Tetrahedron Vol. 36, pp. 1847 to 1850
Pergamon Press Ltd., 1980. Printed in Great Britain

ISOPRENE FUNCTIONALISATION

CHLORINATION OF C10-ISOPRENOID SULFONES WITH HEXACHLOROETHANE

J. J. BURGER, T. B. R. A. CHEN, E. R. DE WAARD* and H. O. HUISMAN
Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

(*Received in UK 14 September 1979*)

Abstract—Lithiation of the sulfones **1-3** in THF at −78° with lithium diisopropyl amide (LDA) is regioselective, since deuteration of the α-lithiosulfone **4** results in formation of the α-monodeuteriated sulfone **7**. Higher temperature causes an intramolecular 1,4-addition of the lithiated sulfone **4** to the lithiated cyclic sulfone **19** and an intermolecular 1,4-addition of the lithiated sulfones **5** and **6**. The cyclisation of *Z*-sulfone **1** has been used for the isolation of the isomeric *E*-sulfone **2** from mixtures of **1** and **2**. The lithiated sulfones **4–6** are chlorinated with hexachloroethane (HCE). Due to acid/base reactions the α,α-dichlorinated cyclic sulfone **23** and α,α′-dichlorinated butadienyl sulfones **13–15** are formed in small amounts.

As part of a broader investigation into the Michael induced Ramberg/Bäcklund (MIRD)[1] isoprene homologation, we have examined the chlorination of the methyl-1,3-butadienyl sulfones **1–3**[2] (Scheme 1).

α-Chlorosulfones are frequently prepared by reaction of sulfonyl carbanions with a chlorine donor. α,β-Unsaturated sulfones, however, are sensitive towards free-radical and anionic polymerisation and require special reaction conditions for the chlorination.

It is therefore not surprising that the usual chlorinating agents (Cl_2, NCS, SO_2Cl_2, $PhICl_2$ and KOH/CCl_4) failed to give the desired α-chlorosulfones **10–12**, when applied to the title compounds, although it should be mentioned that KOH/CCl_4 has been reported to lead to α-halosulfone intermediates in reactions with unsaturated sulfones.[3]

Previously[4] hexachloroethane (HCE) has been used with success in our laboratory for the chlorination of cyclic α-lithiosulfones.

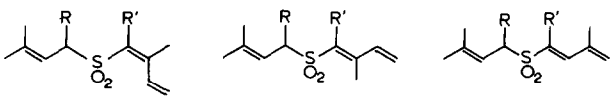
In this communication we wish to report the conversion of the butadienyl sulfones **1–3** into the corresponding α-chloro derivatives **10–12** using HCE as chlorinating agent.

[a]Comparable results were obtained with the methyl-, geranyl-, benzyl-, *Z*-3-methyl-2-pentenyl- and 2-methyl-2-propenylsulfonyl substituted *Z*-2-methyl-1,3-butadienes.

RESULTS AND DISCUSSION

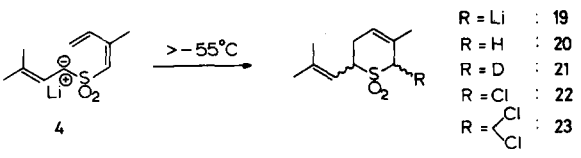
Synthesis of the α-lithiosulfones derived from **1, 2** *and* **3**. Treatment of the sulfones **1–3** with one equivalent of LDA in THF at −78° leads to the α-lithiosulfones **4–6**, respectively. The lithiation is highly regioselective, since acidification of **4** by addition of a well-stirred suspension of DCl/D_2O in THF of −78° resulted in the formation of only **7** under incorporation of one D atom at the allylic position α to the SO_2. The low reaction temperature is essential, because butadienyl sulfones are very susceptible to anionic 1,4-addition-polymerization. At −78°, however, the α-lithiosulfones **4–6** can be kept in THF solutions for several hours. At higher temperatures **5** and **6** gradually polymerise. This polymerisation is complete in a few minutes, when the lithiation is attempted at room temperature. A solution of the α-lithiosulfone **4** is even less stable because of the *Z*-configuration of the 2-methyl-1,3-butadienyl moiety. A rise in temperature to approximately −55° leads to a fast intramolecular 1,4-addition to give the cyclised α-lithiosulfone **19** (Scheme 2). The cyclic sulfone **20** is obtained upon acidification.[a] When DCl/D_2O is used for this purpose, only one D-atom is incorporated at the allylic C2-atom of the Δ^3-dihydrothiapyran-1,1-dioxide **20**. We have not been able to establish the relative configurations at the asymmetric centres.

Separation of **2** *from mixtures of* **1** *and* **2**. We have



R=H , R′=H	1	2	3
R=Li , R′=H	4	5	6
R=D , R′=H	7	8	9
R=Cl , R′=H	10	11	12
R=Cl , R′=Cl	13	14	15
R=H , R′=Cl	16	17	18

Scheme 1.



4

Scheme 2.

reported the laborious separation of the *Z*- and *E*-isomers **1** and **2** from their mixtures by several chromatography techniques.[2] The difference in reactivity of the α-lithiosulfones **4** and **5** can be exploited for the facile isolation of the *E*-isomer by converting mixtures of **1** and **2** into mixtures of **20** and **2**. The cyclic sulfone **20** and its open-chain *E*-isomer **2** are easily separated on a practical scale.

Starting from a mixture, consisting of 20% *Z*- and 80% *E*-sulfone, the corresponding α-lithiosulfones **4** and **5**, were prepared in THF at −78°, as described before. Addition of this α-lithiosulfone mixture to a THF solution of HCl/H_2O produced sufficient heat to trigger the cyclisation of *Z*-sulfone **4**, without intolerable polymerization of the *E*-sulfone **5**. Sulfone **2** was isolated in a purity of over 93%.

HCE-chlorination of α-lithiosulfones **4**, **5** *and* **6**. The general reaction, underlying the HCE-chlorination of sulfonyl carbanions, is shown in eqn (1) (Scheme 3). Sulfonyl carbanions, which carry a second hydrogen at the anionic centre, like in **24**, have the possibility to enter in an acid/base reaction with the more acidic chlorinated product **25**, as can be seen in eqn (2).

When a dilute solution of **24** is added to a concentrated solution of HCE, present in great excess, the main product will be monochlorinated sulfone **25**. Slow addition of one equivalent of HCE, on the other hand, to a concentrated solution of **24** will lead to a 1:1 mixture of the unconverted parent sulfone **26** and the α,α-dichlorosulfone, derived from reaction of the α-chlorosulfonyl carbanion **27** with HCE.

The addition of solutions of the α-lithiosulfones **4–6** of −78° through a "hot" stopcock of a dropping-funnel to a solution of an excess of HCE in THF of −78° already causes appreciable cyclisation of the α-lithiosulfone **4** (Table 1, reaction 1) and polymerisation of **5** and **6**. For this reason, the chlorination of the α-lithiosulfones **4–6** was performed by addition of an excess of precooled solid HCE to the α-lithiosulfone solutions of −78° (Table 1, reactions 2–4). The various products obtained after chromatographic separation of the reaction mixtures are listed in Table 1.

Even at extremely low temperature the intramolecular 1,4-addition of the α-lithiosulfone **4** to give the lithiated cyclic sulfone **19** (Scheme 2) could not be suppressed completely during the chlorination of **4**, as can be seen from reaction 2 (Table 1). The formation of most of the isolated compounds can be explained according to eqns (1) and (2), given in Scheme 3. To our surprise no α,α- but α,α′-dichlorination is observed with the sulfones **1–3**. For reasons not clear to us, the vinylic H at the α′-position of the monohalonagenated product is more acidic than the α-H.[b]

The acid/base reaction shown in Scheme 4 explains the formation of the α-chloro-α′-lithiosulfones which are the presumable precursors of the observed dichlorosulfones.

The α-monochlorosulfones **10–12** were used as Michael acceptors in the head-to-tail and tail-to-tail isoprene homologation. Full details will be published in a forthcoming communication.

EXPERIMENTAL

All reactions were performed under N_2. The content of the n-BuLi in hexane soln (Merck–Schuchardt) was determined by titration.[5] HCE (98%) was purchased from Aldrich, and used without purification. Diisopropyl amide was dried over KOH and distilled. THF was freshly distilled from LAH prior to use. Chromatographic separations were carried out on prepacked columns (Merck, Lobar, LiChroprep Si 60), using EtOAc/P.A. as an eluens at 2 atm pressure. ^1H NMR (TMS, $\delta = 0$, $CDCl_3$) was recorded on a varian A 60 D and a Varian XL-100 NMR Spectrometer; IR on a Perkin–Elmer model 177. M.ps were determined on a Leitz–Wetzlar apparatus and are uncorrected.

Synthesis of the α-lithiosulfones derived from **1**, **2** *and* **3**[2]

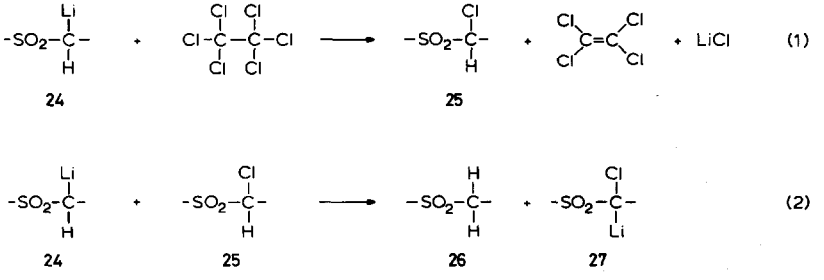
General procedure. A THF soln (80 ml) of 1 g (5 mmole) of the sulfone of −78° was added dropwise to a well-stirred THF soln (40 ml) of LDA[c] (5 mmole) of −78° over a period of 30 min. The so formed dark-red THF soln of the lithiated sulfone was stirred for an additional 30 min at −78° and used either for reprotonation or for HCE-halogenation.

Deuteriation of the α-lithiosulfone **4**

A THF soln (15 ml) of 20% DCl (4 mmole) and D_2O (0.5 ml) of −78° was added in one portion to a well-stirred THF soln (25 ml) of the α-lithiosulfone **4** (1 mmole) of −78°, prepared as described

[b] Hydrolysis of the dianion of sulfone **1** with DCl/D_2O in THF of −78° afforded α,α′-dideuteriated sulfone **1**.

[c] LDA was prepared by dropwise addition from a syringe of a hexane soln of n-BuLi to a well-stirred THF soln of 1 eq. of diisopropyl amide at −78°C, followed by stirring for 20 min.



24 25 25 26 27

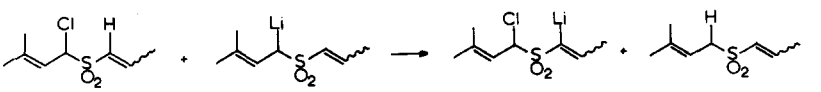
Scheme 3.

Table 1. HCE-chlorination of α-lithiosulfones 4, 5 and 6

Reaction	Compound	Isolated products (% yield) Monochloro sulfones	Dichloro sulfones	Recovered sulfones	Polymeric products
1	4	22(16) 10(5) 16(2)	23(6) 13(14)		
2	4	22(2) 10(22)*	23(6)	20(4) 1(4)	(27)
3	5	11(40) 17(2)†	14(5)	2(5)	(42)
4	6	12(33)	15(3)	3(3)	(50)

*α-Monochlorinated geranyl- and α-cyclogeranyl-Z-2-methyl-1, 3-butadienyl sulfones were obtained in comparable yields upon chlorination.

†Compound 17 was isolated as a chromatographic fraction mixed with 14.



Scheme 4.

above. After warming to r.t. the mixture was diluted with water and extracted with $CHCl_3$. Drying over $MgSO_4$ and evaporation of the solvents afforded the nearly pure α-monodeuteriated 7 in almost quantitative yield. Monodeuteriation could be determined from the sulfonyl methylene-absorption in the ^1H NMR.

3 - *Methyl* - 6 - (2' - *methyl* - 1' - *propenyl*) - Δ^3 - *dihydrothiapyran* - 1,1 - *dioxide* (20)

A THF soln (25 ml) of 4 (1 mmole) of −78° was added dropwise to a well-stirred THF soln (15 ml) of 7% HCl (4 mmole) and H_2O (2 ml) of r.t. After warming to r.t. the mixture was diluted with $CHCl_3$ (50 ml). The $CHCl_3$ soln washed with water and dried over $MgSO_4$. Evaporation of the solvents afforded the crude 20 in 91% yield. Chromatographic purification furnished pure 20 as a colourless oil IR ($CHCl_3$): 2980, 1450 (C–H), 1670 (weak, C=C), 1320, 1270, 1150 and 1120 cm^{-1} (SO_2). ^1H NMR: 5.57 (C4–H, m); 5.09 (C1–H, d, $J_{1'-6}$ 10 Hz); 3.95–3.65 (C6–H, m); 3.51 (C2–H, broad s); 2.73–2.50 (C5–H, m); 1.82 and 1.77 (C3–Me, C2'–Me, C3'–H, two s). (Found: C, 59.92; H, 8.09; S, 15.91, Calcd for $C_{10}H_{16}SO_2$: C, 59.96; H, 8.05; S, 16.01; O, 15.98%).

Addition of the THF soln (25 ml) of 4 (1 mmole) of −78° to a well-stirred THF soln (15 ml) of 20% DCl (4 mmole) and D_2O (0.5 ml) of r.t. afforded 21 in 87% yield.

Separation of sulfone 2 *from mixtures of* 1 *and* 2

A 1 g mixture (5 mmole) of 22% Z-sulfone 1 and 78% E-sulfone 2 was converted into a THF soln (80 ml) of 4 and 5 of −78°, as described before. Addition of this soln to a well-stirred THF soln (20 ml) of conc HCl (7 ml) and H_2O (10 ml) of r.t. over a period of 1 hr was performed through a "hot" stopcock of a dropping-funnel. Warming to r.t. and work-up with $CHCl_3$ furnished the crude E-sulfone 2, contaminated with 20 and polymerisation products, in 95% yield. Chromatographic separation afforded the unstable 2[2] in 38% yield in a purity of over 93%, contaminated with less than 7% of its Z-isomer 1.

HCE-chlorination of the α-lithiosulfones 4, 5 *and* 6

General procedure. 8.3 g (35 mmole; 7 eq excess) solid HCE, precooled in a dispenser[d] with liquid N_2, was added in one portion to a THF soln (120 ml) of the α-lithiosulfone (5 mmole) of −78°, prepared as described before. The mixture was stirred for 30 min. After warming to r.t. the mixture was diluted with 7% HCl (20 ml) and extracted with $CHCl_3$. Evaporation of the solvents and the excess of HCE at 50°/1.5 mm furnished a mixture of the chlorinated sulfones. Chromatographic separation afforded in the order of decreasing R_f value: residual HCE, dichlorobutadienyl, α'-monochlorobutadienyl, cyclic dichloro, cyclic monochloro, α-monochlorobutadienyl, unconverted and cyclic nonchlorinated sulfone. Most compounds were obtained in a colourless crystalline form upon recrystallisation from ether/n-hexane. Nearly all chlorinated sulfones are sensitive towards oxygen at r.t.

HCE-chlorination of 4

Compound 10 was obtained in a crystalline form (m.p. 69–70°). IR ($CHCl_3$): 3060, 1450 (C–H), 1660, 1625, 1570 (C=C), 1340, 1320, 1300 and 1120 cm^{-1} (SO_2). ^1H NMR: 7.59 (C3'–H, X-part of ABX, J_{AX} 11 Hz, J_{BX} 17.5 Hz); 6.12 (C1'–H, broad s); 5.70 (C4'–H, B-part of ABX, J_{AB} 0.5 Hz); 5.58 (C4'–H, A-part of ABX); 5.31 (C1–H and C2–, s, A_2-system); 2.11 (C2'–Me, d, J 0.5 Hz); 1.85 and 1.78 (C4–H and C3–Me, two s) (Found: C, 51.19; H, 6.35; S, 13.72; O, 13.84; Cl, 15.02. Calcd for $C_{10}H_{15}SO_2Cl$: C, 51.17; H, 6.44; S, 13.66; O, 13.63; Cl, 15.10%).

Compound 13. m.p. 67–68.5°; IR ($CHCl_3$): 3040, 1450 (C–H), 1660, 1550 (weak, C=C), 1350, 1320 and 1160 cm^{-1} (SO_2). ^1H NMR: 7.77 (C3'–H, X-part of ABX, J_{AX} 11 Hz, J_{BX} 17.5 Hz); 5.69 (C1–H, d, J_{1-2} 10 Hz); 5.67 (C4'–H), B-part of ABX, J_{AB} 0 Hz); 5.54 (C4'–H, A-part of ABX); 5.36 (C2–H, d with allylic l.r.-coupling); 2.25 (C2'–Me, s); 1.86 and 1.79 (C4–H and C3–Me, two d each with J 0.5 Hz). (Found: C, 44.76; H, 5.21; S, 11.76; Cl, 26.31. Calcd for $C_{10}H_{14}SO_2Cl_2$: C, 44.62; H, 5.24; S, 11.91; O, 11.89; Cl, 26.34%).

Compound 16 was obtained as an oil. ^1H NMR: 7.69 (C3'–H, X-part of ABX, J_{AX} 11 Hz, J_{BX} 17.5 Hz); 5.61 (C4'–H, B-part of ABX); 5.46 (C4'–H, A-part of ABX); 5.33–5.05 (C2–H, apparent t with allylic l.r.-coupling, X-part of ABX); 4.11–3.55 (C1–H, m, AB-part of ABX); 2.19 (C2'–Me, s); 1.86 and 1.76 (C4–H and C3–Me, two d each with J 0.5 Hz).

The cyclic 22 was obtained as a viscous oil (m.p. of *ca* 10–15°). IR ($CHCl_3$): 3040, 2940, 1450 (C–H), 1670 (weak, C=C), 1330, 1160 and 1140 cm^{-1} (SO_2). ^1H NMR: 5.76–5.59 (C4–H, m); 5.03 (C1'–H, d with allylic l.r.-coupling, $J_{1'-6}$ 9 Hz); 4.75 (C2–H, s); 4.44–4.12 (C6–H, m); 2.80–2.50 (C5–H, m); 1.93 (C3–Me, d, J 0.5 Hz); 1.85 and 1.80 (C3'–H and C2'–Me, two d each with J 0.5 Hz). (Found: C, 51.35; H, 6.37; S, 13.51; Cl, 15.07. Calcd for $C_{10}H_{15}SO_2Cl$: C, 51.17; H, 6.44; S, 13.66; O, 13.63; Cl, 15.10%).

Compound 23. m.p. 72.5–74°; IR ($CHCl_3$): 3050, 2930, 1440 (C–H), 1660 (C=C), 1340 and 1150 cm^{-1} (SO_2). ^1HNMR: 5.66–5.49 (C4–H, m); 5.08 (C1'–H, d with l.r.-coupling, $J_{1'-6}$ 9 Hz); 4.76–4.45 (C6–H, m); 2.82–2.53 (C5–H, m); 2.09 (C3–Me, d, J 1 Hz); 1.87 and

[d] Addition of an excess of HCE of r.t. to the THF soln of −78° resulted in complete polymerisation.

1.83 (C3'–H and C2'–Me, two d each with J 1 Hz). (Found: C, 45.04; H, 5.37; S, 11.63; O, 11.55; Cl, 25.97. Calcd for $C_{10}H_{14}SO_2Cl_2$: C, 44.62; H, 5.24; S, 11.91; O, 11.89; Cl, 26.34%).

HCE-chlorination of **5**

Compound **11**. m.p. 59–60°; IR ($CHCl_3$): 3040, 1450 (C–H), 1660, 1630, 1590 (C=C), 1330 and 1145 cm^{-1} (SO_2). ^1H NMR: 6.39 (C3'–H, X-part of ABX, J_{AX} 10.5 Hz, J_{BX} 17 Hz); 6.19 (C1'–H, broad s); 5.72 (C4'–H, B-part of ABX); 5.50 (C4'–H, A-part of ABX); 5.30 (C1–H and C2–H, s, A_2-system); 2.25 (C2'–Me, d, J 0.5 Hz); 1.81 and 1.74 (C4–H and C3–Me, two s). (Found: C, 51.27; H, 6.48; S, 13.52; Cl, 15.21 Calcd for $C_{10}H_{15}SO_2Cl$: C, 51.17; H, 6.44; S, 13.66; O, 13.63; Cl, 15.10%).

Compound **14** was obtained as a colourless oil. ^1H NMR: 7.05 (C3'–H, X-part of ABX, J_{AX} 11 Hz, J_{BX} 17.5 Hz); 5.86 (C4'–H, B-part of ABX); 5.76 (C1–H), d, J_{1-2} 10 Hz); 5.69 (C4'–H, A-part of ABX); 5.41 (C2–H, d with l.r.-coupling); 2.45 (C2'–Me, s); 1.89 and 1.83 (C4–H and C3–Me, two d each with J 1 Hz).

Compound **17** was obtained as a chromatographic fraction mixed with **14**. Its presence was deduced from the C2'-methyl absorption in the ^1H NMR (2.37 ppm, s).

HCE-chlorination of **6**

The α-monochlorosulfone **12** was obtained in a crystalline form (m.p. 67–69°). IR ($CHCl_3$): 3020, 1440 (C–H), 1660, 1625, 1590 (C=C), 1320, 1285 and 1130 cm^{-1} (SO_2). ^1H NMR: 7.32 (C2'–H, d, $J_{1'-2'}$ 15 Hz); 6.39 (C1'–H, d); 5.51 (C4'–H, broad s); 5.33 (C1–H and C2–H, s, A_2-system); 1.90 (C3'–Me, d, J 0.5 Hz); 1.86 and 1.79 (C–4H and C3–Me, two s). (Found: C, 51.22; H, 6.47; S, 13.82; Cl, 15.26. Calcd for $C_{10}H_{15}SO_2Cl$: C, 51.17; H, 6.44; S, 13.66; O, 13.63; Cl, 15.10%).

Compound **15** was obtained as a colourless oil. ^1H NMR: 7.43 (C2'–H, s); 5.71 (C1–H, d, J_{1-2} 10 Hz); 5.60–5.45 (C4'–H, m); 5.37 (C2–H, d with l.r.-coupling); 2.11 (C3'–Me, d, J 0.5 Hz); 1.87 (C4–H) and C3–Me, two d each with J0.5 Hz).

REFERENCES

[1]T. B. R. A. Chen, J. J. Burger, E. R. de Waard and H. O. Huisman, *Tetrahedron Letters* 4527 (1977).

[2]J. J. Burger, T. B. R. A. Chen, E. R. de Waard and H. O. Huisman, *Tetrahedron* **36**, 723 (1980).

[3]P. A. Grieco and D. Boxler, *Synthetic Communications* **5**, 315 (1975).

[4]J. Kattenberg, E. R. de Waard and H. O. Huisman, *Tetrahedron* **29**, 4149 (1973).

[5]W. G. Kofron and L. M. Baclawski, *J. Org. Chem.* **41**, 1879 (1976).