

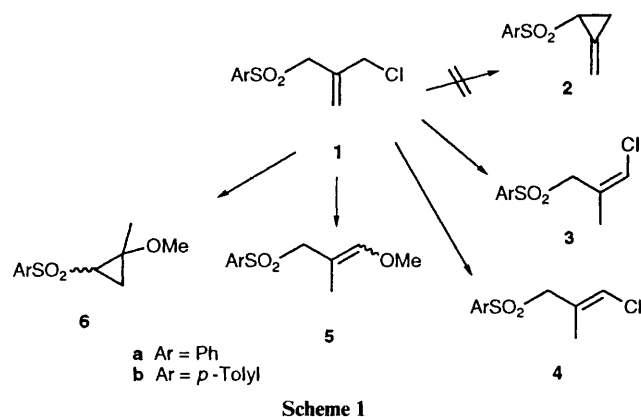
Formation of Cyclopropylsulfones from 1-Arylsulfonyl-2-chloromethyl-prop-2-enes

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Methylenecyclopropyl sulfones are not formed when the title chlorosulfones are treated with methanolic methoxide; instead 1-arylsulfonyl-2-methoxy-2-methylcyclopropanes are formed by an addition–cyclisation sequence involving intramolecular displacement of chloride and not methoxide as suggested by other workers.

As part of an exploration of the limit of excess enthalpy differential (EED) that can be tolerated for intramolecular nucleophilic substitution,¹ we examined the reactions of bases with sulfone **1a**. We were mindful of the fact that cyclisation *via* a sulfonyl-stabilised carbanion leading to methylenecyclopropane **2** would involve an EED of 171 kJ mol⁻¹.[†] In the event, none of **2** was obtained, under a wide variety of conditions (Table 1). When the base was strong but poorly nucleophilic (Bu⁺OK–Bu⁺OH) the isomerisation products **3a** and **4a** were obtained (entry 1) but no cyclisation occurred. When the base was weaker but more nucleophilic (NaOMe–MeOH), the products were initially **3a** and **4a** (entry 2) which were converted under more vigorous conditions into the cyclopropanes **6a** (entries 3 and 4) with small quantities of the ether **5a** (entry 6) (Scheme 1).

A reasonably consistent pathway is outlined in Scheme 2. Isomerisation of **1** to the sulfone-conjugated isomer **9**, probably

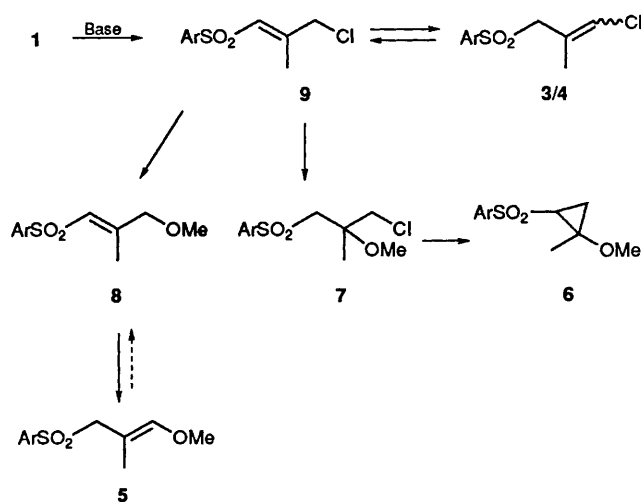


[†] Here the EED between methylenecyclopropane (171 kJ mol⁻¹) (see ref. 2) and an 'unstrained' precursor **1a** is assumed to equal the strain energy of **2**.

Table 1 Product yields from reactions of **1a** with base

Entry	Substrate	Conditions ^a	Products ratio ^b (%)				Isolated yield (%)			
			1a	3a/4a (ratio)	5	6	1a	3a/4a	5	6
1	1a	1 × KOBu ⁺ Bu ⁺ OH, 26 °C	—	100 (2:1)	—	—	—	26 ^c	—	—
2	1a	3 × MeO ⁻ /MeOH, 3 h, 22 °C	66	33 (3:1)	—	—	52	25	—	—
3	1a	3 × MeO ⁻ /MeOH, 18 h, 22 °C	5	85 (4:1)	—	10 ^d	—	76	—	—
4	1a	3 × MeO ⁻ /MeOH, 3 d, 22 °C	—	80 (4:1)	—	20 ^e	—	75	—	5 ^d
5	1a	3 × MeO ⁻ /MeOH, 2 d, 65 °C	—	40 (4:1)	—	60 ^e	—	—	—	—
6	1a	3 × MeO ⁻ /MeOH, 4 d, 65 °C	—	—	10 ^d	90 ^f	—	—	—	81 ^f
7	1a	0.5 × MeO ⁻ /MeOH, 3 d, 65 °C ^g	—	62 (2:1)	9 ^d	29 ^h	—	—	—	—
8	3a/4a (2:1)	3 × MeO ⁻ /MeOH, 3 d, 65 °C	—	—	—	—	10	—	—	76 ⁱ
9	5a	3 × MeO ⁻ /MeOH, 7 d, 65 °C	—	—	75 ^j	—	—	—	—	—
10	(<i>E</i>)-6a	5 × MeO ⁻ /MeOH, 7 d, 65 °C	—	—	—	80 ^{j,k}	—	—	—	—

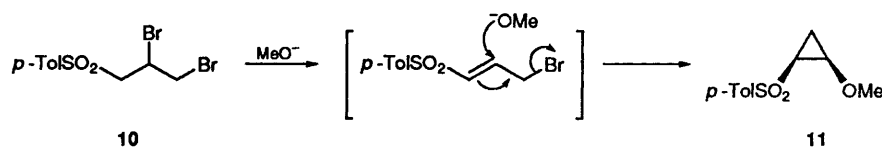
^a Numbers refer to molar ratios of base to substrate. ^b By ¹H NMR. ^c Single isomer by recrystallisation (petrol–ethyl acetate). ^d Observed/isolated as a single isomer. ^e Isomer ratio 9:1. ^f Isomer ratio 6:1. ^g HPLC yields reported. ^h Isomer ratio 18:1. ⁱ Isomer ratio 5:1. ^j Product recovery estimated from HPLC analysis. ^k (*E*)-Isomer only recovered.



in equilibrium with the much-favoured ³ isomer(s), **3** and **4**.[‡] Addition–cyclisation involving methoxide (*cf.* **7**), then gives the cyclopropanes, **6** formed as a mixture of (*E*) and (*Z*) isomers with the (*E*)-**6** favoured. No evidence for formation of methylenecyclopropane, **2**, was found. A minor product, however, was ether **5**, presumably formed by direct substitution on chloride **9**, giving **8**, which then isomerises to the more stable, sulfone-deconjugated isomer, **5** (entry 6). By treatment of **2a**, prepared separately,⁴ with methanolic sodium methoxide we have established that it is not an intermediate in these reaction pathways.

While this work was in progress, reaction of the sulfone **1b** with methanolic sodium methoxide was reported⁵ to give, in 95% yield, a 1:1 mixture of open chain ether (*E*)-**5b** and cyclopropane (*E*)-**6b**. It is implied in this report⁵ that this

[‡] Reactions of **1a** with MeOD/MeO⁻ affords [²H₆]-**3a/4a** supporting equilibration of all double bond isomers of the anion of **1a**.



mixture on prolonged exposure to methanolic sodium methoxide at reflux gives an 84% yield of (*E*)-**5b** and (*E*)-**6b** in a 2:98 ratio. The authors suggest that, in contrast to our work, a single methoxycyclopropane **6** is obtained by a pathway involving addition of methoxide ion to **8** and intramolecular displacement of the distal methoxy-group.*

In earlier work from our laboratories,⁶ formation of cyclopropanes by intramolecular displacement of phenoxide as leaving group was found to be exceedingly slow, with a rate constant of $ca. 5 \times 10^{-13} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 30 °C. Leaving group rank⁷ in such reactions was quantified and shown to correlate excellently with the $pK_a(\text{Bu}^\text{OH})$ of the leaving group. We consider it very improbable therefore that this reaction can occur under the reported conditions. The result of reacting chlorides **3a/4a** gives **6a** (entry 8) but we find that no cyclopropane, **6a** is obtained when the ethers, **5a** react with methanolic sodium methoxide under our conditions (entry 9). We have also established that the cyclopropane (*E*)-**6a** appears not to be involved in subsequent reaction to yield **5a** nor indeed (*Z*)-**6a** over the timescale of these reactions (see Table 1, entry 10). In an analogous situation, the Spanish authors report a timescale of 7 d reflux in 0.4 mol dm^{-3} MeONa/MeOH for reaction of **10** via a related species to afford⁸ cyclopropane **11**.

In the present situation, the origin of such experimental inconsistencies may lie in differing reaction conditions, with our base concentrations typically at $ca. 0.5 \text{ mol dm}^{-3}$. Notwithstanding the differing product ratios, the chlorides **3a** and **4a** appear unequivocally to be the source of cyclopropanes **6a**, as indicated by both the present experiments and the relative leaving group ranks for Cl *vs.* OMe.⁷

Experimental

General Directions.—M.p.s are uncorrected. Petrol refers to light petroleum b.p. 40–60 °C. ¹H NMR spectra were recorded in CDCl₃ at 400 MHz with Me₄Si reference; ¹³C spectra were recorded at 62.9 MHz. Methanol was HPLC grade. *tert*-Butanol was dried (CaH₂) and distilled prior to use. HPLC analysis was performed on 5 μ Spherisorbsilica column (25 cm \times 4.6 mm i.d.) eluting with petrol–ethyl acetate (80:20) and with UV detection at 254 nm. Semi-preparative HPLC was performed on 5 μ Spherisorbsilica (25 cm \times 20 mm i.d.) eluting with petrol–ethyl acetate 85:15, flow rate 15 cm³ min^{−1}; UV detection at 254 nm. The following retention times (min) were observed using semi-preparative HPLC: **4a** (minor isomer), *t_R* 8.90; **3a** (major isomer), *t_R* 11.22; **5a**, *t_R* 13.54; (*Z*)-**6a**, *t_R* 14.57; and (*E*)-**6a**, *t_R* 16.38. No unassigned peaks were observed. 3-Phenylsulfonyl-2-chloromethylprop-1-ene **1a** had m.p. 55–56 °C (lit.,⁹ 54–55 °C) and 1-methylene-2-phenylsulfonylcyclopropane **2a** had m.p. 46–48 °C (lit.,¹⁰ 47.5–48.5 °C).

Reaction of 1a.—(a) *With methanolic sodium methoxide.* 1-Phenylsulfonyl-2-methoxymethylcyclopropane **6a**. A stirred solution of **1a** (2.4 g, 0.01 mol) in methanol (50 cm³) was treated with sodium methoxide (30 cm³, 0.03 mol; 1 mol dm^{-3} solution in methanol). The whole was refluxed for 4 d under argon, quenched with dil. hydrochloric acid, extracted with dichloromethane, concentrated and chromatographed (petrol–ethyl acetate, 7:3) to yield first (*Z*)-**6a** (minor isomer) (0.21 g, 9%),

m.p. 85–87 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 1295 and 1150; δ_{H} 8.0–7.90 (2 H, m) and 7.60–7.40 (3 H, m, PhSO₂), 3.45 (3 H, s, OMe), 2.38 (1 H, dd, *J* 8 and 6 Hz), 1.98 [1 H, dd appears as t, *J* 2 \times 6 Hz, C(3)Ha], 1.40 (3 H, s, CH₃) and 1.25 [1 H, dd, *J* 8 and 6 Hz, C(3)Hb] [NOE observed between C(2)CH₃ and C(1)H] (Found: C, 58.1; H, 6.1. C₁₁H₁₄O₃S requires C, 58.39; H, 6.24%). Next eluted was (*E*)-**6a** (major isomer) (1.62 g, 72%), m.p. 42–44 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 1300 and 1145; δ_{H} 8.0–7.85 (2 H, m), 7.70–7.50 (3 H, m, PhSO₂), 3.24 (3 H, s, OMe), 2.25 (1 H, dd, *J* 8 and 6 Hz) and 1.65–1.50 (2 H, m) [NOE enhancement observed between OMe and C(1)H] (Found: C, 58.3; H, 6.1; S, 14.15. C₁₁H₁₄O₃S requires C, 58.39; H, 6.24; S, 14.17%).

(b) *With potassium tert-butoxide in tert-butanol.* In a similar reaction to that described above in *tert*-butanol with potassium *tert*-butoxide gave **3a/4a**. Major isomer, m.p. 110–112.5 °C (petrol–ethyl acetate), $\nu_{\text{max}}/\text{cm}^{-1}$ 1300 and 1150; δ_{H} 7.90–7.82 (2 H, m), 7.70–7.62 (1 H, m) and 7.60–7.54 (2 H, m, PhSO₂), 5.90–5.88 (1 H, m), 4.89 (2 H, d, *J* 1 Hz, PhSO₂CH₂) and 3.84 (3 H, d, *J* 2 Hz, CH₃); δ_{C} 138.24, 133.90, 129.16, 128.36, 127.21, 122.05, 63.28 and 17.22; *m/z* (CI) 250/248 (M + NH₄⁺, 100%) (Found: C, 52.1; H, 4.6; Cl, 15.4; S, 13.8. C₁₀H₁₁O₂ClS requires: C, 52.06; H, 4.81; Cl, 15.37; S, 13.89%). Minor isomer, m.p. 80–83 °C; δ_{H} 7.92–7.87 (2 H, m), 7.68–7.62 (1 H, m) and 7.56–7.51 (2 H, m, PhSO₂), 5.99–5.97 (1 H, m), 4.04 (2 H, s, PhSO₂CH₂) and 2.00 (3 H, d, *J* 2 Hz, CH₃). (No NOE enhancements observed for either isomer.)

1-Methoxy-2-methyl-3-phenylsulfonylprop-1-ene 5a.—This compound was isolated by semi-preparative HPLC separation of reaction products, m.p. 50–53 °C; δ_{H} 7.95–7.85 (2 H, m), 7.65–7.45 (3 H, m, PhSO₂), 5.80 (1 H, br s), 3.90 (2 H, br s), 3.10 (3 H, s, OMe) and 1.70 (3 H, d, *J* 0.5 Hz, CH₃); *m/z* (EI) 226 (M⁺, 60%) (Found: 226.2902. C₁₁H₁₄O₃S requires 226.2898).

Reaction of 1-Methylene-2-phenylsulfonylcyclopropane 2a with Methanolic Sodium Methoxide.—Under conditions similar to those described above for **1a** a sample of **2a** (0.56 g, 2.88 mmol) in methanolic sodium methoxide was heated under reflux for 3 d. The resulting residue (0.36 g) was shown by ¹H NMR spectroscopy and HPLC analysis to be recovered **2a**. No evidence for the formation of the ether **5a** or the cyclopropanes **6a** was obtained.

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* Note added in proof. Professor Najera tells us in a private communication that the conditions used in her laboratories for the conversion of a 1:1 mixture of compounds **5b** and **6b** into **6b** involved treatment of the mixture with 3 equiv. NaOMe without solvent at 80 °C for 3 days.