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RADICAL-NUCLEOPHILIC SUBSTITUTION ($S_{RN}1$) REACTIONS OF α-NITRO-THIOCYANATES

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Summary: *α-Nitro-thiocyanates undergo substitution by a $S_{RN}1$ mechanism with a range of anions to give loss of thiocyanate, corroborating behaviour observed for the intermediate α-nitro-thiocyanato radical-anions by e.s.r. spectroscopy.*

α-Substituted nitroalkanes have been reported[1,2] to undergo substitution via a radical radical-anion chain mechanism ($S_{RN}1$) with an increasing number of anions. Loss of the α-substituent (Scheme 1, route A) has been observed for X = I, Br, Cl, SO_2R, S(O)R, and SR; and loss of nitrite (equation 2B) in an equivalent $S_{RN}1$ mechanism has been observed for X = COR, CO_2R, NO_2, CN, N_3, and R. To our knowledge, there are no reports of thiocyanate acting as a leaving group in $S_{RN}1$ reactions.

Scheme 1

$$\begin{array}{rcll}
R_2C(X)NO_2 + A^- & \longrightarrow & [R_2C(X)NO_2]^{\dot{-}} + A^{\cdot} & (1)\\
{[R_2C(X)NO_2]^{\dot{-}}} & \longrightarrow & R_2\dot{C}NO_2 + X^- & (2A)\\
{[R_2C(X)NO_2]^{\dot{-}}} & \longrightarrow & R_2\dot{C}X + NO_2^- & (2B)\\
R_2\dot{C}NO_2 + A^- & \longrightarrow & [R_2C(A)NO_2]^{\dot{-}} & (3A)\\
{[R_2C(A)NO_2]^{\dot{-}}} + R_2C(X)NO_2 & \longrightarrow & R_2C(A)NO_2 + [R_2C(X)NO_2]^{\dot{-}} & (4A)
\end{array}$$

Electron spin resonance (e.s.r.) spectroscopy[3] has been used to show that 2-nitro-2-thiocyanatopropane, at low temperature in solid matrices, is able to capture an electron to form a stable radical-anion $[Me_2C(SCN)\dot{N}O_2^-]$ which dissociates to yield $Me_2\dot{C}NO_2$ and thiocyanate (Equation 2A, X = SCN). One of the purposes of this study is to show that e.s.r. spectroscopy can be used to predict the behaviour of radical-anions in solution reactions at room temperature e.g. their stability, and the direction of dissociation (Equation 2A versus 2B). The radical-anion of nitro-thiocyanatomethane has also been observed[4] recently by e.s.r. spectroscopy. Electrochemical studies[5] have shown that thiocyanato radical-anions can dissociate by loss of thiocyanate and/or cyanide.

2-Nitro-2-thiocyanatopropane and 1-nitro-1-thiocyanatocyclohexane were prepared in good yield (40 and 43% resp.) by the oxidative addition of thiocyanate to the anion of 2-nitropropane (Scheme 2). The best yields were obtained when the anion of 2-nitropropane (1 equiv.) was added to a CH_2Cl_2/H_2O solution of thiocyanate (1 equiv.) and ferricyanide (2 equiv.).

Scheme 2

$$\begin{array}{rcll}
R_2CNO_2^- + Fe(III) & \longrightarrow & R_2\dot{C}NO_2 + Fe(II) & (5)\\
R_2\dot{C}NO_2 + {}^-SCN & \longrightarrow & [R_2C(SCN)NO_2]^{\dot{-}} & (6)\\
{[R_2C(SCN)NO_2]^{\dot{-}}} + Fe(III) & \longrightarrow & R_2C(SCN)NO_2 + Fe(II) & (7)
\end{array}$$

Table 1 : $Me_2C(SCN)NO_2 + A^- \longrightarrow Me_2C(A)NO_2 + {}^-SCN$

A^-	Reaction Conditions^a	% yield of $Me_2C(A)NO_2$
$Me_2CNO_2^-$	DMSO (2h), DMF (2h)	72, 51
	DMSO (2h), dark, oxygen atmosphere,	42, 38
	5 molar % *p*-dinitrobenzene, 10 molar % $(t\text{-}Bu)_2NO\cdot$	34, 34
$PhSO_2^-$	DMSO (2h)	49
	DMSO (2h); dark, oxygen atmosphere,	40, 37
	5 molar % *p*-dinitrobenzene, 10 molar % $(t\text{-}Bu)_2NO\cdot$	40, 35
N_3^-	HMPA; fluorescent laboratory lights; 90 min, 5h	8 (39)^b, 8 (27)^b

(a) The reactions were carried out with 3 molar quantities of 2-nitro-2-thiocyanatopropane and the anion under an atmosphere of nitrogen and with irradiation (Tungsten 'white light' lamps, 2 x 150W), unless otherwise stated. (b) Unreacted 2-nitro-2-thiocyanatopropane.

Attempts to prepare 2-nitro-thiocyanatopropane, under various conditions, by an $S_{RN}1$ reaction (Scheme 1, $A^- = {}^-SCN$, X = I, Br) failed, leaving unreacted starting material. Even use of catalytic chain initiation[6] (entrainment) with catalytic amounts of the anion of 2-nitropropane yielded no α-nitro-thiocyanate, but did yield traces of 2,3-dimethyl-2,3-dinitrobutane. The latter compound was also a significant impurity in the synthesis using ferricyanide, suggesting that the anion of 2-nitropropane successfully competes with thiocyanate for addition to the 2-nitropropyl radical.

Similar lack of reactivity of thiocyanate in $S_{RN}1$ reactions with haloquinolines has been reported[7]. The lack of reactivity in our system is surprising because the synthesis of 2-nitro-2-thiocyanatopropane with ferricyanide shows that thiocyanate is able to add to the 2-nitropropyl radical (Equation 5) - the second step of the $S_{RN}1$ chain (Equation 3A, $A^- = {}^-SCN$). Likewise results from e.s.r. spectroscopy suggest that the dissociation of $[Me_2C(SCN)NO_2]^{\dot{-}}$ is reversible (Equation 8),

$$[Me_2C(SCN)NO_2]^{\dot{-}} \rightleftharpoons Me_2\dot{C}NO_2 + {}^-SCN \qquad (8)$$

but that dissociation takes place readily. Similar results for the stability of $[Me_2C(Br)NO_2]^{\dot{-}}$ and $[Me_2C(Cl)NO_2]^{\dot{-}}$ have been suggested from e.s.r. spectroscopy . Bromide and chloride have not been reported to act as nucleophiles in $S_{RN}1$ reactions. We suggest that the equilibrium (Equation 8) lies well over on the side of dissociation thus inhibiting the chain reaction. The lack of $S_{RN}1$ reactivity could also be due to poor electron transfer between thiocyanate and 2-iodo- or 2-bromo-2-nitropropane. The electron transfer is required for initiation of the $S_{RN}1$ chain reaction (Equation 1, $A^- = {}^-SCN$, X = Br, I).

It is of interest to note that thiocyanate is an ambident anion but only adds to the 2-nitropropyl radical via the sulphur atom (Equation 6). We suggest that is phenomena is possibly explained by kinetic control[8] of the addition because the sulphur-anion is more nucleophilic towards carbon than the nitrogen-anion.

Table 2 : $Me_2C(SCN)NO_2 + RS^- \longrightarrow Me_2C(SR)NO_2 + RSSR + {}^-SCN + Me_2C(NO_2)C(NO_2)Me_2$

RS^-	Reaction Conditions[a]	% yields			
		$Me_2C(SR)NO_2$	RSSR	'dimer'	$Me_2C(SCN)NO_2$
4-chlorophenyl	DMSO (2h)	37	14	16	0
	DMSO (2h); dark, oxygen atmosphere,	20, 12	16, 4	20, 10	10, 41
	40 molar % p-dinitrobenzene,	17	26	8	34
	40 molar % $(t\text{-}Bu)_2NO\cdot$	26	0	0	11
phenyl	DMSO (2h), 10 min., 2h	0, 0	36, 52	34, 50	10, 0
	DMSO (2h); dark, oxygen atmosphere,	0, 0	38, 26	41, 11	0, 24
	20 molar % p-dinitrobenzene,	0	38	12	9
	20 molar % $(t\text{-}Bu)_2NO\cdot$	0	37	13	6

(a) The reaction conditions were the same as detailed in Table 1 except that irradiation was with fluorescent laboratory lights.

The results of the reaction of 2-nitro-2-thiocyanatopropane with the anion of 2-nitropropane, phenyl sulphinate, and azide (Table 1) show good yields of the corresponding α-substituted nitro-compound, with loss of thiocyanate. The inhibition studies[2,6] indicate that a radical radical-anion light-catalysed chain mechanism ($S_{RN}1$) is operative (Scheme 1 with X = SCN). The lower yields for azide are due to the steady decomposition of 2-azido-2-nitropropane[1a] with time.

1-Nitro-1-thiocyanatocyclohexane also reacted (DMSO, 4h, hν) with the anion of 2-nitropropane, with loss of thiocyanate, to yield the corresponding α-substituted product [1-(1-methyl-1-nitroethyl)-1-nitrocyclohexane] (61%) by an $S_{RN}1$ mechanism and 2,3-dimethyl-2,3-dinitrobutane (16%) by a radical radical-anion non-chain mechanism[1a,9,10].

The reaction of 2-nitro-2-thiocyanatopropane with thiolates yielded the corresponding α-nitrosulphides and/or disulphides (Scheme 3).

Scheme 3

$$Me_2C(SCN)NO_2 + RS^- \longrightarrow Me_2C(SR)NO_2 + {}^-SCN \qquad (S_{RN}1) \qquad (9)$$

$$\longrightarrow RSSCN + Me_2CNO_2^- \qquad (S_N2) \qquad (10)$$

$$RSSCN + RS^- \longrightarrow RSSR + {}^-SCN \qquad (S_N2) \qquad (11)$$

$$Me_2CNO_2^- + Me_2C(SCN)NO_2 \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + {}^-SCN \qquad (S_{RN}1) \qquad (12)$$

$$Me_2C(SR)NO_2 + RS^- \longrightarrow RSSR + Me_2CNO_2^- \qquad (S_N2) \qquad (13)$$

4-Chlorophenylthiolate yielded largely the α-nitrosulphide. Inhibition studies clearly show lowered yields of α-nitrosulphide and increased recovery of starting material, indicating a $S_{RN}1$ mechanism for the formation of α-nitrosulphide (Equation 9 or Scheme 1, X = ^-SCN, A^- = RS^-). The reaction with phenylthiolate yielded only disulphide, the formation of which was unaltered by p-dinitrobenzene, di-t-butylnitroxide, and the absence of light, suggesting a non-radical mechanism[10] (Equations 10 and 11).

Phenylthiolate is a stronger nucleophile than 4-chlorophenylthiolate and therefore S_N2 attack (Equation 10) by the thiolate on the thiocyanato-substituent to form an intermediate sulphenyl-thiocyanate is favoured over the slower electron-transfer required for the $S_{RN}1$

mechanism. This competition between S_N2 and $S_{RN}1$ mechanisms for the reactions of thiolates with α-substituted nitro-compounds has been described[10]. Sulphenyl-thiocyanates are well known to react rapidly with thiolates to yield disulphides (Equation 11).

2,3-Dimethyl-2,3-dinitrobutane was formed as a by-product in both reactions by an $S_{RN}1$ mechanism (Equation 12) as shown by the inhibition studies. Di-(4-chlorophenyl) disulphide was formed by the abstraction route (Equation 10 and 11) as well as by an equivalent route[10] from the α-nitrosulphide (Equation 13).

Reaction of 2-nitro-2-thiocyanatopropane with 4-nitrophenylthiolate yielded largely the corresponding α-nitrosulphide as well as some disulphide but benzylthiolate yielded disulphide only.

Reaction of 2-nitro-2-thiocyanatopropane with the anion of diethyl ethylmalonate (DMSO, 5h, hν) proceeded with loss of thiocyanate by a redox reaction to give the respective dimers: 2,3-dimethyl-2,3-dinitrobutane (47%) and tetraethyl hexane-3,3,4,4-tetracarboxylate (20%). A radical radical-anion mechanism has been proposed[2] for redox reactions of this type.

$$Me_2C(SCN)NO_2 + Et\bar{C}(CO_2Et)_2 \longrightarrow EtC(CO_2Et)_2C(Et)(CO_2Et)_2 + Me_2C(NO_2)C(NO_2)Me_2 \qquad (14)$$

We have shown that thiocyanate can act as a leaving group in $S_{RN}1$ reactions with a range of different nucleophiles. The behaviour of α-nitrothiocyanates and their radical-anions in solution reactions is in accordance with predictions made from e.s.r. spectroscopy. We *therefore suggest that e.s.r. spectroscopy provides a good probe for predicting the reactivity of radical-anions in* $S_{RN}1$ reactions.

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