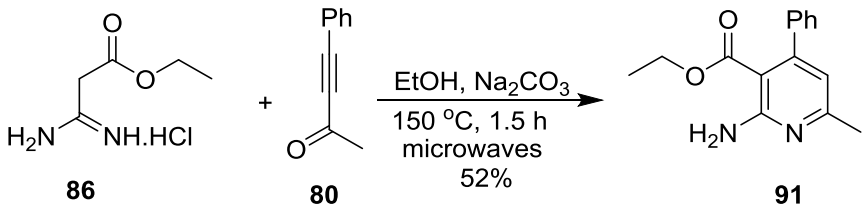
Scheme 51: Synthesis of 2-aminopyridine **85** under basic conditions.

Further studies were carried out under microwave-assisted conditions to attempt to extend the scope of this method to prepare different 2-aminopyridines, substituted at the 4-position. Reaction of 4-phenyl-3-butyn-2-one (**80**) and amidine (**86**) hydrochloride salt, in ethanol as the solvent at 150 °C formed 2-aminopyridine **91** in 70% yield (**Scheme 52**) or 52% yield in the presence of Na_2CO_3 as base (**Scheme 53**).



86 80 91

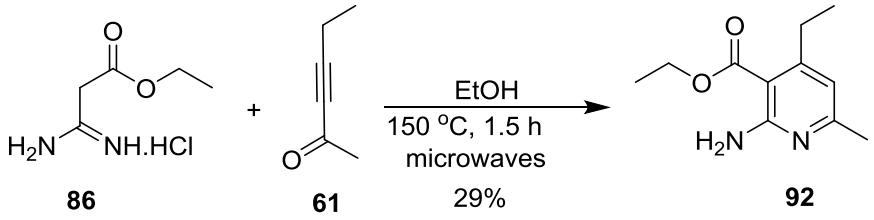
Scheme 52: Synthesis of 2-aminopyridine **91** on changing the ethynyl ketone.



86 80 91

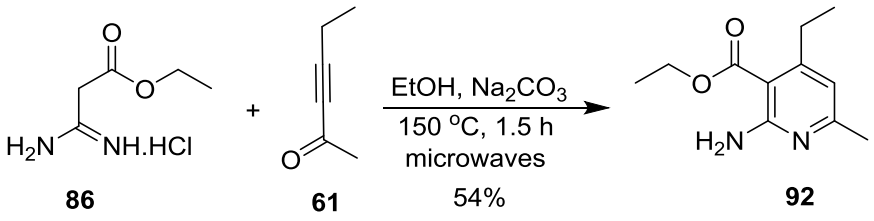
Scheme 53: Synthesis of 2-aminopyridine **91** under basic conditions.

Additionally, reaction of amidine **86** and hex-3-yn-2-one (**61**) gave 2-aminopyridine **92** in 29% yield (**Scheme 54**) or 54% yield in the presence of Na_2CO_3 as base (**Scheme 55**). The lower yields observed here compared with those obtained from the synthesis of **91** (**Scheme 53**) suggesting that substituents at the 4-position hinder the synthesis of the 2-aminopyridines using this method. Nevertheless, these results do suggest that this method for the preparation of 2-aminopyridines can be applied to other substrates, although further optimization may be required.



86 **61** **92**

Scheme 54: A different 2-aminopyridine **92** formed on changing the ethynyl ketone.



86 **61** **92**

Scheme 55: The yield obtained under basic conditions.

The microwave-assisted synthesis of 2-aminopyridines using a Bohlmann-Rahtz type route has prepared four different 2-aminopyridines, albeit in a variety of isolated yields. This is a new reactivity profile that was previously unknown for the Bohlmann-Rahtz pyridine synthesis, that lends itself well to a simple isolation procedure involing catch and release on an acidic resin.

4.2. Synthesis of 2-aminopyridines using flow processing.

As shown in (**Figure 11**) The flow reactor Vapourtec was configured using a combination of the R-2 Pump Module and R-4 Reactor Module. The System Solvent Bottle was filled with solvent, and the Reagent Stock Bottles A and B were filled with solutions of starting material in solvent.

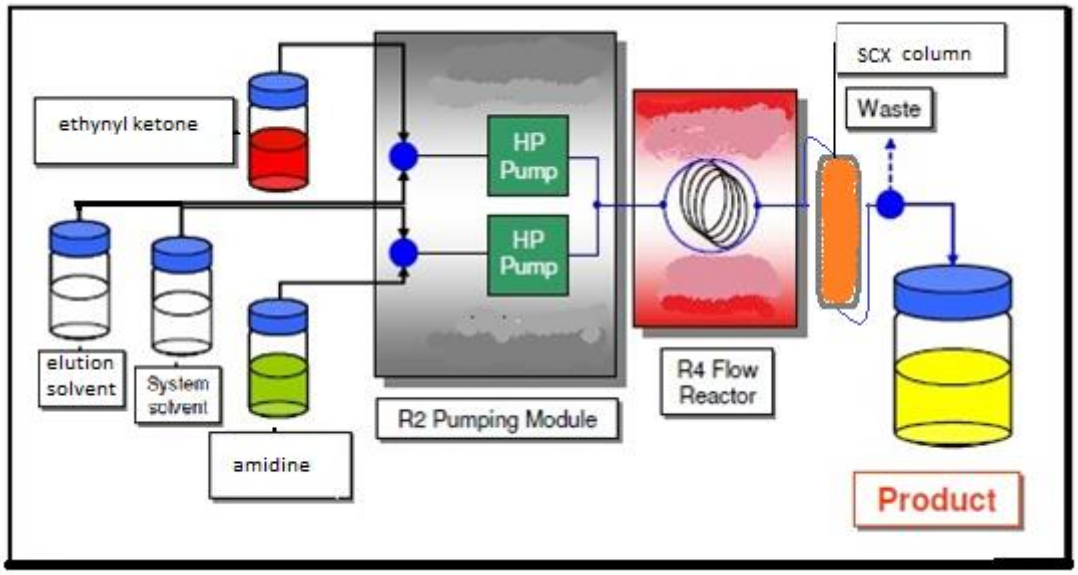
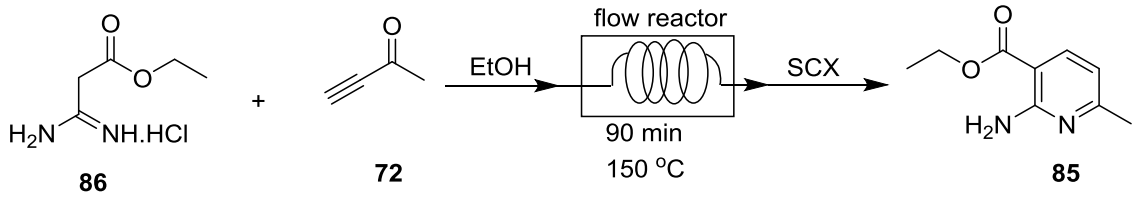


Figure 11: Schematic Flow Reactor Configurations.

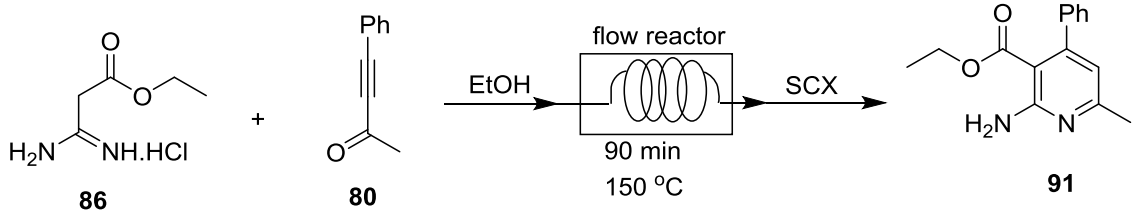
With acetamidine **86** to hand, consideration was given to the Bohlmann-Rahtz pyridine synthesis using a flow reactor to extend the scope of this method to prepare 2-aminopyridines. The flow synthesis of these targets was investigated using a simplified bench-top continuous flow setup and a SCX-2 SPE reagent in column using a low boiling point alcohol (EtOH) at high temperature (150 ^{o}C) reaction of 3-butyn-2-one (**72**) 0.1 M (flow rate 0.057 mL/min) and amidine (**86**) hydrochloride salt 0.1 M (flow rate 0.054 mL/min), in ethanol as the solvent at 150 °C formed 2-aminopyridine **85** in 75% yield

after purification by immobilization on a SCX-2 SPE column and elution with ethanolic ammonia (2 M) (**Scheme 56**). The 2-aminopyrididne **85** prepared by flow technology compared favourably and was indistinguishable to the batch technology product.



Scheme 56: Flow synthesis of 2-aminopyridine **85**.

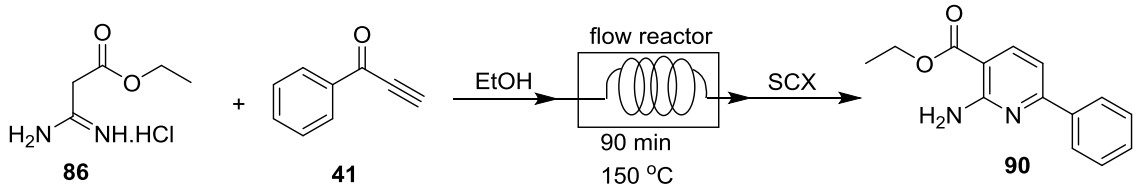
Further studies were carried out under similar conditions to prepare different 2-aminopyridines, substituted at the 4-position. Reaction of 4-phenyl-3-butyn-2-one (**80**) and amidine (**86**) hydrochloride salt, in ethanol as the solvent at 150 °C formed 2-aminopyridine **91** in 69% yield after purification by immobilization on a SCX-2 SPE column and elution with ethanolic ammonia (**Scheme 57**).



Scheme 57: A different 2-aminopyridine **91** formed on changing the ethynyl ketone.

Additionally, reaction of amidine **86** and ethynyl ketone **41** gave 2-aminopyridine **90** in 69% yield (**Scheme 58**). Overall there was a small difference in the yields of these reactions which gave the corresponding 2-aminopyridine under flow reactor conditions.

This could be due to the presence of acid leading to some degradation, a reduction in the efficiency of the isolation procedure or retardation of the reaction rate probably as a consequence of amidine protonation.



Scheme 58: Synthesis of 2-aminopyridine **90** on changing the ethynyl ketone.

The flow method synthesis of 2-aminopyridines using a Bohlmann-Rahtz type route has prepared three different 2-aminopyridines, albeit in a variety of isolated yields. This is a new reactivity profile, previously unknown for the Bohlmann-Rahtz pyridine synthesis, that lends itself well to a simple isolation procedure involing catch and release technology under continuos flow processing.

CHAPTER FIVE

H/D- Exchange in Aminopyridines

5. H/D- Exchange in Aminopyridines.

5.1. Introduction.

Once inside the body, a drug molecule must avoid a multitude of attacks by the metabolic system before it reaches its biological target. The body's metabolic pathways breakdown drug molecules into inactive derivatives and then ejects them, meaning that many drugs need to be taken more frequently than they might otherwise need. One proposed way to improve the metabolic behaviour of a drug is to substitute some of the hydrogen atoms in the molecule with heavier deuterium. Carbon-deuterium bonds are stronger and shorter than the equivalent bonds to hydrogen, leading to differences in reactivity that can be up to six to 10 times slower. So if breaking a C-H bond is responsible for a drug being metabolised faster than is ideal, substituting that hydrogen with deuterium may slow the molecule's breakup. The end result being that the drug can be taken less often, say once a day rather than twice. Because deuterium is an isotope of hydrogen this atom substitution causes little change in the shape, size, charge or the biological effects of the molecule. Only the pharmacokinetics, how the drug is processed by body, should change. In so doing the drug half-life could be improved; reduced variability in the metabolism of the drug molecule between patients and improved tolerability could also potentially be achieved.[156] It has recently been reported that deuterated drug isotopologues may be unexpectedly non obvious in patent law,[162] differentiating these compounds from prior art. This makes deuterated compounds essential targets for study, especially when coupled with interesting biological or pharmacological properties.

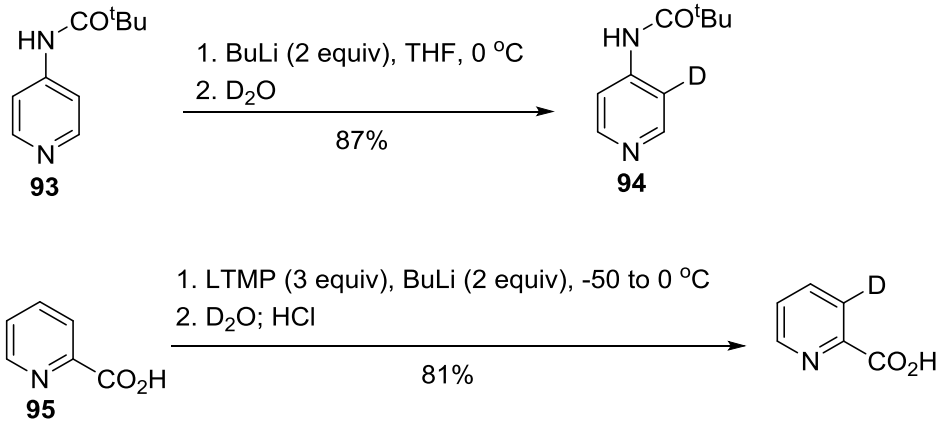
Deuterium is already widely used as an isotopic label to study the metabolism of drug candidates both in the lab and in humans. Previously, however, it had never been used in a final drug molecule but that situation might be about to change. Approval of the first-ever deuterated drug may well be imminent. This idea of using deuterium to shield

pharmaceutical agents against unwanted metabolism is not a new concept: in the 1970s US pharma company Merck & Co put the first deuterated drug into clinical trials.

The demand for compounds multiply-labelled with stable isotopes has increased dramatically in recent years.[157,158] Deuterated derivatives have been used as internal standards for quantifying human and animal pharmacokinetic and metabolism experiments in drug development, and as mechanistic probes to determine reaction pathways. Deuterated standards exhibit similar physical and chemical properties to their non-deuterated isotopologues, but differ on account of their mass difference. If this mass difference is large enough to separate signals from natural isotope patterns, quantitative analysis is possible.[159]

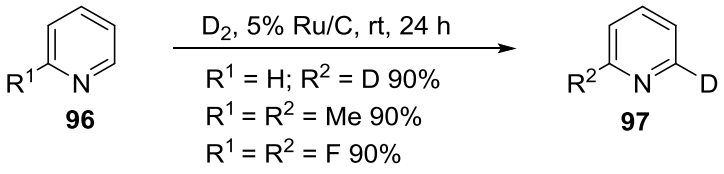
A number of strategies are available for the preparation of compounds containing multiple deuterium atoms.[163-165] It may be easiest to synthesize these compounds using isotopically-labelled precursors. This has the advantage of being predictable, using the route to the 'natural' isotopologue, but can be time consuming and may require expensive reagents and/or the development of additional sequences. The use of protium-deuterium exchange in the target molecule or late-stage intermediate, has the potential to be more rapid, efficient and cost-effective and removes the need for further developmental work, but requires a method to introduce multiple deuterium atoms in an efficient and predictable fashion.[159] H/D exchange can also provide a useful model system for protium-tritium exchange.[157,160,161] Complementary methods are available for carrying out this exchange process such as acid- or base-catalyzed reactions or metal-mediated processes, all of which are possible with aliphatic, aromatic or heteroaromatic compounds. The base-induced hydrogen-deuterium exchange in pyridines is much more facile and rapid than the reaction of benzene, with the hydrogen at the 4-position of pyridine being described

as easier to exchange than H3 or H2.[166,167] Direct hydrogen-deuterium exchange of pyridines with deuterium oxide can be effected at 200 to 400 °C. However, the regioselective base-induced hydrogen-deuterium exchange of pyridines can be achieved by directed deprotonation and subsequent quenching of the metalated (lithiated) pyridine with deuterium oxide; *e.g*. formation of the 3-deuterated derivative **94** from pyridine **93** (**Scheme 59**).[168]



Scheme 59: Directed base-induced hydrogen-deuterium exchange in pyridines.[168,169]

Unprotected pyridine-2-carboxylic acids (picolinic acids), *e.g.* the parent **95**, may be selectively deuterated next to the carboxy function using lithium 2,2,6,6-tetramethylpiperidide (LTMP) followed by treatment with deuterium oxide (**Scheme 59**). Alternatively selective 2- (and 6)-deuteration of pyridines **96** to give isotopologues **97** is possible using heterogeneous catalysis (**Scheme 60**).[170]



Scheme 60: Hydrogen-deuterium exchange using heterogeneous catalysis.[170]

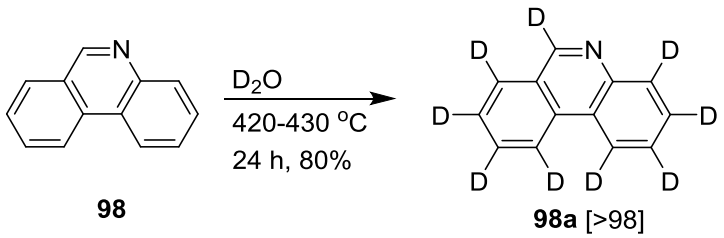
5.2. H/D Exchange Using D_2O.

During the 1960's and 70's the use of H/D-exchange reactions was an area of great interest leading to many significant advances in methods and understanding.[158] After this period, interest in H/D exchange was largely neglected until the mid 1990's in which a renewed surge of interest emerged. This was primarily a consequence of the increase in demand for isotopically labelled compounds for pharmacokinetic and metabolic studies during drug development,[171,172] mechanistic investigations into catalysts and reaction pathways[173,174,175] or research into C-H bond activation.[176,177] For the production of an isotopically labelled compound a method involving H/D exchange is commonly preferable as it avoids multi-step synthesis using labelled precursors which are generally expensive and thus is a lot more efficient and cost-effective. Other related methods include halogen-deuterium exchange[178,179] and reductive deuteration.[180]

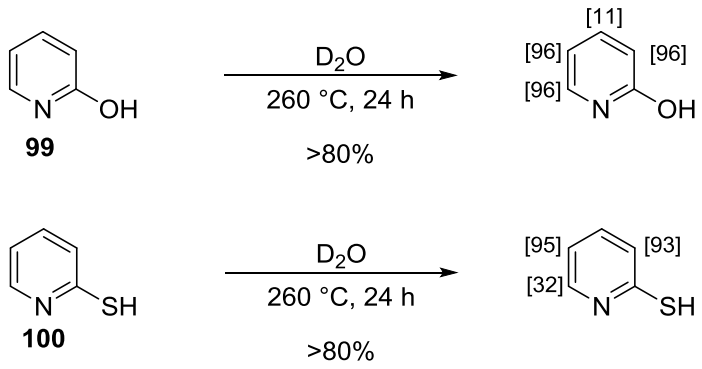
One of oldest known methods for H/D exchange is pH dependent H/D exchange. For example, exchange can occur via the use of a base- or acid-catalysed enolization, with H/D exchange occurring at the active positions in the molecule by application of deuterated Brønsted acids. Such methods often require the deactivation of the compound to prevent the reverse exchange occurring.[158]

H/D exchange can also occur without the presence of a strong acid or base but just using deuterium oxide alone. This exchange occurs on acidic carbon-bonded hydrogen atoms, and works due to the ability of deuterium oxide to act as either an acid or a base. Such exchange is possible with a number of different compounds and the experimental conditions vary dramatically. For example, Junk and Catallo achieved almost complete H/D exchange during the deuteration of phenanthrene (**98**) by carring out the reaction at 380-430 °C (**Scheme 61**).[181] Harsh conditions were used similarly by Werstiuk and Ju to carry out H/D exchange on pyridine derivatives, reporting good yields (>80%) and high

levels of deuteration in the 3-, 5- and 6-positions of 2-hydroxypyridine (**99**) and 2-mercaptopyridine (**100**) (**Scheme 62**).[167]

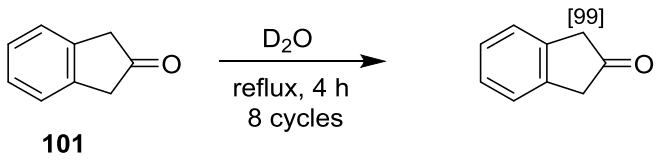


Scheme 61: H/D exchange of phenanthrene (**98**).



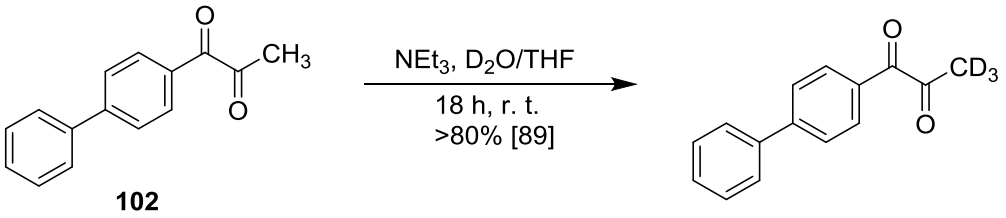
Scheme 62: H/D exchange of pyridine derivatives.

Edlund and Berson showed that it is not always necessary to use such extreme conditions for H/D exchange.[182] During the synthesis of [1,1,3,3-D_4]2-indanone (**101**), exchange occurs by repeatedly heating the precursor in D_2O under reflux, to attain the deuterated product with high % deuteration. The milder conditions again led to high regioselectivity (**Scheme 63**) although quite an involved method was required.



Scheme 63: Highly regioselective deuteration of 2-indanone (**101**)

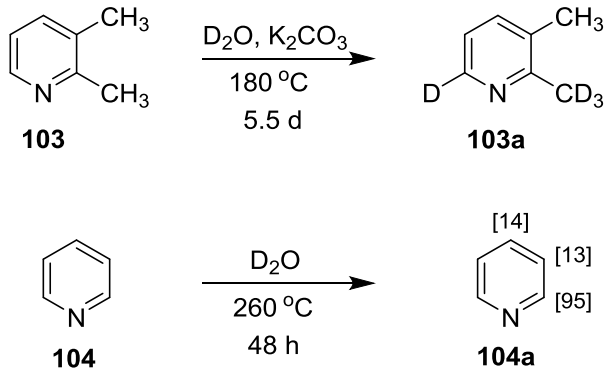
The H/D exchange of methyl ketones has also been reported under base catalysed conditions.[183] Berthelette and Scheigetz achieved such exchange using aryl methyl ketones.[183] The exchange varied greatly with substrate, base and solvent but was achieved in high yield and percentage deuteration using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Deuteration of a base sensitive diketone **102** was also achieved without decomposition by the addition of triethylamine (**Scheme 64**).



Scheme 64: Deuteration of a base-sensitive diketone **102**.

H/D exchange at the α-position of a number of pyridine derivatives was first observed by Zoltewicz,[184] but has also been described recently. When dimethylpyridine **103** was heated under basic conditions at 180 °C in D_2O for 5.5 d (**Scheme 65**), exchange at C-6 occurred more rapidly than at the other ring positions, but very forcing conditions were required.[185] Similarly, pyridine (**104**) when heated to 260 °C for 48 h in D_2O underwent H/D exchange, in high regioselectivity for the α-position, to give dideuterated **104a**. The same process carried out at 200 °C for 24 h gave only 15% D incorporation at this position.[167] Given that many recent efforts have been directed towards H/D exchange of

pyridine derivatives,[186-193] such as the highly site-selective one-step α-labelling of pyridines and *N*-heteroaromatic compounds using deuterium gas and a rhodium or ruthenium catalyst,[194] and the faster H/D exchange observed in 4-pyrrolidino pyridines,[167] we set out to establish a simple one-step method for site-selective protium- deuterium exchange using neutral D_2O that would proceed under microwave irradiation, in a commercial instrument using readily-automated conditions in the absence of any catalyst.



Scheme 65: H/D exchange at the α-position of pyridines using D_2O.[168,186]

Investigating the H/D exchange of 2-aminopyridine (**105**), 3-aminopyridine (**106**), and 4-aminopyridine (**107**) in neutral D_2O under microwave irradiation at 190 °C for just 2 h (**Table 5.1**) established differences in the efficiency of H/D exchange at different positions across this small series of substrates. For 2-aminopyridine (**105**), only moderate H/D exchange was observed at all positions under these relatively mild conditions, as might be expected, with very little overall regioselectivity (entry 1). The reaction of 3-aminopyridine (**106**) under these conditions was much more selective, with good incorporation at C-2 and yet very low levels of H/D exchange at all other positions, including at C-6 (entry 2). Unfortunately, increasing the reaction time gave no further improvement in D incorporation at C-2 (80%). However, 4-aminopyridine (**107**) underwent rapid H/D exchange at the α-positions, even at this relatively low temperature, indicating its unusual high reactivity in the process (entry 3). It is noteworthy that

contrasting behaviour has been described by Zoltewicz in a study of H/D exchange of 4-amino-2,6-dimethylpyridine, with respect to 2,6-lutidine, under neutral and acidic conditions.[184e] Carrying out the H/D exchange in neutral D_2O at lower temperatures 170 (entry 4) or 180 °C (entry 5), gave 4-aminopyridine (**107c** or **107d**) with much less efficient D incorporation at all positions.

Figure 12: %D Incorporation in aminopyridines under neutral conditions.

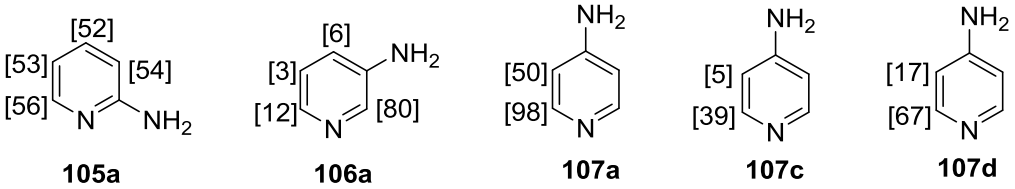


Table 5.1. %D Incorporation after microwave irradiation at 190 °C for 2 h in neutral D_2O[a]

Entry	Substrate	Product	C-2	C-3	C-4	C-5	C-6	Yield[b]
1	**105**	**105a**	-	54	52	53	56	72
2	**106**	**106a**	80	-	6	3	12	66
3	**107**	**107a**	98	50	-	50	98	57
4[c]	**107**	**107c**	39	5	-	5	39	52
5[d]	**107**	**107d**	67	17	-	17	67	57

[a] As determined by ^{1}H NMR spectroscopic analysis after introduction of an internal standard by acetylation (AcCl, K_2CO_3, acetone, RT, 3 h), followed by aqueous work-up.

[b] Yield refers to the isolated yield% of product after microwave irradiation of the substrate in D_2O in a sealed Pyrex™ tube at 190 °C, unless stated otherwise, for 2 h (hold-time) by moderation of the initial magnetron power (300 W), followed by cooling and an acid-base work-up.

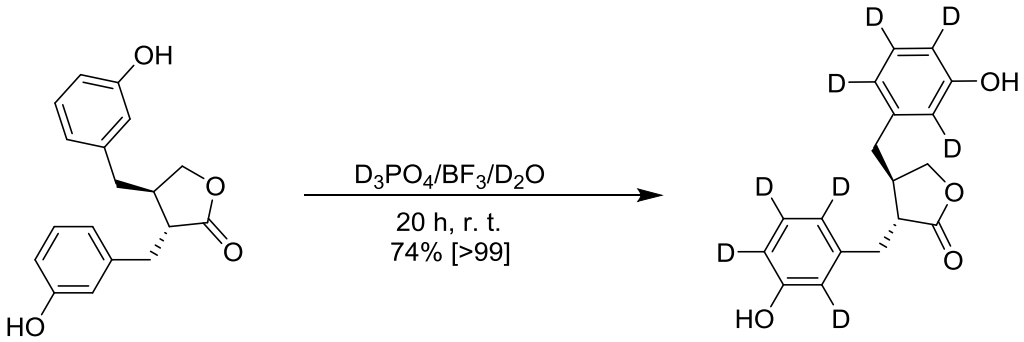
[c] Reaction was carried out at 170 °C.

[d] Reaction was carried out at 180 °C.

5.3. H/D Exchange Using DCl.

There are two possible exchange methods in acid-catalysed exchange: either strong deuterated Brønsted acids or alternatively a Lewis acid with a deuterium source can be used to deuterate an aromatic compound. The use of both of these deuteration methods, combined, has also been described. Wahala and Rasku demonstrated this combination on a number of substrates including flavonoids, isoflavonoids and lignans.[195] With the use of a mixture of D_3PO_4, BF_3, and D_2O, good yields and high levels of deuteration at the activated positions were achieved at temperatures between 20 and 55 °C. The reaction involved many cycles over a period of one to four days.

Rasku and Wahala did further work showing that with more severe conditions it was possible, using diadzein and enterolactone as a substrate, to deuterate at poorly activated positions.[196] The synthesis gave almost full deuteration of d_8-enterolactone (>99%) including at the inactive *meta* positions (**Scheme 66**).



Scheme 66: H/D exchange using both a Brønsted and Lewis acid.

Given the potential of acid-mediated exchange, repeating our studies using acid-mediation under relatively mild conditions could help to understand the high reactivity of 4-aminopyridine (**107**) towards α-exchange (**Table 5.2**). It was expected that this would provide a basis for the site-selectivity of proton-deuteron exchange by electrophilic aromatic substitution and a point of comparison with Zoltewicz's mechanistic studies.

The microwave-assisted exchange reactions were repeated in the presence of DCl. Under these conditions 2-aminopyridine (**105b**) showed D incorporation to a similar degree at C-4 and C-6 but positions activated towards electrophilic aromatic substitution (C-3 and C-5) exhibited a dramatic increase in D incorporation (both 94%), as expected. The same phenomenon was observed in the deuteration of 3-aminopyridine (**106**), with an increase in incorporation at the activated α-positions of **106b** (96% at C-2), making it a useful synthetic procedure. The observation most worthy of note was that H/D exchange of 4-aminopyridine (**107**) completely reversed under acidic conditions, with high levels of incorporation now observed at C-3 and C-5 (positions activated to electrophilic aromatic substitution) and yet minimal incorporation at the pyridine α-carbons of **107b**. This demonstrated that mechanisms operating in neutral D_2O (**Table 5.1**) were distinct from the electrophile-mediated process (**Table 5.2**) for 4-aminopyridine (**107**) and so were worthy of further study as a site-selective method for D-incorporation.

Figure 13: %D Incorporation in aminopyridines under acidic conditions.

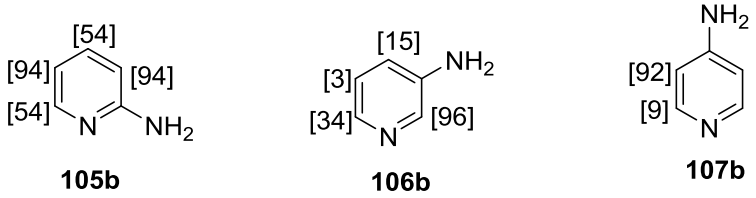


Table 5.2. %D Incorporation after microwave irradiation at 190 °C for 2 h in D_2O in the presence of DCl[a]

Entry	Substrate	Product	C-2	C-3	C-4	C-5	C-6	Yield[b]
1	**105**	**105b**	-	94	54	94	54	70
2	**106**	**106b**	96	-	15	3	34	60
3	**107**	**107b**	9	92	-	92	9	56

[a] As determined by ^{1}H NMR spectroscopic analysis after introduction of an internal standard by acetylation (AcCl, K_2CO_3, acetone, RT, 3 h), followed by aqueous work-up.

[b] Yield refers to the isolated yield% of product after microwave irradiation of the substrate in D_2O in the presence of DCl (4 equiv.) in a sealed Pyrex™ tube at 190 °C for 2 h (hold-time), by moderation of the initial magnetron power (300 W), cooling, and an acid-base work-up.

Given the high site-selectivity for H/D exchange of 4-aminopyridine (**107**) in neutral D_2O, a range of substrates was investigated under the newly-found set of conditions (microwave irradiation at 190 °C, 2 h) to establish the scope of the method. The nature of the substituent, its position, and even the heterocycle were varied (**Table 5.3**). For some substrates, reaction in both the presence and absence of DCl was investigated to see if a reversal of the regioselectivity was observed. It was found that *N*-alkyl groups exhibited minimal side-chain exchange under these conditions (entries 3-7) and their presence slightly retarded H/D exchange at C-3 and C-5, presumably as a consequence of steric effects. Excellent incorporation at C-2 and C-6 (95-98%) was observed for **108**-**110** under neutral conditions, also with high levels of regiocontrol (entries 3, 5 and 6). 4-Aminoquinoline (**111**) showed similar behaviour (entry 8), although the efficiency of incorporation at C-2 in **110a** (89%) was reduced slightly with respect to its pyridine counterpart **107a** (98%). D incorporation in 4-pyrrolidinopyridine (**110b**) and 4-aminoquinoline (**111b**) was seen to reverse by carrying out the procedure in the presence of DCl (entries 7 and 9), demonstrating that this method proceeds by a contrasting mechanism and complements acid-mediated exchange. For quinoline products **111a** and **111b**, minimal exchange was noted in the carbocyclic ring under both sets of conditions. Efficient incorporation was only affected marginally (89%) by the presence of a methyl group, at C-3 in **112a** (entry 10) or at C-2 in **113a** (96%) – the latter also showing efficient incorporation (97%) at C-1' (entry 11). The effect of halogen substituents (**114**-**116**) on H/D efficiency did vary with position: with a halogen at C-3 high efficiency (98%) and regioselectivity for C-2 was observed (entries 12 and 13), but the 2-chloride **116** did not exchange efficiently (entry 14) perhaps as a consequence of its reduced basicity. Interestingly, the 3-iodide **115a** exhibited relatively high D

incorporation at both α-positions (entry 13; 98 and 75%) whereas the 3-bromide did not (entry 12; 98 and 34%).

Finally, exchange in both 4-aminopyrimidine (**117a**) and 2-aminopyrazine (**118a**) was less rapid (entries 14 and 15), the corresponding substrates postulated as being less reactive in the process as a consequence of their reduced basicity (*cf* pK_{aH} 4-aminopyrimidine 5.7l; 2-aminopyridine 6.86; 4-aminopyridine 9.17).[197] In cases for which H/D exchange was efficient and highly-selective the isolated yield of the product was of preparative value (57-97% yield).

Figure 14: %D Incorporation in aminopyridines under neutral or acidic conditions.

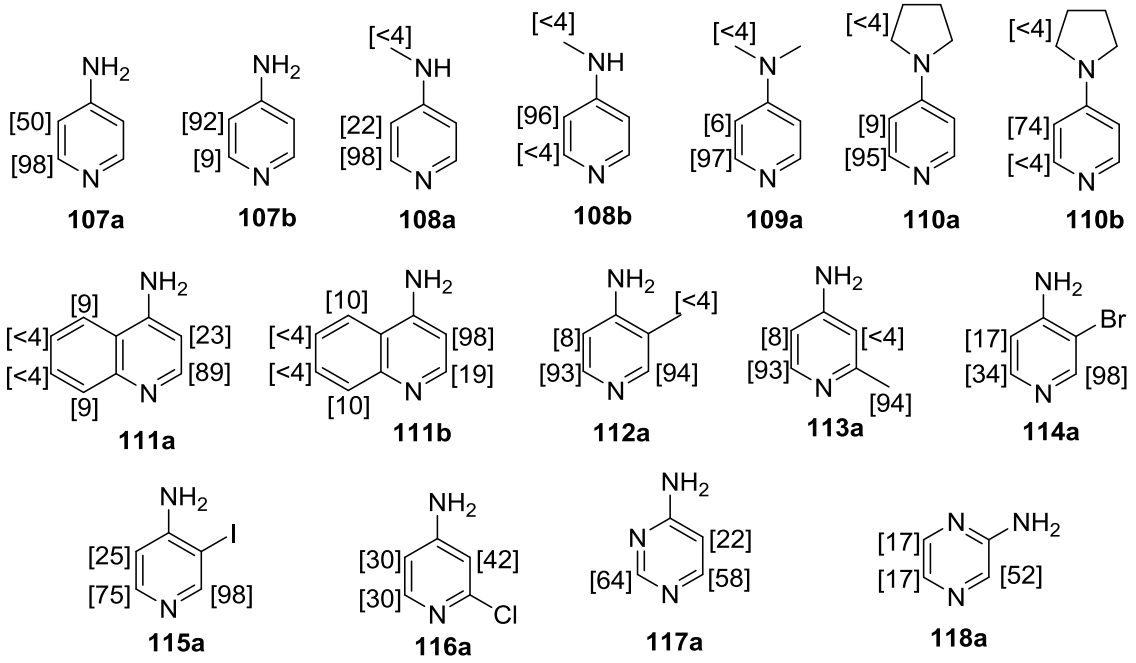


Table 5.3: %D Incorporation of substituted 4-aminopyridines and related heterocycles after microwave irradiation at 190 °C for 2 h in D_2O in the presence or absence of DCl[a].

Entry	DCl	Product	C-2	C-3	C-5	C-6	C-7	C-8	C-1'	C-2'	C-3'	Yield[b]
1	×	**107a**	98	50	50	98	-	-	-	-	-	57
2	√	**107b**	9	92	92	9	-	-	-	-	-	56
3	×	**108a**	98	22	22	98	-	-	<4	-	-	91
4	√	**108b**	<4	96	96	<4	-	-	<4	-	-	82
5	×	**109a**	97	6	6	97	-	-	<4	-	-	97
6	×	**110a**	95	9	9	95	-	-	-	<4	<4	96

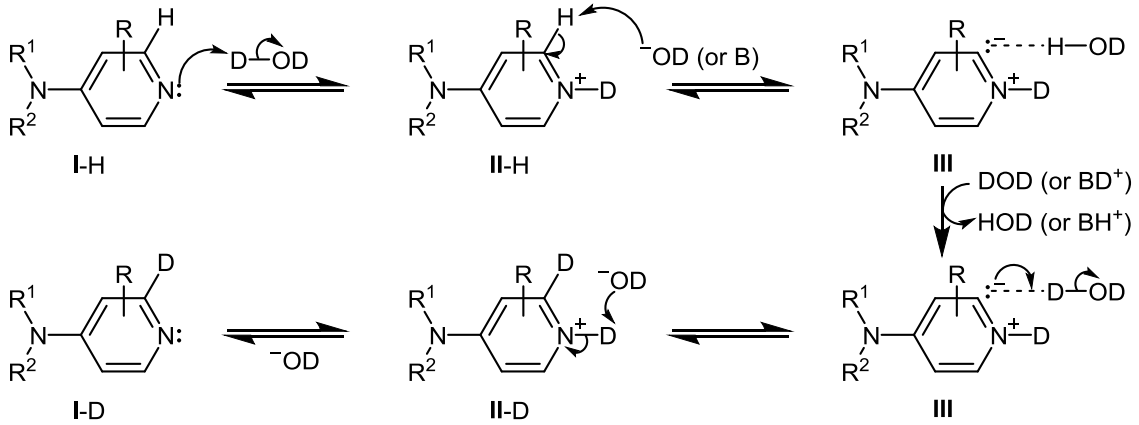
7	√	**110b**	<4	74	74	<4	-	-	-	<4	<4	97
8	×	**111a**	89	23	9	<4	<4	9	-	-	-	69
9	√	**111b**	19	98	10	<4	<4	10	-	-	-	74
10	×	**112a**	94	-	8	93	-	-	<4	-	-	97
11	×	**113a**	-	5	8	96	-	-	97	-	-	84
12	×	**114a**	98	-	17	34	-	-	-	-	-	82
13	×	**115a**	98	-	25	75	-	-	-	-	-	93
14	×	**116a**	-	42	30	30	-	-	-	-	-	98
15	×	**117a**	64	-	22	58	-	-	-	-	-	26
16	×	**118a**	-	52	17	17	-	-	-	-	-	61

[a] As determined by ^{1}H NMR spectroscopic analysis, after introduction of an internal standard (entries 1-3, 7-15) by acetylation (AcCl, K_2CO_3, acetone, RT, 3 h), followed by aqueous work-up and purification by column chromatography on silica if required; or by reference to a known quantity of dioxane as an external standard (entries 4-6).

[b] Yield refers to the isolated yield% of product after microwave irradiation of the substrate in D_2O in a sealed Pyrex™ tube at 190 °C for 2 h (hold-time) in the presence or absence of DCl (4 equiv.), by moderation of the initial magnetron power (300 W), cooling, and an acid-base work-up.

Given the fast kinetics of H/D exchange of 4-aminopyridines under neutral conditions, and the high regioselectivity of the process, which was distinct from acid-mediated exchange[198] a distinct operating mechanism was considered. In accordance with the kinetic and mechanistic studies by Zoltewicz on base-catalyzed H/D exchange of *N*-substituted pyridinium ions,[184d] and exchange of methylpyridines in dilute acid,[184e] this method could be a specific acid-general base catalyzed process influenced by internal return (**Scheme 67**). The equilibrium almost certainly involves protonation of the substrate **I** by the solvent (D_2O), giving a pyridinium conjugate acid **II**, which can then be deprotonated by the lyate anion (or substrate B) to give pyridinium ylide **III**. If this was the case, the efficiency of the exchange process for 4-aminopyridines would be attributed to the increased pyridine basicity in general base catalysis, increased stability of the pyridinium ylides **III** upon deprotonation, or a shift from general base catalysis to an internal return limited process, with no significant general base catalysis and slow dissociation of a hydrogen-bonded ylide **III**-conjugate acid complex, as a consequence

of the reduced acidity of the pyridinium conjugate acid.[184d] A profile of reactivity dependent upon aminopyridine basicity and proceeding in equilibrium via pyridinium ylide **III** explains most of the observations (**Table 5.3**), such as reduced exchange in 4-amino-2-chloropyridine (**116**), 4-aminopyrimidine (**117**) and 2-aminopyrazine (**118**). It is likely other factors are involved. For example, D incorporation at C-2 (80%) vs C-6 (12%) (**Table 5.1**) of 3-aminopyridine (pK_{aH} 5.98) indicates a role of ylide **III** stability, which could also be responsible for the high C-2 selectivity for D incorporation in 3-bromide **16a** and low D incorporation (56%) at C-6 for 2-aminopyridine (pK_{aH} 6.86).[197] It is also possible alternative mechanisms could be in competition. However, no matter what the operating mechanism or mechanisms might be, this relatively-mild method under neutral conditions would seem to tolerate a range of 4-aminopyridine basicities, give quite predictable outcomes and is well-suited to this structural motif, including a benzo-fused analogue.



Scheme 67: Possible mechanism for D incorporation in 4-aminopyridine **I**-H involving H/D exchange equilibria of pyridinium ylide **III**

In conclusion, these studies have shown that H/D exchange for 4-aminopyridines occurs rapidly at the α-position under neutral conditions and is essentially complete in just 2 h in D_2O at 190 °C under microwave irradiation. This single cycle process can provide

deuterated isotopologues in reasonable yield without any added catalyst or specialist equipment. For these substrates this method exhibits complementary selectivity to acid-mediated exchange methods, is mechanistically distinct and thus provides a valuable route to structurally-defined isotopomers or isotopologues based upon this heterocyclic scaffold.

5.4. H/D Exchange Using D_2O and DCl sequentially.

In order to understand the observed phenomena and the high reactivity of 4-aminopyridine (**107**) towards α-exchange under relatively mild conditions, the study was repeated but, this time, the product from α-exchange was irradiated again in presence of DCl (**Table 5.4**). It was anticipated this would provide a new efficient method for incorporating multiple deuterium labels by complementing the site selectivity of α-exchange with the site-selectivity of proton-deuterium exchange by electrophilic aromatic substitution, thus providing a comparison with Zoltewicz's mechanistic studies. A range of substrates was thus submitted to a new one-pot procedure, involving sequential reaction first in D_2O under neutral conditions followed be addition of DCl and a second period of irradiation. Under the 2 step conditions, 4-aminopyridine (**107f**) showed D incorporation at all ring positions, with high levels of incorporation at C-3 and C-5 (positions activated to electrophilic aromatic substitution) and good incorporation at the pyridine α-carbons of **107f**. This demonstrated that mechanisms operating in neutral D_2O complemented the acid-mediated exchange (**Table 5.1**). For some substrates, significant improvements were observed. It was found that *N*-alkyl groups exhibited no side-chain exchange under these conditions (entries 2-5), showed similar behaviour and excellent incorporation at all positions. The effect of halogen substituents (**114**-**116**) did vary with position: with a halogen at C-2 or C-3 high incorporation efficiency (98%) was observed at C-3 or C-2 (entries 8 and 9), respectively, whereas the presence of a methyl group

showed high D incorporation at both α-positions (entry 7). Interestingly, **112** did not exchange efficiently (entry 6) under these conditions other than at the α-position.

Figure 15: %D Incorporation in aminopyridines under neutral conditions then acidic conditions.

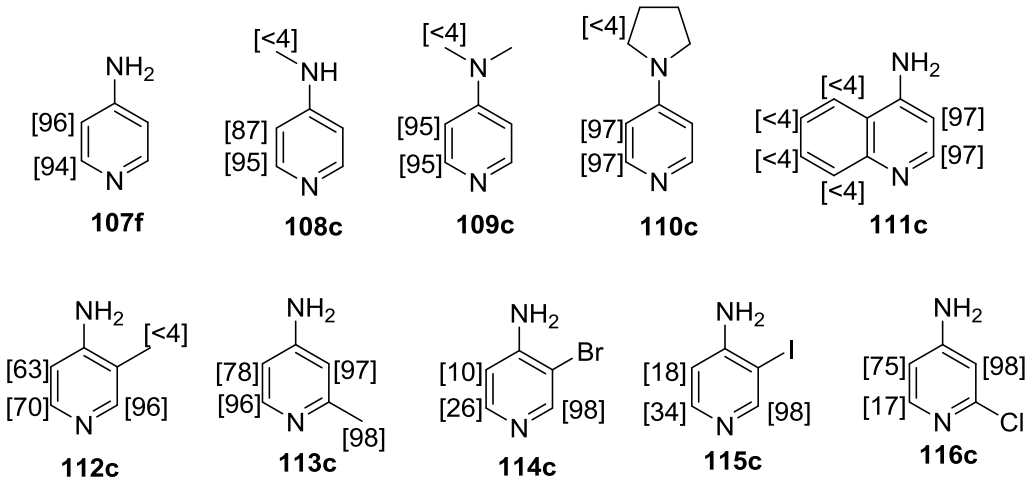


Table 5.4: %D Incorporation of substituted 4-aminopyridines and related heterocycles after microwave irradiation at 190 °C for 2 h in D_2O followed by irradiation in the presence of DCl[a].

Entry	Product	C-2	C-3	C-5	C-6	C-7	C-8	C-1'	C-2'	C-3'	Yield[b]
1	**107f**	94	96	96	94	-	-	-	-	-	58
2	**108c**	95	87	87	95	-	-	<4	-	-	84
3	**109c**	95	95	95	95	-	-	<4	-	-	74
4	**110c**	97	97	97	97	-	-	-	<4	<4	65
5	**111c**	97	97	<4	<4	<4	<4	-	-	-	62
6	**112c**	96	-	63	70	-	-	<4	-	-	75
7	**113c**	-	97	78	96	-	-	98	-	-	67
8	**114c**	98	-	10	26	-	-	-	-	-	86
9	**115c**	98	-	18	34	-	-	-	-	-	96
10	**116c**	-	98	75	17	-	-	-	-	-	92

a As determined by ^1H NMR spectroscopic analysis, after introduction of an internal standard (entries 1-3, 7-15) by acetylation (AcCl, K_2CO_3, acetone, RT, 3 h), followed by aqueous work-up and purification by column chromatography on silica if required; or by reference to a known quantity of dioxane as an external standard (entries 4-6).

b Yield refers to the isolated yield% of product after microwave irradiation of the substrate in D_2O in a sealed Pyrex™ tube at 190 °C for 2 h (hold-time) in the presence or absence of DCl (4 equiv.), by moderation of the initial magnetron power (300 W), cooling, then irradiation again in the presence of DCl under similar conditions, followed by cooling and an acid-base work-up.

These studies demonstrated that 4-aminopyridines can undergo H/D exchange under neutral conditions at comparitively low temperatures and short reaction times. These exchange equilbria complement and can be combined with acid-mediated H/D exchange reactions to give new experimental protocols that are fast, convenient and efficient. Furthermore, they provide isotopologues bearing multible D labels and so may be well suited for application in the study of pharmacokinetic and metabolic properties.

Conclusion.

Recently Bohlmann–Rahtz pyridine synthesis has provided a convenient route for the synthesis of various substituted pyridine products. The process has been modified in this work to be rapid, simple, operate under mild conditions and high yielding. We have shown that substituted pyridines could be synthesized efficiently and in high yields under microwave conditions from readily-available precursors in what is essentially a relatively short reaction time. The use of novel Lewis acids for this process has been investigated and it has been discovered that $FeCl_3$ exhibits a similar profile of reactivity to $ZnBr_2$ in Bohlmann-Rahtz pyridine synthesis, providing the opportunity to improve the yield, rate, catalyst loading and substrate tolerance of this transformation. Furthermore, the behaviour of little studied Lewis acid catalysts containing heteronuclear metal clusters in this reaction has been studied, providing new insights into their chemical properties, new understanding of the catalytic role and new capability for Bohlmann-Rahtz transformations. The application of Bohlmann-Rahtz methods to the synthesis of 2-aminopyridines and pyridine-fused targets has further expanded the scope of this reaction.

The deuteration of pyridine derivatives using microwave irradiation is a valuable process and has provided insights into the selectivity and efficiency of H/D exchange reactions

under both acidic and neutral conditions. Whilst the understanding of acid-mediated electrophilic substitution is reasonably well established, the combination of such reactions with the neutral process, and the remarkable ease with which 4-aminopyridines undergo H/D exchange under neautral conditions, allowed for direct comparison, giving a greater insight into the selectivity and chemistry of exchange processes. It has been shown that the H/D exchange of pyridine derivatives in the absence of DCl proceeds with remarkable ease and is often highly regioselective for exchange at the α-position. In general, the yields for this microwave-assisted procedure are good, the reactions are relatively fast and high levels of deuterium incorporation are observed. In conclusion, this is a useful procedure for the synthesis of deuterated pyridines that should find use in the chemist's modern toolkit.

Future work.

This thesis has revealed new substrate scope for the Bohlmann-Rahtz reaction and shown it can be used in the synthesis of 2-aminopyridines. For this study only a single diamine was investigated, but the scope of this reaction could be expanded in the study of alternative ene-diamines to provide 2-aminopyridines bearing a range of different electron-withdrawing groups at the 3-position. Further work on the synthesis of pyridines bearing alternative *N*-containing groups has been a focus of subsequent work in the group and remains an important goal to widen the applicability of the Bohlmann-Rahtz reaction. However, perhaps the most promising area of study for the future would be the use of heteronuclear metal clusters as catalysts in the Bohlmann-Rahtz reaction. These studies revealed their high activity in cyclodehydration and one-pot pyridine synthesis. Expanding these studies to demonstrate the scope and further applicability of these

methods may reveal new facets of their reactivity and deliver new improved experimental procedures so is worthy of further investigation.

H/D exchange reactions promise to be important in future years and these studies have revealed some intriguing new processes. The findings from H/D exchange under both acidic and neutral conditions could be complemented with metal-catalyzed processes to expand their scope, and even combined with acid-mediated deuterium-protium exchange to deliver highly site-selective methods for poly- or mono-deuteration, respectively. The deuteration of pyridine derivatives using homogenous platinum catalysts would be one system that might be worthy of future investigation to compare results with previous work.

In conclusion, these studies have provided many new methods for the synthesis and functionalization of pyridine-containing compounds. It is anticipated that extending these studies to biologically-relevant scaffolds and other heterocyclic motifs will expand the utility of this work and, it is hoped, will ensure that the discoveries made as part of this thesis will find widespread application in the future.

Experimental

6. Experimental.

6.1. General Procedures.

Commercially available reagents were used without further purification. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254 that were visualised under UV light (at 254 and/or 360 nm). Microwave irradiation experiments were performed using a self-tunable CEM Discover® focused monomodal microwave synthesiser at the given temperature, measured using the instrument's in-built IR sensor, by varying the irradiation power (initial power given in parentheses). Infra-red (IR) spectra were recorded in the range 4000-600 cm^{-1} using a Perkin–Elmer 1600 series FTIR spectrometer using an ATR probe and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded using a Varian VNMRS instrument operating at 400 or 500 MHz in CDCl3 at 25 °C unless stated otherwise and were reported in ppm; *J* values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using electron ionization (EI). In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

6.2. General procedure for microwave-assisted synthesis of 2-aminopyridines using hydrochloride salt **86**·HCl

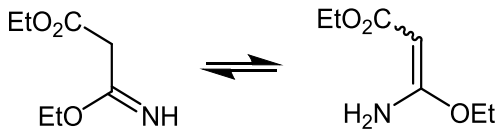
A solution of ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (1 equiv) and the ethynyl ketone (1.05 equiv) in ethanol (3 mL) was irradiated at 150 °C for 1.5 h (hold-time) in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave

synthesizer by moderation of the initial magnetron power (200 W). After cooling in a flow of compressed air, the solution was immobilized on a Biotage ISOLUTE SCX-2 column and eluted with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) to give the title compound.

6.3. General procedure for microwave-assisted synthesis of 2-aminopyridines using free base

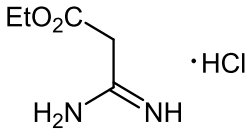
An ethanolic solution of ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (1 equiv) was pre-treated with sodium carbonate (1 equiv) for 10 min. After filtering, the ethynyl ketone (1.05 equiv) was added and the mixture in ethanol (3.5 mL) was irradiated at 150 °C for 1.5 h (hold-time) in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderation of the initial magnetron power (200 W). After cooling in a flow of compressed air, the solution was immobilized on a Biotage ISOLUTE SCX-2 column and eluted with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) or ethanolic ammonia (2 M) to give the title compound.

Synthesis of ethyl 3-amino-3-ethoxypropenoate (ethyl 3-ethoxy-3-iminopropionate).



Ethyl 3-ethoxy-3-iminopropionate hydrochloride (**89**·HCl) (978 mg, 2.22 mmol) and K_2CO_3 (1380 mg, 10.0 mmol) were partitioned between Et_2O (10 mL) and H_2O (10 mL). The organic extract was separated, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (760 mg, 95%) as a colourless oil, which was used without further purification; ν_{max} (neat) /cm^{-1} 3400, 3300, 1741, 1659; δ_H (500 MHz; $CDCl_3$) /ppm 6.16 (2H, s, NH_2), 4.14 (1H, s, CH), 4.07 (2H, q, J = 7.1 Hz, OCH_2), 3.90 (2H, q, J = 7.0 Hz, OCH_2), 1.28 (3H, t, J = 7.1 Hz, Me), 1.21 (3H, t, J = 7.1 Hz, Me); δ_C (125 MHz, $CDCl_3$) /ppm 171.1 (C**)**, 168.4 (C), 64.8 (CH), 63.7 (CH_2), 58.7 (CH_2), 14.7 (Me), 14.4 (Me); *m/z* (EI) 159 ($M^{\bullet+}$, 100%).

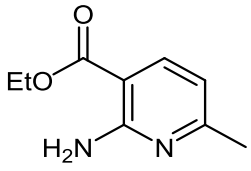
Synthesis of ethyl 3-amino-3-iminopropionate hydrochloride.



A solution of ethyl 3-amino-3-ethoxypropenoate **(86)** (760 mg, 4.78 mmol) and NH_4Cl (270 mg, 5.0 mmol) in EtOH (4.0 mL) was irradiated in a pressure-rated glass tube (10 mL) at 120 °C for 1 h (hold-time) using a CEM Discover® microwave synthesizer by moderation of the initial magnetron power (200 W). After cooling in a flow of compressed air, the solution was filtered, evaporated in vacuo and triturated with diethyl ether to give the *title compound* (923 mg, 78%) as a colourless solid, which was

used without further purification; ν_{max} (neat) /cm^{-1} 3300, 3095, 1738, 1687; δ_H (500 MHz; d_6-DMSO) /ppm 9.16 (2H, bs, N*H*H), 8088 (2H, bs, 2H, N*H*H), 4.15 (2H, q, *J* = 7.1 Hz, OCH_2), 3.63 (2H, s, H-2), 1.22 (3H, t, *J* = 7.1 Hz, Me); δ_C (125 MHz, d_6-DMSO) /ppm 166.7 (C**)**, 163.6 (C), 61.9 (CH_2), 38.2 (CH_2), 14.4 (Me); *m/z* (EI) 130 ($M^{\bullet+}$, 100%).

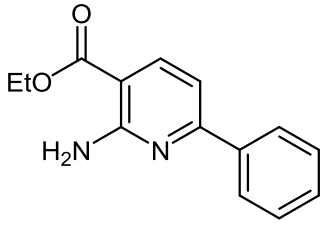
Synthesis of ethyl 2-amino-6-methylnicotinate.



A solution of ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (150 mg, 0.90 mmol) and 3-butyn-2-one (64 mg, 0.95 mmol) in EtOH (3.5 mL) was irradiated at 150 °C for 1.5 h (hold-time) in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderating the initial power (200 W). After cooling in a flow of compressed air the solution was partitioned between aqueous $NaHCO_3$ solution and EtOAc (10 mL). The aqueous layer was further extracted with EtOAc (4 × 10 mL) and the organic extracts were combined and evaporated *in vacuo*. Purification by immobilization on a Biotage ISOLUTE SCX-2 column, eluting with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*), gave the *title compound* (140 mg, 87%) as a brown powder, mp 88 °C (Found MH^+, 181.0971. $C_9H_{13}N_2O_2$ [*MH*] requires 181.0972); ν_{max} (neat)/cm^{-1} 3425, 3263, 2986, 1686, 1616, 1586, 1247, 1106, 841, 781, 721; δ_H (500 MHz; $CDCl_3$)/ppm 8.01 (1H, d, *J* = 8.0 Hz, H-4), 6.90-6.40 (2H, bs, NH_2), 6.46 (1H, d, *J* = 8.0 Hz, H-5), 4.31 (2H, q, *J* = 7.1 Hz, CH_2), 2.38 (3H, s, 6-Me), 1.36 (3H, t, *J* = 7.1

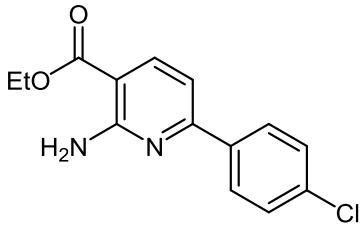
Hz, Me); δ_C (125 MHz, d_6-DMSO/$CDCl_3$)/ppm 171.7 (C**)**, 168.0 (C), 164.2 (C), 145.1 (CH), 116.6 (CH), 107.4 (C), 65.4 (CH_2), 29.1 (Me), 19.3 (Me); *m/z* (EI) 180 ($M^{\bullet+}$, 100%).

Synthesis of ethyl 2-amino-6-phenylnicotinate.



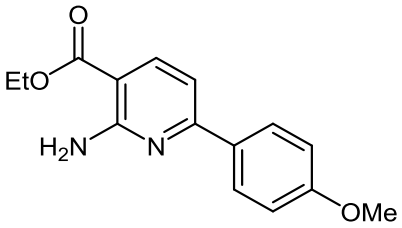
General Procedure I, using ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (250 mg, 1.5 mmol) and 1-phenylpropyn-2-one (205 mg, 1.575 mmol) in EtOH (3.5 mL), gave the *title compound* (268 mg, 73%) as a yellow solid, mp 108 °C (Found MH^+, 243.1129. $C_{14}H_{15}N_2O_2$ [*MH*] requires 243.1128); ν_{max} (neat)/cm^{-1} 3428, 3283, 2980, 1690, 1622, 1583, 1243, 1094, 922, 755, 699; δ_H (500 MHz; $CDCl_3$)/ppm 8.21 (1H, d, *J* = 8.1 Hz, H-4), 8.00 (2H, d, *J* = 7.1 Hz, H-2',6'), 7.48-7.44 (3H, H-3',4',5'), 7.09 (1H, d, *J* = 8.1 Hz, H-5), 7.00-6.00 (2H, bs, NH_2), 4.38 (2H, q, *J* = 7.1 Hz, CH_2), 1.41 (3H, t, *J* = 7.1 Hz, Me); δ_C (125 MHz, $CDCl_3$)/ppm 167.0 (C), 160.8 (C), 159.4 (C**)**, 140.8 (CH), 138.6 (C), 129.7 (CH), 128.6 (CH), 127.3 (CH), 109.6 (CH), 104.9 (C), 60.7 (CH_2), 14.3 (Me); *m/z* (EI) 243 ($M^{\bullet+}$, 25%), 242 (100).

Synthesis of ethyl 2-amino-6-(4-chlorophenyl)nicotinate.



General Procedure II, using ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (150 mg, 0.90 mmol), 1-(4-chlorophenyl)-2-propyn-1-one (156 mg, 0.948 mmol) and sodium carbonate (150 mg, 0.90 mmol) in EtOH (3.5 mL), gave the *title compound* (180 mg, 72%) as a brown solid, mp 122 °C (Found MH^+, 277.0737. $C_{14}H_{14}ClN_2O_2$ [*MH*] requires 277.0738); ν_{max} (neat)/cm^{-1} 3493, 3374, 3007, 2983, 2942, 1684, 1679, 1559; δ_H (500 MHz; $CDCl_3$)/ppm 8.17 (1H, d, *J* = 8.0 Hz, H-4), 7.93 (2H, d, *J* = 8.0 Hz, H-2',6'), 7.40 (2H, d, *J* = 8.0 Hz, H-3',5'), 7.00 (1H, d, *J* = 8.0 Hz, H-5), 6.64 (2H, bs, NH_2), 4.35 (2H, q, *J* = 7.0 Hz, CH_2), 1.39 (3H, t, *J* = 7.0 Hz, Me); δ_C (125 MHz, $CDCl_3$)/ppm 166.9 (C), 160.4 (C), 159.2 (C), 140.9 (CH), 136.9 (C), 135.8 (C), 128.8 (CH), 128.6 (CH), 109.2 (CH), 105.2 (C), 60.9 (CH_2), 13.9 (Me); *m/z* (EI) 277 ($M^{\bullet+}$, 32%), 276 (100).

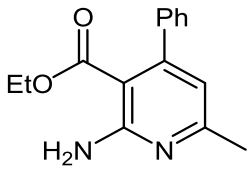
Synthesis of ethyl 2-amino-6-(4-methoxyphenyl)nicotinate.



General Procedure II, using ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (150 mg, 0.90 mmol), 1-(4-methoxyphenyl)-2-propyn-1-one (152 mg, 0.948 mmol), and sodium carbonate (150 mg, 0.90 mmol), in ethanol (3.5 mL), gave the *title compound* (174.2 mg, 71%) as a brown solid, mp 103 °C (Found MH^+, 273.1232. $C_{15}H_{17}N_2O_3$ [*MH*] requires 273.1234); ν_{max} (neat)/cm^{-1} 3490, 3269, 3371, 2965, 2965,

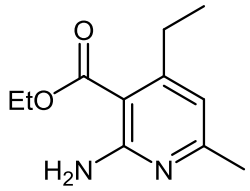
1684, 1606, 1559; δ_H (500 MHz; $CDCl_3$)/ppm 8.13 (1H, d, *J* = 8.1 Hz, 4-H), 7.95 (2H, d, *J* = 7.8 Hz, H-2',6'), 6.98 (1H, d, *J* = 8.1 Hz, H-5), 6.94 (2H, d, *J* = 7.8 Hz, H-3',5'), 6.80-6.20 (2H, bs, NH_2), 4.33 (2H, q, *J* = 7.0 Hz, CH_2), 3.82 (3H, s, OMe), 1.37 (3H, t, *J* = 7.0 Hz, Me); δ_C (125 MHz, $CDCl_3$) 167.1 (C**)**, 161.1 (C), 160.2 (C), 159.3 (C), 140.6 (CH), 131.0 (C), 128.7 (CH), 114.0 (CH), 108.8 (CH), 104.2 (C), 60.6 (CH_2), 55.3 (Me), 14.3 (Me); *m/z* (EI) 272 ($M^{\bullet+}$, 100%).

Synthesis of ethyl 2-amino-6-methyl-4-phenylnicotinate.



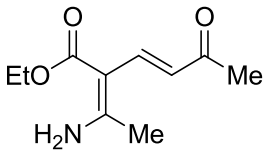
General Procedure II, using ethyl 3-amino-3-iminopropionate hydrochloride (**6**·HCl) (270 mg, 1.62 mmol), 4-phenyl-3-butyn-2-one (270 mg, 1.70 mmol) and sodium carbonate (270 mg, 1.62 mmol), in ethanol (3.5 mL), gave the *title compound* (216 mg, 52%) as a brown solid, mp 139 °C; ν_{max} (neat)/cm^{-1} 3443, 3272, 2977, 1682, 1606, 1582, 1241; δ_H (500 MHz; $CDCl_3$)/ppm 7.33-7.30 (3H, H-3',4',5'), 7.20 (2H, m, H-2',6'), 6.41 (1H, s, H-5), 6.29 (2H, bs, NH_2), 3.88 (2H, q, *J* = 7.1 Hz, OCH_2), 2.37 (3H, s, 6-Me), 0.69 (3H, t, *J* = 7.1 Hz, Me); δ_C (125 MHz, $CDCl_3$)/ppm 168.5 (C), 160.3 (C), 158.7 (C), 153.8 (C), 141.5 (C), 127.9 (CH), 127.4 (CH), 115.2 (CH), 104.7 (C), 60.4 (CH_2), 24.2 (Me), 13.1 (Me); *m/z* (EI) 256 ($M^{\bullet+}$, 100%).

Synthesis of ethyl 2-amino-4-ethyl-6-methylnicotinate.



General Procedure II, using ethyl 3-amino-3-iminopropionate hydrochloride (**86**·HCl) (200 mg, 1.26 mmol), 3-hexyn-2-one (128 mg, 1.32 mmol), and sodium carbonate (200 mg, 1.26 mmol) in ethanol (3.5 mL), gave the *title compound* (133 mg, 54%) as a brown solid, mp 141 °C (Found MH^+, 209.1282. $C_{11}H_{17}N_2O_2$ [*MH*] requires 209.1285); ν_{max} (neat)/cm^{-1} 3450, 3269, 3147, 2972, 1686, 1619, 1586; δ_H (500 MHz; $CDCl_3$)/ppm 6.33 (1H, s, 5-H), 6.19 (2H, bs, NH_2), 4.33 (2H, q, J = 7.0 Hz, OCH_2), 2.78 (2H, q, J = 7.0 Hz, 4-CH_2CH_3), 2.30 (3H, s, 6-Me), 1.36 (3H, t, J = 7.0 Hz, Me), 1.16 (3H, t, J = 7.0 Hz, 4-CH_2Me); δ_c (125 MHz, $CDCl_3$)/ppm 168.3 (C), 160.3 (C), 159.4 (C), 157.2 (C), 114.8 (CH), 104.6 (C), 60.7 (CH_2), 28.6 (CH_2), 23.9 (Me), 15.1 (Me), 14.0 (Me); *m/z* (EI) 208 ($M^{\bullet+}$, 100%).

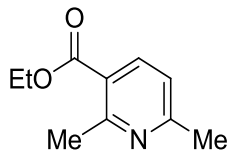
Synthesis of 2-amino-3-ethoxycarbonylhepta-2,4-dien-6-one.



A mixture of ethyl 3-aminocrotonate (0.20 mL, 1.6 mmol) and 4-(trimethylsilyl)but-3-yn-2-one (0.52 mL, 3.2 mmol) in dry ethanol (4 mL) was irradiated at 60 °C for 60 min in a sealed pressure-rated reaction tube (10 mL) using a CEM Discover® microwave synthesizer by moderation of the initial magnetron power (100 W). After cooling in a

flow of compressed air, the solution was evaporated *in vacuo*. Purification by recrystallization from hexane–acetone (7:1 *v*/*v*) gave the *title compound* (310 mg, 100%) as a yellow solid, mp 123–124 °C (lit.[1] mp 125.5–126.4 °C) (Found $M^{\bullet+}$, 197.1053. $C_{10}H_{15}NO_3$ [*M*] requires 197.1052); ν_{max}(neat)/cm^{-1} 3332, 1740, 1554, 1489, 1443, 1352, 1310, 1277, 1200, 1183, 1111, 1023; δ_H (400 MHz; DMSO–*d*$_6$)/ppm 9.20-8.50 (2H, bs, NH_2), 7.45 (1H, d, *J* = 15.0 Hz, C*H*=CHCOCH$_3$), 6.38 (1H, d, *J* = 15.0 Hz, CH=C*H*COCH$_3$), 4.15 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 2.45 (3H, s, Me), 2.10 (3H, s, Me), 1.22 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); δ_C (100 MHz; DMSO–*d*$_6$)/ppm 199.7 (CH$_3$*C*=O), 170.5 (C=O), 166.5 (C-NH_2), 140.4 (*C*H=CHCOCH$_3$), 122.0 (CH=*C*HCOCH$_3$), 95.3 (C=*C*CO$_2$CH$_2$CH$_3$), 59.9 (*C*H$_2$CH$_3$), 29.2 (CO*C*H$_3$), 23.5 (*C*H$_3$C=C), 15.3 (*C*H$_3$CH$_2$); *m/z* (EI) 197 ($M^{\bullet+\cdot}$, 35), 179 (50), 151 (100), 108 (85).

Synthesis of ethyl-2,6-dimethylpyridine-3-carboxylate.



A mixture of 2-amino-3-ethoxycarbonylhepta-2,4-diene-6-one (700 mg, 3.55 mmol) and $ZnBr_2$ (0.131mg, 0.50 mmoL) as a catalyst in toluene (15 mL) was irradiated at 120 °C for 1 h in a sealed pressure-rated reaction tube (10 mL) using a CEM Discover® microwave synthesizer by moderation of the initial magnetron power (100 W). After cooling in a flow of compressed air, water (10 mL) was added and the mixture was stirred for 10 min. The solution was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with light petroleum-EtOAc (3:1 *v*/*v*), gave the *title compound* (610 mg, 99%)

as a light brown oil (Found MH^+, 180.1019. $C_{10}H_{14}NO_2$ [*MH*] requires 180.1019); ν_{max} (neat)/cm^{-1} 3681, 2981, 2866, 2076, 1720, 1591, 1370, 1280, 1149, 1032, 839, 715; δ_H (500 MHz; CD_3OD)/ppm 7.99 (1H, d, *J* = 8.0 Hz, H-4), 6.95 (1H, d, *J* = 8.0 Hz, H-5), 4.27 (2H, q, *J* = 7.1 Hz, CH_2), 2.72 (3H, s, Me), 2.47 (3H, s, Me), 1.30 (3H, t, *J* = 7.1 Hz, CH_2*CH*$_3$); δ_C (125 MHz; CD_3OD)/ppm 166.5 (C=O), 160.9 (C), 159.2 (C), 138.5 (CH), 122.6 (C), 120.2 (CH), 60.8 (CH_2), 24.6 (Me), 24.6 (Me), 14.1 (Me); *m*/*z* (EI) 180 (MH^+, 15%), 179 ($M^{\bullet+}$, 55), 134 (100), 133 (35).

Alternative microwave-assisted method using $FeCl_3$ catalyst.

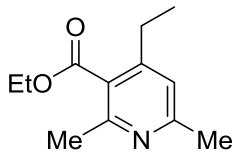
A solution of ethyl 3-aminocrotonate (150 mg, 1.16 mmol), $FeCl_3$ (38 mg, 0.23 mmol) and 3-hexyn-2-one (112 mg, 1.16 mmol) in ethanol (3 mL) was irradiated at 150 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer (initial power 200 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (202 mg, 84%) as a brown oil with identical spectroscopic properties.

Alternative method at reflux using $FeCl_3$ catalyst.

A solution of ethyl acetoacetate (150 mg, 1.15 mmol), $FeCl_3$ (38 mg, 0.23 mmol), ammonium acetate (888 mg, 11.2 mmol) and 3-hexyn-2-one (223 mg, 2.30 mmol) in PhMe (5 mL) was heated under reflux for 15 hours. After cooling, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous was extracted with

EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (193 mg, 93%) as a brown oil with identical spectroscopic properties.

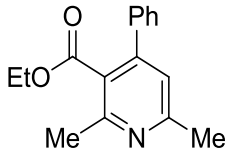
Synthesis of ethyl-2,6-dimethyl-4-ethylpyridine-3-carboxylate.



A solution of ethyl 3-aminocrotonate (150 mg, 1.16 mmol), $FeCl_3$ (38 mg, 0.23 mmol) and 3-hexyn-2-one (134 mg, 1.39 mmol) in ethanol (3 mL) was irradiated at 150 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer (initial power 200 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (206 mg, 86%) as a yellow oil (Found $M^{\bullet+}$, 207.1260. $C_{12}H_{17}NO_2$ [*M*] requires 207.1291); ν_{max} (neat)/ cm^{-1} 3424, 2977, 2076, 1723, 1593, 1446, 1387, 1276, 1188, 1084, 1016, 899, 865, 733; δ_H (500 MHz; CD_3OD)/ppm 6.86 (1H, s, H-5), 4.39 (2H, q, *J* = 7.0 Hz, CH_2), 2.60 (2H, q, *J* = 7.6 Hz, 4-*CH_2*CH_3), 2.50 (3H, s, 6-Me), 1.38 (3H, t, *J* = 7.0 Hz, Me), 1.20 (3H, t, *J* = 7.6 Hz, CH_2*Me*); δ_C (125 MHz; CD_3OD)/ppm 168.9 (C=O), 158.4 (C), 154.3

(C), 150.6 (C), 126.2 (C), 120.2 (CH), 61.1 (CH_2), 26.2 (CH_2), 24.2 (Me), 22.7 (Me), 14.5 (Me) 14.1 (Me); *m*/*z* (EI) 207 ($M^{\bullet+}$, 55%), 162 (100), 161 (50).

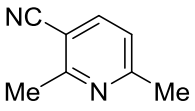
Synthesis of ethyl-2,6-dimethyl-4-phenylpyridine-3-carboxylate.



A solution of ethyl 3-aminocrotonate (150 mg, 1.16 mmol), $FeCl_3$ (38 mg, 0.23 mmol) and 4-phenyl-3-butyn-2-one (167 mg, 1.16 mmol) in ethanol (3 mL) was irradiated at 150 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer (initial power 200 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (245 mg, 84%) as a yellow oil (Found $M^{\bullet+}$, 255.1259. $C_{16}H_{17}NO_2$ [*M*] requires 255.1261); ν_{max} (neat)/cm^{-1} 3060, 2985, 2164, 1721, 1587, 1445, 1262, 1135, 1079, 970, 858, 766, 699; δ_H (500 MHz; CD_3OD)/ppm 7.29 (5H, s, Ph), 6.93 (1H, s, H-5), 4.01 (2H, q, *J* = 7.0 Hz, CH_2), 2.55 (3H, s, Me), 2.49 (3H, s, Me), 0.90 (3H, t, *J* = 7.0 Hz, Me); δ_C (125 MHz; CD_3OD)/ppm 168.8 (C=O), 158.5 (C), 154.9 (C), 148.4 (CH), 138.7 (C), 128.3

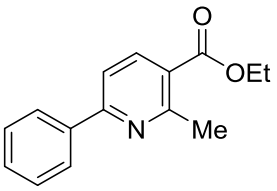
(C), 128.2 (CH), 125.7 (C), 120.9 (CH), 77.2 (CH_2), 61.1 (CH), 24.3 (Me), 22.7 (Me), 13.5 (Me); *m*/*z* (EI) 255 ($M^{\bullet+}$, 45%), 211 (10), 210 (100), 209 (15).

Synthesis of 2,6-dimethylpyridine-3-carbonitrite.



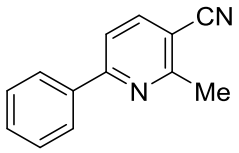
A solution of ethyl 3-aminocrotononitrile (150 mg, 1.83 mmol), $FeCl_3$ (60 mg, 0.36 mmol) and 3-butyn-2-one (124 mg, 1.83 mmol) in ethanol (3 mL) was irradiated at 150 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer (initial power 200 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (202 mg, 84%) as a yellow oil (Found: MH^+, 132.0687. $C_8H_8N_2$ requires [*M*] 132.0687); ν_{max} (neat)/cm^{-1} 3399, 2925, 2198, 1688, 1587, 1435, 1358, 1250, 1159, 972, 799, 735; δ_H (500 MHz; CD_3OD)/ppm 7.87 (1H, d, *J* = 8.0 Hz, H-5), 6.49 (1H, d, *J* = 8.0 Hz, H-4), 2.52 (3H, s, Me), 2.39 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 198.6 (C), 164.1 (C), 158.5 (C), 112.1 (C≡N), 110.9 (C), 26.9 (Me), 24.7 (Me); *m*/*z* (EI) 132 ($M^{\bullet+}$, 100%), 131 (10).

Synthesis of ethyl-2-methyl-6-phenylpyridine-3-carboxylate.



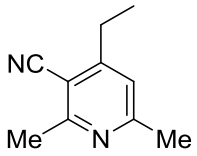
A solution of ethyl 3-aminocrotonate (149 mg, 1.53 mmol), $FeCl_3$ (48 mg, 0.3 mmol) and 1-phenyl-2-propyn-1-one (150 mg, 1.53 mmol) in ethanol (3 mL) was irradiated at 150 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer (initial power 200 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v*), gave the *title compound* (90 mg, 25%) as a orange oil; ν_{max} (neat)/cm^{-1} 3069, 2980, 1716, 1581, 1447, 1262, 1089, 976, 848, 755; δ_H (500 MHz; CD_3OD)/ppm 8.23 (1H, d, *J* = 7.0 Hz, CH), 8.05 (1H, d, *J* = 7.0 Hz, CH), 7.46 (5H, s, Ph), 4.38 (2H, q, *J* = 7.0 Hz, CH_2), 2.66 (3H, s, Me), 1.4 (3H, t, *J* = 7.1 Hz, Me); δ_C (125 MHz; CD_3OD)/ppm 166.6 (C=O), 159.8 (C), 158.9 (C), 139.2 (C), 138.4 (CH), 129.6 (CH), 128.7 (CH), 127.3 (CH), 123.6 (C), 117.2 (CH), 61.1 (CH_2), 25.2 (Me), 14.3 (Me); *m*/*z* (EI) 241 ($M^{\bullet+}$, 100%), 213 (15), 196 (80), 195 (20).

Synthesis of 2-methyl-6-phenylpyridine-3-carbonitrile.



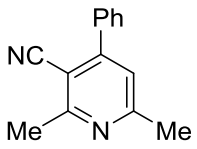
A solution of ethyl 3-aminocrotononitrile (126 mg, 1.53 mmol), $FeCl_3$ (48 mg, 0.3 mmol) and 1-phenyl-2-propyn-1-one (150 mg, 1.53 mmol) in ethanol (3 mL) was irradiated at 150 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer (initial power 200 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (285 mg, 95%) as an orange oil (Found $M^{\bullet+}$, 195.0915. $C_{13}H_{11}N_2$ [*M*] requires 195.0917); ν_{max} (neat)/cm^{-1} 3340, 2222, 2195, 1717, 1638, 1557, 1284, 976, 848, 739; δ_H (500 MHz; CD_3OD)/ppm 8.04 (1H, d, *J* = 7.0 Hz, CH), 7.91 (1H, d, *J* = 7.0 Hz, CH), 7.64 (1H, d, *J* = 7.0 Hz, CH), 7.49 (5H, s, Ph), 2.83 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 161.6 (C), 159.7 (C), 140.6 (C), 137.6 (C), 130.3 (C), 128.9 (CH), 127.4 (CH), 117.3 (C≡N), 106.9 (CH), 76.9 (CH), 74.6 (CH), 23.9 (Me); *m*/*z* (EI) 194 ($M^{\bullet+}$, 100%), 193 (35), 192 (10).

Synthesis of 2,6-dimethyl-4-ethylpyridine-3-carbonitrile.



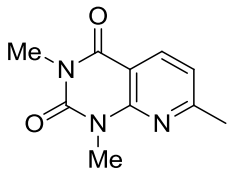
A solution of ethyl 3-aminocrotononitrile (150 mg, 1.83 mmol), $FeCl_3$ (60 mg, 0.36 mmol) and 3-hexyn-2-one (175 mg, 1.83 mmol) in ethanol (3 mL) was irradiated at 150 °C (initial power 200 W) for 1 h in a sealed pressure-rated reaction tube (10 mL) using a CEM Discover® Microwave Synthesizer. After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v*/*v)*, gave the *title compound* (67 mg, 24%) as brown oil; ν_{max} (neat)/cm^{-1} 3424, 2977, 2190, 1561, 1430, 1250, 1188, 964, 834; δ_H (500 MHz; CD_3OD)/ppm 6.88 (1H, s, H-5), 2.65 (2H, q, *J* = 7.6 Hz, 4-*CH*$_2$$CH_3$), 2.50 (3H, s, 6-Me), 2.15 (3H, s, Me), 1.20 (3H, t, *J* = 7.6 Hz, CH_2*Me*); δ_C (125 MHz; CD_3OD)/ppm 158.4 (C), 154.3 (C), 150.6 (C), 126.2 (C), 120.2 (CH), 118.7 (C≡N), 26.2 (CH_2), 24.2 (Me), 22.7 (Me), 14.5 (Me).

Synthesis of 2,6-dimethyl-4-phenylpyridine-3-carbonitrile.



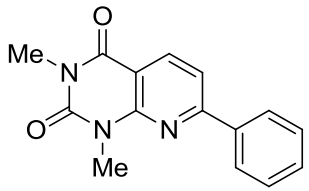
A solution of ethyl 3-aminocrotononitrile (150 mg, 1.83 mmol), $FeCl_3$ (60 mg, 0.36 mmol) and 4-phenyl-3-butyn-2-one (0.26 mL, 1.83 mmol) in ethanol (3 mL) was irradiated at 150 °C (initial power 200 W) for 1 h in a sealed pressure-rated reaction tube (10 mL) using a CEM Discover® Microwave Synthesizer. After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, washed successively with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo.* Purification by column chromatography on silica, eluting with CH_2Cl_2-EtOAc (1:1 *v/v),* gave the *title compound* (124 mg, 33%) as brown oil (Found $M^{\bullet+}$, 208.1040. $C_{14}H_{12}N_2$ [*M*] requires 208.1048); ν_{max} (neat)/cm^{-1} 2963, 2290, 1601, 1570, 1310, 1250, 1117, 1030, 962, 803; δ_H (500 MHz; CD_3OD)/ppm 7.48 (2H, m, H-2´/H-6´), 7.48 (1H, m, H-4´), 7.31 (2H, m, H-3´/H-5´), 5.98 (1H, s, H-5), 2.50 (3H, s, Me), 2.17 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 159.5 (C), 159.1 (C), 150.6 (CH), 139.2 (C), 128.9 (CH), 128.2 (C), 126.1 (C), 117.8 (C≡N), 106.9 (CH), 74.6 (CH), 23.9 (Me), 23.2 (Me), ; *m*/*z* (EI) 208 ($M^{\bullet+}$, 100%).

Synthesis of 1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.



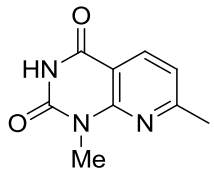
A solution of 6-amino-1,3-dimethyluracil (263 mg, 1.70 mmol) and 3-butyn-2-one (115 mg, 1.70 mmol) in acetic acid (4 mL) was irradiated at 120 °C for 30 min in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 35 mL) and the organic extracts were combined, washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (264 mg, 76%) as a creamy solid (Found $[M\text{-}Me]^{\bullet+}$, 190.0614. $C_{10}H_{11}N_3O_2$ [*M-Me*] requires 190.0617); ν_{max} (neat)/cm^{-1} 1660, 1500; δ_H (500 MHz; CD_3OD)/ppm 8.32 (1H, d, *J* = 8.1 Hz, H-5), 7.03 (1H, d, *J* = 8.1 Hz, H-6), 3.75 (3H, s, Me), 3.45 (3H, s, Me), 2.82 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 162.1 (C), 161.9 (C), 159.2 (C), 149.5 (C), 138.3 (CH), 119.5 (CH), 107.5 (C), 30.1 (Me), 29.1 (Me), 26.3 (Me); *m*/*z* (EI) 191 (MH^+, 13%), 190 ($M^{\bullet+}$, 100%), 164 (33), 163 (46), 110 (7), 85 (73).

Synthesis of 1,3-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.



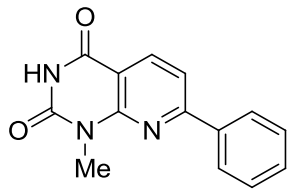
A solution of 6-amino-1,3-dimethyluracil (120 mg, 0.77 mmol) and 1-phenyl-2-propyn-1-one (100 mg, 0.77 mmol) in acetic acid (4 mL) was irradiated at 120 °C for 30 min in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 35 mL) and the organic extracts were combined, washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (200 mg, 98%) as a colourless solid, mp >300 °C; (Found $M^{\bullet+}$, 267.1008. $C_{15}H_{13}N_3O_2$ [*M*] requires 267.1008); ν_{max} (neat)/cm^{-1} 1668, 1592, 1524; δ_H (500 MHz; CD_3OD)/ppm 8.40 (1H, d, *J* = 8.1 Hz, H-5), 8.21 (2H, d, *J* = 7.5 Hz, H-2/H-6 of Ph), 7.91 (1H, d, *J* = 8.1 Hz, H-6), 7.55 (3H, m, H-3/H-4/H-5 of Ph), 3.75 (3H, s, Me), 3.45 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 160.2 (C), 150.9 (C), 150.6 (C), 145.7 (C), 138.3 (CH), 137.8 (C), 131.0 (CH), 129.8 (CH), 128.0 (CH), 113.7 (CH), 109.5 (C), 29.5 (Me), 28.2 (Me); *m*/*z* (EI) 268 (MH^+, 14%), 267 ($M^{\bullet+}$, 100), 226 (39), 165 (52), 77 (80).

Synthesis of 1,7-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.



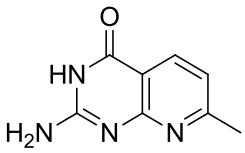
A solution of 6-amino-1-methyluracil (240 mg, 1.70 mmol) and 3-butyn-2-one (115 mg, 1.70 mmol) in acetic acid (4 mL) was irradiated at 120 °C for 30 min in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 35 mL) and the organic extracts were combined, washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (320 mg, 99%) as an orange solid (Found $M^{\bullet+}$, 191.1008. $C_9H_9N_3O_2$ [*M*] requires 191.1007); ν_{max} (neat)/cm^{-1} 1660, 1590, 1522, 970, 880, 723; δ_H (500 MHz; CD_3OD)/ppm 8.33 (1H, d, *J* = 8.1 Hz, H-5), 7.08 (1H, d, *J* = 8.1 Hz, H-6), 3.68 (3H, s, Me), 3.64 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 160.1 (C), 159.8 (C), 148.5 (C), 145.5 (C), 137.3 (CH), 117.5 (CH), 107.5 (C), 29.1 (Me), 26.3 (Me); *m*/*z* (EI) 191 ($M^{\bullet+}$, 15%), 190 (100).

Synthesis of 1-methyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione.



A solution of 6-amino-1-methyluracil (83 mg, 0.59 mmol) and 1-phenyl-2-propyn-1-one (77 mg, 0.59 mmol) in acetic acid (4 mL) was irradiated at 120 °C for 30 min in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 35 mL) and the organic extracts were combined, washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (120 mg, 80%) as a yellow solid (Found $M^{\bullet+}$, 253.1008. $C_{14}H_{11}N_3O_2$ [*M*] requires 253.1007); ν_{max} (neat)/cm^{-1} 1678, 1592, 1424, 950, 882, 723; δ_H (500 MHz; CD_3OD)/ppm 8.38 (1H, d, *J* = 7.1 Hz, H-5), 8.23 (2H, d, *J* = 7.5 Hz, H-2/H-6 of Ph), 8.09 (1H, d, *J* = 7.1 Hz, H-6), 7.55 (3H, m, H-3/H-4/H-5 of Ph), 3.45 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 169.3 (C), 150.5 (C), 149.6 (C), 145.7 (C), 138.3 (CH), 137.8 (C), 131.0 (CH), 129.8 (CH), 128.0 (CH), 113.7 (CH), 109.5 (C), 28.2 (Me); *m*/*z* (EI) 253 ($M^{\bullet+}$, 20%), 252 (100), 226 (30).

Synthesis of 2-amino-7-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one.



A solution of 2,6-diamino-4-hydroxypyridine (214 mg, 1.70 mmol) and 3-butyn-2-one (115 mg, 1.70 mmol) in acetic acid (4 mL) was irradiated at 120 °C for 30 min in a pressure-rated glass tube (10 mL) using a CEM Discover® microwave synthesizer by moderating the initial power (150 W). After cooling in a flow of compressed air, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 35 mL) and the organic extracts were combined, washed successively with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* (263 mg, 90%) as a colourless solid, mp >300 °C; (Found MH^+, 177.0773. $C_8H_9N_4O$ [*MH*] requires 177.0776); ν_{max} (neat)/cm^{-1} 3248, 1666, 1581, 975, 883, 720; δ_H (500 MHz; CD_3OD)/ppm 9.05 (1H, d, *J* = 8.1 Hz, H-5), 7.62 (1H, d, *J* = 8.1 Hz, H-6), 3.04 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 161.6 (C), 156.4 (CH), 154.5 (C), 147.3 (C), 127.5 (CH), 121.8 (C), 113.4 (C), 20.6 (Me); *m*/*z* (EI) 177 ($M^{\bullet+}$, 100%).

6.4. General procedure for H/D exchange of 4-aminopyridines under neutral conditions

A solution of the substrate in D_2O (5 mL) was irradiated in a sealed Pyrex tube at 190 °C for 2 h (hold-time) using a CEM Explorer® microwave synthesizer (maximum pressure 150 psi) by moderation of the initial microwave power (300 W). The mixture was cooled in a stream of compressed air and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the title compound.

6.5. General procedure for H/D exchange of 4-aminopyridines in the presence of DCl

A solution of the substrate in D_2O (5 mL) in the presence of DCl (0.9 mL) was irradiated in a sealed Pyrex tube at 190 °C for 2 h (hold-time) using a CEM Explorer® microwave synthesizer (maximum pressure 150 psi) by moderation of the initial microwave power (300 W). The mixture was cooled in a stream of compressed air, neutralized by the addition of aqueous NaOH solution (1M; 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the title compound.

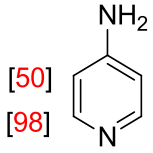
6.6. General procedure for determination of %D incorporation by acetylation.

The deuterated isotopologue was dissolved in acetone (20 mL) and K_2CO_3 (5 equiv.) was added, followed by the dropwise addition of a solution of acetyl chloride (3 equiv.) in acetone (5 mL). The reaction mixture was stirred for 3 h, quenched by the addition of water, evaporated *in vacuo* and extracted with CH_2Cl_2 (3 times). The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the *N*-acetylated derivative.

6.7. General procedure for determination of %D incorporation by the addition of an external standard.

Following general procedure for H/D exchange, ^{1}H NMR spectroscopic analysis of the crude product was quantified by the addition of dioxane (50 mol%) as an external standard.

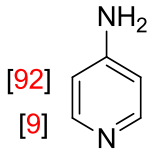
H/D exchange in 4-aminopyridine under neutral conditions.



4-Aminopyridine (300 mg, 3.19 mmol) was reacted according to the general procedure, to give deuterated isotopologues (177 mg, 57%) as a colourless solid, mp 157 ºC; ν_{max} (neat)/ cm^{-1} 3433, 3144, 3036, 2967, 2262, 1686, 1616, 1583, 1519, 1368, 1299, 1279, 1005, 891, 756; δ_H (500 MHz; CD_3OD)/ppm 7.95 (0.04H, d, *J* = 5.0 Hz, H-2,6), 6.55 (1H, s, H-3,5); δ_C (125 MHz; CD_3OD)/ppm 155.3 (C-N), 148.4 (CH*), 148.1 (t_D, *J* = 26 Hz, CD), 108.9 (CH); *m/z* (EI) 96 ($M^{\bullet+}$, 100%), 69 (25), 41 (35).

*Resonance due to H isotopologue

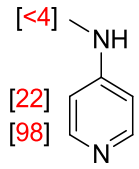
H/D exchange in 4-aminopyridine in the presence of DCl.



4-Aminopyridine (300 mg, 3.19 mmol) was reacted according to the general procedure, to give deuterated isotopologues (174 mg, 56%) as a colourless solid, mp 157 ºC; ν_{max} (neat)/ cm^{-1} 3422, 3309, 3133, 2027, 1583, 1445, 1420, 1210, 970, 814, 700; δ_H (500 MHz; CD_3OD)/ppm 7.95 (1.82H, s, H-2,6), 6.56 (0.17H, d, *J* = 6.0 Hz, H-3,5); δ_C (125 MHz; CD_3OD)/ppm 155.4 (s, C-N), 148.2 (s, CH), 108.9 (s, CH*), 108.7 (t_D, *J* = 25 Hz, CD); *m/z* (EI) 96 ($M^{\bullet+}$, 100%), 69 (34), 41 (25).

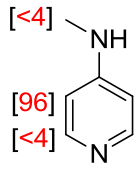
*Resonance due to H isotopologue

H/D exchange in 4-(methylamino)pyridine under neutral conditions.



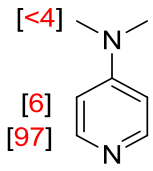
4-(Methylamino)pyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (280 mg, 91%) as a colourless solid, mp 125 ºC; ν_{max} (neat)/ cm^{-1} 3396, 3323, 3269, 3030, 2497, 2402, 2232, 1909, 1635, 1564, 1460, 1301, 1250, 1153, 1042, 914; δ_H (500 MHz; CD_3OD)/ppm 7.99 (0.04H, d, J = 7.0 Hz, H-2,6), 6.51 (1.56H, s, H-3,5), 2.80 (3H, s, Me). δ_C (125 MHz; CD_3OD)/ppm 155.5 (C-N), 147.9 (t_D, J = 27 Hz, CD), 106.7 (CH), 27.8 (Me); *m/z* (EI) 111 (52), 110 ($M^{\bullet+}$, 100%), 109 (69).

H/D exchange in 4-(methylamino)pyridine in the presence of DCl.



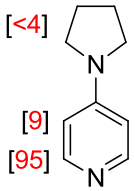
4-(Methylamino)pyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (250 mg, 82%) as a colourless solid, mp 125 ºC; ν_{max} (neat)/ cm^{-1} 3395, 3320, 3267, 3030, 2497, 2402, 2232, 1909, 1635, 1564, 1460, 1303, 1250, 1153, 1040, 914; δ_H (500 MHz; CD_3OD)/ppm 7.96 (2H, s, H-2,6), 6.44 (0.09H, d, J = 6.0 Hz, H-3,5), 2.71 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 155.5 (C-N), 148.1 (CH), 106.5 (t_D, J = 25 Hz, CD), 27.8 (Me); *m/z* (EI) 110 ($M^{\bullet+}$, 100%), 109 (98), 108 (15), 80 (16), 53 (16).

H/D exchange in 4-(dimethylamino)pyridine under neutral conditions.



4-(Dimethylamino)pyridine (300 mg, 2.45 mmol) was reacted according to the general procedure, to give deuterated isotopologues (296 mg, 97%) as a colourless solid, mp 113-114 ºC (Found MH^+, 125.1042. $C_7H_8D_2N_2$ [*MH*] requires 125.1043); ν_{max} (neat)/ cm^{-1} 3286, 3250, 3179, 3045, 2922, 2819, 2236, 1579, 1498, 1350, 1308, 1225, 1068, 993, 750; δ_H (500 MHz; CD_3OD)/ppm 8.06 (0.07H, m, H-2,6), 6.63 (1.88H, s, H-3,5), 3.03 (6H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 155.0 (C-N), 147.7 (t_D, J = 25 Hz, CD), 106.3 (CH), 37.7 (Me); *m/z* (EI) 124 ($M^{\bullet+}$, 86%), 123 (100), 107 (6), 96 (24), 80 (54), 52 (81), 42 (42).

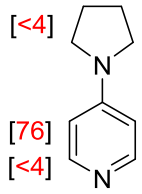
H/D exchange in 4-pyrrolidinopyridine under neutral conditions.



4-Pyrrolidinopyridine (300 mg, 2.02 mmol) was reacted according to the general procedure, to give deuterated isotopologues (293 mg, 96%) as a colourless solid, mp 59 ºC (Found MH^+, 151.1199. $C_9H_{10}D_2N_2$ [*MH*] requires 151.1199); ν_{max} (neat)/cm^{-1} 3074, 2961, 2910, 2845, 2230, 1583, 1532, 1478, 1361, 1286, 1246, 1154, 997, 700; δ_H (500 MHz; $CDCl_3$)/ppm 8.20 (0.10H, d, J = 5.0 Hz, H-2,6), 6.36 (1.82H, s, H-3,5),

3.29 (4H, t, J = 6.0 Hz, H-2′,5′), 2.02 (4H, t, J = 6.0 Hz, H-3′,4′); δ_C (125 MHz; CD_3OD)/ppm 152.4 (C-N), 147.5 (t_D, J = 27 Hz, CD), 106.7 (CH), 46.7 (CH_2), 24.8 (CH_2); *m/z* (EI) 150 ($M^{\bullet+}$, 85%), 149 (100), 121 (15).

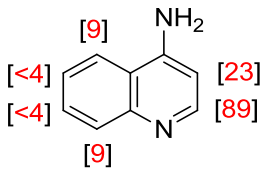
H/D exchange in 4-pyrrolidinopyridine in the presence of DCl.



4-Pyrrolidinopyridine (300 mg, 2.02 mmol) was reacted according to the general procedure, to give deuterated isotopologues (294 mg, 97%) as a colourless solid, mp 59 ºC (Found MH^+, 151.1199. $C_9H_{10}D_2N_2$ [*MH*] requires 151.1199); ν_{max} (neat)/cm^{-1} 3012, 2961, 2918, 2897, 2845, 2297, 1585, 1535, 1455, 1387, 1306, 1285, 1194, 1174, 915, 751; δ_H (500 MHz; $CDCl_3$)/ppm 8.20 (2H, s, H-2,6), 6.36 (0.52H, d, J = 6.0 Hz, H-3,5), 3.29 (4H, t, J = 6.0 Hz, H-2′,5′), 2.02 (4H, t, J = 6.0 Hz, H-3′,4′); δ_C (125 MHz; CD_3OD)/ppm 149.2 (C-N), 147.5 (CH), 106.8 (CH*), 106.6 (t_D, J = 26 Hz, CD), 46.6 (CH_2), 24.8 (CH_2); *m/z* (EI) 150 ($M^{\bullet+}$, 68%), 149 (100), 148 (50), 121 (15).

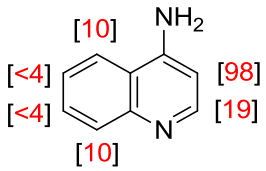
*Resonance due to H isotopologue

H/D exchange in 4-aminoquinoline under neutral conditions.



4-Aminoquinoline (110 mg, 0.76 mmol) was reacted according to the general procedure, to give deuterated isotopologues (77 mg, 69%) as an orange solid, mp 155 ºC (Found MH^+, 146.0824. $C_9H_7DN_2$ [*MH*] requires 146.0823); ν_{max} (neat)/cm^{-1} 3443, 2968, 1683, 1528, 1475, 1339, 1316, 1245, 1009, 917, 751; δ_H (500 MHz; CD_3OD)/ppm 8.25 (0.11H, s, 2-H), 8.06 (0.91H, d, *J* = 8.0 Hz, H-5 or H-8), 7.81 (0.91H, d, *J* = 8.0 Hz, H-5 or H-8), 7.64 (1H, t, *J* = 8.0 Hz, H-6 or H-7) 7.43 (1H, t, *J* = 8.0 Hz, H-6 or H-7), 6.62 (0.77H, s, H-3); δ_C (125 MHz; CD_3OD)/ppm 152.6 (C-N), 149.2 (t_D, *J* = 26 Hz, CD), 147.9 (C-N), 129.2 (CH), 127.4 (CH), 124.0 (CH), 121.4 (CH), 118.6 (C), 102.2 (CH); *m/z* (EI) 145 ($M^{\bullet+}$, 100%), 144 (15), 118 (13).

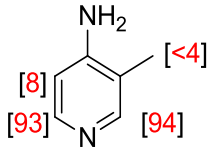
H/D exchange in 4-aminoquinoline in the presence of DCl.



4-Aminoquinoline (200 mg, 1.38 mmol) was reacted according to the general procedure, to give deuterated isotopologues (150 mg, 74%) as an orange solid, mp 155 ºC (Found MH^+, 146.0824. $C_9H_7DN_2$ [*MH*] requires 146.0823); ν_{max} (neat)/cm^{-1} 3443, 2968, 1683, 1528, 1475, 1339, 1316, 1245, 1009, 917, 751; δ_H (500 MHz;

CD_3OD)/ppm 8.27 (0.81H, s, 2-H), 8.06 (0.90H, d, *J* = 8.0 Hz, H-5 or H-8) 7.80 (0.90H, d, *J* = 8.0 Hz, H-5 or H-8), 7.63 (0.97H, t, *J* = 8.0 Hz, H-6 or H-7), 7.43 (0.97H, t, *J* = 8.0 Hz, H-6 or H-7); δ_C (125 MHz; CD_3OD)/ppm 152.5 (C-N), 149.4 (CH) 148.0 (C-N), 129.2 (CH), 127.4 (CH), 123.9 (CH), 121.4 (CH), 118.6 (C), 102.2 (t_D, *J* = 24 Hz, CD); *m/z* (EI) 145 ($M^{\bullet+}$, 100%), 144 (12), 118 (16).

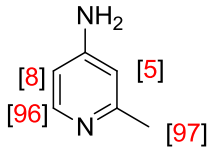
H/D exchange in 4-amino-3-methylpyridine under neutral conditions.



4-Amino-3-methylpyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (298 mg, 97%) as a colourless solid, mp 106 ºC (Found MH^+, 255.1259. $C_{16}H_{17}NO_2$ [*MH*] requires 255.1261); ν_{max} (neat)/cm^{-1} 3345, 3311, 3164, 2536, 2404, 2367, 2288, 2237, 2194, 1631, 1553, 1436, 1264, 1197, 1042, 877; δ_H (500 MHz; CD_3OD)/ppm 7.87 (0.06H, s, H-2), 7.71 (0.07H, d, *J* = 7.0 Hz, H-6), 6.57 (0.92H, s, H-5), 2.08 (2.96H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 153.5 (C-N), 148.3 (CH*), 146.4 (CH*), 146.1 (t_D, *J* = 25 Hz, CD), 116.7 (C), 108.3 (CH), 12.7 (Me); *m/z* (EI) 110 ($M^{\bullet+}$, 100%), 109 (33), 81 (29).

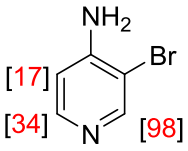
*Resonance due to H isotopologue

H/D exchange in 4-amino-2-methylpyridine under neutral conditions.



4-Amino-2-methylpyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (260 mg, 84%) as a colorless solid, mp 98 °C; ν_{max} (neat)/cm^{-1} 3324, 3065, 2911, 2848, 2366, 1638, 1602, 1559, 1495, 1345, 1297, 1261, 985, 705; δ_H (500 MHz; CD_3OD)/ppm 7.84 (0.04H, d, J = 6.0 Hz, H-6), 6.43 (0.95H, d, J = 2.0 Hz, H-3), 6.39 (0.92H, d, J = 2.0 Hz, H-5), 2.27 (0.08H, m, H-1′); δ_C (125 MHz; CD_3OD) 157.3 (C-N), 155.7 (C), 147.5 (t_D, J = 26 Hz, CD), 108.0 (CH), 106.6 (CH), 21.4 (sep_D, J = 19 Hz, CD_3); *m/z* (EI) 112 ($M^{\bullet+}$, 100%), 111 (22), 110 (11), 83 (22), 69 (23), 41 (25).

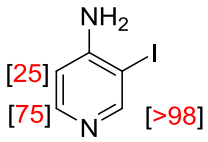
H/D exchange in 4-amino-3-bromopyridine under neutral conditions.



4-Amino-3-bromopyridine (300 mg, 1.73 mmol) was reacted according to the general procedure, to give deuterated isotopologues (250 mg, 82%) as an orange solid, mp 70 °C; ν_{max} (neat)/cm^{-1} 3448, 3149, 2925, 2536, 2156, 1707, 1628, 1589, 1502, 1419, 1339, 1270, 1184, 1074, 1013, 823; δ_H (500 MHz; CD_3OD)/ppm 8.20 (0.02H, s, H-2), 7.90 (0.66H, d, J = 6.0 Hz, H-6), 6.70 (0.83H, d, J = 6.0 Hz, H-5); δ_C (125 MHz;

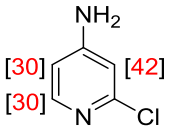
CD_3OD)/ppm 152.3 (C-N), 149.6 (t_D, J = 27 Hz, CD), 147.0 (CH), 109.5 (CH), 105.4 (C); *m/z* (EI) 174 ($M^{\bullet+}$, 60%), 94 (30), 67 (29).

H/D exchange in 4-amino-3-iodopyridine under neutral conditions.



4-Amino-3-iodopyridine (300 mg, 1.36 mmol) was reacted according to the general procedure, to give deuterated isotopologues (283 mg, 93%) as an orange oil, mp 99 ºC; ν_{max} (neat)/cm^{-1} 3421, 3294, 3038, 1639, 1581, 1491, 1412, 1337, 1267, 1185, 820, 725; δ_H (500 MHz; CD_3OD)/ppm 8.38 (0.01H, s, H-2), 7.92 (0.25H, d, J = 6.0 Hz, H-6), 6.68 (0.75H, s, H-5); δ_C (125 MHz; CD_3OD)/ppm 155.4 (t_D, J = 28 Hz, CD), 154.8 (C-N), 147.7 (CH), 108.7 (CH), 79.8 (C); *m/z* (EI) 222 ($M^{\bullet+}$, 100%), 221 (30) 127 (15), 95 (23), 67 (22), 40 (20).

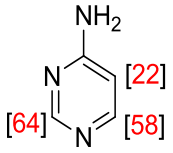
H/D exchange in 4-amino-2-chloropyridine under neutral conditions.



4-Amino-2-chloropyridine (300 mg, 2.33 mmol) was reacted according to the general procedure, to give deuterated isotopologues (298 mg, 98%) as a colourless solid, mp 96 ºC; ν_{max} (neat)/cm^{-1} 3308, 3145, 1656, 1589, 1554, 1479, 1415, 1290, 987, 826, 721; δ_H (500 MHz; CD_3OD)/ppm 7.72 (0.70H, d, J = 6.0 Hz, H-6), 6.54 (0.58H, d, J = 2.0 Hz, H-3), 6.50 (0.70H, dd, J = 2.0 Hz, H-5); δ_C (125 MHz; CD_3OD)/ppm 157.4 (C-

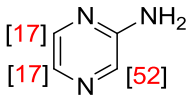
N), 151.1 (C-N), 148.2 (CH), 108.3 (CH), 107.4 (CH); *m/z* (EI) 128 (M[$C_5H_5{}^{35}ClN_2$]$^{\bullet+}$, 100%), 94 (15), 93 (55), 66 (31).

H/D exchange in 4-aminopyrimidine under neutral conditions.



4-Aminopyrimidine (300 mg, 3.15 mmol) was reacted according to the general procedure, to give deuterated isotopologues (80 mg, 26%) as a colourless solid, mp 156 ºC; ν_{max} (neat)/cm^{-1} 3316, 3088, 2734, 2165, 1655, 1586, 1557, 1498, 1407, 1338, 1257, 985, 836; δ_H (500 MHz; CD_3OD)/ppm 8.30 (0.36H, s, H-2), 8.05 (0.42H, d, *J* = 6.0 Hz, H-6), 6.50 (0.78H, m, H-5); δ_C (125 MHz; CD_3OD)/ppm 163.8 (C), 157.5 (CH), 153.8 (CH), 105.1 (CH); *m/z* (EI) 97 (M$^{\bullet+}$, 88%), 96 (100), 95 (33), 69 (35), 41 (75).

H/D exchange in 2-aminopyrazine under neutral conditions.



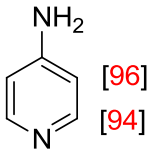
2-Aminopyrazine (250 mg, 2.62 mmol) was reacted according to the general procedure, to give deuterated isotopologues (154 mg, 61%) as a colourless solid, mp 121 ºC; ν_{max} (neat)/cm^{-1} 3327, 3134, 3059, 2709, 2350, 2165, 2026, 1645, 1583, 1480, 1424, 1339, 1203, 1001, 864, δ_H (500 MHz; CD_3OD)/ppm 7.92 (0.48H, s, H-3), 7.90 (0.83H, d, *J* = 2.0 Hz, H-6), 7.70 (0.83H, d, *J* = 2.0 Hz, H-5); δ_C (125 MHz;

CD_3OD)/ppm 156.1 (C-N), 141.6 (CH), 132.5 (CH), 131.4 (CH); *m/z* (EI) 96 ($M^{\bullet+}$, 82%), 95 (100), 69 (46), 68 (70), 41 (55).

6.8. General procedure for H/D Exchange Using D_2O and DCl sequentially.

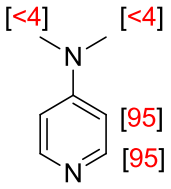
A solution of the substrate in D_2O (3 mL) was irradiated in sealed Pyrex tube (10 mL) at 190 °C for 2 h using a CEM Discover microwave synthesizer (maximum pressure 150 psi) by moderating the initial power (300 W). The reaction mixture was cooled in a stream of compressed air and a solution of DCl 1M; (0.9 mL) was added. The mixture was irradiated at 190 °C for 2 h by moderating the initial power (300 W). and then cooled in a stream of compressed air. The solution was basified to pH 12 by the addition of aqueous NaOH solution (1M; 10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the *title compound*.

H/D exchange in 4-aminopyridine using both neutral and acidic conditions.



4-Aminopyridine (300 mg, 3.19 mmol) was reacted according to the general procedure, to give deuterated isotopologues (177 mg, 57%) as a colourless solid. mp 157 ºC; ν_{max} (neat)/cm^{-1} 3433, 3143, 3036, 2966, 2262, 1686, 1615, 1582, 1519, 1369, 1298, 1279, 1004, 890, 755; δ_H (500 MHz; CD_3OD)/ppm 7.95 (0.12H, s, H-2,6), 6.54 (0.07H, s, H-3,5); δ_C (125 MHz; CD_3OD)/ppm 155.3 (C-N), 147.9 (t_D, J = 27 Hz, CD), 108.5 (t_D, J = 24 Hz, CD); *m/z* (EI) 98 ($M^{\bullet+}$, 100%), 97 (55), 96 (15), 71 (50), 70 (37).

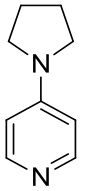
H/D exchange in 4-(dimethylamino)pyridine using both neutral and acidic conditions.



4-(Dimethylamino)pyridine (300 mg, 2.45 mmol) was reacted according to the general procedure, to give deuterated isotopologues (227 mg, 74%) as a colourless solid, mp 113-114 ºC; ν_{max} (neat)/cm^{-1} 3285, 3255, 3179, 3044, 2922, 2819, 2236, 1579, 1498, 1350,1308, 1225, 1068, 990, 750; δ_H (500 MHz; CD_3OD)/ppm 8.04 (0.10H, s, H-2,6), 6.54 (0.10H, s, H-3,5), 2.93 (6H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 154.8 (C-N),

147.7 (t_D, J = 25 Hz, CD), 106.1 (t_D, J = 24 Hz, CD), 37.7 (Me); *m/z* (EI) 126 ($M^{\bullet+}$, 77%), 125 (100), 124 (20), 82 (17), 54 (20).

H/D exchange in 4-pyrrolidinopyridine using both neutral and acidic conditions.



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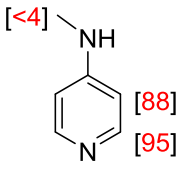
[97]

4-Pyrrolidinopyridine (300 mg, 2.02 mmol) was reacted according to the general procedure, to give deuterated isotopologues (200 mg, 65%) as a colourless solid, mp 59 ºC; ν_{max} (neat)/cm^{-1} 3075, 2960, 2910, 2845, 2230, 1583, 1532, 1478, 1361, 1286, 1246, 1154, 990, 730; δ_H (500 MHz; CD_3OD)/ppm 8.02 (0.06H, s, H-2,6), 6.44 (0.06H, s, H-3,5), 3.26 (4H, t, J = 6.0 Hz, H-2′,5′), 1.99 (4H, t, J = 6.0 Hz, H-3′,4′); δ_C (125 MHz; CD_3OD)/ppm 152.3 (C-N), 147.2 (t_D, J = 26 Hz, CD), 106.5 (t_D, J = 29 Hz, CD), 46.6 (CH_2), 24.8 (CH_2); *m/z* (EI) 152 ($M^{\bullet+}$, 80%), 151 (100), 150 (10), 123 (16), 111 (17), 109 (13), 69 (19), 82 (19).

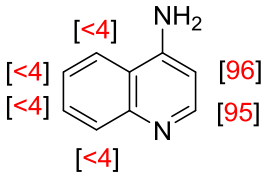
H/D exchange in 4-(methylamino)pyridine using both neutral and acidic conditions.



4-(Methylamino)pyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (258 mg, 84%) as a colourless solid, mp 125 ºC; ν_{max} (neat)/cm^{-1} 3395, 3322, 3266, 3030, 2490, 2402, 2232, 1909, 1635, 1564, 1460, 1301, 1250, 1153, 1042, 914; δ_H (500 MHz; CD_3OD)/ppm 7.96 (0.09H, s, H-2,6), 6.42 (0.23H, s, H-3.5), 2.70 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 155.5 (C-N), 147.8 (t_D, J = 27 Hz, CD), 106.7 (CH*), 106.4 (t_D, J = 24 Hz, CD), 27.9 (Me); *m/z* (EI) 112 ($M^{\bullet+}$, 95%), 111 (100) 110 (55), 109 (11).

*Resonance due to H isotopologue

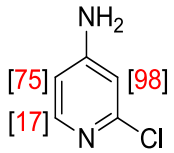
H/D exchange in 4-aminoquinoline using both neutral and acidic conditions.



4-Aminoquinoline (130 mg, 0.90 mmol) was reacted according to the general procedure, to give deuterated isotopologues (81 mg, 62%) as an orange solid, mp 155 ºC; ν_{max} (neat)/cm^{-1} 3443, 2968, 1683, 1528, 1475,1339, 1316, 1245, 1009, 917, 751; δ_H (500 MHz; CD_3OD)/ppm 8.27 (0.05H, s, H-2), 8.05 (1H, d, J = 8.0 Hz, H-5 or

H-8), 7.80 (1H, d, *J* = 8.0 Hz, H-5 or H-8), 7.61 (1H, t, *J* = 8.0 Hz, H-6 or H-7), 7.41 (1H, t, *J* = 8.0 Hz, H-6 or H-7), 6.61 (0.04H, s, H-3); δ_C (125 MHz; CD_3OD)/ppm 152.7 (C-N), 149.2 (t_D, *J* = 26 Hz, CD), 147.9 (CH), 129.2 (CH), 127.3 (CH), 123.9 (CH), 121.4 (C), 118.6 (C) 102.2 (t_D, *J* = 26 Hz, CD); *m/z* (EI) 146 ($M^{\bullet+}$, 100%), 145 (23) 144 (6).

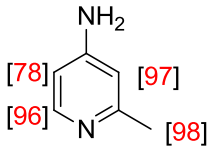
H/D exchange in 4-amino-2-chloropyridine using both neutral and acidic conditions.



4-Amino-2-chloropyridine (**18**) (300 mg, 2.33 mmol) was reacted according to the general procedure, to give deuterated isotopologues (278 mg, 92%) as a colourless solid, mp 96 ºC; ν_{max} (neat)/cm^{-1} 3322, 3140, 1655, 1589, 1544, 1479, 1415, 1290, 987, 826, 721; δ_H (500 MHz; CD_3OD)/ppm 7.75 (0.83H, d, *J* = 6.0 Hz, H-6), 6.56 (0.02H, s, H-3), 6.50 (0.25H, d, *J* = 6.0 Hz, H-5); δ_C (125 MHz; CD_3OD)/ppm 157.3 (C-N), 151.2 (C), 148.1 (CH), 108.3 (CH*), 108.1 (t_D, *J* = 25 Hz, CD), 107.2 (t_D, *J* = 25 Hz, CD); *m/z* (EI) 130 ($M^{\bullet+}$, 100%), 129 (40), 96 (8), 95 (60).

*Resonance due to H isotopologue

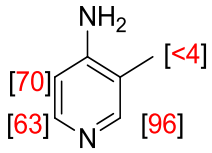
H/D exchange in 4-amino-2-methylpyridine using both neutral and acidic conditions.



4-Amino-2-methylpyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (210 mg, 67%) as a colourless solid, mp 98 ºC; ν_{max} (neat)/cm^{-1} 3322, 3055, 2922, 2844, 2366, 1638, 1602, 1559, 1495, 1345, 1297, 1261, 985, 750; δ_H (500 MHz; CD_3OD)/ppm 7.83 (0.04H, d, *J* = 6.0 Hz, H-6), 6.38 (0.03H, s, H-3), 6.36 (0.22H, d, *J* = 6.0 Hz, H-5), 2.24 (0.07H, m, H-1′); δ_C (125 MHz; CD_3OD)/ppm 157.3 (C-N), 155.9 (C), 147.4 (t_D, *J* = 25 Hz, CD), 107.8 (t_D, *J* = 24 Hz, CD), 106.6 (CH*), 106.3 (t_D, *J* = 25 Hz, CD), 21.4 (sep_D, *J* = 19 Hz, CD_3); *m/z* (EI) 114 (M[$C_6H_2D_6N_2$]$^{\bullet+}$, 100%), 113 (42), 112 (12), 96 (8), 86 (10), 85 (15).

*Resonance due to H isotopologue

H/D exchange in 4-amino-3-methylpyridine using both neutral and acidic conditions.

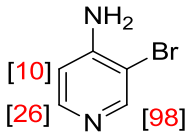


4-Amino-3-methylpyridine (300 mg, 2.77 mmol) was reacted according to the general procedure, to give deuterated isotopologues (230 mg, 75%) as a colourless solid, mp 106 ºC; ν_{max} (neat)/cm^{-1} 3355, 3320, 3144, 2536, 2404, 2367, 2288, 2237, 2194, 1631, 1553, 1436, 1264, 1197, 1042, 870; δ_H (500 MHz; CD_3OD)/ppm 7.76 (0.37H, d, *J* =

6.0 Hz, H-6), 7.69 (0.04H, s, H-2), 6.57 (0.30H, d, *J* = 6.0 Hz, H-5), 2.04 (3H, s, Me); δ_C (125 MHz; CD_3OD)/ppm 153.5 (C-N), 148.3 (CH), 147.9 (CH*), 146.3 (t_D, *J* = 27 Hz, CD), 116.7 (C), 108.3 (CH), 12.7 (Me); *m/z* (EI) 111 ($M[C_6H_5D_3N_2]^{\bullet+}$, 78%), 110 (100), 109 (50), 108 (17).

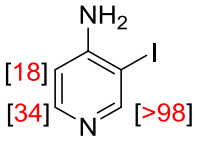
*Resonance due to H isotopologue

H/D exchange in 4-amino-3-bromopyridine using both neutral and acidic conditions.



4-Amino-3-bromopyridine (300 mg, 1.73 mmol) was reacted according to the general procedure, to give deuterated isotopologues (260 mg, 86%) as an orange solid, mp 70 °C; ν_{max} (neat)/cm^{-1} 3448, 3141, 2922, 2530, 2156, 1707, 1628, 1589, 1502, 1419, 1339, 1270, 1184, 1074, 1013, 823, δ_H (500 MHz; CD_3OD)/ppm 8.20 (0.02H, s, H-2), 7.90 (0.74H, d, *J* = 6.0 Hz, H-6), 6.67 (0.90H, d, *J* = 6.0 Hz, H-5); δ_C (125 MHz; CD_3OD)/ppm 152.2 (C-N), 149.8 (t_D, *J* = 27 Hz, CD), 147.1 (CH), 109.5 (CH), 105.5 (C); *m/z* (EI) 175 ($M[C_5H_4DBrN_2]^{\bullet+}$, 100%), 173 (95), 94 (45), 67 (42).

H/D exchange in 4-amino-3-iodopyridine using both neutral and acidic conditions.



4-Amino-3-iodopyridine (300 mg, 1.36 mmol) was reacted according to the general procedure, to give deuterated isotopologues (290 mg, 96%) as an orange oil, mp 99 ºC; ν_{max} (neat)/cm^{-1} 3433, 3244, 3038, 1649, 1581, 1491, 1412, 1337, 1267, 1185, 820, 725; δ_H (500 MHz; CD_3OD)/ppm 8.36 (0.01H, s, H-2), 7.90 (0.66H, d, J = 6.0 Hz, H-6), 6.64 (0.82H, d, J = 6.0 Hz, H-5); δ_C (125 MHz; CD_3OD)/ppm 155.5 (t_D, J = 28 Hz, CD), 154.7 (C-N), 147.7 (CH), 108.8 (CH), 80.2 (C); *m/z* (EI) 221 (M[$C_5H_4DN_2I$]$^{\bullet+}$, 100%), 127 (5) 127 (15), 94 (35), 67 (25), 40 (18).

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