The synthesis of alkyl aryl nitriles from $N$-(1-arylalkylidenecyanomethylamines. Part 2. Mechanism

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The mechanism of the rearrangement of $N$-(1-arylalkylidene)cyanomethylamines $\text{ArC}(-\text{NCHCN})R\,1$ to the corresponding nitriles $\text{ArCH(CN)}R\,2$ (in DMF, at 150 °C, with $K_2\text{CO}_3$) is described. Reaction $1 \rightarrow 2$ was investigated for different types of imine $1$, and it was found that with a leaving group other than CN$^-$ the reaction does not proceed to yield the nitrile, whereas imines such as $\text{PhC}(-\text{NCHCN})\text{H}$, prepared starting from aldehydes rather than ketones, yield the expected phenylacetonitrile even at temperatures as low as 120 °C. Evidence for the mechanism comes from a study of the reactivity of the postulated intermediates: 2-cyano-3-phenylaziridine $4c$, and 2,2-diphenyl-2H-azirine $5b$. The route involving aziridine $4c$ is ruled out, since this compound does not react at all under the investigated conditions. The 2H-azirine $5b$ instead, yields the corresponding diphenylacetonitrile in DMF with $K_2\text{CO}_3$, at 150 °C. The transformation seems to involve an initial deprotonation, followed by an intramolecular ring closure–CN elimination step, which yields the 2H-azirine. The azirine then isomerizes to the nitrile. Additional evidence for the intermediacy of the 2H-azirine, based on $^1$H NMR monitoring of the reaction $1 \rightarrow 2$, is described.

Finally, the results of a simple isotope exchange experiment provide a rationale for the previously observed scrambling of labels, and further confirm the proposed mechanism.

Introduction

We have recently reported a new reaction of $N$-(1-arylalkylidene)cyanomethylamines $\text{ArC}(-\text{NCHCN})R\,1$ when 1 is heated in DMF in the presence of potassium carbonate, it undergoes a clean rearrangement to alkyl aryl nitriles $\text{ArCH-(CN)R}$. This reaction proceeds only at relatively high temperatures ($T \geq 150 \degree \text{C}$), through the formal loss of HCN, and both alkyl aryl-, substituted alkyl aryl-, and diaryl-imines 1 can be used as reagents.

In a previous paper on the mechanism of the $1 \rightarrow 2$ rearrangement, some unequivocal mechanistic evidence was collected through the investigation of the reaction kinetics and through the study of the reactivity of $N$-alkylformimidoyl cyanides $\text{[ArCH(N(-CHCN)]R}$. and of labeled imines $\text{[ArC(-NCHCN)]R}$ and $\text{ArCH-[NCH(CN)]R}$ (1*).1 In particular, it was concluded that:

(1) the first, and rate-determining step of the mechanism was deprotonation at the methylene of imine 1 to yield 1'. This was derived from the Hammett free-energy relationship obtained from the reactions of different $p$-substituted $N$-(1-arylalkylidene)cyanomethylamines 1 ($Ar = p\text{-BrCCH}_2$, $p\text{-ClCCH}_2$, $p\text{-CH}_2\text{CHCH}_2$, and $p\text{-CH}_2\text{OCCH}_2$; $R = \text{CH}_3$). The reaction was first order and fitted the Hammett equation ($log k/k_0 = \rho \sigma$), giving a $\rho$ value of 1.86, consistent with the fact that an electron withdrawing group (EWG) on the aryl ring stabilizes the developing negative charge in 1'. This observation rules out any mechanisms initiated by an $S_N1'$ or $S_N2'$ isomerization, such as the one depicted in Scheme 2.

In compound 7, the aryl ring is not conjugated to the reactive site, a fact not compatible with the large positive $\rho$ value obtained by the Hammett treatment. In addition, when imine 1 (with $K = Ar = Ph$) was deprotonated with $n\text{-BuLi}$ in THF at $-90 \degree \text{C}$, and then heated at the reflux temperature of THF (67 °C), no reaction was observed. However, when THF was replaced with DMF, and the solution refluxed at 150 °C, the usual clean rearrangement to nitrile $\text{PhCH-CN)}R$ was observed.

(2) The cyano group of $\text{ArC}(-\text{NCHCN})R$ acted as the leaving group. In fact cyamide was titrated at the end of the reaction, and when it was replaced with other substituents (e.g. phenyl), reaction $1 \rightarrow 2$ did not take place.

(3) The process was mainly intramolecular and the cyano functionality of nitriles 2 derived primarily from the methylene-imino (-NCH$_2$-) fragment of 1. This was inferred by running a series of reactions using isotopically labeled $\text{PhC(-NCHCN)CH}_3$, and $\text{PhC(-15NCHCN)CH}_3$, under the conditions of Scheme 1. The isotope distribution in the two products $\text{[PhCH(13C)CH}_3\text{CN]$ and [PhCH(13C)C}^{15}\text{N}$ showed enrichments of 32 and 57%, respectively.

Accordingly, two possible reaction pathways were proposed (Scheme 3). They involved the common initial formation of an aziridine ring system, either followed by expulsion of CN$^-$ to give a 2H-azirine, and isomerization to the nitrile (path a), or by loss of cyanide through a symmetrical intermediate, and rearrangement to the nitrile (path b). Although path a appeared more elegant and would somewhat account for the predominant source of CN$^-$, the experimental evidence was not conclusive in its favor. In the present work the proposed
intermediacy of an azirine in the mechanism of the reaction 1 → 2, was tested and the results are reported. The behavior of representative examples of the proposed intermediates, synthesized independently by other routes, is described. The outcome of the reaction on substrates with different leaving groups (other than cyano), as well as extension of the process to aldehyde derivatives [PhC(=NCH₂CN)] were investigated. Finally, a new experiment is described to explain the observed isotope scrambling.

Results and discussion

Before exploring the reactivity of aziridines and azirines—the proposed intermediates—attention was focused on determining how general the examined reaction could be. Thus, functionalized imines of general formula PhC(=NCH₂CN)R were considered. To understand whether nitriles would still be observable as products and consequently, whether azirines were possible intermediates for such compounds, different X groups, as well as an aldehyde derivative, PhC(=NCH₂CN)H, were investigated.

Alternative X groups

In view of the proposed mechanism, whereby the CN moiety of the reagent ArC(=NCH₂CN)R 1 is expelled during the reaction, other groups able to stabilize the negative charge on the methylene were considered in place of CN. Compounds PhC(=NCH₂X)Me (X = CO₂Me, CF₃, Me) were prepared by condensation of acetoephone with hydrochloride salts of glycine methyl ester and of 2,2,2-trifluoroethylamine, respectively. The synthesis of the mesyl (X = Ms), tosyl (X = Ts), and oxazole derivatives was attempted, with no success as of yet.†

Imines 3a,b were made to react under the conditions of Scheme 1, and would have been expected to yield the corresponding nitrile PhCH(CN)CH₂, 2a. Compound 3a proved to be completely unreactive: it was recovered unchanged without any other reaction having taken place; a result likely due to the poor leaving group ability of the –COOCH₃ group.‡ Compound 3b, possessing an electron withdrawing CF₃ group able to promote deprotonation and perhaps to act as a leaving group,§ did not yield the expected nitrile 2a either; however, it did undergo base-promoted HF elimination to the corresponding conjugated product [eqn. (1)].

![Scheme 3](image)

Scheme 3 Two possible pathways for the 1 → 2 rearrangement.

Under the same reaction conditions, a similar product was observed for PhCH(Me)N=CHCCl₃ (3f).§ In this case, compound 3f underwent a 1,4-elimination of HCl to yield PhC(=NCH–CCl₃)Me (3g) as the product; behavior analogous to that of base-promoted reactions of 7α-amino-1-oxacephems.⁷

On the whole, since no other groups but cyano were suitable for this reaction, it appeared that the presence of electron withdrawing groups capable of negative charge stabilization was not enough to promote the examined reaction: the X group must also have leaving group ability. This dual behavior of CN as (a) negative charge stabilizer and (b) leaving group, has an analogy in the benzoin condensation, where cyanide first promotes α-deprotonation, and then acts as a leaving group.⁸

Imines derived from aldehydes

In order to investigate the possible effect of the alkyl group (R) on the iminic carbon, analogs of imines 1 were considered. Specifically, PhC(=NCH₂CN)H 1c (R = H) was prepared starting from benzaldehyde following the usual procedure.¹ When reacted under the conditions of Scheme 1, compound 1c proved much more reactive than methyl aryl imines 1, and it was converted very quickly (10 min) into phenylacetonitrile 2c (66%). The double bond isomer of the reagent PhCH₂N=CHCCN 1c (24%) appeared as a by-product, implying that the isomerization 1c → 1e—forbidden for ketone derivatives—took place in this case. However, the rearrangement of 1e to 2c proved feasible at a lower temperature (80 °C instead of 150 °C; conversion: 84%; 2c: 78%, after 180 min), thereby drastically decreasing 1e formation (6%).

† Compounds 3a and 3b were prepared by the same general procedure used for 1.¹
‡ The syntheses of PhC(=NCH₂X)Me (X = LG) were carried out analogously to the above imines, starting from a ketone and the appropriate amine. However, attempts to synthesize HN=CH₂HCl (X = Ms, Ts, oxazole) proved fruitless.
§ PhCH(Me)N=CHCCl₃ was prepared, rather than its isomer PhC(=NCH₂CCl₃)Me, since its synthesis is easier and since it is known that under the conditions of Scheme 1, R=CHN=CHCN undergoes isomerization to yield R=CH=NCH₂CN.³
Aziridines 4 and azirines 5

Direct and indirect methods were used to probe the intermediacy of the three-membered heterocycles postulated for both pathways a and b in the mechanism of Scheme 3. The following section describes how the search for evidence of the mechanism was approached through the study of these compounds. Indirect tests were carried out by investigating the reactivity of compounds 4 and 5 under the conditions of Scheme 1. Direct evidence of an intermediate was sought through NMR analysis of the reaction 1 → 2.

Reaction of aziridines

For the synthesis of an intermediate in the mechanism shown in Scheme 3, two general considerations led to the choice of 2-cyano-3-phenylaziridine 4c (Scheme 4), as a model compound: (i) as described above, the rearrangement 1 → 2 occurs more readily on the benzaldehyde-derived imine PhC(=NCH2CN)H 1c with respect to ketone-derived imines; (ii) both reaction pathways (a and b) of compounds 1 in Scheme 3, require an aziridine as a common precursor, and 4c was one of the more readily accessible synthetically.7 Thus 2-cyano-3-phenylaziridine was obtained in the cis configuration by a literature method,8 by reacting α,β-dibromocinnaminitrile with dry ammonia. Once prepared, the aziridine 4c was made to react under the same conditions as for 1c. No reaction whatsoever occurred [eqn. (2)] and the reagent was recovered unchanged. This observation allowed us to rule out path b of Scheme 3.

Path a of Scheme 3 implies the initial deprotonation of the reactant imine 1, followed by ring closure and CN− expulsion. The proposed ring closure is thermal, 4-electron, conrotatory, and allowed by the Woodward–Hoffmann rules.9 Scheme 5 shows the allylic anion type HOMO of 1, which controls the course of the reaction, and its conrotatory closure to the intermediate cyclized anion. In this case, the subsequent step of cyanoelimination (path a of Scheme 3), to give the 2H-azirine, must necessarily be favored over protonation at the nitrogen under the investigated conditions, to avoid the bottleneck posed by the aziridine of path b. The mechanistic analogy is again with the benzoin condensation,8 where the intermediate, with a negative charge on a heteroatom in the α position with respect to the CN, prefers to eliminate cyanide, rather than to protonate at the oxygen (Fig. 1). To test this hypothesis the synthesis of an appropriate 2H-azirine was undertaken.

Having established that nitriles 2 can originate from azirines 5, direct evidence for the intermediacy of azirines 5 in the overall rearrangement of Scheme 1 was sought. This was done by 1H NMR monitoring of the reaction of N-(diphenylmethylene)-cyanomethylamine [PhC(=NCH2CN)Ph, 1b] at 150 °C, in DMF-d5, and with K2CO3. The reaction proceeded as expected, with the disappearance of the 2H methylene singlet of 1b (4.5 ppm) and the appearance of the 1H singlet of diphenylacetoni trile 2b (6.0 ppm). The signal at 10.7 ppm—ascribable to the 2H-azirine 5b—was detected, and remained at a constant intensity with respect to the starting material PhC(=NCH2CN)H−Ph, 1b until the reaction was over (Fig. 2).

From a mechanistic standpoint, the general scenario appeared clear: path a of Scheme 3, shown in Scheme 4, was irradiated with diethylvinyl azide 6b. Since 2H-azirines are quite air sensitive, once a 37% yield was reached,9 the solvent (CDCl3) was immediately removed with a stream of nitrogen, and the mixture containing 5b was set to react at 150 °C with K2CO3 in DMF. Rewardingly, the reaction yielded predominantly diphenylacetoni trile 2b [85%, eqn. (3)] along with 15% phenylindole, known to derive from the thermal treatment of 6b.9 This result supported the mechanism delineated in path a of Scheme 3 for the transformation 1 → 2, although some doubt still persisted as to whether the vinyl azide 6b, present in the reaction mixture, might itself have generated diphenylacetoni trile 2b under the same conditions. This hypothesis was ruled out by treating compound 6b at 150 °C with K2CO3, in DMF: benzophenone (74%) and phenylindole (23%) were the only products.

Fig. 1 Comparison between Scheme 4 and the benzoin condensation.

Reaction of 2H-azirine

2,2-Diphenyl-2H-azirine 5b—the proposed intermediate for the rearrangement of PhC(=NCH2CN)Ph 1b to diphenylacetoni trile 2b—was synthesized,4,6,10 as shown in Scheme 6, by reaction of 2

Scheme 4 Synthesis of 2-cyano-3-phenylaziridine 4c.

Scheme 5 Electroyclic ring closure of 1.

Scheme 6 Synthesis of 2,2-diphenyl-2H-azirine 5b.

4 Yield calculated by acquiring a 1H NMR spectrum of the reaction mixture, and by integrating the peak of the proton in the 2-position of the 2H-azirine 5b (10.2 ppm),14 relative to that of the vinyl proton of 6b (6.7 ppm). This experiment also provided direct confirmation of the NMR resonance frequency of the azirine proton, which is reported in the literature, but with some ambiguity on the synthetic procedure.

validated experimentally and offered a plausible pattern for the rearrangement 1 → 2. However, for a definitive explanation, one question remained to be answered. The intramolecular reaction shown in path a implied that the cyanate group of the product nitrile 2 had to originate exclusively from the imine fragment (=N–CH₂≡) of the reactant. By contrast, as determined by the isotope labeling experiments carried out with PhC≡(NCH₂13CN)Me (1a*), a fraction (32%) of the CN incorporated in the nitrile 2a resulted from the starting nitrile functionality of 1a* [eqn. (4)]. This isotope distribution (not explainable by path a, but partially accounted for by path b), was rationalized by means of a simple cross-over experiment.

![Fig. 2](image)

**Fig. 2.** 1H NMR of reaction PhC≡(NCH₂-CN)Ph, 1b → Ph₂CH(CN) 2b, collected at time intervals.

The reaction is very sensitive to the nature of the reacting imines. Imines derived from aldehydes react much faster than those prepared from ketones, indicating that the proposed intramolecular ring closure is influenced by steric factors. However, even the sterically undemanding methyl group in the α position of imine 1 disfavors the intramolecular ring closure to give the 2H-azirine ring, presumably by electron donating effects.

The data available to date seem to indicate that leaving groups other than CN− inhibit the reaction. Current efforts are aimed at extending its scope to other substrates, and some preliminary data indicate that compounds such as PhC≡(NCH₂CO₂CH₃)H, derived from aldehydes, do in fact undergo the same rearrangement to yield phenylacetonitrile. This observation may open the way to a more general application of the reaction, and to its use with reagents possessing poorer leaving groups. To this end, there are significant challenges in the syntheses of imines 1 with such characteristics, which may follow the same rearrangement mechanism, thereby paving the way to new synthetic applications.

**Experimental**

Imine PhC≡(NCH₂CF₃)Me (3b) was obtained through the condensation of acetonophene (2 g, 16.7 mmol) with 2,2,3-trifluoroethylamine hydrochloride (CF₃CH₂NH₂HCl), 10

Yield of distilled product (bp = 65 °C/0.8 mmHg): 1.8 g (54%).

1H NMR (CDCl₃) δ 7.87–7.83 and 7.45–7.35 (m, 4 H, Ph), 4.00 (s, 2H, J = 9.6 Hz, J = 0.98 Hz). Mass spectrum (70 eV) m/z (relative intensity): 201 (M−, 30%), 200 (32), 187 (10), 186 (M−CF₃, 5), 124 (18), 104 (24), 103 (PhCH(Me)=N−), 10, 91 (26), 83 (10), 77 (18), 51 (10).

Compound 3b (0.2 g, 0.99 mmol) was made to react under the conditions of Scheme 1, during which elimination of HF took place. After 310 min in refluxing DMF, the conversion was 54% (by GC) and a mixture of EI3 isomers [PhC≡(NCH₂=CF₂)Me] 3c (45%) and 3e (3%) was obtained. Structures were assigned by GC–MS. Mass spectrum (70 eV) m/z (relative intensity): 3e, 181 (M−, 47%), 166 (M−Me − 100), 154 (15), 104 (25), 103 (12), 77 (38), 51 (13); 3e, 181 (M−, 37%), 104 (M−N≡CH=CF₂), 103 (100), 77 (25), 51 (11).

Imine PhCH(Me)=CHCl₂ (5f) was obtained through the condensation of α-methylbenzylamine (0.5 g, 4.1 mmol) with 2,2,2-trichloroacetaldehyde. 12

Yield of distilled product (bp = 62–65 °C/0.4 mmHg): 0.73 g (70%).

1H NMR (CDCl₃) δ 7.77 (s, 1H, CH=), 7.37–7.32 (m, 4 H, Ph), 4.68 (q, 1H, J = 6.7 Hz, d, 3H, CH₂, J = 6.7 Hz). Mass spectrum (70 eV) m/z (relative intensity): 249 (M−, <1%), 132 (M−CF₃, 7), 106 (11), 105 (100), 77 (14), 51 (10).

Compound 3f (0.2 g, 0.80 mmol) was made to react under the conditions of Scheme 1. As already reported for similar conditions, 15 elimination of HCl took place. After 90 min in refluxing DMF, the conversion was 64% (by GC) and a mixture of EI2 isomers [PhC≡(NCH₂=CCl₂)Me] 3g (41%) and 3g (20%) was obtained. Structures were assigned by GC–MS. Mass spectrum (70 eV) m/z (relative intensity): 3g, 215 (M−, 2, 33), 213 (M−, 50%), 202 (11), 200 (66), 199 (11), 198 (M−CH₂, 100), 180 (11), 178 (33), 138 (11), 136 (17), 104 (63), 103 (22), 102 (16), 77 (45), 51 (32); 3g, 213 (M−, <1%), 164 (2), 106 (10), 105 (100), 77 (15), 51 (10).

Imine PhC≡(NCH₂CN)H (1c) was obtained through the condensation of benzaldehyde (1.0 g, 9.4 mmol) with aminoacetonitrile hydrochloride. 1 Yield of distilled product (bp = 110 °C/0.7 mmHg, lit., 13 92–93 °C/0.1 mmHg; 0.60 g (44%). Characterization data of 1c are in ref. 14.

cis-2-Cyano-3-phenylaziridine (4c) 4c was obtained by saturating a solution of α,β-dibromocinnamoni...
nimonitrile in DMSO (20 ml) with dry ammonia gas for one hour. The mixture was stirred overnight at room temperature, poured into brine, and extracted with dichloromethane. The organic layer was washed twice with 50 ml of water, dried over sodium sulfate and evaporated to dryness. The product solidified (55% yield) upon standing. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.5–7.7 (m, 5H), 3.56 and 3.02 (AB systems, \(J_1 = 9.7\) Hz, \(cis\)-aziridine ring protons)], 1.72 (t, 1H, \(J = 9.7\) Hz).

2-Azido-1,1-diphenylethylene (6b)

Compound 6b was prepared following known methods starting from diphenylethylen oxide, via 1,1-diphenyl-2-azidoethanol.\(^5\) Dehydration of the latter was conducted by the following procedure, adapted from the literature:\(^5\) 1,1-diphenyl-2-azidoethanol (1 g, 4.2 mmol) was dissolved in 7 ml of dry DMF, 3.0 ml of pyridine were added, and the mixture was cooled to 15°C in an ice bath. In a separate flask, SO\(_3\), obtained by the dropwise addition of sulfuric acid to Na\(_2\)SO\(_4\), bubbled through 10 ml of methanesulfonyl chloride (MsCl, Aldrich reagent), until a 5% wt solution of SO\(_3\) was obtained. An aliquot (1 ml, corresponding to 25 mmol of MsCl) of MsCl was added to the 2-azido-1,1-diphenylethylene solution over 15 min, maintaining the temperature of the mixture below 15°C, during which the solution turned deep red. It was allowed to stir overnight at room temperature. Work-up consisted of the dropwise addition of 3 ml water, followed by a large excess (15 ml), and extraction of the mixture with methylene chloride (15 ml). The organic phase was washed successively with saturated brine, half saturated brine, and water, and dried over Na\(_2\)SO\(_4\). It was then filtered, and evaporated to dryness at reduced pressure.

Purification was carried out by flash chromatography eluting with a 1:1 mixture of toluene and petroleum ether (Rf = 0.55).

Yield 300 mg (35%). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.4–7.2 (m, 10H), 6.7 (s, 1H). IR \(\nu_{max}(\text{neat})/\text{cm}^{-1}\): 2102 (N=O), 1612 (C=C). Mass spectrum (70 eV) m/z (relative intensity): 193 (M\(^+\) – N\(_2\), 100), 165 (42), 139 (7).

2,2-Diphenyl-2\(H\)-azirine (5b) and its reaction under the conditions of Scheme 1

2-Azido-1,1-diphenylethylene (200 mg, 0.9 mmol) was dissolved in 10 ml CDCl\(_3\) in a nitrogen atmosphere in a Pyrex jacketed reactor maintained at –20°C by circulating ethanol. The solution was irradiated with a medium pressure Hg lamp (filter cut-off \(\lambda < 350\) nm). The tendency of atmospheric humidity to condense on the reactor was controlled by means of a nitrogen flow over the part exposed to the lamp. After 90 minutes, a portion of the solution was analyzed by \(^1\)H NMR which showed the presence of 37% of the desired 2\(H\)-azirine 5b, the remaining being substrate 6b, indicating that the reaction had proceeded cleanly. 5b: \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 10.2 (s, 1H), 7.4–7.2 (m, 10H).

After removal of the CDCl\(_3\) with a stream of nitrogen (at 0°C), the residue containing 2,2-diphenyl-2\(H\)-azirine 5b was transferred to a 10 ml flask containing 150 mg (1.1 mmol) of K\(_2\)CO\(_3\), using 5 ml of dry DMF. The mixture was heated under nitrogen at 120°C for 2 hours, and then analyzed by GC–MS. Along with 6b, the mixture showed the presence of diphenylecetonitrite 2b (85%) and a small amount of phenylindole (15%), all recognized by comparison with authentic samples. Diphenylvinyl azide 6b was made to react under the same conditions as 5b. After 2 hours at 150°C, at complete conversion, 74% of benzophenone, 23% of phenylindole and <3% of 2b were observed.

Reaction of phenylacetonitrite 2c with \(^1\)CN–

Phenylacetonitrite (50 mg, 0.43 mmol) was set to react at 120°C in a nitrogen atmosphere, with an equimolar amount of Na\(^{13}\)CN in the presence of K\(_2\)CO\(_3\) (90 mg, 0.63 mmol) in 5 ml of dry DMF. After 1 hour the mixture was analyzed by GC–MS, and the phenylacetonitrile showed a 25% isotope enrichment of \(^1\)C.

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