Free Radical Pathways in the Nitrous Acid Deamination of α-Aminonitriles

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Free radicals and carbocations are generated competitively in nitrous acid deamination reactions of α-aminonitriles; in the absence of added scavengers the radicals are trapped by NO_2 and by NO.

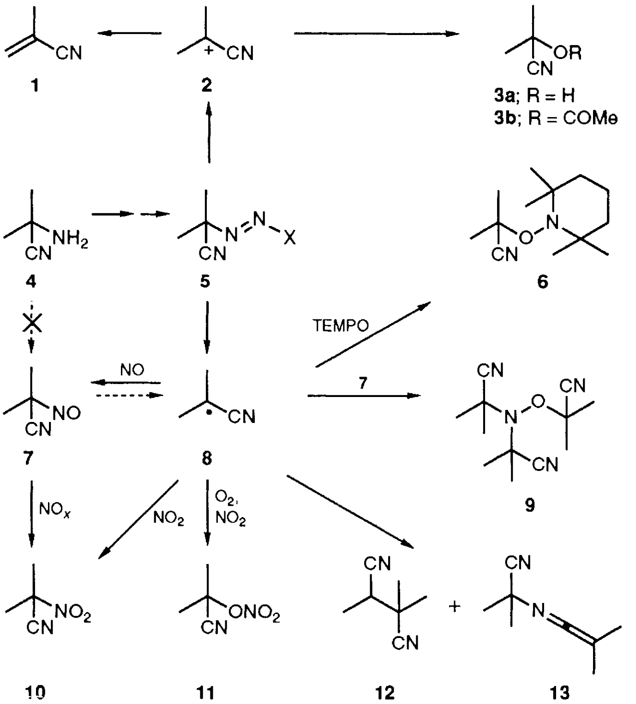
Aliphatic diazonium ions decompose *via* cationic and concerted routes;[1,2] the intervention of free radicals is extremely rare.[3] In contrast, aryl radicals are readily accessible from arenediazonium ions.[4] We now report that the diazotisation of α-aminonitriles generates free radicals as well as carbocations.

The results of nitrous acid deamination reactions of 2-amino-2-methylpropanenitrile **4** are summarised in Scheme 1 and in Table 1. The products of elimination **1** and of nucleophilic substitution **3**, presumably derived from the carbocation **2**, are accompanied by 2-methyl-2-nitropropane-

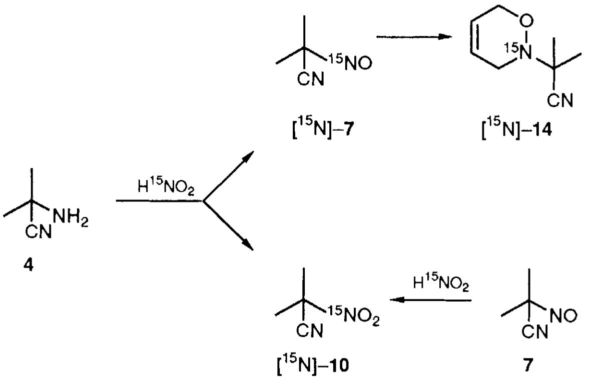
Table 1 Product distribution (%)[a] obtained from deamination reactions of 2-amino-2-methylpropanenitrile **4** at 25 °C

	Conditions[b]	**3a**	**3b**	**6**	**9**	**10**	**11**	**12**	**13**
1	$NaNO_2$, aq. $HClO_4$,[c] N_2	37.3	—	—	13.9	47.4	0.4	—	—
2	$NaNO_2$, aq. $HClO_4$–pentane, N_2	5.2	—	—	13.9	53.6	4.4	9.5	13.4
3	$NaNO_2$, aq. $HClO_4$–pentane, N_2, TEMPO (1 equiv.)	19.1	—	63.7	—	17.2	—	—	—
4	$NaNO_2$,[d] HOAc, N_2	14.3	12.6	—	28.6	41.8	2.7	—	—
5	$NaNO_2$,[d] HOAc, N_2, TEMPO (0.5 equiv.)	2.7	3.6	40.2	—	53.5	—	—	—
6	$NaNO_2$,[d] HOAc, N_2, TEMPO (1 equiv.)	0.5	2.3	50.3	—	46.9	—	—	—
7	$NaNO_2$,[d] HOAc, N_2, TEMPO (2 equiv.)	0.7	1.7	59.1	—	38.5	—	—	—
8	$NaNO_2$,[d] HOAc, N_2, TEMPO (4 equiv.)	0.3	0.3	89.2	—	10.2	—	—	—
9	N_2O_4, HOAc, N_2	2.9	2.0	—	4.6	89.4	1.1	—	—
10	N_2O_4, HOAc, O_2	7.8	7.6	—	—	36.9	47.6	—	—

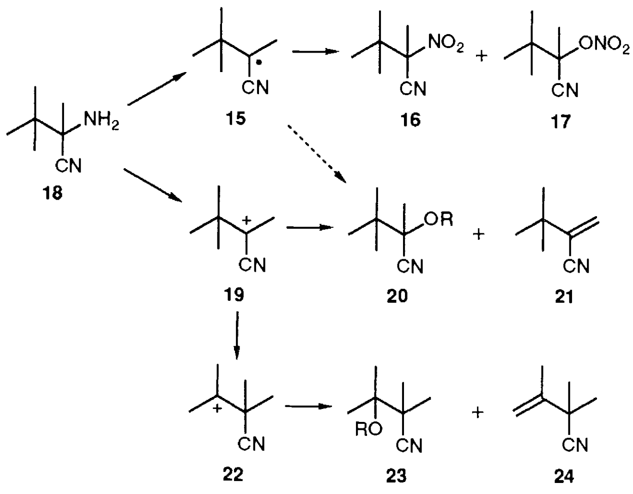
[a] The yields of 2-methylpropenenitrile **1** (15–30% in aq. $HClO_4$, 25–45% in HOAc) varied strongly, owing to the volatility of **1** and to secondary reactions with NO_2. Therefore, **1** was not included in Table 1. [b] Two equivalents of the nitrosating agent were added to 0.2 mol dm^{-3} solutions of **4**. [c] Variation of the pH from 0 to 3.5 had little effect on the product distribution. [d] Added as a concentrated aqueous solution to 0.2 mol dm^{-3} solutions of **4** in anhydrous acetic acid.



Scheme 1



Scheme 2

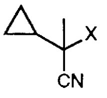


Scheme 3

nitrile **10** and by the trisubstituted hydroxylamine **9**. 2-Cyano-2-propyl radicals **8**, generated by thermolysis of 2,2′-azo-(2-methylpropanenitrile) (AIBN), are known to add NO and NO_2 with formation of **9** and **10**, respectively.[5] In the nitrous acid deamination of **4**, homolysis of covalent diazo species, *e.g.* **5** (X = NO_2), is a likely source of **8**.

The primary product arising from **8** and NO, 2-methyl-2-nitrosopropanenitrile **7**, accounts for the blue colouration of our reaction mixtures. When **7** was continuously extracted with pentane as the deamination of **4** proceeded (see line 2 of Table 1), and buta-1,3-diene was then added to the organic phase, *ca.* 30% of the [4 + 2]cycloadduct **14**[6] was obtained. Dimerisation of **8** to give **12** and **13** also occurs in the organic phase. An analogous experiment (Scheme 2) with $Na^{15}NO_2$ revealed complete (±2%) incorporation of ^{15}N into **7** and **10**. Thus **7** and **10** arise from **4** only by way of **8**; an oxidative route is excluded. Treatment of **7** with NO or HNO_2 gives **10**, again with virtually complete exchange of the nitrogen atom. This transformation is thought to involve the formation and homolysis of **5** (X = NO_3).[7]

Molecular oxygen is known to convert **8** into the 2-cyano-2-propyloxyl radical,[8] which should be trapped by NO_2 under our conditions. In fact, admission of oxygen to the deamination of **4** with N_2O_4–HOAc led to a dramatic increase of the nitrate **11** at the expense of the nitro compound **10** (*cf.* lines 9 and 10 of Table 1). When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was added to nitrous acid deamination reactions of **4**, the 2-cyano-2-propyl radical **8** was scavenged by TEMPO to



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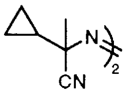

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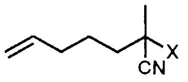

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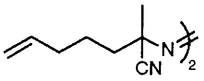

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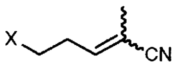

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a; X = NH_2
b; X = NO_2
c; X = OH
d; X = OAc

Table 2 Product distribution (%) obtained from deamination reactions of 2-amino-2,3,3-trimethylbutanenitrile **18** at 25 °C

Conditions[a]	TEMPO (equiv.)	**16**	**17**	**20** + **21**	**23** + **24**
$NaNO_2$, aq. $HClO_4$	0	29.5	3.6	15.1	52.8
$NaNO_2$, HOAc	0	18.8	4.8	4.8	71.6
$NaNO_2$, HOAc	2	36.5	0.3	23.2	40.0

[a] A concentrated aqueous solution of $NaNO_2$ (2 equiv.) was added to 0.2 mol dm^{-3} solutions of **18** under N_2.

give 50–90% of **6**. TEMPO was found to inhibit the formation of **9** very efficiently (*cf.* lines 4 and 5 of Table 1). Much more TEMPO is required for a significant decrease of **10** (see lines 5–8 of Table 1). TEMPO reportedly scavenges free radicals at rates that are close to diffusion-controlled.[9] So does NO_2,[10] while nitroso compounds react more slowly (k = 10^6–10^7 dm^3 mol^{-1} s^{-1}).[11] Our results are consistent with these relative rates. Remarkably, the relative yield of substitution products **3** also decreases in the presence of TEMPO, an observation that raises questions as to the origin of **3**.[12]

For further insight, we studied the nitrous acid deamination of 2-amino-2,3,3-trimethylbutanenitrile **18** (Scheme 3 and Table 2). There is ample precedent for the facile rearrangement of α-cyanocarbocations to β-cyanocarbocations.[13] Free radicals, on the other hand, do not undergo 1,2-alkyl shifts.[14] Accordingly, the deamination of **18** produces a single nitro compound **16** of retained structure whereas Wagner–Meerwein rearrangement is the predominant route to alcohols, acetates and alkenes. Although carbocations are unquestionably the precursors of **23** and **24**, some contribution of free radicals to the formation of **20** cannot be excluded.[12]

TEMPO does not give a stable adduct with the radical **15**, presumably for steric reasons. Nevertheless is appears that the presence of TEMPO enhances the free radical component of the deamination process (for analogous results with **4**, *cf.* Table 1). As a tentative explanation we suggest that TEMPO may intervene at the diazo stage (X = NO_2 → X = TEMPO) and thus affects partitioning of the intermediate **5** (Scheme 1).

Exploratory studies with 'radical clocks' confirm the rapid scavenging of α-cyanoalkyl radicals by NO_2. Nitrous acid deamination reactions of **25a** and **27a**, as well as photolyses of the azo compounds **26** and **28** in the presence of N_2O_4, afforded **25b** and **27b**, respectively, as the only nitro compounds. α-Cyano groups are expected to retard the ring opening of cyclopropylmethyl radicals [k (25 °C) = 1.0×10^8 s^{-1}][15] and the cyclisation of hex-5-enyl radicals [k (25 °C) = 2.5×10^5 s^{-1}].[16] As a consequence, isomerisation of the radicals derived from **25**–**28** cannot compete with trapping by NO_2. On the other hand, the carbocation derived from **25a** produces mixtures of **25c, d** and **29c, d**.

In summary, the diazotisation of α-aminonitriles has been shown to induce the competitive formation of α-cyanoalkyl radicals and of α-cyanoalkyl cations. The radical-stabilizing and cation-destabilizing effects of the cyano group concur to facilitate homolysis and to impede heterolysis of α-cyanodiazo(nium) intermediates.

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