ORGANIC LETTERS

2007
Vol. 9, No. 15
2955−2958

A General and Practical Method of Alkynyl Indole and Benzofuran Synthesis via Tandem Cu- and Pd-Catalyzed Cross-Couplings

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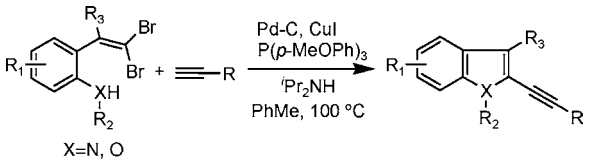
Received June 11, 2007

ABSTRACT



A new tandem coupling approach to synthesize 2-alkynyl indoles and benzofurans is described. This reaction utilizes easily accessible *gem*-dibromovinyl substrates and terminal alkynes and proceeds via Pd/C- and CuI-catalyzed tandem Ullman/Sonogashira couplings.

Transition-metal-catalyzed reactions have increasingly attracted attention in the pharmaceutical and fine chemical industries. Palladium is clearly one of the most versatile metals for numerous transformations in construction of carbon−carbon and carbon−heteroatom bonds.[1] In order to develop and apply new methods to industrial processes, addressing practical issues including reaction generality, robustness, catalyst loadings as well as type of precatalyst and ligand, and metal residue in the product is extremely important but often overlooked.[2]

We now report a simple method to prepare both benzofuran and indole scaffolds bearing an alkyne at the 2-position and show that choice of catalyst is extremely important in achieving high yields.

Recently, we developed a number of new methods for the synthesis of indoles, azaindoles, and thienopyrroles, all very useful subunits found in biologically relevant structures,[3] via Pd-catalyzed tandem cross-coupling strategies using easily accessible *gem*-dihalovinyl substrates.[4] In these processes, homogeneous palladium precatalysts, such as $Pd(OAc)_2$ or $Pd_2(dba)_3$, and a specialized phosphine ligand (e.g., S-Phos) were used which can lead to a high residual metal content in the product. In addition, boronic acids were used as the coupling partner, and while they are among the best of the organometallic reagents, they are not as attractive as feedstock materials such as alkenes or alkynes. Here we report a new general and practical catalyst system using CuI and Pd/C to synthesize 2-alkynyl indoles from *gem*-dibromovinylanilines and terminal alkynes via a tandem Ullman

(1) Tsuji, J. *Palladium Reagents and Catalysis, New Perspective for the 21st Century*; Wiley-VCH: Weinheim, Germany, 2004.

(2) For excellent reviews on Pd-catalyzed reactions from industrial laboratories, see: (a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (b) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (c) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. For general information on process chemistry, see: (d) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, CA, 2000.

(3) For reviews on indole synthesis, see: (a) *Indoles*; Sundberg, R. J., Ed.; Academic Press: San Diego, CA, 1996. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875 and references therein.

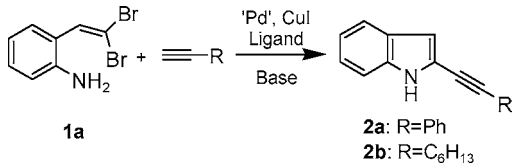
(4) Indole, azaindole, and thienopyrrole synthesis via Pd-catalyzed tandem C−N/Suzuki−Miyaura couplings: (a) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (b) Fang, Y.-Q.; Karisch, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341. (c) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* Published online June 9, 2007 http://dx.doi.org/10.1021/jo07046b. Indole synthesis via tandem C−N/Heck couplings: (d) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. Imidazoindolone synthesis via Cu-catalyzed double intramolecular amidation: (e) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

10.1021/ol071370w CCC: $37.00
Published on Web 06/27/2007

C−N/Sonogashira reaction under relatively mild conditions. We also show that this catalyst system is equally effective for the formation of benzofuran analogues, another family of biologically important heterocycles.[5]

Our preliminary efforts were carried out using *gem*-dibromovinylaniline **1a** with phenylacetylene in the presence of $Pd(PPh_3)_4$ (5 mol %), CuI (5 mol %), and Et_3N in toluene, affording the desired product **2a** in 65% yield (Scheme 1).

Scheme 1



1a **2a**: R=Ph **2b**: R=C_6H_{13}

To our surprise, no double-alkynylated product was observed, despite literature precedent demonstrating that Sonogashira coupling of *gem*-dibromoolefins is a rather unselective process, which would prevent ring formation.[6]

Changing the base (K_2CO_3, K_3PO_4, Cs_2CO_3, DABCO, $^iPr_2NH$, and $^iPr_2NEt$) revealed that organic amine bases were more effective than inorganic bases, and that $^iPr_2NH$ (2.5 equiv) was optimal. Screening a range of palladium catalysts ($Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$, $Pd(PhCN)_2Cl_2$, Na_2PdCl_4, $Pd(acac)_2$, $[Pd(allyl)Cl]_2$, Pd/C) showed that Pd/C[7] gave the cleanest reaction, affording **2a** in 85% isolated yield.[8] Comparing to the homogeneous complexes, Pd/C is an ideal Pd source due to its low cost, easy recovery through simple filtration, and low level of Pd contamination in the product.[9] Other heterogeneous Pd catalysts such as $Pd-Al_2O_3$, $Pd-BaSO_4$, and Lindlar's catalyst worked equally well. Since the solid support did not affect the efficacy of the catalyst system, it is most likely that the reaction itself occurs in a homogeneous organic phase with trace amounts of leached Pd(0).

(5) For reviews on benzo[*b*]furan-containing natural products, see: (a) Donelly, D. M. X.; Meegan, M. J. Furans and Their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, 1984; Vol. 4, pp 657−712. (b) Cagniant, P.; Cagniant, D. *Adv. Heterocycl. Chem.* **1975**, *18*, 337. (c) Bird, C. W.; Cheeseman, G. W. H. Synthesis of Five-membered Rings with One Heteroatom. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, 1984; Vol. 4, pp 89−153. For a recent report on benzo[*b*]furan-containing pharmaceuticals, see: (d) Chen, C; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964.

(6) (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965. (b) Uenishi, J.; Matsui, K.; Ohmiya, H. *J. Organomet. Chem.* **2002**, *653*, 141. (c) Ogasawara, M.; Ikeda, H.; Ohtsuki, K.; Hayashi, T. *Chem. Lett.* **2000**, 776.

(7) 10% Pd/C (Pearlman) provided by Degussa is marginally better than common 10% Pd/C.

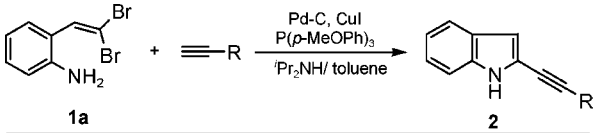
(8) Pd/C-catalyzed Sonogashira coupling reactions: (a) De la Rosa, M. A.; Velarde, E.; Guzmàn, A. *Synth. Commun.* **1990**, *20*, 2059. (b) Bleicher, L; Cosford, N. D. *Synlett* **1995**, 1115. (c) Cosford, N. D.; Bleicher, L.; Herbaut, A.; McCallum, J. S.; Vernier, J.-M.; Dawson, H.; Whitten, J. P.; Adams, P.; Chavez-Noriega, L.; Correa, L. D.; Crona, J. H.; Mahaffy, L. S.; Menzaghi, F.; Rao, T. S.; Reid, R.; Sacaan, A. I.; Santori, E.; Stauderman, K. A.; Whelan, K.; Lloyd, G. K.; McDonald, I. A. *J. Med. Chem.* **1996**, *39*, 3235. (d) Breicher, L. S.; Cosford, N. D.; Herhaut, A.; MacCallum, J. S.; MacDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109.

(9) For reviews, see: (a) Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679. (b) Seki, M. *Synthesis* **2006**, 2975.

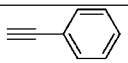
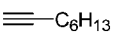
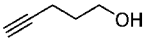
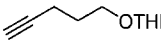
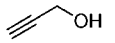
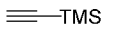
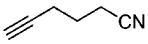
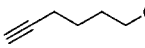
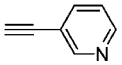
Further fine-tuning of the reaction conditions using **1a** and the more challenging substrate 1-octyne was achieved by varying the phosphine ligand. In general, monodentate triarylphosphines were more effective than electron-rich and sterically hindered phosphines, such as S-Phos or $P(^tBu)_3$, or bidentate ligands, such as DPPF. Moderately electron-rich $P(p\text{-MeOPh})_3$ proved to be the ligand of choice. The ligand to CuI ratio of 2:1 was the most effective to use, affording the product **2b** in 83% yield. Catalyst loading could be reduced to 0.3 mol % of Pd and 2 mol % of CuI; however, a longer reaction time was necessary to obtain full conversion (36 h). The optimal solvent is toluene, and simple degassing is sufficient treatment for solvent-grade toluene.

The optimized conditions were then applied to various aromatic and aliphatic terminal alkynes with different electronic properties using **1a**. In all cases, the expected 2-alkynyl indoles **2** were isolated in moderate to good yields (Table 1, entries 1−9). The reaction tolerated many functional groups including hydroxyl, nitrile, chloro, acetal, and trimethylsilyl, although longer reaction times were required for some cases (entries 8 and 9). Altering the electron-donating and electron-withdrawing groups on the *gem*-dibromovinyl substrate did not affect the efficacy of the tandem reaction, giving the products **2j**−**2m** in 55−84% yields (Table 2, entries 1−4).

Table 1. Scope of Alkyne Reagents



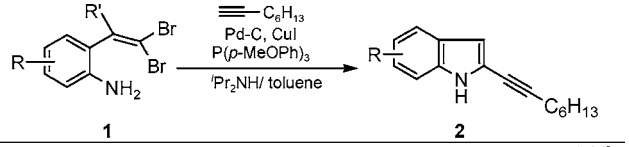
1a **2**

entry	alkyne	product **2**/ yield[a] (%)
1		**2a** 85[b]
2		**2b** 83 (70[b])
3		**2c** 65[b]
4		**2d** 71[b]
5		**2e** 40
6		**2f** 57
7		**2g** 50
8		**2h** 70
9		**2i** 81

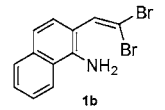
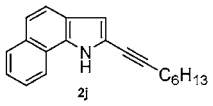
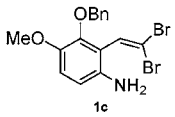
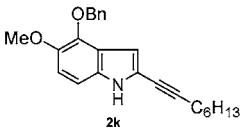
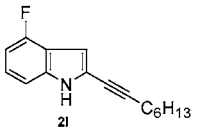
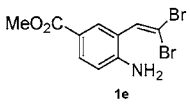
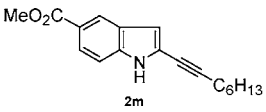
[a] Isolated yields using alkyne (1.5 equiv), Pd/C (2 mol %), CuI (4 mol %), $P(p\text{-MeOPh})_3$ (8 mol %), and $^iPr_2NH$ (2.5 equiv) in toluene at 100 °C for 1.5−48 h. [b] Reaction performed using Pd/C (5 mol %), CuI (5 mol %), PPh_3 (11 mol %), and $^iPr_2NH$ (2.5 equiv) in toluene at 100 °C for 1 h.

In contrast to our previous observations on the Pd-catalyzed tandem C−N/Heck and C−N/Suzuki reaction,[4a,d] alkyl or aryl substituents on the aniline nitrogen of the *gem*-

Table 2. Scope of *ortho-gem*-Dihalovinylaniline Substrates



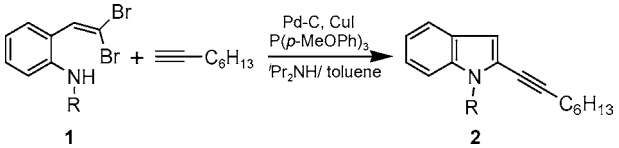
1 2

entry	substrate	product	yield[a] (%)
1	 1b	 2j	55
2	 1c	 2k	81
3	 1d	 2l	72
4	 1e	 2m	84[b]

[a] Isolated yields using 1-octyne (1.5 equiv), Pd/C (2 mol %), CuI (2 mol %), P(*p*-MeOPh)$_3$ (4 mol %), and ^{i}Pr$_2$NH (2.5 equiv) in toluene at 100 °C for 12−24 h. [b] Pd/C (5 mol %), CuI (4 mol %), P(*p*-MeOPh)$_3$ (8 mol %), and ^{i}Pr$_2$NH (2.5 equiv) for 24 h.

dibromovinylaniline in general lowers the yield, although longer reaction times and higher catalyst loadings can be used to force the reaction to completion (Table 3).

Table 3. Scope of Nitrogen Substituents



1 2

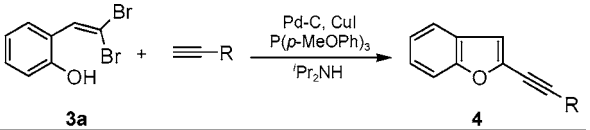
entry	substrate R	product **2**/yield[a] (%)
1	**1g** Me	**2n** 61
2	**1h** ^{i}Pr	**2o** 60
3	**1i** Bn	**2p** 51
4	**1j** Ph	**2q** 65

[a] Isolated yields using alkyne (1.5 equiv), Pd/C (1−7 mol %), CuI (2−10 mol %), ^{i}Pr$_2$NH (2.5 equiv), and P(*p*-MeOPh)$_3$ (4−10 mol %) in toluene at 100 °C.

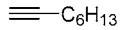
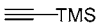
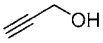
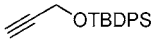
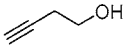
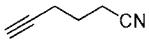
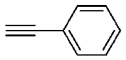
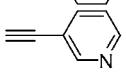
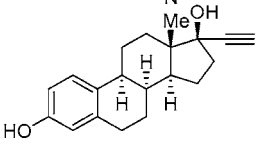
Having developed a novel procedure for the synthesis of 2-alkynyl indoles, we next sought to extend this methodology to the synthesis of 2-alkynylbenzofurans. There have been reports on preparation of this class of compounds using Sonogashira coupling with 2-halobenzofurans and terminal alkynes, but little is known about the synthesis of 2-alkynylbenzofurans directly from easily accessible phenol derivatives. A general, practical, and modular method has not been reported.

Our initial studies using *gem*-dibromovinylphenol **3a**[10] and 1-octyne found that the same catalytic system employed for the indole examples afforded the desired benzofuran **4a** in 69% yield (Table 4, entry 1). Interestingly, use of biphasic

Table 4. Scope of Alkyne Reagents



3a 4

entry	alkyne	product **4**/ yield[a] (%)
1		**4a** 80 (69[b])
2		**4b** 47[b]
3		**4c** 49
4		**4d** 80
5		**4e** 63 (45[b])
6		**4f** 76
7		**4g** 71[b]
8		**4h** 61[b]
9		**4i** 69

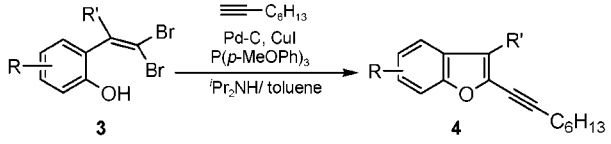
[a] Isolated yields using alkyne (1.5 equiv), Pd/C (1 mol %), CuI (2 mol %), ^{i}Pr$_2$NH (2.5 equiv), and P(*p*-MeOPh)$_3$ (4 mol %) in toluene/H$_2$O (2:1) at 100 °C for 12 h. [b] Toluene was used as solvent instead of a mixture of toluene/H$_2$O.

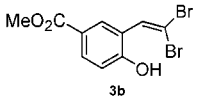
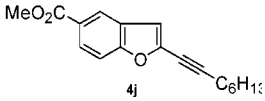
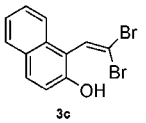
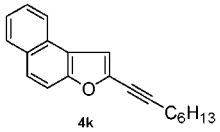
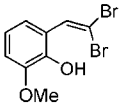
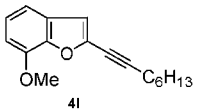
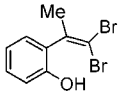
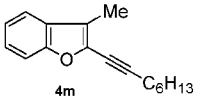
toluene/H$_2$O (2:1) instead of toluene alone was found to improve the yield to 80%. The intriguing beneficial effect of water is presumably due to its ability to remove bromide from the organic phase. A control experiment, in which an external source of bromide (Bu$_4$NBr) was found to inhibit the reaction progress, lends support to this proposal.

The scope of the reaction regarding terminal alkynes is very broad, as shown in Table 4. Substrates containing aryl, heteroaryl, and nitrile groups (entries 6−8) were tolerated, as were alcohols (entries 3 and 5). Even a relatively complicated steroid derivative bearing two acidic hydroxyl groups (entry 9) proceeded in good yield. Similarly, various substitution on the *gem*-dibromovinylphenol was tolerated (Table 5, entries 1−3). Higher catalyst loading and longer reaction time for substrate **3d** was needed to overcome the

(10) For the preparation of **3a**, see: Thilges, S.; Meddah, E.; Bisseret, P; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907.

Table 5. Scope of *ortho-gem*-Dihalovinylphenol Substrates



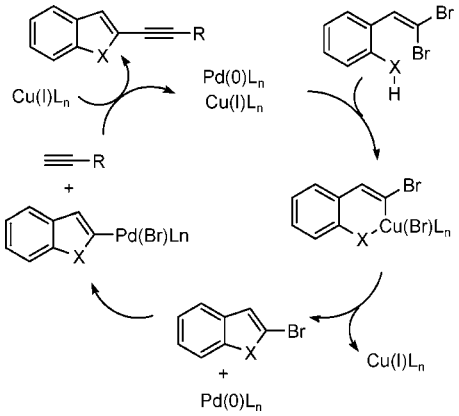
entry	substrate	product	yield[a] (%)
1	 3b	 4j	93
2	 3c	 4k	98[b]
3	 3d	 4l	80[c]
4	 3e	 4m	82

[a] Isolated yield using alkyne (1.5 equiv), Pd/C (2 mol %), CuI (4 mol %), P(*p*-MeOPh)$_3$ (8 mol %), and ^{i}Pr$_2$NH (2.5 equiv) in toluene/H$_2$O, at 100 °C for 12 h. [b] Pd/C (1 mol %), CuI (2 mol %), P(*p*-MeOPh)$_3$ (4 mol %) for 12 h. [c] Pd/C (7 mol %), CuI (5 mol %), P(*p*-MeOPh)$_3$ (10 mol %).

coordination of two adjacent oxygens, which may retard the catalytic cycle. We also showed that 2,3-disubstituted benzofuran **4m** could be obtained from substrate **3e** in 82% yield.

A plausible mechanism, which accounts for the formation of the 2-alkynyl heteroaryl compounds from the dibromovinyl precursors, is shown in Scheme 2. When the tandem C−N/Sonogashira reaction was performed using **1a** in the absence of Pd/C under the optimized conditions, no desired product was observed. However, a significant amount of 2-bromoindole was obtained, presumably formed via an intramolecular Ullman reaction. On the other hand, when the reaction was performed in the presence of Pd/C and PPh$_3$ without CuI, only the starting material **1a** was recovered. On the basis of this evidence, we believe that the

Scheme 2



Cu-catalyzed C−N coupling process occurs prior to the Pd- and Cu-catalyzed Sonogashira coupling in this sequence.

In conclusion, we have established a general and practical CuI and Pd/C catalyst system that provides rapid access to a variety of 2-alkynyl indoles and benzofurans via tandem cross-couplings. This is the first reliable method to stereoselectively functionalize *gem*-dibromoolefins using the Sonogashira reaction. These alkynyl-substituted heterocycles are difficult to obtain using existing indole-forming (e.g., Fischer or Larock's indole synthesis) and benzofuran-forming methods. While the triple bond provides a unique structure motif for biological systems, it can also undergo a rich array of chemical transformations to form other functional groups. Preliminary study shows that both Cu and Pd participate in the C−C bond formation, while Cu is responsible for Ullman C−N bond formation.

Acknowledgment. We thank NSERC (Canada), Merck Frosst, Daiichi Pharmaceutical (Tokyo), and the University of Toronto for the funding of this research. Y.-Q.F. thanks the Ontario Government and University of Toronto for financial support (OGS, OGSST).

Supporting Information Available: Full experimental details and characterization including ^{1}H and ^{13}C spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071370W