Syntheses and Reactions of 2-Ethylthio- or 2-Phenylthio-2-cycloalkenones

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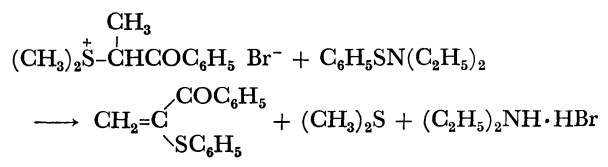
2-Ethylthio- or 2-phenylthio-2-cycloalkenones (five-, six-, or seven-membered ring) were obtained in high yields by the reactions of alicyclic β-ketosulfonium salts with sulfenamides. It was found that dihydrofuran derivatives were obtained in good yields from the sulfonium salts of the cycloalkenones and active methylene compounds.

Recently we found that α-phenylthioacrylophenone was obtained in quantitative yield by the reaction of dimethyl-α-methylphenacyl sulfonium bromide with *N*, *N*-diethylbenzenesulfenamide.[1]

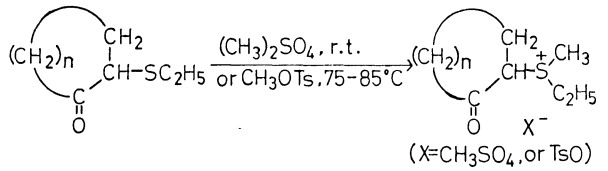


Scheme 1

This indicates that 2-alkylthio- or 2-arylthio-2-cycloalkenones, valuable synthetic intermediates, would be produced from alicyclic β-ketosulfonium salts and sulfenamides.

The preparation of alicyclic β-ketosulfonium salts and the reactions of the salts with sulfenamides were investigated. It is well-known that sulfonium salts are prepared by the reactions of alkyl halides with dimethyl sulfide. However, it was found that the reaction of 2-bromocycloalkanones such as 2-bromocyclohexanone with dimethyl sulfide afforded no corresponding sulfonium salts, except when the reaction was carried out in the presence of silver tetrafluoroborate.[2] Thus, the preparation of the sulfonium salts was attempted by the reactions of β-keto-sulfides with dimethyl sulfate or methyl *p*-tosylate.

When 2-ethylthiocyclohexanone was treated with dimethyl sulfate at room temperature for 1—2 days or with methyl tosylate at 75—85°C for 7—8 hr, the corresponding sulfonium salts were obtained in almost quantitative yields as viscous oil. In a similar way, cyclopentanone and cycloheptanone analogs were prepared in high yields.

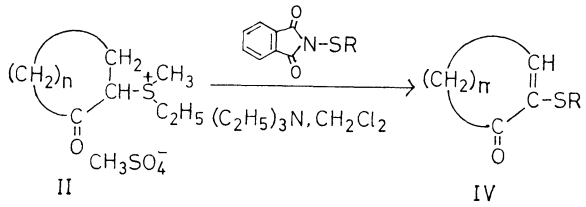


Scheme 2

The reactions of sulfonium salts (IIa—c) thus obtained with several sulfenamides were examined. When methylethyl-2-oxocyclohexylsulfonium tosylate (IIb′) was treated with *N*-phenylthiopyrrolidine[3] (sulfenamides of type *A* in Scheme III) in dichloromethane at room temperature for a day, 2-phenylthio-2-cyclohexenone (IVc) was obtained in 54% yield along with diphenyl disulfide (31%).

The result can be explained as follows. Sulfonium salt (IIb′) reacts with *N*-phenylthiopyrrolidine to afford α-sulfenylated intermediate (III) and pyrrolidine. III is in turn converted to IVc with the elimination of β-hydrogen atom and methyl ethyl sulfide by the influence of pyrrolidine produced at the same time. It was established that IVc was obtained in 78% yield by the reaction of IIb′ with *N*-phenylthiophthalimide (sulfenamides of type *B* in Scheme III) in the presence of triethylamine. These results indicate that sulfenamides of type *B* are preferable to those of type *A* for the synthesis of 2-alkylthio- or 2-arylthio-2-cycloalkenone. In a similar way, reactions of the five- or the seven-membered sulfonium salt with *N*-phenylthio- or *N*-ethylthiophthalimide gave the corresponding 2-phenylthio- or 2-ethylthio-2-cycloalkenones (IVa—f) in good yields (Tabel 1).

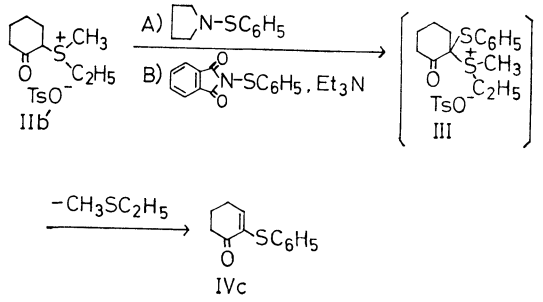
TABLE 1. SYNTHESES OF 2-ETHYLTHIO- OR 2-PHENYLTHIO-2-CYCLOALKENONES



	n	R	Yield (%)	Mp °C (Bp °C/mmHg)	Analyses (%) Found (Calcd) C	H	N
IVa	2	C_6H_5	59	65—66	69.58 (69.46)	5.39 (5.30)	17.12 (16.85)
b	2	C_2H_5	81	(127—128/15)	58.88 (59.14)	7.12 (7.09)	22.30 (22.54)
c	3	C_6H_5	70	57—58	70.31 (70.57)	6.10 (5.92)	15.50 (15.70)
d	3	C_2H_5	80	(110—112/4)	61.57 (61.52)	7.77 (7.75)	20.80 (20.51)
e	4	C_6H_5	76	148—149[a]	71.83 (71.54)	6.29 (6.47)	14.50 (14.69)
f	4	C_2H_5	76	(115—118/5.5)	63.64 (63.51)	8.26 (8.29)	18.79 (18.83)

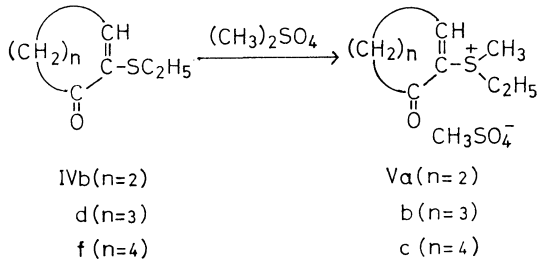
a) Mp of 2,4-dinitrophenylhydrazone

1) T. Mukaiyama, K. Hosoi, S. Inokuma, and T. Kumamoto, This Bulletin, **44**, 2453 (1971).
2) T. Mukaiyama and M. Higo, *Tetrahedron Lett.*, **1970**, 5297.
3) T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *ibid.*, **1970**, 5115.



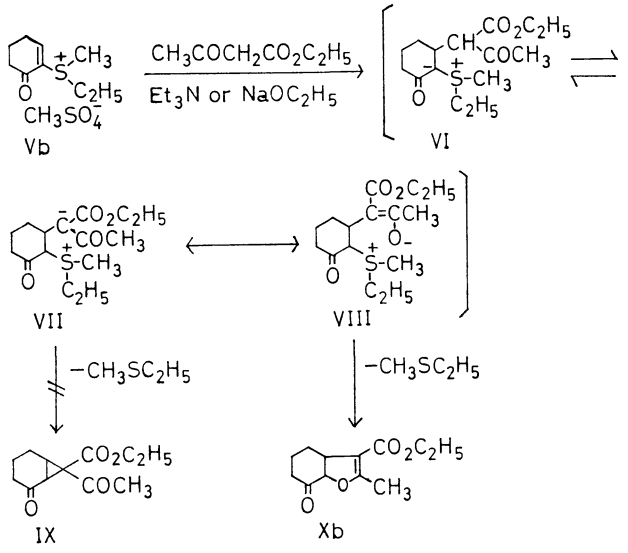
Scheme 3

Reactions of the sulfonium salts (Va—c) of the cycloalkenones with active methylene compounds, such as ethyl acetoacetate or acetylacetone, were attempted. When 2-ethylthio-2-cyclohexenone (IVd) or 2-ethylthio-2-cycloheptenone (IVf) was treated with dimethyl sulfate at 40—50°C for 5 hr, the corresponding sulfonium salts were obtained in almost quantitative yields. In the case of the five-membered analog, the yield of the sulfonium salt (Va) was low.



Scheme 4

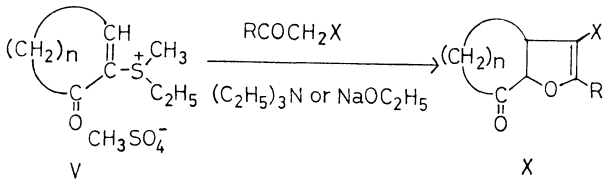
It was found that when the sulfonium salt (Vb) was treated with ethyl acetoacetate in the presence of triethylamine or sodium ethoxide under ice-cooling for 5 hr, the compound, mp 58—59°C, $C_{12}H_{16}O_4$, was obtained along with methyl ethyl sulfide. Its IR spectrum showed the presence of ester group at 1725 cm^{-1}, carbonyl group of cyclohexane ring at 1695 cm^{-1} and the C=C stretching of enol ether at 1640 cm^{-1}, but not a band for acetyl group. The NMR spectrum (60 MHz) exhibited characteristic peaks of two angular hydrogens at 6.1—6.6 τ (1*H*, multiplet) and at 5.4 τ (1*H*, doublet, J=10 Hz), and the UV spectrum in ethanol showed absorption maximum at 255 mμ (ε=12200). Thus, the structure is assigned to the dihydrofuran derivative, 9-ethoxycarbonyl-8-methyl-7-oxabicyclo[4.3.0]-8-nonen-5-one (Xb).



Scheme 5

This result may be explained as follows. First, the intermediate ylide (VI) is produced from the sulfonium salt (Vb) and ethyl acetoacetate by the Michael addition. The ylide (VI) is in turn changed to the betaine form (VII or VIII) by the proton transfer. Subsequent intramolecular nucleophilic attack of enolate anion (VIII) at the α-carbon of sulfonium group affords Xb with the elimination of methyl ethyl sulfide. There is an alternative route for a possible formation of the cyclopropane derivative (IX) involving an attack of the carbanion (VII) at the α-carbon.[4] However, no

Table 2. Preparation of dihydrofuran derivatives



	n	R	X	Yield (%)	Mp °C (Bp °C/mmHg)	λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$)	Analyses (%) Found (Calcd) C	H
Xa	2	CH_3	$CO_2C_2H_5$	18	(127—130/4)		62.55 (62.84)	6.62 (6.71)
b	3	CH_3	$CO_2C_2H_5$	91—98	58—59[a]	255 (1.22)	64.51 (64.27)	7.26 (7.19)
c	3	CH_3	$COCH_3$	70	90—91[a]	274 (1.29)	67.79 (68.02)	6.98 (7.27)
d	3	H	$CO_2C_2H_5$	50	(115—118/4.5)	252 (1.03)	63.11 (62.84)	6.74 (6.71)
e	4	CH_3	$CO_2C_2H_5$	85	64—65[a]	255 (1.21)	65.83 (65.53)	7.63 (7.61)
f	4	CH_3	$COCH_3$	67	86—87[a]	273 (1.36)	68.92 (69.21)	7.44 (7.74)

a) Recrystallized from cyclohexane

4) J. Gosselck, H. Ahlbrecht, F. Dost, H. Schenk, and G. Schmidt, *Tetrahedron Lett.*, **1968**, 995.

such compound could be isolated from the reaction mixture.

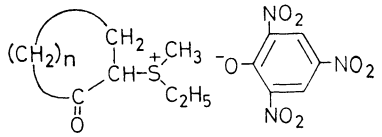
Similarly, dihydrofuran derivatives (Xa—f) were obtained from the sulfonium salts of cyclopentenone or cycloheptenone analog and active methylene compounds as shown in Table 2.

Experimental

Materials. 2-Ethylthiocyclopentanone (Ia, bp 57—59°C/4 mmHg) and 2-ethylthiocycloheptanone (Ic, bp 96.5—97.5°C/5 mmHg) were prepared according to the method of Mousseron.[5]

Preparation of Methylethyl-2-oxocycloalkylsulfonium Salts (II). A mixture of 2-ethylthiocyclohexanone (Ib)[5] (1.58 g, 0.01 mol) and freshly-distilled dimethyl sulfate (1.39 g, 0.011 mol) was stirred at room temperature. After stirring for 1—2 days, methylethyl-2-oxocyclohexylsulfonium methylsulfate (IIb) was obtained in almost quantitative yield as a slightly yellowish viscous oil. Similarly, methylethyl-2-oxocyclopentylsulfonium methylsulfate (IIa) and methylethyl-2-oxocycloheptylsulfonium methylsulfate (IIc) were obtained in good yields. Methylethyl-2-oxocyclohexylsulfonium tosylate (IIb′) was prepared by the treatment of Ib (4.75 g, 0.03 mol) with methyl tosylate (6.15 g, 0.033 mol) at 75—85°C for 7—8 hr as a slightly brownish viscous oil. All of these oily salts were used for the reaction with sulfenamides without further purification, and identified by transformation into their picrates.

Table 3. Methylethyl-2-oxocycloalkyl-sulfomium picrates



n	Mp °C (dec.)	Analyses, Found (Calcd) (%) C	H	N	S
2	109—110	43.90 (43.41)	4.41 (4.42)	10.80 (10.58)	8.14 (8.28)
3	158	45.17 (44.89)	4.61 (4.77)	10.72 (10.47)	8.29 (7.99)
4	129.5	46.51 (46.26)	5.25 (5.10)	10.28 (10.12)	7.68 (7.77)

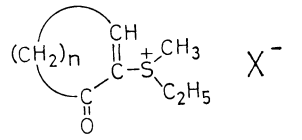
Preparation of 2-Phenylthio-2-cyclohexenone (IVc). (A) The Reaction of IIb′ with N-Phenylthiopyrrolidine: A solution of *N*-phenylthiopyrrolidine (5.37 g, 0.03 mol) in dichloromethane (5 m*l*) was added dropwise to a solution of IIb′ (10.9 g, 0.03 mol) in dichloromethane (10 m*l*) under ice-cooling. The reaction mixture was stirred continuously at room temperature for a day. After removal of the solvent, the resulting dark brown syrup was extracted with ether and the ether layer was chromatogaphed on silica gel. Elution with petroleum ether gave diphenyl disulfide 1.0 g (31%) and that with benzene gave slightly yellowish-green crystals, mp 52—54°C, 3.3 g (54%), which were crystallized from isopropyl alcohol to afford colorless needles (IVc), mp 57—58°C.

(B) The Reaction of IIb′ with N-Phenylthiophthalimide: Into a mixture of IIb′ (7.26 g, 0.02 mol) and *N*-phenylthiophthalimide (5.1 g, 0.02 mol)[6] in dichloromethane (25 m*l*), a solution of triethylamine (2.02 g, 0.02 mol) in dichloromethane (2 m*l*) was added dropwise with stirring under ice-cooling. After additional stirring at room temperature for a day, the precipitate of phthalimide (2.11 g, 72%) was filtered off. The filtrate was concentrated under reduced pressure and the resulting oil was chromatographed on silica gel. Elution with benzene gave slightly brownish crystals, mp 52—55°C, 3.2 g (78%). Recrystallization from isopropyl alcohol gave colorless needles (IVc), mp 57—58°C. In a similar manner, 2-phenylthio-2-cyclopentenone (IVa) or 2-phenythio-2-cycloheptenone (IVe) was obtained by the reaction of the corresponding sulfonium salt (IIa or IIc respectively) with *N*-phenylthiophthalimide as shown in Table 2.

Preparation of 2-Ethylthio-2-cyclohexenone. Into a mixture of IIb (29.7 g, 0.1 mol) and *N*-ethylthiophthalimide (20.7 g, 0.1 mol)[6] in dichloromethane (60 m*l*), a solution of triethylamine (10.1 g, 0.1 mol) in dichloromethane (10 m*l*) was added dropwise under ice-cooling. After additional stirring at room temperature for a day, the white precipitate of phthalimide (14 g) was filtered off and the filtrate was concentrated. The residue was extracted with ether and ether layer was washed with 10% sodium hydroxide, 10% hydrochloric acid and water, and dried over sodium sulfate. After removal of the solvent, the residual liquid was distilled to afford a slightly yellowish-green liquid (IVd), bp 110—112°C/4 mmHg, 12.5 g (80%). Similarly, 2-ethylthio-2-cyclopentenone (IVb) or 2-ethylthio-2-cycloheptenone was obtained. The results are listed in Table 1.

Preparation of the Sulfonium Salt of 2-Ethylthio-2-cycloalkenone. A mixture of 2-ethylthio-2-cycloalkenone and dimethyl sulfate (1:1.1 molar ratio) was stirred at 40—50°C for 5 hr or at room temperature for 3—4 days. The corresponding sulfonium salt was obtained as a viscous oil, which turned crystalline on transformation into its 2,4,6-trinitrobenzenesulfonate or picrate.

Table 4. Sulfonium salts of alicyclic β-ketosulfides



n		Mp °C (dec.)	Analyses, Found (Calcd) (%) C	H	N	S
2	TNBS[a]	191	37.13 (37.41)	3.45 (3.36)	9.45 (9.35)	14.14 (14.27)
3	Pic[b]	113	45.01 (45.12)	4.14 (4.29)	10.50 (10.52)	8.12 (8.03)
4	TNBS	156—157	40.04 (40.24)	4.12 (4.01)	8.58 (8.80)	13.18 (13.43)

a) TNBS: 2,4,6-trinitrobenzenesulfonate
b) Pic: picrate

Preparation of 9-Ethoxycarbonyl-8-methyl-7-oxabicyclo[4.3.0]-*8-nonen-5-one (Xb).* Into a mixture of ethyl acetoacetate (0.98g, 0.0075 mol) and sodium ethoxide [prepared from 0.115 g (0.005 mol) of sodium] in absolute ethanol (5 m*l*), a solution of the sulfonium slat (Vb) (1.47g, 0.005 mol) in absolute ethanol (5 m*l*) was added dropwise under ice-cooling and stirring for 5 hr. White crystals were precipitated during the stirring. After removal of the solvent, water

5) M. Mousseron, R. Jacquier, and A. Fontaine, *Bull. Soc. Chim. Fr.*, **1952**, 767.

6) M. Behforouz and J. E. Kerwood, *J. Org. Chem.*, **34**, 51, (1969).

(10 ml) was added to the residue, and the resulting oil was extracted with ethyl acetate. Ethyl acetate layer was dried over sodium sulfate, followed by evaporation of the solvent giving slightly yellowish brown crystals (Xb), mp 53—55°C, 1.1 g (98%), which were recrystallized from cyclohexane to afford colorless needles, mp 58—59°C. When the sulfonium salt (Vb) was treated with a small excess of ethyl acetoacetate in dichloromethane in the presence of equimolar amount of triethylamine under ice-cooling, Xb was obtained in 91% yield. Similarly, the dihydrofuran derivatives (Xa), (Xc), (Xe) and (Xf) were produced from the corresponding sulfonium salt and active methylene compound. The results are listed in Table 2.

Preparation of 9-Ethoxycarbonyl-7-oxabicyclo[4.3.0]*-8-nonen-5-one (Xd).* Into a suspension of the sodium salt (2.07 g, 0.015 mol)[7] of ethyl formylacetate in absolute ethanol (10 ml), a solution of Vb (2.94 g, 0.01 mol) in ethanol (10 ml) was added dropwise under ice-cooling. After additional stirring for 5 hr, the solvent was evaporated, and the residue was extracted with ethyl acetate. Ethyl acetate layer was chromatographed on silica gel. Elution with benzene-chloroform (1:1) gave the pale yellow oil (Xd), 1.05 g (50%), which was distilled to afford the colorless oil, bp 115—118°C/4.5 mmHg.

7) W. Wislicenus, *Ber.*, **20**, 2930 (1887).