Tetrahedron Letters,Vol.30,No.32,pp 4203-4206,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

ON THE REDUCTION OF α-AMINONITRILES WITH SODIUM

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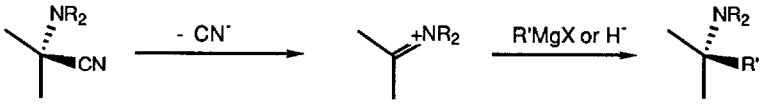
Abstract: *The reduction of α-aminonitriles with sodium proceeds via an α-aminoradical, which can be engaged in intramolecular cyclization. Reduction does not involve prior dissociation of cyanide to form an iminium species.*

The utility of α-aminonitriles as versatile intermediates in organic synthesis is well-established.[1] In addition to the chemical reactivity characteristic of the individual functional groups, α-aminonitriles participate in a number of reactions where the CN moiety is displaced by hydrogen or an alkyl group.[2] Thus, reduction with sodium metal,[2j,k] $NaBH_4$,[2g] or $LiAlH_4$[2e] leads to substitution of H for CN, while the Bruylants reaction[2a-d,f] with Grignard reagents effects the alkylative replacement of CN. These reactions have generally been formulated as proceeding through dissociation of the α-aminonitrile to an iminium ion plus cyanide, followed by reduction or Grignard addition (Eq. 1).



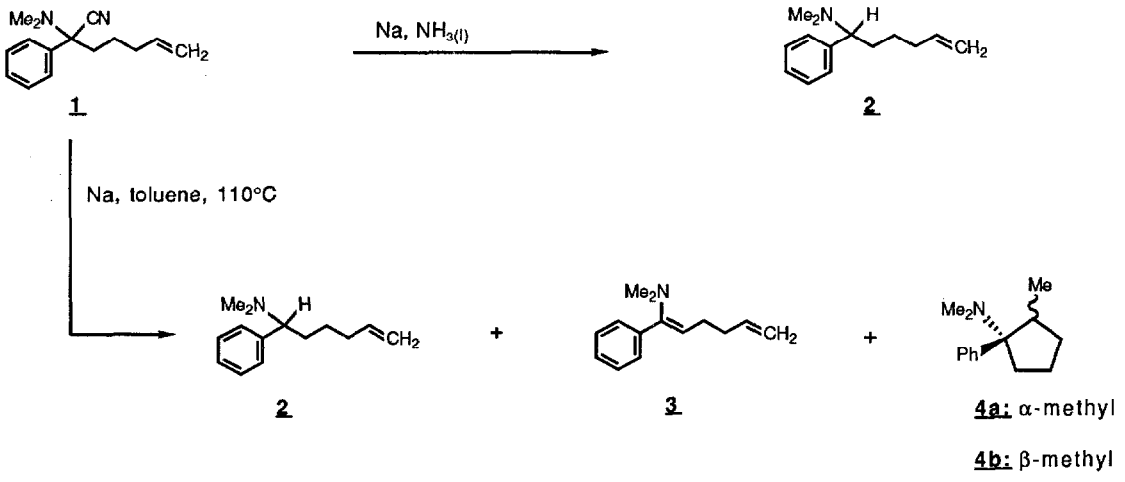
Eq. 1

We became interested in this process because of reports that certain α-aminonitriles formed dimeric vicinal diamines under the Bruylants conditions.[2d,j] This result suggests that α-amino radicals might be involved in the cyanide displacement reactions. Since cyclizations of alkenyl α-amino radicals have demonstrated utility in the preparation of nitrogen heterocycles,[3] we began an investigation to determine whether α-aminonitriles might serve as useful precursors to α-amino radicals. While our work was in progress, Martin and coworkers reported their studies on radicals derived from reduction of iminium salts.[4] Recently, Kudzma and associates have shown that cyanide displacement as in the Bruylants reaction can be effected with various heteroaryllithium reagents, with the very interesting observation that α-aminonitriles do not react equivalently to the corresponding iminium species.[5] This is quite puzzling if the mechanism of Eq. 1 is operable. We have gathered evidence that α-aminonitriles can be reduced directly to α-amino radicals without formation of the iminium ion, and report our results here.

In order to detect a radical intermediate, we utilized an α-aminonitrile incorporating the 5-hexenyl cyclizable probe. Thus, alkylation of the anion of N,N-dimethylphenylacetonitrile[1a-c] with 5-bromopentene[6] gave **1** (Scheme I) in 93% yield. When **1** was treated with Na/NH_3,[2i] clean and rapid conversion to the benzylamine **2** occurred, with no evidence for formation of cyclized products. Apparently, any α-amino radical which is produced is rapidly reduced to the anion and protonated by solvent. With sodium in refluxing toluene or benzene, on the other hand, a mixture of **2** (30%), **3** (trace), **4a** (49%), and **4b** (16%) was obtained. The last two, cyclized products are those expected from ring closure of the α-amino radical (**5**), followed by hydrogen atom abstraction. The structure

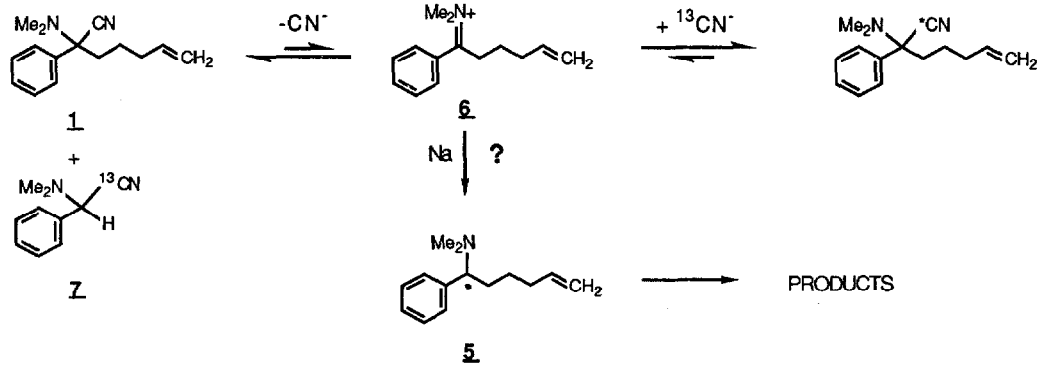
assignments follow from the spectroscopic data[7], and the stereochemical assignments for **4a** and **4b** were made on the basis of the ^1H NOESY spectrum.[8] Cyclization is not entirely efficient, and competing hydrogen abstraction leads to **2**. Enamine **3** could result from disproportionation of the α-amino radical, or simply by base-induced elimination of HCN from **1**.

Scheme I



The most obvious mechanism for formation of the α-amino radical is dissociation of **1** to the iminium ion **6**, followed by electron transfer from Na. There is no evidence by NMR for significant iminium ion formation from **1**, nor is there any indication of a rapid (on the NMR time scale) equilibration of **1** with an achiral species (the diastereotopic protons of **1** are clearly differentiated in the NMR). A slower equilibration, however, cannot be ruled out on this basis. Since the reaction of **1** with sodium in refluxing toluene is complete within 4 hr, we conducted an isotope exchange experiment to determine the involvement of iminium ion under these conditions (Scheme II):

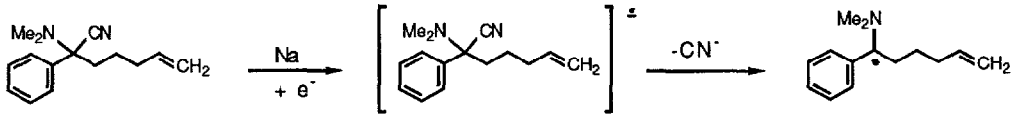
Scheme II



Thus, **1** was treated with an equimolar quantity of labeled $K^{13}CN$ in refluxing toluene for 4 hr. The extent of ^{13}CN incorporation in **1** after this time, as determined by ^{13}C NMR, was only 4%, indicating that the rate of iminium ion formation is too low for that to

be a major pathway in the conversion of 1 to reduced products. Unfortunately, the very low solubility of KCN in toluene raised the possibility that the rate-limiting step of isotope exchange was inefficient scrambling of labelled and unlabelled cyanide in this non-homogeneous system. Essentially the same result was obtained when 5 eq. of 18-crown-6 was added, but since even this additive did not bring all of the labelled CN into solution, a different method was devised. The labelled aminonitrile 7 was prepared, and was shown to react completely with the sodium/toluene system within the 4 hr reflux period, producing N,N-dimethylbenzylamine. If iminium ions are involved in the reduction of 1 and 7, then scrambling of the ^{13}C label between the two compounds should be observed at a rate comparable to the rate of reduction. In the event, after an equimolar solution of 1 and 7 in toluene was heated to reflux for 4 hr, the aminonitriles were recovered quantitatively. Analysis of the mixture by ^{13}C NMR showed that only a small fraction (ca. 3%) of the labelled cyanide had been incorporated into 1 (CN signal at 117.3 and 114.8 ppm for 1 and 7, respectively). This result indicates that the α-aminonitrile ⇌ iminium ion equilibrium is too slow to account for the reduction of 1 under these conditions. Note that we cannot rule out the involvement of an iminium-cyanide tight ion pair, since such a species might not exchange cyanide.

We suggest that the formation of α-aminoradical 5 proceeds by electron transfer to 1 to give the corresponding radical anion. This species fragments with loss of CN^- to give 5, which carries on to the observed products. Of some interest is the electronic character of this radical anion. Similar species have been proposed as intermediates in $S_{RN}1$ reactions,[9] and such arylacetonitrile radical anions



1 5

have been grouped into two categories – those where the excess electron density is largely localized in the aryl system, and those with localization in the nitrile moiety. According to this model, the latter, including that from phenylacetonitrile, cleave to give benzylic radicals. This route to 5, then, has reasonable precedent. It should be noted that we have established the direct electron transfer only for benzylic aminonitriles. Although aliphatic systems react under these conditions, the mechanism may be different.

It is possible that the α-aminoradical 5 is further reduced to give the corresponding anion. Under these reaction conditions, cyclization of the anion could also account for the production of 4a,b. We have been unable to detect deuterium incorporation in 2, 4a, or 4b by quenching the reaction with D_2O, consistent with previous observations with this reaction.[2i] In order to exclude the possibility that any anion produced is quenched by traces of water in the solvent, toluene was saturated with D_2O, then dried as usual and used for reduction of 1. No substantial (<10%) deuterium incorporation in the products was observed. On the other hand, when the reaction is carried out in toluene-d_8, significant (ca. 40%) deuterium incorporation was measured in 4a,b. Similar results were obtained using benzene-d_6 as solvent. When the reaction is repeated in the presence of diisopropyl ether (1.0 M in benzene-d_6), a good hydrogen atom donor but a poor proton source,[10] the level of deuterium incorporation in 4a,b is less than 20%. While not entirely conclusive, this data is more consistent with a radical process.

In summary, we have shown that the reduction of benzylic α-aminonitriles with sodium proceeds via electron transfer to the nitrile, and does not require prior formation of an iminium species. It is quite plausible that other 'nucleophilic' displacements of CN from these compounds (e.g., the Bruylants reaction) involve a similar process. In particular, this may account for the non equivalence of α-aminonitriles with the corresponding iminium salts in these reactions [5] Furthermore, electron transfer-initiated cleavage of α-aminonitriles may have advantage in the preparation of α-aminoradicals for synthesis.

Acknowledgements: We thank the University of Missouri Research Council for partial support of this work.
The NMR facility at the University of Missouri is supported, in part, by the NSF (PCM-815599), and purchase of the GC-MSD instrument used in this work was made possible by a grant from the NIH small instrument program.

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7. NMR spectra of chromatographically homogeneous samples were obtained for solutions in $CDCl_3$ on a JEOL FX90Q spectrometer operating at 90 MHz (^1H) or 22.5 MHz (^{13}C). IR spectra were obtained for neat liquid films using a Nicolet 20 DXB FTIR. Mass spectra were obtained with an HP5890A GC/5970B MSD: **1** (2-Dimethylamino-2-phenyl-6-heptenenitrile): ^1H NMR: δ 7.45 (5H, m), 5.42 (1H, m), 4.95 (2H, m), 2.27 (6H, s), 2.2-0.6 ppm (6H, m); ^{13}C NMR: δ 138.4, 137.5, 128.5, 128.3, 126.4, 117.3, 115.1, 71.8, 40.8, 39.5, 33.1, 23.7 ppm; IR: ν 3079, 2220, 1641 cm^{-1}; **2** (N,N-Dimethyl-1-phenyl-5-hexenamine): ^1H NMR: δ 7.32 (5H, m), 5.70 (1H, m), 4.93 (2H, m), 3.12 (1H, dd, J=8.1, 5.1 Hz), 2.15 (6H, s), 2.1-0.95 ppm (6H, m); ^{13}C NMR: δ 140.5, 138.7, 128.5, 127.9, 126.9, 114.4, 70.8, 42.8, 33.8, 32.6, 25.7 ppm; IR: ν 3026, 1640 cm^{-1}; MS: m/e (%) 203 (2), 134 (100), 91 (10); **3** (N,N-Dimethyl-1-phenyl-1,5-hexadienamine): ^1H NMR: δ 7.3 (5H, m), 5.75 (1H, m), 4.90 (2H, m), 4.48 (1H, t, J=7.1 Hz), 2.45 (6H, s), 2.1-1.8 ppm (4H, m); ^{13}C NMR: δ 150.2, 138.8, 138.5, 129.5, 127.9, 127.2, 114.3, 103.5, 41.5, 35.6, 27.9 ppm; IR: ν 3080, 1628, 1308 cm^{-1}; MS: m/e (%) 201 (8), 160 (100), 117 (46); **4a** (*cis*-N,N,2-trimethyl -1-phenylcyclopentanamine): ^1H NMR: δ 7.27 (5H, m), 2.70 (1H, m), 2.35 (1H, m), 1.95 (6H, s), 1.9-1.2 (5H, m), 1.10 ppm (3H, d, J=7.1 Hz); ^{13}C NMR: δ 136.9, 127.5 (2 lines, not resolved), 126.4, 73.1, 40.7, 38.6, 31.9, 30.2, 19.8, 16.8 ppm; IR: ν 3021, 2956, 1457 cm^{-1}; MS: m/e (%) 203 (15), 202 (11), 160 (100), 91 (13); **4b** (*trans*N,N,2-trimethyl-1-phenylcyclopentanamine): ^1H NMR: δ 7.30 (5H, m), 2.38 (1H, m), 2.15 (6H, s), 2.1-1.6 (5H, m), 1.20 (1H, m), 0.64 ppm (3H, d, J=7.1 Hz); ^{13}C NMR: δ 141.6, 128.8, 127.0, 126.0, 74.2, 39.1, 38.9, 30.8, 26.9, 20.7, 15.7 ppm; IR: ν 3021, 2963, 1457 cm^{-1}; MS: m/e (%) 203 (21), 202 (12), 160 (100), 91 (16); **7** (2-Dimethylamino-2-phenylethanenitrile-^{13}CN): ^1H NMR: δ 7.45 (5H, m), 4.83 (1H, d, J=8 Hz), 2.30 ppm (6H, s); ^{13}C NMR: δ 133.4, 128.5 (2 lines, not resolved), 127.5, 114.8 (CN), 62.8 (d, $^1J_{C\text{-}C}$=52 Hz), 41.4 ppm; IR: ν 3065, 2786, 2228, 1494 cm^{-1}.

8. COSY and NOESY spectra were obtained on a Nicolet NT-300WB spectrometer at 300MHz. For **4a**, the key features of the NOESY spectrum were interactions between the phenyl protons and the ring methine, and between the N-methyl groups and the ring methyl, indicating *cis* relationship within these pairs. For **4b**, off-diagonal peaks connecting the phenyl system and the ring methyl group, as well as between the N-methyl groups and the ring methine, established that the ring methyl was *trans* to the dimethylamino group.

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(Received in USA 19 April 1989)