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SYNTHESIS OF ALKYLARYL- AND DIARYLNITRILES FROM KETONES *VIA* N-(1-ARYLALKYLIDENE)-CYANOMETHYL AMINES

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Abstract: Alkylaryl- and diarylketones (ArCOR; R= alkyl, aryl, **1**) can be converted into nitriles [ArCH(CN)R, **2**] containing an additional carbon atom through a base-promoted reaction of N-(1-arylalkylidene)-cyanomethyl amines [ArC(=NCH_2CN)R, **3**].

The transformation of ketones RR'CO into nitriles RR'CH(CN) represents an useful one carbon homologation for the synthesis of a variety of carboxylic acid

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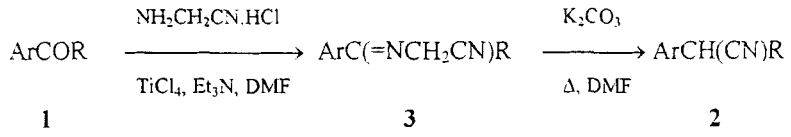
or amine derivatives. This reaction can be carried out by different synthetic methods involving i) the hydrogenation of cyanohydrins, [1-2] ii) the decomposition of HCN adducts of ketone hydrazones, [3-6] iii) the reduction of O-substituted cyano hydrins (cyanophosphates), [2, 7] and iv) the reductive cyanation of ketones with tosylmethyl isocyanide (TosMIC). [8] Although all the methods afford fairly good yields, they appear to be feasible only if certain functional group are absent (i), to be limited to aliphatic ketones (ii), and to use costly reagents and catalysts (iii-iv). Moreover, they operate with a large excess of the cyanide source and therefore a careful waste treatment is needed.

We wish to report here that alkylaryl- and diarylketones may provide the respective nitriles containing an additional carbon atom through a new two-step synthesis involving N-(1-arylalkylidene)-cyanomethyl amines as intermediates, according to Scheme 1.

The reactivity of the ketimines **3** was initially investigated for the derivatives of acetophenone, propiophenone, and benzophenone, respectively; such compounds (**3a-c**; R = Me, Et, Ph) were prepared according to a procedure previously reported by us. [9] In the presence of different bases (K_2CO_3, *t*-BuOK, and MeONa) and using different solvents (DMF, dimethylcarbonate, THF, dioxane), we observed that imines **3a-c** could give a quite general reaction: when heated at temperature of 80-180 °C, they could afford the corresponding nitriles **2**. However, even operating at the lower temperature (80 °C), the use of stronger bases (*t*-BuOK and MeONa) always led to a mixture of **2** and the corresponding ketone **1** (in ≈ 1 : 1 molar ratio) probably because of the easy oxidative



Scheme 1

decyanation of the formed nitrile [10] and/or the hydrolysis of the starting reagent **3**. The better results were obtained using K_2CO_3 (in a 1.5 molar excess with respect to the ketimine) in boiling DMF (≈ 7 mL/g of substrate): they are summarised in Table 1.

The reaction occured only at temperatures ≥ 130 °C (entry 1; shown for the acetophenone derivative) while it did not take place at all in the absence of the base. The corresponding ketone (as a by-product) was less than 5% in all cases. The yields were evaluated by comparison to an internal standard (*n*-tetradecane) and they were moderate for the tested reactions (45-49%), though the total amount of the other products (detected by GC analysis: they were high-boiling compounds whose structure was not identified) was less than 5% (see also later, Table 2).

The chance of using the DMF as the solvent for the reaction **3** → **2** turned out to be quite advantageous because it allowed the nitriles **2** to be prepared from the corresponding ketones without the need of isolating the intermediates **3**. In fact, the DMF was also the solvent of choice for the preparation of the ketimines **3** from ketones **1**. Thus, after ketones were condensed with $NH_2CH_2CN.HCl$ (Scheme 1, reaction **1** → **3**), a simple filtration of the formed solids (Et_3NHCl and

Table 1. Reactions of N-(1-arylalkylidene)-cyanomethylamines in DMF solvent in the presence of K_2CO_3. [a]

Entry	Substrate PhC(=NCH$_2$CN)R	Reaction Time (min)	T (°C)	Convn. (%)	Product PhCH(R)CN	Yield (%)[b]
1	**3a** R: Me	150	100	0		
		120	130	35	R: Me	12
		105	155 [c]	100	"	49 [d]
2	**3b** R: Et	135	155	90	R: Et	45 [d]
3	**3c** R: Ph	115	155	95	R: Ph	46 [d]

[a] All reaction were carried out using substrate / base in a 1 : 1.5 molar ratio. [b] Yields were determined by GC using *n*-tetradecane as the internal standard. [c] Reflux temperature of DMF. [d] The corresponding ketone PhCOR was always less than 5%.

TiO_2) was sufficient to obtain the solutions of the crude ketimines in DMF, ready to be used for the final step of Scheme 1.

In this way, a number of aromatic ketones were reacted. After the formation of the derivatives **3**, the subsequent reactions were run in refluxing DMF (≈10 mL/g substrate) in the presence of K_2CO_3 (ketone / base in 1 : 1.5 molar ratio), under a N_2 atmosphere. Results are shown in Table 2.

The transformation of the ketones **1** into the nitriles **2** appeared to be quite general: different substituents on the aromatic ring and different alkyl chains (bonded to the carbonyl) were allowed, though the increasing of the steric hindrance on the carbonyl resulted in longer reaction times (entries 1, 5 and 6). Instead, halogen substituents moderately favoured the reaction with respect to unsubstituted substrates (compare entries 1-2 and 7-8). Noticeably, the highly

Table 2. Synthesis of Aromatic Nitriles from Ketones *via* N-(1-arylalkylidene)-cyanomethylamines in DMF solvent.

Entry	Substrate: ArCOR Ar, R	Reaction Time (min)	Product ArCH(R)CN	Isolated Yield (%)[b]
1	**1a**: Ph, Me	105	**2a**	40
2	**1b**: Ph, Et	120	**2b**	38
3	**1c**: Ph, Ph	105	**2c**	58
4	**1d**: Ph, Pr	140	**2d**	38
5	**1e**: *p*-BrC_6H_4, Me	85	**2e**	44
6	**1f**: *p*-ClC_6H_4, Ph	95	**2f**	52
7	**1g**: *m*-$CH_3OC_6H_4$, Me	105	**2g**	36
8	**1h**: 2-[(6-CH_3O)-$C_{10}H_6$], Me	80	**2h**	48

[a]All reaction were carried out in refluxing DMF (155°C) and using substrate / K_2CO_3 in a 1 : 1.5 molar ratio. [b] Yields on distilled product (**2a-b**, **2d-e**, and **2g**) or purified by column-chromatography (**2c**, **2f**, and **2h**).

hindered benzophenone reacted as faster as acetophenone, affording the corresponding nitrile **2c** in a relatively higher yield (entries 1 and 3).

The moderate yields probably resulted from a partial decomposition of the ketimine reagents: in fact, after the product purification (by distillation or coloumn chromatography), residual heavy tars were observed.

In conclusion, the proposed method may represent an alternative to the relatively few synthesis for the homologation of aromatic ketones to nitriles. This procedure may offer some synthetic advantages: it uses inexpensive commercially available reagents and the cyanide source ($NH_2CH_2CN.HCl$) is employed in a small excess with respect to the ketone reagents. When methyl aryl ketones are the starting

reagents, this reaction may have a special importance because the corresponding nitriles $ArCH(CN)CH_3$ have a wide pharmacological interest: well-known examples are the 2-(4-isobutylphenyl)proprionitrile and the 2-[(6-methoxy)-naphtyl]proprionitrile which are intermediates for non-steroidal analgesics such as ibuprofen and naproxen, respectively. [11]

EXPERIMENTAL

General. All compounds were ACS grade and used without further purification. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian (400 MHz) spectrometer using $CDCl_3$ and TMS as the internal standard. GC analyses were performed on a Varian GC 3300 using a 30 m, DB5 capillary column. GC-MS analyses were performed on a HP 5971 mass detector at 70 eV coupled to a HP 5890 gas chromatograph fitted with a 30 m, DB5 capillary column. Gravity coloumn chromatography (gradient elution) was performed on Merck silica-gel (Kieselgel 60).

The Reaction of N-(1-arylalkylidene)-cyanomethyl amines 3a-c to Aromatic Nitriles 2a-c (Table 1). N-(1-arylalkylidene)-cyanomethyl amines **3a-c** (R = Me, Et, Ph) were prepared by the condensation of the corresponding ketones (acetophenone, propiophenone and benzophenone, respectively) with $NH_2CH_2CN.HCl$, according to a procedure previously reported by us. [9] Once recrystallized, the ketimines **3** were reacted as follows: a mixture of the substrate, K_2CO_3 (in 1.5 molar excess with respect to the reactant **3**), n-tetradecane (as the internal standard: 0.3 molar with respect to **3**) and DMF (≈10 mL / g substrate) was loaded in a three-necked, round-bottomed flask fitted with an adapter for sample withdrawal, [12] a refluxing condenser capped with a stopcock, and another stopcock. The mixture was degassed under vacuum. N_2 was inlet from a N_2-containing rubber reservoir and kept during all the reaction. Then, the mixture was

heated under stirring at the reflux temperature (155 °C). The reaction course was followed by GC.

General Procedure for The Preparation of Aromatic Nitriles 2a-h (Table 2). According to the above cited procedure, the ketones **1a-h** were condensed with $NH_2CH_2CN.HCl$ in the presence of $TiCl_4$ and Et_3N. In this case, because the DMF was the solvent of choice for both the preparation of **3** and their subsequent reaction to products **2**, the obtained ketimines **3a-h** were not isolated. In particular, once the reaction of **1** was completed (the ketimine formation could be followed by GC; the structure of such compounds was assigned by GC/MS analyses), the crude mixture was quenched with diethyl ether, filtered off to remove the precipitated solids (TiO_2 and Et_3NHCl), and finally rotary-evaporated. Then, the resulting brown solution of the crude compound **3** in DMF solvent was reacted in the presence of K_2CO_3 (in 1.5 molar excess with respect to the ketone) under the above mentioned conditions (no internal standard was used). Once the ketimine **3** had completely reacted, the suspension was cooled to rt, treated in a separatory funnel with water (≈ 70 mL/g substrate) and extracted with diethyl ether (3 x 60 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The brown residue was distilled (products **2a-b** and **2d-e**) or purified by column chromatography (elution solvent: diethyl ether - petroleum ether 80 : 20 v/v for compounds **2c** and **2f**; methylene chloride - petroleum ether 50 : 50 v/v for compound **2h**).

GC-MS spectra are reported for all the compounds **3** which were not isolated. All the products **2a-h** were characterised by GC/MS and ^1H NMR analyses; the literature references are also reported for each of them.

2-Phenylpropionitrile 2a. Acetophenone (3.50 g) was converted into the corresponding **3a** [*m/z* 158 (M^+, 21%), 157 (56), 144 (11), 143 (100), 116 (28), 103 (43), 81 (10), 77 (15), 51 (11)] which affords 1.52 g of distilled nitrile **2a** (40%; purity 95% by GC). [11, 13]

2-Phenylbutyronitrile 2b. Propiophenone (5.00 g) was converted into the corresponding **3b** [*m/z* 172 (M^+, 12%), 171 (43), 144 (12), 143 (100), 116 (20),

103 (37), 77 (11), 51 (7)] which affords 2.06 g of distilled nitrile **2b** (38%; purity 92% by GC). [14a]

Diphenylacetonitrile 2c. Benzophenone (3.50 g) was converted into the corresponding **3c** [*m/z* 220 (M^+, 58%), 219 (100), 193 (25), 180 (62), 166 (10), 165 (36), 116 (25), 103 (53), 77 (31), 76 (14), 51 (22)] which affords 2.14 g of the nitrile **2c** (58%, purity 97% by GC). [8]

2-Phenylvaleronitrile 2d. Butyrophenone (5.00 g) was converted into the corresponding **3d** [*m/z* 186 (M^+, 12%), 185 (41), 158 (47), 144 (21), 143 (100), 117 (16), 116 (35), 104 (24), 103 (63), 91 (12), 77 (30), 76 (18), 51 (17)] which affords 1.65 g of distilled nitrile **2d** (38%; purity 93% by GC). [14b]

2-(*p*-Bromophenyl)propionitrile 2e. *p*-Bromoacetophenone (4.00 g) was converted into the corresponding **3e** [*m/z* 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)] which affords 1.85 g of distilled nitrile **2e** (44%; purity 91% by GC). [8]

***p*-Chloro-diphenylacetonitrile 2f**. *p*-Chlorobenzophenone (3.50 g) was converted into the corresponding **3f** [*m/z* 256 (16), 255 (26), 254 (M^+, 48%), 253 (49), 220 (16), 219 (100), 214 (33), 179 (18), 177 (38), 165 (19), 163 (10), 143 (40), 137 (43), 116 (18), 103 (25), 77 (20), 75 (28), 51 (15)] which affords 1.92 g of the nitrile **2f** (52%; purity 98% by GC). [15]

2-(*m*-Methoxyphenyl)propionitrile 2g. *m*-Methoxyacetophenone (4.00 g) was converted into the corresponding **3g** [*m/z* 188 (M^+, 60%), 187 (100), 173 (36), 157 (12), 146 (11), 133 (63), 103 (14), 81 (12), 77 (10), 54 (10)] which affords 1.55 g of distilled nitrile **2g** (36%; purity 90% by GC). [11]

2-(6-Methoxy-2-naphthyl)propionitrile 2h. 2-(6-Methoxy)acetonaphtone (2.00 g) was converted into the corresponding **3h** [*m/z* 239 (15), 238 (M^+, 92%), 237 (50), 223 (23), 184 (14), 183 (100), 158 (35), 153 (12), 140 (44), 139 (15), 128 (11), 115 (11), 114 (15), 99 (10), 55 (8)] which affords 1.02 g of the nitrile **2h** (48%; purity 95% by GC). [16]

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