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NEW GENERAL SYNTHESES FOR SYMMETRICAL AND UNSYMMETRICAL ORGANIC SULPHIDES

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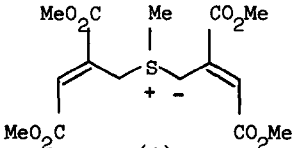
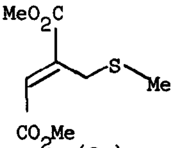
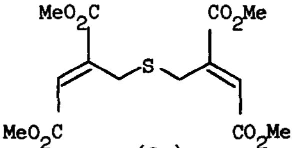
During our recent investigations[1] that centred around a stereospecific sulphonium ylide - salt coupling reaction, and the sigmatropic rearrangement of the bisallylic sulphonium ylide (1) and related sulphides, we had occasion to synthesize the sulphides (2a) and (3a).



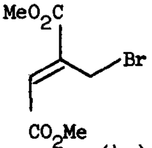
(1)



(2a)



(3a)



(4a)

The most widely used general method for the synthesis of symmetrical and unsymmetrical organic sulphides comprises the reaction of thiolate anions with the appropriate halogen compounds under a variety of reaction conditions.[2] Other general methods for the synthesis of unsymmetrical sulphides include the base-catalyzed reaction of thiols with dialkyl carbonates[3] and phosphate esters,[4] a novel condensation of alcohols with thiols utilizing either aminophosphonium salts[5] or dicyclohexyl carbodiimide.[6]

Symmetrical sulphides are furthermore commonly synthesized by treatment of two moles of the appropriate organic halide with sodium sulphide under a variety of reaction conditions.[7,8,9] Direct treatment of a substrate molecule containing one or more enolic hydrogens with sulphur dichloride may also lead to the corresponding symmetrical sulphides.[10,11]

Since the easily accessible but base-sensitive bromoester (4a) was an obvious choice as starting material for the synthesis of the sulphides (2a) and (3a), utilization of strongly basic thiolate anions was ruled out. The unsymmetrical sulphide (2a) could, however, conveniently be synthesized in high yield under essentially non-basic reaction conditions by treatment of the bromoester (4a) with an excess of dimethyl sulphide. This method was subsequently developed as a general and high yield synthesis for a variety of unsymmetrical alkyl and alkenyl sulphides.

Mixtures of the appropriate halogen compounds (4,a-i) and a four molar excess of dimethyl sulphide were heated in a pyrex pressure vessel at 60°. Trimethylsulphonium bromide, which crystallized from the reaction mixture, was removed by filtration. Distillation of the residues from the filtrates gave the pure sulphides (2, a-i) in excellent yields (see table I).* Only in the syntheses of (2f) and (2g) did the utilization of dimethyl sulphoxide as solvent appear to be

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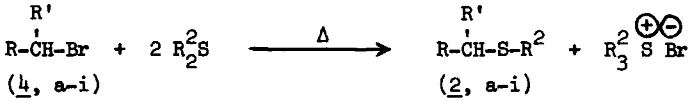
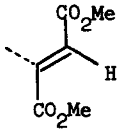
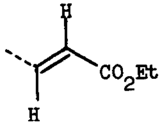
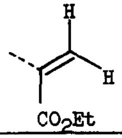
* All new compounds exhibited satisfactory analytical and spectral data.

advantageous. Even the thioacetal ($\underline{2}$i) could be synthesized in reasonable yield by heating methylene bromide with an excess of dimethyl sulphide (molar ratio 1:12). Pertinent to this general synthesis is the observation made by Hunsberger and Tien[12] that the sulphide ($\underline{2}$h) and trimethylsulphonium bromide were formed as undesirable by-products during Kornblum oxidation of ethyl bromoacetate with dimethyl sulphoxide.

TABLE I



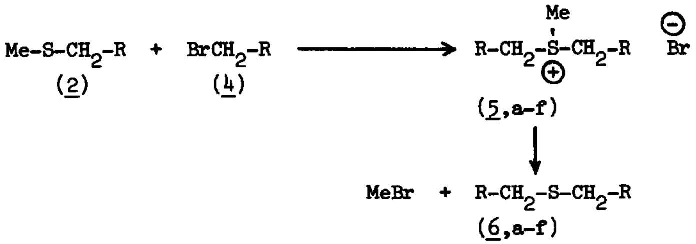
$$\underset{(\underline{4},\ a\text{-}i)}{\overset{R'}{R\text{-}CH\text{-}Br}} + 2\ R^2_2S \xrightarrow{\Delta} \underset{(\underline{2},\ a\text{-}i)}{\overset{R'}{R\text{-}CH\text{-}S\text{-}R^2}} + R^2_3\overset{\oplus}{S}\ \overset{\ominus}{Br}$$

($\underline{4}$)	R	R^2	R^1	Temp.	Time hrs.	($\underline{2}$)	Yield** %
(a)	H	Me		60°	12	(a)	79
(b)	H	Me		60°	48	(b)	94
(c)	H	Me		60°	24	(c)	91
(d)	CO_2Et	Me	CO_2Et	60°	96	(d)	83
(e)	H	Et	CO_2Et	60°	72	(e)	95
(f)	H	Me	CO-Ph	60°	12	(f)	63
(g)	H	Me	Ph	60°	24	(g)	100
(h)	H	Me	CO_2Et	60°	72	(h)	89
(i)	H	Me	S-Me	120°	24	(i)	65

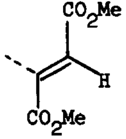
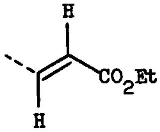
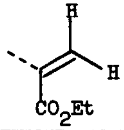
** Isolated yields. No attempts were made to optimize yields.

As an extension of this investigation a general method was elaborated for the synthesis of a number of symmetrical dialkyl and dialkenyl sulphides (6,a-f) under non-basic reaction conditions. This method is based on the known labile character of sulphonium halides in solution,[13] and is carried out simply by heating a mixture of an appropriate unsymmetrical sulphide and the corresponding alkyl or alkenyl halide in a 1:1 molar ratio without solvent. It is believed that the corresponding sulphonium halides (5,a-f) are formed as intermediates under these circumstances. Demethylation[14] of the sulphonium ions by the bromide ions completes the synthesis (see table II) By utilizing this general method, the symmetrical sulphide (6a) could be synthesized in reasonable yield, while no yield was obtained after treatment of the bromoester (4a) with sodium sulphide under standard reaction conditions.[7,8]

TABLE II



$$\underset{(2)}{Me\text{-}S\text{-}CH_2\text{-}R} + \underset{(4)}{BrCH_2\text{-}R} \longrightarrow \underset{(5,a\text{-}f)}{R\text{-}CH_2\text{-}\overset{Me}{\underset{\oplus}{S}}\text{-}CH_2\text{-}R \quad \overset{\ominus}{Br}} \downarrow MeBr + \underset{(6,a\text{-}f)}{R\text{-}CH_2\text{-}S\text{-}CH_2\text{-}R}$$

(2)	R	(4)	Temp.	Time days	(6)	Yield* %
(a)		(a)	60°	7	(a)	66
(b)		(b)	60°	7	(b)	43
(c)		(c)	60°	10	(c)	48
(f)	CO-Ph	(f)	20°	1	(d)	61
(g)	Ph	(g)	80°	5	(e)	75**
(h)	CO_2Et	(h)	60°	10	(f)	76

* Isolated yields. No attempts were made to optimize yields.

** Yield determined by glc.

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REFERENCES

1. (a) C.F. Garbers, A.J.H. Labuschagne, C.J. Meyer, and D.F. Schneider, J.C.S. Perkin I, 1973, 20
   (b) A.J.H. Labuschagne, C.J. Meyer, H.S.C. Spies, and D.F. Schneider, ibid., 1975, 2129.
2. (a) A.W. Herriott and D. Picker, Synthesis, 1975, 447;
   (b) E.G. Wilson Jr. and J.G. Riley, Tetrahedron Letters, 1972, 379.
3. Y. Tamura, T. Saito, H. Ishibashi, and M. Ikeda, Synthesis, 1975, 641.
4. P. Savignag and P. Controt, Synthesis, 1974, 282.
5. Y. Tanigawa, H. Kanamaru, and S.-I. Murahashi, Tetrahedron Letters, 1975, 4655.
6. E. Vowinkel and C. Wolff, Chem. Ber., 1974, 107, 496.
7. L.A. Paquette, R.E. Wingard Jr., J.C. Phillips, G.L. Thompson, L.K. Read, and J. Clardy, J. Amer. Chem. Soc., 1971, 93, 4508.
8. H. Müller, Angew. Chem. Int. Ed., 1971, 10, 652.
9. D. Landini and F. Rolla, Synthesis, 1974, 565.
10. J.J. D'Amico and W.E. Dahl, J. Org. Chem., 1975, 40, 1224.
11. S.K. Gupta, J. Org. Chem., 1974, 39, 1944.
12. I.M. Hunsberger and J.M. Tien, Chem. and Ind., 1959, 88.
13. (a) E.J. Corey and M. Jantelat, Tetrahedron Letters, 1968, 5787;
    (b) P. Mamalis, J. Chem. Soc. (C), 1960, 4747;
    (c) F. Krollpfeiffer and H. Hartmann, Chem. Ber., 1950, 83, 90.
14. J.E. Baldwin, J.A. Walker, A.J.H. Labuschagne, and D.F. Schneider, Chem. Comm., 1971, 1382.