# Synthesis of Benzofuran Derivatives on Solid Support via $SmI_2$-Mediated Radical Cyclization

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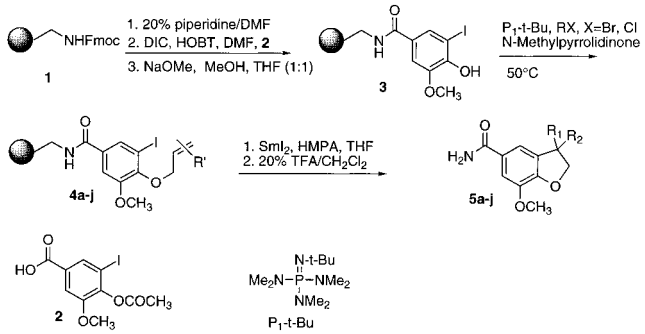
Recently, progress in combinatorial library synthesis has focused on scope and limitations of reactions on solid support.[1] Few studies have been directed toward radical reactions on solid support,[2] although they have emerged as a powerful synthetic strategy in solution in the past decade.[3] Balasubramanian *et al.* reported a study on tributyltin hydride mediated radical cyclization on solid support to generate benzofuran and furan rings.[4] Herein, we wish to report an alternative synthesis of various benzofuran derivatives through $SmI_2$-mediated[5] aryl radical cyclizations on solid support.[6,7] The cyclization is mild, rapid, and easy to carry out at room temperature. It thus offers an advantage over the harsher conditions used in tributyltin hydride-mediated synthesis of benzofuran derivatives in which heating to 80−100 °C for several hours to overnight is usually needed.[4,8]

After Rink resin **1** was coupled to acid **2**[9] (Scheme 1), the acetate group of the resin-bound **2** could be cleanly deprotected by NaOMe in 1 M MeOH/THF solution. Phenol **3** is readily coupled to a variety of allyl halides by using the Schwesinger base[10] $P_1$-t-Bu to generate **4**. Subsequent cyclization of **4a**−**j** by $SmI_2$ and HMPA[11] followed by TFA cleavage generated products **5a**−**j** (Table 1). The coupling between **3** and **4** generally went very well as TFA cleavage of **4a**, **4h**, and **4i** showed clean conversion of the phenol to the corresponding allylic ethers as the only products. For compounds **4c**, **4e**, and **4g**, TFA cleavage yielded only the starting phenol due to the sensitivity of the electron-rich ethers toward TFA. However, the coupling proceeded well for **4b**−**e** as evidenced by the efficiency of the subsequent $SmI_2$-mediated cyclization. In fact, the NMR spectra of the crude products show the predominance of the cyclized products with a small percentage of the reduced products.[12] This coupling method serves as an excellent alternative to existing aryl ether formation reactions on solid support.[1c]

**Scheme 1**




The reactions are run without any special precautions (i.e. solvent degassing, reagent preparations) since the oxygen in the solvent can be consumed by the excess equivalents of $SmI_2$ and are thus readily adaptable to parallel synthesis. A typical procedure for the cyclization of **4** is as follows: A flask with resin-bound **4** and stirrer is dried under high vaccuum at 55 °C for 1−2 h. HMPA (40 equiv) is first added followed by 0.1 M $SmI_2$ solution in THF[13] (10 equiv). The resulting mixture is stirred for 1 h at room temperature. The resin is then filtered, washed with methanol, THF, and $CH_2Cl_2$, before it is cleaved with 20% TFA in $CH_2Cl_2$.

As the coupling between phenol **3** and various halides generally is very clean as mentioned above, the combined yield reported in Table 1 should reflect generally the cyclization step. Several trends are apparent from the table. Cyclizations with a substituent group at the terminal alkene carbon are higher yielding than examples with substitution at the internal alkene carbon. (**b**−**f** vs **h**−**i**). Aryl substituents react with excellent yield and without any radical disproportionation products (**b** and **c**). Methyl substitution (**d**) at the terminal position results in about 11% radical disproportionation product which increases to 30% in the dimethyl case (**e**). The benzofuran derivatives could be functionalized (**f**, **j,** and **i**) and a fused heteroaromatic system could be generated (**g**). However, when COOEt is substituted at the alkene terminal carbon, there is no cyclization. The electron from $SmI_2$ might be transferred to the enoate[14] because

(1) For reviews, see: (a) *Chem. Rev.* **1997**, *97*, whole issue of No. 2, pp 347−510. (b) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (d) *Acc. Chem. Res.* **1996**, *29*, whole issue of No. 3, pp 112−170.

(2) For reduction of halide to alkyl, see: Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221−222. For addition of thiol radical to olefin, see (a) Gasparrini, F.; Misiti, D.; Villani, C.; Borchardt, A.; Burger, M. T.; Still, W. C. *J. Org. Chem.*, **1995**, *60*, 4314−4315. (b) Hodge, P.; Khoshdel, E.; Waterhouse, J.; Frechet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2327−2331.

(3) For reviews in radical reactions in organic synthesis, see: (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306. (b) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519−564. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237−1286. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds. Pergamon: Oxford, 1991; Vol. 4, pp 715−831. (e) Curran, D. P. *Synthesis* **1988**, 417−439, and 489−513.

(4) Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, 61−62.

(5) For a recent review on $SmI_2$-mediated reactions, see: Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(6) For synthesis of indole and benzofuran analogs on solid support via Pd-mediated Heck reaction, see: (a) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189−7192. (b) Zhang, H.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804−1809.

(7) For solution studies of $SmI_2$-mediated cyclization to generate benzofuran derivatives, see: (a) Inanaga, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 1737−1740. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171−6176. (c) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058.

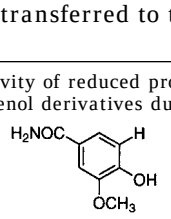
(8) For studies of solution radical cyclizations on related systems using tributyltin hydride, see: (a) Shankaran, K.; Sloan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 6001−6004. (b) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833−2836. (c) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072−4078.

(9) Compound **2** was synthesized from 4-hydroxy-3-iodo-5-methoxybenzaldehyde in 98% yield as follows: (a) $CH_3COCl$, $Et_3N$, $CH_2Cl_2$; (b) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, t-BuOH, THF.

(10) (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070−6071. (b) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmidt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.

(11) HMPA is essential for the reaction on solid support.

(12) Due to the sensitivity of reduced products toward TFA, they are cleaved into their phenol derivatives during removal from resin.



(13) Used as supplied by commercial sources.

S0022-3263(97)00913-4 CCC: $14.00 

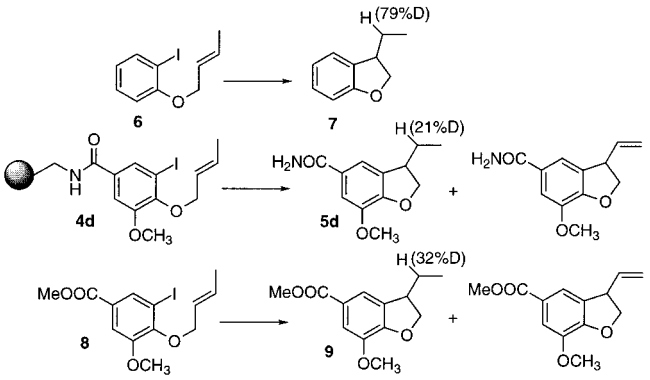



**Figure 1.** $D_2O$ quenching experiments.

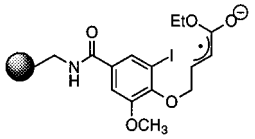
the alkoxy substituent lowers its reduction potential and the aryl ether is reductively cleaved as a result. Similar observations have been reported by Zhou and Bennett in attempts to cyclize alkyl iodides onto enoates.[15] Reduction of the aryl iodide **4** is a minor side reaction except in **i**, where it is the predominant reaction.

The cyclization works equally well when switching to polyethylene glycol grafted resin.[16] Gel phase NMR[17] analysis of the cyclization of **4a** in the presence of t-BuOH indicated excellent conversion to **5a**. One advantage of this resin is that it swells well in aqueous solvents. As a result, the $Sm^{3+}$ impurities in the beads can be washed away by saturated $NaHCO_3$ solution which is more difficult for ungrafted polystyrene resins.

Consistent with literature,[2c] cyclization of *o*-crotyl 2-iodophenol **6** with $D_2O$ added prior to $SmI_2$ generated the cyclized product **7** with 79% deuterium incorporation without radical disproportionation (Figure 1). We then investigated the relatively high degree of radical disproportionation product observed in **4d**. $D_2O$ quenching of **4d** showed 21% deterium incorporation in **5d** with about 13% radical disproportionation. When the parallel solution experiment was run[18] on **8**, 32% deuterium incorporation in **9** was observed with about 17% of the product arising from radical disproportionation. Therefore, radical disproportionation of **4d** appears to be substrate specfic rather than a result of being on resin.

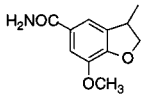
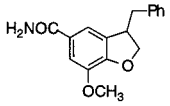
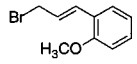
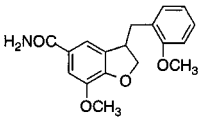
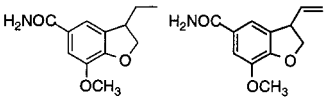
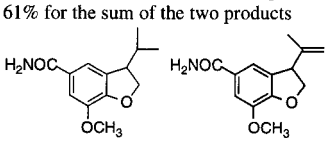
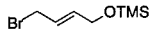
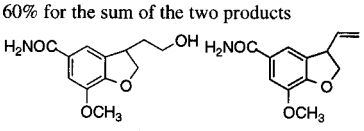
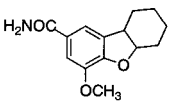
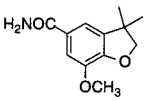
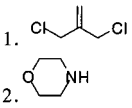
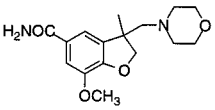
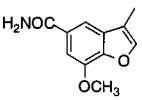
We have developed a mild and efficient synthesis of benzofuran derivatives on solid support via radical cyclization. When this reaction is carried out on PEG-grafted resins, products free of the samarium reagent are formed under mild reaction conditions.

(14) A possible intermediate is:



(15) Zhou, Z.; Bennett, S. M. *Tetrahedron Lett.* **1997**, *38*, 1153−1156.
(16) Purchased from Argonaut Technologies, Inc.
(17) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588−7590.
(18) To preclude the amide proton as a possible proton source in solution, we synthesized the ester **8** instead of the benzamide.

**Table 1: $SmI_2$-Mediated Cyclizations of Resin-Bound 4a−j, Giving 5a−j. The Yields Reported in This Table Are the Combined Yields for Solid-Supported Synthesis of 5a−j Based on the Initial Loading of Rink Resin 1 as Shown in Scheme 1**

| Entry | Halide | Product **5** | Combined Yield (from **1** to **5**) |
|---|---|---|---|
| a |  |  | 57% |
| b |  |  | 63% |
| c |  |  | 58%[a] |
| d |  |  ( 9 : 1 ) inseperable 61% for the sum of the two products | |
| e |  |  ( 7 : 3 ) inseperable 60% for the sum of the two products | |
| f |  |  42%[b] 6% | |
| g |  |  | 51% |
| h |  |  | 41% |
| i |  |  | 11%[c] |
| j |  |  | 37% |

[a] Bromide made from 2-methoxycinnamaldehyde by (1) DIBALH, THF, (2) $PPh_3$, NBS. [b] t-BuOH is added during the cyclization. Bromide made from ethyl 4-bromocrotonate by (1) DIBALH, $CH_2Cl_2$, (2) TMSOTf, $Et_3N$, THF. [c] **3** was first reacted with bischloride and then was heated in morpholine in DMF at 55 °C overnight to generate **4i**.

**Acknowledgment.** This work was supported by NIH grant number 51095.

**Supporting Information Available:** Experimental procedures, compound characterization data, and copies of $^1H$ NMR spectra for **2**, **3**, **4a**, **4i**, **4h**, **5a−j** (21 pages).

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