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Letter

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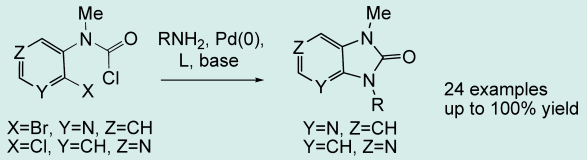
Practical Way to Imidazo[4,5-b] and [4,5-c]Pyridine-2-ones via Cascade Ureidation/Palladium-Catalyzed Cyclization

Franck Lach* and Patrice Koza

AstraZeneca, Centre de Recherches, Z.I. la Pompelle, BP1050, 51689 Reims Cedex.

Supporting Information

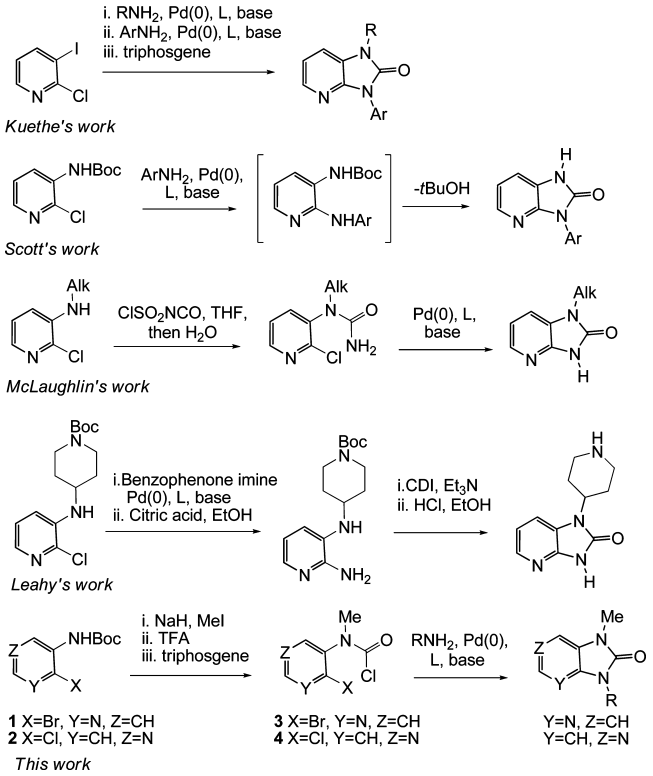
ABSTRACT: We developed an efficient one-pot tandem carbamoyl chloride amination and palladium-catalyzed intramolecular urea cyclization, which furnished high-throughput access to imidazo[4,5-b]pyridine-2-one and related imidazo[4,5-c]pyridine-2-one ring systems. Moderate to excellent yields were reported.



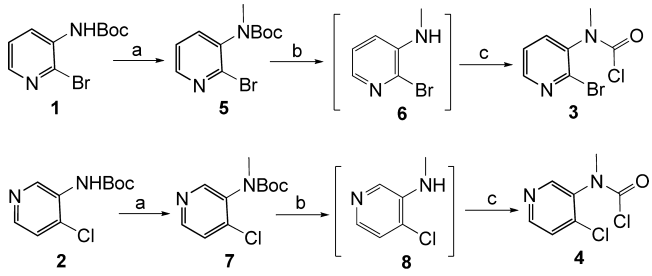
KEYWORDS: *imidazopyridine-2-one, urea cyclization, palladium coupling*

The imidazo[4,5-b]pyridine-2-one and related imidazo[4,5-c]pyridine-2-one ring systems represent the core skeleton of a pharmaceutically important class of heterocyclic compounds possessing a wide range of biological activities: indeed members of this family have demonstrated antidepressant,[1] antimigraine,[2,3] cardiotonic,[4] hypotensive, and antiarrythmic activity[5] but also act as antiviral,[6] antibacterial,[7,8] or non-steroidal antiinflammatory and analgesic agents.[9,10] General approaches that allow facile exploration of SAR within this class are therefore of value. Unsubstituted imidazopyridin-2-ones are typically prepared by reaction of 2,3- and 3,4-diaminopyridine with a variety of acylating reagents.[11,12] The preparation of unsymmetrical 1,3-substituted imidazopyridin-2-ones from 2,3- and 3,4-diaminopyridine is challenging and requires the use of protecting group strategies.[12] Therefore, alternatives based on the ability to generate cyclic urea structures in a regioselective fashion with control of the substituent on each nitrogen atom are desirable. Current approaches relying on Pd catalyzed C−N

Scheme 1. Various Pd-Catalyzed Approaches Towards Substituted Imidazo[4,5-b]pyridine-2-one and Imidazo[4,5-c]pyridine-2-one Ring Systems



Scheme 2. Synthesis of building-blocks 3 and 4[a]



[a]Reagents and conditions: (a) NaH, DMF, MeI, 0−5 °C, 90 min, 77−87%; (b) TFA, DCM, 0−25 °C, 2 h; (c) triphosgene, Et_3N, toluene, 0−25 °C, 2−3 h, 75−86% over two steps.

Scheme 3. Hypothesis for the Formation of Side-Product 9

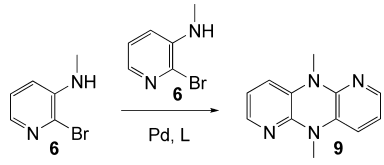


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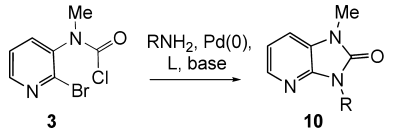
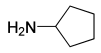
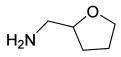
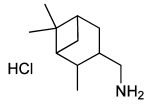
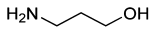
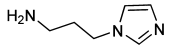
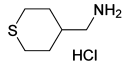
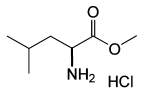
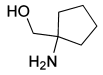
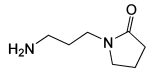
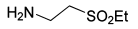
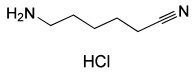
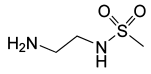
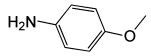
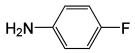
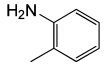
Table 1. Library of Substituted Imidazo[4,5-b]pyridine-2-one via Ureidation of 3 and Pd-Catalyzed Cyclization



Entry	Amine substrate (RNH_2)	Ligand	Cyclized product	Yield (%)[c]
1		PPh_3	**10a**	70[a]
2		PPh_3	**10b**	70[a]
3		PPh_3	**10c**	79[a,d]
4		Xantphos	**10d**	96[b]
5		Xantphos	**10e**	67[b]
6		Xantphos	**10f**	77[b]
7		Xantphos	**10g**	64[b]
8		Xantphos	**10h**	56[b]
9		Xantphos	**10i**	100[b]
10		Xantphos	**10j**	94[b]
11		Xantphos	**10k**	96[b]
12		Xantphos	**10l**	ND[b,e]
13		Xantphos	**10m**	83[b]
14		Xantphos	**10n**	56[b]
15		Xantphos	**10o**	38[b]

[a]Reaction performed in a sealed tube with **3** (0.40 mmol), amine substrate (0.48 mmol), $Pd[PPh_3]_4$ (0.09 mmol), and K_2CO_3 (1.60 mmol) in degassed toluene (2.2−2.3 mL) at 90−95 °C under an inert atmosphere for 4 h. [b]Reaction performed in a sealed tube with **3** (0.40 mmol), amine substrate (0.48 mmol), Xantphos (0.04 mmol), Pd_2dba_3 (0.02 mmol), and Cs_2CO_3 (1.60 mmol) in degassed dioxane (2.2−2.3 mL) at 85−95 °C for 3−5 h. [c]Isolated yields. [d]Reaction run at 55 °C for 16 h. [e]ND = not determined.

bond formation are illustrated in Scheme 1. Kuethe et al. developed a three-step strategy based on sequential chemo and regioselective Buchwald amination of 3-iodo-2-chloropyridine, the scope being limited to anilines for the second amination step.[13] Alternatively, Scott et al., starting from commercially available 3-amino-2-chloropyridine reported a one-pot tandem palladium-catalyzed amination and intramolecular amidation of *tert*-butyl (2-chloropyridin-3-yl)carbamate with primary anilines.[14] This elegant two-step process is unfortunately not suitable for primary alkylamines. Eventually, Mc Laughlin's group found palladium-catalyzed conditions to cyclize a series of primary ureas which were prepared in two steps from 3-

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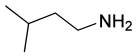
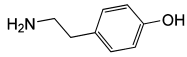
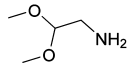
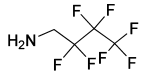
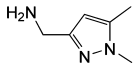
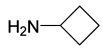
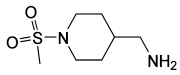
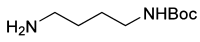
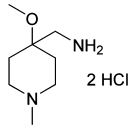
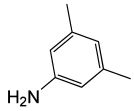
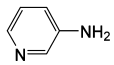
Table 2. Library of Substituted Imidazo[4,5-c]pyridine-2-one via Ureidation of 4 and Pd-Catatalyzed Cyclization

4 11

Entry	Amine substrate (RNH_2)	Cyclized product	Yield (%)[c]
1		**11a**	85[a,e]
2		**11b**	67[a]
3		**11c**	78[a]
4		**11d**	75[b]
5		**11e**	92[a]
6		**11f**	83[b]
7		**11g**	64[a]
8		**11h**	76[a]
9		**11i**	50[d]
10		**11j**	79[a]
11		**11k**	ND[a,f]

[a]Reaction performed in a sealed tube with **4** (0.50 mmol), amine substrate (0.60 mmol), dppb (0.05 mmol), $Pd(OAc)_2$ (0.025 mmol), and $NaHCO_3$ (1.75 mmol) in degassed iPrOH (1.2−1.3 mL) at 80−85 °C under an inert atmosphere for 8−12 h. [b]Reaction mixture was stirred at rt for 16 h prior to heating as in a. [c]Isolated yields. [d]K_2CO_3 (2.75 mmol) was used as the base. Reaction run with $NaHCO_3$ afforded only traces of product according to UPLC (max absorbance at 220 nm). [e]Similar reaction run in toluene afforded only 87% conversion according to UPLC (max absorbance at 220 nm) even after prolonged heating at 110 °C, whereas reaction carried out in dioxane stalled at about 55% conversion. [f]ND = not determined.

amino-2-chloropyridine.[15] This efficient process introduces the diversity at the very first stage through a reductive alkylation. A recent variation of this methodology devised at Bristol-Myers Squibb relies upon palladium-catalyzed amination of 3-alkylamino-2-chloropyridine using an ammonia surrogate followed by CDI-mediated carbonyl installation.[16] Complementary to palladium, two copper-promoted methodologies to access imidazo[4,5-b]pyridine-2-one and related imidazo[4,5-c]pyridine-2-one motifs have been reported, albeit on a single example each.[17,18] Still, the use of iodo- or bromopyridine substrates is required for successful couplings. In this note, we would like to report a practical access to a series of imidazo[4,5-b]pyridine-2-one and related imidazo[4,5-c]pyridine-2-one based on a one-pot tandem ureidation of carbamoyl chlorides **3** and **4** and palladium-catalyzed urea cyclization.

Building-blocks **3** and **4** were prepared in high overall yield on gram scale quantities from readily available precursors **1** and **2**,[19,20] using fairly standard chemistry, according to Scheme 2. We first focused our attention on the imidazo[4,5-b]pyridine-2-one series and considered using Ferraccioli's conditions applied for delivery of dihydroquinazolinones through palladium-catalyzed intramolecular arylation of ureas.[21]

Gratifyingly, a combination of **3**, the primary alkylamine, 3−5% mol $Pd[PPh_3]_4$ and K_2CO_3 in toluene at 90 °C afforded cyclized products **10a−c** in consistent yields (see Table 1, entries 1−3).[22] However, we foresaw that significant amounts

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of triphenylphosphine oxide byproduct would complicate the purification of final products, depending on their polarity. Thus, we turned to a combination of bidendate ligand Xantphos and Cs_2CO_3 in dioxane, a system previously reported for the ureidation of 2-chloropyridine.[23] Table 1 illustrates the scope for this chemistry. Notably, free alkylamines or hydrochlorides (entries 3, 6, and 7) can be used indistinctly although increasing the bulk around amino group led to less efficient couplings (entry 8). Potential palladium coordinating groups such as nitrile or sulfide were also tolerated (entries 6 and 11), whereas a secondary sulfonamide motif, deprotonated under basic conditions, possibly interferes with the ureidation process by competing for metal ligation (entry 12).[24] Primary anilines also delivered the cyclized products **10 m-o** (entries 13−15), although reactions with ortho-substituted or moderately electron-deficient anilines proved sluggish, affording **10n−o** in modest yield. The major side-product isolated from crude mixtures turned out to be the homodimer **9**, likely arising from first disproportionation of intermediate *N*-arylurea to 3-*N*-methylamino-2-bromopyridine **6**, which underwent Pd-catalyzed homocoupling (see Scheme 3).[25]

Those results suggest that the ureidation process was highly sensitive to both steric and electronic effects. We next turned our attention to the imidazo[4,5-c]pyridine-2-one series. Reported intermolecular couplings between 4-chloropyridine and ureas proved low yielding.[23,26] We anticipated the intramolecular palladium-catalyzed ureidation of **4** to be less favorable than for **3**. First, initial oxidative addition to Pd^0 is slower for C−Cl bond than for C−Br bond. More importantly, reductive elimination, reported to be the rate-determining step in the ureidation process,[25] proceeds probably faster from 2-pyridylpalladium amido complex relative to 4-pyridylpalladium amido complex because of a stronger inductive effect of the pyridyl nitrogen. In addition, the base-promoted urea disproportionation side-reaction observed by us and others for the intramolecular Pd catalyzed C−N bond formation was pronounced under more basic conditions, at higher temperatures and under prolonged heating.[15,23] We thus considered limiting the temperature to 80−85 °C and using the system described by McLaughlin: a combination of the mild base $NaHCO_3$, cheap bidendate phosphine ligand 1,4-bis-(diphenylphosphino)butane (dppb) and $Pd(OAc)_2$ as a palladium source.[15] To perform a rapid solvent screen, **4** was first reacted with 3-methylbutylamine: *i*PrOH afforded both a cleaner reaction profile and higher conversion than dioxane or toluene (see Table 2, entry 1, footnote e) and was therefore selected for the parallel synthesis of substituted imidazo[4,5-c]pyridine-2-ones. Table 2 illustrates the scope for this chemistry. A variety of functionalized primary alkylamines underwent smooth coupling via their corresponding urea, even at relatively low temperature. Amine hydrochlorides were also tolerated, but required the use of the stronger base K_2CO_3 (entry 9, footnote d). In addition, volatile amines were first converted into intermediate urea at room temperature and then cyclized at 80−85 °C (entries 4 and 6). A limitation of the method, already mentioned is the previous series, is that sterically hindered alkylamine (entry 9) and electron-deficient aryl and heteroarylamine (entry 11) failed to deliver imidazo-[4,5-c]pyridine-2-ones **11i** and **k** in consistent yield.[27] Notably, we assume that the unfavorable electron-deficient character of the urea moiety, especially for anilines bearing electron-withdrawing groups and heteroarylamines, does prevent the key reductive elimination step of the palladium catalytic cycle, leading to extensive urea cleavage side-products.[28]

In summary, we developed an access to substituted imidazo[4,5-b]pyridine-2-one and relatively unexplored[18,29,30] imidazo[4,5-c]pyridine-2-one ring systems that is both facile an amenable to parallel synthesis. As a general trend and as anticipated, the average yield of this one-pot two-step process synthesis was found to be slightly lower in the latter series, but the described chemistry represents a viable method by which inexpensive starting materials can be rapidly elaborated in synthetically useful yields into more complex heterocycles of pharmaceutical relevance.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization and copies of ^1H NMR, ^{13}C NMR, and LCMS data for all characterized compounds highlighted in the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Email: franck.lach@astrazeneca.com; franck_lach@hotmail.com.

Notes

The authors declare no competing financial interest.

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