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RADICAL-NUCLEOPHILIC SUBSTITUTION ($S_{RN}1$) REACTIONS: PREPARATION AND REACTIONS OF ALIPHATIC α-NITRO-AZIDES

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SUMMARY: α-Nitro-azides were prepared by two routes involving intermediate radical-anions, and undergo substitution by an $S_{RN}1$ mechanism with azides, sulphinates, and thiolates to give loss of nitrite, and with nitronates to give loss of azide.

α-Substituted nitroalkanes have been reported[1,2,3] to undergo substitution via a radical-nucleophilic chain mechanism ($S_{RN}1$, Scheme 1) with a growing list of anions. Route A (loss of X^-) has been observed for X = I, Br, Cl, SO_2R, S(O)R, SR and route B (loss of NO_2^-) for X = COR, CO_2R, NO_2, CN, R. The participation of azide in $S_{RN}1$ reactions has only been reported[4] for the 4-nitrocumyl system (Equat.5). There have been no reports of azido compounds in $S_{RN}1$ substitutions. We report herein our initial results for $S_{RN}1$ reactions with azide and with nitro-azides, and their implications to the $S_{RN}1$ mechanism.

SCHEME 1

(A⁻ = anion)

$$R_2C(X)NO_2 + A^- \longrightarrow [R_2C(X)NO_2]^{\cdot-} + A^\cdot \qquad (1)$$

$$[R_2C(X)NO_2]^{\cdot-} \longrightarrow R_2\dot{C}NO_2 + X^- \qquad (A2)$$

$$R_2\dot{C}NO_2 + A^- \longrightarrow [R_2C(A)NO_2]^{\cdot-} \qquad (A3)$$

$$(R_2C(A)NO_2]^{\cdot-} + R_2C(X)NO_2 \longrightarrow R_2C(A)NO_2 + [R_2C(X)NO_2]^{\cdot-} \qquad (A4)$$

$$[R_2C(X)NO_2]^{\cdot-} \longrightarrow R_2\dot{C}X + NO_2^- \qquad (B2)$$

$$R_2\dot{C}X + A^- \longrightarrow [R_2C(A)X]^{\cdot-} \qquad (B3)$$

$$[R_2C(A)X]^{\cdot-} + R_2C(X)NO_2 \longrightarrow R_2C(A)X + [R_2C(X)NO_2]^{\cdot-} \qquad (B4)$$

$$4\text{-}NO_2PhC(NO_2)Me_2 + N_3^- \longrightarrow 4\text{-}NO_2PhC(N_3)Me_2 + NO_2^- \qquad (5)$$

Preparation of α-Nitro-Azides by Nucleophilic Substitution: We encountered considerable difficult in the preparation of 2-azido-2-nitropropane by nucleophilic substitution. The only good results are shown in Table 1, with a satisfactory yield of 38%. The results of light catalysis and of inhibition by a strong electron-acceptor (*p*-dinitrobenzene) and a radical scavenger (di-t-butylnitroxide) are not clear-cut. These methods are used as criteria[2,5] for assigning the $S_{RN}1$

TABLE 1: $Me_2C(Br)NO_2 + N_3^- \longrightarrow Me_2C(N_3)NO_2 + Br^-$

Conditions	Time (min.)	% Recovery $Me_2C(Br)NO_2$	% Yield of $Me_2C(N_3)NO_2$
Standard	15, 60, 24h	17, 11, 0	25, 22, 38
Dark	15, 60	20, 17	21, 21
5 molar % *p*-dinitrobenzene	15	22	17
10 molar % $(t\text{-}Bu)_2NO^\cdot$	15, 60	28, 13	23, 20

The reactions were carried out in HMPA with equimolar amounts of starting materials, under an atmosphere of N_2 and fluorescent laboratory lighting. The figures are averages of two closely agreeing runs.

mechanism. We however suggest that these small, but significant, inhibitions (especially at shorter times) indicate that $S_{RN}1$ is the most likely mechanism (further work is underway to clarify this assignment).

The use of stronger photolysis lights for catalysis led to rapid consumption of the nitro-azide. The nitro-azide also reacts (see later) with azide to yield the diazide, which is also consumed, even with laboratory lighting. These results are not surprising because the photolysis of azides is well known and certainly complicate conclusions drawn from the results. Reaction in DMF gave only traces of nitro-azide or diazide, at any time, with slow consumption of starting material (i.e. rate of formation equals rate of decomposition).

Preparation of α-Nitro-Azides by Oxidative Addition of Azide to Nitronate Anions: Potassium ferricyanide[6] was used for the oxidative addition (with an excess of azide in CH_2Cl_2/H_2O) as shown in Scheme 2. A 69% yield of pure 1-azido-1-nitrocyclohexane was obtained with cyclohexyl-nitronate; but to our surprise oxidation of propyl-2-nitronate gave a 41% yield of pure 2,2-diazidopropane;

SCHEME 2

$$R_2CNO_2^- + Fe(III) \longrightarrow R_2\dot{C}NO_2 + Fe(II)$$
$$R_2\dot{C}NO_2 + N_3^- \longrightarrow [R_2C(N_3)NO_2]^{\dot{-}}$$
$$[R_2C(N_3)NO_2]^{\dot{-}} + Fe(III) \longrightarrow R_2C(N_3)NO_2 + Fe(II)$$

which suggested that the breakdown of the intermediate radical-anion (Scheme 3) was faster than its oxidation by ferricyanide ($k_2 > k_1$). However when the reaction was analysed (Table 2) at different times it was clear that the diazide was formed from the nitro-azide and not directly by decomposition of the radical-anion. Similarly when the nitronate was added to a solution of ferricyanide (i.e. always in excess) and only one equivalent of azide, a 28% yield of nitro-azide was obtained. The diazide, as shown later, is therefore formed by $S_{RN}1$ reaction of excess azide with the nitro-azide. Our results indicate that the electron is removed from $[Me_2C(N_3)NO_2]^{\dot{-}}$, in either $S_{RN}1$ reaction or ferricyanide oxidation, faster than its breakdown ($k_1 > k_2$).

SCHEME 3

$$\begin{tikzcd}
Me_2CNO_2^- \arrow[r] & Me_2\dot{C}NO_2 \arrow[r, "N_3^-"] & {[Me_2C(N_3)NO_2]^{\dot{-}}} \arrow[r, "k_1"] \arrow[d, "k_2"] & Me_2C(N_3)NO_2 \\
 & & Me_2\dot{C}N_3 + NO_2^- \arrow[d] & \\
 & & {[Me_2C(N_3)_2]^{\dot{-}}} \arrow[r] & Me_2C(N_3)_2
\end{tikzcd}$$

TABLE 2: $Me_2CNO_2^- + 2N_3^- \longrightarrow Me_2C(N_3)NO_2 + Me_2C(N_3)_2$

Time (min.).	1	15	20	40	60
% $Me_2C(N_3)NO_2$	28	24	19	7	0
% $Me_2C(N_3)_2$	19	22	22	38	41

$S_{RN}1$ Reactions of α-Nitro-Azides: The results of the reaction of 2-azido-2-nitropropane with azide, phenylsulphinate, and 4-chlorophenylthiolate (Table 3) show high yields of the α-substituted azides. The inhibition studies strongly indicate that a radical radical-anion light-catalysed chain reaction mechanism ($S_{RN}1$) is operative as illustrated in Scheme 1 (equations 1 B2, B3, and B4 with $X = N_3$); which suggests that:

1. Nitrite is superior to azide as a nucleofugal group in radical-anions. Whilst not strictly comparable, Kornblum's report[4] on the *p*-nitrocumyl series (Equation 5) confirms that loss of

TABLE 3: $Me_2C(N_3)NO_2 + A^- \longrightarrow Me_2C(A)N_3 + NO_2^-$

Anion (A^-)	Conditions*	% Yield of $Me_2C(A)N_3$
N_3^-	DMF, DMSO, HMPA	No product, $Me_2C(N_3)NO_2$ consumed.
	CH_2Cl_2/H_2O, 40 min.	Quantitative.
	CH_2Cl_2/H_2O, 40 min. + dark, 5 molar % *p*-dinitrobenzene, 10 molar % $(t\text{-}Bu)_2NO^{\cdot}$, or O_2	0 %, with 90-95% recovery of $Me_2C(N_3)NO_2$
$PhSO_2^-$	DMSO, 5 min. Control	70
	+ 10 molar % *p*-dinitrobenzene	47
	+ 20 molar % $(t\text{-}Bu)_2NO^{\cdot}$	47
	DMF, 10 & 40 min., 24h.	59 + trace of $Me_2C(N_3)NO_2$; 59; 46
4-ClPhS$^-$	DMF, 40 min.	70

*Carried out under at atmosphere of N_2 and laboratory lighting. Longer reaction times or use of Tungsten (white light) photolysis lamps gave much more lower yields.

nitrite is favoured over loss of azide (the reverse of the reaction shown in Equat.5 is possible but was not observed) in $S_{RN}1$ reactions.

2. The intermediate 2-azidopropyl radical is sufficiently long-lived to be able to participate in chain-reactions without complete decomposition. The radical, although as yet undetected by e.s.r. spectroscopy, is reported[7] to be a π-radical (delocalised onto the nitrogens), short-lived, and to rapidly breakdown with loss of dinitrogen to yield the observed long-lived σ-radical ($Me_2C{=}N^{\cdot}$). We found no signs of this latter decomposition in the form of the usually observed[10] dimer ($Me_2C{=}N{-}N{=}CMe_2$). However, the iminyl radical could abstract a hydrogen radical to form an imine which would hydrolise on work-up to acetone.

3. The 2-azidopropyl radical is able to add to anions via carbon to form a new-species of radical-anions, $[Me_2C(A)N_3]^{\cdot-}$.

4. This $S_{RN}1$ reaction route can be used for the synthesis of α-substituted azides.

Loss of Azide in $S_{RN}1$ Reactions of α-Nitro-Azides: Reactions with propyl-2-nitronate were slow, low-yielding, and gave loss of azide rather than nitrite (Table 4). The results (inhibition and light-catalysis) indicate that some of the product is formed by an $S_{RN}1$ substitution (Scheme 1, equations 1, A2, A3 and A4 with $X{=}N_3$) but that a lot of the 2,3-dimethyl-2,3-dinitrobutane is formed by a radical radical-anion non-chain mechanism (i.e. small amounts of inhibitor will only inhibit chain reactions but large amounts will hinder a non-chain radical reaction). This non-chain mechanism has been observed on numerous occasions[3,8] with the anion of 2-nitropropane.

We suggest that the best explanation for the dual nucleofugal behaviour in the α-nitro-azide radical-anion is that loss of azide is more rapid than nitrite, and that the resulting 2-azidopropyl radical adds rapidly to anions in the absence of steric control (e.g. N_3^-, RS^-). However, when steric control becomes important ($Me_2CNO_2^-$) this addition is blocked and the 2-nitropropyl radical resulting from the less favoured loss of azide, is able to add to the anion instead.

TABLE 4: $R_2C(N_3)NO_2$ + $Me_2CNO_2^-$ $\longrightarrow$ $R_2C(NO_2)C(NO_2)Me_2$

R_2C	Conditions	% $R_2C(N_3)NO_2$	% Yield of $R_2C(NO_2)C(NO_2)Me_2$
Me_2C	HMPA, 1h., N_2, Tungsten Lamps,	0	24
	+ 10 molar % *p*-dinitrobenzene	0	24
	+ 10 molar % $(t\text{-}Bu)_2NO^{\bullet}$	0	24
	+ 40 molar % $(t\text{-}Bu)_2NO^{\bullet}$	trace[a]	trace[a]
	Dark	0	19
Cyclohexyl	DMSO, 2h., N_2, Tungsten Lamps	0	18[a] (8)[a,b]
	Dark	50	0
	Lab. lights + 10 molar % *p*-dinitrobenzene	50[a]	0 (10)[a,b]
	" " + 40 molar % *p*-dinitrobenzene	100	0
	" " + 10 molar % $(t\text{-}Bu)_2NO^{\bullet}$	64	0

a. Analysis by n.m.r. b. % Yield of $Me_2C(NO_2)C(NO_2)Me_2$

We conclude that our results show the reaction of azide as a nucleophile, the dual nucleofugal properties of α-nitro-azides, nitrite as a better nucleofugal group than azide, and the intermediacy of the 2-azidopropyl radical in aliphatic $S_{RN}1$ reactions. While we encountered no explosive properties for any of the compounds, all reactions were carried out with extreme caution.

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