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Report

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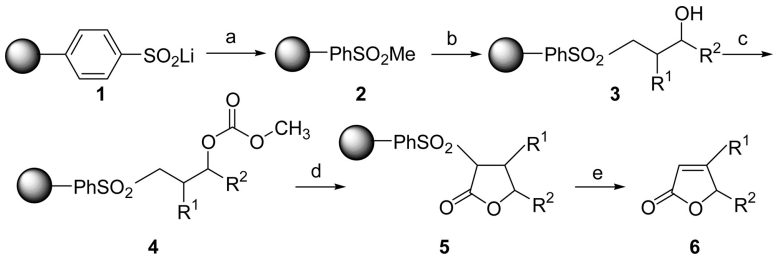

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Solid-Phase Synthesis of Substituted Butenolides and Butyrolactones Using a Traceless Sulfone Linker

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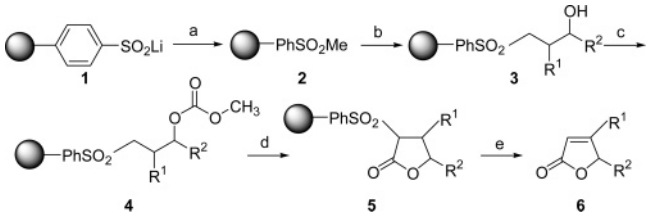
Introduction. Solid-phase organic synthesis (SPOS) has attracted increasing interest in the past few years because of its application in the generation of combinatorial libraries of small organic molecules.[1] SPOS enjoys several advantages over solution-phase synthesis. For example, easy manipulation and purification of the organic products is greatly simplified through the use of polymer-bound reagents. Butenolides and butyrolactones are widespread in a large variety of biologically active natural products.[2] Their occurrence coupled with their pharmacophoric activity has spurred the development of numerous elegant procedures for their preparation.[3] Some solid-phase butenolide[4] and butyrolactone[5] syntheses have been reported by different groups; however, it is still desirable to develop additional efficient solid-phase methodologies for their synthesis. The sulfone linker has been shown to be a robust and versatile tether that offers various on-resin functionalizations or cleavages with additional changes.[6] For example, several research groups recently have demonstrated the use of polystyrene/1% divinylbenzene sodium or lithium sulfinate as a traceless linker for SPOS of heterocyclic compounds, such as 4,5,6,7-tetrahydroisoindoles,[6f] 3,4,6-trisubstituted 2-pyridones,[6e] 3,4-dihydro-1*H*-pyrimidine-2-ones,[6m] and hydantoins,[6o] etc. To the best of our knowledge, there have been no reports about the use of a sulfone linker strategy in solid-phase synthesis of substituted butenolides and butyrolactones. In this paper, we report the extension of this sulfone-based chemistry to a convenient, traceless, solid-phase synthesis of substituted butenolides and butyrolactones. The procedure for the synthesis of target compounds from polystyrene/1% divinylbenzene lithiophenylsulfinate (**1**) includes (a) sulfinate S-alkylation, (b) the sulfonyl anion alkylation with an epoxide, (c) the acylation of the resulting γ-hydroxyl sulfone, (d) the intramolecular acylation-cyclization of the α-sulfonylcarbanion, and (e) traceless product release by desulfonation.

Results and Discussion. As outlined in Scheme 1, the phenylmethylsulfone resin **2**,[7] which was amenable to FT-IR monitoring for the appearance of the sulfone stretch at 1313 and 1150 cm^{-1}, was prepared in 95% yield by treating a THF-swollen suspension of resin **1** (containing a loading of 1.0 mmol/g as determined by titration) with methyl iodide using a procedure that is similar to that used for solution-phase synthesis.[8] Subsequent alkylation of resin **2** with epoxides according to a procedure from Kurth and co-workers[6e] provided γ-hydroxyl sulfone derivatives **3** in good yields (92−94%). The γ-phenylsulfonylalkyl methyl carbonates **4** were easily derived from resin **3** and methyl chloroformate in the presence of pyridine at 0 °C in nearly quantitative yield, as monitored by FT-IR for the appearance of new carbonyl stretches at 1748−1750 cm^{-1}. The intramolecular acylation−cyclization of the α-sulfonylcarbanion of resin **4** would be the key for the success of this protocol. Here, the lactonization was investigated starting with **4a** (R^1 = H, R^2 = C_6H_5). *n*-BuLi was the first base employed in our trial at various temperatures to perform the cyclization. When at −78 °C, 0 °C, and room temperature under nitrogen for 3 h or even for longer time, the lactonization on solid phase was not complete as monitored by a FT-IR study showing a relatively intense band at 1770 cm^{-1}, which corresponds to the lactonic carbonyl group and a weak carbonyl absorption at 1750 cm^{-1}. However, the best result was obtained with LDA at −78 °C. The FT-IR spectrum of resin **5a** showed a single strong carbonyl peak at 1770 cm^{-1} and the complete disappearance of the carbonyl absorption at 1750 cm^{-1}. With resin **5** in hand, a number of elimination conditions were evaluated, and optimal results were obtained by treating resin **5** in CH_2Cl_2 with an excess amount of triethylamine at 25 °C for 10 h. Conventional workup procedures provided γ-substituted 2(5*H*)-furanones (**6a**−**k**) in good yields (75−85%) and purities (90−95%) as shown in Table 1. It should be noted that when (*R*)-styrene oxide was used as a substrate, the expected products, (5*R*)-5-phenyl-2-(5*H*)-furanones (**6k**) (Table 1, entry 11), were obtained with retention of configuration (>99.0% ee) in 81% yield and with purity of 94%. In addition, the use of cyclohexene oxide (Table 1, entry 12) and methylenecyclohexane oxide (Table 1, entry 13) gave 4,5-disubstituted 2(5*H*)-furanone (**6l**) and 5,5-disubstituted 2(5*H*)-furanone (**6m**) in good yields and purities, respectively.

Next, the selected synthesized resin **5** was utilized further for the synthesis of disubstituted butyrolactones. The α-alkylation of the polystyrene-supported α-phenylsulfonylbutyrolactones **5** and the subsequent elimination under the same

Scheme 1. SPOS of Substituted Butenolides[a]



[a] Reagents and conditions: (a) MeI, THF/DMF (2/1), 80 °C, 15 h; (b) (i) $CH_3S(O)CH_2Li$, THF, rt, 0.5 h; (ii) epoxide, THF, rt, 2 h; (c) $ClCO_2CH_3$, pyridine, 0 °C, 1 h; (d) LDA, THF, −78 °C, 1 h, 0 °C, 2 h, then to rt, 1 h; (e) Et_3N, CH_2Cl_2, rt, 10 h.

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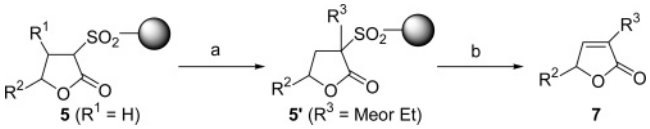
Table 1. Yields and Purities of Substituted Butenolides

entry	R^1, R^2 (epoxide)	product	yield[a] (%)	purity[b] (%)
1	H, Ph	**6a**	80	93
2	H, $C_6H_5OCH_2$	**6b**	82	95
3	H, *p*-$CH_3C_6H_4OCH_2$	**6c**	81	94
4	H, *m*-$CH_3C_6H_4OCH_2$	**6d**	80	94
5	H, $C_6H_5CH_2OCH_2$	**6e**	81	96
6	H, *n*-$BuOCH_2$	**6f**	84	92
7	H, CH_3	**6g**	85	95
8	H, $EtOCH_2$	**6h**	83	94
9	H, $PhSCH_2$	**6i**	75	90
10	H, pyrrolidylmethyl	**6j**	82	93
11	H, Ph [(*R*)-styrene oxide]	**6k**	81	94
12	$-(CH_2)_4-$	**6l**	77	91
13	(methylenecyclohexane oxide)	**6m**	76	90

[a] Overall yield based on the loading of the resin **1**. [b] Purity determined by HPLC of crude cleavage product.

Scheme 2. One-Pot SPOS of 3,5-Disubstituted Butenolides[a]



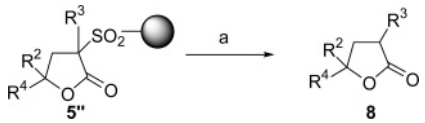
[a] Reagents and conditions: (a) (i) LDA, THF, 0 °C, 0.5 h; (ii) R^3X, rt, 1 h. (b) Et_3N, CH_2Cl_2, rt, 10 h.

Table 2. One-Pot Synthesis of 3,5-Disubstituted Butenolides Starting from Resin **5**

entry	R^2 (resin **5**, R^1 = H)	R^3X	product **7**	yield (%) [a]	purity[b] (%)
1	C_6H_5 (**5a**)	CH_3I	**7a**	76	92
2	*p*-$CH_3C_6H_4OCH_2$ (**5c**)	CH_3I	**7c**	81	93
3	*p*-$CH_3C_6H_4OCH_2$ (**5c**)	EtBr	**7c′**	80	92
4	*m*-$CH_3C_6H_4OCH_2$ (**5d**)	CH_3I	**7d**	78	94
5	CH_3 (**5g**)	CH_3I	**7g**	75	94

[a] Overall yield based on the loading of the resin **1**. [b] Purity determined by HPLC of crude cleavage product.

Scheme 3. SPOS of Substituted Butyrolactones[a]



[a] Reagents and conditions: (a) $Mg/HgCl_2$, EtOH/THF, rt, 16 h.

conditions described above led to the corresponding 3,5-disubstituted 2(5*H*)-furanone derivatives **7** in 75−81% yield and high purity (>90%). Typical examples are shown in Scheme 2 and Table 2. It should be noted that in the cases of α-alkyl-α-phenylsulfonylbutyrolactone resins **5′**, the elimination cleavage of the corresponding resins resulted in the exclusive formation of the corresponding 3,5-disubstituted 2(5*H*)-furanones **7a**−**g**, no α-methylene-γ-butyrolactone being detected by ^1H NMR spectra.

Finally, we switched to another cleavage strategy wherein the polymeric sulfone **5″** was treated with the reducing agent $Mg/HgCl_2$ in EtOH/THF[9] at room temperature for 16 h to give substituted butyrolactones **8** (Scheme 3). Several selected typical examples are described in Table 3. As seen from Table 3, the yields and purities are satisfactory for most of the products. It is obvious that when R^3 is a hydrogen or methyl group that it gives similar results, but the yields of

Table 3. Preparation of Substituted Butyrolactones Starting from Resin **5″**

entry	R^2	R^4	R^3	product **8**	yield (%)[a]	purity (%)[b]
1	C_6H_5	H	H	**8a**	82	94
2	C_6H_5	H	CH_3	**8b**	81	90
3	$C_6H_5OCH_2$	H	H	**8c**	81	93
4	$C_6H_5OCH_2$	H	CH_3	**8d**	80	94
5	CH_3	H	H	**8e**	78	90
6	CH_3	H	CH_3	**8f**	78	90
7	$(CH_2)_5$		H	**8g**	73	91
8	$(CH_2)_5$		CH_3	**8h**	74	92

[a] Overall yield based on the loading of the resin **1**. [b] Purity of crude cleavage product determined by HPLC.

butyrolactone **8g** and **8h** with two substituents at position 5 were slight decreased (Table 3, entry 7 and 8).

In conclusion, we have developed an efficient method for the solid-phase construction of substituted (3- and 5-mono-, 3,4- and 3,5-di, etc.) butenolides and butyrolactones in good yields and high purities employing a sulfone-based traceless linker strategy. Although an excess amount of reagents was required, the considerably simplified workup procedure replaces the time-consuming isolation and purification steps in the corresponding solution-phase synthesis. Furthermore, the described technology and sequence has potential applications in the combinatorial synthesis of butenolide and butyrolactone-containing natural product libraries for biological screening and the drug discovery process.

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Supporting Information Available. General procedures for the synthesis of the library, spectral data for all compounds, and copies of HPLC spectra of some typical compounds: **6e**, **7c**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Preparation of Polymer-Supported Phenylmethylsulfone 2. Polystyrene/1% divinyl benzene lithium sulfinate 1 (1.0 g, 1.0 mmol), prepared according to literature,[6b] was swollen under nitrogen in THF/DMF (2:1, 10 mL). Methyl iodide (5.0 mmol) was added, and the reaction mixture was shaken at 80 °C for 15 h, after which the reaction mixture was cooled to room temperature, quenched with water, and filtered. The resin was washed successively with THF/H_2O (2:1, 3 × 10 mL), THF (2 × 5 mL), CH_2Cl_2 (2 × 5 mL) and ether (2 × 5 mL) and then dried under vacuum overnight to afford the pale yellow resin **2**. FT-IR (single bead reflection): 1600, 1495, 1452, 1380, 1313, 1150 cm^{-1}.

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