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A SIMPLE METHOD TO PREPARE UNSYMMETRICAL DI- TRI- AND TETRASULFIDES

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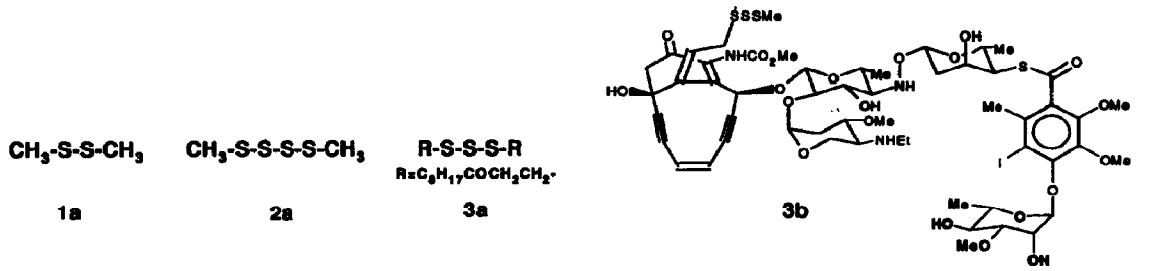
Abstract: *Unsymmetrical di- tri- and tetrasulfides can be prepared in a one-pot reaction using SO_2Cl_2, SCl_2 and S_2Cl_2 respectively to permit coupling of the appropriate thiols.*

A variety of organic di- and trisulfides have been found in natural sources.[1] Among these are examples from the onion family (genus *Allium*),[2a] as well as simple polysulfide derivatives **1a** and **2a** isolated from a Japanese plant.[2b] Trisulfide **3a** has been found in red algae[2c] and of particular recent interest is the extremely unsymmetrical trisulfide represented by Calicheamicin γ_1^I (**3b**).[3]

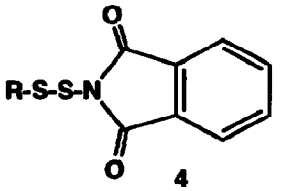


There are several effective procedures for the synthesis of unsymmetrical disulfides.[4] All of them however, first involve the construction of stable derivatives of thiols.[4b-e] The preparation of symmetrical trisulfides is. simple,[5] however the synthesis of the unsymmetrical variety also requires one or more extra steps.

For this class, marginal methodologies have been reported which involve the isolation of chlorodisulfides and their subsequent reaction with thiols[6] as well as N-arylamidothiosulfites in a similar process.[7] Other literature methods use rare hydrodisulfides (RSSH)[8] and an awkward desulfurization reaction employing dialkanesulfonic thioanhydrides (RSO_2SSO_2R').[9]

Some years ago, we reported[10] a useful method of preparation for unsymmetrical trisulfides which requires the preparation of stable alkyl or aryl phthalimido disulfides (4). This procedure has been successfully used in one of the key steps in the preparation of Calicheamicin γ_1[13] (3b), although long reaction times (*ca.* 100 h) are usually required for complete conversion when aliphatic thiols are employed.[10] An effective method was reported in 1984 by Barany[11] which requires preparing methoxycarbonyldisulfenyl chlorides (5) which are then treated with the requisite mercaptan to afford methoxycarbonyl trisulfides 6. While these precursors can generally be prepared in yields of *ca.* 80%, the yields of the next step to give the unsymmetrical trisulfides 3 averages about 60% (Scheme 1).

Scheme 1



4

$$Cl\text{-}S\text{-}S\text{-}CO_2CH_3 \xrightarrow{R\text{-}SH} R\text{-}S\text{-}S\text{-}S\text{-}CO_2CH_3 \xrightarrow{R'\text{-}SH} R\text{-}S\text{-}S\text{-}S\text{-}R'$$

5 6 3

For a separate project we required samples of a number of unsymmetrical trisulfides 3. We report here a simple method which delivers a variety of these molecules generally in good overall yield (25-100%) and purity (Table 1). A major advantage of this procedure is that it is extremely rapid (*ca.* 2 h), does not require the isolation of intermediates and permits the reaction to take place in one vessel. The Table summarizes the data for the trisulfides (as well as di- and tetrasulfides) prepared by similar techniques.[12]

A sample procedure is as follows. A solution of the first thiol (10 mmol) and pyridine (10 mmol) in ether (25 mL) was added dropwise over 0.5 h to a cold (-78°C) stirred solution of sulfur dichloride[13] (10 mmol) in 50 mL of ether. The reaction mixture was stirred for 0.5 h after the addition was complete. The second thiol (10 mmol) and pyridine (10 mmol) in 25 mL of ether was added dropwise over 0.5 h at -78°C and the reaction mixture stirred for an additional 0.5 h. The reaction mixture was transferred to a separatory funnel, washed with 2x25 mL portions of water, 2x25 mL portions of 1 N NaOH solution and with 25 mL portions of water until neutral to pH paper. The organic phase was separated, dried with $CaCl_2$, filtered and evaporated. In all cases studied here, no further purification was necessary.[14]

Apparently, under these specific reaction conditions, the first thiol reacts quantitatively with SCl_2 to give a thiosulfenyl chloride 7 which is stable at -78°C. This then reacts with the second mole of thiol to give the unsymmetrical trisulfide 3 (Scheme 2). *t*-Butylchlorodisulfide was stable enough to be isolated and characterized at room temperature.[15]

Scheme 2

$$R\text{-}SH + SCl_2 \xrightarrow[Et_3N]{-78°C} \left[\, R\text{-}S\text{-}S\text{-}Cl \,\right] \xrightarrow{R'\text{-}SH} R\text{-}S\text{-}S\text{-}S\text{-}R'$$

7 3

Table[a]

Entry	R	R'	% Yield	^{1}H NMR	^{13}C NMR
1b	*t*-Bu	*t*-Bu	100	1.28 (s, 18H)	30.56, 45.97
1c[b]	Trityl	Trityl	98	7.34 (m, 30H)	73.51, 126.96, 127.46 130.57, 143.82
1d	Bz	Bz	100	3.59 (s, 4H), 7.31 (m, 10H)	43.07, 127.26, 128.32, 129.26, 137.18
1e	Adm	Adm	94	1.68 (m, 6H),1.85 (m, 6H) 1.91-2.06 (m, 3H)	30.01, 36.11, 43.04, 47.28
1f	*t*-Bu	*i*-Pr	92	1.25 (d, 6H),1.29 (s, 9H) 2.85 (h, 1H)	22.42, 29.92, 41.61, 47.22
1g	*i*-Pr	*t*-Bu	83	1.24 (d, 6H),1.29 (s, 9H) 2.84 (h, 1H)	22.42, 29.92, 41.61, 47.22
1h	Bz	*t*-Bu	91	1.38 (s, 9H), 3.97 (s, 2H) 7.32 (m, 5H)	29.65, 45.62, 47.95, 127.31 128.44, 129.13, 137.26
2b	*t*-Bu	*t*-Bu	98	1.38 (s, 9H)	30.16, 49.01
2c[c]	*t*-Bu	*i*-Pr	30	1.37 (d, 6H), 1.38 (s, 9H), 3.24 (h, 1H)	22.63, 30.12, 41.97, 49.00
2d	*p*-Cl-Bz	*n*-Bu	43	0.93 (t, 3H),1.42 (m,2H), 1.72 (m, 2H), 2.92 (t, 2H) 4.08 (s, 2H), 7.30 (m, 4H)	13.60, 21.52, 31.01, 39.03 42.61 (CH_2), 128.75 130.71, 133.57, 134.69
3c	*i*-Pr	*i*-Pr	98	1.34 (d,6H), 3.19 (h, 1H)	41.72, 22.44
3d	*n*-Bu	*n*-Bu	94	0.90 (t, 3H), 1.41 (m, 2H) 1.68 (m, 2H), 2.82 (t, 2H)	13.56, 21.55, 30.75, 38.36
3e	*p*-*t*BuPh	*p*-*t*BuPh	98	1.33 (s,18H), 7.42 (AB, 4H)	31.23, 34.63, 151.74 133.11, 130.65, 126.12,
3f	Bz	Bz	100	4.06 (s, 4H), 7.35 (m, 10H)	43.19 (CH_2), 127.64 128.68, 129.34, 135.58
3g	p-Cl-Bz	*p*-Cl-Bz	100	3.98, (s, 4H), 7.68 (m, 8H)	42.10 (CH_2), 128.68 130.66, 133.39, 134.90
3h	*t*-Bu	*t*-Bu	100	1.36 (s, 18H)	29.88, 48.91
i[d]	allyl	allyl	46	3.50 (d, 4H), 5.22 (m, 4H) 5.86 (m, 2H)	41.60, 119.07, 132.65
3j	*t*-Bu	*i*-Pr	96	1.35 (d, 6H), 1.36 (s, 9H) 3.19 (h, 1H)	22.48, 29.85, 41.93, 48.74
3k	*n*-Bu	*p*-Cl-Bz	34	0.93 (t, 3H),1.41 (m, 2H) 1.71 (m, 2H), 2.88 (t,4H) 3.97, (s, 2H), 7.26 (m, 4H)	13.56, 21.55, 30.76 38.39, 42.05, 128.61 130.61, 133.35, 134.90
3l	*n*-Bu	Bz	25	0.91 (t, 3H),1.43 (m,2H), 1.70 (m, 2H), 2.88 (t, 2H) 4.09 (s, 2H), 7.35 (m, 5H)	13.59, 21.54, 30.76 39.39, 42.91 (CH_2), 127.38, 128.44, 129.31 134.69
3m	*p*-Cl-Bz	Bz	40	3.90 (s, 2H), 4.04 (s, 2H) 7.30 (m, 9H)	42.07 (CH_2), 43.02 (CH_2), 127.52, 128.53, 128.66, 129.34, 130.65, 133.38, 134.89, 135.60
3n	*t*-Bu	Bz	75	1.39 (s, 9H), 4.11 (s, 2H) 7.35 (m, 5H)	29.82, 43.07 (CH_2), 127.33, 128.40, 129.34 136.43
3o	*t*-Bu	*p*-Cl-Bz	57	1.38 (s, 9H), 4.01 (s, 2H), 7.27 (m, 4H)	29.81, 42.12,49.08, 128.63 130.62, 133.35, 134.91

[a] All products are isolated and pure (tlc/gc); [b] fails to work with Et_3N; DBU works well; [c] the mixed tetrasulfides were not separable; [d] purified by silica gel chromatography (5% $CHCl_3$/hexanes).

Acknowledgements

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11. A. W. Mott and G. Barany, *Synthesis*, 657 (1984).
12. Unsymmetrical disulfides (**1b-h**) can be prepared by using SO_2Cl_2 following the same general procedure described here. In the same fashion, two unsymmetrical tetrasulfides (**2 c,d**) can be synthesized in moderate yield and good purity by using S_2Cl_2 (see Table). In spite of the many uses o these simple sulfur reagents over the years, there appears to be no reports of successful *in situ* use in the manner described in this paper.
13. Purification was carried out by distillation over phosphorus pentachloride, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley & Sons, Pub., London, Vol. 1, p. 1121 (1967).
14. The only exception was during the preparation of trisulfides where the first thiol was primary; some symmetrical trisulfide was formed (up to 20% for *n*-butyl mercaptan). Silica gel chromatogaphy, using 5% chloroform/hexane allowed a good separation in all cases of these very similar comounds (**3 k-m**).
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