Synthesis of Simple Oxetanes Carrying Reactive 2-Substituents

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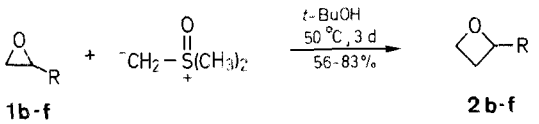
Ring-expansion of substituted epoxides using dimethyloxosulphonium methylide provides a convenient route to oxetanes carrying reactive 2-substituents that are capable of further modification.

Whereas several methods are available for the synthesis of oxetanes,[1-9] no general method exists for the preparation of simple examples carrying a reactive substituent such as hydroxymethyl in the 2-position. Although various substituted 2-hydroxymethyloxetanes have been synthesised from 3,4-epoxyalcohols,[10,11] the method is unsuitable for the synthesis of 2-hydroxymethyloxetane **(2a)** itself, since it proceeds in poor yield, and the product is heavily contaminated with 3-hydroxytetrahydrofuran.

We now report a much improved route to 2-hydroxymethyloxetane **(2a)** and related compounds *via* the ring-expansion of substituted epoxides **1b–f** using dimethyloxosulphonium methylide as methylene transfer agent (Scheme). Okuma et al.[12] have also ring-expanded epoxides, but only to synthesise oxetanes bearing aromatic or cycloalkyl substituents.



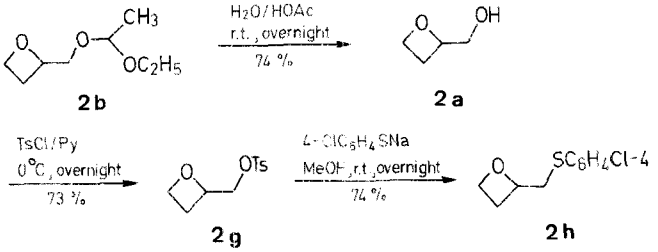
1, 2	R
a	CH_2OH
b	$CH_2OCH(CH_3)OC_2H_5$
c	$CH_2OCH_2CH{=}CH_2$
d	$CH_2OC_6H_5$
e	$CH_2CH_2CH{=}CH_2$
f	$CH(OC_2H_5)_2$

Thus, 2,3-epoxypropan-1-ol **(1a)** was first protected by interaction with ethoxyethene, and the resulting ether **1b** was stirred for 3d at 50°C with dimethyloxosulphonium methylide (prepared from trimethyloxosulphonium iodide and potassium *tert*-butoxide in *tert*-butyl alcohol). This gave the corresponding oxetane ether **2b**, which was readily deprotected in acid to give 2-hydroxymethyloxetane **(2a)**.

Corresponding ring-expansions occurred when the readily available epoxides **1c–e** were similarly treated with dimethyloxosulphonium methylide. The results are shown in the Table.

Epoxide **1f** was prepared from 2,3-dihydroxypropanal diethyl acetal[13] *via* cyclisation of its monotosyl derivative, since both the published methods available[14,15] for **1f** failed in our hands.

The oxetane substituents may be modified whilst preserving the integrity of the oxetane ring. Thus, for example, 2-hydroxymethyloxetane **(2a)** was readily converted *via* its tosylate **2g** into the thioether **2h** by interaction of the latter with 4-chlorobenzenethiol.



The unsaturated side-chains in oxetanes **2c** and **2e** could also be modified. For example, both gave epoxides (**2i** and **2j**, respectively) on treatment with *m*-chloroperoxybenzoic acid (MCPBA) and dibromides (**2k** and **2l**, respectively) on treatment with bromine in the presence of potassium carbonate. Oxetane-2-carbaldehyde could not be isolated from the acetal **2f**, but the latter did give oxetane-2-carbaldehyde 2,4-dinitrophenylhydra-

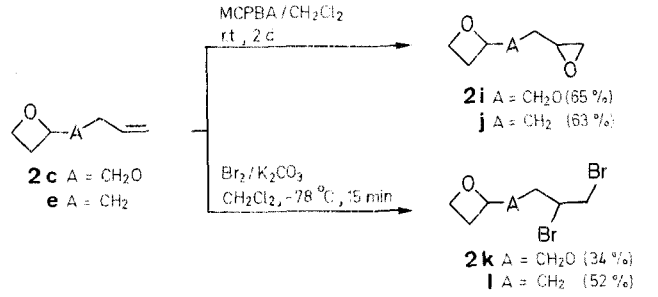


Table. Oxetanes **2a–f** Prepared

Product	Yield (%)	b.p. (°C)/Torr	Molecular Formula[a]	IR (film) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
2a	74	94–98/15	$C_4H_8O_2$ (88.1)	3400, 980, 920	2.7 (m, 2H); 3.8 (m, 3H); 4.4–5.0 (m, 3H)
2b	70	55–58/0.4	$C_8H_{16}O_3$ (160.2)	980, 920	1.2 (m, 6H); 2.7 (m, 2H); 3.6 (m, 4H); 4.7 (m, 4H)
2c	65	52–58/1	$C_7H_{12}O_2$ (128.2)	1640, 980, 920	2.7 (m, 2H); 3.6 (d, 2H, J = 5); 4.0 (d, 2H, J = 5); 4.7 (m, 3H); 5.2 (m, 2H); 5.9 (m, 1H)
2d	83	116–118/0.8[b]	$C_{10}H_{12}O_2$ (164.2)	3060, 1600, 1580, 970, 950	2.7 (m, 2H); 3.9 (m, 2H); 4.7 (m, 2H); 5.0 (m, 1H); 7.1 (m, 5H)
2e	56	62–64/20[b]	$C_7H_{12}O$ (112.2)	3080, 1640, 980, 920	1.6–2.4 (m, 4H); 2.7 (m, 2H); 4.3–5.2 (m, 5H); 6.0 (m, 1H)
2f	59	88–90/10[b]	$C_8H_{16}O_3$ (160.2)	980, 920	1.3 (m, 6H); 2.7 (m, 2H); 3.7 (m, 4H); 4.6 (m, 4H)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.30; except for **2e**: H +0.50.
[b] Product isolated by flash chromatography prior to distillation. Elution solvents: **2d**: ether/pentane (2 : 3); **2e**: ether/pentane (1 : 4); and **2f**: ether/pentane (1 : 3).

zone (**2m**) on stirring overnight with 2,4-dinitrophenylhydrazine in methanol and concentrated sulphuric acid. Attempts to oxidise the acetal to ethyl oxetane-2-carboxylate using either peroxyacetic acid or MCPBA were unsuccessful.

2,3-Epoxy-1-(1-ethoxyethoxy)propane (1b):
To a magnetically stirred solution of 2,3-epoxypropanol (40.0 g, 0.54 mol) in ethyl vinyl ether (200 mL) is added TsOH (1 g) portionwise, keeping the temperature below 40 °C. The mixture is stirred for 3 h and sat. aq. $NaHCO_3$ (100 mL) is then added. The organic layer is separated, dried and evaporated under reduced pressure. Distillation of the residue gives **1b** as a colourless liquid; yield: 72.6 g (92%); b.p. 152–154 °C.

$C_7H_{14}O_3$	calc.	C 57.58	H 9.66
(146.2)	found	57.77	9.55

IR (film): ν = 1350, 1250 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.3 (m, 6H); 2.7 (m, 2H); 3.1 (m, 1H); 3.6 (m, 4H); 4.7 (q, 1H, J = 6 Hz).

2,3-Epoxy-1,1-diethoxypropane (1f):
To a magnetically stirred mixture of TsCl (22.0 g, 0.115 mol) in dry Py (15 mL) is added dropwise a solution of 2,3-dihydroxypropanal diethyl acetal (17.6 g, 0.107 mol) in dry Py (15 mL) keeping the temperature below 0 °C. The mixture is stirred for 4 h then kept in a refrigerator at 2 °C overnight. Ice/water (100 mL) is then added, and the mixture is extracted with CH_2Cl_2 (3 × 100 mL). The extract is washed successively with 10% aq. H_2SO_4 (200 mL) and sat. brine (3 × 100 mL), then dried ($MgSO_4$) and evaporated under reduced pressure to give the monotosylate; yield: 22.1 g (65%).

A solution of the monotosylate (5.00 g, 15.7 mmol) in dry ether (50 mL) is added dropwise to a magnetically stirred solution of KOBu-t (1.94 g, 17.3 mmol) in dry ether (50 mL) keeping the temperature at 0 °C. The mixture is stirred at 0 °C for 6 h, then at room temperature overnight. The mixture is filtered and the solid washed with dry ether (3 × 30 mL). The combined filtrate and washings is dried ($MgSO_4$), and the solvent is carefully evaporated. Distillation of the residue gives **1f** as a colourless liquid; yield: 1.10 g (48%); b.p. 58–62 °C/10 Torr (Lit.[14,15] b.p. 60–64 °C/13 Torr).

Ring-Expansion of Epoxide 1b to Oxetane 2b; Typical Procedure:
A mixture of KOBu-t (61.5 g, 0.548 mol) and trimethyloxosulphonium iodide (120.6 g, 0.548 mol) in dry t-BuOH (700 mL) is stirred magnetically at 50 °C for 1 h. A solution of 2,3-epoxy-1-(1-ethoxyethoxy) propane (**1b**; 40.0 g, 0.274 mol) in dry t-BuOH (100 mL) is then added dropwise over 30 min at 50 °C and stirring is then continued at the same temperature for 3 d. The solvent is carefully evaporated under reduced pressure and water (200 mL) is added to the residual suspension. The mixture is extracted with pentane (4 × 150 mL), and the combined extracts are dried ($MgSO_4$) and evaporated under reduced pressure. Distillation of the residue (after column chromatographic separation in the cases of **2d–f**) gives 2-(1-ethoxyethoxy)methyloxetane **2b** as a colourless liquid; yield: 30.06 g (70%) (see Table).

2-Hydroxymethyloxetane (2a):
A solution of **2b** (10.0 g, 62.5 mmol) in 10% aq. HOAc (50 mL) is magnetically stirred overnight. The reaction mixture is neutralised with solid $NaHCO_3$ (7.5 g), and the mixture is distilled until the distillation temperature reaches 100 °C. The residual solution is cooled, and after addition of an excess of solid K_2CO_3, is extracted with ether (3 × 100 mL). Evaporation of the dried ($MgSO_4$) extract and distillation of the residue gives **2a** as a colourless liquid; yield: 4.07 g (74%) (see Table).

2-(Tosyloxymethyl)oxetane (2g):
To a magnetically stirred solution of TsCl (7.15 g, 37.5 mmol) in Py (10 mL) is added a solution of **2a** (3.00 g, 34.1 mmol) in Py (5 mL) keeping the reaction temperature below 0 °C. The mixture is stirred for a further 1 h at 0 °C and is then left in a refrigerator at 2 °C overnight. Ice/water (75 mL) is added, and the mixture is extracted with ether (3 × 100 mL). The combined extract is washed successively with 10% H_2SO_4 (3 × 100 mL) and sat. brine (3 × 100 mL), then dried ($MgSO_4$) and evaporated. The residue is flash chromatographed on silica gel. Elution with ether/pentane (4:1) gives **2g** as a colourless oil, which gradually gives a white solid; yield: 6.02 g (73%); m.p. 58–59 °C.

$C_{11}H_{14}O_4S$	calc.	C 54.53	H 5.82
(242.3)	found	54.30	5.87

IR ($CHBr_3$): ν = 1600, 1180, 1155, 980, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.4 (s, 3H); 2.7 (m, 2H); 4.2 (m, 2H); 4.5 (m, 2H); 4.9 (m, 1H); 7.3–8.8 (m, 4H).

2-(4-Chlorophenylthiomethyl)oxetane (2h):
To a magnetically stirred solution of NaOMe (0.45 g, 8.33 mmol) in MeOH (10 mL) is added 4-chlorobenzenethiol (1.20 g, 8.31 mmol). The mixture is stirred for 30 min and 2-(tosyloxymethyl)oxetane (**2g**; 2.00 g, 8.27 mmol) is added, stirring then being continued overnight. The reaction mixture is filtered, and the solid washed with MeOH (2 × 5 mL). The combined filtrate and washings are evaporated under reduced pressure, and the residue is flash chromatographed on silica gel. Elution with ether/pentane (1:9) gives **2h** as a colourless oil; yield: 1.31 g (74%).

$C_{10}H_{11}ClOS$	calc.	C 55.94	H 5.16
(214.7)	found	56.08	5.33

IR (film): ν = 3050, 1580, 980, 940 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.3–2.9 (m, 2H); 3.1 (m, 2H); 4.4–5.1 (m, 3H); 7.1–7.3 (m, 4H).

2-(2,3-Epoxypropoxymethyl)oxetane (2i):
To a magnetically stirred solution of 2-(allyloxymethyl)oxetane (**2c**; 1.00 g, 7.8 mmol) in CH_2Cl_2 (100 mL) is added at room temperature dropwise a solution of MCPBA (1.80 g, 10.4 mmol) in CH_2Cl_2 (20 mL) over 5 min. Stirring is continued for 2 d. The solution is washed successively with 10% aq. sodium metabisulphite (75 mL), sat. aq. $NaHCO_3$ (3 × 50 mL) and sat. brine (2 × 50 mL), then dried ($MgSO_4$) and evaporated under reduced pressure. The residue is flash chromatographed on silica gel. Elution with ether/pentane (4:1) gives **2i** as a colourless oil; yield: 0.74 g (65%).

$C_7H_{12}O_3$	calc.	C 58.30	H 8.39
(144.2)	found	58.33	8.56

IR (film): ν = 1350, 1250, 980, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.2–2.8 (m, 4H); 3.1–3.4 (m, 1H); 3.5–3.9 (m, 4H); 4.3–4.7 (m, 2H); 4.8–5.1 (m, 1H).

2-(3,4-Epoxybutyl)oxetane (2j):
Using a similar procedure, 2-(3-butenyl)oxetane (**2e**; 0.60 g, 5.36 mmol) gives **2j** as a colourless oil; yield: 0.43 g (63%); b.p. 70–72 °C/1 Torr, after elution with ether/pentane (9:1) from a silica gel column.

$C_7H_{12}O_2$	calc.	C 65.0	H 9.44
(128.2)	found	65.28	9.57

IR (film): ν = 1350, 1250, 980, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.4–2.0 (m, 4H); 2.2–2.4 (m, 2H); 2.5–3.1 (m, 3H); 4.3–5.0 (m, 3H).

2-(2,3-Dibromopropoxymethyl)oxetane (2k):
To a magnetically stirred mixture of 2-(allyloxymethyl)oxetane (**2c**; 1.00 g, 7.8 mmol) and anhydrous K_2CO_3 (0.60 g) in dry CH_2Cl_2 (50 mL) is added dropwise a solution of bromine (1.27 g, 7.95 mmol) in dry CH_2Cl_2 (41 mL) keeping the temperature at −78 °C. Stirring is continued at −78 °C for 15 min, then 20% aq. sodium metabisulphite (25 mL) is added. The organic layer is separated, and the aqueous phase is extracted with CH_2Cl_2 (2 × 50 mL). The combined organic solution is washed successively with sat. aq. $NaHCO_3$ (3 × 50 mL) and sat. brine (3 × 50 mL), then dried ($MgSO_4$) and evaporated under reduced pressure. The residue is flash chromatographed. Elution with ether/pentane (1:3) gives **2k** as a colourless oil; yield: 0.74 g (34%); b.p. 118–120 °C/0.8 Torr.

$C_7H_{12}Br_2O_2$	calc.	C 29.20	H 4.20
(288.0)	found	29.70	4.55

IR (film): ν = 980, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.2–2.7 (m, 2H); 3.4–3.9 (m, 6H); 3.9–4.1 (m, 1H); 4.2–4.5 (m, 2H); 4.6–4.9 (m, 1H).

2-(3,4-Dibromobutyl)oxetane (2l):
Using a similar procedure, 2-(3-butenyl)oxetane (**2e**; 0.60 g, 5.36 mmol) gives **2l** as a colourless oil; yield: 0.76 g (52%); b.p. 98–100 °C/0.9 Torr, after elution with ether/pentane (1:8) from a silica gel column.

$C_7H_{12}Br_2O$	calc.	C 30.91	H 4.45
(272.0)	found	31.13	4.55

IR (film): ν = 980, 920 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.9–2.6 (m, 6 H); 3.3 (m, 2 H); 3.5–4.2 (m, 3 H); 4.5 (m, 1 H).

Oxetane-2-carbaldehyde 2,4-dinitrophenylhydrazone (2m):
To a solution of 2,4-dinitrophenylhydrazine (0.25 g, 1.26 mmol) in MeOH (5 mL) and conc. H_2SO_4 (0.5 mL) is added oxetane-2-carbaldehyde diethyl acetal (**2f**; 0.10 g, 0.63 mmol) in MeOH (1 mL), and the mixture is stirred overnight. The mixture is filtered and crystallisation of the residue from acetone gives **2m** as orange needles; yield: 0.12 g (72%); m.p. 234–235 °C.

$C_{10}H_{10}N_4O_5$	calc.	C 45.12	H 3.79	N 21.05
(266.2)	found	44.82	3.98	21.29

IR (Nujol): ν = 3250, 1600, 1580, 980, 920 cm^{-1}.

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