Solid-Phase Synthesis of 2-Iodomethyl-2,3-dihydrobenzofurans Using Recyclable Polymer-Supported Selenium Bromide

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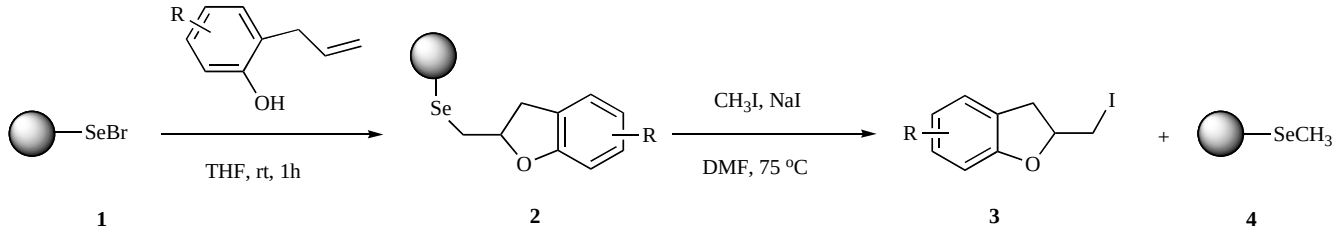
Abstract: Reaction of polymer-supported selenium bromide with *ortho* allylated phenols and subsequent cleavage from the polymer by treatment of methyl iodide efficiently afforded 2-iodomethyl-2,3-dihydrobenzofurans in good yields and high purities. The polymeric reagent can be regenerated and reused as environmentally friendly reagent.

Keywords: Solid-phase organic synthesis, Polymer-supported selenium bromide, Recyclable, Selenium mediated intramolecular cyclization, 2-Iodomethyl-2,3-dihydrobenzofuran, Traceless cleavage.

1. INTRODUCTION

Polymer-supported reagents have attracted growing interest because they can provide attractive and practical methods for combinatorial chemistry and solid-phase organic synthesis (SPOS) in recent years [1]. Synthesis on a polymer support shows a number of advantages as compared to solution chemistry. The most important one is the possibility to apply excesses of reagents and remove them without involving time-consuming separation techniques. Now, the synthesis of highly diverse organic molecule libraries using SPOS methodology is recognized as a valuable tool for acceleration of drug discovery. 2,3-Dihydrobenzofuran derivatives are common in natural products and have attracted considerable attention as a result of their biological activity [2]. In addition, 2,3-dihydrobenzofurans have been developed for the treatment of traumatic and ischemic central nervous system (CNS) injury [3], and are reported to be useful in the treatment of arteriosclerosis, hepatopathy, and cerebrovascular diseases [4]. Consequently, many methods have been developed for the synthesis of 2,3-dihydrobenzofuran ring systems, which involve biomimetic couplings of quinines and phenylpropenyl moieties [5], anionic [6], benzyne [7], dehydrative [8], electrocyclic [9], radical [10], and transition metalmediated [11] cyclizations. Among the 2,3-dihydrobenzofuran derivatives, functionalized 2,3-dihydrobenzofurans have now attracted considerable attention [12], however, to our knowledge, there are few reports about the synthesis of 2-iodomethyl-2,3-dihydrobenzofurans [13]. Since the first organoselenium resin [14] used in SPOS with a combined advantage of decrease volatility and simplification of product work-up was reported in 1976, several research groups [15] and our group [16] have developed selenium-based approaches for SPOS. More recently, we have reported 5-iodoisoxazolines, iodomethyl-substituted dihydrofurans and isoxazolines based on polystyrene-supported selenium reagent [17]. In continuation of our interest in solid-phase organoselenium chemistry, we here wish to describe a simple and efficient waste-free solid-phase synthetic approach to 2-iodomethyl-2,3-dihydrobenzofurans (Scheme **1**).



1 **2** **3** **4**

Scheme 1.

2. EXPERIMENTAL

2.1. General

Melting points were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using $CDCl_3$ as the solvent and TMS as internal standard. Mass spectra (EI, 70eV) were recorded on a HP5989B mass spectrometer. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 elemental analyzer. HPLC was performed on an Agilernt 1100 high performance liquid chromatograph. The ortho allylated phenols were prepared according to the

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reported method [18]. Polystyrene (H 1000, 100-200 mesh, cross-linked with 1% divinylbenzene) for the preparation of polystyrene-supported selenium bromide and other starting materials were purchased from commercial suppliers and used without further purification. THF and benzene were distilled from sodium-benzophenone immediately prior to use.

2.2. General Procedure for the Preparation of 2-Iodomethyl-2,3-dihydrobenzofurans (3)

Under a positive pressure of nitrogen, to polystyrene-supported selenium bromide **1** (1.0 g, 1.18 mmol Br/g) swollen in THF (15 mL) for 30 min was added α-allyl phenol (3 mmol). The suspension was stirred at rt for 1 h. The mixture was filtered and the resin was washed with THF (10 mL×3) and CH_2Cl_2 (10 mL×3) and dried under vacuum to afford dry 2-selenomethyl 2,3-dihydrobenzofuran resin **2**. To a suspension of the swollen resin **2** (1.0 g) in dry DMF (15 mL), NaI (1.5 g) and CH_3I (1.5 mL) were added under nitrogen. The suspension was stirred at 75 °C for 20 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (10 mL×3), the filtrate was washed with saturated $Na_2S_2O_3$ and H_2O respectively and extracted with ethyl acetate (10 mL×3), dried over anhydrous Na_2SO_4, and evaporated to furnish crude products **3a-3i** with 93-97 % purity determined by HPLC, which were further purified by column chromatography [hexane–EtOAc, 20:1 (v/v)] over silica gel to provide pure 2-iodomethyl-2,3-dihydrobenzofurans (**3a-3i**) for their ^{1}HNMR, ^{13}C NMR, MS and elemental analyses.

2-Iodomethyl-2,3-dihydrobenzofuran (3a)

Colorless oil. ^{1}H NMR: δ = 7.37-7.34 (m, 2 H), 7.28-7.24 (m, 2 H), 4.91-4.82 (m, 1 H), 3.44-3.27 (m, 3 H), 2.93 (dd, *J* = 6.5 Hz, 1 H). ^{13}C NMR: δ = 157.6, 127.8, 124.5, 123.3, 121.7, 111.1, 82.3, 36.6, 8.5. IR (neat): ν = 1595, 1455 cm^{-1}. EIMS: *m/z* (%) = 260 (M^+). Anal. Calcd for C_9H_9IO: C, 41.56; H, 3.49. Found: C, 41.63; H, 3.57.

7-Methyl-2-iodomethyl-2,3-dihydrobenzofuran (3b)

Pale brown oil. ^{1}H NMR: δ = 7.05-6.69 (m, 3 H), 4.93-4.85 (m, 1 H), 3.49-3.28 (m, 3 H), 2.99 (dd, *J* = 6.6 Hz, 1 H), 2.23 (s, 3 H). ^{13}C NMR: δ = 158.0, 128.1, 137.8, 125.6, 124.6, 110.5, 82.1, 36.8, 12.1, 9.2. IR (neat): ν = 1596, 1459, 1377 cm^{-1}. EIMS: *m/z* (%) = 274 $(M)^+$

Anal. Calcd for $C_{10}H_{11}IO$: C, 43.82; H, 4.05. Found: C, 43.88; H, 4.12.

6,7-Dimethyl-2-iodomethyl-2,3-dihydrobenzofuran (3c)

Brown solid; Mp: 49-50 °C. ^{1}H NMR: δ = 6.86 (d, *J* = 7.5 Hz, 1 H), 6.65 (d, *J*= 7.5 Hz, 1 H), 4.94-4.85 (m, 1 H), 3.28-3.50 (m, 3 H), 3.02 (dd, *J* = 6.5 Hz, 1 H), 2.25 (s, 3 H), 2.20 (s, 3 H). ^{13}C NMR: δ = 158.2, 137.2, 123.7, 121.7, 118.8, 110.3, 81.8, 36.8, 17.8, 12.3, 9.2. IR (KBr): ν = 1593, 1456 cm^{-1}. EIMS: *m/z* (%) = 289 $(M + H)^+$. Anal. Calcd for $C_{11}H_{13}IO$: C, 45.85; H, 4.55. Found: C, 45.93; H, 4.62.

4,6-Dimethyl-2-iodomethyl-2,3-dihydrobenzofuran (3d)

Colorless oil. ^{1}H NMR: δ = 6.79 (d, *J* = 7.5 Hz, 1 H), 6.53 (d, *J*= 7.5 Hz, 1 H), 4.48-4.52 (m, 1 H), 3.34-3.22 (m, 3 H), 3.01 (dd, *J* = 6.2 Hz, 1 H), 2.25 (s, 3 H), 2.14 (s, 3 H). ^{13}C NMR: δ = 158.2, 128.3, 127.8, 125.9, 125.4, 110.6, 82.3, 36.4, 19.3, 15.8, 9.0. IR (neat): ν = 1589, 1380 cm^{-1}. EIMS: *m/z* (%) = 311 $(M + Na)^+$. Anal. Calcd for $C_{11}H_{13}IO$: C, 45.85; H, 4.55. Found: C, 45.92; H, 4.64.

5-Chloro-2-iodomethyl-2,3-dihydrobenzofuran (3e)

Colorless solid; Mp: 44-45 °C. ^{1}H NMR: δ = 7.09-7.049 (m, 2 H), 6.65 (s, 1 H), 4.92-4.83 (m, 1 H), 3.45-3.26 (m, 3 H), 2.95 (dd, *J*= 6.5 Hz, 1 H). ^{13}C NMR: δ = 158.1, 128.4, 127.8, 126.0, 125.5, 110.7, 82.3, 36.5, 8.8. IR (KBr): ν = 2040, 1857, 1742, 1595 cm^{-1}. EIMS: *m/z* (%) = 317 $(M + Na)^+$. Anal. Calcd for C_9H_8ClIO: C, 36.70; H, 2.74. Found: C, 36.77; H, 2.82.

5,7-Dichloro-2-iodomethyl-2,3-dihydrobenzofuran (3f)

Colourless oil. ^{1}H NMR: δ = 7.14 (s, 1 H), 7.02 (s, 1 H), 5.01-4.95 (m, 1 H), 3.52-3.30 (m, 3 H), 3.13 (dd, *J* = 6.7 Hz, 1 H). ^{13}C NMR: δ = 154.7, 129.1, 128.7, 126.3, 123.8, 116.1, 83.0, 37.0, 8.3.

IR (neat): ν = 1585, 1460 cm^{-1}. EIMS: *m/z* (%) = 329 (M^+). Anal. Calcd for $C_9H_7Cl_2IO$: C, 32.86; H, 2.14. Found: C, 32.93; H, 2.23.

5-Chloro-7-methyl-2-iodomethyl-2,3-dihydrobenzofuran (3g)

Colorless oil. ^{1}H NMR: δ = 7.06 (d, *J* = 8.3 Hz, 1 H), 6.51 (d, *J* = 8.3 Hz, 1 H), 4.94-4.83 (m, 1 H), 3.47-3.25 (m, 3 H), 2.92 (dd, *J* = 6.2 Hz, 1 H), 2.24 (s, 3 H). ^{13}C NMR: δ = 157.5, 128.7, 126.9, 125.2, 112.2, 108.6, 82.4, 36.5, 17.3, 9.0. IR (neat): ν = 1592, 1454, 1375 cm^{-1}. EIMS: *m/z* (%) = 309 (M^+). Anal. Calcd for $C_{10}H_{10}ClIO$: C, 38.93; H, 3.27. Found: C, 38.99; H, 3.35.

5-Cyano-2-iodomethyl-2,3-dihydrobenzofuran (3h)

Colorless solid; Mp: 84-85 °C. ^{1}H NMR: δ = 7.48-7.44 (m, 2 H), 6.81 (d, *J* = 8.7 Hz, 1 H), 5.01-4.95 (m, 1 H), 3.51-3.33 (m, 3 H), 3.02 (dd, *J* = 6.0 Hz, 1 H). ^{13}C NMR: δ = 163.1, 134.2, 129.4, 127.8, 119.5, 110.9, 104.6, 82.8, 35.9, 8.3. IR (KBr): ν = 2225, 1716, 1609, 1483 cm^{-1}.

EIMS: *m/z* (%) = 286 $(M+H)^+$. Anal. Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.83; N, 4.91. Found: C, 42.20; H, 2.90; N, 4.97.

2-Iodomethyl-2,3-dihdro-benzofuran-5-carbaldehyde (3i)

Pale brown oil. ^{1}H NMR: δ = 9.85 (s, 1 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 5.03-4.96 (m, 1 H), 3.52-3.32 (m, 3 H), 3.03 (dd, *J* = 6.4 Hz, 1 H). ^{13}C NMR: δ = 190.1, 164.4, 133.2, 130.8, 127.1, 125.8, 109.9, 82.8, 35.4, 8.1. IR (neat): ν = 1684 cm^{-1}. EIMS: *m/z* (%) = 289 $(M+H)^+$. Anal. Calcd for $C_{10}H_9IO_2$: C, 41.69; H, 3.15. Found: C, 41.77; H, 3.23.

3. RESULTS AND DISCUSSION

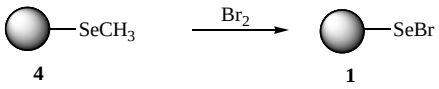
As previously reported [15a], selenenyl bromide resin (**1**) was conveniently prepared from commercial polystyrene by lithiation followed by treatment with dimethyl diselenide to give methyl selenide resin through oxidation with bromine to give (**1**) as a dark red polymer. Simply stirring the resin (**1**) in THF at room temperature with 3.0 equiv of the *ortho* allylated phenols resulted in a rapid decolorization of the resin (<5 min). After stirred for 1 h, the ring-closure reaction

Table 1. The Yields and Purities of 2-Iodomethyl-2,3-dihydrobenzofurans (3)

Entry	R	Product	Yield (%)[a]	Purity (%)[b]
1	H	**3a**	92	97
2	H	**3a**[c]	90	95
3	H	**3a**[d]	88	94
4	2-CH_3	**3b**	90	95
5	2,3-Di-CH_3	**3c**	86	96
6	3,5-Di-CH_3	**3d**	88	95
7	4-Cl	**3e**	86	94
8	2,4-Di-Cl	**3f**	83	93
9	2-CH_3-4-Cl	**3g**	84	95
10	4-CN	**3h**	85	95
11	4-CHO	**3i**	84	94

[a]Overall yields based on polymer-supported selenium bromide **1** (1.18 mmol Br/g).
[b]Determined by HPLC of crude cleavage product.
[c]With the third regenerated resin **1**.
[d]With the fourth regenerated resin **1**.

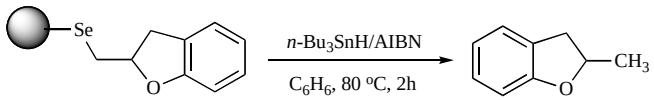
on the solid-phase completed, which was determined by the elemental analysis of 2-selenomethyl 2,3-dihydrobenzofuran resin (**2**) (Br was undetectable). The reaction was also monitored by FT-IR, which showed a strong peak of cyclic ether absorptions at 1020-1032, 1084–1096 cm^{-1}. According to our published method [17], treatment of resin (**2**) with CH_3I-NaI in DMF afforded 2-iodomethyl-2,3-dihydrobenzofurans (**3**) in good yields (83-92%) and with excellent purities greater than 93 % (Table **1**). As seen from Table **1**, the method exhibited broad tolerance toward the substrates *ortho* allylated phenols containing substituents such as halogens (entries 7–9), cyano (entry 10) and aldehyde (entry 11) group. In addition, it should be noted that the polystyrene-supported selenium bromide (**1**) is easily regenerated form the recovered methyl selenide resin (**4**) (Scheme **2**) and can be reused for the conversion of *o*-allylphenol to 2-iodomentyl-2,3-dihydrobenzofurans (**3**). After the fourth regeneration and use, the yield and purity of **3a** (Table **1**, entries 2-3) was about the same as those obtained in the first reaction (entry 1).



4 **1**

Scheme 2.

On the other hand, the other two common cleavage strategies of selenium linkers have been reported: selenoxide *syn*-elimination and agilent hydride transfer [19]. Although a β-H exists in the above molecules, selenoxide *syn*-elimination did not occur when we treated resin **2** with 30 % hydrogen peroxide even when we raised the temperature to 50 °C in THF. Tri-*n*-butyltin hydride could be used here as a good radical hydride transfer reagent. For example, 2,3-dihydro-2-methylbenzofuran (**4a**) [20] was prepared as the described method [19] by cleavage with *n*-Bu_3SnH/AIBN (Scheme **3**) in 90 % overall yields, based on the selenenyl bromide resin **1**. However, we did not apply this reductive cleavage to the other 2,3-dihydro-2-methylbenzofurans because *n*-Bu_3SnH is a toxic reagent.



2a **4a**

Scheme 3.

4. CONCLUSIONS

In summary, we have developed here an efficient and convenient protocol for the traceless solid-phase synthesis of 2-iodomethyl-2,3-dihydrobenzofurans with good yields and purities employing a selenium-based traceless linker strategy. Simple workup procedure replaces the time-consuming isolation and purification steps in the corresponding solution-phase synthesis. Moreover, the polymeric reagent can be recycled without further transformation and reused as environmentally benign reagent.

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[20] Colorless oil. ^{1}H NMR: δ = 7.16 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.82 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 7.8 Hz, 1H), 4.87–4.96 (m, 1H), 3.30 (dd, J = 15.4, 8.8 Hz, 1H), 2.81 (dd, J = 15.4, 7.7 Hz, 1H), 1.46 (d, J = 6.2 Hz, 3H). ^{13}C NMR: δ = 159.7, 128.2, 127.2, 125.2, 120.4, 109.5, 79.7, 37.4, 22.0. IR (neat): ν = 1479, 1463, 1228, 746 cm^{-1}. Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.32; H, 7.29.