[Chem. Pharm. Bull. 27(10)2338—2344(1979)]

UDC 547.442.3.04 : 547.569.3.04

Regioselective Sulfenylation of Dianions derived from 1,3-Dicarbonyl Compounds[1]

Kunio Hiroi, Yuko Matsuda, and Shuko Sato

Tohoku College of Pharmacy[2]

(Received March 26, 1979)

Regioselective sulfenylations of dianions derived from 1,3-dicarbonyl compounds were investigated with readily available sulfenylating agents such as diphenyl disulfide, phenyl benzenethiosulfonate, and phenylsulfenyl chloride, employing sodium hydride and butyl lithium or lithium diisopropylamide as bases.

Sulfenylations of the dianions prepared from the β-ketoesters Ia, Ib and VI, the β-ketoamide Ic, and the 1,3-diketones X and XIII with diphenyl disulfide afforded IIIa, IIIb, VIII, IIIc, XII, and XV, respectively, in fairly good yields.

Keywords——sulfenylation; dianion; diphenyl disulfide; β-keto ester; β-keto amide; 1,3-diketone

Organosulfur groups have a wide synthetic utility for the elaboration of complex organic structures, and many methods for the introduction of organosulfur groups α to a carbonyl group or its derivative have been reported.[3,4]

To utilize organosulfur groups in the total synthesis of natural products, a simple synthetic method is required for the regioselective introduction of organosulfur groups. We therefore investigated the regioselective sulfenylation of dianions derived from 1,3-dicarbonyl compounds, such as β-keto esters, β-keto amides, and 1,3-diketones, with readily available sulfenylating agents. Several workers have already reported regioselective alkylations of dianions derived from β-keto esters,[5] β-keto amides,[6] α-sufinyl ketones,[7] β-ketophosphonium salts,[7] and β-keto phosphonates.[8]

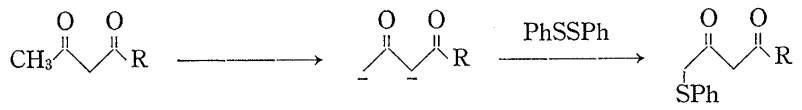
1) For a preliminary report of a portion of this work see K. Hiroi, Y. Matsuda, and S. Sato, *Synthesis*, **1979**, 621.
2) Location: *4-1-1, Komatsushima, Sendai, Miyagi, 983 Japan.*
3) *a*) M.E. Kuehne, *J. Org. Chem.*, **28**, 2124 (1963); *b*) S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *Chem. Commun.*, **1972**, 946; *c*) R.L. Autrey and P.W. Scullard, *J. Am. Chem. Soc.*, **87**, 3284 (1965); *d*) *Idem, ibid.*, **90**, 4917 (1968); *e*) P.A. Grieco and K. Hiroi, *Tetrahedron Lett.*, **1973**, 1831; *f*) S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, *Chem. Pharm. Bull.* (Tokyo), **17**, 419 (1969) and references therein; *g*) T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Lett.*, **1970**, 5115; *h*) T. Kumamoto, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 866 (1972); *i*) K. Hiroi, *Annual Report of Tohoku College of Pharmacy*, **23**, 1 (1976) and references cited therein.
4) Sulfenylation with disulfides; *a*) B.M. Trost and T.N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973); *b*) B.M. Trost and R.A. Kunz, *J. Org. Chem.*, **39**, 2475 (1974); *c*) P.A. Grieco and J.J. Reap, *Tetrahedron Lett.*, **1974**, 1097; *d*) D.N. Brattesani and C.H. Heathcock, *ibid.*, **1974**, 2279; *e*) K. Iwai, M. Kawai, H. Kosugi, and H. Uda, *Chem. Lett.*, **1974**, 385; *f*) B.M. Trost, T.N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976); *g*) P.A. Zoretic and P. Soja, *J. Org. Chem.*, **41**, 3587 (1976); *h*) D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976); *i*) P.A. Zoretic, P. Soja, and N.D. Sinha, *J. Org. Chem.*, **43**, 1379 (1978).
5) *a*) J.F. Wolfe, T.M. Harris, and C.R. Hauser, *J. Org. Chem.*, **29**, 3249 (1964); *b*) C. Mao, C.R. Hauser, and M.L. Miles, *J. Am. Chem. Soc.*, **89**, 5303 (1967); *c*) N. Sugiyama, M. Yamamoto, T. Takano, and C. Kashima, *Bull. Chem. Soc. Jpn.*, **40**, 2909 (1967); *d*) L. Weiler, *J. Am. Chem. Soc.*, **92**, 6702 (1970); *e*) S.N. Huckin and L. Weiler, *ibid.*, **96**, 1082 (1974) and references cited therein; *f*) P-E. Sum and L. Weiler, *Chem. Commun.*, **1977**, 91.
6) J.S. Hubbard and T.M. Harris, *Tetrahedron Lett.*, **1978**, 4601.
7) *a*) P.A. Grieco, D. Boxler, and C.S. Pogonowski, *Chem. Commun.*, **1974**, 497; *b*) I. Kuwajima and H. Iwasawa, *Tetrahedron Lett.*, **1974**, 107; *c*) P.A. Grieco and C.S. Pogonowski, *Chem. Commun.*, **1975**, 72.
8) J.D. Taylor and J.F. Wolf, *Chem. Commun.*, **1972**, 876.
9) *a*) P.A. Grieco and C.S. Pogonowski, *J. Am. Chem. Soc.*, **95**, 3071 (1973); *b*) *Idem, Synthesis*, **1973**, 425.

Sulfenylation of active methylene compounds can easily be achieved by a variety of synthetic methods.[3] However there has been no report on the reaction of sulfenylating agents with dianions. The regioselective sulfenylation of dianions of 1,3-dicarbonyl compounds would provide a facile synthetic method for ketones or esters functionalized regioselectively by modification of the sulfur group.

Initially, sulfenylation reactions of dianions derived from β-keto esters were investigated, employing various bases and sulfenylating agents.

The dianion IIa of methyl acetoacetate (Ia) was prepared according to the general method[5e] for the formation of dianions with one equivalent each of sodium hydride and butyl lithium or two equivalents of lithium diisopropylamide, quenched with a tetrahydrofuran (THF) or HMPA solution of a readily available sulfenylating agent such as diphenyl disulfide, phenylsulfenyl chloride[10] or phenyl benzenethiosulfonate,[11] initially at 0° and subsequently allowed to warm to room temperature.

The dianion IIa prepared from Ia with sodium hydride (1.2 eq) and butyl lithium (1.2 eq) was reacted with one or two equivalents of diphenyl disulfide at 0° for 1.5 hr then at room temperature for 2 hr to give methyl 4-phenylthioacetoacetate (IIIa) in 72 or 74% yield, respectively.



Ia: R=OCH_3
Ib: R=OCH_2CH_3
Ic: R=$N(CH_3)_2$

IIa: R=OCH_3
IIb: R=OCH_2CH_3
IIc: R=$N(CH_3)_2$

IIIa: R=OCH_3
IIIb: R=OCH_2CH_3
IIIc: R=$N(CH_3)_2$

Chart 1

The dianion IIa was also prepared by treatment of Ia with two equivalents of lithium diisopropylamide. Addition of one or two equivalents of diphenyl disulfide to the dianion thus obtained gave IIIa in 78 or 71% yield, respectively.

The nuclear magnetic resonance (NMR) spectrum of IIIa has a two-proton singlet at δ 3.50 due to the C_4 methylene protons. The absence of a three-proton singlet at *ca.* δ 2.0 confirmed that sulfenylation occurred exclusively at the γ carbon.

In general it is well known that the use of HMPA–THF in the sulfenylation of ketones results in an enhanced rate of sulfenylation and an improved product yield.[4f]

In this case, however, HMPA–THF did not increase the yields, as shown in Table I.

In the sulfenylation of ketones, proton transfer from the initially formed sulfenylated material to the unreacted enolate occurred during the reaction (Chart 2), so that two equivalents of bases and diphenyl disulfide were needed to complete the reaction.[4f] To confirm that proton transfer occurred as depicted in Chart 2 in the sulfenylation reaction of the dianion II, the reaction was examined in the presence of excess base.

However the presence of excess base (3.6 eq of lithium diisopropylamide) did not cause any increase of product yield (68%) in the above reaction, as shown in Table I.

This indicates that proton transfer as shown in Chart 2 did not occur in the sulfenylation of the dianion II with diphenyl disulfide.

Reactions of the dianion IIa with other sulfenylating agents such as phenyl benzenethiosulfonate and phenylsulfenyl chloride were carried out as described above to give IIIa, methyl 2-phenylthioacetoacetate (IV), and methyl 2,2-bisphenylthioacetoacetate (V) in rather low yields, as summarized in Table II. The use of phenyl benzenethiosulfonate

10) W.H. Mueller and P.E. Butler, *J. Am. Chem. Soc.*, **90**, 2075 (1968); P.B. Hopkins and P.L. Fuchs, *J. Org. Chem.*, **43**, 1208 (1978).
11) H.J. Shine, M. Rahman, H. Seeger, and G.S. Wu, *J. Org. Chem.*, **32**, 1901 (1967).

Table I. Sulfenylation of the Dianions II with Diphenyl Disulfide

R	Base	eq	Solvent	PhSSPh eq	Yield (%)
OCH_3	NaH	1.2	THF	1.0	72
	n-BuLi	1.2			
			THF	2.0	74
			THF–HMPA	1.0	68
	$LiN(iso\text{-}Pr)_2$	2.4	THF	1.0	78
			THF	2.0	71
			THF–HMPA	1.0	73
	$LiN(iso\text{-}Pr)_2$	3.6	THF	1.0	68
OCH_2CH_3	NaH	1.2	THF	1.0	65
	n-BuLi	1.2			
	$LiN(iso\text{-}Pr)_2$	2.4	THF	1.0	64
$N(CH_3)_2$	NaH	1.2	THF	1.0	52
	n-BuLi	1.2			
	$LiN(iso\text{-}Pr)_2$	2.4	THF	1.0	52

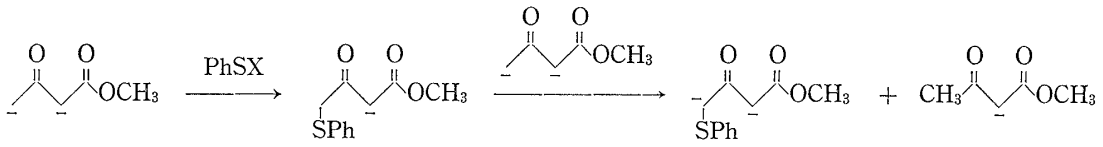
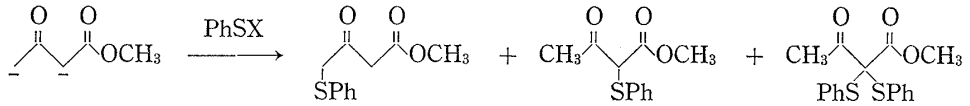


Chart 2

and phenylsulfenyl chloride as sulfenylating agents resulted in reduced yields and lower regioselectivity.



IIIa IV V

Chart 3

Table II. Sulfenylation of the Dianion IIa with PhSX

PhSX X	Base	eq	Yield (%) IIIa	IV	V
SO_2Ph	NaH	1.2	26	33	—
	n-BuLi	1.2			
	$LiN(iso\text{-}Pr)_2$	2.4	37	—	—
Cl	NaH	1.2	35	—	—
	n-BuLi	1.2			
	$LiN(iso\text{-}Pr)_2$	2.4	8	—	4

IIa was reacted with 1.0 eq of PhSX in THF at 0° for 2 hr.

The dianion IIb derived from ethyl acetoacetate (Ib) by treating with sodium hydride (1 eq)–butyl lithium (1 eq) and lithium diisopropylamide (2 eq) was sulfenylated in the same manner with diphenyl disulfide at 0° for 1.5 hr then at room temperature 2 hr to afford ethyl 4-phenylthioacetoacetate (IIIb) in 65% and 64% yields, respectively.

Regioselective sulfenylation of the dianion (VII) of the γ-alkylated β-keto ester, methyl 3-oxovalerate (VI), was investigated with diphenyl disulfide under the reaction conditions given in Table III to produce methyl 3-oxo-4-phenylthiovalerate (VIII) in moderate yields as summarized in Table III.

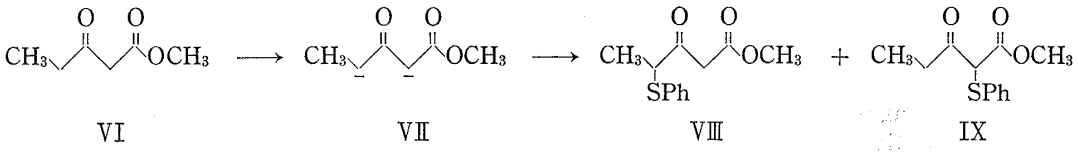
Table III. Sulfenylation of the Dianion VII with Diphenyl Disulfide

Base	eq	Solvent	Yield of VIII (%)
NaH	1.2	THF	72
n-BuLi	1.2		
		THF–HMPA	63
$LiN(iso\text{-}Pr)_2$	2.4	THF	47
		THF–HMPA	42

VII was reacted with 1.0 eq of diphenyl disulfide in THF at 0° for 1.5 hr then at room temperature for 2.0 hr.

In the NMR spectrum of VIII, the C_4 methine proton α to the thio group appears at δ 3.85 as a one-proton quartet and the C_5 methyl protons at δ 1.36 as a three-proton doublet.

The use of phenyl benzenethiosulfonate and phenylsulfenyl chloride in this reaction also resulted in a marked decrease of the product yields, and the employment of phenylsulfenyl chloride made the reaction less regioselective, as shown in Table IV.



VI VII VIII IX

Chart 4

Table IV. Sulfenylation of the Dianion VII with PhSX

PhSX X	Base	eq	Yield (%) VIII	IX
SO_2Ph	NaH	1.2	39	—
	n-BuLi	1.2		
	$LiN(iso\text{-}Pr)_2$	2.4	50	—
Cl	NaH	1.2	30	33
	n-BuLi	1.2		
	$LiN(iso\text{-}Pr)_2$	2.4	17	—

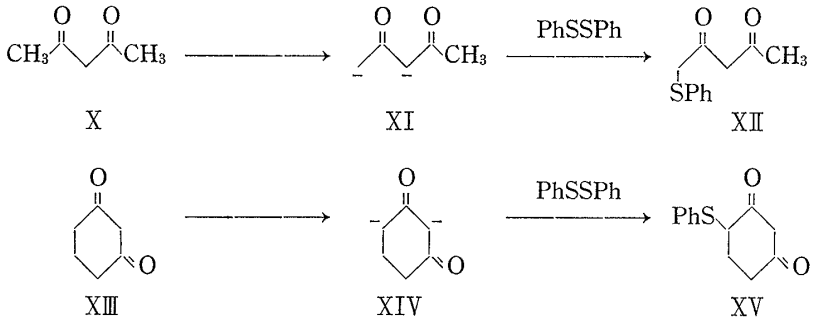
VII was reacted with 1.0 eq of PhSX in THF at 0° for 2 hr.

Thus it appeared that the optimum reaction conditions for γ-sulfenylation of acetoacetic acid esters involve reaction of the dianions with one equivalent of diphenyl disulfide at 0° and then at room temperature for several hours with sodium hydride–butyl lithium or lithium diisopropylamide as bases.

The dianion IIc of the β-ketoamide, N,N-dimethylacetoacetamide (Ic), was also prepared in the same manner according to the general procedure[6] for the formation of dianions and reacted with diphenyl disulfide at 0° for 1.5 hr then at room temperature for 2 hr to give N,N-dimethyl-3-oxo-4-phenylthiobutylamide (IIIc) in 52% yield. In the NMR spectrum of IIIc, the C_4 methylene protons α to the thio group appear at δ 3.50 as a two-proton singlet without methyl protons at δ *ca.* 2.0.

1,3-Diketones were converted to their dianions in the same way either by treatment with one equivalent each of sodium hydride and butyl lithium or by treatment with two equivalents of lithium diisopropylamide.

The dianion XI of 2,4-pentadione (X) was reacted with diphenyl disulfide in THF at 0° for 1.5 hr then warmed to room temperature to produce 1-phenylthio-2,4-pentadione (XII) in 76—79% yield. In the NMR spectrum of XII, the methylene protons α to the thio group



X XI XII XIII XIV XV

Chart 5

appear at δ 3.50 as a two-proton singlet and one of the three-proton singlets due to methyl groups of X is absent.

The dianion XIV of 1,3-cyclohexadione (XIII) was subjected to sulfenylation with diphenyl disulfide at 0° to afford 4-phenylthio-1,3-cyclohexadione (XV) in 47—61% yield. Exceptionally, this reaction required the presence of HMPA together with THF because of the low solubility of the starting material (XIII).

Experimental

General——Melting point was determined on a Yanagimoto melting point apparatus and is uncorrected. Thin-layer or preparative thick layer plates were made of E. Merck Silicagel 60PF-254 activated by drying at 140° for 3.5 hr.

Infrared (IR) spectra were obtained in the indicated state on a Hitachi 215 spectrometer. NMR spectra were determined in the indicated solvent on a Hitachi R-24B high resolution NMR spectrometer; chemical shifts are given in ppm from $(CH_3)_4Si$. Splitting patterns are designated as s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra (MS) were taken on a Hitachi RMU-6MG or RMU-7M spectrometer.

Reaction of Sulfenylating Agents with the Dianion IIa of Methyl Acetoacetate (Ia)——General Procedure: Method A (Sodium Hydride–Butyl Lithium): A dry 25 ml two-necked flask equipped with a septum inlet and magnetic stirrer containing 122 mg (2.6 mmol) of sodium hydride (50% oily, washed with hexane to remove mineral oil) was flushed with nitrogen and maintained under a positive pressure of nitrogen.

Freshly distilled anhydrous THF (3 ml) was added, followed by the dropwise addition (*via* a syringe) of 0.2 ml (1.7 mmol) of methyl acetoacetate (Ia) under ice cooling. The reaction mixture was stirred at room temperature for 10 min to permit formation of the monoanion (white precipitate), then 1.4 ml (2.0 mmol) of 1.5 M butyl lithium hexane solution was added dropwise at −15°, and the resulting solution was stirred for 45 min. The white precipitate of the monoanion disappeared immediately upon addition of the butyl lithium. A solution of 1.7 mmol of sulfenylating agents in 2 ml of THF was added immediately (when HMPA was employed in this reaction, 1 ml of HMPA was added at this step), and the reaction mixture was stirred at 0° for 1.5 hr then at room temperature for 2 hr. The reaction was quenched by the addition of 10% aqueous HCl and the product was extracted with ether. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residual oil was subjected to preparative thin-layer chromatography (TLC) (benzene) to give methyl 4-phenylthioacetoacetate (IIIa) and methyl 2-phenylthioacetoacetate (IV) in the yields given in Tables I and II. IIIa: bp 140° (oil bath) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1740 (ester), 1720 (C=O), 1650, 1620, 1580 (phenyl). NMR (CCl_4) δ: 3.50 (2H, s, CH_2–S), 3.64 (3H, s, CO_2CH_3), 3.70, 4.60, and 5.10 (2H, s, s, and s, $\underset{\underset{O}{\|}}{C}$–$CH_2$ and HO–C=C<u>H</u>CO_2Me), 7.00—7.50 (5H, phenyl). MS *m/e*: 224 (M^+). *Anal.* Calcd. for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.40; S, 14.27. Found: C, 58.72; H, 5.24; S, 14.20. IV: bp 135° (oil bath) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1720 (C=O), 1625 (C=C–OH), 1590 (phenyl). NMR (CCl_4) δ: 2.28 (3H, s, $CH_3\underset{\underset{O}{\|}}{C}$), 3.70 (3H, s, CO_2CH_3), 6.90—7.60 (6H, phenyl and HO–C=C). MS *m/e*: 224 (M^+). *Anal.* Calcd. for $C_{11}H_{12}O_3S$: C, 58.92; H, 5.40; S, 14.27. Found: C, 58.75; H, 5.40; S, 13.91.

Method B (Lithium Diisopropylamide): A solution of 0.57 ml (4.1 mmol) of diisopropylamine in 3 ml of freshly distilled anhydrous THF in a dry 25 ml two-necked flask equipped with a septum inlet was cooled to −15° and 2.7 ml (4.1 mmol) of 1.5 M butyl lithium hexane solution was added under a positive pressure of nitrogen. After stirring at −15° for 30 min, a solution of 0.2 ml (1.7 mmol) of Ia in 2 ml of THF was added dropwise and the mixture was stirred at −10° for 1 hr, then a solution of 1.7 mmol of sulfenylating

agent in 2 ml of THF was added (when HMPA was employed in this reaction, 1 ml of HMPA was added at this stage). The reaction mixture was stirred at 0° for 1.5 hr then at room temperature for 2 hr. It was quenched by the addition of 10% aqueous HCl. The product was isolated by extraction with ether. After drying the combined organic extracts, the solvents were removed under reduced pressure and the crude product was subjected to preparative TLC (benzene) to give IIIa and methyl 2,2-bisphenylthioacetoacetate (V) in the yields listed in Tables I and II. V: mp 74—75° (colorless prisms from hexane–CCl_4). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester), 1715 (ketone). NMR (CCl_4) δ: 2.22 (3H, s, $CH_3\overset{O}{\overset{\|}{C}}$), 3.52 (3H, s, CO_2CH_3), 7.00—7.70 (10H, $2C_6H_5$). MS *m/e*: 332 (M^+). *Anal.* Calcd. for $C_{17}H_{16}O_3S_2$: C, 61.41; H, 4.85; S, 19.30. Found: C, 61.36; H, 4.76; S, 19.45.

Ethyl 4-Phenylthioacetoacetate (IIIb)——Method A: A solution of 335 mg (1.5 mmol) of diphenyl disulfide in 2 ml of THF was added to 2 ml of THF containing the dianion IIb, prepared from 200 mg (1.5 mmol) of ethyl acetoacetate (Ib) with 111 mg (2.3 mmol) of 50% oily sodium hydride and 1.3 ml (2.0 mmol) of 1.5 M butyl lithium hexane solution. The reaction mixture was stirred at 0° for 1.5 hr, warmed to room temperature, stirred for a further 2 hr, and then worked up as described above. The crude product was subjected to preparative TLC (benzene) to give 237 mg (65% yield) of IIIb as a colorless oil of bp 140° (oil bath) (1 mmHg) [lit.[12] bp 140—150° (1 mmHg)]. IR ν_{max}^{film} cm^{-1}: 1740 (ester), 1710 (ketone), 1650, 1620, 1580 (phenyl). NMR (CCl_4) δ: 1.22 (3H, t, $J=7$ Hz, $CO_2CH_2C\underline{H}_3$), 3.50 (2H, s, $\overset{O}{\overset{\|}{C}}-CH_2-CO_2$), 3.70 (2H, s, CH_2S), 4.06 (2H, q, $J=7$ Hz, CO_2CH_2), 7.00—7.40 (5H, C_6H_5). MS *m/e*: 238 (M^+). *Anal.* Calcd. for $C_{12}H_{14}O_3S$: C, 60.50; H, 5.92; S, 13.43. Found: C, 60.43; H, 5.89; S, 13.13.

Method B: The dianion IIb was prepared by treating 200 mg (1.5 mmol) of Ib in 2 ml of THF with lithium diisopropylamide (3.7 mmol) at −15°. A solution of 335 mg (1.5 mmol) of diphenyl disulfide in 2 ml of THF was added to the above mixture. The reaction mixture was stirred at 0° for 1.5 hr then at room temperature for 2 hr, and worked up in the usual way to give 235 mg of IIIb in 64% yield.

N,N-Dimethyl-4-phenylthioacetoacetamide (IIIc)——Method A: A solution of 338 mg (1.6 mmol) of diphenyl disulfide in 2 ml of THF was added at 0° to the dianion IIb prepared from 200 mg (1.6 mmol) of N,N-dimethylacetoacetamide (Ic) in 4 ml of THF with 112 mg (2.3 mmol) of 50% oily sodium hydride and 1.24 ml (1.9 mmol) of 1.5 M butyl lithium hexane solution. The reaction mixture was stirred at 0° for 1.5 hr then at room temperature for a further 2 hr, and worked up as described above. The crude product was subjected to preparative TLC (benzene–ether 3:2) to afford 190 mg (52% yield) of IIIc as a viscous oil of bp 170° (oil bath) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1720 (ketone), 1650 (amide), 1605 (phenyl). NMR (CCl_4) δ: 2.88 (6H, s, $N(CH_3)_2$), 3.50 (2H, s, CH_2S), 3.78, 5.22, and 6.20 (2H, s, s, and bs, $\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}$ and $C\underline{H}=C-O\underline{H}$), 7.0—7.4 (5H, phenyl). MS *m/e*: 237 (M^+). *Anal.* Calcd. for $C_{12}H_{15}NO_2S$: C, 60.75; H, 6.37; N, 5.90; S, 13.49. Found: C, 60.61; H, 6.38; N, 6.11, S, 13.09.

Method B: A solution of 338 mg (1.6 mmol) of diphenyl disulfide in 2 ml of THF was added at 0° to the dianion IIc prepared from 200 mg (1.6 mmol) of Ic in 5 ml of THF with lithium diisoproplyamide (3.7 mmol). After stirring at 0° for 1.5 hr then at room temperature for 2 hr, the reaction mixture was worked up in the usual way to give 191 mg of IIIc in 52% yield.

Reaction of Sulfenylating Agents with the Dianion VII of Methyl 3-Oxovalerate (VI)——Method A: A solution of 200 mg (1.5 mmol) of VI in 2 ml of THF was added at 0° to a suspention of 110 mg (2.3 mmol) of 50% oily sodium hydride in 2 ml of THF and the mixture was stirred at room temperature for 10 min, then 1.2 ml (1.8 mmol) of 1.5 M butyl lithium hexane solution was added dropwise at 0°. After stirring at 0° for 45 min, a solution of sulfenylating agent (1.5 mmol) in 1 ml of THF (and 1 ml of HMPA) was added. The reaction mixture was stirred at 0° for 1.5 hr, warmed to room temperature, and stirred for a further 2 hr. After work-up as described above, the crude product obtained was subjected to preparative TLC (benzene) to afford methyl 3-oxo-4-phenylthiovalerate (VIII) and methyl 3-oxo-2-phenylthiovalerate (IX) in the yields listed in Tables III and IV. VIII: bp 140° (oil bath) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1742 (ester), 1710 (ketone 1650, 1620, 1580 (phenyl). NMR (CCl_4) δ: 1.36 (3H, d, $J=7$ Hz, CH_3), 3.60 (2H, s, $CH_2\overset{O}{\overset{\|}{C}}-$). 3.66 (3H, s,), CO_2CH_3), 3.85 (1H, q, $J=7$ Hz, $C\underline{H}-S$), 7.10—7.45 (5H, phenyl). MS *m/e*: 238 (M^+). *Anal.* Calcd. for $C_{12}H_{14}O_3S$: C, 60.50; H, 5.92; S, 13.43. Found: C, 60.68; H, 6.08; S, 13.17. IX: bp 135° (oil bath) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1740 (ester), 1650, 1600 (phenyl). NMR (CCl_4) δ: 1.15 (3H, t, $J=7$ Hz, CH_3), 2.33 (1H, s, HO–C=C), 2.75 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.72 (3H, s, CO_2CH_3), 6.94—7.43 (5H, phenyl). MS *m/e*: 238 (M^+). *Anal.* Calcd. for $C_{12}H_{14}O_3S$: C, 60.50; H, 5.92; S, 13.43. Found: C, 60.40; H, 5.98; S, 13.60.

Method B: Compound VI (200 mg, 1.5 mmol) in 2 ml of THF was added dropwise at −15° to a solu-

11) F.A. Trofimov, N.G. Tsyshkova, A.N. Grinev, and K.S. Shadurskii, *Khim. Farm. Zh.*, 3, 259 (1969) [*C.A.*, 72, 90181*y* (1970)].

tion of lithium diisopropylamide (3.7 mmol), prepared from 0.52 ml of diisopropylamine and 2.46 ml of 1.5 M butyl lithium hexane solution, in 2 ml of THF. After stirring at −15° for 1 hr, a solution of sulfenylating agent (1.5 mmol) in 2 ml of THF (and 1 ml of HMPA) was added. The reaction mixture was stirred at 0° for 1.5 hr then at room temperature for 2 hr, and worked up as described above to give VIII in the yields shown in Table III and IV.

1-Phenylthio-2,4-pentadione (XII)——Method A: To dianion XI prepared from 200 mg (2.0 mmol) of acetylacetone (X) in 3 ml of THF with 144 mg (3.0 mmol) of 50% oily sodium hydride and 1.6 ml (2.4 mmol) of 1.5 M butyl lithium hexane solution, was added a solution of 436 mg (2.0 mmol) of diphenyl disulfide in 2 ml of THF at 0°. The reaction mixture was stirred at 0° for 1.5 hr then at room temperature for 2 hr. The usual work-up, followed by preparative TLC (benzene) gave 316 mg (76% yield) of XII, bp 132° (oil bath) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1725, 1705 (C=O), 1610 (phenyl). NMR (CCl_4) δ: 1.94 (3H, s, $\overset{O}{\overset{\|}{C}}-CH_3$), 3.50 (2H, s, CH_2–S), 3.58, 3.63, and 5.63 (2H, s,s, and s, $\overset{O}{\overset{\|}{C}}-C\underline{H}_2-\overset{O}{\overset{\|}{C}}$ and $\underline{H}O-C-C\underline{H}-$), 7.05—7.35 (5H, phenyl). MS *m/e*: 208 (M^+). *Anal.* Calcd. for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.14; H, 5.80; S, 15.39.

Method B: A solution of 436 mg (2.0 mmol) of diphenyl disulfide in 2 ml of THF was added at −15° to the dianion XI prepared from 200 mg (2.0 mmol) of X in 3 ml of THF with lithium diisopropylamide (4.8 mmol). The reaction was carried out as described above gave 330 mg of XII in 79% yield.

4-Phenylthio-1,3-cyclohexadione (XV)——Method A: The dianion XIV was prepared from 400 mg (3.6 mmol) of 1,3-cyclohexadione (XIII) in 5 ml of HMPA and 18 ml of THF by treatment with 207 mg (4.3 mmol) of 50% oily sodium hydride and 2.9 ml (4.4 mmol) of 1.5 M butyl lithium hexane solution. A solution of 942 mg (4.3 mmol) of diphenyl disulfide in 3 ml of THF was added at −20° and the reaction mixture was stirred at −20° for 2 hr then at 0° for 3 hr. The usual work-up followed by preparative TLC (ether–benzene 4: 1) gave 479 mg (61% yield) of XV as a viscous oil of bp 170° (oil bath) (1 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O), 1590 (phenyl). NMR ($CDCl_3$) δ: 2.00—2.80 (4H, m), 3.70—4.00 (1H, m, CH–S), 5.53 (1H, s, C=CH), 7.10—7.70 (5H, C_6H_5), 8.20 (1H, bs, HO–C=C). Exact mass determination: 220.0566 (Calcd. for $C_{12}H_{12}O_2S$, 220.0535).

Method B: A solution of 942 mg (4.3 mmol) of diphenyl disulfide in 3 ml of THF was added at −20° to the dianion XIV prepared from 400 mg (3.6 mmol) of XIII in 5 ml of HMPA and 3 ml of THF with lithium diisopropylamide (8.6 mmol). The reaction mixture was stirred at −20° for 2 hr then at 0° for 3 hr and worked up as described above to give 370 mg of XV in 47% yield.