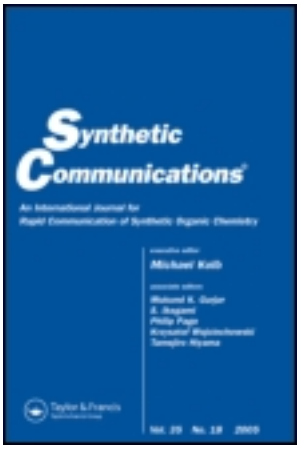



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Simple, Convenient, and Efficient Synthesis of 2-Aryl-substituted Benzo[b]furans

Yong Jiang [a], Botao Gao [a], Wenjuan Huang [a], Yongmin Liang [a], Guosheng Huang [a] & Yongxiang Ma [a]

[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China

Version of record first published: 22 Dec 2008.

To cite this article: Yong Jiang, Botao Gao, Wenjuan Huang, Yongmin Liang, Guosheng Huang & Yongxiang Ma (2008): Simple, Convenient, and Efficient Synthesis of 2-Aryl-substituted Benzo[b]furans, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:2, 197-204

To link to this article: http://dx.doi.org/10.1080/00397910701860323

*Synthetic Communications*®, 39: 197–204, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701860323

Taylor & Francis
Taylor & Francis Group

# Simple, Convenient, and Efficient Synthesis of 2-Aryl-substituted Benzo[b]furans

**Yong Jiang, Botao Gao, Wenjuan Huang, Yongmin Liang, Guosheng Huang, and Yongxiang Ma**
State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China



**Abstract:** A simple, convenient, and efficient one-pot method for the preparation of benzofuran is reported. Sonogashira coupling reaction of aryl iodides with 2-methyl-3-butyn-2-ol was used as an acetylene source in the presence of $Pd(PPh_3)_2Cl_2$ and CuI. Deprotection of the acetylene moiety in the same pot using a strong base and the second Sonogashira coupling/cyclization of and substituted o-iodophenols led to the formation of the appropriate benzo[b]furans. These protocols also can be used in the synthesis of natural products and indoles.

**Keywords:** Aryl iodide, benzo[b]furan, 2-methyl-3-butyn-2-ol, *o*-iodophenol, Sonogashira reaction

Benzo[b]furan derivatives are an important class of organic compounds that occur in many compounds and natural products because of their biological activities,[1] including antitumor properties.[2] They can be used as inhibitors of 5-lipoxygenase,[3] antagonists of the angiotensin II receptor,[4] blood coagulation factor Xa inhibitors,[5] ligands of adenosine A1 receptor[6] and so forth.

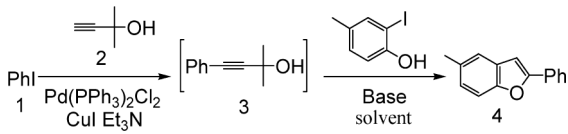
Generally, preparing benzofurans *via* a palladium catalytic reaction is an effective and a widely used method.[7] This is accomplished through a tandem Sonagashira coupling/5-*endo-dig* cyclization starting from either *o*-iodophenols or *o*-ethynyl-phenols. In comparison to the traditional methods, these palladium-based methods offer increased functional group tolerance and improved yields of the desired benzofuran, but

Received March 18, 2007.
Address correspondence to Guosheng Huang, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China. E-mail: hgs2368@163.com

they need expensive acetylenes, or their substrate preparation needs tedious operation and expensive reagents. Recently, many new and efficient methods for the synthesis of benzofuran have been developed, such as cyclization/oxidation of the allyl aryl ether,[8] the cyclization of 2-arylethynyl anisole,[9] and intramolecular *o*-arylation of 2-haloaryl ketones.[10] These methods are very efficient for synthesizing benzofuran; unfortunately, the substrate preparation also needs tedious operation or expensive reagents, and there are some limitations for using substrate extension. So, in the present work, we describe a simple, convenient, and efficient method for the preparation of benzofuran via a one-pot process using a tandem a Sonogashira reaction.

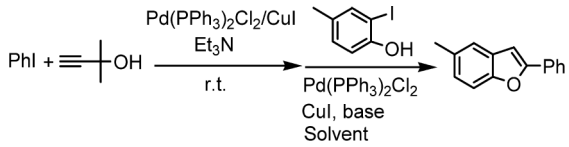
Previously, Novák's group has reported tandem Sonogashira coupling using the cheap reagent 2-methyl-3-butyn-2-ol.[11] Therefore, the first set of experiments was directed toward establishing the feasibility of the reaction. We chose iodobenzene (1) as a model compound and carried out its coupling with 2-methyl-3-butyn-2-ol (2) in the presence of 2 mol% bis(tri-phenylphosphine)palladium dichloride, 2 mol% copper(I) iodide, and $Et_3N$ at room temperature for about 5 h. The intermediate (3) as a yellow solid was isolated first and characterized; then (3) was reacted with 2-iodo-4-methylphenol in the presence of the same catalyst and a strong base $KOBu^t$ to give the desired product (4), 5-methyl-2-phenylbenzo[b]furan, in a yield of 63%. In following experiments, another portion of the catalyst $Pd(PPh_3)_2Cl_2$/CuI, 2-iodo-4-methylphenol, and the strong base $KOBu^t$ were added immediately after completing conversion of (1) and (2) (monitored by thin-layer chromatography, TLC) without isolating the intermediate (3). The addition of another portion of the catalyst is neccessary or lower yield of the desired product will be obtained. Then the mixture was stirred at 110° for 24 h to give the benzo[b]furan (4) in a yield of 75% (as shown in Scheme 1).

To find out the optimum operation, we examined the reaction in various conditions. It can be seen from Table 1 that beneficial base and solvent were used and the isolated yields of 16% for NaOH (entry 1), 45% for KOH (entry 3), 75% for $KOBu^t$ (entry 5), and 8% for $K_3PO_4$ (entry 6) in toluene were obtained. When using $K_2CO_3$ or NaOAc as the base, no desired product was detected by TLC monitoring. A very interesting result appeared when using $KOBu^t$ as the base and benzene as the solvent, and an 80% yield was given. In the following experiments,




***Scheme 1.***

**Table 1.** Various condition effects on the reaction[a]

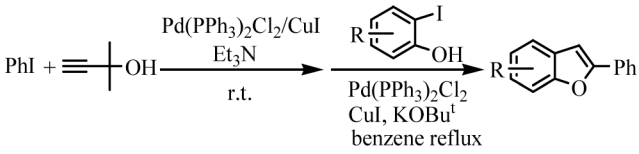


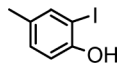
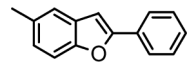
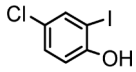
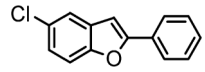
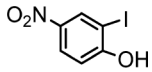
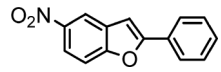
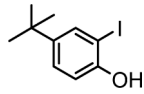
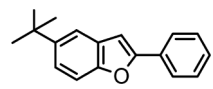
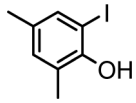
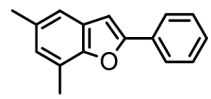

| Entry | Solvent | Base | Isolated yield (%) |
|---|---|---|---|
| 1 | Toluene | NaOH | 16 |
| 2 | Toluene | $K_2CO_3$ | –[b] |
| 3 | Toluene | KOH | 45 |
| 4 | Toluene | NaOAc | –[b] |
| 5 | Toluene | $KOBu^t$ | 75 |
| 6 | Toluene | $K_3PO_4$ | 8 |
| 7 | Toluene | $KOBu^t$ | 80 |

[a]Reacted in a 110 °C oil bath or at the boiling point of the solvent under an argon atmosphere for 24 h.

[b]No benzofuran product was detected by TLC.

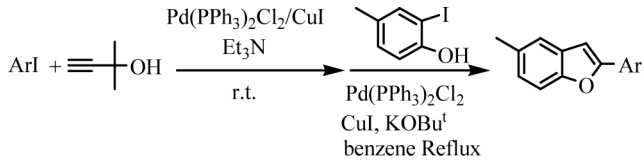
**Table 2.** Synthesis of 2-phenyl substituted benzofurans

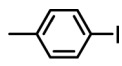
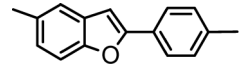
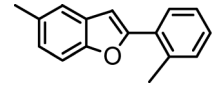
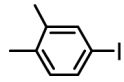
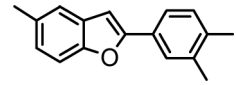
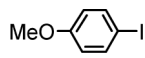
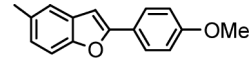
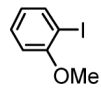
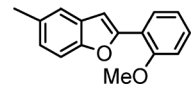
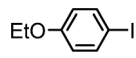
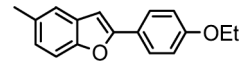
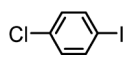
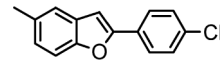
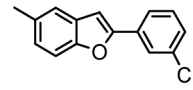
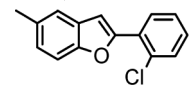
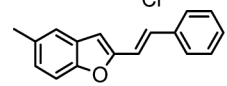



| Entry | *o*-Iodophenol[a] | Product | Isolated yield (%) |
|---|---|---|---|
| 1 |  |  | 80 |
| 2 |  |  | 60 |
| 3 |  |  | 45 |
| 4 |  |  | 75 |
| 5 |  |  | 61 |

[a]*o*-Iodophenols were prepared according to the literature procedure Ref.[13].

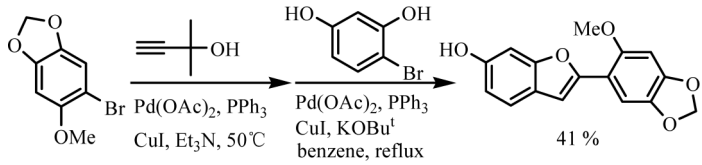
**Table 3.** Synthesis of 5-methyl-2-arylbenzofuran




| Entry | ArI | Product | Isolated yield (%) |
|---|---|---|---|
| 1 |  |  | 81 |
| 2 |  |  | 52 |
| 3 |  |  | 61 |
| 4 |  |  | 51 |
| 5 |  |  | 45 |
| 6 |  |  | 49 |
| 7 |  |  | 69 |
| 8 |  |  | 75 |
| 9 |  |  | 65 |
| 10 | PhCH=CHBr |  | 53 |

[a]0.02 mmol of $Pd(OAc)_2$ and 0.04 mmol of $PPh_3$ were used instead of $Pd(PPh_3)_2Cl_2$ and reacted at 50 °C in the first step.

we chose the $Pd(PPh_3)_2Cl_2$/CuI-KOBu$^t$-benzene system as the standard protocol and aryl iodides,[12] 2-methyl-3-butyn-2-ol and substituted *o*-iodophenols as substrates to synthesize 2-arylbenzo[b]furans.




***Scheme 2.*** Synthesis of cicerfuran.



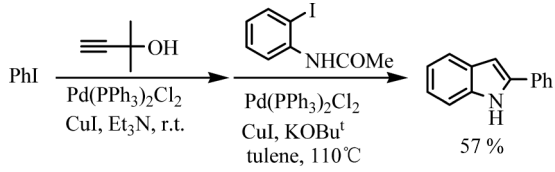
Using this protocol, a series of 5-functional group substituted 2-phenyl-benzo-furans in moderate to good yield (Table 2) can be prepared. From the table, it can be seen that the yield decreases with the increasing electron withdrawing of the functional group. The ortho group of the iodophenol also gives the lower yield of the product (entry 5, Table 2). Furthermore, we successfully synthesized 5-methyl-2-aryl benzo[b]furan in moderate to good yield (Table 3). From the control experiments (entries 1, 2, 4, 5, 7–9, Table 3), it can be seen that the position of functional group of the aryl has a distinct effect on the yield. It is likely that the steric hindrance of the ortho group led to the corresponding yield decrease. In addition, 2-bromovinylbenzene also works in the reaction (entry 10, Table 3). Upon further study, we found that this protocol can be used for the preparation of natural products, cicer-furan (Scheme 2) and indole (Scheme 3).

In summary, a simple, convenient, and efficient method is reported for the one-pot synthesis of various substituted benzo[b]furans starting from easily prepared aryl iodides and *o*-iodophenols and the economical reagent 2-methyl-3-butyn-2-ol. It avoids using expensive reagents, needs no isolation of the intermediate, greatly simplifies the operational steps, and can be used in the preparation of natural products and indole.

## EXPERIMENTAL

### General Procedure for the Preparation of Benzo[b]furan

Under an argon atmosphere, 0.02 mmol of $Pd(PPh_3)_2Cl_2$, 0.02 mmol of CuI, 1 mmol of aryl iodide, 1 mmol of 2-methyl-3-butyn-2-ol, and 1 ml




***Scheme 3.***

of $Et_3$ N were added to a glass tube (2.5 cm in diameter) equipped with a Teflon®-coated stir bar. The mixture was stirred for about 5 h at room temperature until the aryl iodide was converted completely (monitored by TLC). Then 0.02 mmol of $Pd(PPh_3)_2Cl_2$, 0.02 mmol of CuI, 1 mmol of *o*-iodophenol, 3 mmol of $KOBu^t$, and 2 ml of benzene were added and stirred at a reflux condition for 24 h. After cool to rt, the mixture was extracted by ethyl acetate, washed twice by water brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate as eluent to afford the pure product.

**Preparation of 2-(6-Methoxybenzo[d][1,3]dioxol-5-yl) Benzofuran-6-ol (Cicerfuran) (Scheme 2)**

Under an argon atmosphere, 0.02 mmol of $Pd(OAc)_2$, 0.02 mmol of CuI, 0.04 mmol of $PPh_3$, 1 mmol of 5-bromide-6-methoxybenzo[d][1,3]dioxole, 1 mmol of 2-methyl-3-butyn-2-ol, and 1 ml of $Et_3N$ were added to a glass tube (2.5 cm in diameter) equipped with a Teflon®-coated stir bar. The mixture was stirred for about 5 h at 50 °C the until aryl iodide was converted completely (monitored by TLC). Then 0.02 mmol of $Pd(OAc)_2$, 0.02 mmol of CuI, 0.04 mmol of $PPh_3$, 1 mmol of 4-bromobenzene-1, 3-diol, 5 mmol of $KOBu^t$, and 2 ml of benzene were added and stirred at a reflux condition for 24 h. After cooling to rt, the mixture was neutralized with 1 NHCl, extracted by ethyl acetate, washed twice by water brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate as eluent to afford the pure product. White crystals; mp: 145–147 °C (lit.[7i] 145–147 °C). $^1$H NMR (300 MHz, DMSO–$d_6$): $\delta = 9.6$ (br, 1H), 7.38 (d, $J = 8.5$ Hz, 1H), 7.35 (s, 1H), 7.12 (s, 1H), 6.97 (s, 1H), 6.93 (s, 1H), 6.73 (d, $J = 8.5$ Hz, 1H), 6.01 (s, 2 H), 3.91 (s, 3 H). $^{13}$C NMR (75 MHz, MHz, DMSO-$d_6$): $\delta = 155.45$, 154.03, 151.81, 150.16, 147.73, 141.02, 121.33, 120.97, 111.11, 104.62, 104.41, 101.55, 97.22, 95.41, 56.30. MS (EI): $m/z = 284[M^+]$. Anal. calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.78; H, 4.35.

**Preparation of 2-Phenyl-1H-indole (Scheme 3)**

Under an argon atmosphere, 0.02 mmol of $Pd(PPh_3)_2Cl_2$, 0.02 mmol of CuI, 1 mmol of aryl iodide, 1 mmol of 2-methyl-3-butyn-2-ol, and 1 ml of $Et_3N$ were added to a glass tube (2.5 cm in diameter) equipped with

a Teflon®-coated stir bar. The mixture was stirred for about 5 h at room temperature until the aryl iodide was converted completely until (monitored by TLC). Then 0.02 mmol of $Pd(PPh_3)_2Cl_2$, 0.02 mmol of CuI, 1 mmol of N-(2-iodo-phenyl)actamide, and 3 mmol of $KOBu^t$, and 2 ml of benzene were added and stirred at a reflux condition for 24 h. After cooling to rt, the mixture was extracted by ethyl acetate, washed twice by water then brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate as eluent to afford the pure product (yield 57%). Pale yellow solid; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 8.34$ (brs, 1H), 7.64 (t, $J = 7.5$ Hz, 3 H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.39 (d, $J = 7.5$ Hz, 1H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 7.5$ Hz, 1H), 6.83 (s, 1 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 137.92$, 136.95, 132.47, 129.33, 129.01, 127.73, 125.26, 122.45, 120.72, 120.31, 110.93, 100.07. MS(EI): $m/z = 193[M^+]$. Anal. calcd. for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.11; H, 5.69; N, 7.20.



## ACKNOWLEDGMENT

The authors thank the State Key Laboratory of Applied Organic Chemistry for financial support.

## REFERENCES

1. Donnelly, D. M. X.; Meegan, M. J. *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky (Ed.); Pergamon Press: New York, 1984; Vol. 4.
2. Erber, S.; Ringshandl, R.; von Angerer, E. *Anti-Cancer Drug Des.* **1991**, *6*, 417–426.
3. McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67–76.
4. Judd, D. B.; Dowle, M. D.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Jack, T. I.; Pass, M.; Tranquillini, E.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Paton, J. M. S.; Hubbard, T.; Hilditch, A.; Drew, G. M.; Robertson, M. J.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Polly, J.; Eddershaw, P. J.; Bayliss, M. K.; Manchee, G. R.; Donnelly, M. D.; Walker, D. G.; Richards, S. A. *J. Med. Chem.* **1994**, *37*, 3108.
5. Nagahara, T.; Yokoyama, Y.; Inamura, K.; Katakura, S.; Komoriya, S.; Yamaguchi, H.; Hara, T.; Iwamoto, M. *J. Med. Chem.* **1994**, *37*, 1200.
6. Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1993**, *36*, 1425.
7. (a) Areadi, A.; Cacchi, S.; Marinelli, F. *Synthesis* **1986**, 749–751; (b) Torii, S.; Xu, L. H.; Okumoto, H. *Synlett* **1992**, 515–516; (c) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426–6428; (d) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K.

K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271; (e) Areadi, A.; Cacchi, S.; Delrosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280–9288; (f) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311–2314; (g) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101–5104; (h) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299; (i) Novák, Z.; Timári, G.; Kotschy, A. *Tetrahedron* **2003**, *59*, 7509–7513.

8. (a) Esen, B.; Ilia, F.; Peter, L. *Tetrahedron Lett.* **2005**, *46*, 2185–2187; (b) Zhang, H. M.; Eric, M.; Ferreira, B. M. S. *Angew. Chemie. Int. Ed.* **2004**, *43*, 6144–6148; (c) So, W. Y.; Jeong, I. E. *Org. Lett.* **2005**, *7*, 3355–3358.
9. (a) Yue, D. W.; Yao, T. L.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985–9989; (b) Furstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025; (c) Nakamura, I.; Mizushima, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023.
10. (a) Chen, C. Y.; Peter, G. D. *J. Org. Chem.* **2005**, *70*, 6964–6967; (b) Micheal, C. W.; Dawn, T.; Adam, T. G. *Org. Lett.* **2004**, *6*, 4755–4757.
11. (a) Novák, Z.; Nemes, P.; Kotschy, A. *Org. Lett.* **2004**, *6*, 4917; (b) Nagy, A.; Novák, Z.; Kotschy, A. *J. Organometallic Chem.* **2005**, *690*, 4453.
12. The aryl iodides were prepared according to the literature procedure: Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218–4227.
13. Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287–5291.