Reaction between 1,1-Dilithioalkyl Phenyl Sulphones and ω-Bromo-esters. Synthesis of Cyclic Vinyl Ethers

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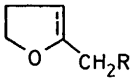
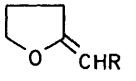
The reaction between 1,1-dilithioalkyl phenyl sulphones (11) and ethyl 4-bromobutyrate affords tetrahydro-2-furylidene derivatives (13) together with minor amounts of the cyclopropyl ketones (15). A mixture of the cyclohexanone and dihydropyran derivatives (17) and (18), respectively, is obtained by the reaction of (11) with ethyl 5-bromovalerate. Treatment of the ω-bromo-β-ketosulphone (19) with various basic reagents also gives a mixture of (17) and (18).

endo- and *exo*-Isomeric five-membered cyclic vinyl ethers [1] (1a and b) are potentially useful intermediates, since they may be subjected to a variety of transformations.[2] In particular, they can be hydrolysed to γ-hydroxyketones,[3] the most direct precursors of γ-diketones.



(1a)



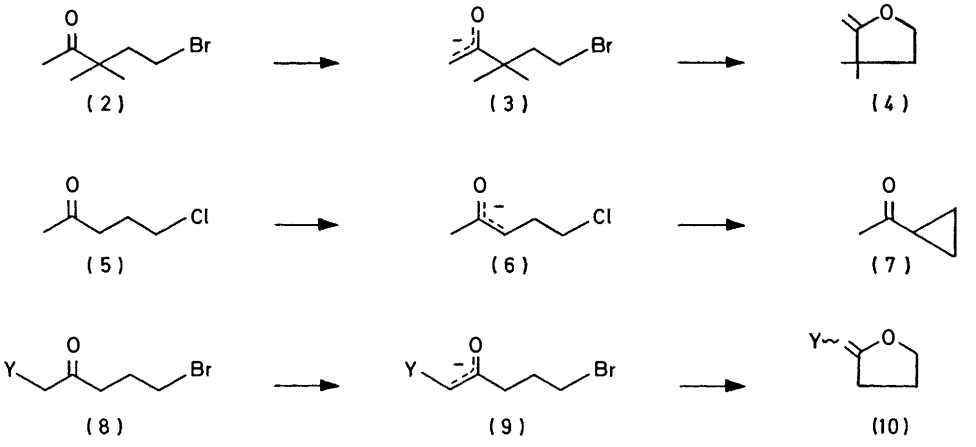
(1b)

Unfortunately the methods commonly used for their preparation are based on the cyclization of compounds such as γ-hydroxyketones [4] and γ-acetylenic alcohols which are not easily prepared.[5]

the cyclopropyl methyl ketone (7) through the enolate (6).[7]

On the basis of these results it is necessary to enhance the acidity of the hydrogen atoms on C(1) in (8) by means of an electron-withdrawing group Y to accomplish regioselective metallation to give (9) and hence to form exclusively the cyclic vinyl ether (10).†

We describe here the reaction of 1,1-dilithioalkyl phenyl sulphones (11) [10] with ethyl 4-bromobutyrate at −60° in tetrahydrofuran to give directly the enolate required for *O*-alkylation, *i.e.* (12), thus avoiding the necessity of going through the ω-bromo-β-ketosulphone (8; Y = $PhSO_2$). The ring closure of (12) provides the expected vinyl ethers (13) as a mixture of *E*- and *Z*-isomers even at low temperature.



SCHEME 1

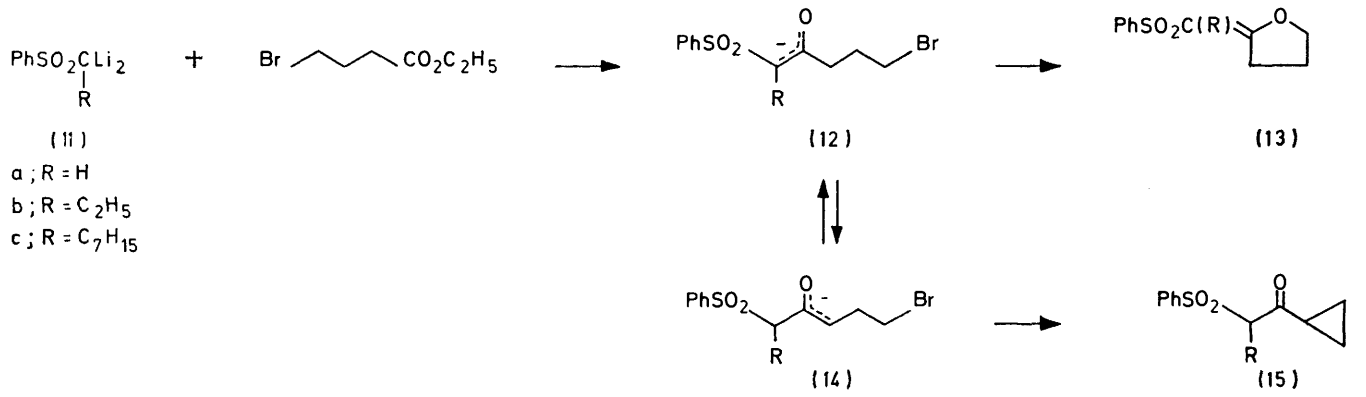
Recently House [6] pointed out that the intramolecular alkylation of the enolate (3) obtained from the bromoketone (2) by treatment with lithium di-isopropylamide in hexane gives exclusively, in the presence of hexamethylphosphoramide, the five-membered cyclic vinyl ether (4). No *C*-alkylated product was detected, supporting the hypothesis that it is difficult to attain the geometry required for the transition state for *C*-alkylation. On the other hand, it is known that base catalysed cyclization of 5-chloropentan-2-one (5) affords only

To a minor extent the reaction follows an alternative pathway to give the cyclopropyl ketone (15), probably through the equilibration of the enolate (12) to (14). Truce *et al.* similarly observed that the relative acidity of the α- and α'-hydrogens in benzyl 5-chloropentyl sulphone was not a decisive factor in the direction of cyclization.[11]

However we cannot exclude that (15) is formed by a previous intramolecular cyclization of the starting bromoester,[12] promoted by (11), followed by attack of the α-sulphonyl carbanion on the cyclopropyl carboxylic ester.

The reaction proved to be satisfactory starting from the 1,1-dianion of methyl, propyl, and octyl phenyl sulphone

† Alternative syntheses of (10) described in the literature are the reactions of the dianion of ethyl acetoacetate with propylene oxide [8] and of the dianion of phenylacetic acid with γ-lactones.[9]



SCHEME 2

(Table 1). The products were separated by column chromatography after the usual work-up.

We have extended our investigation to the reaction of dilithiomethyl phenyl sulphone (11a) with ethyl 5-bromovalerate in tetrahydrofuran. In this case we obtained, after refluxing for a few hours, a mixture of the *C*- and *O*-alkylated products (17) and (18) in 23 and 42% yields, respectively. On the other hand by quenching the intermediate enolate (16) at 0° we obtained the open-chain sulphone (19) in 68% yield together with small amounts of (17) and (18). The *O*-alkylated product was isolated exclusively as the more stable *endo*-isomers.[1b,d] We have also carried out the cyclization of (19) by treating it with various basic reagents in order to check the possibility of orienting the reaction towards either (17) or (18). Magnus observed that the rules governing *C*- *versus* *O*-alkylation in intermolecular reactions could not be applied to the intramolecular cyclization of 6-bromo-3-phenyl-1-phenylsulphonylhexan-2-one.[13]

TABLE 1

Reaction of (11) with ethyl 4-bromobutyrate

Compound	Product yield (%) [a] (13*E*)	(13*Z*)	(15)
(11a)	34	44	10
(11b)	31	33	18
(11c)	39	20	21

[a] Yield refers to pure isolated compounds.

We always obtained (Table 2) mixtures of (17) and (18) with thallium ethoxide [14] (entry e), which is known to give *C*-alkylation of β-diketones, as well as with lithium di-isopropylamide in diglyme (entry b) or sodium hydride in dimethoxyethane (entry c), although Magnus observed only *O*-alkylation under the same conditions.

The cyclic ether (18) was generally formed preferentially, especially under phase-transfer conditions (entry a), but the ketone (17) was predominant in the reaction with potassium hydride in toluene (entry f).

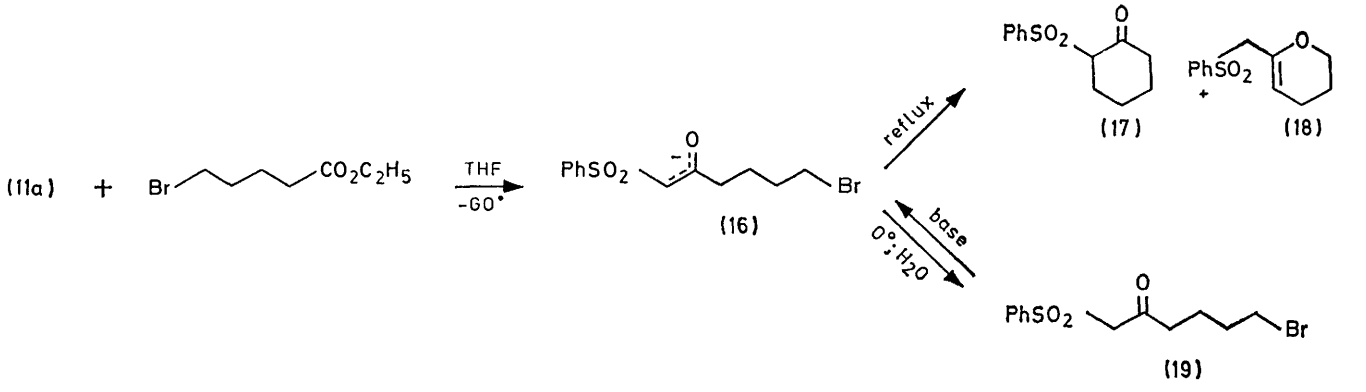
TABLE 2

Intramolecular cyclization of (19)

Entry	Base [a]	Solvent	Temp. (°C)	Product ratio [b] (18) : (17)
a	NaOH–TEBA	CH_2Cl_2	25	75 : 25
b	LiN–Pr^i_2	Diglyme [d]	60	65 : 35
c	NaH	DME [e]	Reflux	60 : 40
d	Bu^tOK	Bu^tOH	55	55 : 45
e	$TlOC_2H_5$	THF	Reflux	50 : 50
f	KH	$C_6H_5CH_3$	Reflux	40 : 60

[a] One equivalent of base was used; under phase-transfer conditions (entry a) an excess of 50% aq NaOH was employed. [b] The reactions reached completion in 2—4 h; the product ratio was evaluated from the n.m.r. spectrum of crude reaction mixtures (yields above 95%). [c] Triethylbenzylammonium chloride. [d] Distilled *in vacuo* over $LiAlH_4$ under argon. [e] Dimethoxyethane, distilled over sodium benzophenone ketyl under argon.

We are currently developing the application of the



SCHEME 3

cyclic vinyl ethers (13) and cyclopropyl ketone (15) * to the synthesis of γ-diketones.

EXPERIMENTAL

I.r. spectra were recorded for NaCl discs with a Perkin-Elmer 710B spectrophotometer, ^1H n.m.r. spectra on a Perkin-Elmer R12B instrument (solvent $CDCl_3$, Me_4Si as internal standard), and mass spectra on a Varian MAT 111 spectrometer (70 eV). T.l.c. was performed on silica gel HF_{254} (Merck) and column chromatography on silica gel (Merck; 0.05—0.20 mesh) with hexane–ethyl acetate as solvent. Tetrahydrofuran was obtained anhydrous and oxygen-free by distillation over sodium benzophenone ketyl under argon. n-Butyl-lithium (2M solution in hexane), ethyl 4-bromobutyrate (97%), and ethyl 5-bromovalerate (97%) were purchased from Fluka. M.p.s are uncorrected.

Preparation of Alkyl Phenyl Sulphones.—Alkyl phenyl sulphones were prepared by the reaction of polymer-supported benzenesulphinate anion with alkyl halides in refluxing benzene.[16]

Reaction of Compound (11) *with Ethyl* 4-*Bromobutyrate.*—In a three-necked flask equipped with mechanical stirrer, dropping funnel, and argon inlet, dry tetrahydrofuran (60 ml) and the alkyl phenyl sulphone (11) (20 mmol) were placed under argon. To the stirred solution n-butyl-lithium (2M, 20 ml, 40 mmol) was added over 15 min at room temperature. After 30 min the flask was cooled at −60° and ethyl 4-bromobutyrate (4 g, 20 mmol) in THF (10 ml) was added with stirring. The temperature was allowed to rise to 0° over 3 h, then water (30 ml) was added, and the mixture extracted with ethyl acetate. The organic phase was washed with aqueous NaCl solution, dried (Na_2SO_4), and evaporated under vacuum. The crude mixture was chromatographed on a silica gel column; the products were eluted with hexane–ethyl acetate in the order (15), (13*E*), (13*Z*).

(*Tetrahydro*-2-*furylidene*)*methyl Phenyl Sulphone* (13a).—The E-*isomer* had m.p. 109° (from CCl_4); δ 7.4—8.1 (5 H, m, aromatic), 5.8 (1 H, s vinylic), 4.25 (2 H, t, OCH_2), 3.15 (2 H, t, allylic), and 2.1 (2 H, m, alicyclic); $\nu_{max.}$ 1 630m, 1 305s, and 1 140s cm^{-1}; *m/e* 224 (M^+). The Z-*isomer* had m.p. 88—90° (from CCl_4); δ 7.4—8.1 (5 H, m, aromatic), 5.5 (1 H, s, vinylic), 4.4 (2 H, t, OCH_2), 2.7 (2 H, t, allylic), and 2.0 (2 H, m, alicyclic); $\nu_{max.}$ 1 630s, 1 305s, and 1 150s cm^{-1}; *m/e* 224 (M^+) (Found: C, 58.8; H, 5.5; S, 14.2. $C_{11}H_{12}O_3S$ requires C, 58.9; H, 5.4; S, 14.3%).

1-(*Tetrahydro*-2-*furylidene*)*propyl Phenyl Sulphone* (13b).—The E-*isomer* was an oil, δ 7.5—8.0 (5 H, m, aromatic), 4.2 (2 H, t, OCH_2), 3.2 (2 H, t, allylic), 2.2 (4 H, m, allylic and alicyclic), and 0.9 (3 H, t, CH_3); $\nu_{max.}$ 1 640s, 1 305s, and 1 135s cm^{-1}; *m/e* 252 (M^+). The Z-*isomer* was an oil, δ 7.4—8.0 (5 H, m, aromatic), 4.1 (2 H, t, OCH_2), 1.8—2.8 (6 H, m, allylic and alicyclic), and 1.0 (3 H, t, CH_3); $\nu_{max.}$ 1 640s, 1 305s, and 1 145s cm^{-1}; *m/e* 252 (M^+) (Found: C, 61.6; H, 6.4. $C_{13}H_{16}O_3S$ requires C, 61.9; H, 6.4%).

1-(*Tetrahydro*-2-*furylidene*)*octyl Phenyl Sulphone* (13c).—The E-*isomer* was an oil, δ 7.4—8.0 (5 H, m, aromatic), 4.2 (2 H, t, OCH_2), 3.2 (2 H, t, allylic), 2.1 (4 H, m, alicyclic and allylic), and 1.2 (10 H, m, aliphatic), and 0.9 (3 H, t, CH_3); $\nu_{max.}$ 1 630m, 1 305s, and 1 150s cm^{-1}; *m/e* 322 (M^+). The Z-*isomer* had m.p. 53° (from CCl_4); δ 7.4—8.0 (5 H, m, aromatic), 4.15 (2 H, t, OCH_2), 1.8—2.8 (6 H, m, allylic and alicyclic), 1.3 (10 H, m, aliphatic), and 0.9 (3 H, t, CH_3); $\nu_{max.}$ 1 630s, 1 300s, and 1 140s cm^{-1}; *m/e* 322 (M^+) (Found: C, 66.7; H, 8.1; S, 9.7. $C_{18}H_{26}O_3S$ requires C, 67.0; H, 8.1; S, 9.9%).

Cyclopropyl (*phenylsulphonyl*)*methyl ketone* (15a) had m.p. 56° (from CCl_4); δ 7.5—8.1 (5 H, m, aromatic), 4.35 (2 H, s, SO_2CH_2), 2.2 (1 H, m, COCH), and 1.0 (4 H, m, cyclopropyl); $\nu_{max.}$ 1 690s, 1 310s, and 1 150s cm^{-1}; *m/e* 224 (M^+) (Found: C, 58.8; H, 5.4. $C_{11}H_{12}O_3S$ requires C, 58.9; H, 5.4%).

Cyclopropyl 1-(*phenylsulphonyl*)*propyl ketone* (15b) was an oil, δ 7.5—8.0 (5 H, m, aromatic), 4.2 (1 H, t, SO_2CH), 2.2, (1 H, m, COCH), 2.0 (2 H, m, aliphatic), 1.0 (4 H, m, cyclopropyl), and 0.9 (3 H, t, CH_3); $\nu_{max.}$ 1 700s, 1 310s, and 1 150s cm^{-1}; *m/e* 252 (M^+) (Found: C, 61.6; H, 6.6. $C_{13}H_{16}O_3S$ requires C, 61.9; H, 6.4%).

Cyclopropyl 1-(*phenylsulphonyl*)*octyl ketone* (15c) had m.p. 71° (from CCl_4); δ 7.5—8.0 (5 H, m, aromatic), 4.2 (1 H, t, SO_2CH), 2.2 (1 H, m, COCH), 2.0 (2 H, m, aliphatic), 1.25 (10 H, m, aliphatic), 1.0 (4 H, m, cyclopropyl), and 0.9 (3 H, t, CH_3); $\nu_{max.}$ 1 700m, 1 310s and 1 150s cm^{-1}; *m/e* 322 (M^+) (Found: C, 67.4; H, 8.3. $C_{18}H_{26}O_3S$ requires C, 67.0; H, 8.1%).

Reaction of Compound (11a) *with Ethyl* 5-*Bromovalerate.*—The procedure previously described for the reaction with ethyl 4-bromobutyrate was followed, but heating at reflux for 3 h was necessary to achieve complete ring closure to (17) (23%) and (18) (42%). When the reaction was quenched with water at 0° mainly the ω-bromo-β-keto-sulphone (19) was obtained in 68% yield together with a little (17) and (18). 2-*Phenylsulphonylcyclohexanone* (17) had m.p. 87° (from CCl_4); δ 7.5—8.0 (5 H, m, aromatic), 3.9 (1 H, t, SO_2CH), and 1.6—2.8 (8 H, m alicyclic); $\nu_{max.}$ 1 720s and 1 310s cm^{-1}; *m/e* 238 (M^+) (Found: C, 60.7; H, 5.8; S, 13.2. $C_{12}H_{14}O_3S$ requires C, 60.5; H, 5.9; S, 13.4%). (5 6-*Dihydro*-4H-*pyran*-2-*yl*)*methyl phenyl sulphone* (18) was an oil; δ 7.5—8.1 (5 H, m, aromatic), 4.7 (1 H, t, vinylic), 3.75 (2 H, s, SO_2CH_2), 3.75 (2 H, t, OCH_2), and 1.8 (4 H, m, alicyclic); $\nu_{max.}$ 1 720s, 1 320s, and 1 150s cm^{-1}; *m/e* 238 (M^+) (Found: C, 60.2; H, 5.9; S, 13.1. $C_{12}H_{14}O_3S$ requires C, 60.5; H, 5.9; S, 13.4%). 6-*Bromo*-1-*phenylsulphonylhexan*-2-*one* (19) had m.p. 83° (from CCl_4); δ 7.5—8.1 (5 H, m, aromatic), 4.2 (2 H, s, SO_2CH_2), 3.4 (2 H, t, $BrCH_2$), 2.8 (2 H, t, $COCH_2$), and 1.8 (4 H, m, aliphatic); $\nu_{max.}$ 1 720s, 1 310s, and 1 140s cm^{-1}; *m/e* 319 (M^+) (Found: C, 45.3; H, 4.7; S, 9.7. $C_{12}H_{15}O_3S$ requires C, 45.2; H, 4.7; S, 10.0%).

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* It is known that cyclopropyl methyl ketone undergoes rearrangement in concentrated sulphuric acid to provide after hydrolysis the same hydroxy-ketone obtained from the hydrolysis of the isomers (1; R = H).[15]

REFERENCES

[1] (*a*) A. Kankaanpera, E. Taskinen, and P. Salomaa, *Acta Chem. Scand.*, 1967, **21**, 2487; E. Taskinen, (*b*) *Ann. Acad. Sci. Fennicae*, 1972, *A*2, 163; (*c*) *Acta Chem. Scand.*, 1975, **B29**, 245; (*d*) E. Taskinen, *Tetrahedron*, 1978, **34**, 433.

[2] M. A. Gianturco, P. Friedel, and V. Flanagan, *Tetrahedron Letters*, 1965, 1847; M. A. Gianturco and P. Friedel, *Canad. J. Chem.*, 1966, **44**, 1083 and references cited therein.

[3] R. Paul and S. Tchelitcheff, *Bull. Soc. chim. France*, 1950, 520; R. Paul, S. Tchelitcheff, and G. Collardeau, *ibid.*, p. 668.

[4] H. Wolgenmuth, *Annalen*, 1914, series IX, **2**, 403.

[5] J. Colange and R. Gelin, *Bull. Soc. chim. France*, 1954, 799.

[6] H. O. House, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.*, 1978, **43**, 700.

[7] R. A. Bartsch and D. M. Cook, *J. Org. Chem.*, 1970, **35**, 1714.

[8] T. A. Bryson, *J. Org. Chem.*, 1973, **38**, 3428.

[9] F. F. Blicke and B. A. Brown, *J. Org. Chem.*, 1961, **26**, 3685.
[10] E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1971, **93**, 4237; W. E. Truce and L. W. Christensen, *Chem. Comm.*, 1971, 558; V. Pascali, N. Tangari, and A. Umani-Ronchi, *J.C.S. Perkin I*, 1973, 1166; N. Bosworth and P. Magnus, *ibid.*, p. 2319; K. Kondo and T. Tunemoto, *Tetrahedron Letters*, 1975, 1397; A. Bongini, D. Savoia, and A. Umani-Ronchi, *J. Organometallic Chem.*, 1976, **112**, 1; P. A. Bartlett, F. R. Green, III, and E. H. Rose, *J. Amer. Chem. Soc.*, 1978, **100**, 4852.
[11] W. E. Truce, K. R. Hollister, L. B. Lindy, and J. E. Parr, *J. Org. Chem.*, 1968, **33**, 43.
[12] M. Julia, S. Julia, and B. Bemont, *Bull. Soc. chim. France*, 1960, 304.
[13] F. Cooke and P. Magnus, *J.C.S. Chem. Comm.*, 1976, 519.
[14] E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 1970, **3**, 338.
[15] C. U. Pittman, jun., and S. P. McManus, *J. Amer. Chem. Soc.*, 1969, **91**, 5915; T. Nakai, E. Wada, and M. Okawara, *Tetrahedron Letters*, 1975, 1531.
[16] F. Manescalchi, M. Orena, and D. Savoia, *Synthesis*, 1979, 445.