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A Concise Synthesis of All Four Possible Benzo[4,5]furopyridines via Palladium-Mediated Reactions

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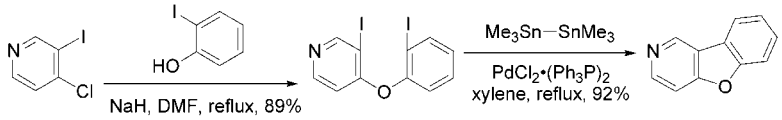
ABSTRACT

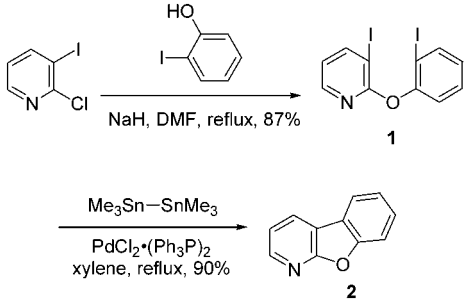


By taking advantage of the α- and γ-activation of chloropyridines as well as palladium-mediated reactions, all four possible benzo[4,5]-furopyridine tricyclic heterocycles, benzo[4,5]furo[2,3-*b*]pyridine, benzo[4,5]furo[2,3-*c*]pyridine, benzo[4,5]furo[3,2-*c*]pyridine, and benzo[4,5]-furo[3,2-*b*]pyridine, are efficiently synthesized from 2-chloro-3-iodopyridine, 3-chloro-4-stannylpyridine, 4-chloro-3-iodopyridine, and 2-chloro-3-hydroxypyridine, respectively.

The advent of palladium chemistry has exerted a profound impact on the synthesis of heterocycles.[1] During the course of our research, we investigated the utility of palladium chemistry in the synthesis of benzo[4,5]furopyridines. These heterocycles often display important biological activities[2] and are also useful biosteres for dibenzofuran. Ames and Opalko synthesized benzo[4,5]furo[2,3-*b*]pyridine (**2**) in 10% yield employing an intramolecular Heck reaction of 2-(2-bromophenoxy)pyridine.[3] Abramovitch et al. also reported the synthesis of **2** via a six-step sequence from an *N*-(aryloxy)-pyridinium salt.[4] Furthermore, Lai and co-workers adapted an S_NAr cyclization strategy to prepare benzo[4,5]furo[2,3-*c*]pyridine (**5**) in 63% yield from 3-fluoro-4-(2-methoxyphenyl)-pyridine.[5] Herein we report our efforts in accomplishing an efficient synthesis of benzo[4,5]furo[2,3-*b*]-pyridine (**2**), benzo[4,5]furo[2,3-*c*]pyridine (**5**), benzo[4,5]-furo[3,2-*c*]pyridine (**7**), and benzo[4,5]furo[3,2-*b*]pyridine (**10**) via palladium-mediated reactions[6] while taking advantage of the α- and γ-activation of chloropyridines.

The synthesis of benzo[4,5]furo[2,3-*b*]pyridine (**2**) was readily achieved. 2-Chloro-3-iodopyridine[7] was prepared in 65% yield by lithiation of 2-chloropyridine followed by treatment with I_2. Because of the α-activation, a result of the inductive effect of the N-atom on the pyridine ring, chemoselective S_NAr displacement of the 2-chloro substituent with a nucleophile was expected to proceed smoothly. As illustrated in Scheme 1, refluxing 2-chloro-3-iodopyridine with sodium *o*-iodophenoxide, derived from exposing iodophenol to NaH, in DMF gave heterobiaryl ether **1** in 87%

Scheme 1. Synthesis of Benzo[4,5]furo[2,3-*b*]pyridine (**2**)



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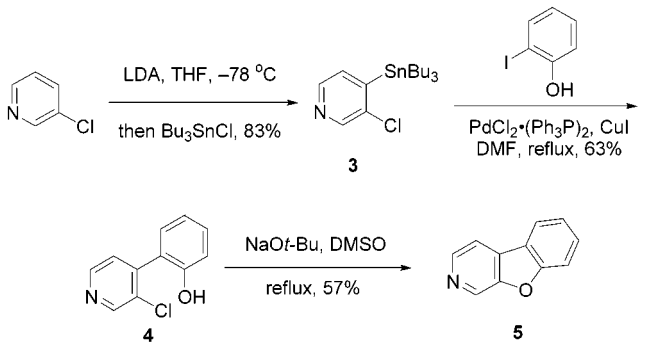
yield. Subsequent Stille−Kelly reaction[8] of ether **1** using hexamethylditin in the presence of catalytic $PdCl_2$•$(Ph_3P)_2$ in refluxing xylene furnished benzo[4,5]furo[2,3-*b*]pyridine (**2**)[9] in 90% yield.

The synthesis of benzo[4,5]furo[2,3-*c*]pyridine (**5**) began with preparation of stannane **3** (Scheme 2). Applying

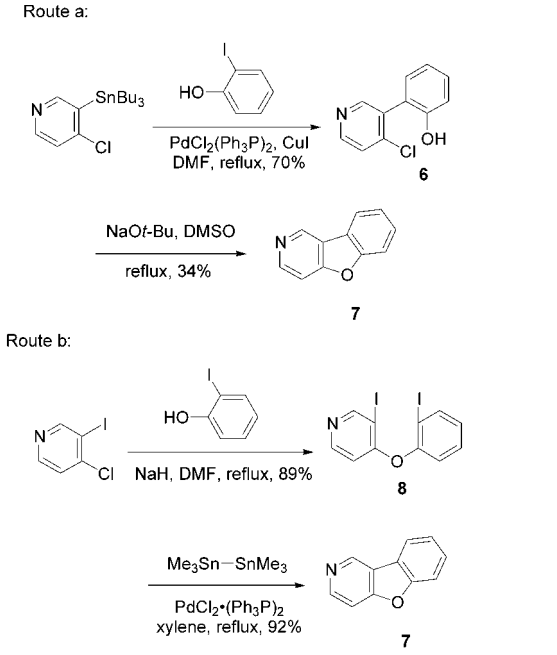
Scheme 2. Synthesis of Benzo[4,5]furo[2,3-*c*]pyridine (**5**)



Gribble's *ortho*-lithiation tactic,[10] 3-chloropyridine was deprotonated at the most acidic position, C(4). Subsequent exposure of the resulting 3-chloro-4-lithiopyridine to tributyltin chloride gave 3-chloro-4-tributylstannylpyridine (**3**). The Stille coupling of stannane **3** with *o*-iodophenol in the presence of catalytic $PdCl_2$•$(Ph_3P)_2$ and CuI in refluxing DMF then produced heterobiaryl **4** in 63% yield. Only small amounts of **4** were observed when the reaction was carried out using THF, dioxane, or toluene as the solvent. Finally, the intramolecular S_NAr etherification was accomplished by treatment of biaryl **4** with NaO*t*-Bu in refluxing DMSO to afford benzo[4,5]furo[2,3-*c*]pyridine (**5**)[11] in 57% yield.

The Stille coupling of 4-chloro-3-tributylstannylpyridine and *o*-iodophenol under the same conditions for the transformation **3** → **4** led to two products in 70% combined yield. The major product was the desired adduct **6**, along with the cyclized product, benzo[4,5]furo[3,2-*c*]pyridine (**7**) as a minor product (Scheme 3, route a). The discrepancy of

Scheme 3. Synthesis of Benzo[4,5]furo[3,2-*c*]pyridine (**7**)



reactivities between heterobiaryls **4** and **6** relies upon the fact that the 4-chloro substituent on **6** is more activated as a result of γ-activation than the 3-chloro substituent on **4**. Subjecting the reaction mixture to NaO*t*-Bu in refluxing DMSO furnished benzo[4,5]furo[3,2-*c*]pyridine (**7**)[12] in only 34% yield. As a consequence, an alternative route to **7** was pursued.

4-Chloro-3-iodopyridine was prepared in 65−80% yield by *ortho*-lithiation of 4-chloropyridine followed by treatment with iodine (Scheme 3, route b).[13] Taking advantage of the γ-activation, also a consequence of the inductive effect of the N-atom on the pyridine ring, regioselective S_NAr displacement of the 4-chloro substituent was accomplished by refluxing 4-chloro-3- iodopyridine with sodium *o*-iodophenoxide in DMF to construct heterobiaryl ether **8** in

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(9) **Data for 2**: mp = 68−69 °C; R_f = 0.47 (1:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$) δ 8.43 (dd, J = 1.8, 5.1 Hz, 1H), 8.24 (dd, J = 1.7, 7.6 Hz, 1H), 7.93 (m, 1H), 7.61 (m, 1H), 7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 163.4, 154.7, 146.6, 129.8, 128.5, 123.6, 122.6, 121.5, 119.3, 117.1, 112.4; MS (ACPI) *m*/*z* 170.1 ($M^+ + 1$). Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 77.96; H, 4.22; N, 8.19.
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(11) **Data for 5**: mp = 93−95 °C; R_f = 0.28 (1:1 hex/EtOAc); IR (KBr, cm^{-1}) 3042, 1626, 1577, 1450, 1421, 1182, 1016, 823, 750, 728; ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.57 (d, J = 6.0 Hz, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.60 (m, 2H), 7.60 (t, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) 156.8, 152.9, 143.0, 134.4, 130.9, 129.8, 123.4, 122.3, 122.0, 115.0, 122.4; MS (ACPI) *m*/*z* 169.9 ($M^+ + 1$). Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 77.92; H, 4.26; N, 8.16.
(12) **Data for 7**: mp = 72−74 °C.; R_f = 0.20 (1:1 hex/EtOAc); ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.2, 156.1, 147.7, 143.8, 128.5, 124.1, 121.8, 121.3, 107.1; MS (ACPI) *m*/*z* 170.0 ($M^+ + 1$). Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.02; H, 4.13; N, 8.17.
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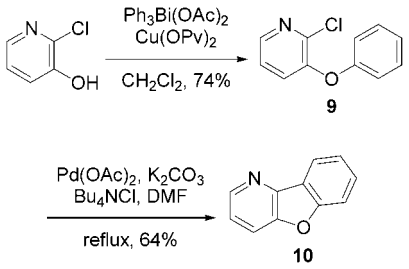
89% yield. Employing the Stille−Kelly conditions,[8] di-iodide **8** was treated with hexamethylditin in the presence of catalytic $PdCl_2$•$(Ph_3P)_2$ in refluxing xylene to give benzo[4,5]furo[3,2-*c*]pyridine (**7**) in 92% yield.

The assembly of benzo[4,5]furo[3,2-*b*]pyridine (**10**) proved to be a challenging enterprise. Several initial routes that applied the Stille coupling strategy were either too lengthy or met with failure. An "intramolecular aryl-Heck" reaction[15] eventually allowed us to successfully prepare tricycle **10**. As depicted in Scheme 4, commercially available 2-chloro-3-hydroxypyridine was phenylated using triphenylbismuth(V) diacetate in the presence of Cu(II) pivaloate to provide diaryl ether **9** in 74% yield.[14] Subsequently, the heteroaryl-aryl C−C bond connection was achieved using an intramolecular aryl-Heck reaction under Jeffery's ligand-free conditions.[16] The desired benzo[4,5]furo[3,2-*b*]pyridine (**10**)[17] was isolated in 64% yield.

Scheme 4. Synthesis of Benzo[4,5]furo[3,2-*b*]pyridine (**10**)



In conclusion, by taking advantage of the α- and γ-activation of chloropyridines and utilizing palladium-mediated reactions, we have synthesized all four possible benzofuropyridines: benzo[4,5]furo[2,3-*b*]pyridine (**2**), benzo[4,5]furo[2,3-*c*]pyridine (**5**), benzo[4,5]furo[3,2-*c*]pyridine (**7**), and benzo[4,5]furo[3,2-*b*]pyridine (**10**). Our method provides an alternative to literature methods where metalation of pyridine was followed by palladium-catalyzed coupling approach for pyridine derivative synthesis.[18] The aforementioned success is also a testimony to the utility of palladium chemistry as a powerful tool in solving otherwise lengthy synthetic problems with great efficiency.

Acknowledgment. The authors are indebted to Mr. Roderick J. Sorenson for helpful discussions on bismuth chemistry and to Drs. Michelle M. Bruendl and Drago R. Sliskovic for proofreading the manuscript.

Supporting Information Available: ^1H and ^{13}C NMR spectra of benzo[4,5]furopyridines **2**, **5**, **7**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) **Data for 10**: mp = 62−64 °C; R_f = 0.46 (1:1 hex/EtOAc); ^1H NMR ($CDCl_3$) δ 8.40 (dd, J = 3.7, 0.9 Hz, 1H), 8.15 (dt, J = 7.6, 0.7 Hz, 1H), 7.72 (dd, J = 7.1, 0.8 Hz, 1H), 7.50−7.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 157.9, 150.1, 145.4, 144.3, 129.4, 123.8, 123.1, 121.45, 121.36, 118.8, 112.3; MS (ACPI) m/z 170.0 ($M^+ + 1$).

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