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Pd/C mediated synthesis of 2-substituted benzo[*b*]furans/nitrobenzo[*b*]furans in water☆

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Abstract—An efficient synthesis of 2-alkyl/aryl substituted benzo[*b*]furans/nitrobenzo[*b*]furans in water has been accomplished via Pd/C catalyzed reaction of *o*-iodophenols with terminal alkynes in the presence of PPh_3, CuI and prolinol. This method can tolerate a variety of functional groups present in the alkynes as well as base labile nitro group in the *o*-iodophenols. The protocol does not require the use of a phase transfer catalyst or water-soluble phosphine ligands and is free from the use of any organic co-solvent.

Benzo[*b*]furans are of considerable interest due to their occurrence in nature as well as their biological activities,[1,2] especially as anti-tumor agents,[3a] as calcium entry blockers[3b] or as potent inhibitors of protein tyrosine phosphatase 1B[3c] for the treatment of type 2 diabetes. They are also known to be useful inhibitors of 5-lipoxygenase (5-LO)[4a] and cyclooxygenase-2 (COX-2)[4b] for the treatment of inflammation and pain. Nitrobenzofurans also display interesting pharmacological properties.[4c–d]

In continuation of our research in a new drug discovery program, we have recently reported the synthesis of 3,4-diarylfuranones,[5] 3,4-diarylmaleic anhydrides,[6a] 1,5-diarylpyrazoles[6b] along with other heterocycles.[6c–d] In further pursuance of our research on the development of general methods for the synthesis of various oxygen containing heterocycles we became interested in the synthesis of benzofurans.[7] Various methods are known for the synthesis of benzo[*b*]furan and its derivatives of which the intramolecular cyclization of a suitably substituted benzene is the most commonly employed.[1,8] However, benzo[*b*]furans are the focus of many recent reports on transition metal-mediated heteroannulation especially alkyne-based palladium catalyzed reactions.[9]

In most of these cases the synthesis of the benzo[*b*]furans is accomplished through a tandem Sonogashira coupling/5-*endo*-*dig* cyclization starting from either *o*-alkynylphenols or *o*-iodophenols. Typically these reactions are carried out using a palladium catalyst and a copper salt[10] as co-catalyst in the presence of an amine base in an organic solvent. These one-pot palladium mediated protocols have advantages over the multi-step traditional methods in terms of functional group tolerability and yields. However, this single step coupling-cyclization was found to be less efficient when the starting *o*-iodophenols contain additional substitutents[11] especially base-labile nitro groups.[11a] In a few cases, formation of 1,3-diynes was observed to predominate over the normal coupling product.[11d]

Palladium catalyzed reactions in aqueous media have attracted much attention[12] recently because water based synthetic processes are inherently safer as well as inexpensive. Therefore, the use of water-soluble catalysts[12g] and water-soluble phosphine ligands, e.g. sulfonated phosphines[12f] have been explored successfully. The use of Pd/C-CuI-PPh_3 as catalyst system for efficient Sonogashira coupling of aryl halides with terminal alkynes has also been reported.[12e] When compared to the most frequently used expensive palladium catalysts [e.g. $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$ etc.], Pd/C-based methods have an economic advantage and hence remain attractive in large or industrial scale preparations. Nevertheless, all these Pd-catalyzed reactions are usually carried out in an aqueous-organic media and a co-solvent such as acetonitrile[12f] or DME[12e] is often required for these coupling reactions.

Keywords: benzo[*b*]furans; Sonogashira coupling/5-*endo*-*dig* cyclization; palladium catalyst; water.
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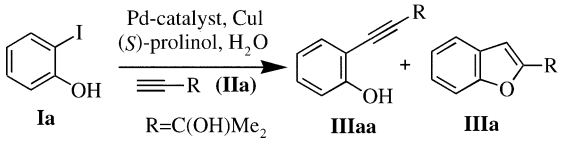
While the use of prolinol in the transition metal catalyzed Michael reaction in organic/aqueous media has been investigated,[13] its use in palladium catalyzed reactions is not common. Our continuing interest in palladium catalyzed reactions[14] prompted us to develop a mild and efficient method for the synthesis of 2-substitutedbenzo[*b*]furans via Pd/C catalyzed C–C bond formation reaction in water[9r] in the presence of prolinol.

Very recently we have developed an efficient method for the Sonogashira coupling of 3-iodoflavone with terminal alkynes in aqueous–dimethylformamide (H_2O–DMF) using prolinol as a base.[14e] To extend the scope and generality of this protocol we examined the reaction of *o*-iodophenol **Ia** with 2-methyl-3-butyn-2-ol **IIa** under various reaction conditions in the presence of (*S*)-prolinol (Table 1) in water. As can be seen, the *o*-ethynyl phenol derivative[9b,h] **IIIaa** was isolated as the major product[15] when the reaction was carried out in the presence of a Pd(0) complex and CuI for 3 h at 25°C (entry 1, Table 1). The cyclized product **IIIa** was isolated when the reaction temperature was increased to 80°C (entry 2, Table 1). The best result for the synthesis of **IIIa**, however, was achieved by using 10% Pd/C, PPh_3 along with CuI as a catalyst system (entry 5, Table 1) in a ratio of 1:4:2. Any change in this ratio resulted in inferior yields. Interestingly, unlike Pd(0) compounds the Pd/C mediated method required a higher temperature to afford **IIIaa** (entry 1 versus 4, Table 1) and no reaction was observed at 25°C (entry 3, Table 1). This clearly indicates that a new Pd(0) species generated in situ from Pd/C–PPh_3 at higher temperature is responsible for the coupling reactions.

Using the optimized protocol as detailed above (entry 5, Table 1), several 2-substituted benzo[*b*]furans and nitrobenzo[*b*]furans (previous synthesis of which often required a separation of regio-isomers or multi-step procedures)[16] were prepared in aqueous media. Thus, when *o*-iodophenol I[17a,b] was treated with 2–3 equivalents of terminal alkyne (**II**, R = alkyl, hydroxyalkyl etc.)[17c] in water in the presence of 10% Pd/C (0.03 equiv.), PPh_3 (0.12 equiv.), CuI (0.06 equiv.) and (*S*)-prolinol (3 equiv.) under nitrogen, benzofurans **III** were obtained as desired products.[17d] The results are summarized in Table 2.

While the yields were not optimized, the heteroannulation of acetylenic compounds in a single synthetic operation afforded the desired benzofurans **III** in good to excellent yields. By the use of this palladium catalyzed reaction a variety of terminal acetylenes were reacted with *o*-iodophenol (Table 2). Various substituents (including alkyl, hydroxyl, phenyl etc.) present in acetylenic compounds **II** were well tolerated during the course of the reaction and yields were generally high irrespective of the nature of the substituents present in the acetylenic component (entries 1–6, Table 2). Yields were also found to be good irrespective of the presence of nitro group in the starting *o*-iodophenol (Table 2 versus Table 3). This is in sharp contrast to an earlier report where the synthesis of nitrobenzofurans via a single step coupling-cyclization method using $(PPh_3)_2PdCl_2$–CuI as catalyst system afforded only low

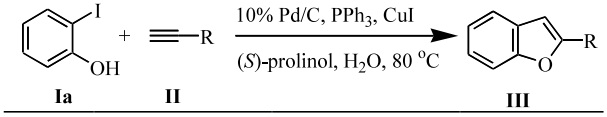
Table 1. Effect of base on the palladium catalyzed coupling reaction of *o*-iodophenol with 2-methyl-3-butyn-2-ol in aqueous media[a]

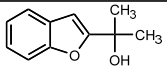
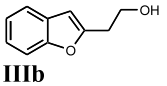
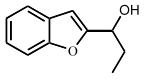
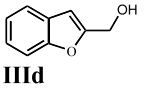
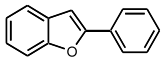
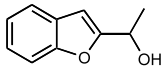


Entry	Pd-catalyst	Temp.(°C); time (h)	Yield (%)[c]	
			IIIaa[b]	**IIIa**[b]
1	$Pd(PPh_3)_4$	25; 3	50	21
2	$Pd(PPh_3)_4$	80; 3	n.d.	70
3[d]	10% Pd/C-PPh_3	25; 18	n.d.	n.d.
4[d]	10% Pd/C-PPh_3	50; 18	46	17
5[d]	10% Pd/C-PPh_3	80; 3	n.d.	85

[a] Reaction conditions: **Ia** (1.0 equiv), **II** (3.0 equiv), Pd-catalyst (0.05 equiv), CuI (0.10 equiv), (*S*)-prolinol (3 equiv) in water under N_2.
[b] Identified by ^1H NMR, ^{13}C NMR, IR, MS.
[c] Isolated yields.
[d] The reaction was carried out using 1:4:2 ratio of Pd/C:PPh_3:CuI. n.d. = not detected.

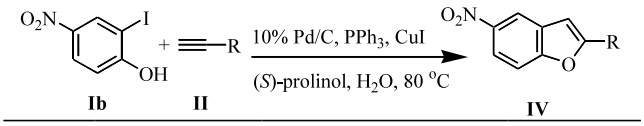
Table 2. Pd/C catalyzed synthesis of 2-substituted benzo[*b*]furans in aqueous media[a]



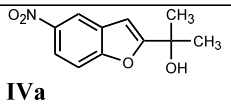
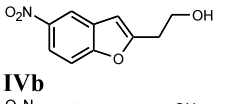
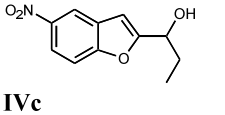
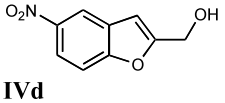
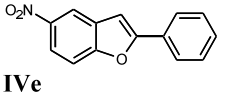
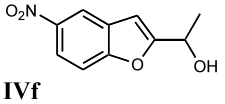
Entry	Substrate **II** R =	Products[b] **III**	Yield (%)[c] **III**
1	$C(OH)Me_2$ **IIa**	 **IIIa**	85
2	CH_2CH_2OH **IIb**	 **IIIb**	88
3	$CH(OH)C_2H_5$ **IIc**	 **IIIc**	87
4	CH_2OH **IId**	 **IIId**	76
5	C_6H_5 **IIe**	 **IIIe**	86
6	$CH(OH)CH_3$ **IIf**	 **IIIf**	87

[a] All reactions were carried out by using **Ia** (1.0 equiv), **II** (3.0 equiv), 1:4:2 ratio of Pd/C:PPh_3:CuI, (*S*)-prolinol (3 equiv) in water for 3 h. [b] Identified by ^1H NMR, ^{13}C NMR, IR, MS. [c] Isolated yields.

Table 3. Pd/C catalyzed synthesis of 2-substituted nitrobenzo[*b*]furans in aqueous media[a]

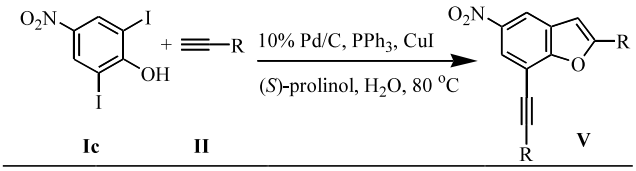


Ib **II** **IV**

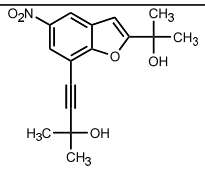
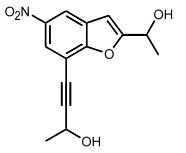
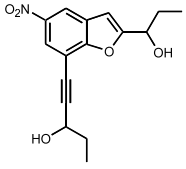
Entry	Substrate **II** R =	Products[b] **IV**	Yield (%)[c] **IV**
1	$C(OH)Me_2$ **IIa**	 **IVa**	79
2	CH_2CH_2OH **IIb**	 **IVb**	75
3	$CH(OH)C_2H_5$ **IIc**	 **IVc**	78
4	CH_2OH **IId**	 **IVd**	68
5	C_6H_5 **IIe**	 **IVe**	77
6	$CH(OH)CH_3$ **IIf**	 **IVf**	70

[a]All reactions were carried out by using **Ib**. For reaction condition see footnote 'a' of Table 1. [b]Identified by ^1H NMR, ^{13}C NMR, IR, MS. [c]Isolated yields.

Table 4. Pd/C catalyzed synthesis of 2-substituted-7-alkynylbenzo[*b*]furans in aqueous media[a]



Ic **II** **V**

Entry	Substrate **II** R =	Products[b] (**V**)	Yield (%)[c] **V**
1	$C(OH)Me_2$ **IIa**	 **Va**	75
2	$CH(OH)CH_3$ **IIf**	 **Vb**	70
3	$CH(OH)C_2H_5$ **IIc**	 **Vc**	75

[a]All reactions were carried out using **Ic**. For reaction condition see footnote 'a' of Table 1. [b]Identified by ^1H NMR, ^{13}C NMR, IR, MS. [c]Isolated yields.

to moderate yields of the desired products.[11a] Furthermore we successfully coupled terminal alkynes with 4-nitro-2,6-diiodophenol to give the expected 7-alkynyl benzofurans as the only products in good yields (Table 4).

The coupling reactions were usually carried out using 10%Pd/C–PPh_3 as catalyst and CuI as a co-catalyst in water. Apart from the low cost and stability, the use of Pd/C has advantages of ease of use and facilitation of reaction mixture work-up. It is noteworthy that the use of an organic co-solvent[12c] is not required in the present case and this eliminates recyclability (waste handling) problems. Moreover, neither a phase transfer catalyst[18a] nor water soluble phosphine ligands[12b,f] are required for the successful single step coupling–cyclization reaction.

While prolinol was used as a base in the present cases, the use of triethylamine was also investigated. Prolinol possesses better miscibility with water and therefore facilitated the coupling reaction affording better yields of products. Moreover, due to its lower volatility (thereby avoiding internal pressure development as well as ensuring its maximum recovery) in comparison to triethylamine, prolinol has advantages over the other amine bases[18b–c] especially in the large-scale preparation.

Mechanistically, the reaction may proceed[9h] via in situ generation of a prolinol-stabilized Pd(0)-complex which perhaps facilitates the reaction in aqueous media due to its interaction with the water molecules (via the hydroxyl group of prolinol). Further study is in progress to confirm the nature of the actual catalytic species involved in this coupling reaction.

In summary, we have described the first palladium on carbon mediated synthesis of 2-alkyl/aryl substituted benzo[*b*]furans/nitrobenzo[*b*]furans in water in the presence of prolinol. Since the water based syntheses are safer and inexpensive, the described methodology holds promise in modern organic synthesis. Some of the benzofurans synthesized were converted to compounds of potential biological interest.[19]

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15. The *o*-hydroxytolan **IIIaa** isolated was found to be a stable compound and no spontaneous cyclization was observed upon storage at room temperature as reported earlier in other cases. For example *o*-hydroxytolan used for the synthesis of XH-14, a benzofuran derivative isolated from the plant *Salvia miltiorrhiza*, showed a strong tendency to cyclize even upon storage at 4°C. See Lutjens, H.; Scammells, P. J. *Synlett* **1999**, 1079–1081.
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Scholz, T. H.; Schwam, H.; Shepard, K. L.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Sugrue, M. F. *J. Med. Chem.* **1990**, *33*, 749–754. For alternative access to nitrobenzo[*b*]furans via intramolecular condensation of suitably substituted nitrobenzenes, including intramolecular Wittig olefinations, see: (b) Chilin, A.; Rodighiero, P.; Guitto, A. *Synthesis* **1998**, 309–313; (c) Kaminsky, D.; Shavel, F.; Meitzer, I. *Tetrahedron Lett.* **1967**, 859–861; (d) Mooradian, A. *Tetrahedron Lett.* **1967**, 407–408. (e) Mooradian, A.; Dupont, P. E. *J. Heterocycl. Chem.* **1967**, *4*, 441–444.

17. *o*-Iodophenols were prepared according to the known procedure, see: (a) Kometani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 2043–2046; (b) Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287–5291; (c) All the terminal alkynes used are commercially available. (d) **General procedure for the preparation of 2-substituted benzo[*b*]furans (III, IV, V)**: A mixture of **I** (1 mmol), 10% Pd/C (32 mg, 0.03 mmol), PPh_3 (32 mg, 0.12 mmol), CuI (12 mg, 0.06 mmol) and (*S*)-prolinol (3.0 mmol) in H_2O (3 mL) was stirred at 25°C for 1 h under nitrogen. The acetylenic compound **II** (2–3 mmol) was added slowly to the mixture with stirring. The reaction mixture was then stirred at 80°C for 3 h. The mixture was cooled to room temperature, diluted with EtOAc (100 mL) and filtered through celite. The filtrate was collected, washed with cold water (2×50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by column chromatography (petroleum ether-EtOAc) to afford the desired product.
Spectral and analytical data for **IVa**: yellow solid; yield 79%; mp 60–62°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.46 (d, $J=1.9$ Hz, 1H), 8.20 (dd, $J=8.9$, 2.0 Hz, 1H), 7.53 (d, $J=8.9$ Hz, 1H), 6.73 (s, 1H), 2.18 (bs, D_2O exchangeable, OH), 1.70 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) 166.7, 157.5, 144.1, 128.7, 119.9, 117.4, 111.4, 101.2, 69.3 (C(OH)Me_2), 28.7 (2C, CH_3); IR (neat, cm^{-1}) 3394.4 (bs, OH), 1522.7; *m*/*z* (CI) 222 (M+1, 100); UV (MeOH, nm) 285, 243.5; HPLC: 99%, INERTSIL ODS 3V, 0.01M KH_2PO_4/CH_3CN, 1 mL/min, 243 nm, retention time 13.39 min. Elemental analysis found C, 59.49; H, 5.05; $C_{11}H_{11}NO_4$ requires C, 59.73; H, 5.01%.
IVb: light brown solid; yield 75%; mp 56–58°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.42 (d, $J=2.1$ Hz, 1H), 8.17 (dd, $J=9.1$, 2.1 Hz, 1H), 7.50 (d, $J=9.1$ Hz, 1H), 6.67 (s, 1H), 4.04 (t, $J=6.2$ Hz, 2H, CH_2OH), 3.09 (t, $J=6.2$ Hz, 2H, CH_2), 1.65 (bs, D_2O exchangeable, OH); IR (neat, cm^{-1}) 3115.0 (bs, OH), 1511.1; *m*/*z* (CI) 208 (M+1, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 159.9, 157.5, 143.8, 129.1, 119.3, 116.7, 110.9, 104.2, 59.9 (CH_2OH), 31.8 (CH_2); UV (MeOH, nm) 286.5, 244; HPLC: 99%. INERTSIL ODS 3V, 0.01M KH_2PO_4/CH_3CN, 1mL/min, 243 nm, retention time 11.86 min. Elemental analysis found C, 57.88; H, 4.40; $C_{10}H_9NO_4$ requires C, 57.97; H, 4.38%.
Va: light yellow solid; yield 75%; DSC: 137.80°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.38 (d, $J=1.9$ Hz, 1H), 8.24 (d, $J=1.9$ Hz), 6.74 (s, 1H), 2.30 (bs, D_2O exchangeable, OH), 1.72 (s, 6H, $2CH_3$), 1.70 (s, 6H, $2CH_3$); IR (neat, cm^{-1}) 3353.6 (bs, OH), 1531.3; *m*/*z* (CI) 304 (M+1, 80), 286 (M^+–OH, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 166.9, 157.0, 143.8, 128.6, 128.4, 123.0, 117.2, 107.8, 101.5, 74.7, 69.3 (C(OH)Me_2), 65.7 (C(OH)Me_2), 31.3 (2C, Me), 28.7 (2C, Me); UV (MeOH, nm) 260.5, 226.5, 221.5; HPLC: 99%, INERTSIL ODS 3V, 0.01M KH_2PO_4/CH_3CN, 1 mL/min, 260 nm, retention time = 13.54 min. Elemental analysis found C, 63.38; H, 5.55; $C_{16}H_{17}NO_5$ requires C, 63.36; H, 5.65%.

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