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Synthesis of Disubstituted Imidazo[4,5-*b*]pyridin-2-ones

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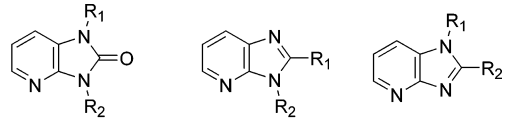
Abstract: Regioselective palladium-catalyzed amination of 2-chloro-3-iodopyridine followed by a subsequent palladium-catalyzed amination leads to 2,3-diaminopyridines. Treatment with triphosgene affords highly functionalized unsymmetrical imidazo[4,5-*b*]pyridin-2-ones in just three synthetic steps. A two-step synthesis of pseudosymmetrically disubstituted imidazo[4,5-*b*]pyridin-2-ones, 1,4-disubstituted pyrido[2,3-*b*]pyrazinediones, and 1,3-disubstituted thiadiazolo-[3,4-*b*]pyridin-2-ones is also described.

The 1,3-dihydro-imidazo[4,5-*b*]pyridin-2-one ring system (**1**) and related imidazo[4,5-*b*]pyridines (**2**, **3**) represent the core skeletons of a pharmaceutically important class of heterocyclic compounds possessing a range of biological activities.[1−5] Compounds within the imidazo-[4,5-*b*]pyridin-2-one class (**1**) have been shown by Merck to be nonsteroidal antiinflammatory and analgesic agents,[6] and by others to possess antidepressant,[7] antiphlogistic,[8] cardiotonic,[9] hypotensive and antiarrhythmic,[10] and antisecretory activity.[11] In addition, certain members of this class have post-emergence applications on broad-leaved plants.[12] Unsubstituted imidazo[4,5-*b*]pyridin-2-ones of type **1a** are typically prepared by the reaction of 2,3-diaminopyridines with a variety of acylating reagents[13,14] and often serve as precursors to imidazo[4,5-*b*]pyridines **2** and **3**. Preparation of 1,3-disubstituted imidazo[4,5-*b*]-pyridin-2-ones (**1b**) via the selective functionalization of either nitrogen atom of 2,3-diaminopyridine or **1a** is difficult and often requires protecting group stategies.[14] While access to substituted imidazo[4,5-*b*]pyridin-2-ones (**1b**) beginning with 2-chloro-3-nitropyridine has been described, the overall sequence is limited in scope, requires harsh reaction conditions leading to unstable intermediates, and provides the desired products in low overall yield.[7,8] To fully define biological profiles, strategies which give rapid access to highly functionalized imidazo[4,5-*b*]pyridin-2-ones not obtainable through current synthetic methods are important synthetic tools. In this Note, we wish to report a general synthesis of symmetrically and unsymmetrically 1,3-disubstituted imidazo[4,5-*b*]pyridin-2-ones **1b** through palladium-catalyzed cross coupling.



1a R_1=R_2 = H
1b R_1;R_2 = alkyl, aryl

2 **3**

Aminopyridine derivatives are important synthetic intermediates that have been used as acyl transfer reagents,[15] ligands in inorganic and organometallic chemistry,[16] and fluorescent dyes.[17] Aminopyridines have also received a considerable amount of attention due to their presence in biologically active pharmaceuticals and many natural products.[18] Recent advances by Buchwald,[19] Maes

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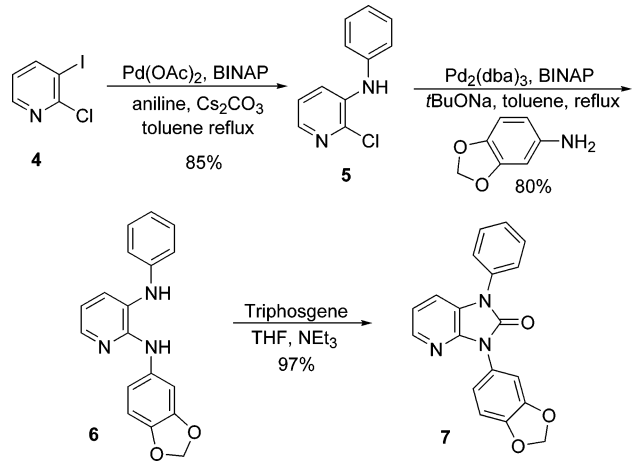
SCHEME 1



and Dommisse,[20] and Ji[21] have allowed for the chemo- and regioselective palladium-catalyzed aminations of dihalopyridines which avoids the harsh reaction conditions often associated with modest yielding aromatic substitutions of activated pyridine substrates.[22] Our approach to 1,3-disubstituted imidazo[4,5-*b*]pyridin-2-ones **1b** was inspired by these advances and is outlined in Scheme 1. Reaction of 2-chloro-3-iodopyridine **4**[23] (1.0 equiv) and aniline (0.95 equiv) in the presence of palladium acetate (3 mol %) and BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] (3 mol %) in refluxing toluene employing cesium carbonate (5 equiv)[20] and catalytic NEt_3[24] as the base gave aminopyridine **5** in 85% isolated yield. The molar ratio of **4** to aniline was found to be crucial for chemoselective substitution of the iodide. An excess of aniline often led to increased amounts of diaminopyridines (vida infra). The use of alkylamines did not affect the chemo- or regioselectivity of the reaction and afforded the monoaminated products in good yield (Table 1). Coupling of **5** with 3,4-(methylenedioxy)aniline in the presence of $Pd_2(dba)_3$ (1.5 mol %) and BINAP (4.5 mol %) employing sodium *tert*-butoxide[19] as the base gave diaminopyridine **6** in 80% isolated yield. Subsequent reaction with triphosgene/NEt_3 in tetrahydrofuran gave the unsymmetrically substituted 1,3-dihydro-3-[3,4-(methylenedioxy)phenyl]-1-phenyl-imidazo[4,5-*b*]pyridin-2-one **7** in near quantitative yield. The three-step reaction sequence proved to be general and afforded a diverse array of unsymmetrically substituted imidazo[4,5-*b*]-pyridin-2-ones bearing a variety of functional groups (Table 1). In most cases, the aminochloropyridines and diaminopyridine intermediates could be either isolated by direct crystallization from the crude reaction mixture

TABLE 1. Preparation of Unsymmetrical Imidazo[4,5-*b*]pyridine-2-ones

Entry	Aminochloropyridine	Diaminopyridine	Imidazo[4,5-*b*]pyridin-2-one
1	**8** 75%	**9** 63%	**10** 72%
2	**8**	**11** 67%	**12** 90%
3	**13** 74%	**14** 78%	**15** 65%
4	**16** 74%	**17** 87%	**18** 80%
5	**19** 84%	**20** 56%	**21** 88%
6	**22** 85%	**23** 95%	**24** 94%
7	**25** 83%	**26** 79%	**27**[7] 92%

(20) (a) Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemiére, G. L. F.; Dommisse, R. A. *Synlett* **2002**, 1995. (b) Jonckers, T. H. M.; Maes, B. U. W.; Lemiére, G. L. F.; Dommisse, R. A. *Tetrahedron* **2001**, *57*, 7027.

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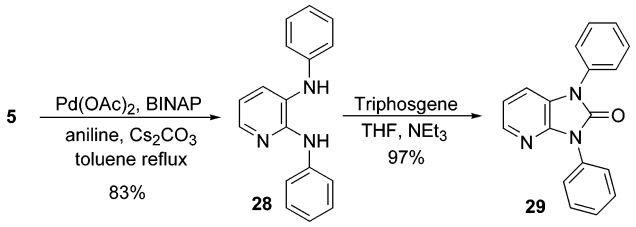
(23) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 4764. For an improved procedure describing the preparation of **4** see the Supporting Information.

(24) The use of triethylamine has been shown to provide significant rate enhancement in palladium-catalyzed aminations of aryl iodides when cesium carbonate is employed as the base. For a leading reference see: Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560.

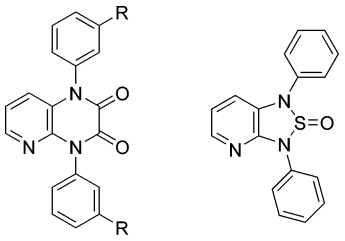
SCHEME 2



or were used directly in subsequent transformations without further purification.[25]

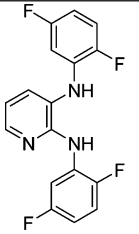
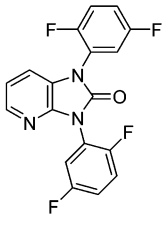
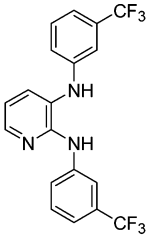
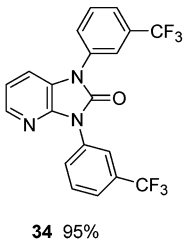
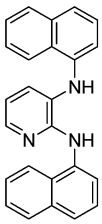
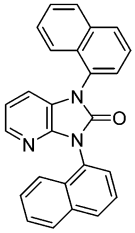
Having established a three-step protocol for the preparation of unsymmetrically substituted products, our attention turned to the preparation of pseudosymmetrically disubstituted imidazo[4,5-*b*]pyridin-2-ones. For example, reaction of **4** with aniline (2.5 equiv) in the presence of palladium acetate (3 mol %)/BINAP (3 mol %) in refluxing toluene with 5 equiv of Cs_2CO_3 as the base gave diaminopyridine **28** as the sole reaction product that could be crystallized from the crude reaction mixture in 83% isolated yield (Scheme 2). Cyclization of **28** with triphosgene/NEt_3 afforded **29** in 98% yield. In similar fashion, reaction of **4** with an excess of 2,5-difluoroaniline, 3-trifluoromethylaniline, and 1-naphthylamine yielded diaminopyridines **30**−**32** in high yield (Table 2). Cyclization with triphosgene gave the symmetrically disubstituted imidazo[4,5-*b*]pyridin-2-ones **33**−**35** in just two synthetic steps and excellent overall yield (Scheme 2).

Finally, access to other novel heterocyclic ring systems through reaction of **28** and **31** with oxalyl chloride or thionyl chloride was demonstrated. For example, reaction of **28** or **31** with oxalyl chloride afforded the 1,4-disubstituted pyrido[2,3-*b*]pyrazinediones **36** and **37** in 95% and 97% yields, respectively.[26] Reaction of **28** with thionyl chloride furnished 1,3-diphenylthiadiazolo[3,4-*b*]pyridin-2-one **38** in 89% yield.



In summary, a general, high-yielding method for the preparation of symmetrically and unsymmetrically 1,3-disubstituted-1,3-dihydro-imidazo[4,5-*b*]pyridin-2-ones through a sequential palladium-catalyzed coupling protocol has been demonstrated. The reaction conditions are mild and tolerant of a wide range of functional groups. This method allows for the preparation of novel heterocycles that are pharmaceutically interesting in two or three synthetic steps which are not accessible through current synthetic methods.

TABLE 2. Preparation of Symmetrical Imidazo[4,5-*b*]pyridin-2-ones

Entry	Diaminopyridine	Imidazo[4,5-*b*]pyridin-2-one
1	 **30** 89%	 **33** 81%
2	 **31** 89%	 **34** 95%
3	 **32** 80%	 **35** 84%

Supporting Information Available: Experimental procedures and compound characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) In certain cases where the reaction product was used crude, minor amounts of unreacted starting materials were present. The presence of these impurities had no detrimental affect on the outcome of subsequent transformations.

(26) Unsubstituted pyrido[2,3-*b*]pyrazinediones have been shown to possess antagonistic activity at the glycine site on the *N*-methyl-D-aspartate (NMDA) receptor which has been implicated in several neurodegenerative disorders such as Alzheimer's diesease, epilepsy, and stroke. For a leading reference, see: Cugola, A.; Donati, D.; Guarneri, M.; Micheli, F.; Missio, A.; Pecunioso, A.; Reggiani, A.; Tarzia, G.; Zanirato, V. *Bioorg., Med. Chem. Lett.* **1996**, *6*, 2749 and references therein.