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Efficient synthesis of 5-nitro-benzo[*b*]furans via 2-bromo-4-nitro-phenyl acetates

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In memoriam of Professor Antonio Mario Tamburro, great man and tireless scientist

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ABSTRACT

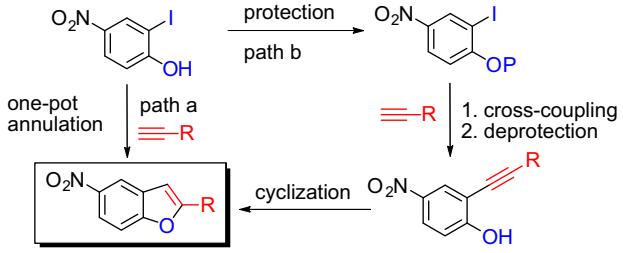
Acetylation/Sonogashira cross-coupling reaction/cyclization has been carried out in one-pot using a Na_2PdCl_4/2-(di-*tert*-butylphosphino)-*N*-phenylindole/CuI system in TMEDA to give 5-nitro-2-substituted benzo[*b*]furans in excellent yields. We also describe the extension of this method to 4-EWG-2-bromo-phenols obtaining 2,5-disubstituted-benzo[*b*]furans in good yields.

Benzo[*b*]furan derivatives are found abundantly in nature and are well known to possess various biological activities.[1–3] Benzo[*b*]-furan-based molecules have been also disclosed as the inhibitors of β-amyloid (Aβ) aggregation[4] and cyclooxygenase-2 (COX-2).[5] Consequently, there is an increasing interest in the synthesis of compounds containing benzo[*b*]furan moiety and a number of synthetic methods for their synthesis have been described in the literature.[6]

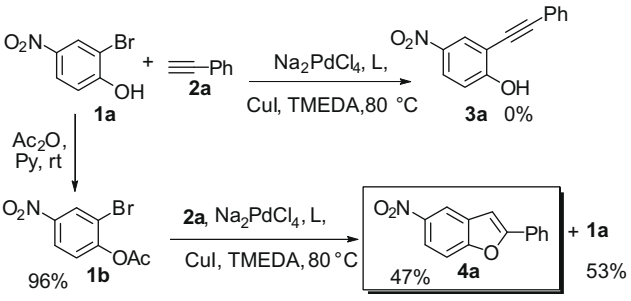
5-Nitro-benzofurans possess antibacterial and anti-cancer activities and recently have been used as a synthetical precursor of the new antiarrhythmic agent, dronedarone.[7] In connection with our research for the synthesis of biologically active compounds, we decided to evaluate a Sonogashira-based process[8] to access to 5-nitro-2-substituted-benzo[*b*]furans. They have been mostly obtained using Pd-catalyzed reactions: via a one-pot annulation of terminal alkynes and 2-iodophenols (path a)[9] or via cyclization of 2-alkynyl-phenols, prepared in three steps including O-protection, Sonogashira coupling, and O-deprotecting (path b),[10] (Scheme 1).

However, to the best of our knowledge, there are no examples of the synthesis of benzofurans using 2-bromo-4-nitrophenol derivatives as substrates.

Recently, highly efficient Sonogashira couplings have been obtained on aryl and heteroaryl bromides using 0.5 mol % of Na_2PdCl_4 in the presence of 1 mol% of 2-(di-*tert*-butyl phosphino)-*N*-indole as the ligand, with CuI as the co-catalyst and tetramethylethylenediamine (TMEDA) as the solvent at 80 °C.[11]



Scheme 1. General routes to 5-nitro-benzo[*b*]furans.



Scheme 2. Reactions of 2-bromo-4-nitrophenol derivatives with phenylacetylene **2a**.

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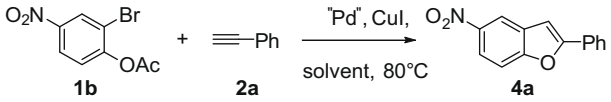
Table 1
Sonogashira coupling of 2-bromo-4-nitrophenyl acetate (**1b**) with phenylacetylene (**2a**) under various conditions[a]



Entry	Equiv of **2a**	Pd source	Solvent	*t* (h)	**4a** Yield[b] (%)
1	1.2	Na_2PdCl_4/L	TMEDA	5	47
2	4	Na_2PdCl_4/L	TMEDA	1	98
3	4	Na_2PdCl_4/L	Et_3N	7	98
4	4	$PdCl_2(PPh_3)_2$	TMEDA	4	23
5	1.2	$PdCl_2(PPh_3)_2$	Et_3N	24	Trace[c]
6[d]	2	Na_2PdCl_4/L	TMEDA	8	0[c]

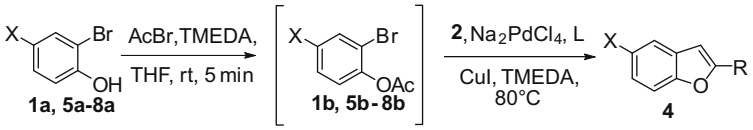
[a] Reactions were carried out with **1b** (1 equiv), phenylacetylene **2a**, 'Pd' (0.5 mol %), ligand (1 mol %), CuI (1 mol %) in solvent (1 M) at 80 °C and were monitored by TLC and GC–MS analysis.
[b] Isolated yield.
[c] Compound **1a** was obtained as the product.
[d] Reaction was carried out without CuI.

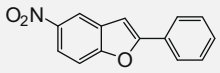
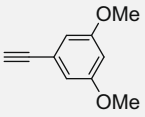
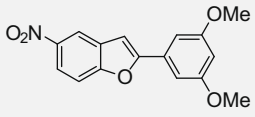
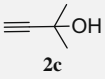
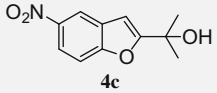
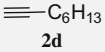
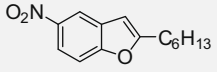
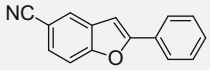
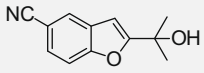
Herein we report the first application of the latter conditions for the synthesis of 5-nitro-2-substituted benzofurans using 2-bromo-4-nitro-phenol acetates as substrates. Firstly we examined this reaction protocol on 2-bromo-4-nitrophenol **1a** with phenylacetylene **2a**. However, no reaction occurred (Scheme 2).

It has been shown by Kotschy and co-workers[12] that acetylated bromophenols give very good results in terms of cross-coupling products if used in Sonogashira reaction, so we decided to use the acetate derivative **1b** as the substrate. The reaction of the latter with **2a** (1.2 equiv) gave after 5 h a mixture of the deacetylated bromide **1a** (53%) and benzo[*b*]furan **4a** (47%, Scheme 2 and Table 1, entry 1).

This result shows that **1b** can indeed afford the coupling product, which then undergoes in situ deacetylation followed by heteroannulation. The in situ deacetylation of the phenol group can be ascribed to the presence of the nitro group at the *para* position as well as to the basicity of TMEDA. In order to optimize the results avoiding the competitive deprotection reaction on **1b**, we used an excess of **2a**. More than 2 equiv was necessary to obtain **4a** in high selectivity (98% yield after 1 h, Table 2, entry 2). Na_2PdCl_4 in Et_3N also gave **4a** in high yield, but with longer reaction time (entry 3). It should be noted that $PdCl_2(PPh_3)_2$, used as the catalyst, afforded **4a** in only 23% yield if used in the TMEDA and only trace in Et_3N (Table 1, entries 4 and 5). With the aim of reducing the

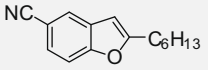
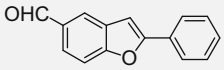
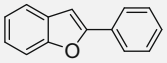
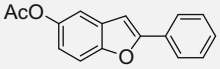
Table 2
One-pot synthesis of 2,5-disubstituted-benzofurans (**4**) starting from 2-bromo-4-substituted phenols (**1a**, **5a**–**8a**)[a]



Entry	X	Bromide	Alkyne **2**	*t* (h)	Benzofuran **4**	Yield[b] (%)
1	NO_2	**1a**	**2a**	1.5	 **4a**	99
2	NO_2	**1a**	 **2b**	9	 **4b**	79
3	NO_2	**1a**	 **2c**	7	 **4c**	99[c]
4	NO_2	**1a**	 **2d**	4	 **4d**	97
5	CN	**5a**	**2a**	5.5	 **4e**	94
6	CN	**5a**	**2c**	23	 **4f**	89[c]

(*continued on next page*)

Table 2 (*continued*)

Entry	X	Bromide	Alkyne **2**	*t* (h)	Benzofuran **4**	Yield[b] (%)
7	CN	**5a**	**2d**	16	 **4g**	90
8	CHO	**6a**	**2a**	26	 **4h**	24
9	H	**7a**	**2a**	12	 **4i**	87[e]
10[d]	OH	**8a**	**2a**	14	 **4j**	23[e]

[a] Reactions were carried out with **1a**, **5a**–**8a** (1 equiv), acetyl bromide (1 equiv), TMEDA (1 equiv), THF (1 M), **2** (4 equiv), Na_2PdCl_4 (0.5 mol %), 2-(di-*tert*-butyl phosphino)-*N*-indole (1 mol %), CuI (1 mol %) in TMEDA (1 M) at 80 °C and were monitored by TLC and GC–MS analysis. All products were characterized by NMR spectroscopy and mass spectrometry (EI MS).

[b] All yields are isolated yields after column chromatography.

[c] Conversion evaluated by GC–MS analysis.

[d] Reaction was carried out with 2 equiv of acetyl bromide and 8 equiv in all of **2a**.

[e] After 10 h was added KO^{t}Bu (2 equiv) to convert the cross-coupling products **9** and **10** into the cyclic ones.

Glazer-type oxidative dimerization of terminal alkyne due to the presence of copper(I) co-catalyst, the copper-free condition was tested without any success (Table 1, entry 6).

The one-pot acetylation/coupling/cyclization of 2-bromo-4-nitrophenol **1a** to **4a** was equally successful.[13] Acetylation of **1a** was complete in 5 min at room temperature (monitored by TLC) using acetyl bromide (1 equiv), TMEDA (1 equiv), and THF (1 M). After the addition of **2a** (4 equiv), TMEDA (1 M), and the catalyst system the Sonogashira coupling/cyclization reached full conversion in less than 2 h affording **4a** in 99% yield (starting from **1a**, entry 1 in Table 2).

The generality of this protocol was then investigated under the optimized reaction conditions. Table 2 shows that several commercial alkynes can react with bromide **1a** to give compounds **4b**–**d** in very good yields (entries 2–4). It can be noted that bromide **1b** was completely transformed into **4c** only when 1.2 equiv of **2c** was used (Table 2, entry 3), but significant decomposition during the purification occurred.

Encouraged by these results we further investigated the reaction of EWG-substituted bromides under similar conditions. When the substituents were the cyano- and the formyl-group acetates **5b** and **6b** afforded benzofurans **4e** and **4h** in 94% and 24% yields, respectively. The formation of **4h** was in competition with the hydrolysis of the acetyl group of **6b**, as the other product of the reaction was the deacetylated bromophenol **6a.**

Unfortunately but unsurprisingly, unsubstituted *o*-bromophenol **7a** and 2-bromo-1,4-dihydroxybenzene **8a** gave under these reaction conditions lower yields of benzofurans **4i** and **4j** along with cross-coupling products **9** and **10** (Fig. 1). Adding 2 equiv of KO^{t}Bu in the same vessel compounds **9** and **10** were converted into benzofurans **4i** and **4j** (87% and 23% yields, respectively; Table 2 entries 9 and 10). In the case of the reaction of **8b** the main reaction product corresponded to the fully hydrolyzed bromide **8a**.

From the results obtained, it is clear that substrates **1a** and **5a** are the most reactive in these coupling/cyclization sequences. Although 4 equiv of alkynes has been used, this protocol provides a facile access to a large number of 5-nitro-2-substituted-benzofurans in excellent yields, starting from commercially available aryl bromide **1a** and alkynes **2a**–**d**.

The synthesis of benzo[*b*]furans is strongly limited by the nature of the substituents on the aromatic ring, which can be regarded as switches of the reaction direction. Phenols bearing electron-withdrawing groups led exclusively to the target benzofurans while their analogues with electron-donating substituents (or without any substituent) gave previously the cross-coupling products and after the addition of a base the desired cyclic ones.

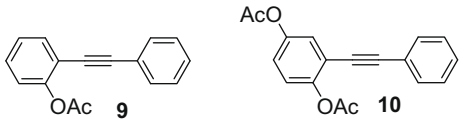


Figure 1. Cross-coupling products **9** and **10**.

4-EWG-2-bromophenols are valuable synthetic tools for a one-pot preparation of 2,5-disubstituted-benzofurans using Na_2PdCl_4/L/CuI/TMEDA system.

Further investigations to utilize this method and these compounds for more complex molecules are currently underway in our laboratory.

Acknowledgment

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13. *General procedure for the one-pot synthesis of 2,5-disubstituted-benzofurans*. AcBr (1 equiv) was added dropwise to a solution of bromophenol **1a**, **5a–8a** (1 equiv) and TMEDA (1 equiv) in dry THF and the resulting mixture was stirred at room temperature for 5 min. After total conversion of starting bromophenol to the corresponding acetylated product **1b**, **5b–8b** (monitored by TLC), the flask was charged with Na_2PdCl_4 (0.5 mol %), 2-(di-*tert*-butyl phosphino)-*N*-indole (1 mol%), and copper iodide (1 mol %). TMEDA (1 M) and the acetylene substrates **2a–e** (4 equiv) were added successively under argon atmosphere and the resulting mixture was stirred at 80 °C. After cooling to room temperature, water was added and the mixture was extracted with diethyl ether. The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude was purified by silica gel column chromatography to provide the desired products **4a–h** in moderate to excellent yields (24–99%). Compounds **4i** and **4j** were obtained by base-promoted cyclization of acetylated alkynylphenols **9** and **10**. Two equivalents of KO^{t}Bu were added in the same pot for 2 h before cooling the mixture. *2-(3,5-Dimethoxy-phenyl)-5-nitro-benzo[b]furan* **4b**. Yield 79%; (found: C, 64.18; H, 4.70. $C_{16}H_{13}NO_5$ requires C, 64.21; H, 4.68); pale yellow solid; mp 178–180 °C; ν (KBr, cm^{-1}) 3020, 1562, 1260, 1138, 1113; δ_H (500 MHz, $CDCl_3$) 3.91 (6H, s, OC*H*$_3$), 6.55 (1H, s, C*H*), 7.04 (2H, s, C*H*), 7.14 (1H, s, C*H*), 7.62 (1H, d, *J* 9.0, C*H*), 8.24 (1H, d, *J* 9.0, C*H*), 8.56 (1H, s, C*H*); δ_C (125 MHz, $CDCl_3$) 55.5, 101.9, 102.1, 103.4, 111.4, 117.3, 120.2, 129.5, 130.8, 144.3, 157.5, 159.0, 161.2; *m*/*z* (EI) M$^+$ 299 (100), 283 (5), 269 (10), 253 (15). *2-Hexyl-5-nitro-benzo[b]furan* **4d**. Yield 97%; (found: C, 68.30; H, 5.69. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 5.66); yellow oil; ν (KBr, cm^{-1}) 3018, 1592, 1524, 1346, 1265, 754; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, m, C*H*$_3$), 1.35 (6H, m, C*H*$_2$), 1.75 (2H, m, C*H*$_2$), 2.81 (2H, t, *J* 8, C*H*$_2$), 6.52 (1H, s, C*H*), 7.47 (1H, d, *J* 8.8, C*H*), 8.16 (1H, d, *J* 8.8, C*H*), 8.42 (1H, s, C*H*); δ_C (125 MHz, $CDCl_3$) 14.1, 22.5, 28.5, 28.8, 31.5, 102.6, 110.9, 116.6, 119.2, 128.8, 129.4, 130.9, 157.6, 163.5; *m*/*z* (EI) M$^+$ 247 (50), 176 (100), 130 (70), 95 (98). *2-Hexyl-benzo[b]furan-5-carbonitrile* **4g**. Yield 90%; (found: C, 79.40; H, 7.57. $C_{15}H_{17}NO$ requires C, 79.26; H, 7.54); pale yellow oil; ν (KBr, cm^{-1}) 2190, 1590, 1340, 790, 720; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C*H*$_3$), 1.32 (6H, m, C*H*$_2$), 1.73 (2H, m, C*H*$_2$), 2.77 (2H, t, *J* 8, C*H*$_2$), 6.41 (1H, s, C*H*), 7.45 (2H, s, C*H*), 7.78 (1H, s, C*H*); δ_C (125 MHz, $CDCl_3$) 14.1, 22.5, 27.4, 28.4, 28.8, 31.5, 101.7, 106.2, 111.8, 119.7, 125.0, 126.9, 129.7, 156.4, 162.5; *m*/*z* (EI) M$^+$ 227(30), 156 (100), 95(70).