SYNTHESIS
COMMUNICATIONS

Concise, complete papers on

- New or improved synthetic methods
- Key intermediates for organic synthesis

Including full experimental and analytical data

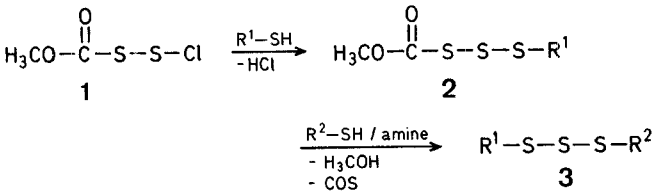
A New Method for the Synthesis of Unsymmetrical Trisulfanes[1]

Andrew W. MOTT, George BARANY*

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, U.S.A.

The biological importance of the sulfur-sulfur bond extends to organic trisulfanes, several of which have been isolated from natural sources[2,3,4]. These include a variety of symmetrical and unsymmetrical trisulfanes from plants in the onion family (genus *Allium*)[3,4]. Although the preparation of symmetrical trisulfanes is straightforward and well documented[5], the synthesis of unsymmetrical trisulfanes is more complex. Previous methods include the reaction of the relatively unstable disulfanyl chlorides with thiols[6], the reaction of sulfenyl chlorides with hydrodisulfanes[7], the reaction of a thiol with an *N*-arylamidothiosulfite[8], and the deoxygenation of dialkylsulfonic thioanhydrides[9]. Somewhat better is the reaction of thiols with phthalimido disulfanes[10,11] but this method has only been applied to the preparation of trisulfanes containing simple alkyl and aryl groups. We now report a widely applicable method for the preparation of unsymmetrical trisulfanes.

By an extension of the method of Brois et al.[12] to prepare unsymmetrical disulfanes, methoxycarbonyldisulfanyl chloride **(1)**[13] was reacted with a variety of thiols to give methoxycarbonyl trisulfanes **(2)** in good yields (Table 1). These were reacted in the presence of an amine catalyst with a second thiol to yield the desired unsymmetrical trisulfane **(3)** (Table 2), the only other products being carbonyl sulfide and methanol.



Triethylamine, the catalyst employed by Brois et al. for the disulfane series, was found to give unsatisfactory results in that considerable disproportionation of the products occurred with formation of both symmetrical and unsymmetrical polysulfanes. *N*-Methylmorpholine was generally found to be the most suitable catalyst except in some of the more reactive systems where the reaction was so rapid (complete in less than 1 h) that a mixture of tri- and di-sulfanes was formed. Disulfanes presumably arise by the thiol displacing carbonyl sulfide, methanol, and sulfur. For these reactive systems aniline or *N,N*-dimethylaniline were found to be better catalysts (Table 2).

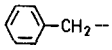
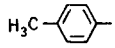
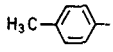
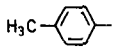
Generally the yields of purified trisulfanes were in the range 50–80% except in two cases where the yields were much lower. The first of these was the reaction of methoxycarbonyl methyl trisulfane **(2a)** with benzyl mercaptan. The crude reaction product contained (by ^{1}H-N.M.R.) a mixture of methyl benzyl disulfane and trisulfane **(3f)** in a ratio of 2:3 from which the pure trisulfane was distilled. When the catalyst was *N,N*-dimethylaniline the reaction was slower (complete in 16 h) but a similar amount of disulfane was formed. The alternative route to benzyl trisulfanes, namely from methoxycarbonyl benzyl trisulfane **(2d)** and a thiol, was better as shown by the synthesis of benzyl 2-propyl tri-

Table 1. Methoxycarbonyl Trisulfanes **2a–g** prepared

Product No.	R^1	Reaction Temp. [°C]	Yield [%]	b.p. [°C]/torr	Molecular Formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm] H_3CO	R^1
2a	H_3C	0°	69	50–51°/0.14	$C_3H_6O_2S_3$ (170.3)	3.95	2.66 (s, 3H)
2b	i-C_3H_7	0°	86	82–85°/0.09	$C_5H_{10}O_2S_3$ (198.3)	3.91	1.38 (d, 6H, J = 6.4 Hz); 3.30 (m, 1H)
2c	H_3C–C$_6$H$_4$–	−78°	~100	–[b]	$C_9H_{10}O_2S_3$ (246.4)	3.82[c]	2.35 (s, 3H); 7.33 (AB, 4H, ν_{AB} = 26.6 Hz, J_{AB} = 8.3 Hz)
2d	C$_6$H$_5$–CH_2–	−78°	~100	–[b]	$C_9H_{10}O_2S_3$ (246.4)	3.91	4.18 (s, 2H); 7.33 (s, 5H)
2e	HO–CH_2–CH_2–	0°	85	95–100°/0.08	$C_4H_8O_3S_3$ (200.3)	3.92	3.13 (t, 2H, J = 5.8 Hz); 4.00 (t, 2H, J = 5.8 Hz)
2f	H_2N–CH_2–CH_2– · HCl	0°	72	m.p. 116–118°[d]	$C_4H_{10}ClNO_2S_3$ (235.8)	3.96	3.29 (br., 4H); 8.4 (br., 3H)[f]
2g	C$_6$H$_5$–C(=O)–	0°	49	m.p. 51–53°[e]	$C_9H_8O_3S_3$ (260.4)	3.93	7.5–8.0 (m, 5H)

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.20, N +0.13, S ±0.18.
[b] Decomposed during an attempted distillation (0.05 torr).
[c] H_3CO— of disulfane δ = 3.88 ppm.
[d] The crude product was collected by filtration, washed with petroleum ether and dried.
[e] The crude product was triturated with petroleum ether, collected by filtration, washed with petroleum ether and dried.
[f] In DMSO-d_6.

Table 2. Unsymmetrical Trisulfanes **3a–l** prepared

Product No.	R^1 (from **2**)	R^2 (from thiol)	Catalyst[a]	Reaction Time	Yield [%]	b.p. [°C]/torr or m.p. [°C]	Molecular Formula[b] or Lit. Data	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
3a	i-C_3H_7	t-C_4H_9	NMM	120 h	71	38–44°/0.11	$C_7H_{16}S_3$ (196.4)	1.35 (d, 6H, J = 6.7 Hz); 1.38 (s, 9H); 3.20 (m, 1H)
3b	i-C_3H_7	HO–CH_2–CH_2–	NMM	20 h	71	64–74°/0.06	$C_5H_{12}OS_3$ (184.3)	1.38 (d, 6H, J = 6.7 Hz); 3.06 (t, 2H, J = 5.4 Hz); 3.27 (m, 1H); 3.8–4.1 (m, 2H)
3b	HO–CH_2–CH_2–	i-C_3H_7	DMA	350 h	59	63–70°/0.05	as above	as above
3c	H_3C		An	16 h	66	58–70°/0.07	$C_7H_8S_3$ (188.3)	2.50 (s, 3H); 7.2–7.7 (m, 5H)
3d	H_3C		none	2 h	59	–[c]	$C_7H_9NS_3$ (203.3)	2.50 (s, 3H); 6.7–7.5 (m, 4H)
3e	H_3C	H_2C=CH–CH_2–	NMM	16 h	60	28–30°/0.05	$C_4H_8S_3$ (152.3)	2.56 (s, 3H); 3.5 (dd, 2H, J = 7.3 Hz, 0.9 Hz); 5.0–5.3 (m, 2H); 5.8–6.0 (m, 1H)
3f	H_3C		NMM	4 h	33	70–80°/0.07	84°/0.2[6]	2.48 (s, 3H); 4.09 (s, 2H); 7.32 (s, 5H)[d]
3g		i-C_3H_7	NMM	16 h	79	70–80°/0.05	111–116°/0.4[11]	1.35 (d, 6H, J = 6.7 Hz); 3.14 (m, 1H); 4.09 (s, 2H); 7.31 (s, 5H)
3h			DMA	16 h	57	–[e]	–[f]	2.35 (s, 3H); 4.02[g] (s, 2H); 7.27 (s, 5H); 7.34 (AB, 4H, ν_{AB} = 28.6 Hz, J_{AB} = 8.3 Hz)
3i		i-C_3H_7	NMM	4 h	25	70–80°/0.07[h]	$C_{10}H_{14}S_3$ (230.4)	1.31 (d, 6H, J = 6.7 Hz); 2.35 (s, 3H); 3.17 (m, 1H); 7.32 (AB, 4H, ν_{AB} = 28.6 Hz, J_{AB} = 8.7 Hz)
3j			none	16 h	55	–[e]	–[i]	2.33 (s, 3H); 4.0–4.4 (br. s, 2H); 6.5–7.5 (m, 8H)
3k	i-C_3H_7	HOOC–CH_2–CH_2–	NMM	16 h	53	90–96°/0.07	$C_6H_{12}O_2S_3$ (212.4)	1.37 (d, 6H, J = 6.7 Hz); 2.7–3.3 (m, 4H)
3l	i-C_3H_7	Ac–NH–CH(COOH)–CH_2–	NMM	16 h	69	m.p. 132–134°	$C_8H_{15}NO_3S_3$ (269.4)	1.34 (d, 6H, J = 6.7 Hz); 1.90 (s, 3H); 3.1–3.4 (m, 2H); 4.62 (dt, 1H, J_d = 5.1 Hz, J_t = 7.9 Hz)[j]

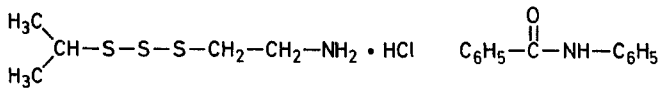
[a] NMM, *N*-methylmorpholine; DMA, *N*,*N*-dimethylaniline; An, Aniline.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.25, N ±0.13, S ±0.16.
[c] Purified by liquid chromatography (dichloromethane/petroleum ether 1/1).
[d] Corresponding disulfane: 2.11 (s, 3H); 3.90 (s, 2H).
[e] Purified by liquid chromatography (petroleum ether).
[f] Readily disproportionated, see text.
[g] Lit.[10], δ = 4.00 (s, 2H).
[h] Distillation subsequent to purification as per note e.
[i] Unstable; m/e (M^+) = 279.0186 (calc. 279.0209).
[j] In DMSO-d_6.

sulfane (**3g**). Problems in the synthesis of benzyl-containing di- and tri-sulfanes have been previously reported. Hiskey et al.[14] found that benzyl 2-hydroxyethyl disulfane disproportionated very rapidly. Our finding that 2-propyl 2-hydroxyethyl trisulfane (**3b**) was unchanged after 3 months at 25°C suggests that the instability of Hiskey's compound was due to the benzyl rather than the hydroxyethyl group. Furthermore, Harpp et al.[11] reported that the attempted preparation of benzyl 4-methylphenyl trisulfane (**3h**) from either benzyl mercaptan and 4-methylphenyl phthalimido disulfane or from *p*-thiocresol with benzyl phthalimido disulfane yielded mixtures containing both of the symmetrical trisulfanes as well as the desired product. Similarly, the crude product of our preparation of **3h** contained (by H.P.L.C.) 10% each of the two symmetrical trisulfanes.

The second reaction to give low yields was the reaction of 2-propanethiol with methoxycarbonyl 4-methylphenyl trisulfane (**2c**). When this reaction was carried out in chloroform-*d* (followed by ^{1}H-N.M.R.), methoxycarbonyl 4-methylphenyl disulfane was observed to form as the major contaminant of the crude product, with 2-propyl 4-methylphenyl disulfane being formed as well. The best route to aryl trisulfanes appears to involve the alternative where the thiol component is aryl, as demonstrated by the preparation of methyl phenyl trisulfane (**3c**).

Attempts to prepare, by the general method, 2-propyl 2-aminoethyl trisulfane hydrochloride (**4**) from either methoxycarbonyl 2-propyl trisulfane (**2b**) plus 2-aminoethanethiol hydrochloride, or from methoxycarbonyl 2-aminoethyl

trisulfane hydrochloride (**2f**) plus 2-propanethiol, proved unsuccessful. In both cases a product was isolated which was believed to have undergone some disproportionation to the two symmetrical trisulfanes. Any bis[2-propyl] trisulfane would have been removed during washing of the product hydrochloride salt with petroleum ether giving rise to a product with a low carbon and a high nitrogen microanalysis together with a low integration for the 2-propyl group in the ^{1}H-N.M.R. However, trisulfanes containing the less basic aromatic amino group, for example **3d**, were prepared by the standard procedure as was a cysteine-containing trisulfane (**3l**) where the amino group was protected by an acetyl group. Finally, an attempt to prepare 2-propyl benzoyl trisulfane from methoxycarbonyl benzoyl trisulfane (**2g**) and 2-propanethiol was unsuccessful. The only products isolated from this reaction were methoxycarbonyl 2-propyl polysulfanes, principally the trisulfane (**2b**), and benzanilide (**5**). The latter was probably formed from reaction of the aniline catalyst with thiobenzoic acid[15] which was apparently displaced from trisulfane **2g** in place of carbonyl sulfide and methanol.



4 **5**

In conclusion, the method described offers a clean entry to a wide variety of trisulfanes, with methanol and carbonyl sulfide being the only by-products. Since two alternative routes exist for each unsymmetrical trisulfane, these may have to be compared to obtain the best yields and product purities. The wide application of the method was shown by the preparation of methyl 2-propenyl trisulfane (**3e**), a natural product isolated from garlic[3] which reduces blood platelet aggregation and has been recently patented[16] for use as an antithrombotic pharmaceutical. The previous low-yield method[3] of preparing this compound involves heating bis[methyl] disulfane, bis[2-propenyl] disulfane and elemental sulfur with *N,N*-dibutylamine followed by fractionation of the complex product mixture.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. ^{1}H-N.M.R. spectra were recorded on a Varian HFT 80 spectrometer at 80 MHz. Liquid chromatography was performed on a Lobar Size B (310–25 mm) LiChroprep™ Si60 column with flow rates of 2–3 ml min^{-1}. Solvents and chemicals were reagent grade and used without further purification, except for 2-propenyl mercaptan which was freshly distilled (b.p. 67–68 °C) before use. The homogeneity of the trisulfanes **3** was confirmed by normal phase H.P.L.C. on an Ultrasphere-Si column (4.6 mm × 25 cm) eluting with hexane except for **3b, 3d, 3j** with hexane/dichloromethane (7/3) and **3k, 3l** with dichloromethane/methanol (4/1). The product purities were generally over 90% although several of the trisulfanes developed higher levels of the symmetrical trisulfane disproportionation products after storing for several months at 25 °C.

Methoxycarbonyl Trisulfanes 2; General Procedure:
A solution of the thiol (7 mmol) in dichloromethane (5 ml) is added dropwise to a cooled solution of methoxycarbonyldisulfanyl chloride[13] (**1**; 1 g, 6.3 mmol) in dichloromethane (10 ml). Hydrogen chloride is evolved and the yellow color of **1** fades. After stirring for 1 h the mixture is warmed to 25 °C and is evaporated to yield the crude **2** in almost quantitative yields. The crude products are purified as described in Table 1.

Trisulfanes 3; General Procedure:
The thiol (1.1 equiv.) is added to a solution of methoxycarbonyl trisulfane **2** (0.5 g) in chloroform (5 ml). The optimum catalyst (20 mg), which is determined by preliminary small scale experiments in chloroform-*d*, is added and the mixture is stirred at 25 °C until all of the starting material is consumed (disappearance of the methoxycarbonyl peak in ^{1}H-N.M.R.). The solution is washed with hydrochloric acid (20 ml, 0.1 normal) and water (20 ml), the organic phase is separated, and dried with magnesium sulfate. Evaporation yields the crude trisulfanes **3** which are purified by bulb-to-bulb distillation or by liquid chromatography (Table 2).

Trisulfanes 3k and 3l Containing a Carboxyl Group:
Bis[trimethylsilyl]acetamide (1.1 equiv.) is added to a solution/suspension of the carboxyl-containing thiol (0.5 g) in chloroform (10 ml). After stirring for 30 min, methoxycarbonyl 2-propyl trisulfane (**2b**; 1.0 equiv.) is added together with *N*-methylmorpholine (20 µl). After stirring for 16 h, the solution is evaporated, dissolved in ether (20 ml), and stirred with hydrochloric acid (20 ml, 0.5 normal) for 1 h. The organic layer is separated, dried with magnesium sulfate, and evaporated to yield the crude trisulfane which is purified by distillation (for **3k**) or by washing several times with petroleum ether (for **3l**).

Reaction of Methoxycarbonyl Benzoyl Trisulfane (2g) with 2-Propanethiol:
Aniline (30 mg, 0.32 mmol) is added to a solution of 2-propanethiol (0.18 ml, 2 mmol) and **2g** (0.5 g, 1.9 mmol) in chloroform (5 ml). After 170 h, the solution is evaporated to give 0.49 g of an oily solid which is shown to comprise of two components by T.L.C. (dichloromethane/petroleum ether 1/1). Separation by liquid chromatography with the same solvent system gives a mixture of methoxycarbonyl 2-propyl polysulfanes (0.18 g), and a white solid which is identified as benzanilide (**5**; 0.06 g, 0.3 mmol) by I.R. spectroscopy; m.p. 162–163 °C (Lit.[17], m.p. 163 °C).

The authors thank Ms. Lori J. Enloe for technical assistance, and the National Institutes of Health (GM 28934 and AM 01099) and Chicago Community Trust (Searle Scholars Program) for financial support.

Received: March 11, 1984

[1] A preliminary report was presented at the 187th National Meeting of the American Chemical Society, St. Louis, Missouri, April 8–13, 1984, ORGN 33.
[2] J.D. Sandy, R.C. Davies, A. Neuberger, *Biochem. J.* **150**, 245 (1975).
K. Morita, S. Kobayashi, *Tetrahedron Lett.* **1966**, 573.
R. Hodges, J.S. Shannon, *Aust. J. Chem.* **19**, 1059 (1966).
[3] D.M. Oaks, H. Hartmann, K.P. Dimick, *Anal. Chem.* **36**, 1560 (1964).
[4] L. Schregen, P. Diriack, F. Van Wassehove, N. Schamp, *J. Agric. Food Chem.* **24**, 336 (1976).
H. Nishimura, K. Fujiwasa, J. Mizutani, Y. Obata, *J. Agric. Food Chem.* **19**, 992 (1971).
[5] A. Schöberl, A. Wagner, in Houben-Weyl, *Methoden der Organischen Chemie* 4th. Edn., E. Müller, Ed., Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, p. 87–90.
[6] H. Böhme, G. Van Ham, *Justus Liebigs Ann. Chem.* **617**, 62 (1958).
C. Von Szczepanski, J. Heindl, E. Schroeder, H.J. Kessler, U. Redmann, *German Patent*, 2114653, (1972); *C.A.* **78**, 3942 (1973).
[7] T. Nakabayashi, J. Tsurugi, *J. Org. Chem.* **26**, 2482 (1961).
[8] G. Kresze, H.P. Patzschke, *Chem. Ber.* **93**, 380 (1960).
[9] S. Hayashi, M. Furukawa, J. Yamomoto, K. Hamamura, *Chem. Pharm. Bull.* **15**, 1310 (1967).
[10] A.B. Sullivan, K. Boustany, *Int. J. Sulfur Chem.*, [A] **1**, 207 (1971).
[11] D.N. Harpp, D.K. Ash, *Int. J. Sulfur Chem.* [A] **1**, 211 (1971).
[12] S.J. Brois, J.F. Pilot, H.W. Barnum, *J. Am. Chem. Soc.* **92**, 7629 (1970).
[13] G. Barany, A.W. Mott, *J. Org. Chem.* **49**, 1043 (1984).
H. Böhme, H.P. Steudel, *Justus Liebigs Ann. Chem.* **730**, 121 (1969).

[14] R.G. Hiskey, F.I. Carroll, R.M. Babb, J.O. Bledsoe, R.T. Puckett, B.W. Roberts, *J. Org. Chem.* **26**, 1152 (1961).
[15] P.J. Hawkins, D.S. Tarbell, P. Noble, Jr., *J. Am. Chem. Soc.* **75**, 4462 (1953).
[16] *Japan Patent* 57209218, (1982) Japan Alcon Ltd.; *C.A.*, **98**, 95692 (1983).
[17] *CRC Handbook of Chemistry and Physics*, R.C. Weast, Ed., CRC Press, Florida, 1979, Vol. 60, p. C-181.