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$S_{RN}1$ AND OXIDATIVE ADDITION REACTIONS OF NITROIMIDAZOLE ANIONS

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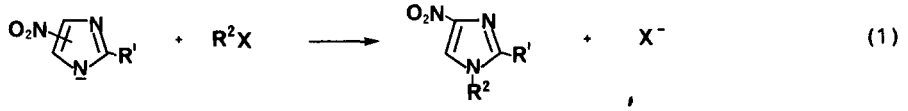
Summary: The anions of 2- and 4(5)-nitroimidazoles react with aliphatic substituted nitro compounds and p-nitrobenzyl chloride by a $S_{RN}1$ mechanism, or by oxidative addition to the anion of 2-nitropropane, to yield 1-alkyl-2-(or 4-)-nitroimidazoles.

A wide range of anions have been reported to react with aliphatic substituted nitro compounds, and nitrobenzyl derivatives and their heterocyclic analogues.[1,2] A singular lack of success has been reported[1,3] for N-centred anions, or amines. An exception is the facile reaction between amide ($^-NH_2$) and substituted arenes.[3] Kornblum[1a] has also reported the reaction between p-nitrocumyl chloride and quinuclidine, and nitrite. Azide anion also undergoes $S_{RN}1$ type reactions.[4] We report the $S_{RN}1$ reactions of a new group of N-centred anions.

Nitroimidazoles are important because of their excellent antibiotic activity against anaerobic micro-organisms. $S_{RN}1$ reactions between 2-(chloromethyl)-1-methyl-5-nitro-imidazole and nitronates have been reported.[5] Our studies use the $S_{RN}1$ and related reactions to functionalise the nitrogen to produce new and otherwise inaccessible nitroimidazole analogues.

The anions of 4(5)-nitroimidazole and 2-methyl-4(5)-nitroimidazole were reacted with various electron-accepting nitro compounds to yield 1-alkyl-4-nitroimidazoles as shown by equation 1 (the results are tabulated in the Table).

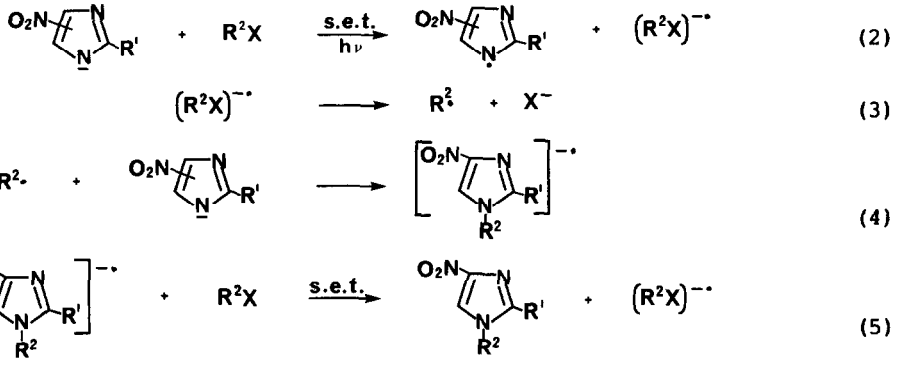


(1)

R^1 = H, Me

R^2X = $Me_2C(X)NO_2$ (X = Br, Cl, NO_2), p-NO_2-$C_6H_4CH_2Cl$, 5-bromo-5-nitro-1,3-dioxane

Scheme 1



(2)

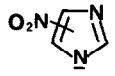
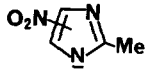
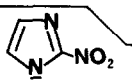
(3)

(4)

(5)

Using the normal criteria for establishing the $S_{RN}1$ mechanism[1,6] (results are tabulated in the Table), we conclude that $S_{RN}1$ is the most probable mechanism, as shown in Scheme 1. Strong inhibition was observed with oxygen and di-t-butyl nitroxide but not by p-dinitrobenzene which suggests that oxygen largely acts as a radical scavenger rather than a

$S_{RN}1$ Reactions between Nitroimidazoles Anions and Electron Acceptors (RX).

Nitroimidazole anion	RX	Conditions[a]	% Yields[b] 1-alkyl-2(or 4)-nitroimidazole	% Yields[b] unaltered RX	% Yields[b] unaltered nitroimidazole[c]
	$Me_2C(Br)NO_2$	44 h, 8 h	92 (59), 68	0, 0	0, 0
		6 h; 6 h/O_2	41; 0, 0	25; 3, 28	0; 40, 27
		6 h/ 5 mol% pDNB	49, 52	20, 8	3, 0
		6 h/ 10 mol% DTBN	3	3	62
		6 h/ dark	28, 28	58, 23	0, 0
	$Me_2C(Cl)NO_2$	30 h	11 (6)	50	-
	p-$NO_2C_6H_4CH_2Cl$	8 h	100 (75)	0	-
		5 h, 2 h	60, 55	0, 0	0, 0
		2 h/O_2, 2 h/dark	1, 30	0, 16	48, 0
		2 h/ 10 mol% pDNB	35	0	0
		2 h/ 10,25 mol% DTBN	38, 3	10, 11	4, 57
5-bromo-5-nitro-1,3-dioxane		27 h	81 (42)	0	-
	PhI	24 h	0	58	1
	$Me_2C(Br)NO_2$	72 h	41 (37)	0	-
	$Me_2C(NO_2)_2$	48 h	80 (37)	0	-
	$Me_2C(Cl)NO_2$	96 h	12 (5)	0	-
	p-NO_2-$C_6H_4CH_2Cl$	22 h	100 (73)	0	-
	$BrCH_2NO_2$	36 h	0	0	45
	p-$NO_2C_6H_4CH_2Cl$	26 h	(26)	-	-

a) All reactions were carried out in DMSO under nitrogen and irradiation with fluorescent lamps (2 x 150 W), with nitroimidazole (1 equiv.), t-BuOK (1.5 equiv.), and RX (1.5 equiv.). b) % Yields are based on nitroimidazole and were calculated by n.m.r spectroscopy using an internal standard, isolated yields are in parenthesis. c) % Nitroimidazole recovered by filtration after pouring the reaction into water (a large amount stays in solution).

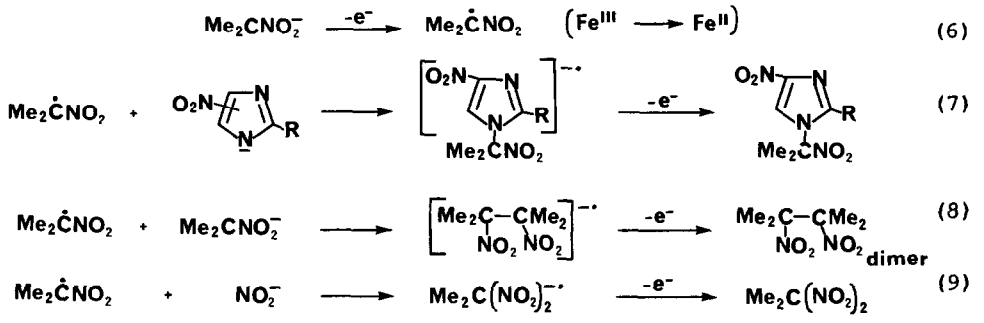
strong electron-acceptor. The lack of inhibition by p-dinitrobenzene may be due to strong electron affinity of the dinitro-product, i.e. its radical-anion, which is an intermediate in the propagation steps, may not readily undergo single electron transfer (s.e.t.) with p-dinitrobenzene.[6] All the reaction solutions exhibit a red colour after a few minutes which disappears on completion, indicative of a charge-transfer complex between reactants prior to light catalysed s.e.t.

4(5)-Nitroimidazole anions are ambident and therefore can react to form 4- or 5-nitro-imidazole radical-anion intermediates (equation 4) and hence 4- or 5-nitroimidazole products. The 4-isomer is exclusively formed with no indication of the 5-isomer in the $Me_2C(X)NO_2$ reactions. The 4-isomer is also the major product in the reaction of 4(5)-nitro-imidazoles anions with p-nitrobenzyl chloride but a small amount of the 5-isomer was observed by ^{13}C n.m.r. spectroscopy. The position of the nitro group was determined by spectroscopy (^1H n.m.r. and u.v./vis.) but particularly by ^{13}C n.m.r. spectroscopy,[7] (i.e. the ^{13}C n.m.r signal for C_4 in the 5-nitro-isomer ranges between 131-134 p.p.m., whereas the signal for C_5 in the

4-nitro-isomer is 119-123 p.p.m.)

4-Nitroimidazoles are also formed exclusively over the 5-nitro-isomer in the oxidative addition of the nitroimidazole anions to the anion of 2-nitropropane (equations 6 and 7, Scheme 2). Addition of the nitroimidazole anion to the 2-nitroprop-2-yl radical is the crucial step in both $S_{RN}1$ and oxidative addition. The oxidations using potassium ferricyanide[2,8] gave low yields of 1-alkyl-4-nitroimidazoles and a considerable amount of 2,3-dimethyl-2,3-dinitrobutane (equations 6 and 7) and traces of 2,2-dinitropropane (equations 6 and 9) arising from nitrite formed during decomposition of the 2-nitroprop-2-yl radical. However when persulphate and ferricyanide were used[9] the yield improved considerably with no 2,2-dinitropropane.

Scheme 2



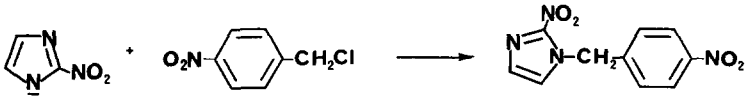
R = Me,	$K_3Fe(CN)_6$ (2 equiv.),	$Me_2CNO_2^-$ (1.2 equiv.),	10 min,	9-17%,	2-14% dimer
R = H,	"	"	1 h,	(21%) 9%	"
= H,	" (0.2 equiv.),	"	"	63(34)%,	20% "

plus sodium persulphate (2 equiv.).

An interesting comparison of the selectivity of this reaction can be made with the reaction between the anion of 4(5)-nitroimidazole and the electrophilic dimethyl sulphate.[10] In this reaction the relative rate of formation of 4:5-nitroimidazole, of *ca* 8:1 is explained by the greater nucleophilicity of the 4-nitroimidazole anion (the nitro group is further away from the *N*-anion than in the 5-nitro-isomer, causing higher electron-density on the *N*-anion). We suggest that this reasoning also applies to radical reactions, *i.e.* kinetic control of the attack by the nitroimidazole anion on the intermediate radical (equation 4). In $S_{RN}1$ reactions involving ambident anions, exclusive formation of a product *via* the most nucleophilic ambident anion is usually observed.[2] Our results therefore provide further evidence that the addition of anions to radicals in $S_{RN}1$ reactions is under kinetic control.[2,3]

Steric hindrance is also possibly a factor in determining the selectivity of formation of the 4-isomer even though $S_{RN}1$ reactions are not easily influenced by steric factors.[11b,12] The nitro group in the 5-nitroimidazole ambident anion is adjacent to the reacting *N*-anion and will hinder the approach of the bulky 2-nitroprop-2-yl radical, whereas the nitro group in the 4-nitro ambident anion is away from the reacting *N*-anion. Evidence for this proposal is provided by: a) Reactions with 2-methyl-4(5)-nitroimidazole are slower than with 4(5)-nitroimidazole. b) A small amount of the 5-nitroimidazole is formed in the reaction between the anion of 4(5)-nitroimidazole and *p*-nitrobenzyl chloride. In this reaction the intermediate *p*-nitrobenzyl radical should not be greatly influenced by steric hindrance. However, the predominance of the 4-nitro-isomer in this reaction indicates that electronic factors are probably dominant.

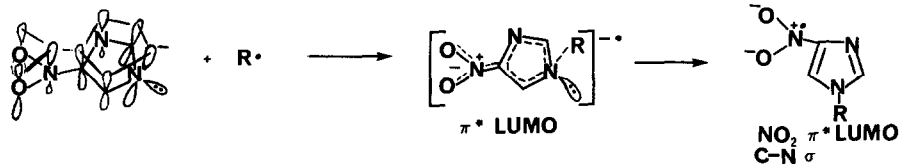
c) The anion of 2-nitroimidazole (which also has the nitro group adjacent to the reacting N-anion) does not undergo oxidative addition to $Me_2CNO_2^-$ or undergo $S_{RN}1$ reaction with 2-substituted-2-nitropropanes, even under forcing conditions, but does react with p-nitrobenzyl chloride (equation 10).



(10)

An interesting point is why these N-anions react in $S_{RN}1$ reactions whereas other N-anions or amines do not. A possible explanation[13] for the lack of reactivity is that the energy of the LUMO in the intermediate radical-anion is too high (i.e. the unpaired electron is in a C-N σ^* MO). A similar lack of $S_{RN}1$ reactivity, observed for O-centred anions, has been explained by the high energy of the C-O σ^* MO in the intermediate radical-anion.[14] The electrons in the imidazole anion are symmetrically delocalised[15] in the imidazole ring in the π MO's). We therefore propose that when the nitroimidazole anion attacks the intermediate radical to form a radical-anion that the radical-anion initially formed has the unpaired electron in a π^* MO (of relatively low energy) and not in a σ^* MO, thereby allowing the reaction to proceed. The conjugated nitro group will further lower the LUMO energy of the radical-anion. The initial radical-anion probably undergoes a smooth transition with rearrangement of MO's to a radical-anion with a C-N σ-bond in which the the unpaired electron is localised in the π^* LUMO of the aromatic nitro group as illustrated in Scheme 3.

Scheme 3



The $S_{RN}1$ reactions of the anions of other five-atom NH-heterocycles are under investigation. The antibiotic activity of these and related compounds against anaerobic micro-organisms will be reported elsewhere in the near future.

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