Facile β-Sulfenylation of α,β-Unsaturated Lactones and Esters

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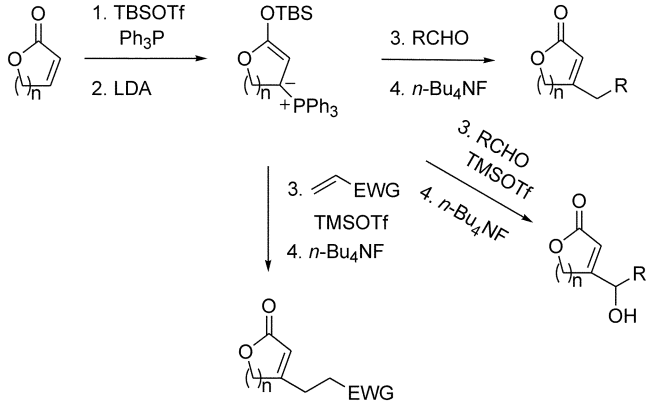
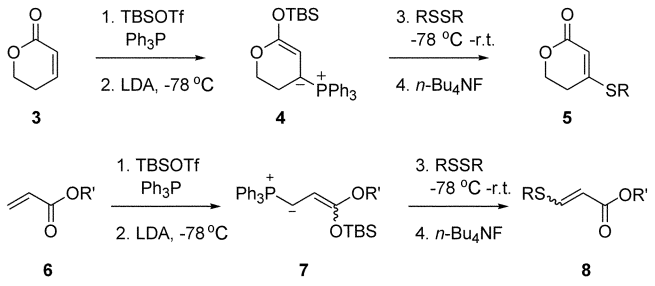
β-Functionalization of α,β-unsaturated carbonyl compounds *via* the organometallic conjugate addition process is one of the most useful methods for carbon-carbon bond formation. However, organometallic conjugate addition procedures followed by enolate trapping and subsequent oxidation are sometimes inadequate and the requisite organocuprates are difficult to obtain.[1] In the case of enones, very efficient and practical β-functionalization methods utilizing the phosphoniosilylation process, one of the dipole reversal processes, have been previously developed by Kozikowski, Kim and Lee (Scheme 1).[2-4] In this process, the ylides (**2**), generated from phosphoniosilylation products (**1**) of enones, serve as β-acylvinyl anion equivalents. Recently, we have shown that such procedure can also be employed to α,β-unsaturated lactones and esters by effecting β-alkylation, β-hydroxyalkylation and β-conjugate addition of them (Scheme 2).[5] The feasible ylide formation from phosphoniosilylation products of α,β-unsaturated lactones and esters by using lithium diisopropylamide (LDA) as a base was the key to the success in these β-functionalizations. These results prompted us to study the possibility of β-sulfenylation of α,β-unsaturated lactones and esters. There are no general methods for the synthesis of β-sulfenylated α,β-unsaturated lactones and esters, and thioethers are useful synthetic intermediates in organic synthesis. We now wish to report facile β-sulfenylation of α,β-unsaturated lactones and esters.

Lee has demonstrated that sulfenylation of enones at β-position can be achieved by the reaction of ylides (**2**) derived from the phosphoniosilylation products (**1**) of enones with disulfides to yield β-sulfenyl-α,β-unsaturated enones.[4(a)] Since β-alkylation, β-hydroxyalkylation and β-conjugate addition of α,β-unsaturated lactones and esters could be executed by the phosphoniosilylation process,[5] we envisaged that the sulfenylation of ylides (**4**, **7**) with various disulfides can also be achieved. Thus, we examined β-sulfenylation of α,β-unsaturated lactones and esters by employing the phosphoniosilylation reaction (Scheme 3).

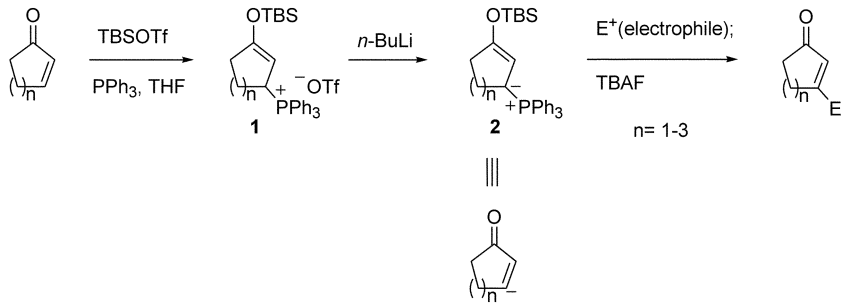
Upon examining various reaction conditions with 5,6-



Scheme 2



Scheme 3



Scheme 1

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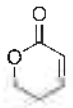
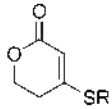
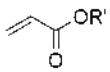
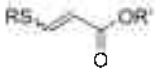
Table 1. β-Sulfenylation of α,β-Unsaturated Lactones (Esters)

entry	Unsaturated lactone (ester)	RSSR	Product	Yield (%)[a]
				
1	"	R= Ph	R= Ph	69(67)[a]
2	"	R= CH_3	R= CH_3	71
3	"	R= $CH_2CH=CH_2$	R= $CH_2CH=CH_2$	55
4	"	R= CH_2Ph	R= CH_2Ph	53
				
5	R=CH_3	R= Ph	R= Ph	60(84:16)[b]
6	"	R= $(CH_2)_3CH_3$	R= $(CH_2)_3CH_3$	40(78:22)[b]
7	"	R=$CH(CH_3)CH_2CH_3$	R=$CH(CH_3)CH_2CH_3$	31(75:25)[b]
8	"	R= CH_3	R= CH_3	22(90:10)[b]
9	R=$(CH_2)_5CH_3$	R= Ph	R= Ph	67(80:20)[b]
10	"	R= $(CH_2)_3CH_3$	R= $(CH_2)_3CH_3$	57(61:39)[b]
11	"	R= CH_3	R= CH_3	54(89:11)[b]

[a]saturated ammonium chloride solution was used as a desilylating agent instead of TBAF. [b]the ratio of *E*:*Z* isomers: determined by the ^{1}H NMR analysis.

dihydro-2*H*-pyran-2-one (**3**) and phenyl disulfide as model unsaturated lactone and disulfide, respectively, it was found that the efficient β-sulfenylation of **3** could be accomplished by the reaction of the *in situ* generated ylide (**4**)[5] with 1.3 equivalents of phenyl disulfide at -78 °C ~ rt and the subsequent treatment with tetra-*n*-butylammonium fluoride (TBAF) at rt in the same pot. The results of β-sulfenylation of α,β-unsaturated lactones and esters, employing these reaction conditions, are shown in Table 1. This process works well with aromatic, aliphatic, and unsaturated disulfides in six-membered lactone, 5,6-dihydro-2*H*-pyran-2-one (**3**) series (entries 1-4), in which products were obtained in moderate to good yields (53-71%). Encouraged by the successful β-sulfenylation of 5,6-dihydro-2*H*-pyran-2-one (**3**), this four-step one pot procedure was employed to α,β-unsaturated esters (**6**). In these cases (entry 5-11), a mixture of (*E*)- and (*Z*)-isomers was obtained, in which (*E*)-isomers were major products with the selectivity of 61 : 39 (entry 10) to 90 : 10 (entry 8).[6] This chemistry also works well with aromatic and aliphatic disulfides in most cases (entries 5, 6, 9-11). However, with *s*-butyl disulfide and methyl disulfide in case of methyl acrylate (**6**, R=Me), the yields which attend this procedure were relatively low (entries 7, 8). The low yield, with *s*-butyl disulfide (entry 7), was assumed to be due to the bulkier nature of *s*-butyl group and/or the poorer leaving ability of *s*-butyl thiolate than other groups. With methyl disulfide (entry 8), the low yield was presumed to be due to relatively high volatility of products.

The results illustrate the efficiency and the applicability of the present method. Especially, it is noteworthy that these overall conversions can be accomplished by one-pot procedure from α,β-unsaturated lactones and esters without any isolation of the intermediates.

In summary, we have shown that the phosphoniosilylation of α,β-unsaturated lactones and esters, in combination with sulfenylation, provides an efficient tool for β-sulfenylation of α,β-unsaturated lactones and esters. Currently we are exploring other β-functionalizations of α,β-unsaturated lactones and esters.

Experimental Section

The general procedure for β-sulfenylation of α,β-unsaturated lactones (esters). To a solution of triphenylphosphine (302.0 mg, 1.14 mmol) in tetrahydrofuran (3.0 mL) was added TBSOTf (262 μL, 1.14 mmol) and 5,6-dihydro-2*H*-pyran-2-one (89.6 μL, 1.04 mmol) at 0 °C. After being stirred at room temperature for 30 min, the reaction mixture was cooled to -78 °C and LDA, prepared from diisopropylamine (210 μL, 1.44 mmol) and *n*-butyllithium (845 μL of 1.48 *M* solution in hexanes, 1.25 mmol) in THF, was added dropwise to give a dark brown-colored solution. The mixture was stirred at -78 °C for 1 h and a solution of phenyl disulfide (298 mg, 1.35 mmol) in tetrahydrofuran (3.0 mL) was added to the ylide solution. After being warmed to room temperature, the reaction mixture was stirred for 1 h. TBAF (1.56 mL of 1 *M* solution in THF, 1.56 mmol) was added and the reaction mixture was stirred for 2 h. The extractive work-up and flash column chromatography gave 4-phenylsulfenyl-5,6-dihydropyran-2-one (entry 1) (148 mg, 69%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54-7.51 (m, 5H), 5.35 (s, 1H), 4.44 (t, J = 6.1 Hz, 2H), 2.64 (t, J = 6.1 Hz, 2H). IR (CCl_4) 2948, 2829 (C-H), 1712 (C=O), 1472 (aromatic C=C), 1214 (C-O) cm^{-1}.

4-Methylsulfenyl-5,6-dihydropyran-2-one (entry 2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67 (s, 1H), 4.43 (t, J = 6.1 Hz, 2H), 2.54 (t, J = 6.1 Hz, 2H), 2.40 (s, 3H). IR (CCl_4) 2948 (C-H), 1714 (C=O), 1470 (C=C), 1212 (C-O) cm^{-1}.

4-Allylsulfenyl-5,6-dihydropyran-2-one (entry 3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.98-5.78 (m, 1H), 5.75 (s, 1H),

5.37 (d, J = 17.1 Hz, 1H), 5.29 (d, J = 11.2 Hz, 1H), 4.41 (t, J = 6.1 Hz, 2H), 3.55 (d, J = 6.34 Hz, 2H), 2.56 (t, J = 6.1 Hz, 2H). IR (CCl_4) 2980, 2940 (C-H), 1710 (C=O), 1650, 1470 (C=C), 1270 (C-O) cm^{-1}.

4-Benzylsulfenyl-5,6-dihydropyran-2-one (entry 4). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 5.80 (s, 1H), 4.42 (t, J = 5.9 Hz, 2H), 4.11 (s, 2H), 2.57 (t, J = 5.9 Hz, 2H). IR (CCl_4) 2950, 2890 (C-H), 1710 (C=O), 1460 (aromatic C=C), 1300, 1210 (C-O) cm^{-1}.

3-Phenylsulfenylacrylic acid methyl ester (entry 5). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (d, J = 15.1 Hz, 1H), 7.54-7.42 (m, 5H), 5.69 (d, J = 15.1 Hz, 1H), 3.73 (s, 3H). IR (CCl_4) 2950 (C-H), 1714 (C=O), 1478 (aromatic C=C), 1300, 1262 (C-O) cm^{-1}.

3-Butylsulfenylacrylic acid methyl ester (entry 6). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (d, J = 15.1 Hz, 1H), 5.77 (d, J = 15.1 Hz, 1H), 3.75 (s, 3H), 2.82 (t, J = 7.1 Hz, 2H), 1.55-1.41 (m, 2H), 0.96 (t, J = 7.1 Hz, 3H). IR (CCl_4) 2958 (C-H), 1714 (C=O), 1434 (C=C), 1256, 1164, 1018 (C-O) cm^{-1}.

3-*sec*-Butylsulfenylacrylic acid methyl ester (entry 7). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, J = 15.6 Hz, 1H), 5.84 (d, J = 15.6 Hz, 1H), 3.75 (s, 3H), 3.13-3.10 (m, 2H), 1.39 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 6.8 Hz, 3H). IR (CCl_4) 2958, 2887 (C-H), 1714 (C=O), 1434 (C=C), 1256, 1164, 1018 (C-O) cm^{-1}.

3-Methylsulfenylacrylic acid methyl ester (entry 8). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (d, J = 15.1 Hz, 1H), 5.69 (d, J = 15.1 Hz, 1H), 3.76 (s, 3H), 2.36 (s, 3H). IR (CCl_4) 2950, 2924 (C-H), 1714 (C=O), 1330, 1254, 1166 (C-O) cm^{-1}.

3-Phenylsulfenylacrylic acid hexyl ester (entry 9). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (d, J = 15.1 Hz, 1H), 7.48-7.31 (m, 5H), 5.68 (d, J = 15.1 Hz, 1H), 4.11 (t, J = 6.6 Hz, 2H), 1.64-1.60 (m, 2H), 1.56-1.31 (m, 6H), 0.98-0.81 (m, 3H). IR (CCl_4) 2956, 2858 (C-H), 1714 (C=O), 1582 (C=C), 1470 (aromatic C=C), 1296, 1248, 1162 (C-O) cm^{-1}.

3-Butylsulfenylacrylic acid hexyl ester (entry 10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, J = 15.1 Hz, 1H), 5.76 (d, J = 15.1 Hz, 1H), 4.13 (t, J = 6.8 Hz, 2H), 2.81 (t, J = 7.3 Hz, 2H), 1.73-1.59 (m, 4H), 1.52-1.28 (m, 8H), 0.99-0.88 (m, 6H). IR (CCl_4) 2928 (C-H), 1714, 1650 (C=O), 1288, 1162, 1082 (C-O) cm^{-1}.

3-Methylsulfenylacrylic acid hexyl ester (entry 11). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, J = 15.1 Hz, 1H), 5.68 (d, J = 15.1 Hz, 1H), 4.14 (t, J = 6.6 Hz, 2H), 2.35 (s, 3H), 1.67-1.63 (m, 2H), 1.58-1.33 (m, 6H), 0.91-0.88 (m, 3H). IR (CCl_4) 2956, 2930 (C-H), 1714 (C=O), 1468 (C-H), 1298, 1252, 1164 (C-O) cm^{-1}.

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6. The ratio of *E*:*Z* isomers was determined by the ^{1}H NMR analysis. And the stereochemistry of *E*- and *Z*-isomers was assigned based on the ^{1}H NMR coupling constants between the olefinic hydrogens. While *E*-isomers exhibit coupling constants of ~15.5 Hz, *Z*-isomers exhibit coupling constants of ~10.0 Hz.