Sultone Formation from α-Hydroxycyclopentanones and Alkanesulfonyl Chloride

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Reaction of alkanesulfonyl chloride with α-hydroxycyclopentanones in the presence of triethylamine in CH_2Cl_2 at room temperature afforded the sultones and α,β-unsaturated sultones; the usual alkanesulfonate was not obtained.

Keywords alkanesulfonyl chloride; sultone; α,β-unsaturated sultone; α-hydroxycyclopentanone; methanesulfonyl chloride

Sultones, so named by Erdmann,[1] are the internal esters of hydroxy sulfonic acids, and certain sultones[2] are known to have cellular immunosuppressive properties, like the analogous sultams. The general procedure for the synthesis[3] of sultones is either by cyclization of the halogeno or hydroxy sulfonic acids or by sulfonation of olefins with SO_3–dioxane. α,β-Unsaturated sultones[3] were synthesized from sodium2-alkene sulfonates, which could be obtained by sulfonation of 1-alkenes with SO_3–dioxane (2:1-complex) followed by neutralization, *via* treatment with bromine and subsequent dehydrobromination with triethylamine (Chart 1). These methods are considered to be rather limited, because of vigorous reaction conditions and difficulty in the selection of substrates.

During synthetic studies on biologically active compounds containing a five-membered ring, we found that certain α-hydroxycyclopentanones afford the sultones under usual mesylation reaction conditions,[4] and the mesylates are not obtained (Chart 2). Treatment of compound **1**[5] with methanesulfonyl chloride–triethylamine–CH_2Cl_2 at room temperature afforded the α,β-unsaturated sultone (**2a**) in 56% yield. The structure of **2** was confirmed on the basis of spectroscopic analysis. In the mass spectrum (MS), **2a** showed the molecular ion peak at *m/z* 364, suggesting dehydration from the usual mesylate. The infrared (IR) spectra showed the absorption bands of OSO_2 at 1360 and 1190 cm^{-1}. In addition, the signals of an olefinic proton at δ 6.59 (1H) assignable to $C=CH-SO_2O$, CH_a at δ 3.51 (1H, $J=18$ Hz) and CH_b at δ 3.72 (1H, $J=18$ Hz), CH_3 at δ 2.21 (3H), and $COOCH_3$ at δ 3.84 (3H) were observed in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. In a similar manner, treatment of **1** with ethanesulfonyl chloride afforded the sultone (**2b**), which was supported by spectroscopic data. However, 1-propanesulfonyl chloride afforded two products (**3**, **4**), and independent treatment of each product with triethylamine–CH_2Cl_2 under refluxing conditions afforded **2c**. The structure of **2c** was determined by comparison of the spectroscopic data with those of **2a** and **2b**, and **3** was decided to be an intermediate for **2c** based on the absorption band of OH at 3400 cm^{-1} in the IR

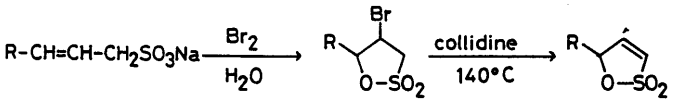
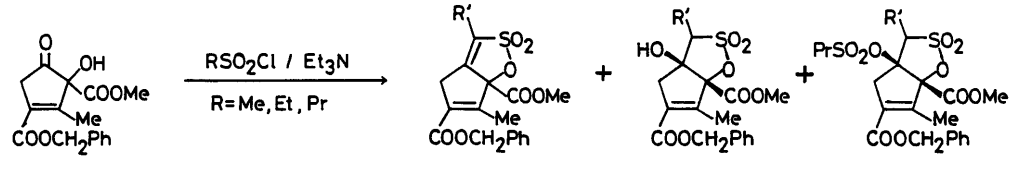


Chart 1

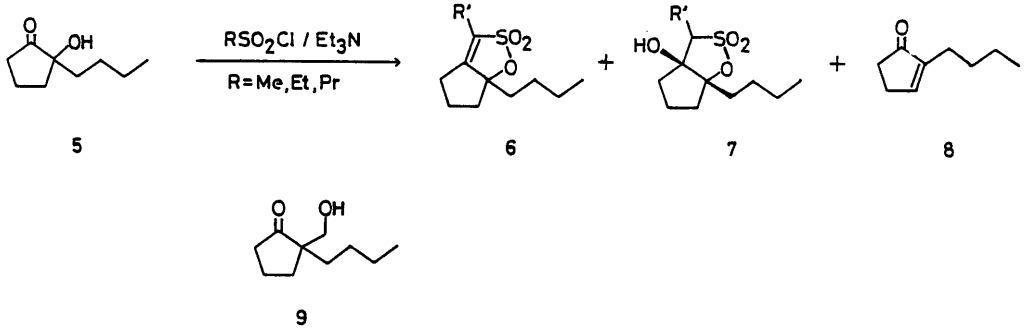
TABLE I

Entry	RSO_2Cl R	R′	Yields (%)		
			2	3	4
1	Me	a(R′=H)	56	0	0
2	Et	b(R′=Me)	50	0	0
3	Pr	c(R′=Et)	0	22	34



1 2 3 4

Chart 2



5 6 7 8 9

Chart 3

TABLE II

Entry	RSO_2Cl R	R′	Yields (%)		
			6	7	8
1	Me	a(R′=H)	12	5	40
2	Et	b(R′=Me)	0	23	42
3	Pr	c(R′=Et)	0	25	41

spectrum, in addition to the molecular ion peak at *m/z* 410 in the MS and rational assignment of signals in the ^{1}H-NMR spectrum to the protons of the proposed structure. In compound **4**, disappearance of OH absorption in the IR spectrum and the molecular ion peak at *m/z* 516 in the MS, as well as the analysis of the ^{1}H-NMR spectrum supported the proposed structure (Table I). Although the stereochemical assignment for each product was difficult, it seems reasonable to assign the *cis*-ring fusion for the bicyclosultone skeleton.

The above findings prompted us to examine the mesylation of a tertiary alcohol[6] in a simpler structure (Chart 3). Reactions of compound **5** with RSO_2Cl are summarized in Table II. Although the formation of sultones was observed for each RSO_2Cl, the yields were unsatisfactory. That is to say, the existence of hydrogen at the β-position of the carbonyl function favors elimination of sulfonate, leading to the formation of sultones. However, compound **9** afforded only the mesylate and the sultone was not obtained, even under reflux in $MeSO_2Cl$–triethylamine–CH_2Cl_2.

Experimental

IR spectra were measured on a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-FX 100, and MS on a JEOL-D 300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were washed with saturated brine and dried on anhydrous sodium sulfate. Each compound was obtained as a colorless oil.

General Procedure $MeSO_2Cl$ (2.4 mmol) in CH_2Cl_2 (2 ml) was added to a stirred solution of a mixture of **1** (1 mmol) and triethylamine (6 mmol) in CH_2Cl_2 (10 ml) under ice-water cooling. The whole was stirred at room temperature for 48 h, and the reaction mixture was washed successively with 3% HCl, 5% $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to silica gel column chromatography. The fraction eluted with 5% AcOEt in hexane (v/v) afforded **2a** as a colorless oil.

2a: IR (neat): 1760 (sh), 1720, 1500, 1360, 1190, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, dd, J=2.7, 2.0 Hz, =–Me), 3.51 (1H, d, J=18 Hz, CH_a), 3.72 (1H, J=18 Hz, CH_b), 3.84 (3H, s, OMe), 5.24 (2H, s, CH_2Ph), 6.59 (1H, br d, J=2.0 Hz, =CH), 7.38 (5H, m, aromatic-H). MS *m/z*: 364 (M^+), 305, 257, 229.

2b: IR (neat): 1760 (sh), 1720, 1350, 1220, 1180, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, d, J=1.3 Hz, =–Me), 2.19 (3H, dd, J=2.4, 1.6 Hz, =–Me), 3.40 (1H, d, J=18 Hz, CH_a), 3.56 (1H, d, J=18 Hz, CH_b). MS *m/z*: 378 (M^+), 346, 319, 304, 270.

2c: IR (neat): 1760 (sh), 1720, 1350, 1220, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=6.3 Hz, Me), 2.19 (3H, dd, J=2.5, 1.7 Hz, =–Me), 2.54 (2H, m, CH_2), 3.46, 3.56 (each 1H, m, CH_2).

3c: IR (neat): 3460, 1760 (sh), 1720, 1360, 1240, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz, Me), 2.07 (3H, dd, J=2.2, 2.0 Hz, =–Me), 2.97 (2H, m, CH_2), 3.06 (1H, m, CH), 3.86 (3H, s, OMe). MS *m/z*: 411 (M^++1), 321, 303.

4c: IR (neat): 1770 (sh), 1730, 1360, 1240, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7.4 Hz, Me), 1.23 (3H, m, Me), 2.06 (3H, dd, J=2.5, 1.8 Hz, =–Me), 3.12 (3H, m, SO_2–CH, –CH_2), 3.47, 3.50 (each 1H, m, CH_2), 3.87 (3H, s, OMe). MS *m/z*: 516 (M^+), 409, 333, 301, 137.

6a: IR (neat): 1370 (sh), 1340, 1180, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6.8 Hz, Me), 1.04—2.87 (12H, m), 6.55 (1H, t, J=7.6, 2.7 Hz, =CH). MS *m/z*: 217 (M^++1), 199, 161.

7a: IR (neat): 3500, 1350, 1330, 1180, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=6.8 Hz, Me), 1.10—2.86 (12H, m), 3.40 (2H, dd, J=13.7, 2.0 Hz, CH_2SO_2). MS *m/z*: 235 (M^++1), 199, 102.

7b: IR (neat): 3500, 1450, 1340, 1170, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz, Me), 1.44 (3H, d, J=6.9 Hz, Me), 3.15[7] (H, q, J=6.9 Hz, CH), 3.51[7] (H, q, J=6.9 Hz, CH). MS *m/z*: 249 (M^++1), 233, 207, 184.

7c: IR (neat): 3400, 1460, 1340, 1170, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.1 Hz, Me), 1.21 (3H, t, J=7.4 Hz, Me), 2.96[7] (H, t, J=4.8 Hz, CH), 3.35[7] (H, t, J=4.8 Hz, CH). MS *m/z*: 262 (M^+), 244, 198, 183, 169.

8: IR (neat): 1720, 1690, 1640, 1460, 1320, 1190, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.6 Hz, Me), 6.55 (1H, t, J=7.6 Hz, =CH). MS *m/z*: 138 (M^+), 123, 95.

References and Notes

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7) Proton signals (SO_2CH) at δ 3.15 and 3.51 of **7b**, and at δ 2.96 and 3.35 of **7c** were observed in ratio of 3 to 1, suggesting a mixture of stereoisomers.