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# Regioselective Synthesis of 3-(2-Hydroxyaryl)pyridines via Arynes and Pyridine *N*-Oxides

Cristiano Raminelli, Zhijian Liu, and Richard C. Larock*

*Department of Chemistry, Iowa State University, Ames, Iowa 50011*

*larock@iastate.edu*

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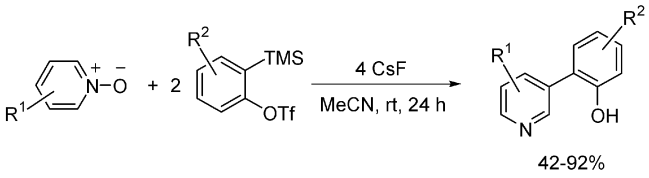
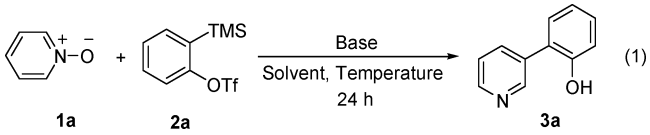



A variety of substituted 3-(2-hydroxyphenyl)pyridines have been prepared regioselectively by a transition-metal-free, mild, one-step route, which involves the reaction of pyridine *N*-oxides with silylaryl triflates in the presence of CsF in acetonitrile at room temperature. These reactions proceed in good yields through what appears to be a series of rearrangements.

Heterocycles are considered a very important class of organic compounds because of their wide application in medicine, agriculture, and technology.[1] Among nitrogen heterocycles, alkaloids stand out as biologically active compounds presenting a broad spectrum of activities.[1,2] Accordingly, synthetic methods for the construction of alkaloids are particularly valuable.

3-Arylpyridines are a particularly interesting class of alkaloids, which can be prepared via intermolecular radical addition using pyridine derivatives.[3] However, transition-metal-catalyzed cross-coupling reactions have more commonly been chosen to prepare such heterobiaryls.[4] Some time ago, Abramovitch reported that benzyne reacts with pyridine *N*-oxides to afford mixtures of 3- and 2-(2-hydroxyphenyl)pyridines in low yields.[5] Several approaches to the generation of benzyne were explored, and a mechanism was proposed involving a series of rearrangements based on prior literature (see the later mechanistic discussion). Considering the importance of such pyridine derivatives, a method to generate only one single isomer, namely, 3-(2-hydroxyphenyl)pyridines, in high yields in a single step would be highly desirable.

**TABLE 1. Optimization of the Synthesis of 3-(2-Hydroxyphenyl)Pyridine (3a) (Eq 1)[a]**




1a 2a 3a

| entry | 2a (equiv) | base (equiv) | solvent | temp (°C) | % isolated yield |
|---|---|---|---|---|---|
| 1 | 1.5 | CsF (3) | MeCN | rt | 74 |
| 2 | 1.5 | CsF (3) | MeCN | 80 | 65 |
| 3 | 2 | CsF (3) | MeCN | rt | 78 |
| **4** | **2** | **CsF (4)** | **MeCN** | **rt** | **88** |
| 5 | 2 | | MeCN | rt | 0 |
| 6 | 1.5 | $Bu_4NF$ (1.8) | THF | rt | 64 |

[a] Reaction conditions: 0.2 mmol of pyridine *N*-oxide (**1a**), the indicated amount of benzyne precursor **2a**, the indicated amount of base, and 3 mL of solvent were stirred at the temperature shown for 24 h.

In view of our recent success using arynes prepared from *o*-(trimethylsilyl)aryl triflates and CsF in organic synthesis,[6] we decided to examine their reaction with pyridine *N*-oxide because this approach generates benzyne under very mild reaction conditions.[7] Allowing pyridine *N*-oxide (**1a**) to react with 2 equiv of *o*-(trimethylsilyl)phenyl triflate (**2a**) and 3 equiv of CsF in MeCN at room temperature, we obtained 3-(2-hydroxyphenyl)pyridine (**3a**) in a 74% yield as a single isomer (Table 1, entry 1). The formation of regioisomers was not observed. In an attempt to improve the yield, subsequent work focused on optimization of these reaction conditions (Table 1). When the transformation was performed at 80 °C, compound **3a** was obtained in a lower yield (65%) (entry 2) because of the formation of byproducts. No attempts were made to identify the byproducts. By using 2 equiv of benzyne precursor **2a** at room temperature, we isolated **3a** in a slightly better yield of 78% (entry 3). Treatment of pyridine *N*-oxide (**1a**) with 2 equiv of benzyne precursor **2a** and 4 equiv of CsF in acetonitrile at room temperature gave 3-(2-hydroxyphenyl)pyridine (**3a**) in an 88% yield (entry 4). As can be seen in Table 1, entry 5, the heterobiaryl **3a** was not obtained and the starting materials **1a** and **2a** were recovered when the reaction was carried out in the absence of CsF. This experiment shows that the success of our reaction depends dramatically on the presence of fluoride. To explore the effect of the fluoride source on the reaction, tetrabutylammonium fluoride (TBAF) was added to a mixture of pyridine *N*-oxide (**1a**) and silylaryl triflate **2a** in THF at room temperature. After 24 h, heterobiaryl **3a** was obtained in a 64% isolated yield (entry 6). No further attempts were made to optimize this TBAF procedure.

(1) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. In *Heterocycles in Life and Society − An Introduction to Heterocyclic Chemsitry and Biochemistry and the Role of Heterocycles in Science, Technology, Medicine and Agriculture*; John Wiley & Sons: Chichester, England, 1997.

(2) *Foye's Principles of Medicinal Chemistry*; Williams, D. A., Lemke, T. L., Eds.; Lippincott Williams & Wilkins: Baltimore, 2002.

(3) (a) McLoughlin, P. T. F.; Clyne, M. A.; Aldabbagh, F. *Tetrahedron* **2004**, *60*, 8065. (b) Núñes, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217. (c) Crich, D.; Patel, M. *Heterocycles* **2004**, *64*, 499. (d) Martínez-Barrasa, V.; Viedma, A. G.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933.

(4) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang P. J., Eds.; Willey-VCH: Weinheim, 1998. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Meijere, A., Diederich, F., Eds.; Willey-VCH: Weinheim, 2004; Vols. 1 and 2. (c) Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835. (d) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(5) Abramovitch, R. A.; Shinkai, I. *J. Am. Chem. Soc.* **1974**, *96*, 5265.

(6) (a) Liu, Z.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 15716. (b) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (c) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273. (d) Zhang, X.; Larock, R. C. *Org. Lett.* **2005**, *7*, 3973. (e) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3937. (f) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99−102. (g) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673.

(7) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

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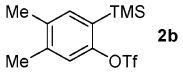
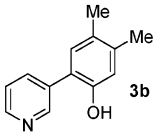
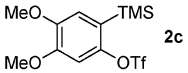
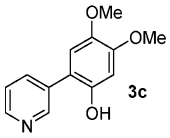
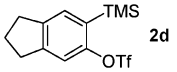
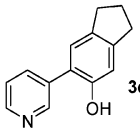
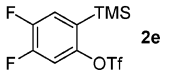
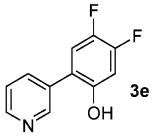
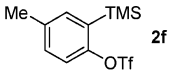
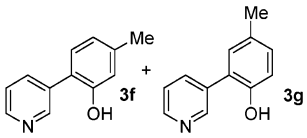
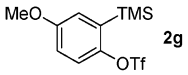
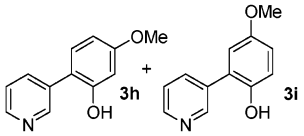
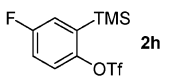
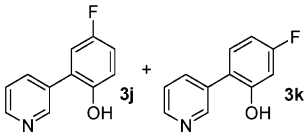
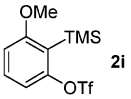
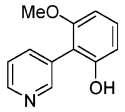
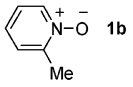
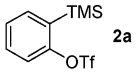
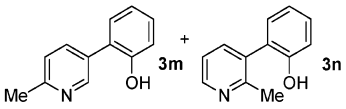
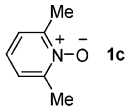
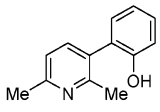
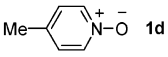
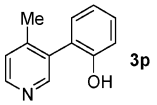
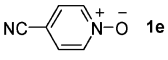
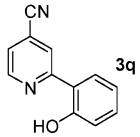
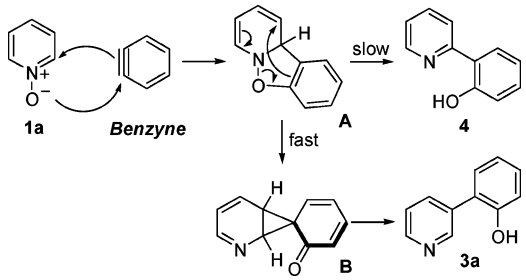
**TABLE 2. Synthesis of 3-(2-Hydroxyphenyl)pyridines by the Reaction of Pyridine *N*-Oxides and Aryne Precursors in the Presence of CsF[a]**

| entry | pyridine *N*-oxide | benzyne precursor | product(s) | % isolated yield |
|---|---|---|---|---|
| 1 |  **1a** |  **2b** |  **3b** | 84 |
| 2 | **1a** |  **2c** |  **3c** | 84 |
| 3 | **1a** |  **2d** |  **3d** | 90 |
| 4 | **1a** |  **2e** |  **3e** | 92 |
| 5 | **1a** |  **2f** |  **3f** + **3g** | 77 (1.4:1)[b] |
| 6 | **1a** |  **2g** |  **3h** + **3i** | 75 (1:1)[b] |
| 7 | **1a** |  **2h** |  **3j** + **3k** | 83 (2:1)[b] |
| 8 | **1a** |  **2i** |  **3l** | 82 |
| 9 |  **1b** |  **2a** |  **3m** + **3n** | 81 (6.7:1)[b] |
| 10 |  **1c** | **2a** |  **3o** | 78 |
| 11 |  **1d** | **2a** |  **3p** | 52 |
| 12 |  **1e** | **2a** |  **3q** | 42 |

[a] Reaction conditions: 0.2 mmol of pyridine *N*-oxide **1**, 0.4 mmol of benzyne precursor **2**, 0.8 mmol of CsF, and 3 mL of MeCN were stirred at room temperature for 24 h. [b] The ratio was determined by $^1$H NMR spectroscopy.

Employing the optimal conditions shown in Table 1, entry 4, we examined the scope of this process using various aryne precursors and aromatic *N*-oxides (Table 2). The reaction between pyridine *N*-oxide (**1a**) and the electron-rich benzyne precursor **2b** gave the biaryl **3b** in an 84% isolated yield (Table 2, entry 1). The same yield was obtained for biaryl **3c**, when the reaction was carried out using the silylaryl triflate **2c** bearing two methoxy groups (entry 2). By performing the reaction between **1a** and the benzyne precursor **2d** derived from 5-indanol, we prepared compound **3d** in a 90% yield (entry 3).

**SCHEME 1**



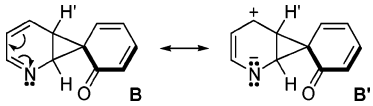

When the electron-poor benzyne precursor **2e** was allowed to react with pyridine *N*-oxide (**1a**), compound **3e** was isolated in a 92% yield. The high yields indicate that both electron-rich and electron-poor arynes can be successfully utilized in this chemistry.

To better understand the regioselectivity of the reaction when unsymmetrical arynes are employed, pyridine *N*-oxide (**1a**) was allowed to react with 4-methyl-2-(trimethylsilyl)phenyl triflate (**2f**), using our optimized conditions. A mixture of two isomers **3f** and **3g** was obtained in a 1.4:1 ratio in a total yield of 77% (Table 2, entry 5). When the reaction was carried out using the 4-methoxy silylaryl triflate **2g**, a 1:1 mixture of heterobiaryls **3h** and **3i** was isolated in a 75% yield (entry 6). For entries 5 and 6, only a slight or no effect of the electron-donating groups present in the aryne was observed on the ratio of the isomers. On the other hand, when the reaction between pyridine *N*-oxide (**1a**) and the 4-fluoro aryne precursor **2h** was performed, this electron-withdrawing group produced a 2:1 mixture of isomers **3j** and **3k** in an 83% yield (entry 7). In this case, the major product was the heterobiaryl **3j** with the fluoro substituent in the 5-position. When pyridine *N*-oxide (**1a**) was subjected to the reaction with the 3-methoxy aryne precursor **2i**, the product of attack of the oxygen at the less electron-rich position of the benzyne was formed as the only regioisomer in an 82% isolated yield (entry 8).

Turning our attention to the effect of substituted *N*-oxides on the reaction course, we treated 2-picoline *N*-oxide (**1b**) with benzyne precursor **2a** to give a 6.7:1 mixture of two regioisomers **3m** and **3n** in an overall 81% yield (entry 9). Presumably, the regioselectivity for this transformation is governed by the steric bulk of the methyl group present in substrate **1b**. When the coupling between 2,6-lutidine *N*-oxide (**1c**) and silylaryl triflate **2a** was performed, the desired product **3o** was still isolated in an excellent 78% yield (entry 10). A moderate yield of 52% was obtained when 4-picoline *N*-oxide (**1d**) was treated with benzyne precursor **2a**. In this case, the electron-donating effect of the methyl group at the 4-position of the pyridine ring may have disfavored the sequence of rearrangements necessary to form the biaryl product (see the later mechanistic discussion). Interestingly, the treatment of 4-cyanopyridine *N*-oxide (**1e**) with silylaryl triflate **2a** gave only the regioisomer **3q** in a respectable 42% yield (entry 12).

Compounds **3a**−**p** are presumably obtained through the proposed mechanism illustrated in Scheme 1.[5] To explain the formation of the observed products, it is necessary to consider the resonance structures B and B′ shown in Scheme 2. Through the positive charge present in B′, one would expect that hydrogen H′ is more acidic than H. Thus, the carbonyl group present in the intermediate B attacks the hydrogen H′, instead of H, affording 3-substituted pyridines. On the other hand, the

**SCHEME 2**




resonance structure B′ (Scheme 2) is unfavorable when the cyano-substituted amine oxide **1e** is employed and compound **3q** is formed instead. For this reaction, the hydrogen next to the nitrogen atom is more acidic, and formation of a 2-substituted pyridine takes place.

The structures of the biaryls have been assigned on the basis of a variety of spectroscopic techniques. The structure of compound **3a** was assigned according to its HRMS, IR, $^1$H, and $^{13}$C NMR spectra and confirmed afterward by X-ray analysis. The structures for compounds **3b**−**p** were assigned by carefully comparing their spectral data with the spectral data obtained for **3a**. The structure of compound **3q** was assigned on the basis of HRMS, IR, $^1$H, and $^{13}$C NMR spectra and confirmed by X-ray analysis.

In summary, a simple, regioselective coupling reaction between pyridine *N*-oxides and arynes has been developed, which provides hydroxyphenylpyridines in excellent yields. Through this transition-metal-free process, a carbon−carbon bond is formed presumably by means of a series of rearrangements. The synthetic method described in this manuscript provides an alternative preparation of aryl-substituted pyridines and should find use in the construction of molecules with interesting biological properties and applications in material science.

## Experimental Section

To a vial (20 mL) were added the appropriate pyridine *N*-oxide **1a**−**e** (0.2 mmol), the appropriate silylaryl triflate **2a**−**i** (0.4 mmol), acetonitrile (3 mL), and CsF (0.1215 g, 0.8 mmol). The vial was sealed using a cap, and the mixture was stirred for 24 h at room temperature. Afterward, brine (20 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was impregnated with silica gel and purified by column chromatography on silica gel using 2:1 hexane/acetone as eluent unless otherwise indicated, affording the desired products **3a**−**q**.

**3-(2-Hydroxyphenyl)pyridine (3a):**[7] yield 30.0 mg (88%); light yellow solid; mp 173−175 °C (lit.[7] mp 171−172 °C); $^1$H NMR (DMSO-$d_6$) $\delta$ 9.77 (s, 1H), 8.75 (d, $J$ = 1.5 Hz, 1H), 8.50 (dd, $J$ = 4.8, 1.5 Hz, 1H), 7.95 (dt, $J$ = 7.8, 1.9 Hz, 1H), 7.43 (ddd, $J$ = 7.9, 4.8, 0.7 Hz, 1H), 7.32 (dd, $J$ = 7.5, 1.5 Hz, 1H), 7.22 (td, $J$ = 7.6, 1.5 Hz, 1H), 6.99 (dd, $J$ = 8.2, 0.7 Hz, 1H), 6.92 (td, $J$ = 7.5, 1.2 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 154.5, 149.5, 147.5, 136.3, 134.1, 130.3, 129.3, 124.3, 123.1, 119.6, 116.1; IR (KBr, cm$^{-1}$) 3445, 3039−2426, 1450, 1394, 1267, 758; HRMS calcd for $C_{11}H_9NO$ 171.0684, found 171.0687.

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**Supporting Information Available:** General methods, experimental procedures, characterization data, as well as copies of $^1$H and $^{13}$C NMR spectra for compounds **3a**−**q** and crystallographic information files (CIF) are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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