SCIENTIFIC LETTER N°10

Edito

Au cours de ces 12 dernières années nous vous avons accompagné sur plus de 1300 projets allant du milligramme à la dizaine de grammes, et nous savons bien que seule la mobilisation de toute une entreprise et de son équipe a des effets sur votre satisfaction et votre fidélité. Chaque jour grâce aux études que vous nous avez confié nous avons renforcé notre expertise sur les différents domaines de la chimie et à travers la réalisation de vos contrats, nous avons pu expérimenter et **développer un savoir faire pratique** en synthèse. C'est pour cela que nous vous dédions cette lettre scientifique!

Dans le cadre de notre veille scientifique, le Professeur **Jacques LEBRETON** vous propose en cette fin d'année un article sur la chimie de la pyridine à travers une série d'exemples récents, principalement issus de travaux en chimie médicinale et qui illustre la réactivité de cet hétérocycle.

Vous trouverez à la suite de cet article le portrait de Grégory Sautejeau, technicien chimiste, qui a rejoint récemment l'équipe **d'AtlanChim Pharma**.

Nous profitons également de cette lettre pour vous annoncer la mise en ligne de notre tout nouveau site internet. Ce site a été pensé pour nos clients, mais aussi pour nos partenaires. Vous y trouverez des informations sur notre expertise, l'historique de la société ainsi que toute l'actualité de notre entreprise.

www.atlanchimpharma.com

Enfin dans le cadre de notre processus d'amélioration continue nous avons également mis en place un cahier de laboratoire électronique.

Nous vous souhaitons une bonne lecture!

Editorial

Over the past 12 years we have collaborated with you on over 1,300 projects ranging from milligrams to tens grams, and we know that only the mobilization of a company and its team have effects on your satisfaction and loyalty. Every single day thanks to the studies you have entrusted us with, we have strengthen our expertise on different types of chemistry and through the production of your contracts, we were able to experience and develop knowledge in chemical synthesis practice. This is why we dedicate this scientific letter to you!

As part of our scientific monitoring work, Professor **Jacques LEBRETON** would like to share with you in this end-of-year period an article about the chemistry of pyridine in a series of recent examples, mainly from work in medicinal chemistry and illustrates the reactivity of this heterocyclic.

To conclude this scientific letter you will find the portrait of Gregory Sautejeau, chemistry technician, who has recently joined **AtlanChim Pharma**'s team.

We are pleased to announce the launch of our new website. It has been designed for our customers as well as for our partners. You can find information about our expertise, the company's history as well as our latest news.

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Finally as part of our continuous improvement process we have also set up an internal electronic laboratory notebook.

Enjoy the reading!

Synthesis of pyridine derivatives through recent examples of pharmaceuticals

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Pyridines have a range of applications from pharmaceutical compounds[1] to new materials[2]. In particular, pyridine forms the nucleus of many important drugs as shown in Figure 1. Consequently, due to their therapeutic and pharmacological properties, efficient access to substituted pyridine derivatives is still a challenging problem of current interest[3].

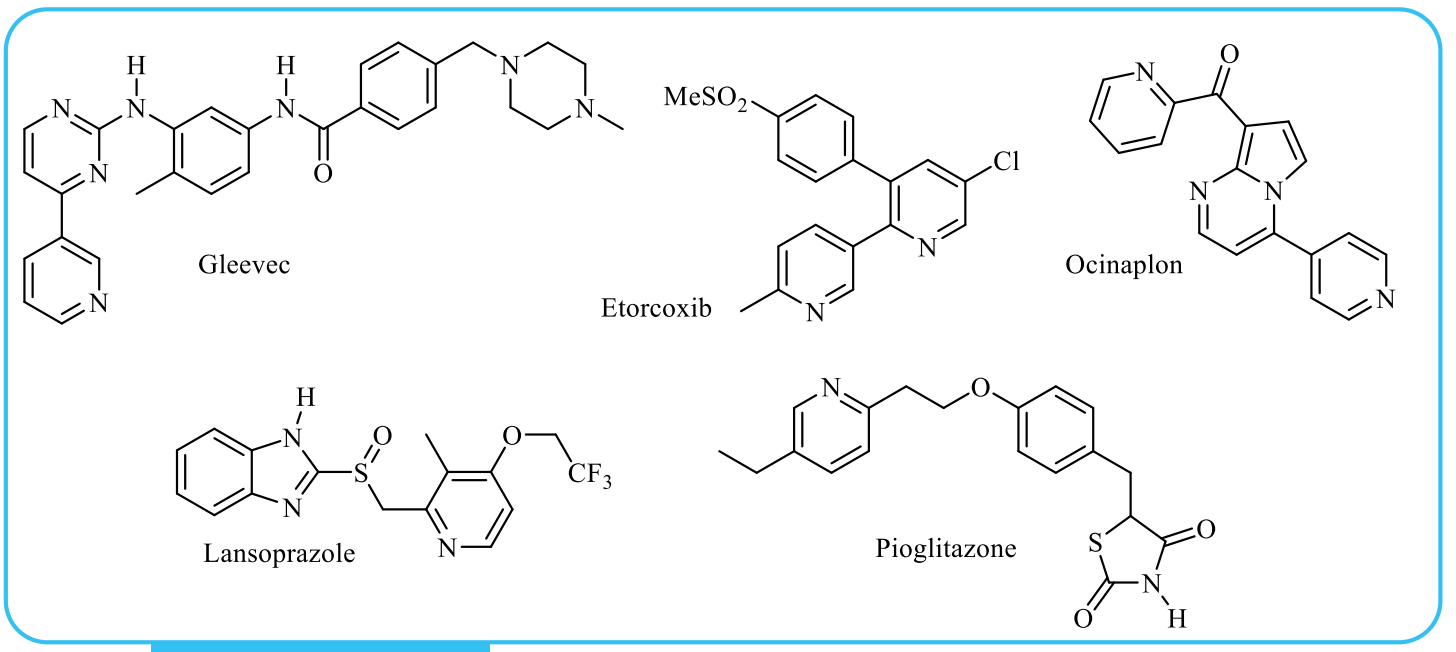


Figure 1

This letter focuses on major methodologies which have impacted pyridine chemistry in the field of Medicinal Chemistry, including scale-up, through recent examples. It is organized according to the strategy used to construct or to functionalize the pyridine core of the target molecule.

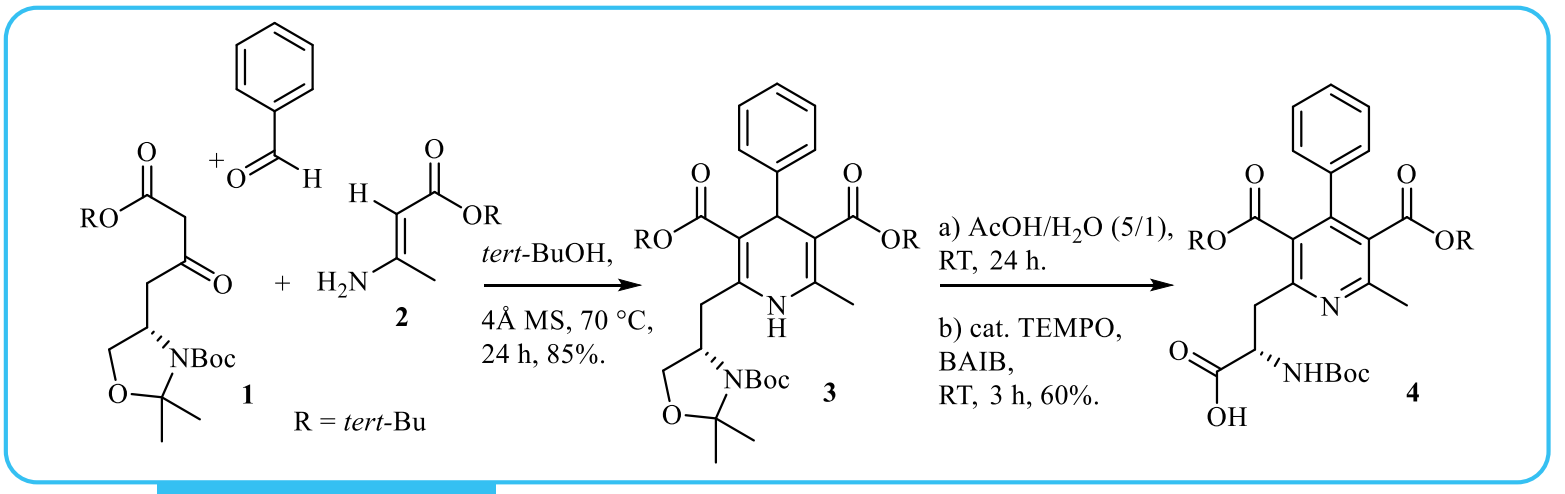
[1] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem*. **2013**, *9*, 2265-2319.
[2] I. Sasaki, J.-C. Daran, G. Commenges, *Beilstein J. Org. Chem.* **2015,** *11*, 1781-1785 and cited literature.
[3] For reviews, see: (a) G. D. Henry, *Tetrahedron* **2004**, *60*, 6043-6061. (b) M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052-12062 and cited literature.

Construction of pyridine ring systems

Preparation of substituted pyridines using classical heterocyclic chemistry is a valuable alternative to disconnection of pyridine-aryl system *via* metal-catalyzed cross coupling.

Hantzsch pyridine synthesis

Published in 1881, the Hantzsch pyridine synthesis is a cyclocondensation of an aldehyde and two equivalents of a 1,3-dicarbonyl compound in the presence of ammonia to give the 1,4-dihydropyridine which readily undergoes oxidation with various oxidative agents to the corresponding symmetric pyridine[4]. Using an enamine, the unsymmetrical 2,3,4,5,6-substituted pyridines could be efficiently prepared as presented in Scheme **1**.[5] Nevertheless, this one-pot three-component synthesis is limited to the preparation of 3,5-carbonyl substituted pyridines. Condensation of benzaldehyde, oxazolidinyl ketoester **1** and methyl aminocrotonate **2** in *tert*-butanol containing 4Å molecular sieves gave the corresponding dihydropyridyl-cycloadduct **3** as a 1.5:1 mixture of diastereoisomers in 85% yield. Subsequently, chemoselective acidic cleavage of the acetonide in intermediate **3** followed by oxidation of the resulting primary alcohol into a carboxylic acid using catalytic 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) with *bis*(acetoxy)iodobenzene (BAIB) and concomitant aromatization under these oxidative conditions furnished the targeted substituted pyridine **4** in 60% overall yield.



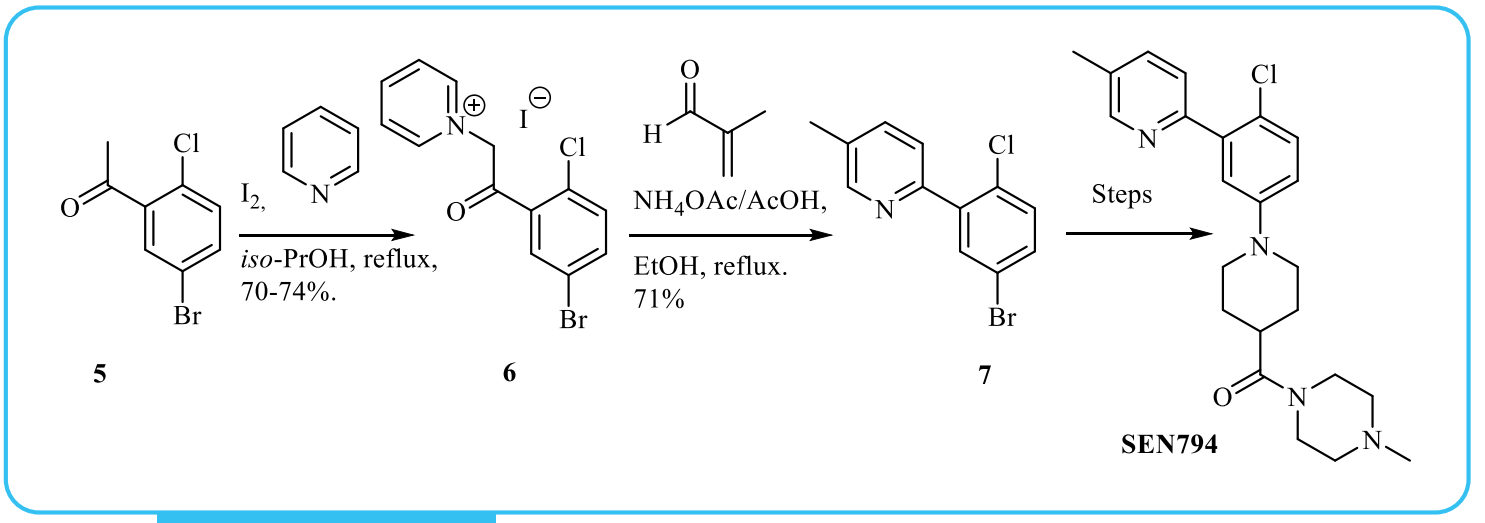
SCHEME 1

[4] For a review, see: D. M. Stout, A. I. Meyers, *Chem. Rev.* **1982**, *82*, 223-243 and cited literature.
[5] A. Dondoni, A. Massi, E. Minghini, S. Sabbatini, V. Bertolasi, *J. Org. Chem.* **2003**, *68*, 6172-6183.

Kröhnke pyridine synthesis

Condensation of *N*-phenacylpyridinium salts with α,β-unsaturated carbonyl compounds *via* a Michael-type addition in the presence of ammonium acetate and acetic acid provide the corresponding 2,4,6-trisubstituted pyridines in high yields under mild reaction conditions.[6] The Kröhnke pyridine synthesis has been largely used for the preparation of a variety of polysubstituted pyridines, and presents distinct advantages over other related reactions, such as the Hantzsch pyridine synthesis, as no oxidation of a dihydropyridine intermediate is required.

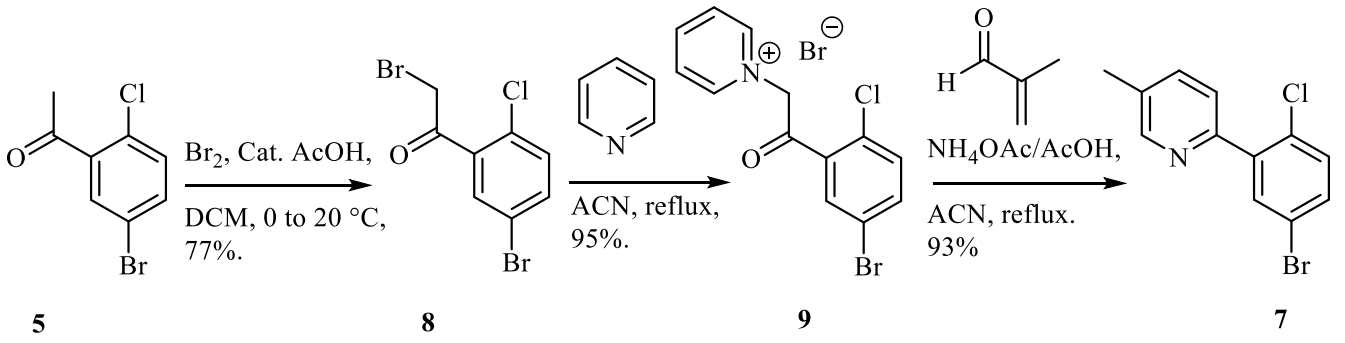
A practical and scalable route to the Smoothened (SMO) receptor antagonist **SEN794** has been developed using a Kröhnke reaction to prepare the key substituted pyridine **7**, as outlined in Scheme 2.[7] *N*-Phenacylpyridinium salt **6** was prepared in 70-74% yield by refluxing methyl ketone **5** in *iso*-propanol in presence of iodine and pyridine. Under optimized conditions, this pyridinium salt **6** was reacted with methacrolein and ammonium acetate in refluxing ethanol to afford the desired substituted pyridine **7** in 71% yield (152 g).



SCHEME 2

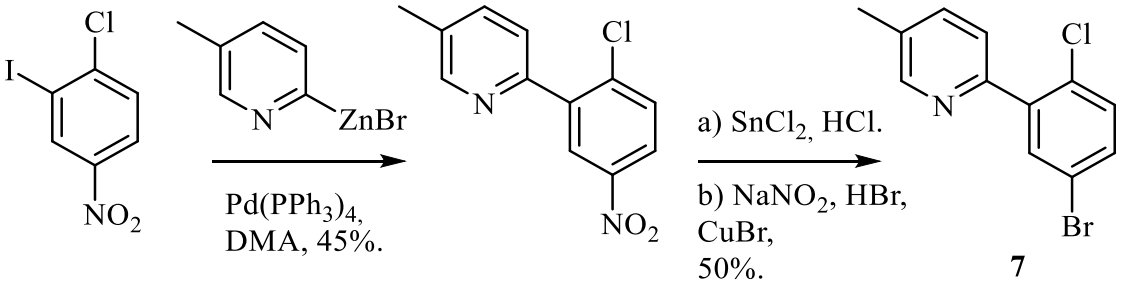
[6] For a review, see: F. Kröhnke, Synthesis, 1976, 1-24.
[7] M. Betti, G. Castagnoli, A. Panico, S. S. Coccone, P. Wiedenau, *Org. Process Res. Dev*. **2012**, *16*, 1739-1745.

For large scale preparation of substituted pyridine **7**, a more efficient synthesis was carried out as presented in Scheme 3. Bromination of acetophenone **5** using bromine in DCM containing AcOH (0.1 equiv) afforded the corresponding α-bromoketone **8** as a white solid in 77% yield, which was then treated with one equivalent of pyridine in hot ACN to give the *N*-phenacylpyridinium salts **9** in 95% yield. This latter salt was engaged, as previously described in Kröhnke reaction in refluxing ACN to furnish substituted pyridine **7** in 93% yield (200 g).



SCHEME 3

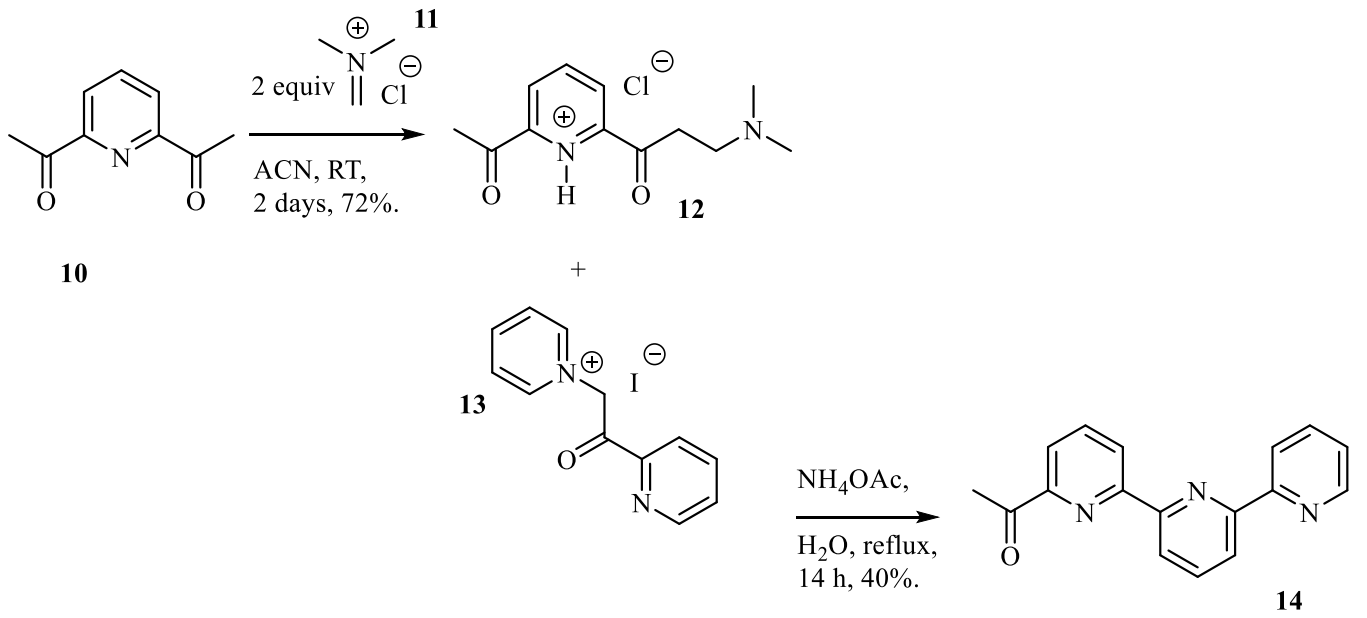
This route was found to be more efficient than the previous bench synthesis using Pd-catalyzed Negishi coupling with the expensive 5-methyl-2-pyridylzinc bromide followed by a potentially hazardous diazotization, as reported in Scheme 4.[8]



SCHEME 4

[8] Pericot, M. G.; Thomas, R. J.; Minetto, G.; Bellini, M.; Wiedenau, P. H.; Betti, M. PCT Int. Appl. WO 2012/076413 14/06/2012.

An elegant and efficient preparation of non-symmetric terpyridines such as 6-acetyl-2,2':6',2''-terpyridine **14** starting from 2,6-diacetylpyridine **10** has been published by Sasaki and coll. using a modified Kröhnke pyridine synthesis, as described in Scheme 5.[2] Treatment of 2,6-diacetylpyridine **10** with an excess of the Eschenmoser's salt **11** ((*N*,*N*-dimethyl)methyliminium chloride) in ACN at room temperature gave the nonsymmetric pyridinium salt **12**, as the masked enone, in 72% yield (5.52 g). This latter salt **12** was then reacted with α-pyridinium ketone salt **13** and ammonium acetate in refluxing water to furnish the targeted 6-acetyl-2,2':6',2''-terpyridine **14** in 40% yield (1.06 g). This route to oligopyridylimines was found to be more efficient, as compared to the previous route utilizing Stille-type cross-coupling.[9]

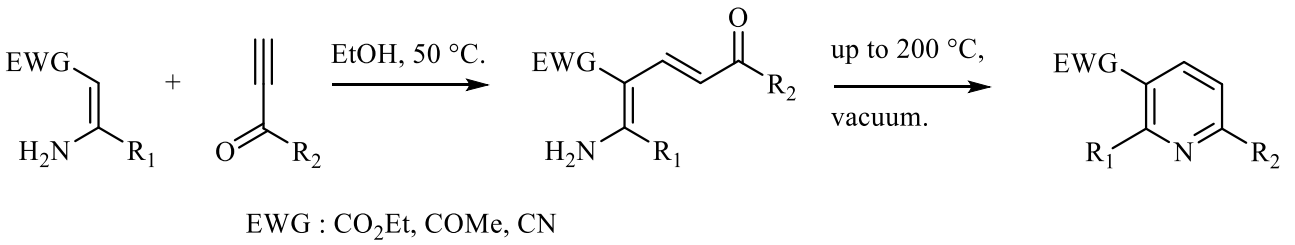


SCHEME 5

[9] Y. D. M. Champouret, R. K. Chaggar, I. Dadhiwala, J. Fawcett, G. A. Solan, *Tetrahedron* **2006**, *62*, 79-89.

Bohlmann-Rahtz pyridine synthesis.

In 1957, Bohlmann and Rahtz reported the preparation of 2,3,6-trisubstituted pyridines by condensation of acetylenic ketones or aldehydes with enamines, *via* a Michael-type addition followed by cyclodehydration of the resulting δ-amino-ketones or -aldehydes at high temperatures (up to 200°C under *vacuum*) to promote E/Z isomerization and spontaneous cyclodehydration as depicted in Scheme 6.[10]

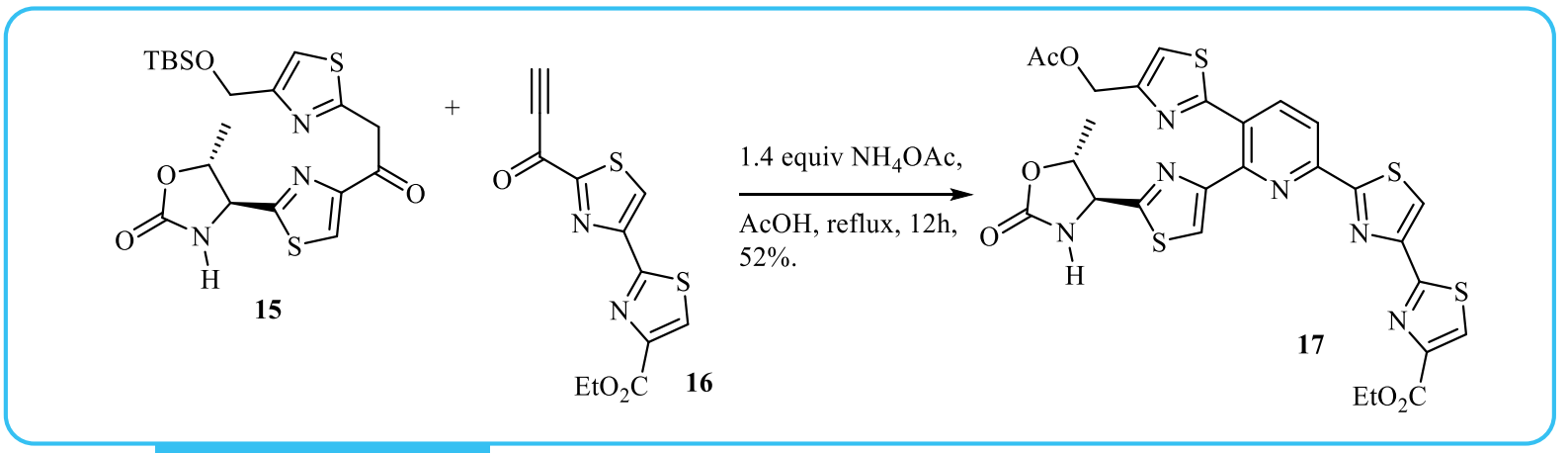


SCHEME 6

To circumvent these thermal conditions for the cyclodehydration step, Bagley developed a three-component condensation of β-ketoesters, acetylenic ketones and a source of ammonia, such as ammonium acetate in refluxing toluene in the presence of either acetic acid or zinc(II) bromine, to provide directly the desired pyridines with excellent yields.[11] Compared to the Hantzsch pyridine synthesis, Bohlmann-Rahtz reaction with the use of ethylnyl ketones or aldehydes gave directly the pyridine derivatives without aromatizing oxidative step.

[10] F. Bohlmann, D. Rahtz, *Chem. Ber*. **1957**, *90*, 2265-2272.
[11] M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459-2482.

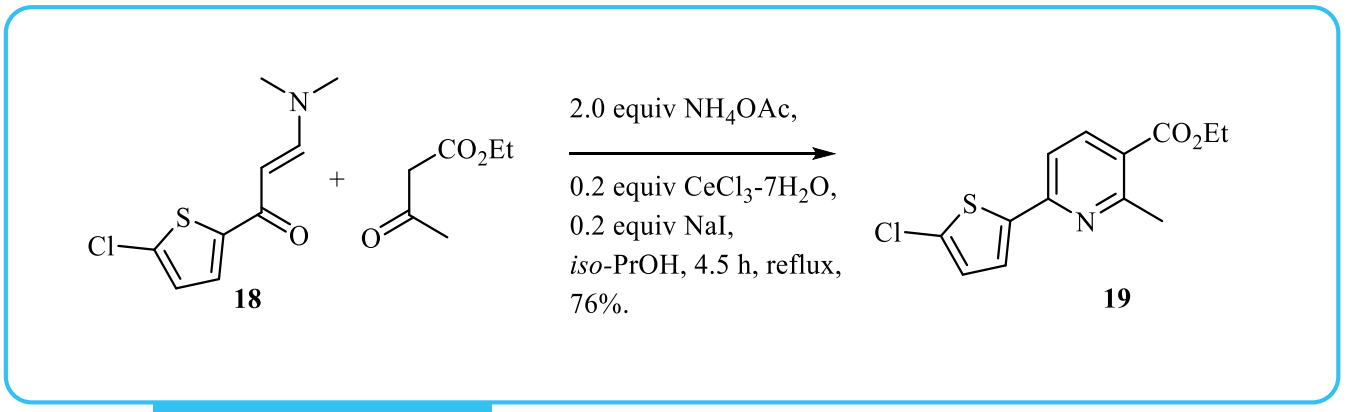
In 2011, Aulakh and Ciufolini published a total synthesis and complete structural assignment of Thiocillin I, a thiopeptide antibiotic isolated from *Bacillus cereus*.[12] In this elegant synthesis, the pyridine-containing central domain of Thiocillin I was built using a Bohlmann-Rahtz reaction as outlined in Scheme 7. Under Bagley conditions, the enolizable ketone **15**, the ynone **16** and NH_4OAc combination in refluxing acetic acid led to the formation of the trisubstituted pyridine **17** in 52% yield (285 mg). It should be noticed that during this reaction, acid-promoted desilylation of the *tert*-butyldimethylsilyl (TBS) protective group provided the corresponding alcohol which was *in situ* acetylated by Fischer esterification.



SCHEME 7

[12] V. S. Aulakh, M. A. Ciufolini, *J. Am. Chem. Soc*. **2011**, *133*, 5900-5904.

A set of novel aryl and heteroaryl tethered pyridines has been synthesized and evaluated for their *in vitro* anti-mycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB).[13] These compounds have been efficiently prepared using a $CeCl_3$-$7H_2O$/NaI catalyzed variant of the Bohlmann-Rahtz reaction as presented in Scheme 8 through one example. β-Enaminone **18**, derived from the corresponding methyl ketone precursor by simple reaction with *N,N*-dimethylformamide dimethylacetal (DMF-DMA) in hot xylene, was regioselectively reacted with ethyl acetoacetate in the presence ammonium acetate and $CeCl_3$-$7H_2O$/NaI as catalyst in refluxing *iso*-propanol to provide the pyridine derivative **19** in 76% yield. A plausible mechanism for this tandem Michael addition-cyclodehydration-elimination sequence has been proposed *via* a regioselective Michael addition of a cerium-activated 1,3-dicarbonyl with ammonium species on the polarized β-enaminone partner followed by cyclodehydration.[14] It should be pointed out that in this related Bohlmann-Rahtz catalyzed reaction, the use of β-enaminones instead of acetylenic ketones as Michael acceptors facilitated the aromatization step which is promoted by elimination of dimethylamine.



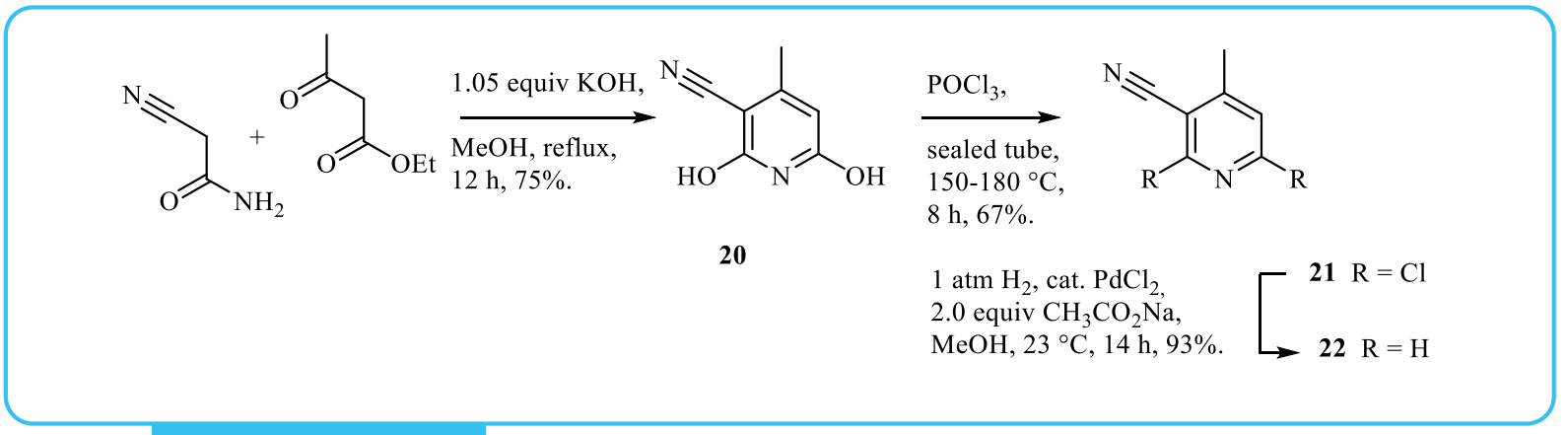
SCHEME 8

[13] S. Kantevari, S. R. Patpi, D. Addla, S.l R. Putapatri, B. Sridhar, P. Yogeeswari, D. Sriram, *ACS Comb. Sci*. **2011**, *13*, 427-435.
[14] S. Kantevari, D. Addla, B. Sridhar, *Synthesis* **2010**, 3745-3754.

Guareschi-Thorpe condensation

Condensation of 1,3-dicarbonyl compounds with cyanoacetic ester in the presence of ammonia or directly with cyanoacetamide, known as Guareschi-Thorpe condensation, lead to the formation of 2-pyridone derivatives.[15] Guareschi-Thorpe condensation has been largely applied to the preparation of various pyridine building blocks, as presented in this paragraph.

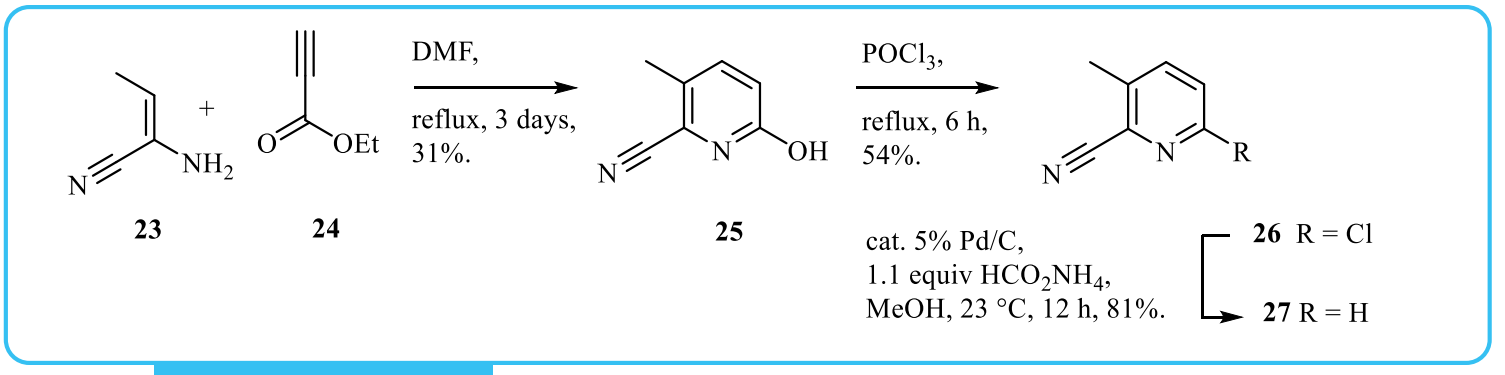
In the context of the synthesis of azaindenoisoquinolines as topoisomerase I inhibitors and potential anticancer agents, the 4-methylnicotinonitrile **22** has been prepared as explained in Scheme 9.[16] Condensation of ethyl acetoacetate and cyanoacetamide under refluxing methanolic potassium hydroxide solution provided in 75% crude yield the 2-hydroxy-3-cyano-4-methyl-6-pyridone **20** which was heated in $POCl_3$ in a sealed tube up to 180 °C to afford the 2,6-dichloro-4-methylnicotinonitrile **21** in 67% yield. It should be noted that Scipione used $POBr_3$, for this latter step, pointing out that bromination was more selective than chlorination.[17] Hydrogenolysis of the dichloropyridine **21** was carried out under atmospheric pressure of hydrogen in the presence of palladium chloride to furnish the 4-methylnicotinonitrile **22** in 93% yield (2.9 g).



SCHEME 9

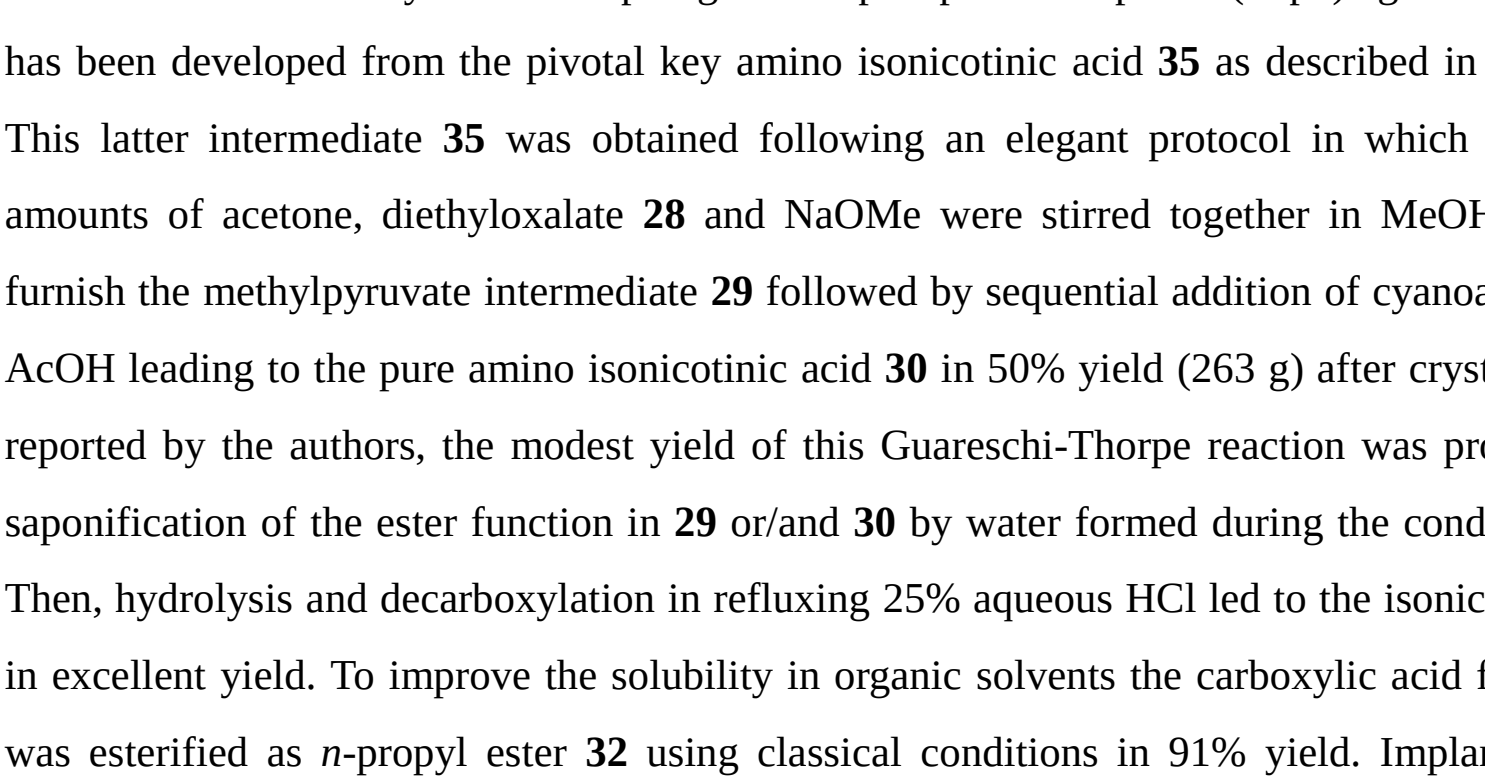
[15] For a representative example, see: J. M. Bobbit, D. A. Scola, *J. Org. Chem*. **1960**, *25*, 560-564.
[16] E. Kiselev, K. Agama, Y. Pommier, M. Cushman, *J. Med. Chem*. **2012**, *55*, 1682-1697.
[17] B. Di Rienzo, P. Mellini, S. Tortorella, D. De Vita, L. Scipione, *Synthesis* **2010**, 3835-3838.

Interestingly, the 2-methyl-3-cyanopyridine isomer required for the preparation of 10-azaindenoisoquinoline derivatives has been obtained using a Bohlmann-Rahtz pyridine synthesis as depicted in Scheme 10. Condensation of enamine **23** with acetylenic ester **24** in refluxing DMF yielded the corresponding 2-pyridone **25** in low yield (31%, 1.5 g). Following a similar two-step sequence as described for the 2-hydroxy-3-cyano-4-methyl-6-pyridone **22**, the 2-methyl-3-cyanopyridine **27** was isolated in 50% overall yield.



SCHEME 10

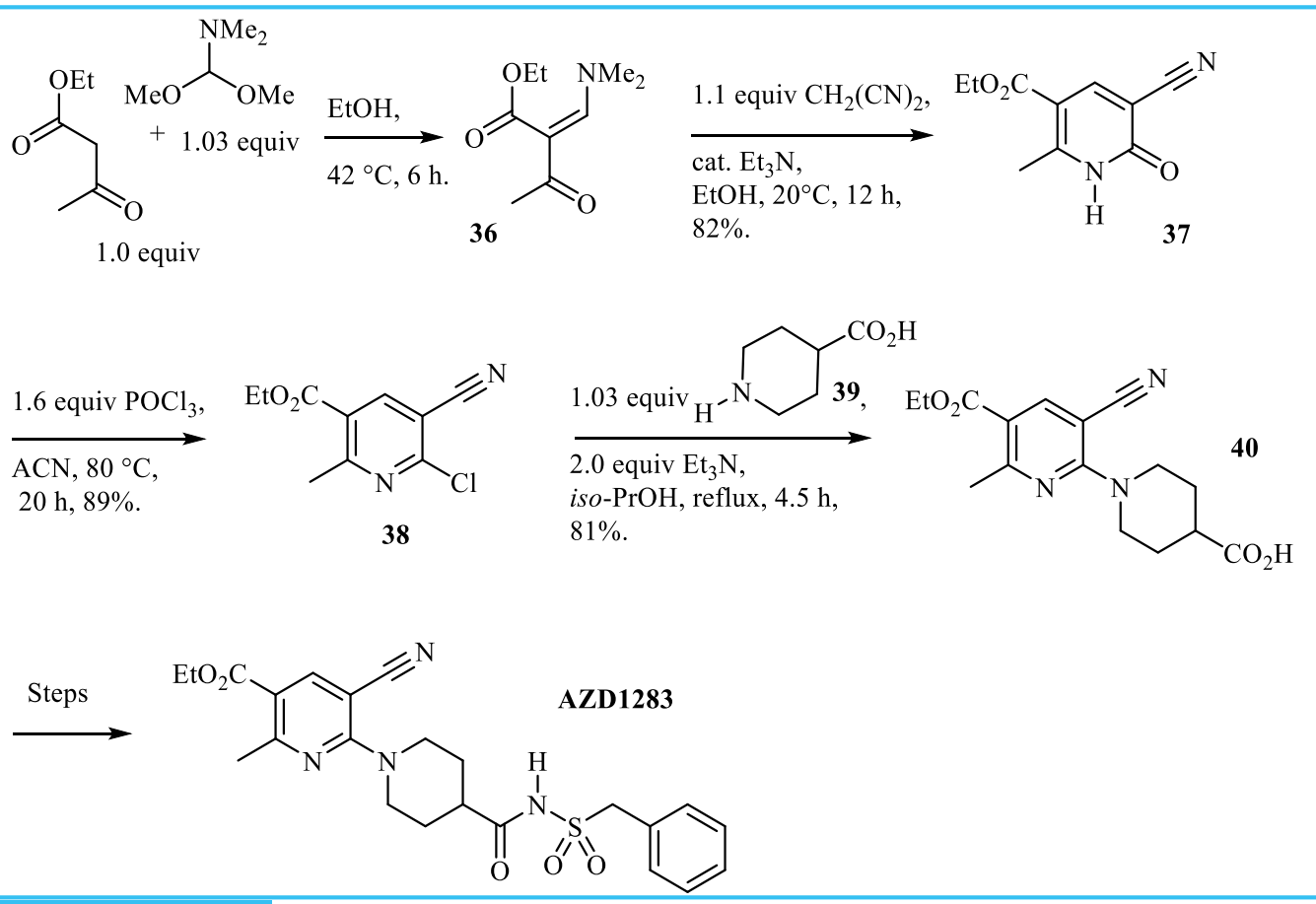
A scalable synthesis of sphingosine-1-phosphate receptor 1 (S1p1) agonist **ACT-209905** has been developed from the pivotal key amino isonicotinic acid **35** as described in Scheme 11.[18] This latter intermediate **35** was obtained following an elegant protocol in which an equimolar amounts of acetone, diethyloxalate **28** and NaOMe were stirred together in MeOH at 60 °C to furnish the methylpyruvate intermediate **29** followed by sequential addition of cyanoacetamide and AcOH leading to the pure amino isonicotinic acid **30** in 50% yield (263 g) after crystallization. As reported by the authors, the modest yield of this Guareschi-Thorpe reaction was probably due to saponification of the ester function in **29** or/and **30** by water formed during the condensation step. Then, hydrolysis and decarboxylation in refluxing 25% aqueous HCl led to the isonicotinic acid **31** in excellent yield. To improve the solubility in organic solvents the carboxylic acid function in **31** was esterified as *n*-propyl ester **32** using classical conditions in 91% yield. Implantation of the diethylamino moiety in compound **34** was carried out first by treatment of the 2-pyridone intermediate **32** with triflic anhydride and pyridine in DCM following by aromatic nucleophilic substitution of the resulting triflate **33** by diethylamine in DMSO at 50 °C. Acidic hydrolysis of the ester function in **34** afforded the key amino isonicotinic acid **35** in 87% overall yield (481 g). It should be pointed out that attempts to run this previous sequence on commercially available 2-chloro-6-methyl isonicotinic ester by aromatic nucleophilic substitution with diethylamine or employing palladium-catalyzed Buchwald-Hartwig amination failed: no conversion took place.



SCHEME 11

[18] G. Schmidt, S. Reber, M. H. Bolli, S. Abele, *Org. Process Res. Dev.* **2012**, *16*, 595-604.

For the treatment of thromboembolisms and other clotting disorders, a kilogram-scale route to **AZD-1283**, a potent antagonist of the P2Y12 receptor which is involved in platelet aggregation, has been established as depicted in Scheme 12.[19] Condensation of ethyl acetoacetate and *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) in ethanol without any catalytic amount of acid gave the enaminone intermediate **36**. In an elegant investigation concerning a robust and scalable procedure for the preparation of pyridone **37**, the chemists from Almac and AtraZeneca established that malononitrile was more efficient compared to cyanoacetamide in the condensation step.[20] Thus, ethyl acetoacetate and *N*,*N*-dimethylformamide dimethylacetal were stirred in ethanol and after 6 hours, triethylamine followed by malononitrile were added to give after 12 hours the desired ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate **37** which was isolated as an orange solid in 82% yield (539 g). Subsequent treatment of the previous cyanopyridinone **37** with $POCl_3$ furnished the corresponding 2-chloropyridine **38** in 89% yield (484 g). During the manufacturing process, this sequence was carried out on 25 kg scale! Finally, aromatic nucleophilic substitution of 2-chloropyridine **38** with isonipecotic acid **39** was run in *iso*-PrOH instead of EtOH, to minimize the formation of diester, to give the key acid intermediate **40** in 81% yield (21.4 kg).

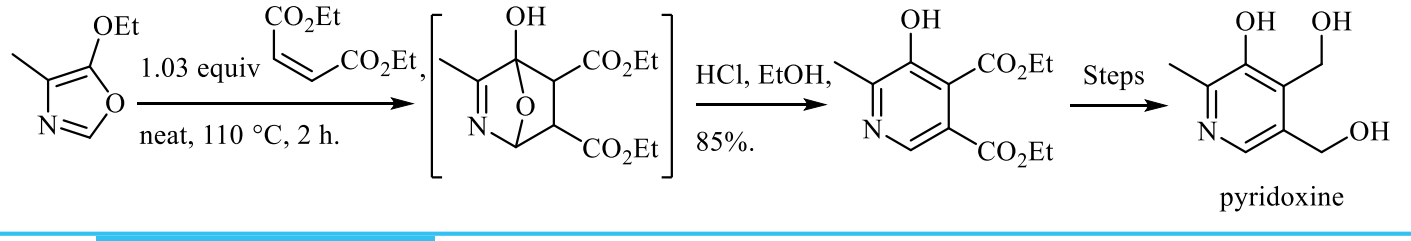


SCHEME 12

[19] S. M. Andersen, C.-J. Aurell, F. Zetterberg, M. Bollmark, R. Ehrl, P. Schuisky, A. Witt, *Org. Process Res. Dev.* **2013**, *17*, 1543-1551.
[20] S. J. Bell, S. McIntyre, C. F. Garcia, S. L Kitson, F. Therkelsen, S. M Andersen, F. Zetterberg, C.-J. Aurell, M. Bollmark, R. Ehrl, *Org. Process Res. Dev.* **2012**, *16*, 819-823.

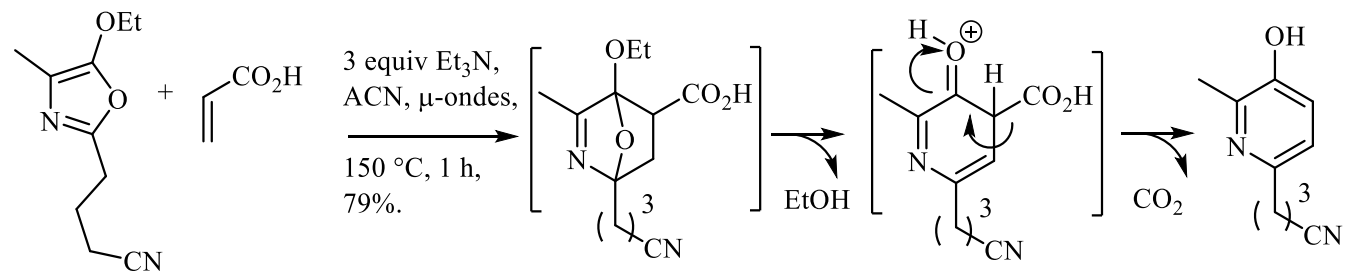
Electrocyclic additions

To construct the pyridine core, a plethora of electrocyclic additions with subsequent extrusion of volatile small molecules (e.g. H_2O, N_2, HCN) have been used, as reported in the literature.[21] For example, inter- and intramolecular Kondrat'eva [4+2] cycloaddition[22] of a dienophile, having an electron-withdrawing group on the double bond, with an oxazole to provide 3-hydroxypyridines derivatives has been employed as illustrated with the industrial synthesis of pyridoxine (vitamin B6, a water-soluble essential vitamin) (see Scheme 13).[23]



SCHEME 13

Very recently, Sabot, Renard and coll. published a succinct and original preparation of 3-hydroxypyridines *via* a thermally controlled decarboxylative modified Kondrat'eva [4+2] cycloaddition between alkoxyoxazoles and acrylic acid under microwave activation.[24] Under optimized reaction conditions as outlined in Scheme 14, this decarboxylative cycloaddition methodology provided an efficient access to 3-hydroxypyridines. It should be pointed out that in this [4+2] cycloaddition, acrylic acid partner acted as a dienophile equivalent of ethylene.



SCHEME 14

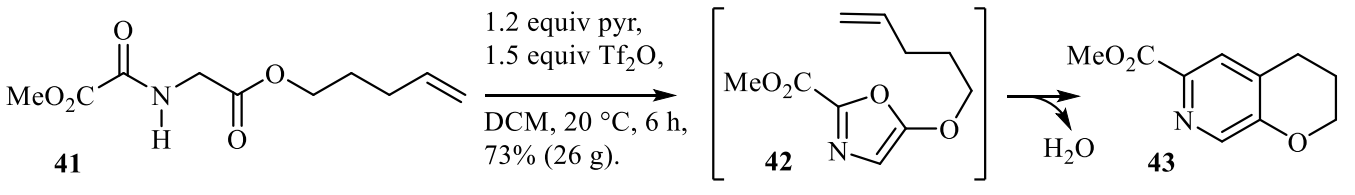
[21] T. Eicher, S. Hauptmann, A. Speicher, The Chemistry of Heterocycles:Structure, Reactions, Synthesis, and Applications, October 2012, ISBN 978-3-527-32868-0-Wiley-VCH, Weinheim.

[22] G. Y. Kondrat'eva, *Khim. Nauka Prom.* **1957**, *2*, 666-667 [Chem Abstr. **1958**, *52*, 35255].

[23] (a) For the seminal reference, see: E. E. Harris, R. A. Firestone, K. Pfister, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, W. Reuter, *J. Org. Chem*. **1962**, *27*, 2705-2706 (Surprisingly, an electronic version of this paper is not accessible on the ACS web site (8th September 2016, http://pubs.acs.org/)). (b) Y. R. Dumond, A. G. Gum, *Molecules* **2003**, *8*, 873-881.

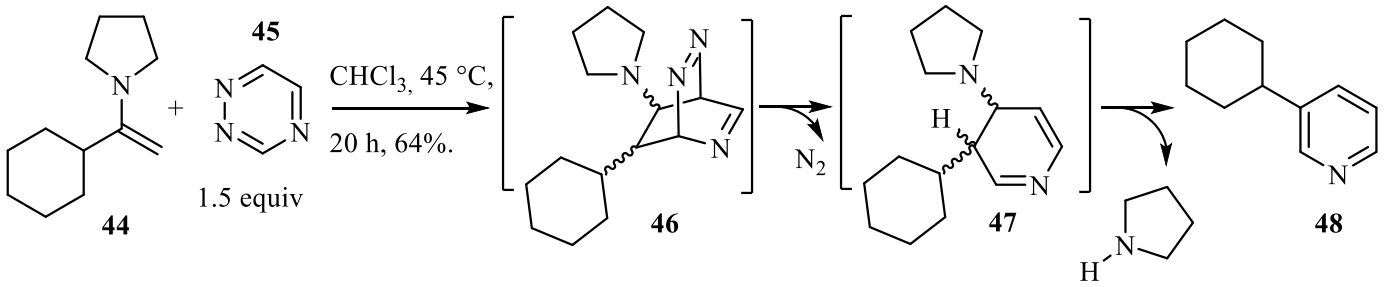
[24] L.-A. Jouanno, V. Tognetti, L. Joubert, C. Sabot, P.-Y. Renard, *Org. Lett.* **2013**, *15*, 2530-2533.

Mans and Coll. developed an efficient synthesis of fused pyridine derivatives from oxamate derivatives as presented in Scheme 15.[25] Following a one-pot multistep process, cyclodehydration of the oxamate **41** under treatment with triflic anhydride and pyridine in DCM at room temperature led to the formation of the oxazole intermediate **42**, which by intramolecular Kondrat'eva [4+2] cycloaddition and concomitant dehydration-aromatization yielded the desired dihydropyrano[2,3-c]pyridine **43**.



SCHEME 15

Boger and Panek developed in 1981 a synthetic route to pyridine core based on a Diels-Alder reaction between a 1,2,4-triazine **45**, acting as electron-demand azadien and an enamine **44**, an electron-rich olefin prepared from ketone.[26] As presented in Scheme 16, this inverse electron-demand Diels-Alder reaction afforded regioselectively the adduct **46** which by subsequent loss of nitrogen led to the azadiene **47**, and then aromatization occurred by elimination of pyrrolidine giving the desired pyridine **48** in good yield.



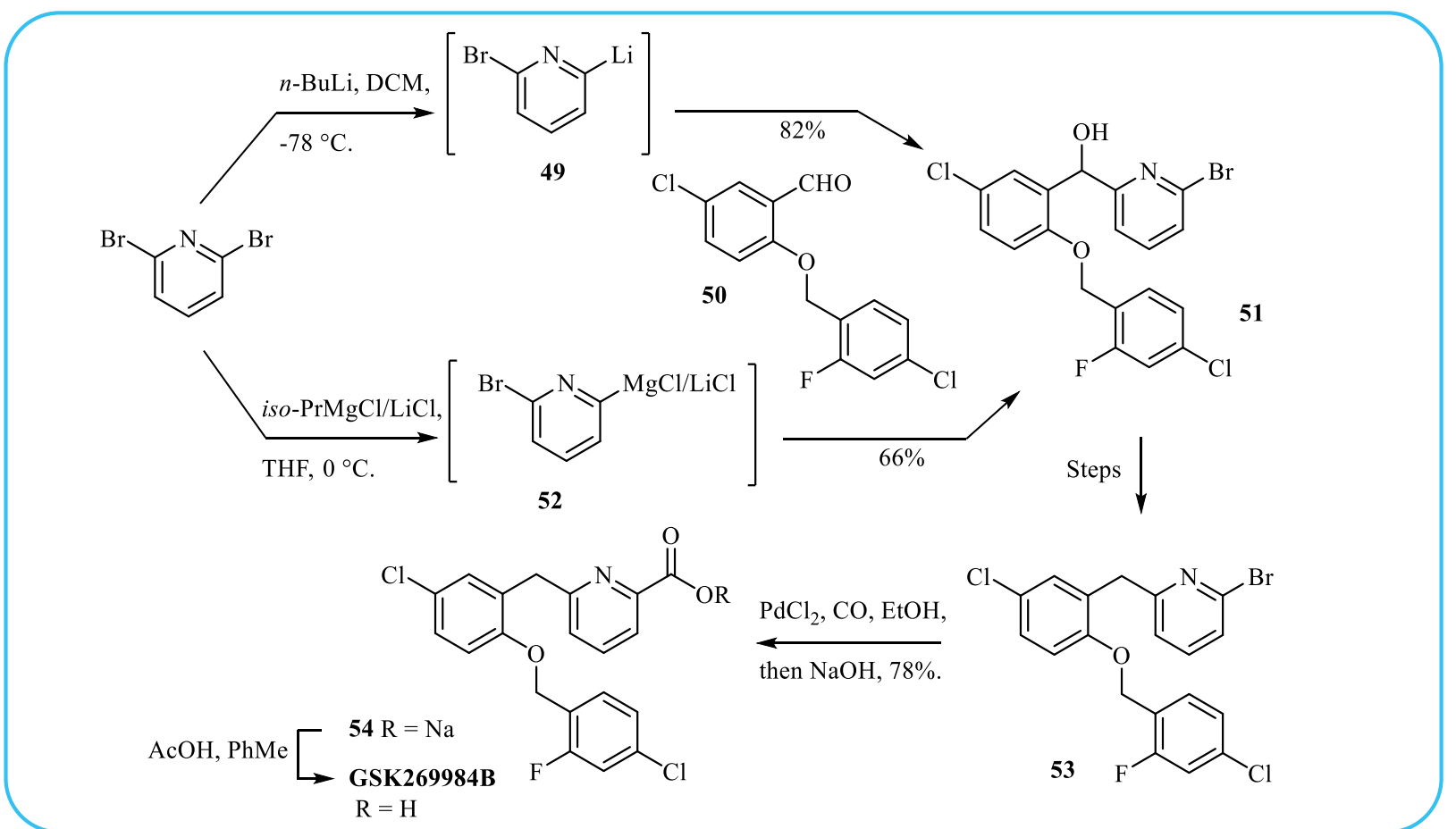
SCHEME 16

[25] S. N. Goodman, D. M. Mans, J. Sisko, H. Yin, *Org. Lett.* **2012**, *14*, 1604-1607.
[26] D. L. Boger, J. S. Panek, *J. Org. Chem*. **1981**, *46*, 2179-2182.

Functionalization of pyridine ring systems

Pyridine synthesis *via* metaled intermediates

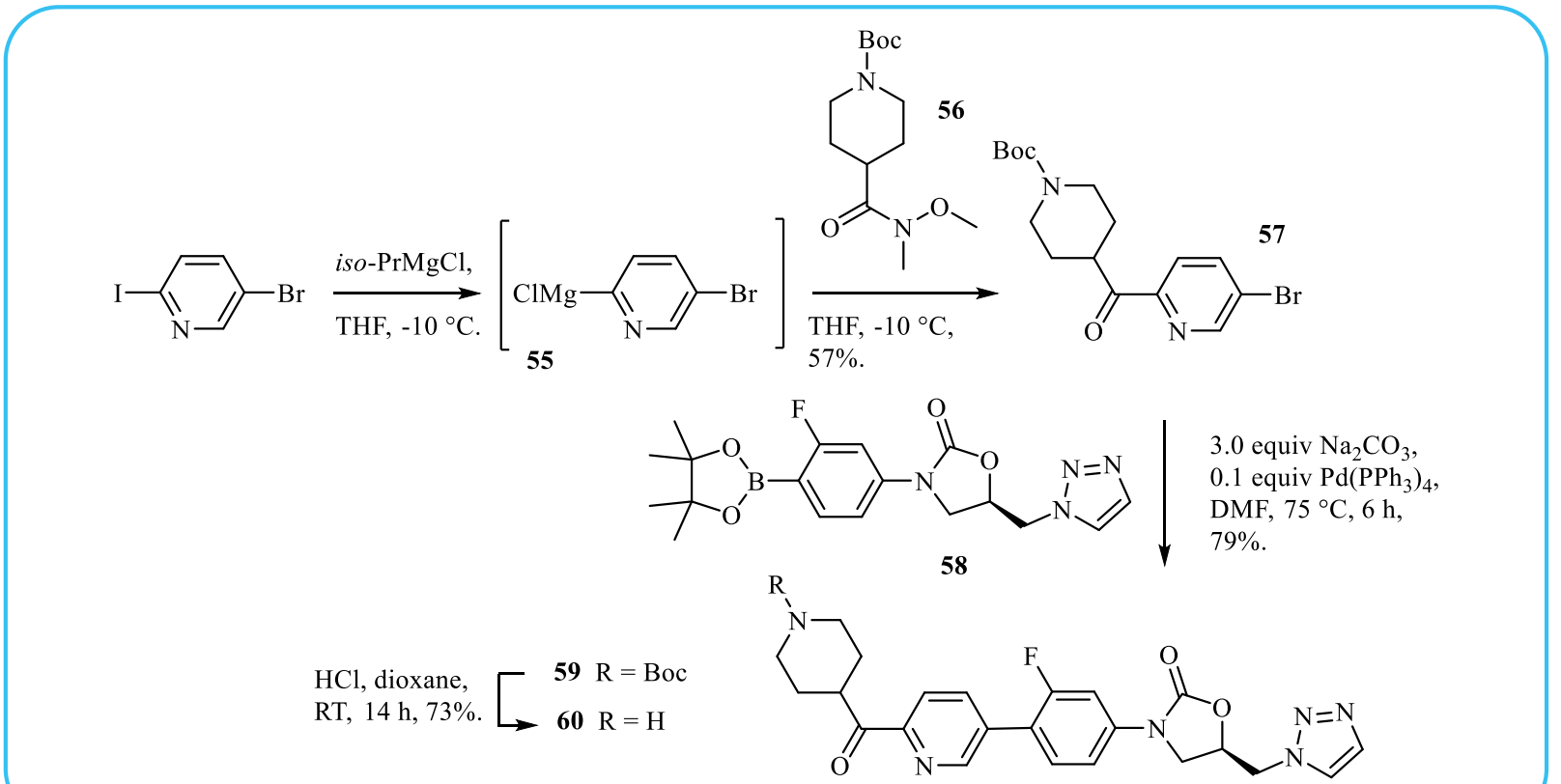
During the identification of an optimal route for long-term manufacture of the Prostaglandin E_1 receptor 1 (EP_1) antagonist **GSK269984B**, a clinical candidate for the treatment of inflammatory pain, a preparation was evaluated from 2,6-dibromopyridine, as outlined in Scheme 17.[27] Condensation of the aldehyde **50** with the monolithiated pyridine **49**, formed under cryogenic conditions with *n*-Buli in DCM[28] from 2,6-dibromopyridine, provided the desired diarylmethanol adduct **51** in 82% yield (20 g) as a white solid. In parallel, the same sequence was carried out by metal-halogen exchange with the commercially available *iso*-PrMgCl/LiCl known as "Turbo" Grignard, instead of *n*-Buli, to furnish the compound **51** with lower efficiency (66% yield, 3.42 g). At the final stage, Pd-catalyzed carbonylation in ethanol permitted the functionalization of the 2-bromopyridine compound **53** into the target acid **GSK269984B**, isolated as sodium salt **54** in 78% yield (1.57 g).



SCHEME 17

[27] M. Whiting, K. Harwood, F. Hossner, P. G. Turner, M. C. Wilkinson, *Org. Process Res. Dev.* **2010**, *14*, 820-831.
[28] For the reference concerning the first report of dichloromethane as solvent for a lithium-bromine exchange, see: M. A. Peterson, J. R. Mitchell, *J. Org. Chem.* **1997,** *62*, 8237-8239.

In the quest of a new class of antibacterial compounds, 16 oxazolidinones bearing a (pyridin-3-yl)phenyl moiety have been synthetized and evaluated.[29] A representative example of the synthesis is described in Scheme 18. From the 5-bromo-2-iodopyridine, the corresponding 5-bromopyridyl-2-magnesium chloride **55** was formed by iodo-magnesium exchange reaction using *iso*-propylmagnesium chloride reagent following a known procedure[30], and then reacted with the Weinreb amide **56** to give the ketone **57** in correct yield. Then, this pyridyl bromide intermediate **57** was engaged in a Suzuki cross-coupling reaction with the boronic ester **58** to furnish the protected target **59** in 79% yield. At the last step, acidic cleavage of the *tert*-butoxycarbonyl (Boc) group in the latter intermediate ***59*** yielded the desired acyl-pyridylphenyloxazolidinone ***60***.



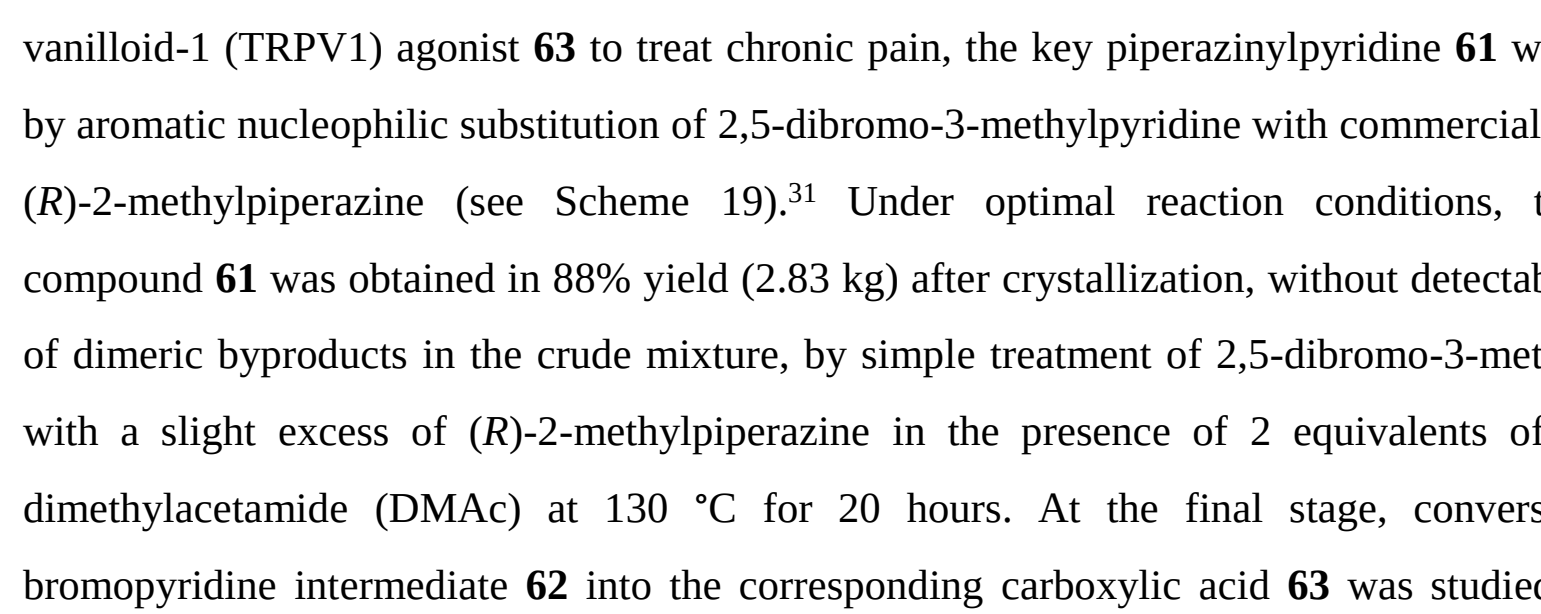
SCHEME 18

[29] F. Reck, F. Zhou, C. J. Eyermann, G. Kern, D. Carcanague, G. Ioannidis, R. Illingworth, G. Poon, M. B. Gravestock, *J. Med. Chem.* **2007,** *50*, 4868-4881.

[30] J. J. Song, N. K. Yee, Z. Tan, J. Xu, S. R. Kapadia, C. H. Senanayake, *Org. Lett*., **2004**, *6*, 4905-4907.

Aromatic nucleophilic substitution (S_NAr)

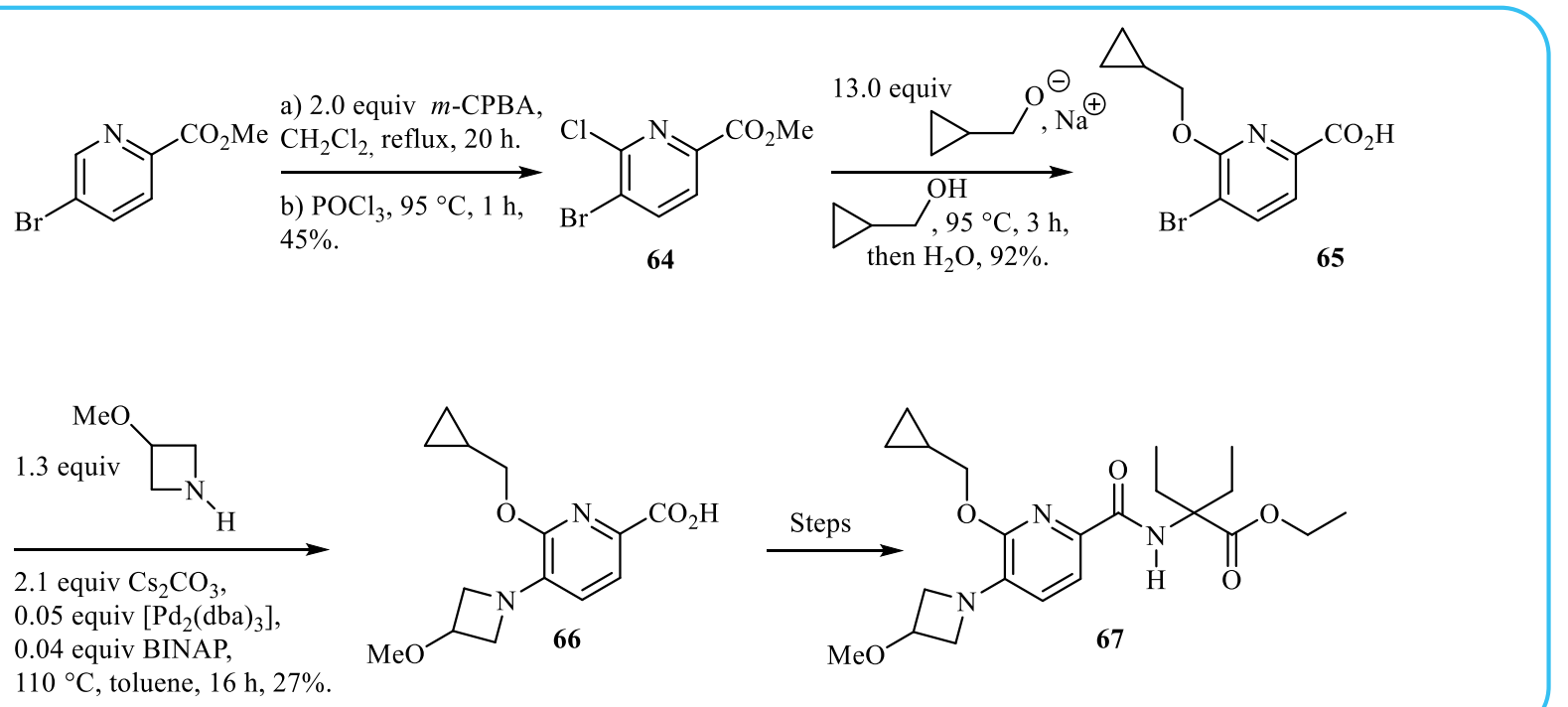
During the development of a multikilogram scale synthesis of the transient receptor potential vanilloid-1 (TRPV1) agonist **63** to treat chronic pain, the key piperazinylpyridine **61** was prepared by aromatic nucleophilic substitution of 2,5-dibromo-3-methylpyridine with commercially available (*R*)-2-methylpiperazine (see Scheme 19).[31] Under optimal reaction conditions, the desired compound **61** was obtained in 88% yield (2.83 kg) after crystallization, without detectable amounts of dimeric byproducts in the crude mixture, by simple treatment of 2,5-dibromo-3-methylpyridine with a slight excess of (*R*)-2-methylpiperazine in the presence of 2 equivalents of K_2CO_3 in dimethylacetamide (DMAc) at 130 °C for 20 hours. At the final stage, conversion of the bromopyridine intermediate **62** into the corresponding carboxylic acid **63** was studied by metal-halogen exchange followed by trapping with CO_2. Attempted metal-halogen exchange under standard Knochel conditions with *iso*-PrMgCl led to complete recovery of the starting bromide pyridine **62** unchanged. In sharp contrast, with a *n*-Buli rapid metal-halogen exchange occurred and subsequent bubbling of CO_2 into the reaction mixture gave the desired carboxylic acid **63** in modest yield. Finally, the formation of a magnesium ate complex,[32] which is more stable than the corresponding organolithium species was successful. Under noncryogenic conditions, the bromopyridine intermediate **62** was sequentially treated by addition of *iso*-PrMgCl and *n*-BuLi at -25°C, followed by reverse quenching of the resulting magnesium ate complex into CO_2/THF solution at -10 °C to give after workup the target acid **63** in 95% yield (3.08 kg).



SCHEME 19

[31] J. T. Kuethe, M. Journet, Z. Peng, D. Zhao, A. McKeown, G. R. Humphrey, *Org. Process Res. Dev*. **2016**, *20*, 227-232.
[32] Q. Tian, Z. Cheng, H. M. Yajima, S. J. Savage, K. L. Green, T. Humphries, M. E. Reynolds, S. Babu, F. Gosselin, D. Askin, *Org. Process Res. Dev*. **2013**, *17*, 97-107.

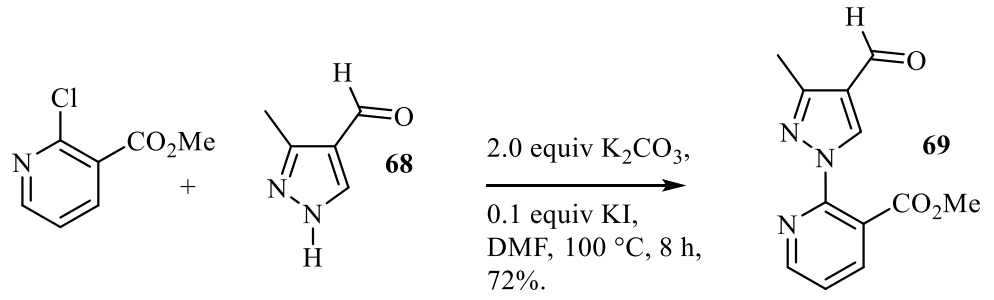
Novel 2,5,6-substituted pyridines have been synthesized and evaluated as a potential positron emission tomography imaging agent for cannabinoid type 2 receptor.[33] The synthesis of a representative ligand **67** is presented in Scheme 20 from commercially available methyl-5-bromopicolinate. Methyl-5-bromopicolinate was first treated with *m*-CPBA and the resulting *N*-oxide was transformed into the 6-chloropyridine derivative **64** with $POCl_3$ in 45% overall yield. This latter derivative **64** was engaged in an aromatic nucleophilic substitution with the sodium salt of cyclopropylmethanol to furnish in 92% yield the carboxylic acid intermediate **65** (formed by hydrolysis of the methyl ester during the workup). This latter bromopyridine derivative **65** was then coupled with 3-methoxyazetidine in a Buchwald-Hartwig amination process to give the key building block **66** in modest overall yield.



SCHEME 20

[33] R. Slavik, U. Grether, A. Müller Herde, L. Gobbi, J. Fingerle, C. Ullmer, S. D. Krämer, R. Schibli, L. Mu, S. M. Ametamey, *J. Med. Chem*. **2015**, *58*, 4266-4277.

In the course of the development of a multikilogram scale synthesis of an opioid receptor like-1 antagonist, the key ethyl 2-(4-formyl-3-methyl-1*H*-pyrazol-1-yl)nicotinate **69** was obtained in 6 kg scale as depicted in Scheme 21.[34] Under optimized conditions, treatment of ethylnicotinate and pyrazole derivative **68** with K_2CO_3 in the presence of catalytic amounts of KI in high concentrated solution of DMF at 100 °C led to the desired compound **69** in 72% yield as a single isomer after crystallization.



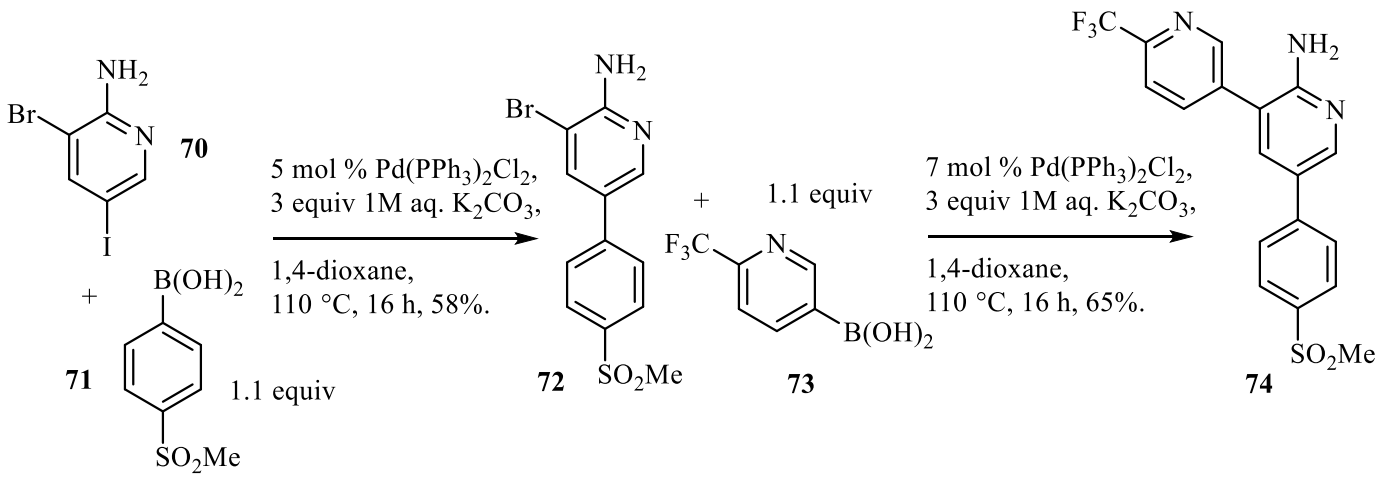
SCHEME 21

[34] A. C. DeBaillie, C. D. Jones, N. A. Magnus, C. Mateos, A. Torrado, J. P. Wepsiec, R. Tokala, P. Raje, *Org. Process Res. Dev*. **2015**, *19*, 1568-1575.

Palladium-catalyzed reactions

During the past few decades, extensive effort has led to the development of a wide variety of Pd-catalyzed methodologies for the preparation of substituted pyridines.

An efficient two-step general synthetic route to 3,5-diaryl-2-aminopyridines, a novel class of orally active antimalarial agents, has been developed through two successive Pd-catalyzed Suzuki-Myaura cross coupling reactions from 3-bromo-5-iodopyridin-2-amine **70** as outlined in Scheme 22.[35] Due to the different reactivity of iodine and bromine groups toward the Suzuki reaction[36], the selective coupling occurred at the C-5 position with a second one at C-3. Thus, under standard Suzuki reaction conditions, iodo derivative **70** was reacted with 4-methylsulfonyl-phenyl boronic acid **71** to provide the substituted 3-bromopyridin-2-amine intermediate **72** in correct yield. This bromo intermediate **72** was then involved into a second Suzuki cross-coupling reaction with the pyridinylboronic acid **73** to give the desired target **74** in 65% yield. In this study, around 30 boronic acids have been engaged with success in this latter step.



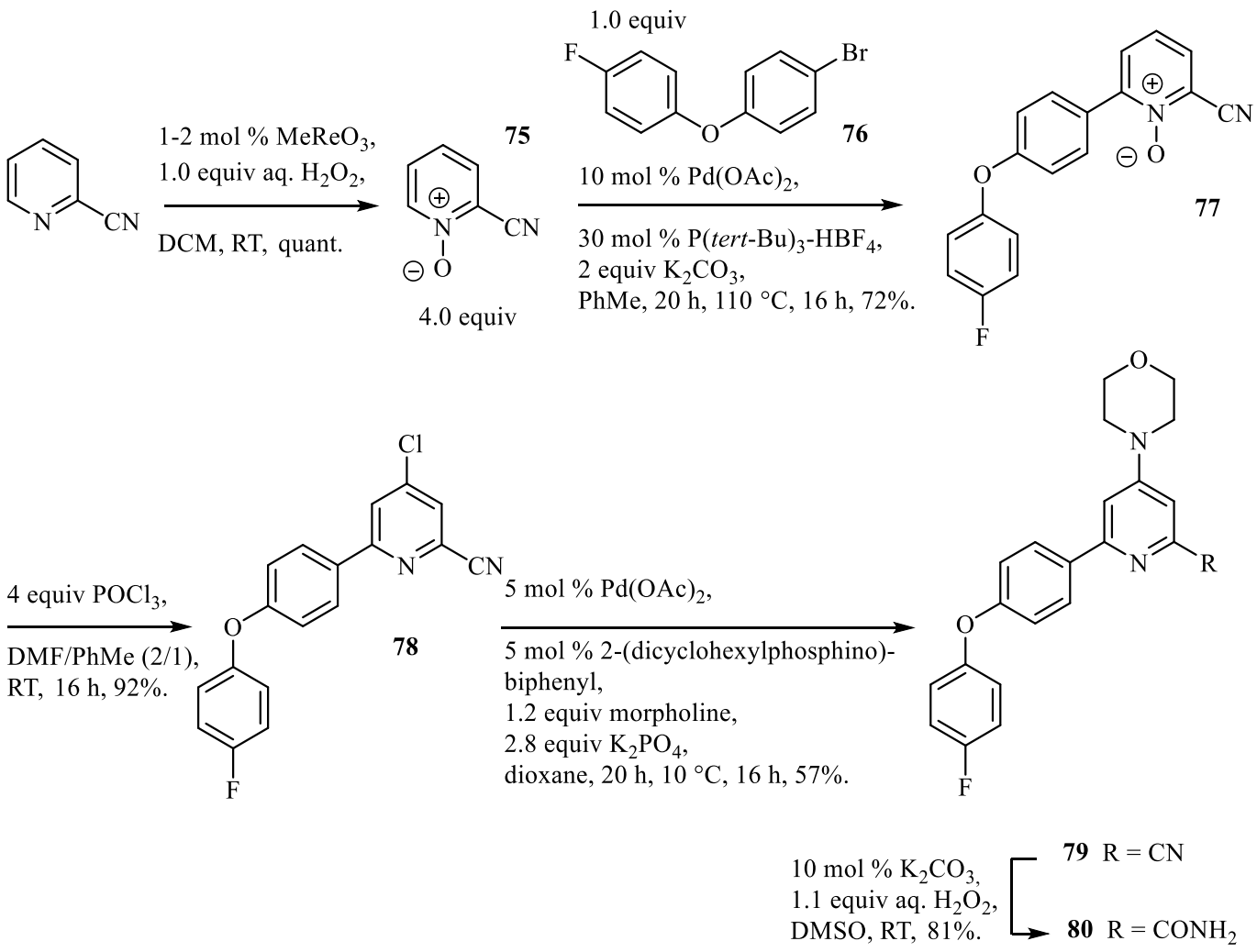
SCHEME 22

[35] K. Chibale and Coll., *J. Med. Chem*. **2012**, *55*, 3479-3487.
[36] F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc*. **2005**, *127*, 6944-6945.

Recently, direct C-H activation has emerged as an alternative to the use of stoichiometric organometallic reagents in standard cross-coupling reactions. In this context, C-H activation strategy using pyridine *N*-oxide intermediates, as first introduced by Fagnou,[37] opened a new avenue for the preparation of 2-functionalized pyridine derivatives. It should be pointed out that this transformation is highly site-selective at C-2 position owing mainly to the fact that, the *N*-oxide moiety increases the electron-density of the electron-deficient pyridine ring system, whilst simultaneously enhancing the Brönsted acidity of the adjacent protons. This C2-H activation of pyridine *N*-oxide derivatives solved the major drawback concerning the instability and demanding preparation of 2-pyridyl organometallic intermediates which greatly limited their use.[38]

State-dependent sodium channel inhibitors have been recognized as a potential strategy for the treatment of neuropathic pain through a mechanism involving the blocking of these channels[39]. In this context, a novel family of the state-dependent Na^+ channel blocker was discovered by Purdue Pharma.[40] The more promising inhibitor **80** (see Scheme 23) was synthetized in seven steps with an overall yield around 7%.[40] Based on Pd-catalyzed direct arylation of pyridine *N*-oxides, Fagnou[37] described an efficient alternative route to this inhibitor **80** on small scale. Conversion of 2-cyanopyridine into its corresponding *N*-oxide **75** was carried out quantitatively by treatment with catalytic amounts of methyltrioxorhenium and aqueous hydrogen peroxide in DCM. This latter *N*-oxide **75** was then engaged in Pd-catalyzed direct arylation under standard conditions with the bromofluoro diarylether **76** to provide the coupled compound **77** in 72% yield. The required chloropyridine derivative **78** was prepared in 92% yield from the *N*-oxide **77** in an astute fashion by treatment with $POCl_3$. Interestingly, the treatment of *N*-oxide **77** with the 2- and 6-position blocked led to the implantation of the chlorine atom at C-4 with concomitant deoxygenation process. Under standard Buchwald-Hartwig amination, the newly installed chlorine in **78** was replaced by morpholine to provide the compound **79** in 57% yield. Nevertheless, during the original preparation,[40] this latter step was run on a related substrate by reaction of NaH and morpholine at elevated temperature in sealed tube to furnish the desired adduct in 100% yield (3.2 g). At the final stage, the nitrile functional group of **79** was hydrolyzed with aqueous hydrogen peroxide to yield the target inhibitor **80** in five steps and an overall yield of 31% from 2-cyanopyridine.

[37] L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc*. **2009**, *131*, 3291-3306.
[38] D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc*. **2009**, *131*, 6961-6963 and cited literature.
[39] M. Rogers, L. Tang, D. J. Madge, E. B. Stevens, *Semin. Cell. Dev. Biol*. **2006**, *17*, 571-581.
[40] R. B. Carter *and Coll.*, *J. Med. Chem*. **2004**, *47*, 4277-4285.


1.0 equiv
F
Br
O
76
1-2 mol % $MeReO_3$,
1.0 equiv aq. H_2O_2,
DCM, RT, quant.
75
N
CN
O
4.0 equiv
10 mol % $Pd(OAc)_2$,
30 mol % P(*tert*-Bu)$_3$-HBF_4,
2 equiv K_2CO_3,
PhMe, 20 h, 110 °C, 16 h, 72%.
77
4 equiv $POCl_3$,
DMF/PhMe (2/1),
RT, 16 h, 92%.
Cl
78
5 mol % $Pd(OAc)_2$,
5 mol % 2-(dicyclohexylphosphino)-biphenyl,
1.2 equiv morpholine,
2.8 equiv K_2PO_4,
dioxane, 20 h, 10 °C, 16 h, 57%.
R
10 mol % K_2CO_3,
1.1 equiv aq. H_2O_2,
DMSO, RT, 81%.
79 R = CN
80 R = $CONH_2$

SCHEME 23

Conclusion

It is anticipated that, in the future, further developments in Pd-catalyzed reaction in particular in oxidative C-H[41] as well as C-H/C-H[42] cross-coupling reaction with pyridine *N*-oxides, will open up new routes to reach this class of important compounds in Medicinal Chemistry.

I would like to thank Ruairi O. M^{c} Court and Professor François-Xavier Felpin for fruitful discussions and comments. I also thank all my colleagues from Atlanchim Pharma for their valuable suggestions during the preparation of this manuscript.

[41]For a recent work concerning a green and selective preparation of biaryl compounds through C-H arylation of heterocyclic *N*-oxides, see: A. P. Colleville, R. A. J. Horan, S. Olazabal, N. C. O. Tomkinson, *Org. Process Res. Dev*. **2016**, *20*, 1283-129.
[42] W. Liu, X. Yu, Y. Li, C. Kuang, *Chem*. *Commun.* **2014**, *50*, 9291-9294.

PORTRAIT

Grégory SAUTEJEAU, technicien chimiste chez AtlanChim Pharma depuis 2015 est titulaire d'un DUT Chimie obtenu à Poitiers et d'une licence professionnelle en chimie organique et bioorganique (Orsay), réalisée en alternance.

Avant de rejoindre notre équipe, Grégory a travaillé dans l'industrie pharmaceutique, notamment sur des composés hétérocycliques d'intérêts thérapeutiques. Actuellement Grégory travaille en association avec un chef de projet sur des contrats de synthèse à façon, lui permettant de travailler sur une grande diversité de molécules et de réactions chimiques.

Grégory SAUTEJEAU, chemistry technician at AtlanChim Pharma since 2015, holds a Diploma of Higher Education in Chemistry obtained at the University of Poitiers and a BSC degree in organic synthesis and bioorganique (Orsay), with a work placement.

Before to join our team, Grégory has been working in the pharmaceutical industry, in particular on heterocyclic compounds of therapeutic value. Grégory currently works in association with a project manager on custom synthesis contracts, allowing him to work on a wide variety of molecules and chemical reactions.