Olefinic Cyclisations Initiated by Pummerer Rearrangement Products; Synthesis of Cyclic Ketones

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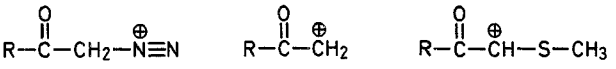
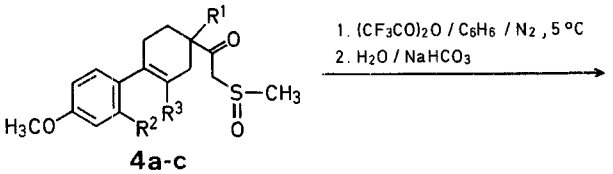
The protonated diazomethylcarbonyl function **1** serves as a valuable operational equivalent to the α-oxocarbenium ion **2** in intramolecular reactions with aromatic and olefinic π bonds[1]. These processes have been very usefully exploited in a variety of preparations, including our recent total syntheses of the gibberellin phytohormones[2]. Unfortunately, the hyperactivity of **1** often leads to isomeric products[3], and allows only limited discrimination between the π bond and competing nucleophiles, including neighbouring groups[4,5] and solvent[6]. We have therefore examined the effect of substituents which would attenuate the reactivity of **2** and now communicate the results of a study on olefinic cyclisations initiated (formally) by **3**. The choice of group was made on the basis of earlier reports[7] on the preparation of β-tetralone derivatives, *inter alia*, and in the expectation that the sulphur substituent could be readily hydrogenolysed subsequently.

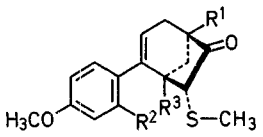


1 **2** **3**

Access to the desired intermediates was obtained through Pummerer rearrangement[8] of β-keto sulphoxides, formed by treatment of the parent methyl ester[9] with lithium dimsyl[10] (see Experimental). Thus, sulphoxides **4a–c, 7a, b** (Table 1) were prepared in good yields, dissolved in benzene, and 1.1 equivalents of trifluoroacetic anhydride added. In each of the examples studied, the N.M.R. spectra showed that diastereomeric hemithioacetal trifluoroacetates, were obtained in less than one minute [e.g. from **4a**, resonances at $\delta = 5.58$ and 5.62 ppm, —CO—CH(SCH$_3$)—O—CO—CF$_3$, were observed], followed by formation of a single cyclic α-methylthio ketone at variable rates (Table 2). The structures of products **5a–c** (obtained as glasses, which could not be distilled and analysed) were consistent with spectroscopic data and substantiated by desulphurisation (W2 Raney nickel)[11] to the parent ketones **6a**[12], **6b**[13], and **6c**, respectively. In the ^{1}H-N.M.R. spectrum of **5a**, the proton adjacent to the S—CH$_3$ substituent gave rise to a singlet resonance, indicating the *exo*-configuration for the thio group (*cf.* **8a** and **8b**). The chemical shifts of the equivalent protons in spectra of **5b** and **5c** were consistent with shielding by the aryl ring and therefore with an *exo*-methylthio substituent also.

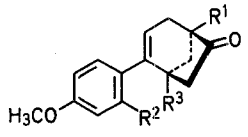


4a-c

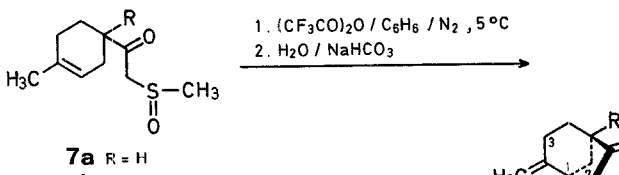


5a-c

4-6	R^1	R^2	R^3
a	H	H	H
b	H	—CH$_2$—CH$_2$—	
c	OCH$_3$	—CH$_2$—CH$_2$—	



6a-c



7a R = H
b R = CH$_3$

8a,b

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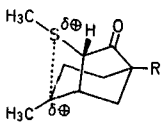
Table 1. Preparation and Physical Data of β-Ketosulphoxides **4a–c, 7a, b**

Product	Yield [%]	m.p./b.p. [°C]/torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/100 MHz) δ [ppm]
4a	65	125–126°	$C_{16}H_{20}O_3S$ (242.3)	2.56 (s, 3H); 3.64 (s, 3H); 3.83 (s, 2H); 5.84 (e, 1H, $W_{h/2}$=10 Hz); 6.7 (d, 2H, J=8 Hz); 7.17 (d, 2H, J=8 Hz)
4b	70	100–101°	$C_{18}H_{22}O_3S$ (318.4)	2.58 (s, 3H); 3.64 (s, 3H); 3.84 (s, 2H); 6.5 (m, 2H); 6.9 (d, 1H, J=8 Hz)
4c	84	120°/0.05 torr	$C_{19}H_{24}O_4S$ (348.4)	2.75 (s, 3H); 3.25 (s, 3H); 3.76 (s, 3H); 3.82, 4.32 (ABq, 2H, J=16 Hz); 6.66 (m, 2H); 7.04 (d, 1H, J=8 Hz)
7a	70	60–61°	$C_{10}H_{16}O_2S$ (200.2)	1.6 (s, 3H); 2.6 (s, 3H); 3.86 (s, 2H); 5.3 (e, 1H, $W_{h/2}$=8 Hz)
7b	82	71°	$C_{11}H_{18}O_2S$ (214.2)	1.14 (s, 3H); 1.6 (s, 3H); 2.66 (s, 3H); 3.68–4.28 (2×ABq, 2H, J=16 Hz); 5.3 (e, 1H, $W_{h/2}$=8 Hz)

[a] All compounds gave satisfactory microanalyses (C ±0.36, H ±0.21, S ±0.36).

In products **8a** and **8b**, however, a value of 7 Hz for $J_{H\text{-}1,H\text{-}7}$ clearly indicated a 7-*endo*-substituent. This feature was associated with significantly higher rates of reaction and with the selective formation of exocyclic olefins. Since the aryl substituent in examples **4a–c** would have been expected to have provided greater activation, it may be assumed that cyclisation to *endo*-products is favoured in all cases, but that an aryl group allows retrocyclisation and equilibration to the more stable *exo*-isomers. Moreover, to explain the observed kinetic preference for the *endo*-epimers, bonding between the cationic centre and sulphur (*cf.* structure **9**)[14] is invoked, an inference which is supported by the specificity of olefin formation: i.e. antiperiplanar proton elimination may be achieved readily from the methyl substituent in **9**, but not from the C-3 methylene group.



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Thus, cyclisations initiated by the structural unit **3** are shown to have a significant synthetic utility and may provide a useful alternative to the related diazoketone initiated processes. Example **4c** demonstrates that a neighbouring nucleophilic substituent may be tolerated, thereby eliminating the need for temporary masking[5,13] of such groups. Finally, the methylthio group has considerable potential for subsequent manipulations[15].

1,4-Dimethylcyclohex-3-en-1-yl Methylsulphinylmethyl Ketone (7b); Typical Procedure:

A solution of methyl 1,4-dimethylcyclohex-3-ene-1-carboxylate (8 g, 0.048 mol) is added over 10 min to an ice-cooled suspension of lithium dimsyl (18.6 g, 0.10 mol) in a mixture of tetrahydrofuran (200 ml) and dimethyl sulphoxide [10 ml, containing a trace of triphenylmethane as indicator (pink→colourless)] under an argon atmosphere. The reaction mixture is poured on to a mixture of 10 molar hydrochloric acid (10 ml) and ice (100 g) and then extracted with benzene (3×50 ml). The combined extracts are washed with brine, dried with magnesium sulphate, and concentrated to a colourless oil. Trituration with ether affords white crystals of sulphoxide **7b**; yield 8.0 g (82%); m.p. 71 °C.

$C_{11}H_{18}O_2S$	calc.	C 61.66	H 8.47	S 14.95
(214.2)	found	61.54	8.68	14.80

I.R. (Nujol): ν = 1720 cm^{-1}.

(1*RS*,5*RS*,7*RS*)-5-Methyl-2-methylene-7-methylthiobicyclo[3.2.1]octan-6-one (8b); Typical Procedure:

Trifluoroacetic anhydride (3.6 ml, 0.026 mol) is added over 5 min to a stirred degassed solution of sulphoxide **7b** (5 g, 0.023 mol) in anhydrous benzene (70 ml) at 5 °C under an atmosphere of nitrogen. After 30 min at 5 °C, water (70 ml) is added followed by sodium hydrogen carbonate solution until the mixture is neutral. The aqueous phase is separated, extracted with ether (100 ml), the organic layers are combined, and washed with brine, then dried with magnesium sulphate.

Table 2. Preparation and Physical Data of Cyclic Ketones **5a–c, 8a, b**

Product	$T_{1/2}$ [min][a]	b.p. [°C]/torr	Yield [%]	High-Resolution M.S. *m/e*	^{1}H-N.M.R. ($CDCl_3$, 100 MHz) δ [ppm]
5a	85	—[b]	70	274.1025 (M^+, 70%) (calc. for $C_{16}H_{18}O_2S$: 274.1027)	1.96 (s, 3H); 3.5 (s, 1H); 3.70 (s, 3H); 5.70 (t, 1H, J=4 Hz); 6.80 (d, 2H, J=8 Hz); 7.40 (d, 2H, J=8 Hz)
5b	85	—[b]	65	300.1185 (M^+, 70%) (calc. for $C_{18}H_{20}O_2S$: 300.1184)	2.10 (s, 3H); 3.02 (s, 1H); 3.70 (s, 3H); 5.80 (t, 1H, J=4 Hz); 6.66 (m, 2H); 7.40 (d, 1H, J=8 Hz)
5c	15	—[b]	76	330.1291 (M^+, 92%) (calc. for $C_{19}H_{22}O_3S$: 330.1289)	2.15 (s, 3H); 3.00 (s, 1H); 3.41 (s, 3H); 3.79 (s, 3H); 5.98 (t, 1H, J=4 Hz); 6.72 (m, 2H); 7.40 (d, 1H, J=8 Hz)
8a	12	95 °C/2	80[c]	182.0762 (M^+, 55%) (calc. for $C_{10}H_{14}OS$: 182.0765)	2.20 (s, 3H); 3.30 (d, 1H, J=7 Hz); 4.80 (e, 2H, $W_{h/2}$=6 Hz)
8b	0.75	87 °C/0.5	70	see experimental	

[a] Estimated from the peak height of the H_3C—S resonance in the ^{1}H-N.M.R. spectra on 0.3 molar solutions in benzene-d_6 at 35 °C.
[b] Decomposed on distillation (kugelrohr); could not be analysed; converted to known compounds **6a–c**.
[c]

$C_{10}H_{14}OS$	calc.	C 65.91	H 7.74	S 17.56
(182.1)	found	65.65	7.58	17.27

Removal of solvent and chromatography of the residue on florisil (100 g) furnishes the ketone **8b** as a pale yellow oil; yield 3.2 g (70%); b.p. (kugelrohr): 87 °C/0.5 torr.

$C_{11}H_{16}OS$	calc.	C 67.32	H 8.22	S 16.31
(196.1)	found	67.04	8.10	16.17

M.S.: $m/e = 196.0923$ (M^+, 40%); calc. 196.0922.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.06$ (s, 3H); 2.22 (s, 3H); 3.30 (d, 1H, $J = 7$ Hz); 4.70 ppm (s, 2H, $W_{h/2} = 4$ Hz).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 15.3$ (SCH_3); 20.4 (CH_3); 28.7 (C-3); 38.7 (C-4); 43.0 (C-8); 45.2 (C-1); 48.2 (C-5); 57.0 (C-7); 110.4 (=CH_2); 146.0 (C-2); 218.6 ppm (C-6).

I.R. (Nujol): $\nu = 1740$ cm^{-1}.

Hydrogenolysis of 5c; Typical Procedure:

Raney nickel (W2, 0.5 g) is added to a solution of **5c** (55 mg) in acetone (10 ml) and the mixture heated under reflux for 3 h. Filtration, removal of solvent, and extraction of the residue into dichloromethane gives **6c**; yield: 48 mg (~100%); colourless crystals from ether/pentane; m.p. 95–96 °C. The product is identical with a sample (m.p., m.m.p., I.R., ^{1}H-N.M.R.) prepared from **6d** (R^1=OH, R^2—R^3=—CH_2—CH_2—)[13] by treatment with sodium hydride (1.1 equiv) in tetrahydrofuran for 10 min followed by methyl iodide (5 equiv) for 10 min.

$C_{18}H_{20}O_3$	calc.	C 76.03	H 7.09
(284.3)	found	75.81	7.37

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.41$ (s, 3H); 3.79 (s, 3H); 6.07 (t, 1H, $J = 4$ Hz); 6.68 (m, 2H); 7.51 ppm (d, 1H, $J = 8$ Hz).

I.R. (Nujol): $\nu = 1740$ cm^{-1}.

M.S.: m/e (relative intensity) = 284 (M^+ 100%), 256 (12), 241 (55), 212 (25), 199 (17), 186 (11), 165 (10).

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