Intermolecular and Intramolecular Alkylation of Mono- and Di-anions Derived from a β-Ketosulphone

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Summary Alkylation of the 1,3-dianion of the β-ketosulphone (**1**) with 1,3-dibromopropane gave (**3**) which under appropriate conditions can be converted into either (**6**; *C*-alkylation) or (**7**; *O*-alkylation) without contamination with the other *C*- or *O*-alkylated isomer.

WHILST the 1,3-dianions of β-dicarbonyl compounds,[1] β-ketophosphonates,[2] and β-ketosulphoxides[3] have been extensively studied, the 1,3-dianion derived from a β-ketosulphone has received scant attention.[4] We were interested in the 1,3-dianions of β-ketosulphones as intermediates in the construction of carbocyclic systems for the synthesis of certain natural products.†

Treatment of methyl phenyl sulphone carbanion (NaH–THF) with ethyl phenylacetate gave the β-ketosulphone (**1**).[5] Lithium di-isopropylamide (2 equiv.) [or NaH (1 equiv.) followed by Bu^nLi (1 equiv.) at −70 °C] in glyme at −55 °C reacted with the sulphone (**1**) to give a species formulated as (**2**). When the 1,3-dianion (**2**) was quenched at −40 °C with 1,3-dibromopropane the alkylated product (**3**) was rapidly formed (60—75%). In contrast, treatment of (**1**) with NaH (1 equiv) in glyme, followed by 1,3-dibromopropane, gave the enol-ether (**5**); no other products were detected. The mono-anion of (**1**) is pale yellow and the dianion (**2**) is crimson. If the initial monoanion (**5**), M = Na), from quenching (**2**) with 1,3-dibromopropane, is allowed to warm to room temperature several compounds are formed and the *C*- and *O*-alkylated products (**6**)‡ and (**7**)§ respectively can be detected, whereas treatment of the monoanion (**5**, M = Li) at −40 °C with 1 equiv. further of $LiNPr^i_2$ and warming to room temperature gave (**6**); no

TABLE

Cyclisation of (**3**) to (**6**) and (**7**)

	Reagents and conditions[a]	Products (approximate % yields or proportions)
(a)	NaH(1·5 equiv.), dry Me_2SO, 24 °C	(**6**) (90%); (**7**) (10%)
(b)	NaH (1·0 equiv.), dry DME or HMPA, 40—50 °C	(**7**) (95%)
(c)	Alumina 'Woelm neutral' Gl in toluene, R.T.	(**7**) (95%)
(d)	KOBu^t (1 equiv.) in Bu^{t}OH, 50—60 °C NaOBu^t or LiOBu^t (1 equiv.) in Bu^{t}OH–THF	(**6**) (70%); (**7**) (30%)
(e)	Sat. aqueous Na_2CO_3, Me_2CO, 25 °C 10% aqueous NaOH, toluene, 28 °C 10% aqueous NaOH,DMF, 25 °C Sat. aqueous Li_2CO_3, DMF, 25 °C 28% NH_4OH, THF, R.T.	(**6**) (80%); (**7**) (20%)
(f)	NaI–Li_2CO_3, aqueous Me_2SO	(**6**) (60%); (**7**) (40%)
(g)	Thallium ethoxide—glyme, reflux	(**7**) (90%)
(h)	$LiNPr^i_2$ (1 equiv), glyme, −55 to 0 °C	(**6**) (90%)

[a] DME = 1,2-dimethoxyethane; HMPA = hexamethylphosphoric triamide; THF = tetrahydrofuran; DMF = dimethylformamide; glyme = methoxymethyl methyl ether; R.T. = room temperature.

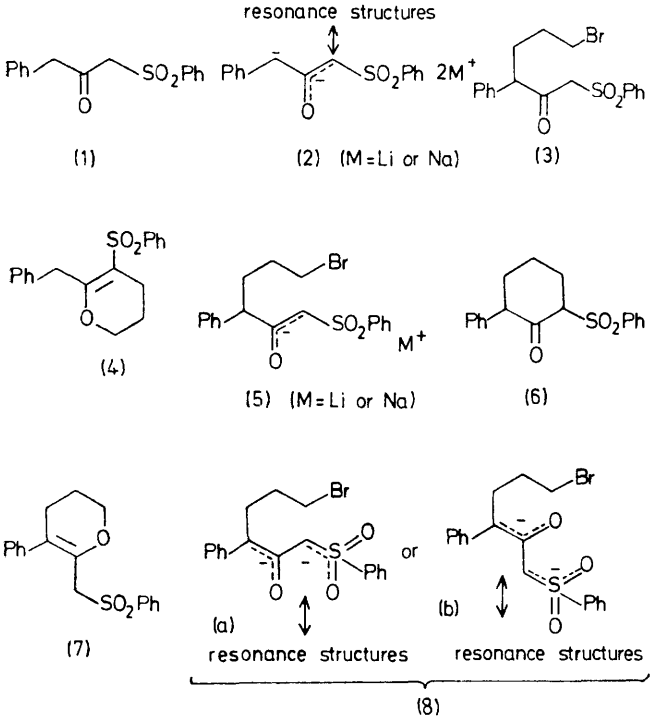
† Details of this work and the use of sulphones as nucleophilic acylating reagents will be reported elsewhere.

‡ Attempts to prepare an authentic sample of (**6**) *via* 2-phenylcyclohexanone–$LiNPr^i_2$–$(PhS)_2$ and oxidation with *m*-chloroperoxybenzoic acid gave the isomer 2-phenyl-2-(phenylsulphonyl)cyclohexanone as the only isolable product. The structure of (**6**) was confirmed by reduction (Al–Hg) to 2-phenylcyclohexanone.

§ Presumably (**7**) arises from its exocyclic double isomer which would be expected to isomerize to the thermodynamically more stable endocyclic isomer (**7**).

O-alkylation product was detected. The sulphone (**3**) was treated with a variety of reagents to examine its intramolecular alkylation to either (**6**) or (**7**); the results are given in the Table.

Some of the results in the Table are unexpected.[6] Entry (b) is in keeping with currently accepted views that alkylation at the more electronegative atom of an ambient anion is favoured by polar aprotic solvents.[7] The heterogeneous *O*-alkylation (c) is unusual since heterogeneous conditions usually, for an intermolecular system, favour *C*-alkylation.[8]



(1) (2) (M=Li or Na) (3)

(4) (5) (M=Li or Na) (6)

(7) (8)

The conditions used in (a) were expected to give predominantly *O*-alkylation, whereas mostly *C*-alkylation was observed. The Me_2SO solution in (a) became dark crimson, a colour associated with a dianionic intermediate. If the dianion (**8**) is formed, then only one of its possible conformations, (**8b**), can lead to *O*-alkylation. The W-shaped conformer (**8a**) is said to be preferred in aprotic polar solvents such as Me_2SO,[9] providing a possible explanation for *C*-alkylation as the major pathway. Entries (d), (e), and (f) are according to expectations. Solvation of the oxygen atom of the enolate increases *C*-alkylation.

Unexpectedly, entry (g), with thallium ethoxide, a reagent reputed to lead to almost exclusive *C*-alkylation with β diketones,[10] gave predominantly the *O*-alkylation product. This observation shows that the reasoning used to explain *C*- versus *O*-alkylation cannot be applied *per se* to intramolecular situations.

Lithium di-isopropylamide, entry (h), in glyme, again unexpectedly, led to exclusive *C*-alkylation.¶ (No *O*-alkylation product was detected.) It appears that the conformation of (**5**) can vary so markedly with the nature of the cation and solvent that either *C*- or *O*-alkylation may be observed exclusively under appropriate conditions.[11]

All new compounds gave spectral and microanalytical data in agreement with the proposed structures.

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¶ This reagent system would be expected to parallel entry (b).

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