Tetrahedron Letters No.41, pp. 3551-3554, 1970. Pergamon Press. Printed in Great Britain.

A NEW SYNTHESIS OF UNSYMMETRICAL DISULFIDES[1]

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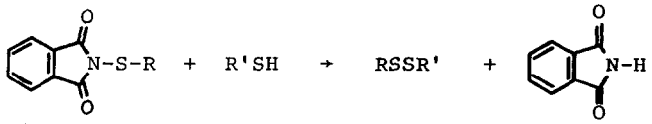
(Received in USA 15 June 1970; received in UK for publication 30 July 1970)

The synthesis of pure unsymmetrical disulfides is often a difficult problem in organo-sulfur chemistry. While several methods of preparation are known[3], no one technique suffices for all synthetic situations. We wish to report a method for obtaining unsymmetrical disulfides which, with the exception of diaryl systems, is rapid, clean and proceeds in excellent yield.

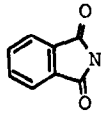
When thiophthalimides (1)[4] are treated with thiols, a wide variety of aralkyl and dialkyl disulfides can be generated in yields ranging from 71-92% (Table I). Only in a few cases (6 - 8) were even traces (ca. 2%) of the



1 2

symmetrical disulfide by-products observed (tlc,vpc) in the reaction mixture. The cysteine and glutathione derivatives (8, 9) are of special interest as this method may be applicable to the construction of disulfide-containing molecules of biological significance[5]. It is conceivable that the phthalimide group may serve both as a protective and an activating group in such syntheses. Further work in this area is in progress.

An exception to the generality of the reaction occurs where R and R' are aryl substituents. For example, efforts to obtain p-fluorophenyl tolyl (11) and phenyl tolyl (12) disulfides result in each case in a mixture of the three possible disulfides (1:2:1 and 1:5:1 respectively). Rapid mercaptan-disulfide interchange would not be unexpected in those systems where there is both a nucleophilic thiol and a disulfide in which each arythio- half can serve as an effective leaving group.



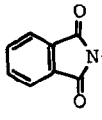
$$\text{N-S-R} + \text{R'SH} \rightarrow \text{RSSR} + \text{RSSR'} + \text{R'SSR'} + \underline{2}$$

11 R= p$CH_3C_6H_4$-; R'= pFC_6H_4-

12 R= C_6H_5-; R'= p$CH_3C_6H_4$-

A typical experimental procedure is as follows. Thiophthalimide (0.01 mole) and thiol (0.01 mole) are refluxed in 40 ml of benzene (1 - 20 hr). After filtering the phthalimide (ca. 90%), the product is obtained by crystallizing (or distilling) the concentrated filtrate. Monitoring the reaction by tlc or vpc ensures optimum reaction time.

This reaction also provides a useful method for the preparation of trisulfides. Addition of benzyl hydrodisulfide to benzyl thiophthalimide affords the corresponding trisulfide in 98% yield.



$$\text{N-S-}CH_2C_6H_5 + C_6H_5CH_2SSH \rightarrow C_6H_5CH_2SSSCH_2C_6H_5 + \underline{2}$$

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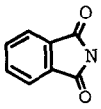
Thus the method is versatile and has the particular advantage that precursor thiophthalimides are easy to prepare and have unlimited shelf stability.

TABLE I

Preparation of Disulfides and Trisulfides



→ RSSR' + 2

compound	R	R'	% yield	Reaction Time(hr)[a,b]	[bp] or mp °C [c]	lit [bp] or mp
3	$C_6H_5CH_2$-	$C_6H_5CH_2$-	86	20	70.5-71	71.5[6]
4	$C_6H_5CH_2$-	p$BrC_6H_4CH_2$-	80	4	49-52	54-55[7]
5	C_6H_5-	$CH_3CH_2CH_2$-	71	18	[87-93/ 0.1mm]	-
6	$(CH_3)_2CH$-	p$CH_3C_6H_4$-	88	17	[76-80/ 0.01mm]	[93-94/[8] 0.1mm]
7	$CH_3O_2CCH_2$-	C_6H_{11}-	91	12	[94-98/ 0.005mm]	-
8	$C_6H_5CH_2$-	L-Cy-HCl	89	16[d]	178 dec.	175-180[9]
9	$C_6H_5CH_2$-	Glu-Cy-Gly	92	1[d]	206-207 dec.	-
10	$C_6H_5CH_2$-	$C_6H_5CH_2S$-	98	20[e]	47-48.5	47[10]
11	p$CH_3C_6H_4$-	pFC_6H_4-	f	1	-	-
12	C_6H_5-	p$CH_3C_6H_4$-	e,g	2	-	-

a) benzene solvent at reflux unless otherwise noted; b) in most cases reaction conditions were not optimized; c) satisfactory analyses or mass spectra and purity criteria (tlc and/or vpc) were obtained for all new compounds; d) ethanol solvent; e) benzene, room temperature; f) mixtures of disulfides (1:2:1); g) mixture of disulfides (1:5:1).

References

1. a. Organic Sulfur Chemistry. Part VIII. Part VII, submitted for publication; b. Abstracted from the M.Sc. thesis of B. A. Orwig, McGill University, 1970.

2. a. NRCC Bursary Holder 1969-70; b. NRCC Studentship Holder 1968-70; c. Visiting Scientist, Bishops University, Lennoxville, Quebec.

3. I.B. Douglass, T.T. Martin and R.J. Adder, J. Org. Chem., 16, 1297 (1951); R.G. Hiskey, F.I. Carroll, R.M. Babb, R.M. Bledsoe, R.T. Pückett, and B.W. Roberts, J. Org. Chem., 26, 1152 (1961); L. Field, H. Harle, T.C. Owen and A. Ferretti, J. Org. Chem., 29, 1632 (1964); T. Mukaiyama and K. Takahashi, Tetrahedron Letters, 5907 (1968); K.S. Boustany and A.B. Sullivan, Tetrahedron Letters, this issue.

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

5. E. Schröder and K. Lübke, "The Peptides", Vol. II, Academic Press, New York, N. Y., 1965.

6. F.M. McMillan and J.A. King, J. Am. Chem. Soc., 70, 4143 (1948).

7. J.G. Gleason, Ph.D. Thesis, McGill University, 1970.

8. J.L. Kice and E.H. Morkved, J. Am. Chem. Soc., 86, 2270 (1964).

9. H. Bretschneider and W. Klötzer, Monatsh. Chem., 81, 589 (1950).

10. S. Hayashi, M. Furukawa, J. Yamamoto and K. Hamamura, Chem. Pharm. Bull., 15, 1310 (1967).

Acknowledgements

We wish to thank the National Research Council and the Defense Research Board of Canada for support of this work.