Pergamon

Tetrahedron Letters 43 (2002) 9377–9380

TETRAHEDRON LETTERS

Chemistry of aminophenols. Part 3: First synthesis of nitrobenzo[*b*]furans via a coupling–cyclization approach†

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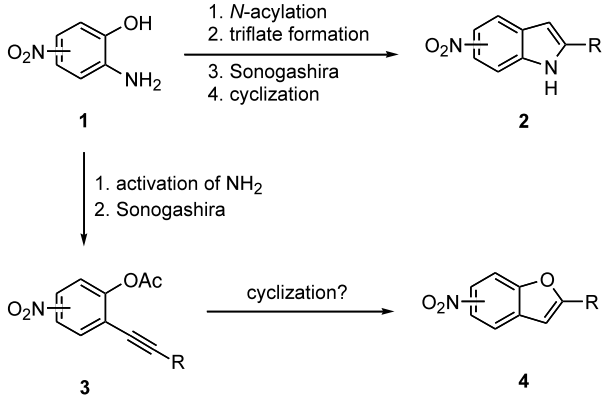
Received 30 September 2002; accepted 11 October 2002

Abstract—The first synthesis of 4-, 5-, and 6-nitrobenzo[*b*]furans has been achieved via the Sonogashira cross-coupling reaction of 2-iodonitrophenol acetates prepared from commercially available and inexpensive 2-aminonitrophenols. The obtained 2-alkynylnitrophenol acetates were subjected to a KO^{t}Bu-promoted cyclization at room temperature to form nitrobenzo[*b*]furans. Examples of the synthesis of other substituted benzo[*b*]furans and the one-pot coupling–cyclization are given.

Benzo[*b*]furans[1] are the focus of many recent reports on transition metal-mediated heteroannulation. They can be synthesized via the reactions of 2-halophenols with copper(I) acetylides[1b–c,2] and via the palladium-catalyzed heteroannulation of 2-halophenols with terminal[3] or internal alkynes.[4] In particular, the carbonylative heteroannulation of 2-alkynylphenols is very useful for the synthesis of benzo[*b*]furans possessing a 3-acyl moiety.[3e,5] Moreover, benzo[*b*]furans exhibit diverse biological activities. For example, they have been reported as ligands of the adenosine A_1 receptor[2,6a] and mitochondrial DBI (diazepam binding inhibitor) receptor complex (mDRC),[6b] and as antagonists for the angiotensin II receptor,[6c–e] the brain CB1 receptor,[6f] the central and peripheral $GABA_B$-receptor,[6g] and oxytocin (OT), a neurophyseal hormone.[6h,i] Benzo[*b*]furan-based molecules have been disclosed as the inhibitors of β-amyloid (Aβ) aggregation,[6j,k] and cyclooxygenase-2 (COX-2).[6l]

Because direct nitration of benzo[*b*]furans often gives mixtures of isomers,[7] the best access to nitrobenzo[*b*]furans is the intramolecular condensation of suitably substituted nitrobenzenes, including the intramolecular Wittig olefinations.[8,9] To the best of our knowledge, the palladium-catalyzed heteroannulation has not been applied to the synthesis of nitrobenzo[*b*]furans. This may be attributed to the difficulty in promoting cyclization of 2-alkynylnitrophenol derivatives, such as **3**, due to the base-labile nitro group (Scheme 1). Recently, we have established a general synthesis of indoles from 2-aminophenols, including nitroindoles **2** from 2-aminonitrophenols **1**, by converting the phenolic OH into the triflate for the Sonogashira cross-coupling followed by a KO^{t}Bu-promoted cyclization.[10] We report here on the first synthesis of nitrobenzo[*b*]furans **4** via a coupling–cyclization approach from **1**.

As shown in Scheme 1, the key step in the synthesis of **4** relies on the successful cyclization of **3** under a



Scheme 1. Synthesis of nitroindoles and nitrobenzo[*b*]furans from common 2-aminonitrophenols.

Keywords: coupling reactions; benzofurans; phenols; aryl iodides.

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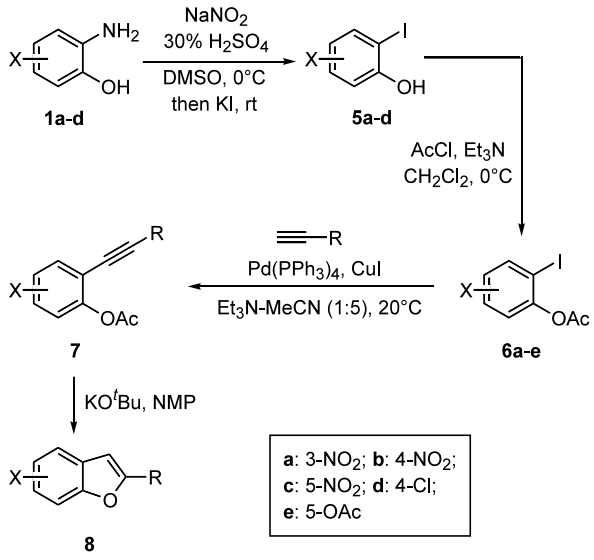
† The Institute of Molecular Technology for Drug Discovery and Synthesis is supported by The Areas of Excellence Scheme (AoE/P-10/01) established under The University Grants Committee of Hong Kong SAR, China.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02333-X

suitable set of conditions since the nitro group is sensitive to strong basic conditions at high temperature. Various bases such as NaOEt,[11a,b] CuO^{t}Bu,[11c] TMG (in refluxing toluene),[11d] or Et_3N (60°C)[11e] are known to facilitate the cyclization of 2-alkynylphenols. Arcadi and Cacchi reported the cyclization of 2-alkynylphenol acetates using hot piperidine (MeOH, 60°C) or KO^{t}Bu (NMP, 70°C).[3a] Similarly, NaOEt in refluxing EtOH was used for the cyclization of a simple 2-alkynylphenol acetate.[11a] For the cyclization of 2-alkynylphenol mesylate, silyl ether, and methyl ethers, KOH,[12a] TBAF,[12b,c] $Hg(OAc)_2$,[12d] and pyridinium chloride (at 200°C)[12e] were used, respectively. However, the nitro-substituted substrates were not examined in these previous studies described above. Recently, an iodocyclization of 2-alkynylphenols[13a] or acetates[13b] was disclosed by Arcadi and Cacchi to form 3-iodobenzo[*b*]furans, which allow further cross-coupling reactions at the C3 position. Unfortunately, all reported examples include only moderately electron-withdrawing PhC(O)- and EtO_2C-groups. Therefore, it is desirable to explore the coupling–cyclization method for the synthesis of nitrobenzo[*b*]furans.[3a]

Scheme 2 illustrates the synthesis of 4-, 5-, and 6-nitrobenzo[*b*]furans starting from 2-amino-3-nitrophenol **1a**, 2-amino-4-nitrophenol **1b**, and 2-amino-5-nitrophenol **1c**.[14] Selective activation of the amino group in **1a–c** was achieved via a one-pot diazotization–iodination sequence to give 2-iodonitrophenols **5a–c** in 95–97% yields.[15] Similarly, the 4-Cl analog **5d** was prepared in 89% yield. Because direct cross-coupling of **5a–c** with 1-alkynes gave low yields of nitrobenzo[*b*]furans (vide infra), the phenols **5a–c** were first converted to the corresponding acetates **6a–c**, which were then subjected to the Sonogashira cross-coupling catalyzed by Pd(0)–Cu(I). In general, iodobenzenes possessing an additional nitro group are very reactive substrates for the Pd-catalyzed cross-coupling reactions. We noted that the reactivity of **6a–c** was dependent on the position of the nitro group. For 2-iodo-3-nitrophenol acetate **6a**, the cross-coupling reactions with phenylacetylene and 1-pentyne took place at 70°C to afford **7a** and **7d** in 83% and 76% yields, respectively, whereas the products **7b**,**c**,**e**,**f** were formed from **6b**,**c** at 20°C in 86–100% yields (entries 1–6, Table 1). Under similar cross-coupling conditions at 20°C, the alkynes **7g–j** were obtained from **6d**,**e**[16] in 83–96% yields (entries 7–10, Table 1).

Next, the cyclization of 2-alkynylphenol acetates **7** was investigated (Table 1).[14] For the nitro-substituted substrates **7a-f**, the ring closure reaction was carried out at 20°C using KO^{t}Bu[3a,10] as the base. We observed significant decomposition at high temperature and the starting materials disappeared rapidly. The phenylethynyl-substituted compounds **7a–c** afforded the nitrobenzo[*b*]furans **8a–c** in good to excellent yields when 1 equiv. of KO^{t}Bu was employed (entries 1–3, Table 1). Similarly, the pentyn-1′-yl-substituted **7f** underwent the cyclization to produce **8f** in 67% yield. In contrast, **7d**,**e** gave lower yields of 4- and 5-nitrobenzo[*b*]furans **8d**,**e** in the presence of 2 equiv. of KO^{t}Bu



Scheme 2. Synthesis of C4-, C5-, and C6-nitrobenzo[*b*]furans.

Table 1. KO^{t}Bu-promoted cyclization of **7**

Entry	**7**: X;[a] R	KO^{t}Bu (equiv.)	T (°C); t (h)	**8** (%)[b]
1	**7a**: 4-NO_2; Ph[c]	1	20; 2.5	**8a** (76)
2	**7b**: 5-NO_2; Ph	1	20; 7	**8b** (56)
3	**7c**: 6-NO_2; Ph	1	20; 1	**8c** (93)
4	**7d**: 4-NO_2; ^{n}Pr[c,d]	2	20; 2	**8d** (12)
5	**7e**: 5-NO_2; ^{n}Pr	2	20; 2	**8e** (53)
6	**7f**: 6-NO_2; ^{n}Pr	1	20; 5	**8f** (67)
7	**7g**: 5-Cl; Ph	2	80; 0.3	**8g** (92)
8	**7h**: 6-OAc; Ph	2	80; 1	**8h** (58)[e]
9	**7i**: 5-Cl; ^{n}Pr	2	80; 0.3	**8i** (71)
10	**7j**: 6-OAc; ^{n}Pr	2	80; 1	**8j** (92)[e]
11	**7k**: 5-NH_2; Ph	2.5	20; 7	**8k** (75)

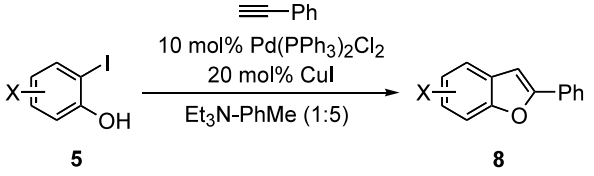
[a] Benzo[*b*]furan numbering.
[b] Isolated yield.
[c] Formed at 70°C.
[d] $Pd(PPh_3)_2Cl_2$ was used in place of $Pd(PPh_3)_4$.
[e] 6-OH.

(entries 4–6, Table 1). Prolonged reaction time or high temperature usually resulted in complete decomposition and no products could be identified from the reaction mixtures. For example, the isolated yield of **8e** upon treatment of **7e** with 2 equiv. of KO^{t}Bu was 0% (80°C, 15 min), 28% (20°C, 24 h), 31% (20°C, 4 h), and 53% (20°C, 2 h), respectively. 4-Nitro-substituted **7d** completely decomposed in the presence of 1 equiv. of KO^{t}Bu at 20°C for 4 h. On the basis of these results, it seems that low yields of nitrobenzo[*b*]furans from the KO^{t}Bu-promoted cyclization are attributed to the instability of the products under the basic conditions. Fur-

ther evidence was obtained to support the above argument. For the Cl- and OAc-substituted substrates **7g–j**, cyclization occurred at 80°C with 2 equiv. of the base to form the 5-Cl and 6-OH benzo[*b*]furans **8g–j** in 58–92% yields (entries 7–10, Table 1). Furthermore, the 5-aminobenzo[*b*]furan **8k** was obtained in a higher yield than the 5-nitro analog **8b** (entry 11, Table 1).

We examined the one-pot coupling–cyclization of 2-iodonitrophenols **5a–c** (Table 2).[14] We found that toluene is a better solvent for the reactions of **5a–c** and that the reaction temperature had a negligible effect on the yield of the product (entries 3–5, Table 2). The 4-, 5-, and 6-nitrobenzo[*b*]furans **8a–c** were obtained via the one-pot synthesis at 20°C in 12%, 66%, and 28% yields, respectively (entries 1–3, Table 2). For comparison, we carried out the reactions of 2-iodophenols **5f** and **5g** in DMF–Et_3N at 80°C and isolated **8l** and **8m** in 89% and 85% yields, respectively (entries 6 and 7, Table 2). Compound **8m** is a useful intermediate for the synthesis of 5-nitrogen-substituted 2,3-diarylbenzo[*b*]furan **9** of the known selective COX-2 inhibitor (Scheme 3).[6l]

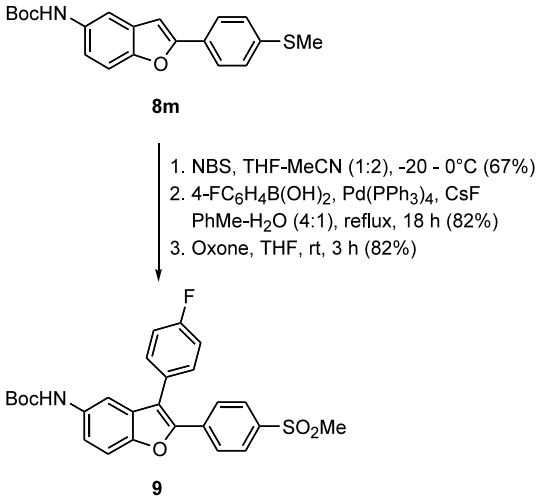
Table 2. One-pot synthesis of benzo[*b*]furans **8**



5 **8**

Entry	X[a]	5	T (°C)	*t* (h)	8 (%)[b]
1	4-NO_2	**5a**	20	1/4	**8a** (12)
2	5-NO_2	**5b**	20	1/3	**8b** (66)
3	6-NO_2	**5c**	20	2	**8c** (28)
4	6-NO_2	**5c**	55–60	1/4	**8c** (29)
5	6-NO_2	**5c**	110	1	**8c** (25)
6	H	**5f**	80[c,d]	18	**8l** (89)
7	5-X[e]	**5g**	80[c,f]	24	**8m** (85)

[a] Benzo[*b*]furan numbering.
[b] Isolated yield.
[c] DMF was used instead of PhMe.
[d] 5 mol% $Pd(PPh_3)_2Cl_2$ and 10 mol% CuI were used.
[e] X = NHBoc.
[f] 4-$MeSC_6H_4C{\equiv}CH$ was used instead of $PhC{\equiv}CH$.



Scheme 3. Synthesis of 2,3-diarylbenzo[*b*]furan **9**.

In summary, we have synthesized, for the first time, 4-, 5-, and 6-nitrobenzo[*b*]furans using inexpensive 2-aminonitrophenols **1a–c** via coupling–cyclization reactions.[3a] Both stepwise and one-pot reactions were examined and good yields of nitrobenzo[*b*]furans were obtained for the reactions of selected 2-iodonitrophenols and 1-alkynes. This method can be applied to the synthesis of the nitrogen-substituted analogs of bioactive benzo[*b*]furans[6] and thus deserves further optimization.

Acknowledgements

This work is supported in part by The Areas of Excellence Scheme (AoE/P-10/01) of Hong Kong SAR, China.

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