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THE ALKYLATION OF AN α,α'-DIANION IN A β-KETOSULPHONE LEADING TO THE PREPARATION OF AXIAL 2-SUBSTITUTED THIANE-1,1-DIOXIDES.

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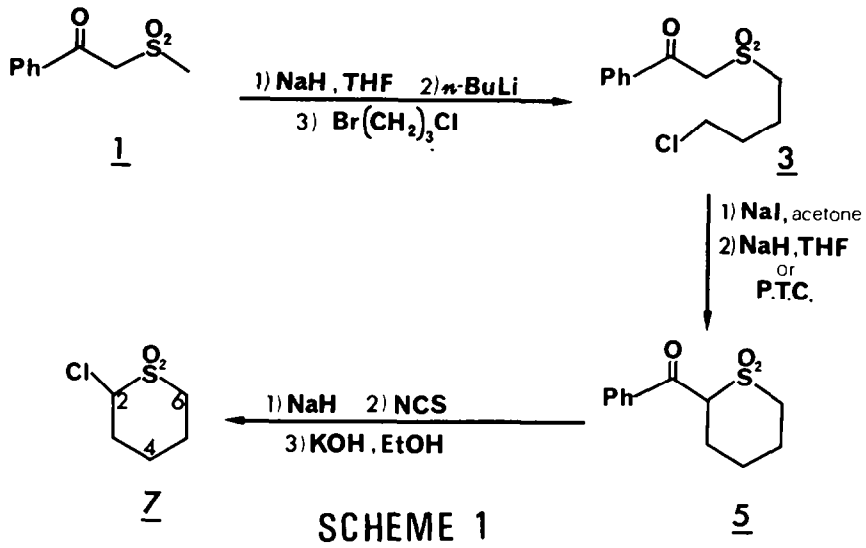
Abstract--The 1,3-dianion formed across the sulphone of a β-ketosulphone may be selectively dialkylated in a controlled way with an α,ω-difunctional electrophile to give a 2-ketothiane-1,1-dioxide. Polar groups in the 2-position of thiane-1,1-dioxides preferentially adopt an axial orientation as shown by detailed nmr studies. In cyclic sulphones such conformational preferences, arising from polar rather than steric effects are rare.

Introduction

The α-sulphonyl carbanion is a good nucleophile for reaction with alkyl halides [1,2] although its utility is limited by the observed tendency to give polyalkylated products, especially with a reactive and unhindered electrophile, such as methyl iodide.[3] By contrast, the less reactive enolate anions derived from β-ketosulphones have considerable potential for use in synthetic sequences requiring alkylation steps, as monoalkylation is normally observed in the reaction of these anions with alkyl halides.[1,4]

The study of the chemistry of 1,3-dianions across the sulphonyl group of a β-ketosulphone is a natural extension of other work from this laboratory concerning the preparation and reactions of β-ketosulphones.[5] The chemistry of 1,3-dianions across ketones is well developed [6,7] although reactions across the ketone group of β-ketosulphones [8] and β-ketosulphoxides [9,10] are less well known. Although the reactions of 1,3-dianions across sulphones have been investigated [1,2,11] little such work has been reported on 1,3-dianions across the sulphone group of a β-ketosulphone.[1] It occured to us that dialkylation of such an anion with an α,ω-difunctional electrophile could be a useful route to substituted thiane-1,1-dioxides. We had previously used a similar approach to prepare substituted thianes.[12] The preparation of thiane-1,1-dioxides has received some impetus from extensive conformational studies,[13] syntheses generally proceeding from 1,5-diols through to the thiane which is then oxidised to the thiane-1,1-dioxide. Overall yields for such a multi-step sequence can be quite poor and it is not easy to functionalise the different ring positions.

Scheme 1 shows the proposed sequence of reaction, begining with **1**; formation of the dianion **2** would be followed by selective reaction to **3** which could then be cyclised to 2-benzoylthiane-1,1-dioxide, **5**, by standard procedures. Since **5** could be readily halogenated, alkylated and/or cleaved, it would be a precursor for a useful range of 2-substituted thianes. Alternatively, dianion formation of **5** would lead to a range of 2,6-disubstituted thianes.



SCHEME 1

Results and Discussion

The synthetic sequence as depicted in Scheme 1 proceeded relatively smoothly. We found that the cyclisation of **3** to **5** did not proceed easily, but this was circumvented by conversion of **3** into the iodide **4**.

Attempted halogenations of **5** using regular halogenation reagents (SO_2Cl_2, SO_2Cl_2/Et_3N, Br_2) were unsuccessful, in contrast to the ease of these reactions for acyclic β-ketosulphones[5] . The methine proton in **5** was acidic and could be exchanged by D_2O /Et_3N in $CDCl_3$. Our route for the conversion of **5** into **7** lay in discretely forming the anion of **5** and reacting this with NCS.

The structures of the products **5** and **7** were confirmed by the usual spectroscopic methods. The complexity of the strongly coupled 9-spin system of the thiane-1,1-dioxide ring protons meant that the highest field strength available was required for the ^1H spectra. At 360 MHz dispersion of signals is sufficient to allow observation, without overlap, of all the ^1H resonances. Tables 1 and 2 report these spectra, including a systematic homonuclear decoupling study of each compound.

H2 was easily assigned from its chemical shift and this provided the starting place for the analysis. In addition to the vicinal coupling to H3, there is a doublet splitting caused by long-range coupling. Long-range coupling through the sulphone in acyclic sulphones is in the range 0.5-0.8 Hz. [14] In a more rigid cyclic system the value $^4J_{eq-eq} = 2.3\pm0.4$ has been reported, [15] and in butadiene sulphone the observed [16] values are $^4J_{trans} = 1.265\pm0.015$ Hz and $^4J_{cis} = 1.940\pm0.015$ Hz. The observation of ^4J = 1.85 Hz and ^4J = 2.23 Hz in **5** and **7** respectively is then good evidence for the predominantly axial orientation of the benzoyl and chloro groups at C2.

The $H6_{ax}$ group is identified as the member of the $H6_{ax}$ - $H6_{eq}$ pair which is not affected by irradiation of H2. The protons at C3 and C5 were then assigned from consideration of chemical shifts and as the result of irradiation experiments. This leaves $H4_{ax}$ and $H4_{eq}$ as the lowest frequency proton absorptions of each spectrum. Satisfactory agreement of computer simulations of the H4 and H5 patterns, for conditions of H3 irradiation, was obtained only if the $H4_{eq}$ signal was assigned a lower frequency than the $H4_{ax}$ signal. This is in contrast with the general result of Lambert and Goldstein [17] who found that axial

TABLE 1. ^{1}H NMR results for 2-benzoylthiane-1,1-dioxide, 5, in $CDCl_3$ at 25°C.

Observed ^{1}H / ^{1}H Irradiated	H2	$H6_{ax}$	$H6_{eq}$	H3	H5	$H4_{ax}$	$H4_{eq}$
none	4.94 dt	3.55 ddd	3.12 ddt	2.37 m	2.11 m	1.86 m	1.62 m
H2	X	no change	dt	simpf m	no change	no change	no change
$H6_{ax}$	no change	X	dt no J_{gem}	no change	simpf m	no change	no change
$H6_{eq}$	t J_{vic}=5.25	dd no J_{gem}	X	no change	simpf m	no change	no change
H3	d ^4J=1.83	no change	no change	X	no change	simpf m	simpf m
H5	no change	d J_{gem}=13.9	dd	no change	X	simpf m	simpf m
$H4_{ax}$	no change	no change	no change	simpf m	simpf m	X	simpf m
$H4_{eq}$	no change	no change	no change	simpf m	simpf m	simpf m	X

TABLE 2. ^{1}H NMR results for 2-chlorothiane-1,1-dioxide, 7, in $CDCl_3$ at 25°C.

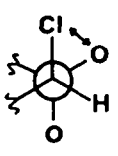
Observed ^{1}H / ^{1}H Irradiated	H2	$H6_{ax}$	$H6_{eq}$	$H3_{ax}$	$H3_{eq}$	H5	$H4_{ax}$	$H4_{eq}$
none	4.73 ddd*	3.42 ddd	2.95 ddt	2.60 dddd	2.30 ddt	2.10 m	1.93 m	1.67 m
H2	X	no change	dt	simpf m	no change	no change	no change	no change
$H6_{ax}$	no change	X	dt	no change	no change	simpf m	no change	no change
$H6_{eq}$	dd	dd	X	no change	no change	simpf m	no change	no change
$H3_{ax}$	dd	no change	no change	X	dt	no change	simpf m	simpf m
$H3_{eq}$	dd	no change	no change	ddd	X	no change	simpf m	simpf m

* J_{vic} = 3.3 Hz, J_{vic} = 6.6 Hz, ^4J = 2.23 Hz.

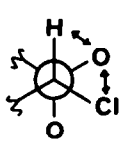
protons of thiane-1,1-dioxides usually resonate at higher fields than do the equatorial protons at the same carbon. In support of our conclusion, the spectrum at -65°C showed that the only changes observed were a broadening of the aromatic resonances together with the resonances at 3.55 and 1.86 ppm, thus requiring $H4_{eq}$ to be at a higher field than $H4_{ax}$.

Dissolution of **5** in d_5-nitrobenzene permitted the observation of separate resonances for $H3_{ax}$ and $H3_{eq}$ at 2.15 and 2.05 ppm whilst the rest of the spectrum was very similar to that obtained in $CDCl_3$. There was no change in chemical shifts when the nitrobenzene solution was warmed up to 60°C.

These results require that the equilibrium for an axial *versus* an equatorial benzoyl or chloro substituent is significantly biased towards the axial conformer. Since the barrier to ring-inversion of thiane-1,1-dioxides is similar to that of cyclohexanes,[18] it would be quite extraordinary if this had been affected to a significant extent by the introduction of an α-benzoyl or α-chloro group. We propose that in **5** and **7** the observed conformational effects result from an energy difference of at least 12 kJ mol^{-1} between the axial and the equatorial substituents. An axial substituent has the polar group *gauche* to only *one* of the polar sulphone-oxygen bonds *vs* two in the case of an equatorial substituent. In acyclic systems this appears to be the favoured orientation both in the solid state and in solution.[19,20]



axial



equatorial

From the ^{13}C nmr data of **5** and **7** we have found the size of the γ-gauche effects of a chloro and a benzoyl group across the sulphonyl group in a thiane-1,1-dioxide ring system to be -4.2 and -0.2 ppm respectively. There are at present no data to compare these figures with.

The present work introduces a facile, high-yield synthesis for 2-substituted thiane-1,1-dioxides and also provides examples of conformational preference, in a 6-membered ring, arising from polar rather than steric forces. In cyclic sulphones such occurrences are rare.[21]

Experimental

Variable-temperature, high resolution ^1H NMR spectra were obtained on a Nicolet 360 NB spectrometer whilst routine ^1H and ^{13}C NMR spectra were obtained on a Varian CFT-20. ^1H and ^{13}C NMR spectra are reported as δ-values in $CDCl_3$, with respect to TMS = 0. Infra-red spectra were recorded on a Perkin-Elmer model 283B spectrophotometer and melting points were taken on a Fisher-Johns apparatus and are uncorrected. Mass spectra were recorded on a CEC-DuPont 21-104 mass specrometer, equiped with a glass direct-introduction probe, and operated at 70 eV and 150°C.

Preparation of 2-(4-chlorobutyl)sulphonyl-1-phenylethanone, **3**.

A solution of **1** (1.74g, 8.8 mMol) in THF (25ml) was added to the dry grey solid produced from washing NaH (0.423g 50% suspension in oil, 8.8 mMol) with dry ligroin b.p. 40-60°C; the resulting mixture was stirred at 0°C under dry nitrogen for 30 min. Addition of n-butyllithium (4ml, 2.2M in hexane, 8.8 mMol) gave a yellow solution to which 1-bromo-3-chloropropane (0.87ml, 8.8 mMol) in THF (2ml) was added dropwise. The reaction mixture was stirred at 0°C (3h) and then allowed to warm to room temp. After filtration to remove inorganic salts, the mixture was

acidified (HCl), extracted with CH_2Cl_2 (4x20ml), dried and evaporated to a residue which was triturated with ligroin b.p. 40-60°C . Crystallisation of the remaining off-white solid, from MeOH, gave **3** as microcrystals (1.9g, 79%), m.p. 97.5-98.5°C, ν_{max} 2970, 2930, 1690, 1340, 1330, 1140; ^1H NMR 1.8-2.2(m,4H), 3.30(t,2H), 3.57(t,2H), 4.57(s,2H), 7.4-8.1(m,5H); ^{13}C NMR 19.4, 30.8, 43.7, 52.7, 59.5, 128.9(2C), 129.1(2C), 134.6, 135.6, 189.1; ms m/z 276(0.3), 274(0.9), 239(8), 120(43), 106(15), 105(100), 77(31), 55(27), 51(15).

Preparation of 2-(4-iodobutyl)sulphonyl-1-phenylethanone, **4**.

A mixture of **3** (5.17g, 19 mMol) and NaI (3.0g, slight excess) was refluxed in acetone (200ml) for 3h. The resulting two-phase mixture was cooled and rotary evaporated to dryness. The residue was triturated with CH_2Cl_2 which was washed with $Na_2S_2O_3$ solution (20ml, 5%), dried and evaporated in a flask protected from light. Crystallisation of the crude product, from MeOH, gave **4** as fine colourless crystals (6.4g, 93%), m.p. 99-101°C, ν_{max} 2960, 2920, 1685, 1595, 1330, 1130, 1120; ^1H NMR 1.8-2.2(m,4H), 3.0-3.6(m,4H), 4.55(s,2H), 7.4-8.1(m,5H); ^{13}C NMR 19.4, 22.9, 31.6, 43.6, 59.6, 128.9(2C), 129.1(2C), 134.5, 135.7, 189.1; ms m/z 366(0.2), 240(9.5), 239(50), 120(37), 106(13), 105(100), 103(29), 91(34), 78(11), 77(32), 65(16), 55(23), 51(12).

Preparation of 2-benzoylthiane-1,1-dioxide, **5**.

A: Basic conditions in soln.

A solution of **4** (1.25g, 3.4 mMol) in dry DMSO (55ml) was added to dry NaH (0.17g, 50% suspension in oil, 3.5 mMol). The resulting mixture was stirred (4h, under nitrogen) poured into iced water (30ml), acidified with 1M HCl and extracted with CH_2Cl_2 (3x35ml). The combined organic layers were washed with copious quantities of water to remove residual DMSO, dried with $MgSO_4$ and rotary evaporated to dryness. Crystallisation of the crude product, from EtOAc, gave **5** as colourless needles (0.70g, 87%), m.p. 139-141°C, ν_{max} 2960, 2930, 1670, 1595, 1580, 1450, 1360, 1335, 1290, 1270, 1250, 1220, 1165, 1120, 1070, 1000, 930, 850, 785, 730, 715, 680, 655, 550, 490, 470; ^1H NMR see Table 1; ^{13}C NMR 20.3, 24.1, 28.2, 51.4, 65.0, 128.8(4C), 134.2, 135.7, 192.2; ms m/z 238(13), 106(9), 105(100), 77(21).

B: Phase-transfer conditions

A mixture of **4** (0.18g, 0.49 mMol) and ethylhexadecyldimethyl ammonium bromide (0.15g, catalyst) was dissolved in CH_2Cl_2 (5ml) to which NaOH (8ml, 0.063M in water) was added. The resulting two-phase mixture was stirred vigorously until the pH of the aqueous layer was about 7 (ca 1h). The two layers were separated and the volume of the organic layer was increased to 20ml by addition of CH_2Cl_2. This was washed with water (3x20ml), $Na_2S_2O_3$ solution (2x25ml, 5%) and evaporated to an off-white solid which gave **5** (0.11g, 90%) after several recrystallisations from EtOAc.

Preparation of 2-benzoyl-2-chlorothiane-1,1-dioxide, **6**.

A solution of **5** (0.1308g, 0.55 mMol) in dry THF (6ml) was added to dry NaH (263mg, 50% suspension in oil, 0.55 mMol). The mixture was stirred at room temperature under an atmosphere of dry nitrogen for 30 minutes during which time the rapid evolution of hydrogen ceased. To this two-phase mixture was added N-chlorosuccinimide (0.0734g, 0.55 mMol) in one batch followed by a further portion of THF (6ml). The mixture was refluxed for 90 minutes, cooled, poured into water (10ml), extracted with CH_2Cl_2 (3x15ml) and evaporated to dryness. The residue was dissolved in ether (50ml) which was washed with saturated sodium chloride solution (2x25ml), dried and evaporated to a yellow residue containing ca 85% of **6** (^1H NMR). This mixture was separated by vacuum-assisted column chromatography using tlc grade silica

gel as stationary phase and CH_2Cl_2 as eluant, [22] to give **6** as stout prisms (0.11g, 73%) after recrystalisation from EtOAc/ligroin b.p. 40-60°C, m.p. 94.5-96°C, ν_{max} 2960, 2940, 2920, 1690, 1600, 1580, 1450, 1430, 1405, 1320, 1295, 1235, 1180, 1145, 1135, 1060, 1050, 1015, 940, 920, 850, 825, 790, 740, 720, 700, 695, 660, 560, 530, 500, 480, 440, 395, 295; ^{1}H NMR 1.8-2.1(m,4H), 2.5-3.5(m,4H), 7.3-8.5(m,5H); ^{13}C NMR 19.7, 23.7, 37.4, 49.7, 85.2, 127.9(2C), 130.8(2C), 133.4, 134.4, 189.7; ms m/z 274(1.5), 272(4), 237(0.6), 106(10), 105(100), 77(21), 51(8).

Preparation of 2-chlorothiane-1,1-dioxide, **7**.

A solution of KOH (19.2mg, 0.34mMol) in 95% EtOH (10ml) was added to **6** (91mg, 0.34 mmol). This mixture was refluxed (2h) and evaporated to dryness *in vacuo*. The resulting residue was triturated with CH_2Cl_2 which was dried and evaporated to yield **7** as colourless needles after recrystallisation from CH_2Cl_2-pentane(56mg, 94%),m.p. 72-73°C, ν_{max} 2970, 2960, 2935, 1320, 1300, 1165, 1135,; ^{1}H NMR see Table 2 ; ^{13}C NMR 19.7, 23.6, 33.4, 48.1, 70.2; ms m/z 170(4), 168(11), 133(22), 105(17), 103(50), 77(14), 76(23), 75(36), 69(16), 68(22), 67(54), 55(31), 42(100), 41(82), 40(75). A mixed melting point with an authentic sample of **7** gave an identical melting point range.[23]

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