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REACTIONS OF THIOLATE ANIONS WITH 2-SUBSTITUTED-2-NITROPROPANES

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Summary: Thiolates undergo substitution reactions with 2-substituted-2-nitropropanes by an $S_{RN}1$ mechanism or are oxidised to disulphides by an ionic mechanism.

A growing list of α-substituted nitroalkanes have been found to undergo nucleophilic substitution with various anions by a radical, radical-anion chain mechanism[1] ($S_{RN}1$, Scheme 1).

Scheme 1 X = I, Br, Cl, $-NO_2$, $-SO_2R$, $-S(O)R$, $-SR$

$$R_2C(X)NO_2 + A^- \longrightarrow [R_2C(X)NO_2]^{\cdot -} + A\cdot \quad \text{(initiation)}$$
$$[R_2C(X)NO_2]^{\cdot -} \longrightarrow R_2CNO_2\cdot + X^-$$
$$R_2CNO_2\cdot + A^- \longrightarrow [R_2C(A)NO_2]^{\cdot -}$$
$$[R_2C(A)NO_2]^{\cdot -} + R_2C(X)NO_2 \longrightarrow R_2C(A)NO_2 + [R_2C(X)NO_2]^{\cdot -}$$

This mechanism has been shown to operate in the reactions of thiolates with a variety of substrates (aromatic,[2] benzylic,[1b] and aliphatic[3,4,5]). In contrast there are also a number of reports[1c 4,6,7] that similar reactions give disulphides as products. Russell[1c,8] has proposed a radical mechanism (Scheme 2) to account for this oxidative dimerisation.

Scheme 2
$$Me_2C(X)NO_2 + RS^- \longrightarrow [Me_2C(X)NO_2]^{\cdot -} + RS\cdot$$
$$[Me_2C(X)NO_2]^{\cdot -} \longrightarrow Me_2CNO_2\cdot + X^-$$
$$Me_2CNO_2\cdot + RS^- \longrightarrow Me_2CNO_2^- + RS\cdot$$
$$2RS\cdot \longrightarrow RSSR$$

We have studied the reactions of a wide variety of thiolates with 2-substituted-2-nitropropanes and the results are summarised in the Table. In general the oxidations are rapid (several minutes) while the substitutions require several hours.

In most cases the production of disulphide was accompanied by the formation of a similar yield of 2,3-dimethyl-2,3-dinitrobutane. We believe this compound arises from the reaction of nitronate anion with the 2-substituted-2-nitropropane (E1, E2), a well known[1,8] $S_{RN}1$ reaction. In accordance with this proposal the formation of this dinitrobutane was largely inhibited by the addition of p-dinitrobenzene, the use of an O_2 atmosphere, or by the exclusion of light. These are well established devices for the inhibition of $S_{RN}1$ reactions.[1]

$$Me_2C(X)NO_2 + 2RS^- \longrightarrow Me_2CNO_2^- + RSSR \qquad \text{(E1)}$$
$$Me_2CNO_2^- + Me_2C(X)NO_2 \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + X^- \qquad \text{(E2)}$$

Evidence for the stoichiometry of the oxidation as shown in E1 and also for the formation of nitronate was obtained in several reactions. The reaction of 2 equivs of phenyl-thiolate with 2-bromo-2-nitropropane in methanol for 5 min produced diphenyl-disulphide (96%) and the anion of 2-nitropropane (96%). The reaction to form the dinitrobutane (E2) is very slow in methanol at room temperature.[9] The reaction of 2 equivs of the same thiolate with 1-bromo-1,1-dinitroethane gave disulphide (92%) and the anion of 1,1-dinitroethane (89%). This anion does not participate in $S_{RN}1$ reactions.[9] Similarly 2 equivs of benzyl thiolate reacted with 2-bromo-2-nitropropane to

Table: $Me_2C(X)NO_2$ + RS^- ⟶ $Me_2C(SR)NO_2$ + RSSR

R	X, reaction conditions[a]	% yield α-nitrosulphide	% yield disulphide
2-benzothiazolyl	Br	89	—
4-nitrophenyl	Br	83	—
2-nitrophenyl	I (30 min); Cl (5 h); NO_2 (24 h)	0;34;55	98;14(57)[b];9(27)[b]
	Br; Br (oxygen atmosphere[c])	75;0	14;80
	Br, p-dinitrobenzene (10 & 30 mol %)[c]	36,0	32,50
	Br, galvinoxyl (10 mol %)[c]	37	27
	Br, light excluded	41	57
4-chlorophenyl	I; Br (2 h); Cl; SO_2Ph	0;0;35;59	75;70;32;0
	NO_2 (18 h)	69	—
	NO_2 (18 h), oxygen atmosphere[c]	—	30
	4-chlorophenylthio[d]	—	84
Phenyl	Br (MeOH, 5 min), (DMF 2 h)	—	96,87
	Cl; NO_2 (16 h); SO_2Ph	—	52;92;48(38)[b]
p-tolyl	I (30 min); Br; 2,4-dinitrophenylthio (2 h)[d]	—	78;90;94
benzyl	Br; Cl; NO_2; SO_2Ph	—	80;86;87;58(54)[b]
2-hydroxyethyl	Br (MeOH, 1 h)	—	80
$AcNHCH(CO_2Me)CH_2$-	Br (MeOH, 30 min)	—	60

(a) The reaction conditions used were as illustrated in the sample procedure unless otherwise stated: Sodium 4-nitrophenylthiolate (540 mg, 3 mmol) and 2-bromo-2-nitropropane (500 mg, 3 mmol) in DMF (25 ml) were irradiated with fluorescent lamps (2 x 15 W) under an atmosphere of nitrogen and anhydrous conditions. Analysis of the products was by n.m.r. of the worked up crudes and subsequent separation, purification and characterisation. The % yields were calculated from thiolate. (b) (%) of starting $Me_2C(X)NO_2$ recovered. (c) Blank reactions of inhibitors and thiolates alone gave only small yields of disulphides and do not significantly alter the results. (d) Molar ratio of RS^-: $Me_2C(X)NO_2$ = 10:1

give only disulphide and the anion of 2-nitropropane.

Further consideration of the results in the Table reveals that thiolates derived from the more acidic thiols reacted to give α-nitrosulphides (we have shown this to be a $S_{RN}1$ process[4]) while those thiolates derived from the less acidic thiols (more nucleophilic) are oxidised to disulphides. This difference in reactivity could be explained if the intermediate nitropropyl-radical either adds to thiolate (Scheme 1) to yield α-nitrosulphide or undergoes electron transfer (Scheme 2) with thiolate to yield disulphide. Thiolates of the less acidic thiols are more easily oxidised and electron transfer (Scheme 2) could therefore predominate.

However attempts to trap a possible thiyl radical intermediate during the oxidation of phenyl-thiolate with 2-bromo-2-nitropropane using norbornadiene[10] (1 equiv) were unsuccessful. Diphenyl-disulphide (86%) was the only isolable product and no trace of norbornadiene-thioether adduct could be detected. The diene did however inhibit the formation of 2,3-dimethyl-2,3-dinitrobutane, thus indicating its potential to trap radicals. Similarly, carrying out the reaction

in styrene[11] did not produce a significantly higher yield of polystyrene than blank experiments.

Further evidence against a radical mechanism is provided by the following rationalisation. If the competition is as shown in Schemes 1 and 2 then the product obtained should be independent of the nature of the α-substituent, since both processes have a common intermediate - the 2-nitropropyl radical. Our results show that for thiolates of intermediate reactivity 4-chlorophenyl and 2-nitrophenyl) the nature of the α-substituent does determine the route of reaction, i.e. the reaction between the thiolate and the α-substituted nitropropane is the point of divergence between the paths to form either α-nitrosulphide or disulphide, not the reaction with the 2-nitropropyl radical.

Furthermore, oxidation of the anion of 2-nitropropane with $K_3Fe(CN)_6$[12] (Scheme 3) in the presence of 4-chlorophenyl-thiolate gave only α-nitrosulphide (72%) and no disulphide. The 2-nitropropyl radical is generated by the oxidation and this result clearly shows that the radical and thiolate react by addition and not by electron transfer. In view of the above data we consider that a mechanism for the production of disulphide as shown by Scheme 2 is unlikely.

Scheme 3

$$Me_2CNO_2^- + Fe^{III}(CN)_6 \longrightarrow Me_2CNO_2\cdot + Fe^{II}(CN)_6$$

$$Me_2CNO_2\cdot + RS^- \longrightarrow [Me_2C(SR)NO_2]^{\cdot-}$$

$$[Me_2C(SR)NO_2]^{\cdot-} + Fe^{III}(CN)_6 \longrightarrow Me_2C(SR)NO_2 + Fe^{II}(CN)_6 \quad (R=4\text{-chlorophenyl})$$

We suggest that the oxidation is best explained by an ionic mechanism involving nucleophilic attack by the thiolate anion on the α-substituent (E3) and subsequent reaction of a second thiolate with the sulphenyl intermediate (E4). Thus the distribution of products depends on competition between a S_N2 mechanism and the $S_{RN}1$ one. This proposal is able to account for all the results in the Table; the more nucleophilic the thiolate and the easier the abstraction of the 2-substituent (I>Br>Cl>NO_2>SO_2Ph), the more disulphide formation is favoured, and vice versa.

$$RS^- + X\text{-}CMe_2NO_2 \longrightarrow RSX + Me_2CNO_2^- \qquad (E3)$$

$$RS^- + RSX \longrightarrow RSSR + X^- \qquad (E4)$$

Similar competition between S_N2 and $S_{RN}1$ has been proposed in the reactions of p-nitrobenzyl derivatives[13] and in the reactions of 2-substituted-2-nitropropanes with malonates[14] (E5).

$$RC^-(CO_2Et)_2 + Me_2C(X)NO_2 \longrightarrow RC(X)(CO_2Et)_2 \ (X=I, Br) \text{ or } Me_2C(NO_2)C(R)(CO_2Et)_2 \ (X=Cl, SO_2Ph) \qquad (E5)$$

Sulphenyl halides are well known reactive species which react rapidly with thiolates to form disulphides, and it is therefore not surprising that attempts to isolate them failed. However when triphenylmethyl-thiolate was reacted with 2-chloro-2-nitropropane in MeOH (E6) the sterically hindered triphenylmethylsulphenyl chloride was isolated (63%) and no disulphide detected. The disulphide should have been formed if thiyl radicals were present. The equivalent reaction with 2-bromo-2-nitropropane was attempted but the instability of the sulphenyl bromide led to unreliable results.

$$Ph_3CS^- + Me_2C(Cl)NO_2 \longrightarrow Ph_3CSCl + Me_2CNO_2^- \qquad (E6)$$

Of the other required sulphenyl intermediates, thionitrates ($RSNO_2$) have recently been prepared and shown to be highly reactive compounds.[15] Similar properties for thiolsulphonates ($RSSO_2R$) are well known.

We obtained evidence for the competition between the $S_{RN}1$ (Scheme 1) and S_N2 (E3, E4) routes by trapping the radicals and radical anions involved in the former. When the reaction of 2-nitrophenylthiolate with 2-bromo-2-nitropropane was carried out under O_2, in the presence of

p-dinitrobenzene, or with the exclusion of light the yield of disulphide was substantially increased at the expense of the α-nitrosulphide. Similarly when the reaction of 4-chlorophenylthiolate with 2,2-dinitropropane was carried out under O_2 only disulphide was formed.

Precedent for an ionic mechanism for the oxidation of thiolates is provided by their reaction with acetylene halides[16] (E7). Bunnett[17] has shown that this reaction yields disulphide in the dark but with light catalysis yields a $S_{RN}1$ product.

$$PhC{\equiv}CX + RS^- \longrightarrow PhC{\equiv}C^- + RSX \xrightarrow{RS^-} RSSR \qquad (E7)$$

Another possible mechanism (E8) for the oxidation, with the α-nitrosulphide as intermediate, can be eliminated since inhibition of the formation of α-nitrosulphides should also prevent formation of disulphides. This is evidently not the case, as the reactions of p-tolyl-, 4-chlorophenyl-, or phenyl-thiolate with 2-bromo-2-nitropropane under O_2 gave an undiminished yield of disulphide (see Table, note c).

$$RS^- + Me_2C(X)NO_2 \xrightarrow{S_{RN}1} Me_2C(SR)NO_2 \xrightarrow{RS^-\,(S_N2)} RSSR + Me_2CNO_2^- \qquad (E8)$$

We conclude that our results provide considerable evidence that certain thiolates undergo oxidative dimerisation with α-substituted aliphatic nitro compounds by an ionic mechanism (E3, E4) via a reactive sulphenyl intermediate (RSX) to yield disulphides. We also suggest that in the reactions of anions with α-substituted nitro compounds three reaction pathways are possible, depending on the nature of the α-substituent and the anion; $S_{RN}1$ (Scheme 1), nucleophilic attack by the anion on the α-substituent, or oxidative dimerisation by a radical route (Scheme 2).

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