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One-Pot Iodination of Hydroxypyridines

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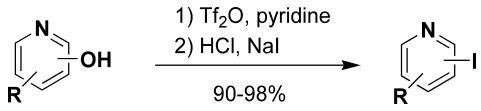
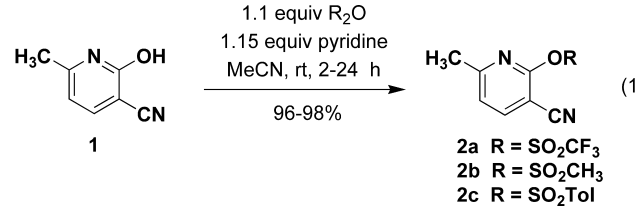


A one-pot, high-yielding iodination of hydroxypyridines and hydroxyquinolines is described. The iodination proceeds under mild conditions, and the products are obtained in high yield without the need for chromatographic purification. In addition, the iodination works on both 2- and 4-hydroxypyridines and -hydroxyquinolines.

Iodopyridines are important and valuable intermediates for the synthesis of both natural products and pharmaceutically important compounds. Iodopyridines often serve as convenient precursors for the generation of reactive organometallics such as organomagnesium and organolithium reagents.[1] Alternatively, iodopyridines and iodoquinolines participate in carbon−carbon, carbon−oxygen, and carbon−nitrogen bond formation via cross-coupling reactions such as the Suzuki−Miyaira,[2] Negishi,[3] and Buchwald−Hartwig[4] reactions. Iodopyridines also undergo substitution with (trifluoromethyl) copper reagents to give trifluoromethyl-substituted heterocycles.[5] While iodopyridines are versatile intermediates, their limited commercial availability requires that they be synthesized from readily available precursors. One of the most common methods for the preparation of iodopyridines involves lithiation of activated pyridines followed by quenching with iodine.[6] The major disadvantage of this protocol is that sensitive functional groups are not well tolerated leading to either competing side reactions or decomposition of either the starting materials or products.[7] Given the wealth of commercially available hydroxypyridines, we reasoned that suitable activation followed by displacment with iodide would serve as an attractive method for the construction of both 2- and 4-iodopyridines. Although several methods exist for the chlorination[8] and bromination[9] of hydroxypyridines, to the best of our knowledge a direct method for the related iodination does not exist. The most common method involves a two-step sequence involving chlorination followed by iodide displacement.[10] Given the superior reactivity of iodides versus chlorides and bromides, methods which provide rapid access to iodopyridines and tolerate a wide range of functional groups are important synthetic tools. Therefore, we set out to develop a mild, one-pot, high-yielding iodination of 2- and 4-hydroxypyridines. In this paper, we report a general synthesis of 2- and 4-iodopyridines and extend the methodology to the preparation of both iodoquinolines and iodoisoquinolines.

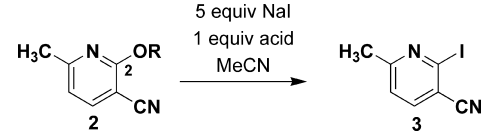
Our investigations began with hydroxypyridine **1** as shown in eq 1. We envisioned that conversion of **1** to a sulfonate ester would sufficiently activate the hydroxyl group for iodide displacement under mild conditions.[11] Sulfonate esters **2a**−**c** were prepared in excellent yield by reaction of **1** with the corresponding sulfonic anhydride (Ms_2O, Ts_2O, and Tf_2O) in the presence of pyridine.

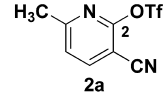
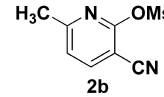


(1)

With **2a**,**b** in hand, efforts were focused on the iodination reaction as shown in Table 1. For example, reaction of **2a**,**b** with 5 equiv of sodium iodide in refluxing acetonitrile for up

TABLE 1. Optimization Studies for the Iodination of Pyridine 2



entry	substrate	acid	pka(H_2O)	time	conversion[a]
1		no acid		18 h	< 5%
		TFA	0	18 h	< 5%
		MsOH	-3	18 h	100%
		HCl	-8	10 min	100%
		TfOH	-14	10 min	100%
2		no acid			< 5%
		TfOH			< 5%
3		no acid			< 5%
		TfOH			< 5%

[a] Determined by HPLC analysis.

(1) For reviews, see: (a) Schlosser, M. In *Organometallics in Synthesis: A Manual*, 2nd ed.; Wiley: Chichester, 2002; pp 1−353. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. *Angew Chem., Int. Ed.* **2003**, *42*, 4302–4320. (c) Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *204*, 2667–2722.

(2) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

(3) Negishi, A. *Acc. Chem. Res.* **1982**, *15*, 340–348.

(4) For reviews, see: (a) Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. (b) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; pp 699−760.

(5) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 3277–330.

(6) For examples, see: (a) Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2002**, 3375–3383. (b) Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156–4158.

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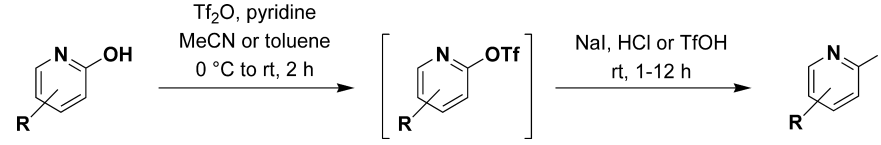
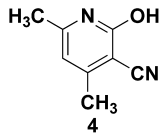
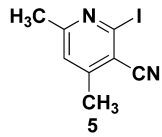
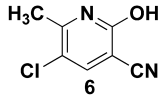
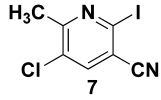
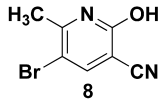
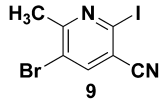
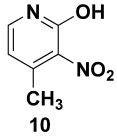
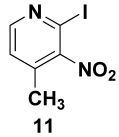
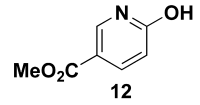
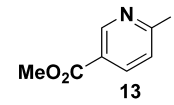
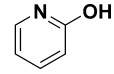
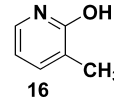
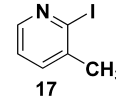
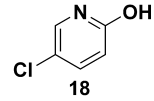
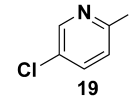
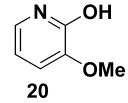
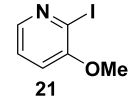
TABLE 2. One-Pot Iodination of 2-Hydroxypyridines to 2-Iodopyridines

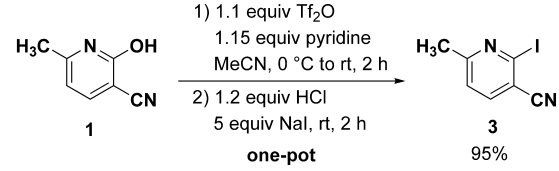


entry	substrate	product	yield (%)[a]
1	 **4**	 **5**	94[b]
2	 **6**	 **7**	95[b]
3	 **8**	 **9**	98[b]
4	 **10**	 **11**	92[c]
5	 **12**	 **13**	97[d]
6	 **14**	 **15**	90[d]
7	 **16**	 **17**	95[d]
8	 **18**	 **19**	94[d]
9	 **20**	 **21**	90[d]

[a] Isolated yields. [b] Reactions were carried out at room temperature using 1.1 equiv of concd HCl and 5 equiv of NaI in MeCN. [c] Reaction was carried out at room temperature using 1.1 equiv of HCl (2 M solution in Et_2O) and 5 equiv of NaI in MeCN. [d] Reactions were carried out at room temperature using 1.1 equiv of HCl (2 M solution in Et_2O) and 5 equiv of NaI in toluene.

to 24 h only afforded trace amounts (<5%) of the desired iodide **3**. In each case, the starting material was recovered virtually unchanged, despite the presence of the activating cyano group present in the 3-position of the ring. In an attempt to further activate the pyridine ring toward nucleophilic displacement, it was decided to screen the effect of Brønsted acids in the reaction of **2a** with sodium iodide.[12] As shown in Table 1, it was discovered that concd HCl, MsOH, and TfOH led to **3** with complete conversion when **2** was treated with 1 equiv of acid in the presence of 5 equiv of NaI at room temperature in acetonitrile. Interestingly, activation of **2a** with TFA resulted in no detectable reaction, suggesting that the pK_a of the acid employed for activation of the pyridine was crucial for success.[13] We also observed that 1 equiv of acid (HCl, MsOH, or TfOH) was needed for complete conversion. In the presence of less than 1 equiv, conversion corresponded to the amount of acid added.[14] This confirmed that protonation of the pyridine nitrogen was in fact activating the C-2 carbon of **2a** for subsequent iodide addition. Unfortunately, mesylate **2b** and tosylate **2c** were completely unreactive under these conditions.

Having identified conditions for the iodination of sulfonate ester **2a**, we investigated the possibility of developing a one-pot procedure for the direct conversion of **1** to **3** (eq 2). It was discovered that treatment of crude triflate **2a** with 5 equiv of sodium iodide and 1.1 equiv of concd HCl afforded quantitative conversion to **3** for the one-pot process. The workup of the reaction involved a simple pH adjustment with 10 M NaOH, extraction into toluene, and solvent removal to give **3** in 95% isolated yield and excellent purity[15] (>98%) avoiding the need for further purification by chromatography.[16]



(2)

The scope and generality of the one-pot iodination procedure was next examined. As shown in Table 2, the one-pot iodination

(7) For a review, see: Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161–1172.

(8) See, for example: Sugimoto, O.; Mori, M.; Tanji, K. *Tetrahedron Lett.* **1999**, *40*, 7477–7478.

(9) See, for example: (a) Kato, Y.; Okada, S.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4849–4851. (b) Katritzky, A. *Org. Prep. Proced. Int.* **1994**, *26*, 436–444.

(10) See, for example: Schlosser, M.; Cottet, F. *Eur. J. Org. Chem.* **2002**, 4181–4184.

(11) For examples of the two-step transformation of phenols to aryl iodides via sulfonate esters, see: (a) Wang, Z.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, 213–216. (b) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094–6100. (c) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Wiggins, J. M. *J. Med. Chem.* **1990**, *33*, 758–765.

(12) For examples of Brønsted acid activation of pyridines, see: Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, F. V., McKillop, A., Eds.; Pergamon Press: New York, 1996; Vol. 5, pp 37−86.

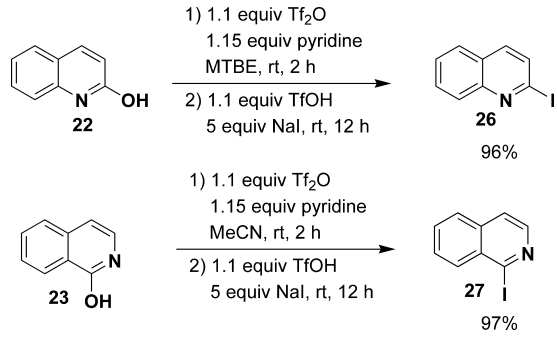
(13) The pK_a of **2a** was calculated to be−4.7 (pK_a calculation program from Advanced Chemistry Development, Inc., Version 11.01).

(14) With catalytic acid, the iodination could be pushed to completion with increased temperature (reflux) and reaction time (>7 days).

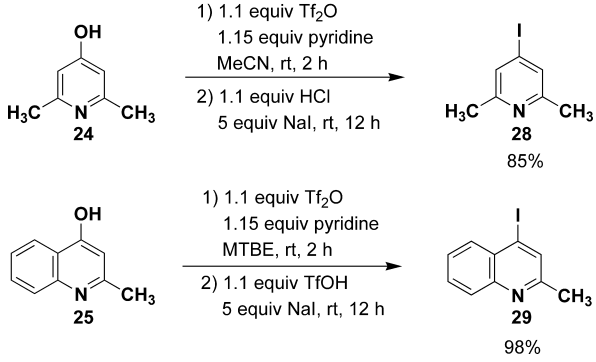
(15) Purity determined by HPLC and NMR (^{1}H and ^{13}C) analysis.

(16) Attempts to conduct the one-pot iodination without pyridine were unsuccessful due to incomplete triflate (**2a**) formation.

SCHEME 1. Iodination of Hydroxyquinolines



SCHEME 2. Iodination of 4-Hydroxypyridines and 4-Hydroxyquinolines

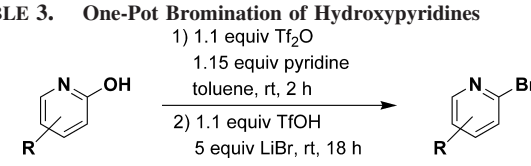


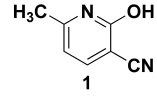
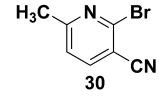
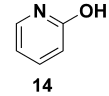
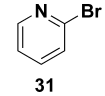
of several electronically and structurally diverse hydroxypyridines afforded the desired iodides in excellent yields. In general, pyridines bearing electron-deficient groups (entries 1−5) reacted with sodium iodide within 1 h and gave the iodide products in high yield. On the other hand, reaction of substrates lacking electron-withdrawing substituents (entries 6−9) proved sluggish. For example, reaction of the intermediate triflate of pyridine **14** with sodium iodide in the presence of concd HCl resulted in the formation of **15** in only 15% yield after 12 h at room temperature. The mass balance of the reaction was identified as remaining triflate and **14**. Under the reaction conditions, hydrolysis of the triflate intermediate back to hydroxypyridine **14** was competitive with iodide displacemnt. It was speculated that water from the conc. HCl was leading to the formation of **14** and in order to circumvent this competitive process, modified reaction conditions were investigated. It was discovered that replacing acetonitrile with toluene and using anhydrous acid (anhydrous HCl or TfOH) afforded **15** in 90% yield. In a similar fashion, reaction of **16**, **18**, and **20** provided access to iodides **17**, **19**, and **21** in 95%, 94%, and 90% yields, respectively.

Next, we set out to explore the reactivity of hydroxyquinolines. As shown in Scheme 1, 2-hydroxyquinoline **22** and isoquinoline **23** afforded the desired iodides **26** and **27** in 96% and 97% yield. Interestingly, we noticed that HCl afforded a mixture of the 2-chloro and 2-iodo products which was not seen in the related hydroxypyridine cases. However, we found that replacement of HCl with TfOH completely eliminated the 2-chloroquinoline byproduct.

As shown in Scheme 2, we were also interested in extending this methodology to 4-hyrdoxypyridines. Historically, the preparation of 4-iodopyridines has been fairly challenging, often requiring several synthetic steps.[11] However, utilization of our one-pot iodination procedure on pyridone **24** afforded iodide **28** in 85% yield. As expected, we were able to extend this protocol to 4-hydroxyquinolines as demonstrated by the preparation of iodide **29** in 98% yield. Unfortunately, attempts to extend this methodology to unhindered pyridones such as 4-hydroxypyridine were unsuccessful due to competing *N*-triflation.[17]

TABLE 3. One-Pot Bromination of Hydroxypyridines



entry	substrate	product	yield(%)[a]	literature yield(%)[b]
1	 1	 30	98	75
2	 14	 31	90	75

[a] Isolated yields. [b] See ref.[9a] Reactions were carried out using TBAB and P_2O_5 in refluxing toluene (entry 1) or refluxing 1,2-Cl_2Ph (entry 2).

Lastly, we explored the possibility of utilizing a similar procedure for the bromination of hydroxypyridines. We envisioned that simply replacing sodium iodide with lithium bromide in our standard protocol would provide an efficient bromination procedure. Although direct methods exist for the bromination of hydroxypyridines,[9] we felt our methodology would provide a mild and high-yielding alternative. As shown in Table 3, we were pleased to find that our modified conditions efficiently converted pyridones **1** and **14** to the desired bromides **30** and **31** in 98% and 90% yield. This proved to be a substantial improvement over current methodologies with regard to yield (90−98% versus 75%) and reaction conditions (room temperature versus 100−180 °C).[9a] It should also be mentioned that both TfOH and HCl efficiently promoted the bromination; however, trace amounts of 2-chloro products were seen in HCl-promoted reactions.

In conclusion, we have developed an efficient one-pot procedure for the iodination of hydroxypyridines and hydroxyquinolines. The iodination proceeds under mild conditions, and the products are obtained in high yield without the need for chromatographic purification. The reaction is also amenable to large scale applications as exemplified in the Experimental Section. In addition, the iodination works on both 2- and 4-hydroxypyridines and hydroxyquinolines.

Experimental Section

Representative Procedure: Preparation of 4-Chloro-3-cyano-2-iodo-6-methylpyridine (7). A 100-L, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, 5-L addition funnel, thermocouple, and mechanical stirrer was charged with pyridine (2.48 L, 30.7 mol) and 18 L of MeCN. Pyridone **6** (4.5 kg, 26.7 mol) was added in one portion, and the reaction mixture (brown slurry) was cooled at 5 °C. Tf_2O (4.96 L, 29.4 mol) was then added via addition funnel over 1.5 h keeping the internal temperature

(17) Giudice, M. R.; Settimj, G. *Tetrahedron* **1984**, *40*, 4067–4080.

below 25 °C. After complete addition, the reaction mixture (black solution) was stirred at 20−25 °C for 30 min and then charged with NaI in five portions over 15 min keeping the internal temperature below 40 °C. HCl was then added via addition funnel over 15 min keeping the internal temperature below 40 °C. The reaction mixture (orange slurry) was stirred for 1 h and then cooled to 10 °C. The reaction mixture was diluted with 22.5 L of water and slowly quenched with 10 M NaOH to reach a pH of ca. 10. The resulting brown solution was transferred to a 100-L extractor with the aid of toluene (45 L, 10 vol). The resulting organic layer was separated and washed with 5% sodium thiosulfate (12 L), 1 M NaOH (12 L), and 20 L of water. The organic layer was dried (azeotroped with 50 L of toluene) and concentrated to give 7.06 kg (95% yield) of yellow crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1 H), 2.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 140.5, 131.5, 118.4, 116.7, 116.6, 23.1. Anal. Calcd for $C_7H_4N_2ClI$: C, 30.19; H, 1.45; N, 10.06. Found: C, 30.47; H, 1.14; N, 9.90.

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Supporting Information Available: Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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