Synthesis of Ene-Sulfides of 2-Methoxycarbonylcyclopentanone: Interconversion of Ene-Sulfides via the Corresponding *S*-Oxides

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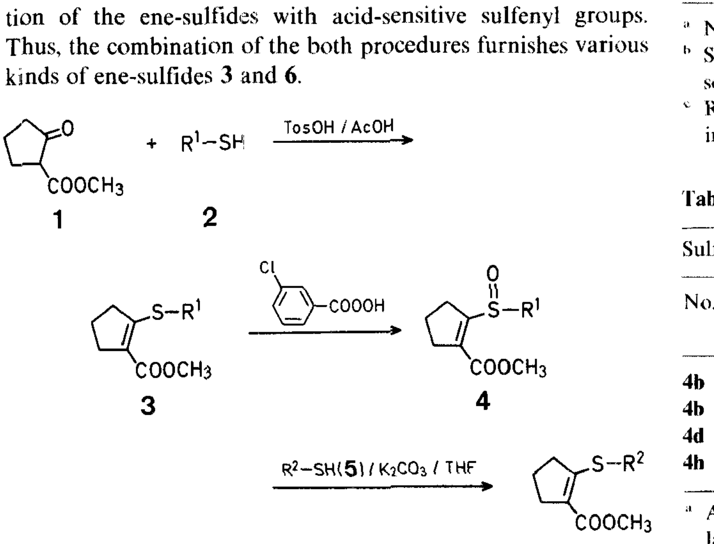
Ene-sulfides recently received increased attention as reagents in organic synthesis[1,2,3] and also in organosulfur-mediated reactions[4,5]. In the course of our study on the reactions of ene-sulfides, we have found a convenient synthesis of various ene-sulfides (**3** and **6**) of 2-methoxycarbonylcyclopentanone (**1**) by both direct and indirect processes. The former consists in the coupling of **1** with a mercaptan **2** under acidic conditions to give **3**, and the latter involves the exchange of the sulfur group in the ene-sulfide **3** with another sulfenyl group from mercaptan **5** via the corresponding *S*-oxide **4** under basic conditions to give **6**. The latter interconversion is an efficient method for the preparation of the ene-sulfides with acid-sensitive sulfenyl groups. Thus, the combination of the both procedures furnishes various kinds of ene-sulfides **3** and **6**.



The reaction of 2-methoxycarbonylcyclopentanone (**1**) with a series of mercaptans **2** is carried out in the presence of *p*-toluenesulfonic acid in acetic acid at room temperature. For example, the coupling of isopropyl mercaptan with **1** occurred on treatment with one equivalent of *p*-toluenesulfonic acid in acetic acid to give **3a** in 84% yield. The bifunctional 2-hydroxyethyl mercaptan underwent reaction under similar conditions to give the *O*-acetylated derivative **3g** in 95% yield. Similarly, an *N*-acetylcysteamine moiety was introduced into **1** to give **3h** in 51% yield. Additional examples are listed in Table 1.

The alternative, indirect procedure was performed by initial oxidation of **3** to **4** and subsequent displacement of sulfinyl group in **4** by another sulfenyl group. When the sulfenyl group in **3** (R^1S) is oxidized to the sulfoxide, the C-2 position of **4** is activated to attack of a nucleophile such as a mercaptan in the presence of base. The *S*-oxides (**4b**, **4d**, and **4h**) were obtained in ~90% yields by treatment of **3b**, **3d**, and **3h** with *m*-chloroperbenzoic acid in dichloromethane at −40 °C. When **4d** was treated with benzyl mercaptan (**5**; $R^2 = C_6H_5CH_2$) in the presence of potassium carbonate in dry tetrahydrofuran at room temperature, the substitution reaction took place almost immediately to give **6b** ($R^2 = C_6H_5CH_2$, ≡**3c**) in 90% yield. Some examples are listed in Table 2. By this procedure, the sulfenyl groups in the ene-sulfide can be easily exchanged with other sulfenyl groups, thus, this method constitutes a facile method for the interconversion of ene-sulfides.

Table 1. Ene-Sulfides **3a-g** Prepared from **1** under Acidic Conditions

Product No.	R^1	Yield [%]	m.p. [°C][a]	Molecular formula[b]
3a	i-C_3H_7	84	oil	$C_{10}H_{16}O_2S$ (200.3)
3b	n-C_4H_9	64	oil	$C_{11}H_{18}O_2S$ (214.3)
3c	$C_6H_5CH_2$	92	34–36°	$C_{14}H_{16}O_2S$ (248.3)
3d	C_6H_5	70	oil	$C_{13}H_{14}O_2S$ (234.3)
3e	2-naphthyl	99	81–83°	$C_{17}H_{16}O_2S$ (284.4)
3f	$C_2H_5O—CO—CH_2$	67	19–21°	$C_{11}H_{16}O_4S$ (244.3)
3g[c]	$H_3C—CO—O—CH_2—CH_2$	95	oil	$C_{11}H_{16}O_4S$ (244.3)
3h	$H_3C—CO—NH—CH_2—CH_2$	51	66–68°	$C_{11}H_{17}NO_3S$ (243.3)

[a] Not corrected.

[b] Satisfactory microanalyses (C ±0.26, H ±0.23, S ±0.26) and high resolution mass spectra for M^+ (±0.0021 mass units) obtained.

[c] R^1 in **2** = $HO—CH_2—CH_2$, *O*-acetylation of the OH group occurs during the reaction.

Table 2. Ene-Sulfides **6** Prepared from **4** under Basic Conditions

Sulfoxide **4**[a]			Mercaptan **5**	Ene-Sulfide **6**	
No.	R^1	Yield [%]	R^2	No.	Yield [%]
4b	n-C_4H_9	90	C_6H_5	**6a**≡**3d**	90
4b	n-C_4H_9	90	$C_6H_5CH_2$	**6b**≡**3c**	90
4d	C_6H_5	82	$C_6H_5CH_2$	**6b**≡**3c**	82
4h	$H_3C—CO—NH—CH_2—CH_2$	75	$C_6H_5CH_2$	**6b**≡**3c**	70

[a] All *S*-oxides listed gave satisfactory spectra and their chemical formulae were confirmed by high resolution mass spectrometry (±0.003 mass unit).

2-Isopropylsulfenyl-1-methoxycarbonylcyclopentene (3a); Typical Procedure under Acidic Conditions:

To a solution of 2-methoxycarbonylcyclopentanone (**1**; 142 mg, 1 mmol) and isopropyl mercaptan (**2**; $R^1 = i$-C_3H_7; 91.2 mg, 1.2 mmol) in acetic acid (8 ml) is added *p*-toluenesulfonic acid (190 mg, 1 mmol). After stirring of the solution for 20 h at room temperature, the acetic acid is removed in vacuo and then the residue is dissolved in chloroform (100 ml). The solution is shaken with cold 2 normal sodium hydroxide solution (20 ml), washed with water (3 × 50 ml), and dried with anhydrous sodium sulfate. After removal of the solvent, the residue is distilled in a bulb-to-bulb apparatus at 80–90 °C (oven temperature)/1 torr, affording 2-isopropylsulfenyl-1-methoxycarbonylcyclopentene (**3a**); yield: 195.4 mg (84%).

$C_{10}H_{16}O_2S$	calc.	C 59.97	H 8.05	S 16.01
(200.3)	found	59.99	8.22	16.23

I.R. ($CHCl_3$): $\nu = 1680\ cm^{-1}$ (C=O).

U.V. (ethanol): $\lambda_{max} = 291$ nm ($\varepsilon = 11\,800$).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.34$ [d, 6H, $J = 7$ Hz, $CH(C\underline{H}_3)_2$]; 1.8–2.1 (m, 2H, CH_2); 2.5–3.0 (m, 4H, $C\underline{H}_2—C=C—C\underline{H}_2$); 3.37 [sept, 1H, $J = 7$ Hz, $C\underline{H}(CH_3)_2$]; 3.70 ppm (s, 3H, $OC\underline{H}_3$).

1-Methoxycarbonyl-2-phenylsulfinylcyclopentene (4d); Typical Procedure:

A solution of *m*-chloroperbenzoic acid (8.6 g, 0.05 mol) in dry dichloromethane (90 ml) is added dropwise over 10 min to a solution of 1-methoxycarbonyl-2-phenylsulfenylcyclopentene (**3d**; 11.7 g, 0.05 mol) in dry dichloromethane (150 ml) with stirring at −40 °C. After the completion of the addition, stirring is continued for 2.5 h. The reaction mixture is

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then shaken with 10% sodium thiosulfate solution (50 ml) and with saturated sodium hydrogen carbonate solution (100 ml). The solvent is removed under reduced pressure and the residue is chromatographed (flash chromatography) on a column of silica gel (Merck, silica gel 60, 230–400 mesh) using ethyl acetate/*n*-hexane (1:2) as eluent to give 1-methoxycarbonyl-2-phenylsulfinylcyclopentene (**4d**); yield: 10.3 g (82%); m.p. 50–51 °C (from *n*-hexane/ethyl acetate).

$C_{13}H_{14}O_3S$	calc.	C 62.38	H 5.64	S 12.81
(250.3)	found	62.50	5.66	12.63

High resolution M.S.: *m/e* = 250.0683 (calc. for M^+: 250.0664).

I.R. ($CHCl_3$): $\nu = 1710$ (C=O); 1620 cm^{-1} (>C=C<).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.6–2.2$ (m, 2H, CH_2); 2.4–3.2 (m, 4H, $C\underline{H}_2-C=C-C\underline{H}_2$); 3.84 (s, 3H, CO–$OCH_3$); 7.3–7.9 ppm (m, 5H, C_6H_5).

2-Benzylsulfenyl-1-methoxycarbonylcyclopentene (6b; $R^2 = C_6H_5CH_2$, ≡3c); Typical Procedure for Exchange Reaction under Basic Conditions:

To a mixture of 1-methoxycarbonyl-2-phenylsulfinylcyclopentene (**4d**; 125 mg, 0.5 mmol) and potassium carbonate (384 mg, 2.8 mmol) in dry tetrahydrofuran (1 ml) is added dropwise a solution of benzylmercaptan (**5**; $R^2 = C_6H_5CH_2$; 310 mg, 2.5 mmol) in dry tetrahydrofuran (1 ml) with stirring at room temperature. After stirring for 10 min, the mixture is diluted with chloroform (100 ml), and the solution is washed with water (3 × 50 ml), and dried with anhydrous sodium sulfate. The solvent is removed under reduced pressure to give a residual oil which is chromatographed (flash chromatography) on a column of silica gel using ethyl acetate/*n*-hexane (1:5) as eluent to give **1-methoxycarbonyl-2-benzylsulfenylcyclopentene**; yield: 102 mg (82%).

$C_{14}H_{16}O_2S$	calc.	C 67.71	H 6.49	S 12.91
(248.3)	found	67.50	6.26	13.13

I.R. ($CHCl_3$): $\nu = 1680$ cm^{-1} (C=O).

U.V. (ethanol): $\lambda_{max} = 290$ nm ($\varepsilon = 11200$).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.7–2.1$ (m, 2H, $C\underline{H}_2$); 2.5–2.9 (m, 4H, $C\underline{H}_2-C=C-C\underline{H}_2$); 3.70 (s, 3H, CO–$OCH_3$); 4.07 (s, 2H, $C\underline{H}_2-C_6H_5$); 7.2–7.5 ppm (m, 5H, C_6H_5).

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[1] R. W. Ratcliff, T. N. Salzmann, B. G. Christensen, *Tetrahedron Lett.* **21**, 31 (1980).

[2] D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, M. Sletzinger, *Tetrahedron Lett.* **21**, 2783 (1980).

[3] R. J. Ponsford, P. M. Roberts, R. Southgate, *J. Chem. Soc. Chem. Commun.* **1979**, 847.

[4] H. Okamura, M. Miura, H. Takei, *Tetrahedron Lett.* **1979**, 43.

[5] B. M. Trost, *Acc. Chem. Res.* **11**, 453 (1978).