Tetrahedron Letters 51 (2010) 4755–4758

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A versatile route to 3-(pyrimidin-4-yl)-imidazo[1,2-*a*]pyridines and 3-(pyrimidin-4-yl)-pyrazolo[1,5-*a*]pyridines

Richard Ducray [a,*], Pascal Boutron [a], Myriam Didelot [a], Hervé Germain [a], Franck Lach [a], Maryannick Lamorlette [a], Antoine Legriffon [a], Mickael Maudet [a], Morgan Ménard [a], Georges Pasquet [a], Fabrice Renaud [a], Iain Simpson [b], Gail L. Young [b]

[a] *AstraZeneca, Research Centre, Z.I. la Pompelle, 51689 Reims Cedex 2, France*
[b] *AstraZeneca, Cancer Medicinal Chemistry, Mereside, Alderley Park, Macclesfield SK10 4TG, UK*

ARTICLE INFO

Article history:
Received 2 June 2010
Revised 2 July 2010
Accepted 5 July 2010

ABSTRACT

A two-step synthesis of 3-(2-chloropyrimidin-4-yl)imidazo[1,2-*a*]pyridines is presented. The late stage elaboration of the imidazopyridine through a cyclocondensation allows a rapid access to a variety of substitution patterns. The intermediate enol ethers were obtained from inexpensive reagents in a ligand-free Heck coupling. This methodology has been extended to the formation of pyrazolo[1,5-*a*]pyridines via a formal 1,3-dipolar cycloaddition.

The imidazo[1,2-*a*]pyridine ring is found in many bioactive substances including pharmaceutical drugs such as the GABA receptor antagonist Zolpidem (**1**), (Fig. 1), the phosphodiesterase III inhibitor Olprinone (**2**), or the bisphosphonate Minodronic acid (**3**). In particular, the 3-pyrimidin-4-yl-imidazo[1,2-*a*]pyridine scaffold has been used in anti-viral compounds,[1] anticoccidial agents,[2] and kinase inhibitors.[3]

Following up the work from colleagues at AstraZeneca on CDK2 inhibitors,[3a,b] we have been interested in expanding the substitution pattern on the imidazopyridine ring as well as the C5 position of the central pyrimidine. For this purpose, we had to access 2-chloropyrimidine building blocks which allow the introduction of various arylamines using either a nucleophilic aromatic substitution or a Buchwald reaction (Scheme 1). The traditional approach to build compounds of general structure **6** is based on the condensation of enamine **4** with guanidine to afford a 2-aminopyrimidine which is converted to the desired chloropyrimidine **5a** by a Sandmeyer reaction followed by $POCl_3$-mediated chlorination.

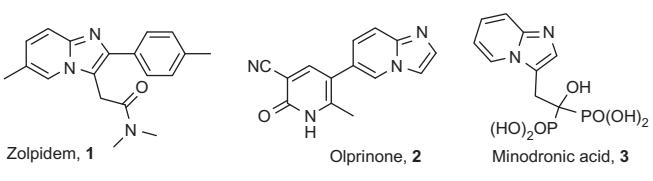
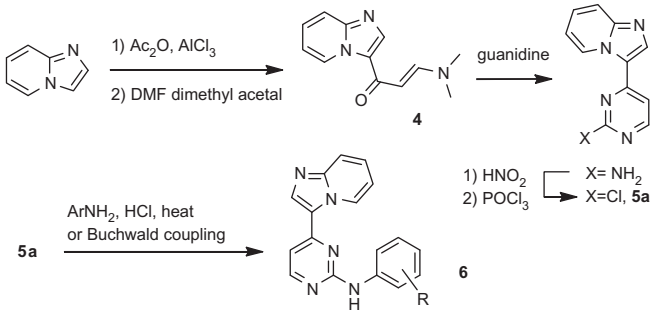


Figure 1. Structures of some pharmaceutical drugs containing the imidazo[1,2-*a*]pyridine motif.

Although this route could in principle be applied to substituted imidazopyridines, the length of the synthesis of each building block would require a significant effort to explore the structure–activity relationships of the final compounds. Furthermore some of the modifications intended on the C5 position of the pyrimidine ring were anticipated to be challenging using this strategy. In the need for a shorter, more convergent, and a more versatile route to structure **6** and analogs, we started to investigate a possible biaryl coupling to assemble imidazopyridine and pyrimidine synthons.

Our first approach based on a Suzuki coupling with 2,4,5-trichloropyrimidine was rapidly abandoned in light of the difficulty to generate the required boronic acid or ester using conventional methods.[4] Alternatively, the reported Negishi coupling[3c] between the imidazopyridinyl zinc reagent and trichloropyrimidine (Scheme 2) afforded the desired product in a modest yield. How-



Scheme 1. Reported synthesis of imidazopyridines **6**.

* Corresponding author.
E-mail address: richard.ducray@astrazeneca.com (R. Ducray).

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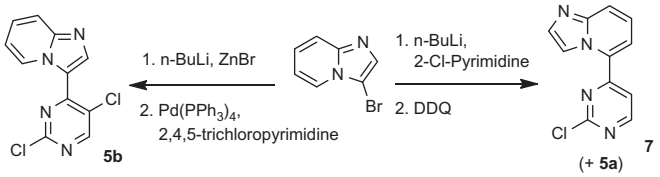
doi:10.1016/j.tetlet.2010.07.024

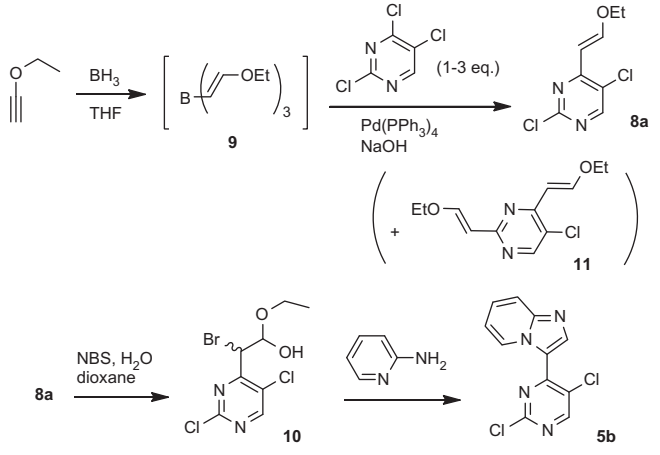


Scheme 2. Negishi and Strekowski approaches.

ever, in our hands, this procedure proved to be difficult to reproduce and we were unable to obtain a satisfactory yield when scaling up the reaction. We then turned our attention toward the method described by Strekowski and co-workers[5] using 3-bromo-imidazo[1,2-*a*]pyridine and 2-chloropyrimidine as starting materials. Unfortunately this method was not conveniently applicable to our synthesis since we isolated a 1:1 mixture of the expected product **5a** and the isomeric compound **7**, presumably arising from a proton shift on the lithiated species to form a more stable aryllithium intermediate.[6]

Faced with the difficulty of coupling the two heterocycles, we started to investigate the possible formation of the imidazopyridine ring at a late stage. A careful survey of the patent literature indicated that such an approach is indeed possible using a two-steps, one-pot procedure.[7] Indeed, bromination of the vinyl ether **8a** with NBS in dioxane–water (Scheme 3) followed by a cyclocondensation with 2-aminopyridine provided the desired imidazopyridine **5b** in 40% yield, presumably via the α-bromo hemiacetal **10**. Compound **8a** is obtained in 47% yield from 2,4,5-trichloropyrimidine by a Suzuki type reaction with the trivinylborane **9**.[8] Although we were able to reproduce this sequence, we found it difficult to control the course of the reaction on a multi-gram scale, in part because of an increased amount of the bis-vinylic product **11**. Adjusting the stoichiometry of the reaction up to 3 equiv of pyrimidine did not avoid the formation of **11** and led to an incomplete conversion. In addition, ethynyl ethyl ether is an expensive reagent which was difficult to obtain in large amount from our chemicals suppliers. From our perspective, this represented the most important limitation of this method.

Recognizing the value of vinyl ether **8a** for our purpose, we needed an alternative method for its preparation, which would be cost effective and applicable to a large scale synthesis. The Heck reaction, an atom-economic transformation for arylation of terminal alkenes, was an attractive option for us. Although selective β-arylation of vinyl ethers is a challenging reaction, recent advances have provided favorable conditions for this transformation.[9] We



Scheme 3. Vinyl borane route to imidazopyridine **5b**.

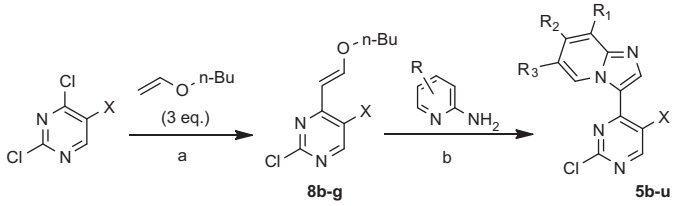
discovered that such a β-arylation of 4-chloropyrimidines could be achieved using a phosphine-free Heck reaction in polyethyleneglycol.[10] The reaction of 2,4,5-trichloro-pyrimidine with ethyl vinyl ether (3 equiv) in the presence of triethylamine (1 equiv) and palladium acetate (7 mol %) using PEG-400 as a solvent provided a 2:1 mixture of **8a** and the starting trichloropyrimidine (30% corrected yield). We found that replacing the ethyl ether by the less volatile *n*-butyl ether (Scheme 4) led to the completion of the reaction and provided compound **8b** in 53% yield (Table 1, entry 1).[11]

The use of an inexpensive, readily available vinyl ether in conjunction with a ligand-free catalytic process removed constraints associated with the previous method. Moreover the synthesis of **8b** using this new procedure was conducted on a 100 g scale without loss of chemical yield. We applied this process to 2,4-dichloropyrimidines with various C5 substituents (Table 1). The reaction proceeded under similar conditions with either electron-withdrawing (entries 1–3) or electron-donating substituents (entries 4–6), with the exception of the trifluoromethyl group for which no product was isolated (entry 7).

With a robust route to our key 2-chloropyrimidine building blocks, we embarked on the preparation of a variety of substituted 3-(2-chloropyrimidin-4-yl)-imidazo[1,2-*a*]pyridines. The one-pot sequence of bromination and cyclocondensation with 2-aminopyridine (Scheme 4) was successfully applied to compounds **8b–f** (Table 2, entries 1–5) with consistent yields, the inductive character of the pyrimidine C5 substituent having little impact on the reaction. Compound **8b** was then reacted with a number of substituted 2-aminopyridines (Table 2, entries 6–20) to provide imidazopyridines substituted on the 6, 7, or 8 positions.

Interestingly, the electron-donating or -withdrawing nature of the substituent on the 3-position of the starting pyridine (R_1) did not significantly impact the course of the reaction, the desired products being generally obtained in 40–60% yield (compounds **5g**–**m**). A similar trend was observed with 4-substituted 2-aminopyridines (compounds **5n**–**s**) with the notable exception of 4-amino-pyridines, such as 4-(pyrrolidin-1-yl)pyridin-2-amine, which failed to provide the desired product. Presumably the higher basicity of these compounds is not compatible with our reaction conditions. Finally 5-fluoro- and 3,5-difluoro-2-aminopyridines provided the desired products (compounds **5t** and **5u**) in excellent yields.

With the aim of accessing novel kinase inhibitors, we became interested in the replacement of the imidazopyridine ring by a



Scheme 4. Heck route to imidazopyridines **5b**–**u**. Reagents and conditions: (a) triethylamine, $Pd(OAc)_2$ (7 mol %), PEG-400, 80 °C, 2 h, see Table 1 for isolated yields; (b) *N*-bromosuccinimide, dioxane, water, rt, 1 h, then 2-aminopyridine, 60–80 °C, 2–4 h, see Table 2 for isolated yields.

Table 1
Synthesis of vinyl ethers **8b**–**g**

Entry	Product	X	Yield (%)
1	**8b**	Cl	53
2	**8c**	F	51
3	**8d**	Br	39
4	**8e**	Me	55
5	**8f**	OMe	51
6	**8g**	cy-Pr	47
7	**8h**	CF_3	0

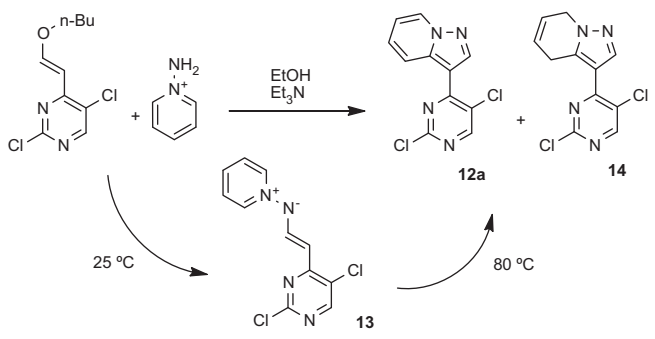
Table 2
Synthesis of compounds **5b–u** from vinyl ethers **8**

Entry	Product	X	R_1	R_2	R_3	Yield (%)
1	**5b**	Cl	H	H	H	67
2	**5c**	F	H	H	H	70
3	**5d**	Br	H	H	H	43
4	**5e**	Me	H	H	H	63
5	**5f**	OMe	H	H	H	53
6	**5g**	Cl	NH_2	H	H	37[a]
7	**5h**	Cl	MeO	H	H	53
8	**5i**	Cl	Me	H	H	49
9	**5j**	Cl	CH_2OH	H	H	56
10	**5k**	Cl	F	H	H	59[a]
11	**5l**	Cl	CN	H	H	61
12	**5m**	Cl	NO_2	H	H	59
13	**5n**	Cl	H	MeO	H	21
14	**5o**	Cl	H	Me	H	45[a]
15	**5p**	Cl	H	F	H	44
16	**5q**	Cl	H	Cl	H	61
17	**5r**	Cl	H	Br	H	51[a]
18	**5s**	Cl	H	CN	H	39
19	**5t**	Cl	H	H	F	73
20	**5u**	Cl	F	H	F	88

[a] The cyclization was performed at room temperature for 16 h.

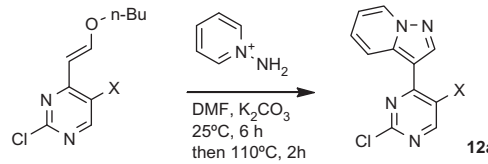
pyrazolo[1,5-*a*]pyridine. We expected that such pyrazolopyridines could be obtained via a 1,3-dipolar cycloaddition between vinyl ethers **8** and the azomethine imine formed by deprotonation of a 1-amino-pyridinium ion, followed by an oxidative aromatization. Indeed, when compound **8b** was reacted, in the presence of air, with 1-amino-pyridinium iodide and triethylamine in refluxing ethanol, we obtained a 9:1 mixture of the desired 3-(pyrimidin-4-yl)-pyrazolo[1,5-*a*]pyridine **12a** and a by-product that we assigned as the dihydro-pyrazolopyridine **14** based on mass spectrometry and ^{1}H NMR (Scheme 5). Since a prolonged reaction time in the presence of atmospheric oxygen did not reduce the amount of compound **14** we concluded that the latter is not the precursor of **12a**.

A closer look at the course of the reaction revealed that this transformation does not follow a concerted mechanism but occurs in a stepwise fashion through a Michael addition of the amino-pyridinium onto the activated olefin and the subsequent elimination of butanol as the first step. This was confirmed by the isolation at room temperature of intermediate **13** which was characterized by an X-ray crystallography. Heating the reaction mixture allows this intermediate to undergo a cyclization–oxidation process for which the exact mechanism remains unclear. Indeed performing the reaction under strict anaerobic conditions did not lead exclusively to compound **14**, suggesting that the oxidation step is not a simple oxygen-mediated aromatization. Finally we found that a polar aprotic solvent (DMF) and an inorganic base (potassium carbonate) improved the yield of **12a** while limiting the formation of **14**, which proved difficult to separate from the desired product by



Scheme 5. Formation of pyrazolopyridine **12a** and by-product **14**.

Table 3
Synthesis of pyrazolopyridines **12a–e**



12a-e

Entry	Product	X	Yield (%)
1	**12a**	Cl	41
2	**12b**	F	49
3	**12c**	Br	24
4	**12d**	Me	48
5	**12e**	cy-Pr	52

silica gel chromatography. These optimized conditions were applied to the synthesis of compounds **12a–e** (Table 3) from the vinyl ethers **8b–e** and **8g**.

In conclusion, we have elaborated a fast, convenient, and economic route to 3-(2-chloropyrimidin-4-yl)imidazo[1,2-*a*]-pyridines and the corresponding pyrazolo[1,5-*a*]pyridines, in only two steps from readily available starting materials. The first step involves the formation of vinyl ethers using an unusual, phosphine-free, Heck reaction. The reaction of the 2-chloropyrimidines described herein with arylamines and the biological activity of the resulting compounds will be reported in due course.

Acknowledgments

We thank Dominique Boucherot and Aurélien Peru for providing useful intermediates and Christian Delvare for NMR studies.

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11. Experimental procedures and ^{1}H NMR characterization for compounds **8b**, **5b** and **12a**:
Vinyl ether **8b**. Triethylamine (166 ml, 1.19 mol), 1-(vinyloxy)butane (176 ml, 1.36 mol),[12] and palladium(II) acetate (16 g, 71 mmol) were added to a stirred solution of 2,4,5-trichloropyrimidine (208 g, 1.13 mol) in polyethylene glycol 400 (800 ml). The solution was heated at 80 °C for 2 h (*CAUTION*: exotherm[13]). After cooling to 0 °C, diethylether was added and the etheral layer separated by decantation (2 L, twice). The organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford an orange oil which was purified by chromatography on silica gel using 15% EtOAc/petroleum ether as eluent. (*E*)-4-(2-Butoxyvinyl)-2,5-dichloropyrimidine **8b** (147 g, 53%); ^{1}H NMR ($CDCl_3$) 0.97 (t, 3H), 1.41–1.50 (m, 2H), 1.70–1.78 (m, 2H), 4.03 (t, 2H), 6.09 (d, 1H), 8.07 (d, 1H), 8.33 (s, 1H).
Compound **5b**. *N*-Bromosuccinimide (12.9 g, 72.8 mmol) was added to a stirred solution of **8b** (18.0 g, 72.8 mmol) in dioxane (400 ml) and water (150 ml). The resulting solution was stirred for 1 h at room temperature; then 2-aminopyridine (6.86 g, 72.8 mmol) was added and the solution was heated at 65 °C for 4 h. Dioxane was evaporated and a saturated solution of sodium bicarbonate was added until pH 7. The mixture was extracted with methylene chloride and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. Purification on silica gel, eluting with 5% MeOH in methylene chloride afforded 3-(2,5-dichloropyrimidin-4-yl)imidazo[1,2-*a*]pyridine **5b** in 54% yield; ^{1}H NMR ($CDCl_3$) 7.15 (dd, 1H), 7.53 (ddd, 1H), 7.83 (d, 1H), 8.60 (s, 1H), 9.01 (s, 1H), 9.87 (d, 1H); Mass spectrum (ESI) 265 (MH^+).
Compound **12a**. 1-Aminopyridinium iodide (68.8 g, 309 mmol) and potassium carbonate (42.8 g, 309 mmol) were added to a solution of **8b** (88 g, 309 mmol) in DMF (800 mL) at 25 °C. The resulting dark orange suspension was stirred at 25 °C for 6 h and then heated at 110 °C for 2 h. After cooling, the reaction mixture was diluted with water (4 L) and a red-orange solid was collected by filtration. This solid was dissolved in methylene chloride (3 L) and the solution was dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography on silica gel eluting from 0% to 10% Et_2O in CH_2Cl_2 to afford 3-(2,5-dichloropyrimidin-4-yl)pyrazolo[1,5-*a*]pyridine **12a** (33.6 g, 41%); ^{1}H NMR ($CDCl_3$) 7.07 (ddd, 1H), 7.54 (ddd, 1H), 8.51 (s, 1H), 8.61 (d, 1H), 8.74 (d, 1H), 9.05 (s, 1H); Mass spectrum (ESI) 265 (MH^+).
12. When performed on a large scale, we were able to reduce the amount of 1-(vinyloxy)butane down to 1.2 equiv.
13. When performed on such a scale, an exothermic reaction was observed with an onset temperature of about 70 °C, leading to an internal temperature of up to 120 °C. It is therefore recommended to perform this reaction on a smaller scale unless appropriate control measures are in place.