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NEW SIMPLE SYNTHESES OF UNSYMMETRICAL DISULFIDES AND THIOLSULFONATES

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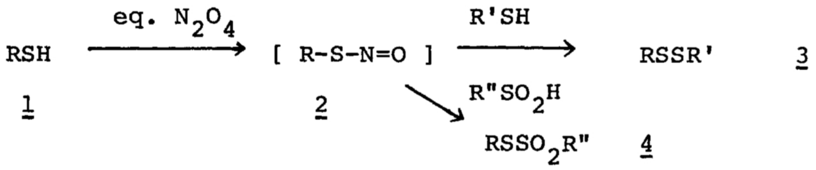
New one-pot syntheses of both unsymmetrical disulfides and thiolsulfonates by treatment of thionitrites with thiols and sulfinic acids are reported.

We have recently reported that the reaction of both aromatic and alkyl thiols with an equimolar amount of N_2O_4 readily afforded isolable thionitrites(2)[1], which upon treatment in situ with other thiols(R'SH) or with sulfinic acids give the corresponding unsymmetrical disulfides(3) or the thiolsulfonates(4) in good yields.



$$\begin{tikzcd}
RSH \arrow[r, "eq.\ N_2O_4"] & {[\ R\text{-}S\text{-}N{=}O\ ]} \arrow[r, "R'SH"] \arrow[dr, "R''SO_2H"] & RSSR' \quad 3 \\
1 & 2 & RSSO_2R'' \quad 4
\end{tikzcd}$$

Since disulfides constitute an important part of biomedical, industrial and coordination chemistry, various methods which use activated sulfenyl derivatives to synthesize unsymmetrical disulfides have been developed. Common active sulfenyl derivatives are sulfenyl halide[2], sulfenyl thiocyanate[3], sulfenyl hydrazide[4], sulfenyl thiocarbonate[5], sulfenimide[6], thiosulfate[7], thiolsulfonate[8], thiolsulfinate[9], and alkylthio-dialkylsulfonium salt[10]. Most of these methods, however, involve at least two or three reaction steps when thiols are the starting materials. For the synthesis of unsymmetrical disulfides, the sulfenyl halides would be the most often used intermediate which can be prepared by treating thiols with halogen. However, it is not easy to obtain pure alkanesulfenyl halides by the reaction of the corresponding thiols or disulfides with halogen.

Meanwhile, both aromatic and alkyl thionitrites can be readily obtained in pure form by treating thiols and N_2O_4 under mild conditions in such inert solvent as carbon tetrachloride, ether or acetonitrile and hence used for subsequent reactions to prepare unsymmetrical disulfides without isolation.

When a solution of N_2O_4[1)] (N_2O_4: 2.0 mmol, CCl_4: 1 ml, -20°C) was added to the solution of a thiol (RSH: 2.0 mmol, anhydrous ether: 20 ml) at ca. -20°C with vigorous stirring in dark, immediately the solution is colored, usually bright red and an ethereal solution of the corresponding thionitrite is obtained. The second thiol solution (R'SH: 2.0 mmol, ether: 10 ml) was slowly added to the solution of the thionitrite at ca. -5°C. After keeping the reaction mixture at 0°C for 1 h, the mixture was washed with 5% sodium bicarbonate solution to remove nitric acid formed during the reaction and then dried. After removing ether, the crude products were purified either by distillation or by column chromatography (silica-gel, 1x15 cm, solvent: 2-propanol/hexane = 1/20). All these products were identified by compairing their ir, nmr, glc and llc with those of the authentic samples.

The results are summarized in Table 1.

Table 1 The Yields of Unsymmetrical Disulfides

Run	R	R'	$[N_2O_4/RSH]$	RSSR' (%)[a)]	RSSR (%)[a)]
1	Ph	$(CH_3)_3C$	1	98[b)]	1
2	Ph	$(CH_3)_2CH$	1	85	7
3	Ph	$CH_3(CH_2)_7$	1	87	6
4	Ph	CH_3CH_2	1	81	9
5	Ph	$p-CH_3-C_6H_4$	1	81	9
6	$p-CH_3-C_6H_4$	$(CH_3)_3C$	1	91[b)]	1
7	$CH_3(CH_2)_7$	$CH_3(CH_2)_3$	1	81	6
8	$(CH_3)_3C$	Ph	1	50	11
9	CH_3CH_2	Ph	1	73	--
10	Ph	$(CH_3)_3C$	1.5[c)]	70	1
11	Ph	$CH_3(CH_2)_7$	1.5[c)]	55	9
12	Ph	$(CH_3)_2CH$	1.5[c)]	66	1
13	Ph	$p-CH_3-C_6H_4$	1.5[c)]	21	--
14	$(CH_3)_3C$	Ph	1.5[c)]	42	20
15	$CH_3(CH_2)_7$	Ph	1.5[c)]	27	7

a) The yields were determined by glc using callibration curves of authentic samples. b) Yields isolated. c) When an excess N_2O_4 was used, the yields of unsymmetrical disulfides were low and small amount of unsymmetrical thiolsulfonates were given.

The yields (Run 1-9) of unsymmetrical disulfides (3) are markedly high when an equimolar mixture of N_2O_4 and RSH is used to prepare the thionitrite which is then treated in situ with another thiols. However, the yields (Run 10-15 of 3) are low when excess N_2O_4 was used. These results and the amount of consumption of the thionitrite revealed that a maximum yield of the thionitrites (2) can be achieved when equimolar amounts of both N_2O_4 and the thiols were used as the starting materials. When the amount of N_2O_4 was in excess, the thionitrite once formed appears to be oxidized quickly to give further oxidation derivatives of the thionitrite which are readily decomposed.

The thionitrites are highly reactive and reacted readily with sulfinic acids in ether at ca. -5°C to afford the unsymmetrical thiolsulfonates (4) in good yields. In general, unsymmetrical thiolsulfonates are prepared by the treatment of sulfenyl chlorides with sulfinic acids11), of sulfonyl halides with silver thiolates12), of sulfonyl chlorides with iron pentacarbonyl13), or of nitroarenesulfenyl halides with silver nitrate14). However, these procedures also require at least two or three reaction steps when thiols are used as starting materials. Unique syntheses of unsymmetrical aromatic mono-thiolsulfonates15) and alkyl thiolsulfonates16) by the reaction of thiols and nitrites with sulfinic acids were introduced. Our new methods can provide thiolsulfonates by only one-step, namely mixing thiols, N_2O_4 and sulfinic acids under cooling. The HNO_3 and HNO formed during the reaction can be readily removed by washing with $NaHCO_3$ solution (5%). The crude products were easily purified by column chromatography (silica-gel, 1x15 cm, solvent: 2-propanol/hexane=1/20). This method can be used for the syntheses of both aryl arenethiolsulfonates and alkyl arenethiolsulfonates.

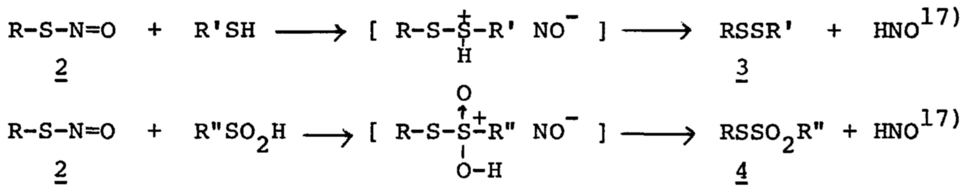
The results are summarized in table 2.

Table 2 The yields of Unsymmetrical Thiolsulfonates

Run	R	R"	$[N_2O_4/RSH]$	$RSSO_2R"$ (%)a)	RSSR (%)a)
1	Ph	$p\text{-}CH_3\text{-}C_6H_4$	1	80b)	2
2	Ph	$p\text{-}CH_3\text{-}C_6H_4$	1	74	5
3	$p\text{-}CH_3\text{-}C_6H_4$	Ph	1	82	3
4	$p\text{-}Cl\text{-}C_6H_4$	Ph	1	73	12
5	$CH_3(CH_2)_4$	$p\text{-}CH_3\text{-}C_6H_4$	1	61b)	6

a) Yields isolated. b) $RSH/R"SO_2H = 1/1.5$

The formation of unsymmetrical disulfides or thiolsulfonates undoubtedly proceeds via the nucleophilic attacks of another thiol (R'SH) or sulfinic acids on the sulfur atom of the thionitrites as shown below.



$$\underset{\mathbf{2}}{\text{R-S-N=O}} + \text{R'SH} \longrightarrow [\ \text{R-S-}\underset{\text{H}}{\overset{+}{\text{S}}}\text{-R' NO}^-\ ] \longrightarrow \underset{\mathbf{3}}{\text{RSSR'}} + \text{HNO}^{17)}$$

$$\underset{\mathbf{2}}{\text{R-S-N=O}} + \text{R''SO}_2\text{H} \longrightarrow [\ \text{R-S-}\underset{\text{O-H}}{\overset{\substack{\text{O}\\ \uparrow +}}{\text{S}}}\text{-R'' NO}^-\ ] \longrightarrow \underset{\mathbf{4}}{\text{RSSO}_2\text{R''}} + \text{HNO}^{17)}$$

Small amount of symmetrical disulfides are derived probably by the intermolecular reaction of the thionitrite with a thyl radical which is formed by the facile decomposition of the thionitrites together with nitric oxide radicals as suggested by Barrett[18].

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