Tetrahedron Letters 50 (2009) 4492–4494

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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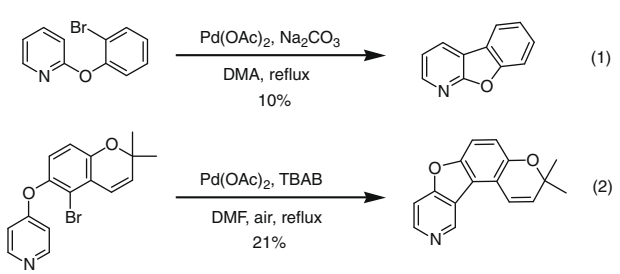
ARTICLE INFO

Article history:
Received 7 April 2009
Revised 15 May 2009
Accepted 19 May 2009
Available online 23 May 2009

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.

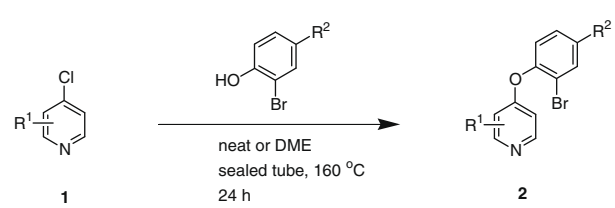
Benzo[4,5]furo[3,2-c]pyridines are a common structural motif in medicinal chemistry and often display important biological activity.[1] These heterocycles are also used as organic electroluminescent material.[2] Pd-catalyzed intramolecular Heck reaction of suitably tethered aryl halides has been utilized 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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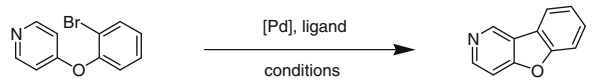
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.063

Table 1
Optimization of cyclization conditions

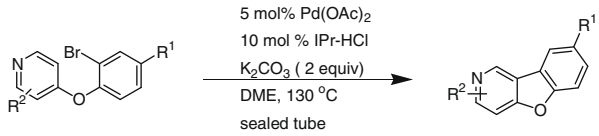


2a **3a**

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*-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**

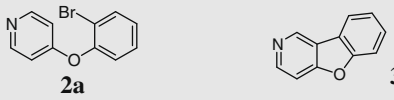
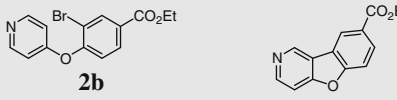
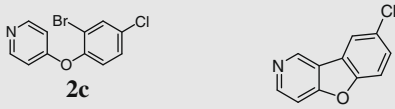
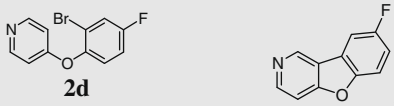
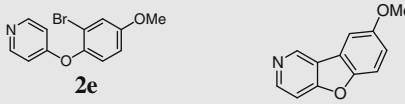
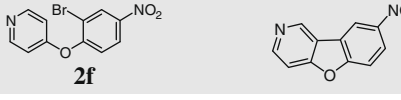
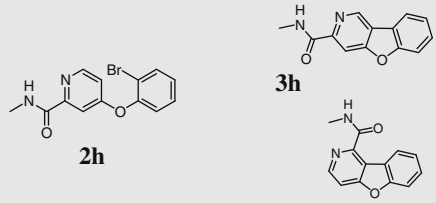
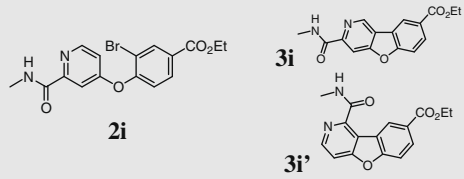
Entry	3	Yield[a] (%)
1	 **2a** **3a**	95
2	 **2b** **3b**	95
3	 **2c** **3c**	85
4	 **2d** **3d**	85
5	 **2e** **3e**	80
6	 **2f** **3f**	<5

Table 2 (*continued*)

Entry	3	Yield[a] (%)
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.

Acknowledgment

We are grateful to the Korea Research Institute of Chemical Technology for financial support.

References and notes

1. (a) Wakelin, L. P. G.; Waring, M. J. In *Comprehensive Medicinal Chemisty*; Sammes, P. G., Ed.; Pergamon: Oxford, 1990; pp 703–724; (b) Gharat, L. A.; Gajera, J. M.; Patil, S. D.; Kadam, S. M. PCT Int. Appl. WO 2008142542.; (c) Yue, W. S.; Li, J. J. *Org. Lett.* **2002**, *4*, 2201.
2. Oshiyama, T.; Sugino, M.; Otsu, S.; JP 2008074939.
3. a J.T. Link, Organic Reactions, John Wiley & Sons: Hoboken, NJ, United States, 2002, 60.; (b) Gajera, J. M.; Gopalan, B.; Yadav, P. S.; Patil, S. D.; Gharat, L. A. *J. Heterocyclic Chem.* **2009**, *45*, 797; (c) Arava, V. R.; Siripalli, U. B. R.; Dubey, P. K.; Reddanna, P.; Reddy, D. B. *Indian J. Chem. B Org.* **2007**, *46B*, 1343; (d) Ebisawa, M.;

Ueno, M.; Oshima, Y.; Kondo, Y. *Tetrahedron Lett.* **2007**, *48*, 8918; (e) Gopalan, B.; Gharat, L. A.; Lakdawala, A. D.; Karaunakaran, U. PCT Int. Appl. WO 2004089940.; (f) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347; (g) Ames, D. E.; Opalko, A. *Synthesis* **1983**, 235.

4. Zhang, Y.-M.; Razler, T.; Jackson, P. F. *Tetrahedron Lett.* **2002**, *43*, 8235.
5. (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505; (b) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403; (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253.
6. Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.
7. Prado, S.; Toum, V.; Saint-Joanis, B.; Michel, S.; Koch, M.; Cole, S. T.; Tillequin, F.; Janin, Y. L. *Synthesis* **2007**, 1566.
8. (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240; (b) Cheon, J.-D.; Mutai, T.; Araki, K. *Tetrahedron Lett.* **2006**, *47*, 5079.
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).