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Facile synthesis of benzo[4,5]furo[3,2-*c*]pyridines via palladium-catalyzed intramolecular Heck reaction

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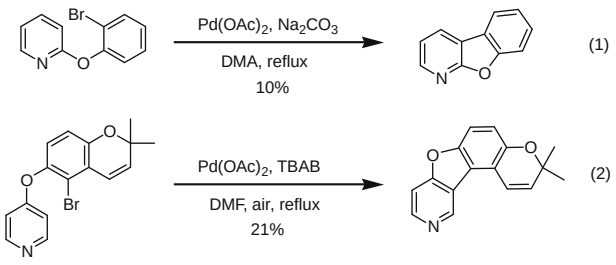
ABSTRACT

The heating of 4-chloropyridine with 2-bromophenol in either neat or DME as solvent gives rise to 2-bromophenoxy pyridines, which were treated with $Pd(OAc)_2$ and various ligands to afford functionalized benzo[4,5]furo[3,2-*c*]pyridines.

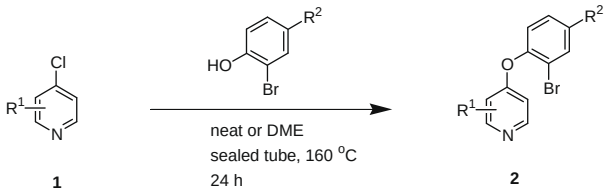
Benzo[4,5]furo[3,2-c]pyridines are a common structural motif in medicinal chemistry and often display important biological activity.[1] These heterocycles are also used as organic electroluminescent material.[2] Pd-catalyzed intramolecular Heck reaction of suitably tethered aryl halides has been utilized in the preparation of dibenzofurans,[3,5] benzo[4,5]furo heterocycles,[4] and carbazoles,[5] the corresponding application with halogenated phenoxy pyridines has seen scant use in the synthesis of benzo[4,5]furo[3,2-*c*]pyridines. There are only two reports[6,7] on the Pd-catalyzed intramolecular Heck reaction of halogenated phenoxy pyridines. We now report a convenient synthesis of benzo[4,5]furo[3,2-*c*]pyridines bearing several substituents on both rings by adaptation of the Heck reaction.



Rapid access to 2-bromophenoxy pyridines was found in coupling of 4-chloropyridines with 2-bromophenols neat or in DME as solvent at 160 °C (sealed tube) for 24 h (Scheme 1). The reaction proceeded satisfactorily in typical yields of 40–75%, but **2f** was isolated only in 13% yield.

Various catalysts, ligands, and bases were screened for the Heck cyclization (Table 1). First, we examined reaction conditions reported in the two literature precedents (Eqs. 1 and 2).[6,7] When 2-bromophenoxy pyridine was treated with 10 mol % $Pd(OAc)_2$ in refluxing DMA in the presence of Na_2CO_3 (Eq. 1), benzo[4,5]-furo[3,2-*c*]pyridine **3a** was obtained in 59% yield (entry 1). Cyclization of **2a** under Janin's conditions [5 mol % $Pd(OAc)_2$, K_2CO_3, and tetrabutylammonium bromide as promoter in refluxing DMF under air, eq. 2] afforded **3a** in significantly lower yield (31%, entry 2). When the reaction was conducted in sealed tube at 130 °C, the yield improved to 65% (entry 3). A survey of different ligands such as dppf (entry 4), palladacyclic precatalyst (entry 5), Josiphos type ligand (entry 6), tricyclohexylphosphine (entry 7), and an imidazole ligand (1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride, IPr–HCl) (entry 8), suggested that IPr–HCl was most effective for this cyclization in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % IPr–HCl, and K_2CO_3 in DME at 130 °C (sealed tube) to provide product **3a** in 95% isolated yield (entry 7).

By utilizing optimized conditions, we examined an intramolecular Heck reaction of various 2-bromophenoxy pyridines as summarized in Table 2. Under optimized conditions, both electron-deficient (entries 2, 3, and 4) and electron-donating (entry 5) substrates gave good yields of the desired products. Although the scope is generally broad, several limitations have been noted.



Scheme 1. Synthesis of 2-(2-bromophenoxy)pyridines.

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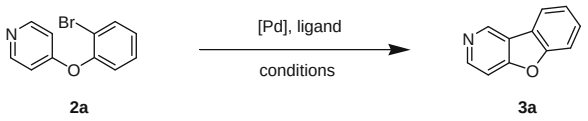
Table 1
Optimization of cyclization conditions

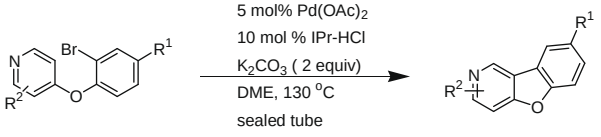


2a 3a

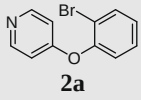
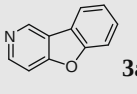
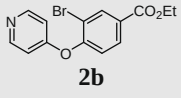
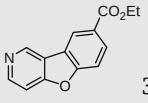
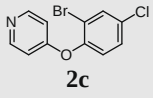
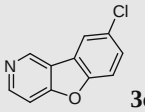
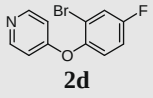
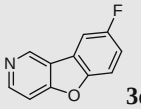
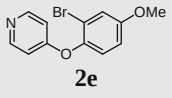
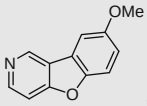
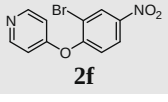
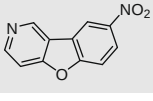
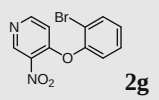
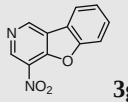
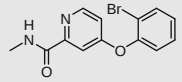
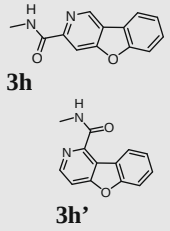
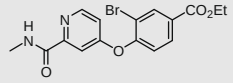
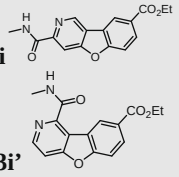
Entry	Palladium/ligand	Conditions	Yields (%)
1[a]	$Pd(OAc)_2$	Na_2CO_3 DMA Reflux	59
2[b]	$Pd(OAc)_2$	K_2CO_3, TBAB DMF, air Reflux	31
3	$Pd(OAc)_2$	K_2CO_3, TBAB DMF, 130 °C Sealed tube	65
4	$PdCl_2$ [dppf]	Et_3N DMA, 130 °C Sealed tube	72
5	Pd_2 ($P(o\text{-}Tol)_3)_2$ (u-$OAc)_2$	NaOAc DMA,130 °C Sealed tube	80
6	$Pd(OAc)_2$/Josiphos	K_2CO_3 DME,130 °C Sealed tube	82
7	$Pd(OAc)_2/Cy_3P{\cdot}HBF_4$	K_2CO_3 DME,130 °C Sealed tube	85
8	$Pd(OAc)_2$/IPr–HCl	K_2CO_3 DME,130 °C Sealed tube	95

[a] Following the condition described by Ames.
[b] Following the condition described by Janin.

Table 2
Preparation of Benzo[4,5]furo[3,2-*c*]pyridines



2 3

Entry	3	Yield[a] (%)
1	 2a  3a	95
2	 2b  3b	95
3	 2c  3c	85
4	 2d  3d	85
5	 2e  3e	80
6	 2f  3f	<5
7	 2g  3g	29
8	 2h  3h 3h’	50[b]
9	 2i  3i 3i’	22[c] (1:1)

[a] Isolated yields following purification by silica gel column chromatography.
[b] The reaction was carried out with 10 mol % Josiphos type ligand and a trace amount of **3h**′ was observed in its crude ^{1}NMR spectrum.
[c] The reaction was carried out with 10 mol % $Cy_3P{\cdot}HBF_4$ as a ligand.

Substrates bearing strong electron-withdrawing groups on either phenoxy (entry 6) or pyridine (entry 7) rings such as a nitro group furnished **3f** and **3g** in <5% and 29% yields, respectively.

In addition, cyclization of 2-methylamide-substituted phenoxypyridines (entries 8 and 9) proved to be problematic. Cyclization of **2h** and **2i** was very sluggish and gave only trace amounts of the desired products. Poor yields obtained for substrates **2h** and **2i** were presumably due to strong coordination of palladium with 2-pyridine methylamide moiety to shut down a catalytic cycle.[8] However, use of bidendate Josiphos ((*S*)-1-[(1*R*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine) as the ligand was found to be effective, and the product **3h** (entry 8) was prepared in 50% yields along with very small amounts of the regio-isomer **3h**′ (determined by crude ^{1}H NMR). Cyclization of **2i** bearing an electron-deficient phenyl ring employing various bidendate ligands, such as Josiphos, dppf, and BINAP, was unsuccessful. In conclusion, we have developed a convenient method for preparing functionalized benzo[4,5]furo[3,2-*c*]pyridines.[9] The key intermediate, 2-bromophenoxy pyridines[9] was readily prepared from nucleophilic displacement of chloropyridines with 2-bromophenols. Subsequent Pd-catalyzed intramolecular Heck reaction afforded benzo[4,5]furo[3,2-*c*]pyridine derivatives. This route should be applicable for the preparation of many pharmacologically useful molecules.

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9. *Representative spectroscopic data*. Compound **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.8, 1.5 Hz, 2H), 8.37 (d, J = 2.1 Hz, 1H), 8.06 (dd, J = 8.4, 2.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 4.8, 1.5 Hz, 2H), 4.44 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H). **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.76 (d, J = 1.8 Hz, 1H), 8.72 (d, J = 5.7 Hz, 1H), 8.29 (dd, J = 8.7, 1.8 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.58 (dd, J = 5.7, 0.8 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H).Compound **2e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 4.5, 1.5 Hz, 2H),7.19 (d, J = 3.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 6.91 (dd, J = 9.0, 3.0 Hz, 1H), 6.85 (dd, J = 4.5, 1.5 Hz, 2H), 3.83 (s, 3H). **3e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.63 (d, J = 5.7 Hz, 1H), 7.53–7.48 (m, 3H), 7.12 (dd, J = 9.0, 1.8 Hz, 1H), 3.93 (s, 3H). Compound **2h**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 5.6 Hz, 1H), 8.03 (br s, 1H), 7.69 (dd, J = 7.8, 1.5 Hz, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.40 (td, J = 7.8, 1.5 Hz, 1H), 7.22–7.15 (m, 2H), 6.96 (dd, J = 5.5, 2.5 Hz, 1H), 3.02 (d, J = 5.1 Hz, 3H). Compound **3h**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.42 (s, 1H), 8.18 (br s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.58 (td, J = 7.3, 1.0 Hz, 1H), 7.45 (t, J = 7.3 Hz, 1H), 3.09 (d, J = 5.1 Hz, 3H). **2i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 5.5 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 5.6, 2.0 Hz, 1H), 8.01 (br s, 1H), 7.66 (d, J = 2.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 5.6, 2.5 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.01 (d, J = 5.1 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H). Compound **3i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.80 (d, J = 1.5 Hz, 1H), 8.47 (s, 1H), 8.33 (dd, J = 8.6, 1.8 Hz, 1H), 8.15 (br s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.12(d, J = 5.1 Hz, 3H), 1.48 (t, J = 7.1 Hz, 3H). Compound **3i′**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (d, J = 1.8 Hz, 1H), 8.63 (d, J = 5.4 Hz, 1H), 8.35 (dd, J = 8.6, 1.8 Hz, 1H), 8.33 (br s, 1H), 7.70 (d, J = 5.4 Hz, 1H), 7.67 (d, J = 8.6 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.16 (d, J = 5.1 Hz, 3H), 1.47 (t, J = 7.1 Hz, 3H).