JOC*Note*

# A Rapid Synthesis of 2-Aryl-5-substituted-2,3-dihydrobenzofurans

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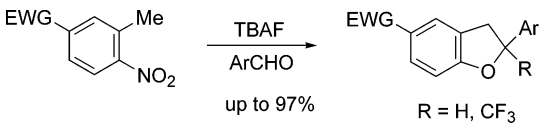
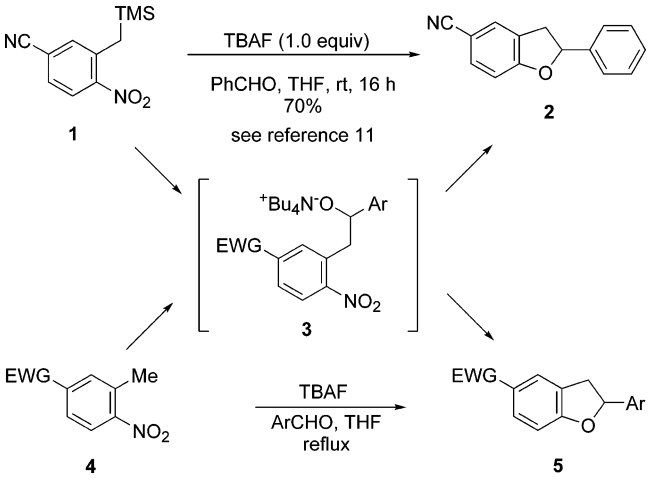



An effective strategy has been developed for the rapid and efficient one-pot synthesis of 2-aryl-5-substituted-2,3-dihydrobenzofurans from readily available *o*-nitrotoluenes and aromatic aldehydes. This strategy allows access to a structurally diverse array of products for further manipulation.

The 2,3-dihydrobenzofuran ring system constitutes the core skeleton of an increasing number of neolignan natural products that have been identified possessing a range of biological activity.[1] In addition, 2,3-dihydrobenzofurans have been developed for the treatment of traumatic and ischemic central nervous system (CNS) injury,[2] and are reported to be useful in the treatment of arteriosclerosis, hepatopathy, and cerebrovascular disease.[3] Common approaches to the 2,3-dihydrobenzofuran ring system involve biomimetic couplings of quinones and phenylpropenyl moieties,[4] anionic,[5] benzyne,[6] dehydrative,[7] electrocyclic,[8] radical,[9] and transition metal-mediated[10] cyclizations. To fully define biological profiles, strategies which provide rapid access to highly functionalized 2,3-dihydrobenzofurans not accessible through current techniques are important synthetic tools. Our general approach to the 2,3-dihydrobenzofuran ring system was guided by the work of Bartoli, who investigated the reaction of 4-cyano-1-nitro-2-[(trimethylsilyl)-methyl]benzene **1** with benzaldehyde. In the presence of an equimolar amount of TBAF, the 5-cyano-2,3-dihydro-2-phenylbenzofuran **2** was obtained in 70% yield (Scheme 1).[11] In connection with our ongoing programs involving the reactions of *o*-trimethylsilylmethylnitrobenzenes,[12] we began to investigate the Bartoli methodology in greater detail. On the basis of our own observations, it was apparent that tetrabutylammonium fluoride (TBAF)

**SCHEME 1**




(1) (a) Donnelly, B. J.; Donnelly, M. X.; O'Sullivan, A. M.; Prendergast, J. P. *Tetrahedron* **1969**, *25*, 4409. (b) Hayashi, T.; Thomson, R. H. *Phytochemistry* **1975**, *14*, 1085. (c) Gregson, M.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Dietrichs, H. H.; Gottlieb, O. R. *Phytochemistry* **1978**, *17*, 1395. (d) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183. (e) Ward, R. S. *Nat. Prod. Rep*. **1997**, *14*, 43. (f) Benevides, P. J. C.; Sartorelli, P.; Kato, M. J. *Phytochemistry* **1999**, *52*, 339. (g) Nascimento, I. R.; Lopes, L. M. X. *Phytochemistry* **1999**, *52*, 345. (h) Gordaliza, M.; Castro, M.; Corral, J. M.; Lopez-Vazquez, M.; Feliciano, A. S.; Faircloth, G. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2781. (i) Tsai, I.-L.; Hsieh, C.-F.; Duh, C.-Y. *Phytochemistry* **1998**, *48*, 1371. (j) Chen, C.-H.; Shaw, C.-Y.; Chen, C.-C.; Tsai, Y.-C. *J. Nat. Prod.* **2002**, *65*, 740. (k) Apers, S.; Paper, D.; Bürgermeister, J.; Baronikova, S.; Van Dyck, S.; Lemière, G.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2002**, *65*, 718. (l) Satorelli, P.; Benevides. P. J. C.; Ellensohn, R. M.; Rocha, M. V. A. F.; Moreno, P. R. H.; Kato, M. J. *Plant Sci.* **2001**, *161*, 1083.

(2) Ohkawa, S.; Fukatsu, K.; Miki, S.; Hashimoto, T.; Sakamoto, J.; Doi, T.; Nagai, Y.; Aono, T. *J. Med. Chem.* **1997**, *40*, 559.

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(5) Solladié, G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1995**, *51*, 9559.

(6) (a) Birkett, M. A.; Knight, D. W.; Mitchel, M. B. *Tetrahedron Lett.* **1993**, *34*, 6939. (b) Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchel, M. B. *Tetrahedron* **2000**, *56*, 1013.

(7) (a) Yamashita, M.; Ono, Y.; Tawada, H. *Tetrahedron* **2004**, *60*, 2843. (b) Stafford, J. A.; Valvano, N, L. *J. Org. Chem.* **1994**, *59*, 4346. (c) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1993**, *34*, 7483.

(8) Ponpipom, M. M.; Yue, B. Z.; Bugianesi, R. L.; Brooker, D. R.; Chang, M. N.; Shen, T. Y. *Tetrahedron Lett.* **1986**, *27*, 309.

(9) (a) Jiménez, M. C.; Miranda, M. A.; Tormos, R. *J. Org. Chem.* **1998**, *63*, 1323. (b) Meijs, G. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 5890.

(10) (a) Larock, R. C.; Berrios-Pēna, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. (b) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (c) Larock, R. C.; Yang, H.; Pace, P.; Narayanan, K.; Russell, C. E. *Tetrahedron* **1998**, *54*, 7343. (d) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett*. **2002**, *4*, 3887. (e) Szlosek-Pinaud, M.; Diaz, P.; Martinez, J.; Lamaty, F. *Tetrahedron Lett.* **2003**, *44*, 8657. (f) Zheng, S.-L.; Yu, W.-Y.; Xu, M.-X.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 1445. (g) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615. (h) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237.

(11) Bartoli, G.; Bosco, M.; Caretti, D.; Dalpozzo, R.; Todesco, P. E. *J. Org. Chem.* **1987**, *52*, 4381.

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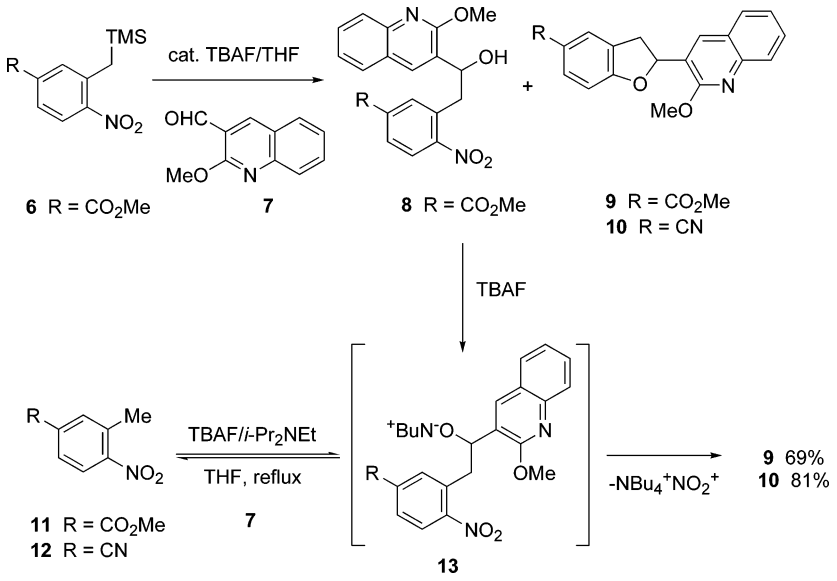
**SCHEME 2**




might be basic enough to promote the direct formation of the expected tetrabutylammonium alkoxide intermediate **3** from unfunctionalized *o*-nitrotoluenes **4**. The direct use of simple and often commercially available *o*-nitrotoluenes for the preparation of highly functionalized 2,3-dihydrobenzofurans of type **5** would greatly simplify the Bartoli two-step sequence and promote wider application in the synthesis of dihydrobenzofurans. In this Note, we document the realization of this approach with a practical, high-yielding, one-pot procedure for the preparation of 2-aryl-5-substituted-2,3-dihydrobenzofurans.

Investigations began with trimethylsilymethylnitrobenzene **6**.[13] Reaction of a mixture of **6** and aldehyde **7**[14] with a catalytic amount of TBAF afforded the expected alcohol **8** in 79% yield together with a trace amount of dihydrobenzofuran **9** (Scheme 2).[15] Treatment of alcohol **8** with TBAF (1.5 equiv) at room temperature gave a mixture of aldehyde **7** (20%), dihydrobenzofuran **9** (40%), and nitrotoluene **11** (20%). This product distribution suggested that a reversible carbonyl addition process may be occurring leading to the possibility that reaction of nitrotoluene **11** with **7** in the presence of TBAF may provide **9** directly. In a simple validation of this hypothesis, reaction of **11** and **7** with 1.5 equiv of TBAF in refluxing THF for 3 h furnished **9** in 57% yield. However, when the reaction was conducted in the presence of 2 equiv of Hünig's base, which effectively removed the liberated HF from the reaction mixture, the yield of **10** increased to 69%. The major byproduct observed was hydrolysis of the methyl ester of **11** to give the corresponding benzoic acid.[16] There was no significant amount of ester hydrolysis of **9** observed under the reaction conditions even after prolonged reaction times. Reaction of 3-methyl-4-nitrobenzonitrile **12** with aldehyde **7** furnished dihydrobenzofuran **10** in 81% yield. The overall sequence was general and gave access to a structurally diverse array of substituted 2,3-dihydrobenzofurans in good to excellent yields in a one-pot operation from commercially available nitrotoluenes **11** and **12** (Table 1). Other bases and conditions were also examined. For example, reaction of **12** with aldehyde **33** in the presence of benzyltrimethylammonium hydroxide (Triton B)[17] gave **34** in similar yield and reaction profile as when TBAF was employed (Table 1, entry 12). While reaction of **12** and **33** in the presence of NaOMe in DMSO[18–20] furnished **34** in low yield (<60%), cyclization of the alcohol intermediate remained incomplete and the formation of numerous byproducts was observed. The use of Hünig's base, $CsCO_3$/MeOH,[21] NaOMe, or KO*t*-Bu in refluxing THF, $NH_4OH$, $Bu_4NCl$, and DBU/DMSO resulted in no reaction ($CsCO_3$/MeOH, $NH_4OH$, and Hünig's base), formation of multiple reaction products (NaOMe or KO*t*-Bu in refluxing THF), or stalling at the alcohol interme-

(12) (a) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3721. (b) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3975. (c) Wong, A.; Kuethe, J. T.; Davies, I. W.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 7761.

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(15) 2,4,6-Trinitrotoluene (TNT) has been reported to undergo a stepwise conversion to 2,3-dihydrobenzofurans, see: Rozhkov, V. V.; Kuvshinov, A. M.; Shevelev, S. A. *Synth. Commun.* **2002**, *32*, 1465.

(16) Reaction of **11** under the reaction conditions (1.5 equiv of TBAF, THF, reflux) in the absence of any aldehyde gave nearly quantitative conversion to 3-methyl-4-nitrobenzoic acid.

(17) For the reaction of nitrotoluenes with aldehydes in the presence of Triton B, see: Tsuji, Y.; Kotachi, S.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580.

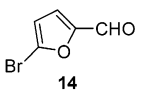
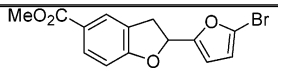
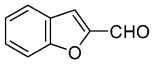
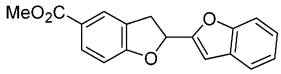
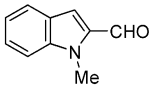
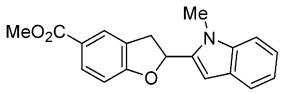
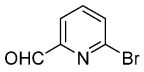
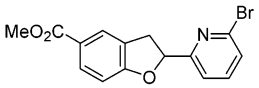
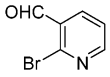
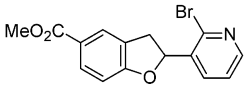
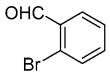
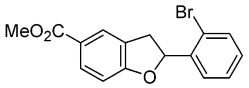
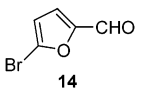
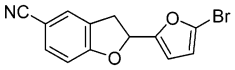
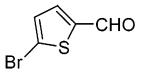
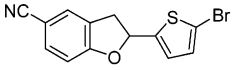
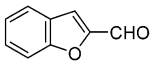
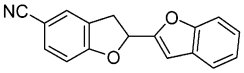
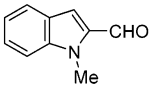
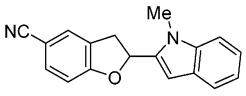
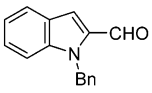
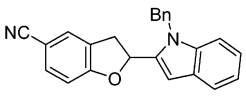
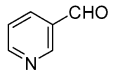
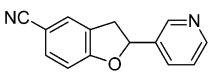
(18) For the reaction of nitrotoluenes with aldehydes in the presence of NaOMe/DMSO, see: (a) Bakke, J. *Acta Chem. Scand.* **1967**, *21*, 1967. (b) Izumi, T.; Yokota, T. *J. Heterocycl. Chem.* **1992**, *29*, 1085.

(19) For the reaction of nitrotoluenes with aldehydes in the presence of NaOMe/DMF, see: (a) Rollins, S. B.; Williams, R. M. *Tetrahedron Lett.* **1997**, *38*, 4033. (b) Williams, R. M.; Rollins, S. B.; Judd, T. C. *Tetrahedron* **2000**, *56*, 521. (c) Judd, T. C.; Williams, R. M. *Org. Lett.* **2002**, *4*, 3711.

(20) For the reaction of a nitrotoluene with formaldehyde in the presence of KOH/DMSO, see: Yasuda, N.; Williams, R. M. *Tetrahedron Lett.* **1989**, *30*, 3397.

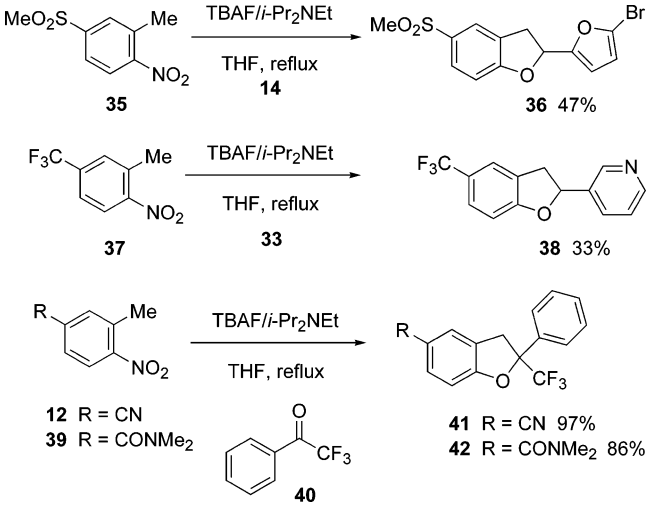
(21) Masubuchi, K.; Taniguchi, M.; Umeda, I.; Hattori, K.; Suda, H.; Kohchi, Y.; Isshiki, Y.; Sakai, T.; Kohchi, M.; Shirai, M.; Okabe, H.; Sudoh, M.; Yamazaki, T.; Shimma, N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1459.

**TABLE 1. Preparation of 2,3-Dihydrobenzofurans**

| Entry | Nitrotoluene | Aldehyde | 2,3-Dihydrobenzofuran |
|---|---|---|---|
| 1 | **11** |  **14** |  **15** 79% |
| 2 | **11** |  **16** |  **17** 82% |
| 3 | **11** |  **18** |  **19** 68% |
| 4 | **11** |  **20** |  **21** 77% |
| 5 | **11** |  **22** |  **23** 85% |
| 6 | **11** |  **24** |  **25** 83% |
| 7 | **12** |  **14** |  **26** 88% |
| 8 | **12** |  **27** |  **28** 82% |
| 9 | **12** |  **16** |  **29** 82% |
| 10 | **12** |  **18** |  **30** 79% |
| 11 | **12** |  **31** |  **32** 79% |
| 12 | **12** |  **33** |  **34** 93% |

diate to give incomplete conversion to dihydrobenzofuran products ($Bu_4NCl$ and DBU/DMSO).

**SCHEME 3**




A range of electron-withdrawing substituents in the 4-position of the nitrotoluene ring was examined (Scheme 3). For example, reaction of nitrotoluene **35** with aldehyde **14** furnished **36** in 47% yield.[22] In similar fashion, the trifluoromethyl-substituted nitrotoluene **37**[23] gave dihydrobenzofuran **38** in 33% unoptimized yield when allowed to react with aldehyde **33**.[24] While the reaction of nitrotoluenes **11** or **12** with aldehydes and ketones bearing acidic protons only resulted in enolization,[11] reaction of **12** with 2,2,2-trifluoroacetophenone **40** gave the interesting trifluoromethylated derivative **41** in 97% isolated yield. Reaction of **39** with **40** under the identical reaction conditions gave **42** in 86%, which also demonstrates that the reaction proceeds with amides in the 4-position of the nitrotoluene ring.

In conclusion, we have outlined an efficient one-pot procedure for the preparation of highly functionalized 2-aryl-5-substituted-2,3-dihydrobenzofurans from readily available *o*-nitrotoluenes. The dihydrobenzofuran products may serve as a platform for further manipulation leading to structurally unique benzofurans and other pharmaceutically intriguing compounds. In addition, there may be multiple applications to parallel and diversity oriented syntheses.

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**Supporting Information Available:** Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Unidentified reaction byproducts, most likely arrising from deprotonation of the methyl sulfone, account for the mass balance.

(23) Zumstein sen, F.; Assmann, E.; Koenigsferger, R.; Holzbauer, R.; Zumstein jun, F. German Patent DE2750170, 1978.

(24) Significant amounts of starting materials, in addition to some decomposition, account for the mass balance.