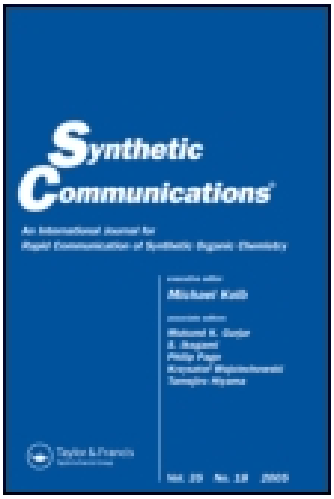

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SOLID-PHASE ORGANIC SYNTHESIS OF 5-IODOMETHYL-DIHYDROFURAN-2-ONES WITH RECYCLABLE POLYMER-SUPPORTED SELENIUM BROMIDE

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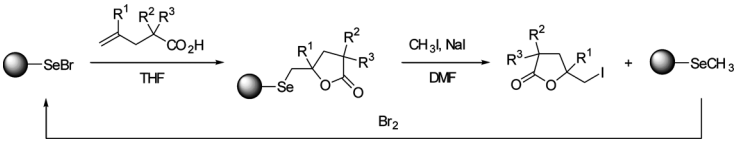
GRAPHICAL ABSTRACT



Abstract *Reaction of polystyrene-supported selenium bromide with γ,δ-unsaturated acids and subsequent cleavage from the polymer by treatment with methyl iodide efficiently afforded 5-iodomethyl-dihydrofuran-2-ones in excellent yields. The polymeric reagent can be regenerated and reused as an environmentally friendly reagent.*

Keywords 5-Iodomethyl-dihydrofuran-2-one; polystyrene-supported selenium bromide; recyclable; selenium-mediated intramolecular cyclization; solid-phase organic synthesis

INTRODUCTION

Over the past few years, combinatorial chemistry has emerged as a powerful tool in organic synthesis. As a result, the development of new methodology and the adaptation of already existing methods to make them amenable to parallel synthesis have become very active research topics.[1] Solid-phase organic synthesis (SPOS) using insoluble solid supports such as polystyrene resins shows a number of advantages as compared to solution chemistry. The most salient one is the possibility of applying excesses of reagents and removing them without involving time-consuming separation techniques.[2] Compounds bearing the substituted γ-butyrolactone moiety are widespread in nature and have received much interest because of their physiological properties.[3] Moreover, functionalized γ-butyrolactones have important biological properties and are also known as starting material for the preparation

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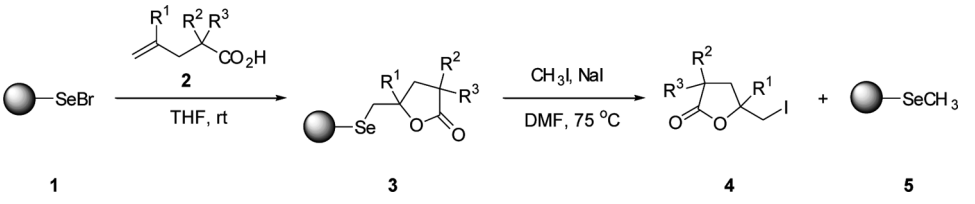
of pharmacologically active compounds.[4] So, many methods have been developed for the synthesis of γ-butyrolactone ring systems.[5] Among these methods, seleno-promoted cyclization reactions of olefinic carboxylic acids are useful methods for the construction of functionalized γ-butyrolactones.[5a–5c,6] However, organoselenium reagents always have a foul smell and are quite toxic, which is often problematic in organic synthesis. Since the first organoselenium resin[7] used in SPOS with a combined advantage of decrease volatility and simplification of product workup was reported in 1976, several research groups[8] have developed selenium-based approaches for SPOS. Recently, our research group has been interested in the application of organic selenium resins for the synthesis of some functional heterocyclic compounds such as 5-iodoisoxazolines,[9] 2-iodomethyl-2,3-dihydrobenzofurans,[10] and vinyl-substituted 1,3,4-oxadiazoles.[11] As part of an ongoing research program focused on the use of polymeric organoselenium reagents in SPOS, we here describe a simple and efficient synthetic approach to 5-iodomethyl-dihydrofuran-2-ones (Scheme 1). To our knowledge, there has no report concerning the preparation of 5-iodomethyl-dihydrofuran-2-ones using this technology.

As previous reported,[8a] polymer-supported selenium bromide resin (**1**) was conveniently prepared from commercial polystyrene by lithiation followed by treatment with dimethyl diselenide to give methyl selenide resin via oxidation with bromine to give reagent (**1**) as a dark red polymer.

Obviously, polymer-supported selenolactonization would be the key step for the success of this protocol. Interestingly, simply stirring the resin **1** in tetrohydrofuran (THF) at room temperature with 3.0 equiv of the γ,δ-unsaturated acids (**2**) resulted in a rapid decolorization of the resin. After stirring for 2 h, the ring-closure reaction on the solid phase was completed, which was determined by the elemental analysis of 5-selenomethyl-dihydrofuran-2-ones (**3**) (Br was undetectable). Additionally, the reaction was also monitored by Fourier transform–infrared (FT-IR) of resin (**3**), showing a single strong peak around 1770 cm^{-1}, which indicated that the lactonization was complete. Furthermore, increasing the amount of γ,δ-unsaturated acid to 4 or 5 equiv, replacing THF with other solvents such as CH_2Cl_2 and CH_3CN, or prolonging the reaction time had little affect on the cyclization.

Finally, following our published method[9,10] for traceless cleavage of selenium resin, the target compound 5-iodomethyl-dihydrofuran-2-one (**4**) was obtained in excellent isolated yields (90–96%) by treatment of resin (**3**) with CH_3I-NaI in dimethylformamide (DMF) at 70 °C for 20 h. The generality and efficiency of the reaction were established by studying various substrates (Table 1).

As seen from Table 1, the only 5-*exo*-*trig* ring-closing reaction induced by selenium bromide resin was preferred because the other possible regioisomer from

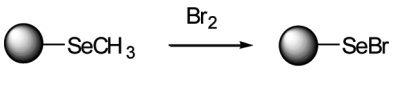


Scheme 1. Solid-phase synthetic route to 5-iodomethyl-dihydrofuran-2-ones.

Table 1. Preparation of 5-iodomethyl-dihydrofuran-2-ones (**4a–4h**)

Entry	R^1	R^2	R^3	Product	Yield (%)[a]
1	H	H	H	**4a**	96
2	H	H	H	**4a**[b]	94
3	H	H	H	**4a**[c]	92
4	H	H	Me	**4b**	94 (dr 6:1)
5	H	H	Et	**4c**	95 (dr 6:1)
6	H	H	$C_6H_5CH_2$	**4d**	93 (dr 5:1)
7	H	Me	Me	**4e**	90
8	H	C_6H_5	C_6H_5	**4f**	90
9	Me	H	H	**4g**	94
10	C_6H_5	H	H	**4h**	92

[a]Overall yields based on polymer-supported selenium bromide **1** (1.18 mmol Br/g).
[b]With the third regenerated resin **1**.
[c]With the fourth regenerated resin **1**.



5 **1**

Scheme 2. Conversion of methyl selenide resin (**5**) to **1**.

a 6-*endo-trig* closure was not observed. For the α-substituted acids (**2b, 2c**, and **2d**), a mixture of two diastereoisomers was obtained, and NMR studies showed that *syn* lactones were the major isomers (Table 1, entries 4–6). For α,α-disubstituted substrates (**2e** and **2f**), the cycliation also proceeded well, although with a little bit lower yields of target compounds (**4e** and **4f**) (Table 1, entries 7 and 8).

In addition, it should be noted that the polystyrene-supported selenium bromide (**1**) is easily regenerated form the recovered methyl selenide resin (**5**) (Scheme 2) and can be reused for the conversion of γ,δ-unsaturated acids to 5-iodomethyl-dihydrofuran-2-ones (**4**). For example, after the fourth regeneration and use, the yield of 5-iodomethyl-dihydrofuran-2-one (**4a**) (Table 1, entry 3) was almost same as when freshly prepared selenium bromide resin was used.

In summary, we have developed an efficient protocol for the traceless solid-phase synthesis of 5-iodomethyl-dihydrofuran-2-ones with excellent yields and easy workup procedure, employing a selenium-based traceless linker strategy. Moreover, the polymeric reagent can be recycled without further transformation and reused as an environmentally benign reagent.

EXPERIMENTAL

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. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 elemental analyzer. Polystyrene for the preparation of

polystyrene-supported selenium bromide according to the procedure described by Nicolaou[8a] was purchased from Aldrich (100–200 mesh, cross-linked with 1% divinylbenzene). 4-Pentenoic acid (**2a**) is commercially available, and the other γ,δ-unsaturated acids such as 2-methylpent-4-enoic acid (**2b**),[12] 2-ethylpent-4-enoic acid (**2c**),[13] 2-allyl-3-bezenepropanoic acid (**2d**),[14] 2,2-dimethylpent-4-enoic acid (**2e**),[15] 2,2-diphenylpent-4-enoic acid (**2f**),[16] 4-methyl-4-pentenoic acid (**2g**),[17] and 4-phenyl-4-pentenoic acid (**2h**)[18] were prepared according to the reported method.[16] DMF was distilled from calcium hydride, and THF was distilled from sodium benzophenone immediately prior to use. Other reagents were obtained from commercial suppliers and used without further purification.

Preparation of 5-Iodomethyl-dihydrofuran-2-ones: General Procedure

Under a positive pressure of nitrogen, γ,δ-unsaturated acid **2** (3 mmol) was added to polystyrene-supported selenium bromide **1** (1.0 g, 1.18 mmol Br/g) swollen in THF (15 mL) for 30 min. The suspension was stirred at room temperature for 2 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 5-selenomethyl-dihydrofuran-2-one resin **3**. NaI (1.5 g) and CH_3I (1.5 mL) were added to a suspension of the swollen resin **3** (1.0 g) in dry DMF (15 mL) under nitrogen. The suspension was stirred at 75 °C for 20 h. The mixture was filtered, and the residual resin **5** was washed with CH_2Cl_2 (10 mL × 3). The filtrate was washed with saturated $Na_2S_2O_3$ and H_2O, extracted with ethyl acetate (10 mL × 3), dried over anhydrous Na_2SO_4, and evaporated to furnish crude products **4a**–**4h** with 93–98% purity as determined by high-performance liquid chromatography (HPLC), which were further purified by column chromatography (EtOAc/hexane, 20/1–12/1, v/v) over silica gel to provide pure 5-iodomethyl-dihydrofuran-2-ones (**4a**–**4h**) for their ^{1}H NMR, ^{13}C NMR, and elemental analyses.

Selected Data

5-Iodomethyl-dihydrofuran-2-one (4a). Colorless oil (lit.[19] oil); ^{1}H NMR: δ = 4.60–4.55 (m, 1 H), 3.46–3.41 (m, 1 H), 3.34–3.30 (m, 1 H), 2.68–2.47 (m, 3 H), 2.05–1.94 (m, 1 H); ^{13}C NMR: δ = 176.1, 78.5, 28.8, 28.0, 7.3; IR (neat): $\nu = 1775\ cm^{-1}$. Anal. calcd. for $C_5H_7IO_2$: C, 26.57; H, 3.12. Found: C, 26.38; H, 3.32.

3-Methyl-5-iodomethyl-dihydrofuran-2-one (*trans/cis* = 1:6) (4b). Colorless oil (lit.[20] oil); IR (neat): $\nu = 1770\ cm^{-1}$. Anal. calcd. for $C_6H_9IO_2$: C, 30.02; H, 3.78. Found: C, 29.78; H, 3.93. *Cis*-3-methyl-5-iodomethyl-dihydrofuran-2-one (major): ^{1}H NMR: δ = 4.39–4.36 (m, 1 H), 3.41 (dd, J = 5.7, 10.1 Hz, 1 H), 3.28–3.24 (m, 1 H), 2.78–2.68 (m, 2 H), 1.58 (q, J = 10.7 Hz, 1 H), 1.31 (d, J = 6.3 Hz, 3 H); ^{13}C NMR: δ = 178.4, 76.4, 37.6, 36.1, 15.1, 6.8. *Trans*-3-methyl-5-iodomethyl-dihydrofuran-2-one (minor): ^{1}H NMR: δ = 4.61–4.57 (m, 1 H), 3.37 (dd, J = 10.6, 4.4 Hz, 1 H), 3.27–3.25 (m, 1 H), 2.84–2.80 (m, 1 H), 2.34–2.30 (m, 1 H), 2.14–2.09 (m, 1 H), 1.30 (d, J = 6.5 Hz, 3 H); ^{13}C NMR: δ = 179.0, 76.6, 35.3, 34.2, 16.0, 7.0.

3-Ethyl-5-iodomethyl-dihydrofuran-2-one (*trans/cis* = 1:6) (4c). Colorless oil (lit.[5g] oil); IR (neat): $\nu = 1776\,cm^{-1}$. Anal. calcd. for $C_7H_{11}IO_2$: C, 30.09; H, 4.36. Found: C, 29.80; H, 4.57. *Cis*-3-ethyl-5-iodomethyl-dihydrofuran-2-one (major): ^1H NMR: $\delta = 4.43–4.35$ (m, 1 H), 3.45 (dd, $J = 4.6$, 10.1 Hz, 1 H), 3.27–3.25 (m, 1 H), 2.70–2.61 (m, 2 H), 1.95–1.63 (m, 2 H), 1.60–1.53 (m, 1 H), 1.01 (t, $J = 7.7$ Hz, 3 H); ^{13}C NMR: $\delta = 178.4$, 76.6, 40.6, 33.2, 24.3, 11.6, 7.5. *Trans*-3-ethyl-5-iodomethyl-dihydrofuran-2-one (minor): ^1H NMR: $\delta = 4.60–4.55$ (m, 1 H), 3.40–3.35 (m, 1 H), 3.25 (d, $J = 7.4$ Hz, 1 H), 2.72–2.60 (m, 1 H), 2.24–2.15 (m, 2 H), 1.61–1.50 (m, 2 H), 1.02 (t, $J = 7.7$ Hz, 3 H); ^{13}C NMR: $\delta = 177.9$, 76.5, 42.6, 35.1, 23.4, 11.5, 6.8.

3-Benzyl-5-iodomethyl-dihydrofuran-2-one (*trans/cis* = 1:5) (4d). Colorless oil (lit.[20] oil); IR (neat): $\nu = 1778\,cm^{-1}$. Anal. calcd. for $C_{12}H_{13}IO_2$: C, 45.59; H, 4.15. Found: C, 45.38; H, 4.38; *Cis*-3-benzyl-5-iodomethyl-dihydrofuran-2-one (major): ^1H NMR: $\delta = 7.35–7.24$ (m, 5 H), 4.43–4.37 (m, 1 H), 3.37 (dd, $J = 10.6$, 4.5 Hz, 1 H), 3.30 (dd, $J = 14.5$, 4.5 Hz, 1 H), 3.21 (dd, $J = 10.6$, 7.5 Hz, 1 H), 3.06–3.00 (m, 1 H), 2.84 (dd, $J = 14.5$, 9.4 Hz, 1 H), 2.55–2.50 (m, 1 H), 1.72–1.65 (m, 1 H); ^{13}C NMR: $\delta = 177.3$, 138.1, 128.9, 128.8, 127.0, 76.7, 43.0, 36.2, 34.8, 6.6. *Trans*-3-benzyl-5-iodomethyl-dihydrofuran-2-one (minor): ^1H NMR: $\delta = 7.36–7.20$ (m, 5 H), 4.37–4.31 (m, 1 H), 3.24–3.14 (m, 2 H), 3.11–3.02 (m, 1 H), 2.84 (dd, $J = 13.5$, 8.7 Hz, 1 H), 2.25–2.04 (m, 2 H), 1.73–1.67 (m, 1 H); ^{13}C NMR: $\delta = 177.7$, 137.8, 129.0, 128.8, 127.1, 76.8, 41.4, 36.7, 32.5, 7.2.

3,3-Dimethyl-5-iodomethyl-dihydrofuran-2-one (4e). White solid, mp 54–55 °C (lit.[5g] 53.7–55.0 °C); ^1H NMR: $\delta = 4.45–4.40$ (m, 1 H), 3.39 (dd, $J = 10.5$, 4.8 Hz, 1 H), 3.25 (dd, $J = 10.5$, 7.3 Hz, 1 H), 2.34 (dd, $J = 12.8$, 6.4 Hz, 1 H), 1.90 (dd, $J = 12.8$, 9.5 Hz, 1 H), 1.30 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR: $\delta = 180.7$, 75.0, 43.9, 41.0, 24.7, 7.2; IR (neat): $\nu = 1777\,cm^{-1}$. Anal. calcd. for $C_7H_{11}IO_2$: C, 33.09; H, 4.36. Found: C, 32.94; H, 4.52.

3,3-Diphenyl-5-iodomethyl-dihydrofuran-2-one (4f). White solid; mp 115–116 °C (lit.[21] 116–117 °C); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.28$ (m, 10 H), 4.44–4.34 (m, 1 H), 3.45–4.41 (m, 1 H), 3.32–3.29 (m, 1 H), 3.25–3.18 (m, 1 H), 2.70–2.63 (m, 1 H); ^{13}C NMR: $\delta = 176.5$, 141.6, 139.4, 129.2, 128.6, 128.1, 127.8, 127.5, 127.2, 75.5, 58.8, 44.1, 5.9; IR (neat): $\nu = 1765\,cm^{-1}$. Anal. calcd. for $C_{17}H_{15}IO_2$: C, 53.99; H, 4.00. Found: C, 53.78; H, 4.24.

5-Iodomethyl-5-methyl-dihydrofuran-2-one (4g). White solid; mp 45–46 °C (lit.[22] 44–45 °C); ^1H NMR: $\delta = 3.43$ (d, $J = 10.5$ Hz, 1 H), 3.36 (d, $J = 10.5$ Hz, 1 H), 2.68–2.66 (m, 2 H), 2.35–2.32 (m, 1 H), 2.16–2.14 (m, 1 H), 1.63 (s, 3 H); ^{13}C NMR: $\delta = 175.5$, 83.6, 32.7, 29.2, 25.8, 14.0; IR (neat): $\nu = 1768\,cm^{-1}$. Anal. calcd. for $C_6H_9IO_2$: C, 30.02; H, 3.78. Found: C, 29.80; H, 3.95.

5-Iodomethyl-5-phenyl-dihydrofuran-2-one (4h). White solid; mp 75–76 °C (lit.[22] 73–74 °C); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40–7.36$ (m, 5 H), 3.65 (s, 2 H), 2.84–2.45 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.3$, 140.5, 128.9, 128.5, 124.7, 85.9, 33.8, 29.1, 16.2; IR (neat): $\nu = 1779\,cm^{-1}$. Anal. calcd. for $C_{11}H_{11}IO_2$: C, 43.73; H, 3.67. Found: C, 43.50; H, 3.45.

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