The synthesis of alkyl aryl nitriles from *N*-(1-arylalkylidene)-cyanomethyl amines: some mechanistic conclusions

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A mechanistic investigation of the rearrangement of *N*-(1-arylalkylidene)cyanomethylamines [**1**, ArC(=NCH$_2$CN)R; R = alkyl, aryl] to alkyl aryl nitriles [**2**, ArCH(R)CN] in refluxing DMF in the presence of a base is reported.

Under these conditions, *p*-phenyl substituted *N*-(1-arylethylidene)cyanomethylamines (Ar = *p*-BrC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-CH$_3$C$_6$H$_4$ and *p*-CH$_3$OC$_6$H$_4$; R = CH$_3$) follow the Hammett linear free-energy relationship, with a large positive ρ value (1.86), implying that electron-withdrawing substituents enhance the reaction rate by an initial deprotonation step. However, *C*-alkylated imines [Ph$_2$C=NCH(R′)CN; R′ = Me, *n*-Bu] do not yield the corresponding nitriles [Ph$_2$C(R′)CN], indicating the need for both methylene protons in order for the reaction to begin.
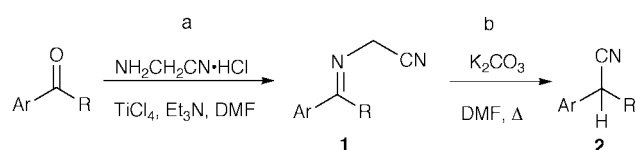
Different mechanistic pathways are then discussed. A base-catalysed imine double bond isomerisation, considered plausible, is excluded, since *N*-alkylformimidoyl cyanides [ArCH(N=CHCN)R] interconvert quantitatively to imines **1** prior to the formation of nitriles **2**. The photochemical activation of the reaction is also ruled out. The results of isotope labelling experiments, using ^{13}C- and ^{15}N-labelled *N*-(1-phenylethylidene)cyanomethylamines [PhC(=NCH$_2$-^{13}CN)CH$_3$ and PhC(=^{15}NCH$_2$CN)CH$_3$] are consistent with a mechanism based upon an intramolecular nucleophilic substitution reaction, since the cyano groups of the products **2** appear to come in preference from the methylene-iminic fragment (=NCH$_2$–) of the reagents.

The mechanism is proposed to proceed *via* an intermediate three-membered nitrogen heterocycle, generated by a nucleophilic intramolecular attack, which eliminates cyanide to afford the product nitrile.

Introduction

Alkyl aryl nitriles [ArCH(R)CN, **2**] are widely used intermediates for the syntheses of a number of carboxylic acids or amines.[1] A well-known example of their pharmaceutical relevance is the class of 2-arylpropionitriles [ArCH(CH$_3$)CN] which are intermediates for the preparation of hydratropic acids (2-arylpropionic acids), important non-steroidal analgesics such as Naproxen, Ibuprofen and Ketoprofen.[2]

We recently reported that nitriles **2** could be synthesised by a new two-step one-carbon homologation, starting from the corresponding ketone (ArCOR), *via* an intermediate *N*-(1-arylalkylidene)cyanomethylamine (**1**, Scheme 1).[3]

Scheme 1 A two-step homologation of alkyl aryl ketones to nitriles.

The alkyl aryl ketones were condensed with the hydrochloride salt of aminoacetonitrile to yield derivatives **1** [reaction (a)].[4] The resulting imines rearranged to nitriles **2** when heated in refluxing DMF, in the presence of a base [K$_2$CO$_3$; reaction (b)], through a loss of HCN (see the Results and Discussion sections). The reaction (b) proceeded only at relatively high temperature ($T \geq 150$ °C) and although it turned out to be feasible both for alkyl aryl and diaryl ketones, the conditions appeared to be quite stringent. For example, both organic (*i.e.* Et$_3$N, Bu$_3$N, DMAP) and inorganic (*i.e.* KF) bases, in the presence of different solvents such as polyethylene glycols, aromatic hydrocarbons, acetonitrile, THF, *etc.*, were ineffective. Also, radical pathways were excluded: although photoactivation was reported for other imines and nitriles,[5] compounds **1** yielded no
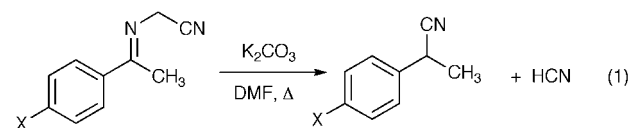
reaction under photochemical activation (UV radiation: 500 W lamp). However, the influence of the specific reaction conditions was beyond the scope of the present study.

The novelty of such a transformation prompted us to undertake a mechanistic study of the reaction **1**→**2**. This paper reports some conclusive results of the investigation.

Results

(i) Hammett free-energy relationship

Different *p*-substituted *N*-(1-arylethylidene)cyanomethyl amines [aryl = *p*-XC$_6$H$_4$; X = Br (**1a**), Cl (**1b**), H (**1c**), CH$_3$O (**1d**), CH$_3$ (**1e**)] were synthesised and reacted under the conditions of Scheme 1 (K$_2$CO$_3$ in refluxing DMF):[3] solutions of **1a**–**e** (0.12 M) in 10 mL DMF were heated at reflux (153 °C), under nitrogen, in the presence of a 1.5 molar excess of K$_2$CO$_3$ [eqn. (1)].

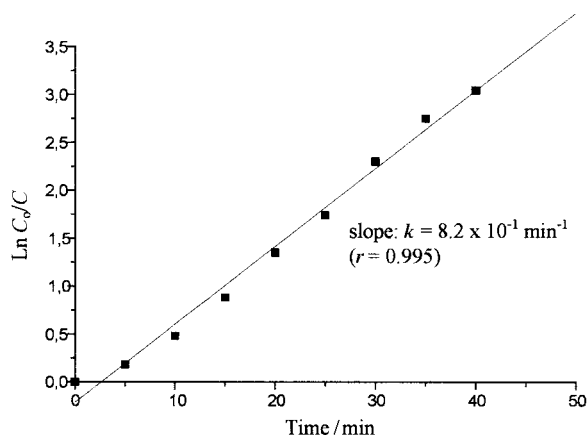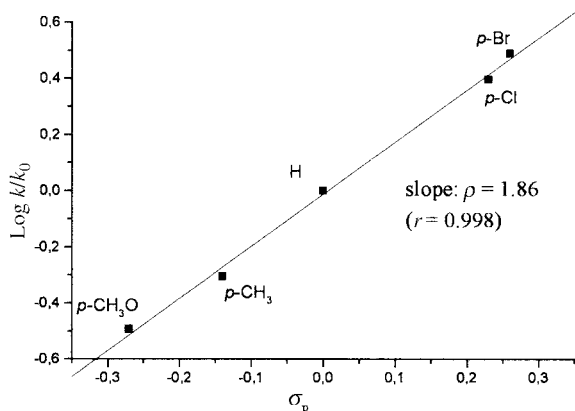X = **1a**: Br; **1b**: Cl; **1c**: H; **1d**: CH$_3$O; **1e**: CH$_3$

The reactions were followed by GLC and showed that the related concentration *versus* time plots fitted well the first-order rate law expression ln (C_0/C) = kt (C_0 and C = substrate concentrations at $t = 0$ and at a later time t, respectively).

As an example, by applying the integrated form of the first-order kinetic equation to the disappearance curve of *N*-(1-phenylethylidene)cyanomethyl amine **1c**,[6] the resulting plot of ln (C_0/C) against time gave a straight line ($r > 0.99$), whose slope was the rate constant k_{obs} of substrate disappearance (Fig. 1; $k_{obs} = 8.1 \times 10^{-2}$ min^{-1}).

Table 1 The reaction of $XC_6H_4C(=NCH_2CN)CH_3$ in DMF solvent, in the presence of K_2CO_3[a]

Entry	Substrate (X)	k_{obs}[b]/10^{-2} min^{-1}	σ_p[c]	Product	Yield (%) by GC[d]
1	**1a** (*p*-Br)	25.0	0.26	*p*-BrC$_6$H$_4$CH(CH$_3$)CN **2a**	64
2	**1b** (*p*-Cl)	20.2	0.24	*p*-ClC$_6$H$_4$CH(CH$_3$)CN **2b**	47
3	**1c** (H)	8.1	0	PhCH(CH$_3$)CN **2c**	41
4	**1d** (*p*-CH$_3$)	4.0	−0.14	*p*-CH$_3$C$_6$H$_4$CH(CH$_3$)CN **2d**	38
5	**1e** (*p*-CH$_3$O)	2.6	−0.28	*p*-CH$_3$OC$_6$H$_4$CH(CH$_3$)CN **2e**	41

[a] All reactions were carried out in refluxing DMF (153 °C) and using a 1.5 molar excess of the base. [b] First-order rate constants for the disappearance of the substrate. [c] Hammett σ constants for *p*-phenyl substituents; from ref. 7. [d] Yields are referred to the internal standards used: *n*-tetradecane (entries 1,3,4), *n*-hexadecane (entry 2) and *n*-dodecane (entry 5).

Fig. 1 Plot of ln C_0/C against time for imine **1c**.

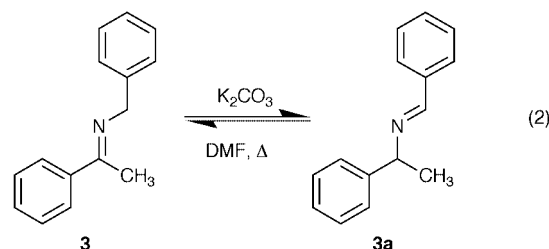**Fig. 2** Hammett plot for compounds **1a–1e**.

Under the same conditions as for **1c**, the first-order rate constants were evaluated for the disappearance of all imines **1a–e**. Table 1 reports the results.

The reaction fitted the Hammett relationship equation, log $(k/k_0) = \sigma\rho$ [where k and k_0 are the rate constants for the *p*-phenyl substituted (**1a–b, d–e**) and the unsubstituted imines **1c**, respectively, and σ_p constants are from ref. 7], giving a positive ρ value of 1.86. Fig. 2 shows the results.

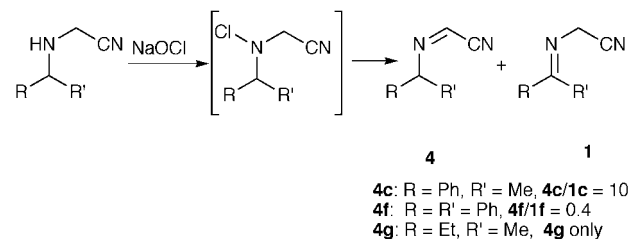**(ii) Isomerisation of the iminic double bond under basic conditions**

To investigate how deprotonation and, possibly, isomerisation of ketimines could take place under the condition of Scheme 1, *N*-(1-phenylethylidene)benzylamine [**3**; PhC(=NCH$_2$Ph)CH$_3$] was subjected to the same reaction conditions as for derivatives **1a–e**,[3] and a 40:60 mixture of isomers **3** and **3a** † was obtained at equilibrium after 7.5 h [eqn. (2)], a result analogous to the reported base-catalysed interconversion between Ph$_2$C=N–

† **3a** was identified by comparison with an authentic sample prepared by condensing α-methylbenzylamine with benzaldehyde.

CH$_2$Ph and Ph$_2$CH–N=CHPh.[7] No rearrangement to 2-phenyl-propionitrile was observed.

On the other hand, the double bond isomers of imines **1**, *N*-alkylformimidoyl cyanides [RR′CH–N=CHCN; **4**] behaved differently. Compounds **4** [RR′CH–N=CHCN; **4c**: R = Me, R′ = Ph; **4f**: R = R′ = Ph; **4g**: R = Et, R′ = Me] were synthesised by oxidising the appropriate amine [RR′CHNHCH$_2$CN] with aqueous NaOCl, in a one-pot *N*-chlorination–hydrodechlorination sequence.‡ The procedure afforded compound **4g** as a pure product, while, in the cases of **4f** and **4c**, a mixture of isomers was obtained (Scheme 2): **4c** and PhC(=NCH$_2$CN)CH$_3$ **1c** (44:1 ratio), and **4f** and Ph$_2$C=NCH$_2$CN **1f** (4:10 ratio).

Scheme 2 Synthesis of *N*-alkylformimidoyl cyanides **4**.

Both imines **4c** and **4g** were reacted under the conditions of Scheme 1. Initially, they underwent a rapid and quantitative isomerisation to the corresponding imines **1** [PhC(=NCH$_2$CN)-CH$_3$ **1c** and CH$_3$CH$_2$C(=NCH$_2$CN)CH$_3$ **1g**, respectively]. While the further reaction of **1g** afforded a mixture of high boiling compounds with no 2-methylbutanonitrile (the expected product according to Scheme 1), **1c** underwent the previously observed rearrangement, after a 15 min induction time, affording **2c** (Fig. 3 and Scheme 3).

The imine **1g** was also synthesised independently,[4] and reacted under the same conditions to afford the same high boiling products observed in the case of **4g**. The 4:6 mixture of **4f** and **1f** was not reacted.

‡ The syntheses of compounds **4** is reported in the literature as a two step preparation:[8] (i) the treatment of secondary amines with Ca(OCl)$_2$, to isolate the corresponding *N*-chloro adduct, and (ii) the successive reaction of the chlorinated intermediate with a base to afford a single product, or mixture of isomers, depending on the substrate. In this work, the reported imines **4** were synthesized in one pot using a novel procedure, by treating cyanomethyleneamines directly with a commercial aqueous solution of NaOCl (10–13% available chlorine).[20]
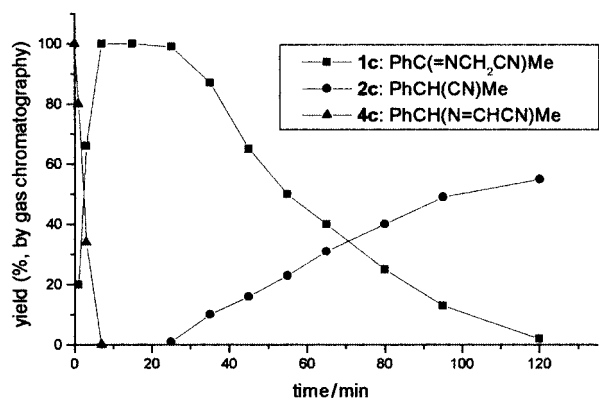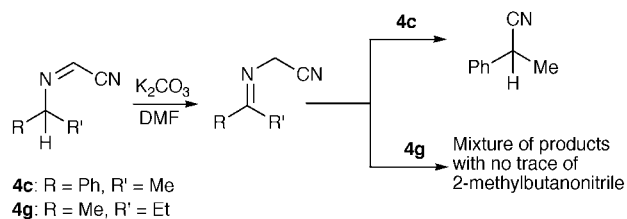
Fig. 3 Reaction of **4c** under the rearrangement conditions of eqn. (1).

4c: R = Ph, R' = Me
4g: R = Me, R' = Et

Scheme 3 Isomerization of *N*-alkylformimidoyl cyanides.

(iii) Reaction of 1f with *n*-BuLi

Imine **1f** was treated with *n*-BuLi in THF at −90 °C. The brown–red coloured solution was then heated at the reflux temperature of THF (67 °C): no reaction was observed. However, when THF was distilled off and replaced with DMF, and the solution refluxed at 150 °C, the usual clean rearrangement to nitrile $Ph_2CH(CN)$ **2f** was observed. If, instead of replacing the solvent, the solution was quenched with either *n*-bromobutane or methyl iodide, it yielded the two alkylated imines $Ph_2C=$ $NCH(n\text{-Bu})CN$ **5a** and $Ph_2C=NCH(CH_3)CN$ **5b**, respectively. Both **5a** and **5b** were subjected to the conditions of Scheme 1: only a mixture of products was detected, with no $Ph_2C(n\text{-Bu})$-CN or $Ph_2C(CH_3)CN$ among them.

(iv) Isotope labelling experiments

A series of reactions was conducted using isotope labelled substrates. ^{13}C- and ^{15}N-labelled *N*-(1-phenylethylidene)cyano-methylamines [$PhC(=NCH_2{}^{13}CN)CH_3$: ***1c**, and $PhC(=^{15}NCH_2$-$CN)CH_3$: **1c***, respectively] were synthesised independently, by condensing acetophenone with $NH_2CH_2{}^{13}CN \cdot H_2SO_4$ (^{13}C, 99%) and $^{15}NH_2CH_2CN \cdot H_2SO_4$ (^{15}N, 99%).[4]§

The imines ***1c** and **1c*** were then reacted under the conditions of eqn. (1), and the outcome was monitored by GC/MS. In order to quantitatively evaluate the labelled isotopic enrichment of the resulting nitriles [$PhCH(CH_3){}^{13}CN$: ***2c** and $PhCH(CH_3)C^{15}N$: **2c***], two reference compounds were prepared: labelled (^{13}C, 99%) and unlabelled 2-phenylpropionitriles were synthesised by nucleophilic substitution with $Na^{13}CN$ (^{13}C, 99%) and $NaCN$, on 1-chloro-1-phenylethane [$PhCH$-$(CH_3)Cl$], according to reported conditions.[9] The isotope distribution in the products of the rearrangement reactions conducted using the isotope enriched substrates is reported in Table 2.

The most significant mass peaks [$M^+ + 1$, M^+, $M^+ − 1$, $(M^+ + 1) − CH_3$, $M^+ − CH_3$ and $(M^+ − 1) − CH_3$] are shown for both compounds ***2c** and **2c*** (entries 1,2), and for the

§ The structure of the imines ***1c** and **1c*** was confirmed by comparison of their mass spectra with that of the unlabelled compound **1c**. The identification peaks of ***1c** and **1c*** ($M^+ = 158$, $M^+ + 1 = 159$ and $M^+ − CH_3 = 144$) were shifted by one mass unit with respect to **1c**, while their relative intensity was unchanged (see Experimental).

2-phenylpropionitrile standards (entries 3,4, respectively). We assumed the same response for ***2c** and **2c***, which have equal molecular masses, with respect to the standards.

(v) Titration of the cyanide released by the reaction 1→2

Titration by $AgNO_3$ of the aqueous extracts of the reaction of compound $Ph_2C=NCH_2CN$ **1f**, under the conditions of Scheme 1, yielded a molar amount of cyanide (51%) corresponding to the isolated molar yield of diphenylacetonitrile **2f** (48%).

Discussion

(i)–(iii) Hammett free-energy relationship, isomerisation of the iminic double bond, and reactions with *n*-BuLi

The investigation of the mechanism of the transformation 1→2 was first addressed by considering the effect of a series of *para*-substituents on the aryl ring of **1**. The trend of first-order rate constants k_{obs} for the disappearance of imines **1a–e** (Table 1) clearly shows that electron-withdrawing *p*-phenyl substituents enhance the reaction rate, while electron-donating ones decrease it with an overall variation (from *p*-Br to *p*-CH₃O) by a factor of 10. Also, the positive ρ value (1.86) obtained from the Hammett equation (Fig. 2) can be associated with a developing negative charge in a transition state more stabilised by electron-withdrawing substituents.[10–12] If this is the case, the negative charge may develop initially by proton abstraction by the base on the methylene carbon; an hypothesis which seems further verified by both the equilibrium of eqn. (2) (whose establishment implies proton abstraction–migration from a methylene to an imine carbon), and the reaction of **1f** with *n*-BuLi which yields an anion capable of affording diphenylacetonitrile upon reflux in a DMF solution. In both cases, the initial occurrence of a species such as $PhC(=N\bar{C}HR)R'$ (**3**: R = Ph, R' = Me; **1f**: R = CN, R' = Ph) seems more than reasonable.

Moreover, the proton shift of eqn. (2) suggests that the double bond isomers of imines **1**, namely *N*-alkylformimidoyl cyanides **4** [formed in analogy to eqn. (2)], should also be expected to afford nitriles **2**.

However, the study of the reactivity of imines **4** proves that any mechanistic hypothesis based upon an initial isomerisation of **1** to **4** must be excluded. Under the conditions of Scheme 1, compounds **4c** and **4g** (c: R = Ph, R' = Me; g: R = Et, R' = Me) first undergo complete isomerisation to the corresponding imines **1**. Then, while **1c** gives the usual clean rearrangement to 2-phenylpropionitrile, the dialkyl compound **1g** furnishes only high boiling products with none of the expected nitrile (Scheme 3 and Fig. 3).

Further indirect evidence can be inferred by the preparation of the imines **4**: while the dialkyl imine **4g** and the alkylaryl imine **4c** are obtained as single products, the attempt to synthesise the diaryl derivative **4f** gives a mixture of **4f/1f** in a 4:10 ratio. In the alkaline environment (NaOCl aq.), **1f** clearly represents the more stable highly conjugated structure.

However, the formation of nitriles **2** requires both protons at the methylene position: in fact, alkylated imines **5a** and **5b** [$Ph_2C(=NCHRCN)$; R = *n*-Bu, Me] do not undergo the desired rearrangement, and yield a mixture of products.

(iv–v) Isotope labelling experiments, and titration of the cyanide released by the reaction 1→2

A different approach to the mechanistic investigation was aimed at establishing which part of the iminomethylenenitrile moiety (=NCH₂–CN) of the reacting imines **1** is incorporated as the cyano functionality in nitriles **2**.

As was noted earlier, *N*-(1-phenylethylidene)benzylamine **3** does not rearrange to 2-phenylpropionitrile, which means that the cyano fragment (=NCH₂–CN) of the iminomethylene moiety of compounds **1a–e** is necessary for the reaction to

Table 2 Isotopic enrichment of 2-phenylpropionitrile produced from different source compounds[a]

Entry	product	Identifying mass peaks (%, relative intensity)						Isotopic enrichment (%)	Source compound
		$M^+ + 1$	M^+	$M^+ - 1$	$(M^+ + 1) - CH_3$	$M^+ - CH_3$	$(M^+ - 1) - CH_3$		
1	PhCH(CH$_3$)^{13}CN *2c	133 (1)	132 (17)	131 (27)	118 (5)	117 (65)	116 (100)	(^{13}C, 32)[b]	Ph(=NCH$_2$^{13}CN)CH$_3$
2	PhCH(CH$_3$)C^{15}N 2c*	133 (3)	132 (37)	131 (34)	118 (6)	117 (100)	116 (83)	(^{15}N, 57)[b]	Ph(=^{15}NCH$_2$CN)CH$_3$
3	PhCH(CH$_3$)^{13}CN (standard)	133 (3)	132 (37)	131 (4)	118 (8)	117 (100)	116 (−)	(^{13}C, 99)	PhCH(CH$_3$)Cl
4	PhCH(CH$_3$)CN (standard)	132 (4)	131 (38)	130 (4)	117 (10)	116 (100)	115 (−)	[c]	PhCH(CH$_3$)Cl
5	PhCH(CH$_3$)^{13}CN	133 (1)	132 (10)	131 (33)	118 (2)	117 (30)	116 (100)	(^{13}C, 15)[b]	Ph(=NCH$_2$CN)CH$_3$

[a] Entries 1,2: products of the reactions of the imines *1c and 1c* carried out in refluxing DMF solutions in the presence of K$_2$CO$_3$, according to conditions of eqn. (1). Entries 3,4: products synthesised from PhCH(CH$_3$)Cl and Na^{13}CN (^{13}C, 99%; entry 3) or NaCN (entry 4). Entry 5: product obtained from the reaction of Ph(=NCH$_2$CN)CH$_3$ in the presence of an equimolar amount of Na^{13}CN (^{13}C, 99%), under the conditions of eqn. (1). [b] Evaluated from mass spectra of labelled and unlabelled 2-phenylpropionitrile standards [PhCH(CH$_3$)^{13}CN and PhCH(CH$_3$)CN] reported in entries 3 and 4, respectively. [c] Natural abundance of ^{13}C.

proceed. Moreover, the CN⁻ molar amount released by the reaction $1 \rightarrow 2$ was shown to be equal to the molar yield of products **2**: that is, the overall rearrangement proceeds *via* the loss of HCN.

These facts lead us to believe that cyanide may act as a leaving group along the reaction pathway. If this is the case, the cyano functionality of nitriles **2** may perhaps derive from the iminomethylene fragment (=**NCH$_2$**–CN) of the reacting imines **1**.
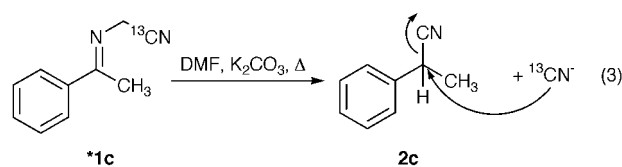
In this sense, further evidence is provided by the fact that *C*-alkylated imines **5a,b** do not rearrange to the respective nitriles, suggesting that the =NCH$_2$– is likely incorporated in nitriles **2** through an intramolecular mechanism.

To study these aspects in detail, labelled imines PhC-(=NCH$_2$^{13}CN)CH$_3$ (*1c) and PhC(=^{15}NCH$_2$CN)CH$_3$ (1c*) were prepared and reacted under the usual conditions. The outcome of the reaction was monitored by GC/MS.

From the data in Table 2, isotopic enrichments of 32 and 57% can be calculated for the two obtained products *2c [PhCH-(CH$_3$)^{13}CN] and 2c* [PhCH(CH$_3$)C^{15}N], respectively (entries 1,2). These results indicate that the cyano functionality of nitriles **2** derives from both the cyano [CN, (**A**)] and the iminomethylene [=NCH$_2$–, (**B**)] fragments of the reagents. However, a definite regioselectivity is observed: the values of the isotopic enrichments for *2c and 2c* (32 and 57%, respectively) indicate that the cyano group originates mainly from the iminomethylene part (**B**) of the reagent, in a 2:1 ratio with respect to portion (**A**). Since it is hardly imaginable that fragment **B** can be lost from the substrate (and successively re-introduced in the product), this behaviour suggests that the reaction has to proceed mainly *via* an intramolecular process. However, the labelled minor product coming from **A** does not exclude an intermolecular reaction involving a labelled cyanide fragment previously eliminated from the substrate.

A crossover experiment was therefore carried out in order to elucidate whether the reaction proceeds through an intra- or an intermolecular process. In particular, the unlabelled imine **1c** [PhC(=NCH$_2$CN)CH$_3$] was reacted according to the conditions of eqn. (1) (refluxing DMF, 1.5 molar excess of K$_2$CO$_3$) in the presence of an equimolar amount of Na^{13}CN (^{13}C, 99%). Entry 5 of Table 2 reports the mass peak abundances of the obtained 2-phenylpropionitrile, which corresponds to a labelled isotopic enrichment of 15%. Although the occurrence of the crossover reaction shows that an intermolecular process operates, the low isotopic enrichment (15%) of the product also indicates that the intermolecular reaction occurs only to a low extent.

In order to explain formation of *2c, we propose that the ^{13}CN⁻ generated from the reaction of *1c [eqn. (3)] can undergo exchange with the –CN of 2c. This kind of isotopic crossover is documented for acetonitrile, which undergoes nitrile exchange with labelled cyanide.[13]

$$+ \,^{13}CN^- \quad (3)$$

In our opinion, this exchange determines the degree of scrambling. The apparent contradiction of the lower enrichment observed by adding labelled cyanide to the reaction of **1c** (^{13}C, 15%), compared with the reaction of *1c without added labelled cyanide [eqn. (3): ^{13}C, 32%] might be accounted for by a solvent cage effect, which favours attack of ^{13}CN⁻ on **2c** with respect to its diffusion [eqn. (3)]. Thus, exchange becomes preferred with respect to the case where ^{13}CN⁻ is added to the reaction mixture.

Mechanistic pattern

The conclusions drawn from (i) the Hammett equation applied to *p*-phenyl substituted imines **1**, (ii) the study of the reactivity of *N*-alkylformimidoyl cyanides **4**, and (iii) the reaction of imines **1** with *n*-BuLi and their subsequent alkylation, strongly suggest that the initial rate-determining step of the mechanism is deprotonation at the methylene carbon to yield **1⁻**, while a double bond isomerisation can be excluded.

In addition, the reaction is dramatically sensitive to the structure of imines **1**. Under the same reaction conditions, similar compounds such as PhC(=NCH$_2$Ph)CH$_3$ do not give either PhCH(R)CN or PhCH(CH$_3$)Ph. This observation, together with the recovery of cyanide from the reaction mixture, strengthens the hypothesis that the cyano group of imines **1** behaves as a leaving group which is not found later in the product nitrile, unless by a CN exchange on the final nitrile **2**.
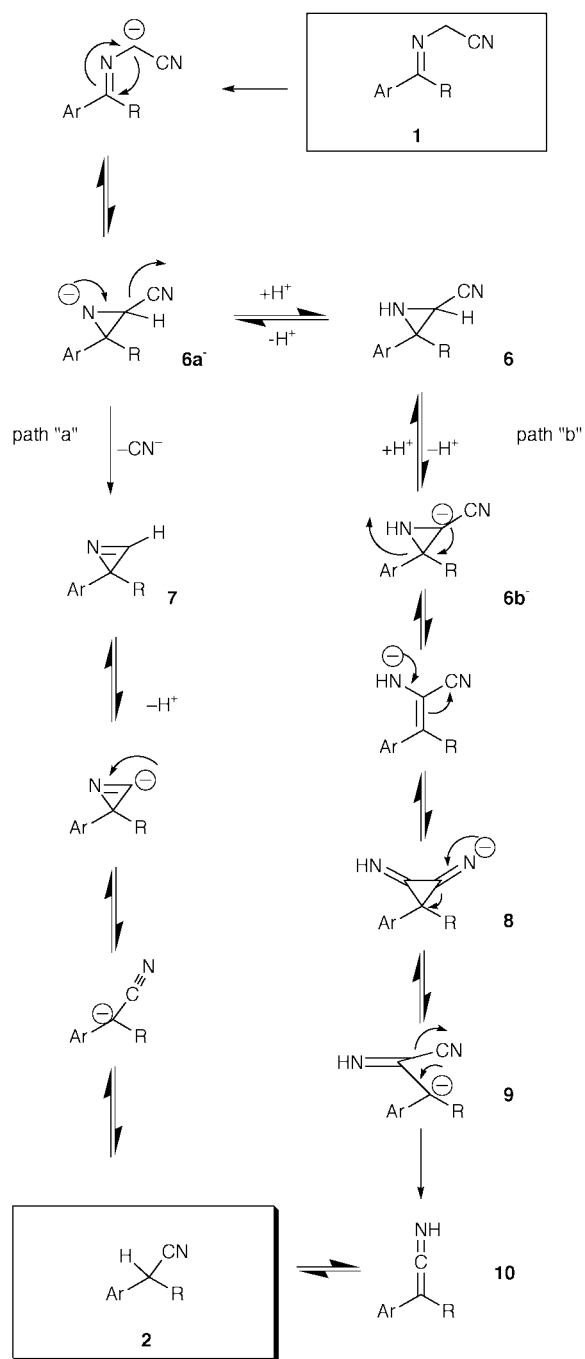
The tests carried out on isotopically labelled imines **1** suggest that the reaction proceeds through a mechanism mainly based upon an intramolecular process: in particular, the iminomethylene fragment (=NCH$_2$–) of the reagent is the primary source of cyano groups into the product **2**.

In our view, these combined observations justify a general mechanistic hypothesis, which involves an intramolecular nucleophilic attack by the carbanion **1⁻** on the imine carbon to form an azirine ring system (Scheme 4).

The analogous spiro(2*H*-azirine-2,9′-fluorene) intermediate was previously isolated in the reaction of 9-(azidomethylene)-fluorene, and further reacted to yield a mixture of 9-cyano- and 9-isocyanofluorene.[14]

The formation of the aziridine **6** is the common starting point for the two following different pathways.

Route "a". The aziridine **6** deprotonates on the nitrogen, to

second route lies in the degree of symmetry of intermediate **8**: this would provide a complete scrambling of the isotopes, and therefore does not account for the iminomethylene fragment as the preferential source of the cyano group, according to the isotope labelling studies.

The two suggested pathways for the rearrangement also rationalise the fact that alkylated imines **5a** and **5b** do not undergo the rearrangement. Neither the intermediate aziridine **6** nor the azirine of route "a", nor the intermediate **6b**[-] of route "b" would be able to rearrange to the nitrile because of the missing proton on the heterocycle.

At this stage it is not possible to choose one mechanism *vs.* another, though our preference goes to path "a" of Scheme 4, which better justifies the observed degree of isotopic scrambling. Additional work is therefore in progress, aimed at the synthesis and study of the reactivity of the postulated azirine and aziridine intermediates.

The moderate yields (40–65%) of nitriles **2**, which are reported in Table 1, may perhaps be explained based on the previous considerations. An initial anionic species, such as the proposed one, may undergo intermolecular reactions, leading to the formation of uncharacterisable tars, which are observed as by-products of our reaction (except for minor amounts, ≤5%, of the corresponding ketones, ArCOR). Also *N*-alkylimino-acetonitriles (R–N=CHCN) have been claimed to form oligomers by an anionic mechanism under mildly alkaline conditions at room temperature.[15]

Therefore, the starting CN content present in reagent **1** is distributed in two portions: it either ends up as cyanide when the intramolecular rearrangement occurs and **2** is formed (as observed by titration) or it may form organic polymers *via* an intermolecular process.

Conclusions

The reported experimental evidence sketches out a working hypothesis toward the final determination of the reaction pathway, through the mechanism of Scheme 4. Future work will fill in the reaction steps by independently synthesising some of the proposed intermediates, and subjecting them to the reaction conditions of Scheme 1.

The significance of the studied transformation lies in its synthetic applicability, and in its mechanistic relevance. More importantly, the reaction is unprecedented, and it opens an unexplored area of investigation which hopefully will allow expansion of its scope, by using functional groups other than CN.

Experimental

General

All compounds were ACS grade and used without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian Unity Spectrometer, using CDCl$_3$ as solvent and TMS as the internal standard. GC analyses were performed using a 30 m DB5 capillary column. GC-MS analyses were carried out using an HP mass detector at 70 eV coupled to a gas chromatograph fitted with a 30 m DB5 capillary column. The fitting curves of experimental data were obtained using the Microcal Origin software.

Preparation of *N*-(1-arylethylidene)cyanomethyl amines (1a–e) and labelled *N*-(1-phenylethylidene)cyanomethyl amines (*1c, 1c*)

N-(1-Arylethylidene)cyanomethyl amines **1a–e** were prepared by the condensation of the corresponding ketones (*p*-XC$_6$H$_4$-COCH$_3$; X = Br, Cl, H, CH$_3$O and CH$_3$, respectively) with NH$_2$CH$_2$CN·HCl according to a procedure previously reported by us.[4] Likewise, labelled *N*-(1-phenylethylidene)cyanomethyl

Scheme 4 Hypotheses for the mechanisms of the base catalysed rearrangement of imines **1** to nitriles **2**.

yield anion **6a**[-], which expels cyanide to form the azirine **7** (the CN group here behaves somewhat like in the benzoin condensation: it favours deprotonation of **6** and then acts as a leaving group), which isomerises by protonation–reprotonation and yields nitrile **2**. This pathway requires that 100% of the final CN derives from the iminomethylene fragment of the starting imine. The observed label scrambling must therefore take place in a second step, as proposed earlier [eqn. (3)].

In addition, 2*H*-azirines have been proposed as intermediates also in the conversion of vinyl azides to nitriles.[14]

Route "b". The aziridine **6** deprotonates on the carbon, to yield anion **6b**[-], which by successive rearrangements forms the intermediate **8**. This intermediate offers, by prototropy, a pathway for both the cyano and iminomethylene functions to contribute to the retained and expelled cyano groups in the product. Finally, intermediate **9** may expel CN^{-} and provide **10**, which rearranges to the product **2**. The major drawback of this

amines [*1c: PhC(=NCH$_2$^{13}CN)CH$_3$; 1c*: PhC(=^{15}NCH$_2$CN)-CH$_3$] were prepared using NH$_2$CH$_2$^{13}CN·H$_2$SO$_4$ (^{13}C, 99%) and ^{15}NH$_2$CH$_2$CN·H$_2$SO$_4$ (^{15}N, 99%), respectively, as the iminating agents of acetophenone. In turn, the labelled aminoacetonitrile salts were synthesised by using ^{13}NaCN (^{13}C, 99%) or ^{15}NH$_4$Cl (^{15}N, 99%), according to reported procedures.[16] Both the imines *1c and 1c* were not isolated; they were directly reacted to yield the corresponding nitriles *2c and 2c*, respectively.

N-[1-(p-Bromophenyl)ethylidene]cyanomethyl amine 1a.

Starting from 6.0 g of p-bromoacetophenone, 3.7 g of 1a was obtained (96% pure by GC; 52% yield); mp 96–98 °C. The product was recrystallised from n-pentane–diethyl ether (95:5 v/v). ^{1}H NMR (CDCl$_3$) δ: 2.29 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 7.54 (dd, 2H, Ar; J 8.8 Hz, J' 2.0 Hz), 7.70 (dd, 2H, Ar; J 8.8 Hz, J' 2.0 Hz). Mass spectrum (70 eV) m/z (relative intensity): 238 (29), 237 (M$^+$, 40), 236 (29), 235 (39), 223 (96), 221 (100), 183 (55), 181 (54), 157 (18), 102 (41), 75 (22), 76 (17).

N-[1-(p-Chlorophenyl)ethylidene]cyanomethyl amine 1b.

Starting from 5.0 g of p-chloroacetophenone, 4.4 g of 1b was obtained (99% pure by GC; 71% yield); mp 60–64 °C. The product was recrystallised from n-pentane–diethyl ether (95:5 v/v). ^{1}H NMR (CDCl$_3$) δ: 2.29 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 7.38 (d, 2H, Ar; J 8.8 Hz), 7.77 (d, 2H, Ar; J 8.8 Hz). Mass spectrum (70 eV) m/z (relative intensity): 194 (9), 193 (15), 192 (M$^+$, 28), 191 (38), 180 (4), 179 (34), 178 (11), 177 (100), 152 (8), 150 (11), 139 (18), 137 (55), 102 (12), 75 (12).

N-(1-Phenylethylidene)cyanomethyl amine 1c.

Full data are in ref. 4.

N-[1-(p-Methoxyphenyl)ethylidene]cyanomethyl amine 1d.

Starting from 5.0 g of p-methoxyacetophenone, 5.0 g of 1d was obtained (98% pure by GC; 80% yield); mp 46–47.5 °C. The product was recrystallised from n-hexane–CHCl$_3$ (95:5 v/v). ^{1}H NMR (CDCl$_3$) δ: 2.29 (s, 3H, CH$_3$), 3.85 (s, 3H, OCH$_3$), 4.38 (s, 2H, CH$_2$), 6.91 (dd, 2H, Ar; J 9.2, J' 2.0 Hz), 7.8 (dd, 2H, Ar; J 9.2, J' 2.0 Hz). Mass spectrum (70 eV) m/z (relative intensity): 189 (6), 188 (M$^+$, 50), 187 (31), 174 (8), 173 (68), 134 (10), 133 (100), 103 (8), 90 (8), 80 (9), 77 (7), 55 (8).

N-[1-(p-Methylphenyl)ethylidene]cyanomethyl amine 1e.

Starting from 5.0 g of p-methylacetophenone, 3.5 g of 1e was obtained (98% pure by GC; 55% yield); mp 29–31 °C. The product was recrystallised from n-hexane. ^{1}H NMR (CDCl$_3$) δ: 2.29 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 4.38 (s, 2H, CH$_2$), 7.47 (d, 2H, Ar), 7.71 (d, 2H, Ar). Mass spectrum (70 eV) m/z (relative intensity): 172 (M$^+$, 17), 171 (20), 158 (11), 157 (100), 130 (16), 117 (58), 116 (24), 91 (12), 89 (12), 77 (6), 65 (12). The product decomposes on standing.

^{13}C-labelled N-(1-phenylethylidene)cyanomethyl amine *1c, PhC(=NCH$_2$^{13}CN)CH$_3$.

Under the conditions reported in ref. 4, acetophenone (0.25 g) was reacted with NH$_2$CH$_2$^{13}CN·H$_2$SO$_4$ (^{13}C, 99%; 0.51 g), affording *1c in 88% yield (by GC). The product *1c was not isolated. The structure was confirmed by GC/MS. Mass spectrum (70 eV) m/z (relative intensity): 159 (M$^+$, 17), 158 (43), 145 (9), 144 (100), 117 (8), 116 (22), 103 (31), 82 (8), 77 (16), 76 (8), 51 (12).

^{15}N-labelled N-(1-phenylethylidene)cyanomethyl amine 1c*, PhC(=^{15}NCH$_2$CN)CH$_3$.

Under the conditions reported in ref. 4, acetophenone (0.25 g) was reacted with ^{15}NH$_2$CH$_2$CN·H$_2$SO$_4$ (^{15}N, 99%; 0.51 g), affording 1c* in 83% yield (by GC). The product 1c* was not isolated. The structure was confirmed by GC/MS. Mass spectrum (70 eV) m/z (relative intensity): 159 (M$^+$, 22), 158 (52), 145 (10), 144 (100), 118 (6), 117 (23), 104 (31), 82 (9), 77 (13), 51 (9). The peaks 117 and 104 of compound 1c* represent the (PhC=^{15}NCH)$^+$ and (PhC=^{15}N)$^+$ frag-

ments; they confirm the position of labelled isotope ^{15}N. In fact, for both compounds 1c and *1c, the same fragments appear shifted by one mass unit at m/z 116 and 103, respectively.

Preparation of N-[1-(ethyl)ethylidene]cyanomethyl amine 1g.

According to the above reported procedure,[4] the dialkyl imine 1g (1.15 g, 10.5 mmol; 75%) was obtained as a dense yellow liquid by condensing methyl ethyl ketone (1.0 g, 13.9 mmol) with NH$_2$CH$_2$CN·HCl. ^{1}H NMR (CDCl$_3$) δ: 1.09 (t, 3H, CH$_3$, J 7.32), 1.90 (s, 3H, CH$_3$), 2.33 (q, 2H, CH$_2$, J 7.32), 4.15 (s, 1H, CH$_2$CN). Mass spectrum (70 eV) m/z (relative intensity): 11 (M$^+$, 110), 95 (14), 81 (100), 70 (14), 68 (22), 67 (11), 54 (60). The product turned to a brown colour on standing.

General procedure for the transformation of imines 1a–e into the corresponding nitriles 2a–e

A DMF (10 mL) solution of the substrate (0.13 M; 10 mL) containing the internal standard (0.3 molar with respect to 1; n-tetradecane for 1a,c,d, n-hexadecane for 1b, and n-dodecane for 1e, respectively) and K$_2$CO$_3$ (in 1.5 molar excess with respect to the reactant 1) was loaded in a three-necked, round-bottomed flask fitted with a silicone septum for sampling, a refluxing condenser capped with a stopcock, and another stop-cock. The mixture was degassed by vacuum/N$_2$ cycles and nitrogen was admitted from a rubber reservoir and maintained throughout the reaction. Then, the mixture was heated under stirring at the reflux temperature (153 °C); after a few minutes the solution becomes a characteristic dark brown–red colour. The reaction course was followed by GC. **ATTENTION!** The reaction mixture contains cyanide, great care must be used for all further operations.

Under the same conditions, the imine 1c [PhC(=NCH$_2$CN)-CH$_3$] was also reacted in the presence of an equimolar amount of Na^{13}CN (^{13}C, 99%).

Compounds 2a–e were not isolated: their characterisation was through GC/MS analysis by comparison with authentic samples.[2c,3]

The reactions of labelled imines *1c and 1c*. As above described, solutions of the crude imines *1c and 1c* in DMF were obtained by condensing acetophenone with NH$_2$CH$_2$-^{13}CN·H$_2$SO$_4$ (^{13}C, 99%) and ^{15}NH$_2$CH$_2$CN·H$_2$SO$_4$ (^{15}N, 99%), respectively. According to the same procedure used for compounds 1a–e, the solutions of *1c and 1c* were then added to K$_2$CO$_3$ (1.5 molar excess with respect to the reacting imine), and heated under stirring at the reflux temperature.

The labelled 2-phenylpropionitriles (*2c and 2c*) were not isolated and they were characterized by GC/MS as described in Table 2.

Preparation of N-alkylformimidoyl cyanides (4c,f,g)

N-Alkylformimidoyl cyanides 4c,f,g were prepared by a new method[20] devised as a modification of reported N-chlorination and dehydrochlorination procedures.[8] Accordingly, the appropriate amines RR'CHNHCH$_2$CN (R = Ph, R' = CH$_3$; R = Et, R' = CH$_3$)[8,17] were added dropwise to a vigorously stirred aqueous solution of NaOCl (1.5 M; 10–13% available chlorine; 1.2 molar equiv. with respect to the amine), providing that the reaction temperature was kept below 10 °C. Then, the mixture was allowed to warm to room temperature, stirred for 1 h, and extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over Na$_2$SO$_4$, and, after filtration, the diethyl ether was carefully removed by rotary evaporation. Compound 4g was further purified by distillation.

In the case of the solid amine Ph$_2$CHNHCH$_2$CN (0.5 g), the reaction was run dissolving the amine in dioxane (4 mL). When used neat, no reaction took place at all.

N-sec-Butylformimidoyl cyanide 4g.

Starting from N-sec-

butylaminoacetonitrile (5.0 g, 44.6 mmol),[17] a mixture of **4g** and starting amine was obtained in a 95 : 5 ratio, respectively (2.68 g; bp 66–69 °C, 20 mmHg). **4g**, *E* isomer: ^{1}H NMR (CDCl$_3$) δ: 0.81 (t, 3H, CH$_3$, *J* 7.2 Hz), 1.22 (d, 3H, CH$_3$, *J* 7.2 Hz), 1.60 (quintet, 2H, CH$_2$, *J* 7.2 Hz), 3.26 (q, 1H, CH, *J* 7.2 Hz), 7.35 (s, 1H, N=CH); traces ($\leq$5%) of the *Z* isomer were also detected. Mass spectrum (70 eV) *m/z* (relative intensity): 95 (M$^+$ − CH$_3$, 18), 82 (16), 81 (100), 68 (13), 57 (22), 54 (44). The product rapidly decomposed on standing.

N-(α-Methyl)benzylformimidoyl cyanide 4c. Starting from *N*-(α-methyl)benzylaminoacetonitrile (1.0 g, 6.3 mmol),[18] a mixture of **4c**, starting amine and **1c** was obtained in an 88 : 10 : 2 ratio, respectively (0.65 g; not distilled). **4c**, *E* isomer: ^{1}H NMR (CDCl$_3$) δ: 1.59 (d, 3H, CH$_3$, *J* 6.6 Hz), 4.59 (q, 1H, CH, *J* 6.6 Hz), 7.29–7.39 (m, Ph and N=CH); traces of the *Z* isomer were also detected. Mass spectrum (70 eV) *m/z* (relative intensity): 158 (M$^+$, 6), 116 (20), 106 (10), 105 (100), 103 (12), 79 (12), 77 (21), 51 (9). The initially pale yellow liquid turned to brown in 24 h, even when stored at +4 °C.

The reaction of Ph$_2$CHNHCH$_2$CN gave a mixture of **1f** (60%), **4f** (25%) and *N*-(α-methyl)benzylaminoacetonitrile (15%). Products were not separated. **4f**: mass spectrum (70 eV) *m/z* (relative intensity): 220 (M$^+$, 7), 168 (15), 167 (100), 166 (12), 165 (34), 152 (19), 116 (8), 89 (7), 77 (7), 51 (5).

Spectroscopic data of the secondary amines

N-sec-Butylaminoacetonitrile.[17] Starting from 10 g (137 mmol) of *sec*-butylamine, 9.95 g was obtained (65%; bp 38 °C, 0.3 mmHg; 95% pure by GC). ^{1}H NMR (CDCl$_3$) δ: 0.91 (t, 3H, CH$_3$, *J* 7.2 Hz), 1.05 (d, 3H, CH$_3$, *J* 6.6 Hz), 1.28 (br s, 1H, NH), 1.35 (dq, 1H, CH$_2$, *J* 7.2 Hz), 1.47 (dq, 1H, CH$_2$, *J* 7.2 Hz), 2.81 (sextet, 1H, CH, *J* 6.6 Hz), 3.66 (dd, 2H, CH$_2$CN, *J* 8.2 Hz); mass spectrum (70 eV) *m/z* (relative intensity): 158 (M$^+$, 6), 116 (20), 106 (10), 105 (100), 103 (12), 79 (12), 77 (21), 51 (9); IR (CCl$_4$): v/cm^{-1} 2243 (CN), 3357 (NH).

N-(α-Methyl)benzylaminoacetonitrile.[18] Starting from 5 g (41.3 mmol) of (α-methyl)benzylamine, 2.5 g was obtained (38%; bp 86–88 °C, 0.2 mmHg). ^{1}H NMR (CDCl$_3$) δ: 1.41 (d, 3H, CH$_3$, *J* 7.8 Hz), 2.4 (br s, 1H, NH), 3.42 (dd, 2H, CH$_2$CN, *J* 17 Hz), 4.09 (q, 1H, CH, *J* 7.8 Hz), 7.28–7.38 (m, 5H, Ph); mass spectrum (70 eV) *m/z* (relative intensity): 158 (M$^+$, 6), 116 (20), 106 (10), 105 (100), 103 (12), 79 (12), 77 (21), 51 (9); IR (CCl$_4$): v/cm^{-1} 2235 (CN), 3334 (NH).

N-Benzhydrylaminoacetonitrile. Starting from 3 g (16.4 mmol) of benzhydrylamine, 2.4 g was obtained (65%; mp 73–74.5 °C). The product was crystallised from *n*-hexane–diethyl ether (2 : 1 v/v). ^{1}H NMR (CDCl$_3$) δ: 2.00 (br s, 1H, NH), 3.58 (s, 2H, CH$_2$CN), 5.10 (s, 1H, CH), 7.25–7.55 (m, 10H, 2Ph); mass spectrum (70 eV) *m/z* (relative intensity): 222 (M$^+$, 19), 168 (12), 167 (70), 166 (13), 165 (39), 152 (21), 146 (11), 145 (100), 144 (19), 104 (39), 77 (17), 67 (24), 51 (11); IR (KBr): v/cm^{-1} 2243 (CN), 3342 (NH).

Titration of the cyanide released by the reaction 1→2

The particular case of Ph$_2$C=NCH$_2$CN **1f** was considered. **1f** (0.30 g, 1.4 mmol) was reacted under the conditions of Scheme 1, and once the reaction was completed, the DMF solvent (10 mL) was distilled off under vacuum. To the solid brown residue was added ultrapure water (40 mL, produced by a Millipore Milli-Q-plus system). The mixture was then extracted with diethyl ether (3 × 20 mL). The aqueous phase was titrated by aq. AgNO$_3$ (0.01 M volumetric standard) using established procedures:[19] the concentration of the resulting cyanide solution was 1.8 × 10^{-2} M (0.72 mmol of CN$^-$ in 40 mL).

The combined organic layers were dried over Na$_2$SO$_4$ and filtered. After removal of the solvent by rotary evaporation, the product (Ph$_2$CHCN, **2f**) was purified by column chromatography: 48% yield (0.13 g, 0.65 mmol).

The molar ratio CN$^-$/**2f** was 1.1.

Reaction of 1f with *n*-BuLi

Ph$_2$C=NCH$_2$CN **1f** (0.50 g, 2.3 mmol) dissolved in 15 mL of anhydrous THF was treated with 0.95 mL of *n*-BuLi (2.5 M in hexanes; 2.4 mmol) at –90 °C, under N$_2$. The solution turned brown.

Procedure A. The solution was warmed slowly to room temperature, THF was distilled off under vacuum and replaced with an equal amount of anhydrous DMF, and brought to the reflux temperature. The reaction was followed by GC: **2f** was the sole product, identified by GC/MS by comparison with a known sample.

Procedure B. The solution was warmed to room temperature and quenched with 1.0 equiv. of either *n*-BuBr or MeI. The mixture was cooled to 0 °C, treated with water, washed with half saturated brine (3 × 20 mL), the organic layer was dried over Na$_2$SO$_4$, filtered and the solvent removed by rotary evaporation. The products **5a** and **5b** were obtained as yellow oils, and were characterised by GC-MS and ^{1}H NMR.

5a. Yield = 90%. ^{1}H NMR (CDCl$_3$) δ: 7.16–7.86 (m, 10H, aromatic), 4.22 (t, 1H, *J* 6.6 Hz, CH), 2.08–1.76 (m, 2H), 1.52–1.20 (m, 4H), 0.89 (t, 3H, *J* 7.5 Hz); mass spectrum (70 eV) *m/z* (relative intensity): 276 (M$^+$, 34), 275 (92), 233 (12), 222 (12), 220 (24), 219 (80), 209 (18), 208 (100), 194 (11), 165 (37), 117 (10), 116 (93), 104 (34), 103 (13), 89 (14), 77 (32).

5b. Yield = 92%. Mass spectrum (70 eV) *m/z* (relative intensity): 234 (M$^+$, 62), 233 (74), 219 (12), 207 (25), 180 (48), 166 (23), 165 (37), 157 (20), 156 (12), 116 (100), 104 (78), 103 (14), 77 (71).

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