A Comparative Study of the Synthetic Methods for Nitriles

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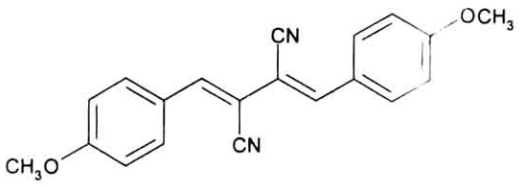
Summary: Different methods used for the synthesis of nitriles are being compared with respect to the yields of the nitriles synthesized. It is observed that the method using tosylmethylisocyanide to convert ketones to nitriles although gives only moderate yields but is advantageous as it is a single step reaction. The cyanation using acetonitrile followed by reductive dehydration also gives an excellent yield of the nitrile and introduces two carbon atoms in one step. In alkylation of nitriles, the best yields were obtained using lithium diiospopylamide as a base. To the best of our knowledge of the nitriles synthesized, 2-(1-naphthyl)propionitrile, 3-(2,4,6-trimethylphenyl)butyronitrile and 3-(2,4,6-trimethoxyphenyl) butyronitrile, have not been reported in the literature so far.

Introduction

Nitriles is a class of compounds which has been used extensively in organic synthesis. These are among the versatile synthetic intermediates in organic chemistry especially when chain elongation is required [1,2]. They can be reduced by a variety of reagents to amines [3] and may undergo acidic or basic hydrolysis to amides [4,5]. They offer an alternative rout [6,7] to the Grignard's synthesis using carbon dioxide in the synthesis of carboxylic acids. Nitriles are also a very promising route for the preparation of optically active carboxylic acids. The α-carbon of the nitriles has acidic hydrogens and can be converted to carbanions which are donor synthons in organic synthesis. The reaction with acceptor synthons produces new carbon-carbon bonds [8,9]. Hydrolysis of cyanohydrins provides a convenient route to α-hydroxyacids [10]. The nitriles also occur occasionally in natural products. For example, a dicyano analogue of the xanthocillins, emerin **(1)**, has been isolated from *Aspergillus* nidulans [11].



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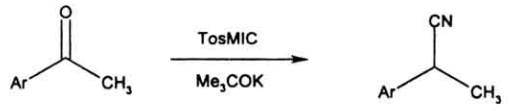
As a part of a project on chiral recognition [12,13] of nitriles, we synthesized a number of nitriles with different structural features using different synthetic strategies. In the present paper we wish to report a comparative account of the synthesis of these nitriles.

Results and Discussion

One of the methods reported for the synthesis of nitriles involves the direct conversion of a ketone to a nitrile by the use of tosylmethylisocyanide (TosMIC) in presence of potassium ter-butoxide [14]. We used this method for the synthesis of five different nitriles.



Ar = C_6H_5, 1-naphthyl, 2-naphthyl, 4-$OCH_3C_6H_4$ and 4-$NO_2C_6H_4$

The yields of the nitriles obtained were moderate (44-62 %). The overall yields of the alternative classical method involving the reduction of ketone to alcohol and then cyanation followed by tosylation or halogenation are also not higher than this single step reaction. To our observation the method works only for methyl ketones as the attempts to convert higher ketones to nitriles failed. The method

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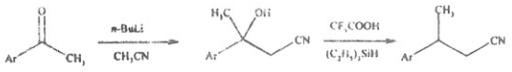
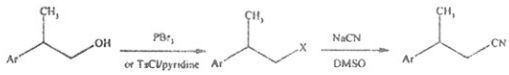
also failed for the conversion of 2-(2-methoxyphenyl)propionitrile and 2-(9-anthryl) propionitrile.

Another method for the conversion of ketones to nitriles introducing two carbon atoms in one step is the reaction of the carbanion of acetonitrile to ketone followed by reductive dehydration [15]. This method gives a very good yield of the nitrile (> 80 % from ketone) and has the added advantage of introducing two carbon atoms in one step. This method was used for the synthesis of 3-(2-naphtyl)butyronitrile and 3-(2,4,6-trimethoxyphenyl)butyronitrile. The yields obtained were 84 and 89 %, respectively. It is also noteworthy that the reaction is clean and purification of the products is easier.



Ar = 2-naphtyl and 2,4,6-trimetoxyphenyl

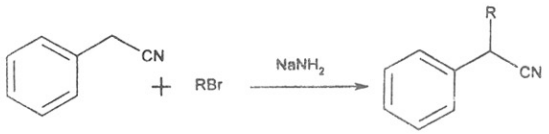
The nucleophilic substitution of the halides or tosylates by the cyanide ion was found to be the most general method [16] for the synthesis of nitriles. A number of nitriles were synthesized using this method in 60-71 % yield except 3-(4-nitrophenyl) butyronitrile in which case the yield was lower (20 %). The yields in this method are only moderate.



X = Br, tosyl

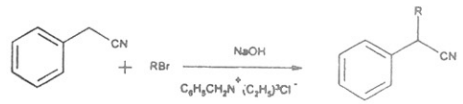
Ar = Ph, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$NO_2C_6H_4$, 2,4,6-$(CH_3)_3C_6H_2$, 2-$OCH_3C_6H_4$

The acidity of the α-hydrogen atoms of nitriles can be utilized to make the carbanion and this method is used for preparation of nitriles from other nitriles by alkylation. One of the earlier reported methods [8] involves the use of $NaNH_2$ as a base followed by treatment with an alkyl halide. We have noted in the synthesis of 2-phenylbutyronitrile and 2-phenyl-2-cylohexylacetonitrile that this method gives poor yields (43 and 50 %, respectively). Furthermore, polyalkylation was also observed in these reactions.



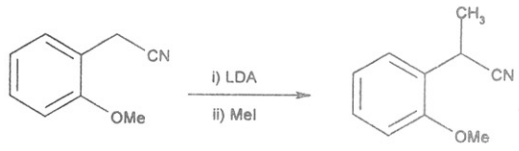
R = $-C_2H_5$, $-C_6H_{11}$

Another method utilized for this purpose uses triethylbenzylammonium chloride and sodium hydroxide in phase transfer catalysis [17]. This method gives moderate to high yields (61-76 %). This method was used for the synthesis of nitriles having varying length of the chain. In this method, only a trace of the dialkylated product was encountered.



R = $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$

The best yields (86 %) in alkylations of nitriles were, however, obtained when lithium diisopropyl amide was used [18] as a base for the synthesis of 2-(2-methoxyphenyl)propionitrile. It was observed that in this case the purification of the product was also easier and no polyalkylation was observed.



$C_6H_5CH_2N^+(C_2H_5)_3Cl^-$

Experimental

General

All the chemicals used in the present work were of analytical grade. IR spectra were recorded on a Perkin-Elmer 1710, FT instrument. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker WP-200 and Brüker AM-400. Deuterated chloroform (with tetramethylsilane as an internal standard) was used as a solvent. For MS spectra Finnigan MAT 312 was used. The elemental analysis was carried out on a Heraeus CHN Rapid. The tlc plates used were from Merck chemical company, Germany. For column chromatography Kieselgel 60 from Merck was used. All the solvents were distilled before use. Petroleum ether used refers to the fraction b.p. 36 °C - 60 °C.

General method for synthesis of nitriles by reaction of the ketone with TosMIC

To an ice-cooled solution of TosMIC (6.5 mmol ; 1.3 g) in dry DMSO (10 ml) was added solid potassium *tert*-butoxide (1.12 g, 10 mmol) all at once with stirring. The solution was allowed to come to

room temperature for ten minutes, when it was cooled again. Methanol (0.25 ml) and then the ketone (5mmoles) was added. The reaction mixture was stirred for half an hour at 0 °C and then allowed to warm up to room temperature while stirring was continued. After completion of the reaction (tlc), the reaction mixture was diluted with water and acidified by hydrochloric acid (2N) to pH ≈ 6 and extracted with ether (3 × 25 ml). The combined ether extracts were washed with saturated sodium chloride solution and dried ($MgSO_4$). Column chromatography gave the pure product.

2-Phenylpropionitrile

Yield = 62 %, IR (νmax, film, cm^{-1}): 3066, 3032, 2987, 2242, 1601, 1495, 1453, 759,699. ^{1}H-NMR ($CDCl_3$, δ): 7.22-7.37 (5H, m, Ar-*H*), 3.86 (1H, q, -C*H*-, *J*= 7.0 Hz), 1.58 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 21.40 (-CH_3), 31.14 (-CH-), 121.63 (-CN), 126.69 (C-3′, 5′), 128.00 (C-4′), 129.12 (C-2′, 6′), 137.13 (C-1′). MS (*m/z*): 131 (M^+), 116 (100 %), 105, 104, 77. HREIMS M^+ 131.0732 (calcd. 131.0734)].

2-(1-Naphthyl)propionitrile

Yield = 49 %, IR (ν_{max}, film, cm^{-1}): 3052, 2987, 2939, 2241, 1598, 1511, 1454, 1397, 800, 777. ^{1}H-NMR ($CDCl_3$, δ): 7.41-7.97 (7H, m, Ar-*H*), 4.59 (1H, q, -C*H*-, J = 7.0 Hz), 1.76 (3H, d, -CH_3, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 20.46 (-CH_3), 28.14 (-CH-), 121.73 (-CN), 121.99 (C-9′), 124.59 (C-7′), 125.46 (C-3′), 126.03 (C-8′), 126.83 (C-4′), 128.85 (C-2′), 129.21 (C-6′), 129.69 (C-10′), 132.58 (C-5′), 133.91 (C-1′). EI (*m/z*): 181 (M^+), 166 (100 %), 155, 154, 153, 140, 139, 127, 113, 90, 77, 76. HREIMS: M^+ 181.0891 (calcd. 181.0891).

2-(2-Naphthyl)propionitrile

Yield = 44 %; m.p. = 62-64 °C {lit [19] 63-65 °C}. IR (ν_{max}, film, cm^{-1}): 3055, 2992, 2942, 2241, 1600, 1508, 1455, 1368, 823, 754. ^{1}H-NMR ($CDCl_3$, δ): 7.73-7.88 (4H, m, Ar-*H*), 7.32-7.55 (3H, m, Ar-H), 3.98 (1H, q, -C*H*-, *J* = 7.0 Hz), 1.66 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 21.32 (-CH_3), 31.32 (-CH-), 121.59 (-CN), 124.37 (C-7′), 125.52 (C-8′), 126.43 (C-2′), 126.68 (C-4′), 127.68 (C-9′), 127.81 (C-6′), 129.08 (C-3′), 132.72 (C-5′), 133.27 (C-10′), 134.31 (1′). EIMS (*m/z*): 181 (M^+), 166 (100 %), 155, 154, 153, 139, 127, 115, 113, 90, 77.

2-(4-Methoxyphenyl)propionitrile

Yield = 48.2 %, IR (ν_{max}, film, cm^{-1}): 3072, 3036, 2984, 2836, 2240, 1612, 1584, 1456, 1304, 1248, 1180, 832, 804. ^{1}H-NMR ($CDCl_3$, δ): 6.80-6.90 (2H, m, 3′,5′-Ar-*H*), 7.15-7.25 (2H, m, 2′,6′-Ar-*H*), 3.85 (1H, q, -C*H*-, *J* = 8.0 Hz), 3.81 (3H, s, -OCH_3), 1.62 (3H, d, -CH_3, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, δ): 21.48 (-CH_3), 30.41 (-CH-), 55.32 (-OCH_3), 114.46 (C-3′), 121.90 (-CN), 127.83 (C-2′), 129.10 (C-1′), 159.29 (C-4′). EIMS (*m/z*): 161 (M^+), 146 (100 %), 135, 134, 117, 90, 77.

2-(4-Nitrophenyl)propionitrile

Yield = 44.3 %, m.p. = 74-76 °C {lit [20] 73-75 °C}. IR (ν_{max}, film, cm^{-1}): 3110, 2994, 2247, 1608, 1522, 1493, 1463, 1347, 1090, 861, 752, 701. ^{1}H-NMR ($CDCl_3$, δ): 7.61-7.66 (2H, dt, 2′,6′-Ar-*H*), 8.32-8.37 (2H, dt, 3′,5′-Ar-*H*), 4.10 (1H, q, -C*H*-, *J* = 7.0 Hz), 1.77 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 21.00 (-CH_3), 30.95 (-CH-), 120.20 (-CN), 124.23 (C-3′, 5′), 127.75 (C-2′, 6′), 143.93 (C-1′), 147.49 (C-4′). EIMS (*m/z*): 176 (M^+), 161, 159, 146, 130 (100 %), 115, 103, 77.

General method for the synthesis of nitriles using condensation followed by reductive dehydration.

a) Synthesis of 3-hydroxy-3-arylbutyronitriles

To a 1.6 M solution of *n*-butyllithium (7.4 mmol, 4.6 ml in *n*-hexane) in anhydrous THF (20 ml) at -78 °C under argon was added anhydrous acetonitrile (7.44 mmol, 0.303 g, 0.38 ml) over five minutes with stirring. After the mixture was stirred at -78 °C for half an hour, the resulting white suspen-sion was treated with a solution of the ketone (6.89 mmol) in anhydrous THF (10 ml) during 15-20 minutes. The mixture was stirred at this temperature for one hour. The cold bath was removed and the mixture was stirred for 15 minutes before it was poured into ice/water/hydrochloric acid (150 g) and extracted with diethyl ether (3 × 25 ml). The organic extracts were washed with water (3 × 20 ml) and dried ($MgSO_4$). The purification of the product was carried out by column chromatography using petroleum ether and diethyl ether as eluent.

3-Hydroxy-3-naphthylbutyronitrile

Yield = 87.6 %, IR (ν_{max}, film, cm^{-1}): 3448, 3056, 3020, 2976, 2932, 2256, 1632, 1600, 1452,

1380, 1272, 1128, 860, 820, 748. ^{1}H-NMR ($CDCl_3$, δ): 7.78-7.92 (4H, m, Ar-H), 7.45-7.51 (3H, m, Ar-H), 3.08 (1H, b, -O*H*), 2.81 (2H, d, -CH_2CN, *J* = 2.0 Hz), 1.75 (3H, s, -CH_3). ^{13}C-NMR ($CDCl_3$, δ): 29.01 (-CH_3), 33.44 (-CH_2-), 72.51 (-CH-), 117.40 (-CN), 122.56 (C-7′), 123.34 (C-8′), 126.39 (C-2′), 126.48 (C-4′), 127.52 (C-9′), 128.29 (C-6′), 128.54 (C-3′), 132.68 (C-5′), 132.98 (C-10′), 141.95 (C-1′). EIMS (*m/z*): 211 (M^+), 193, 171 (100 %), 155, 145, 127, 115, 103, 76.

3-Hydroxy-3-(2, 4, 6-trimethoxyphenyl) buty-ronitrile

Yield = 83.9 %, IR (ν_{max}, film, cm^{-1}): 3448, 3008, 2972, 2944, 2244, 1612, 1588, 1472, 1440, 1416, 1380, 1228, 1208, 1160, 1112, 1096, 812. ^{1}H-NMR ($CDCl_3$, δ): 6.19 (2H, s, Ar-*H*), 3.86 (6H, s, 2′, 6′-OCH_3), 3.80 (3H, s, 4′-OCH_3), 3.27 (1H, dd, -C$H_a$$H_b$CN), 2.84 (1H, dd, -CH$_a$$H_b$CN), 1.65 (3H, s, -$CH_3$). ^{13}C-NMR ($CDCl_3$, δ): 29.74 (-$CH_3$), 32.72 (-$CH_2$-), 55.33 (4′-$OCH_3$), 56.22 (2′, 6′-$OCH_3$), 74.12 (-CH-), 92.47 (C-3′, 5′), 112.28 (C-1′), 118.91 (-CN), 158.32 (C-2′, 6′), 160.26 (C-4′). EIMS (*m/z*): 251 (M^+), 233, 211 (100 %), 195, 181, 169, 152, 137, 105, 91, 77. Elemental analysis [found (calculated)]: C = 62.15 (62.15), H = 6.78 (6.77), N = 5.62 (5.57).

b) Synthesis of nitriles by reductive dehydration

Trifluoroacetic acid (12 mmol, 1.37 g, 0.92 ml) was added with stirring to a solution of 3-hydroxyarylbutyronitrile (2 mmol) and triethylsilane (5 mmol, 0.58 g, 0.79 ml) in methylene chloride (10 ml) at -78 °C. The reaction mixture was brought to room temperature over a period of one hour, during which time trifluoroacetic acid melted and reaction occured. The contents of the flask were then poured cautiously into saturated aqueous sodiumhydrogen-carbonate solution (50 ml), with careful avoidance of excess effervescence. The resulting mixture was extracted with ether (3 × 25 ml). The combined organic extracts were washed with water (3 × 25 ml) and dried ($MgSO_4$). The product was purified by column chromatography using petroleum ether and ethyl acetate as an eluent.

3-(2-Naphthyl)butyronitrile

Yield = 83.6 %, IR (ν_{max}, film, cm^{-1}): 3056, 2956, 2912, 2212, 1608, 1500, 1456, 808, 752. ^{1}H-NMR ($CDCl_3$, δ): 7.32-7.86 (7H, m, Ar-H), 3.31 (1H, sex, -C*H*-, *J* = 7.0 Hz), 2.65 (2H, ddd, -CH_2-), 1.52 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 20.70 (-CH_3), 26.25 (-CH_2-), 36.65 (-CH-), 118.54 (-CN), 124.74 (C-7′), 125.12 (C-8′), 125.92 (C-2′), 126.34 (C-4′), 127.65 (C-9′), 127.77 (C-6′), 128.67 (C-3′), 132.65 (C-5′), 133.47 (C-10′), 140.51 (C-1′). EIMS (*m/z*): 195 (M^+), 180, 165, 155 (100 %), 128, 127, 76.

3-(2,4,6-Trimethoxyphenyl)butyronitrile

Yield = 88.9 %, IR (ν_{max}, film, cm^{-1}): 3008, 2960, 2940, 2836, 2244, 1608, 1588, 1496, 1468, 1416, 1228, 1204, 1152, 1124, 812. ^{1}H-NMR ($CDCl_3$, δ): 6.11 (2H, s, Ar-*H*), 3.80 (1H, m, -C*H*-), 3.79 (6H, s, 2′,6′-OCH_3), 2.80 (3H, s, 4′-OCH_3), 2.75 (2H, ddd, -CH_2-), 1.34 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 18.58 (-CH_3), 22.59 (-CH_2-), 26.65 (-CH-), 55.28 (4′-OCH_3), 55.62 (2′, 6′-OCH_3), 90.99 (C-3′, 5′), 111.42 (C-1′), 120.23 (-CN), 159.02 and 160.04 (C-2′, 4′, 6′). EIMS (*m/z*): 235 (M^+), 220, 208, 204, 195 (100 %), 167, 165, 105, 91, 77. Elemental analysis [found (calculated)]: C = 66.30 (66.38), H = 7.22 (7.23), N = 6.01 (5.99).

General method for the synthesis of nitriles through tosylates

a) Synthesis of tosylates

The alcohol (0.001 moles) and *p*-toluene-sulfonylchloride (0.0011 mol, 220 mg) in pyridine (2 ml) were stirred at 0 °C for three hours. Ice was added to the reaction mixture and extracted with diethyl ether (3 × 20 ml). The combined ether extracts were washed twice with 6N hydrochloric acid, twice with water and dried ($MgSO_4$). After filtration the solvent was evaporated *in vacuo* and the crude tosylate was converted to nitriles.

b) Synthesis of nitriles from tosylates

Crude tosylate (from 0.001 moles of alcohol) in dry DMSO (1 ml) was added drop wise to stirred slurry of sodium cyanide (0.003 moles, 140 mg) in dry DMSO (3 ml) at 90 °C. The resulting solution was stirred for three hours at this temperature, cooled to room temperature, diluted with water (20 ml) and extracted with diethyl ether (3 × 20 ml). The combined ether extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave almost a colourless oil which was purified by column chromatography.

3-(4-Methylphenyl)butyronitrile

Yield = 64.1 %, IR (ν_{max}, film, cm^{-1}): 3022, 2964, 2923, 2878, 2244, 1517, 1458, 1421, 1379,

1018, 817. ^{1}H-NMR ($CDCl_3$, δ): 7.09-7.16 (4H, m, Ar-*H*), 3.10 (1H, sex, -C*H*-, *J* = 7.3 Hz), 2.52 (2H, ddd, -CH_2-), 2.31 (3H, s, 4′-CH_3), 1.41 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 20.71 and 20.99 (2 X -CH_3), 26.37 (-CH_2-), 36.11 (-CH-), 118.67 (-CN), 126.40 (C-3′, 5′), 129.48 (C-2′, 6′), 136.87 (C-4′), 140.19 (C-1′). MS (*m/z*): 159 (M^+), 144, 119 (100 %), 118, 115, 91, 77. EIHR: M^+ 159.1048 (cacld. 159.1048).

3-(4-Methoxyphenyl)butyronitrile

Yield = 54.7 %, IR (ν_{max}, film, cm^{-1}): 2963, 2937, 2839, 2243, 1614, 1515, 1460, 1251, 1180, 1035, 830. ^{1}H-NMR ($CDCl_3$, δ): 7.12-7.19 (2H, m, Ar-*H*), 6.83-6.90 (2H, m, Ar-H), 3.77 (3H, s, -OCH_3), 3.10 (1H, sex, -C*H*-, *J* = 7.0 Hz), 2.52 (2H, ddd, -CH_2-), 1.40 (3H, d, -CH_3, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 20.77 (-CH_3), 26.55 (-CH_2-), 35.72 (-CH-), 55.24 (-OCH_3), 114.16 (C-3′, 5′), 118.70 (-CN), 127.56 (C-2′, 6′), 135.23 (C-1′), 158.70 (C-4′). MS (*m/z*): 175 (M^+), 160, 144, 135 (100 %), 134, 120, 108, 105, 91, 77. HREIMS: M^+ 175.0996 (calcd. 175.0997).

3-(4-Nitrophenyl)butyronitrile

Yield = 19.6 %, IR (ν_{max}, film, cm^{-1}): 3072, 2968, 2936, 2252, 1596, 1516, 1456, 1344, 1108, 852, 696. ^{1}H-NMR ($CDCl_3$, δ): 8.20-8.24 (2H, dt, Ar-*H*), 7.43-7.48 (2H, dt, Ar-H), 3.31 (1H, sex, -C*H*-, J = 6.8 Hz), 2.65 (1H, d, -C$H_a$$H_b$CN, *J* = 1.1 Hz), 2.67 (1H, d, -C$H_a$$H_b$CN, *J* = 1.1 Hz), 1.50 (3H, d, -CH_3, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 20.45 (-CH_3), 25.89 (-CH_2-), 36.43 (-CH-), 117.77 (-CN), 124.15 (C-3′, 5′), 127.73 (C-2′, 6′), 150.32 (C-4′). EIMS (*m/z*): 190 (M^+), 175, 174, 163, 150 (100 %), 144, 143, 115, 91, 90, 76.

3-(2,4,6-Trimethylphenyl)butyronitrile

Yield = 62.4 %, IR (ν_{max}, film, cm^{-1}): 2968, 2924, 2876, 2248, 1612, 1572, 1468, 1452, 852, 740. ^{1}H-NMR ($CDCl_3$, δ): 6.82 (2H, s, Ar-*H*), 3.66 (1H, sex, -CH-, J = 7.2 Hz), 2.34 (6H, s, 2′, 6′-CH_3), 2.23 (3H, s, 4′-CH_3), 2.71 (2H, ddd, -CH_2-), 1.46 (3H, d,-CH_3, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, δ): 18.60 (-CH_3), 20.61 (4′-CH_3), 21.34 (2′,6′-CH_3), 22.98 (-CH_2-), 32.15 (-CH-), 119.20 (-CN), 135.91 and 136.32 (aromatic carbons). MS (*m/z*): 187 (M^+), 172, 157, 147 (100 %), 131, 119, 115, 105, 91, 77.

3-(2-Methoxyphenyl)butyronitrile

Yield = 62.7 %, IR (ν_{max}, film, cm^{-1}): 2968, 2939, 2839, 2243, 1601, 1586, 1493, 1462, 1245, 1126, 1030, 754. ^{1}H-NMR ($CDCl_3$, δ): 7.17-7.26 (2H, m, Ar-*H*), 6.84-6.98 (2H, m, Ar-*H*), 3.81 (3H, s, -OCH_3), 3.53 (1H, sex, -C*H*-, J = 6.6 Hz), 2.60 (2H, ddd, -CH_2-), 1.42 (3H, d, -CH_3, J = 6.8 Hz). ^{13}C-NMR ($CDCl_3$, δ): 18.76 (-CH_3), 24.46 (-CH_2-), 30.06 (-CH-), 55.25 (-OCH_3), 110.54 (C-3′), 119.05 (-CN), 120.76 (C-1′), 126.76 (C-5′), 128.20 (C-4′), 130.94 (C-6′), 156.72 (C-2′). MS (*m/z*): 175 (M^+), 160, 149, 148, 145, 135 (100 %), 120, 108, 105, 91, 77. HR: M [found (calculated)] = [175.0996905 (175.0997144)].

4-Phenylpentanenitrile

Yield = 70.7 %, IR (ν_{max}, film, cm^{-1}): 3025, 2961, 2930, 2875, 2245, 1603, 1493, 1452, 1029, 764, 703. ^{1}H-NMR ($CDCl_3$, δ): 7.16-7.37 (5H, m, Ar-*H*), 2.86 (1H, m, -C*H*-), 2.16 (2H, m, -CH_2CN), 1.92 (2H, m, -CHCH_2-), 1.31 (3H, d, -CH_3, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, δ): 15.41 (C-2), 21.92 (C-5), 33.51 (C-3), 38.89 (C-4), 119.64 (-CN), 126.74 (C-4′), 126.90 (C-3′, 5′), 128.76 (C-2′, 6′), 144.57 (C-1′). MS (*m/z*): 159 (M^+), 144, 118, 105 (100 %), 91, 77. HR: M [found (calculated)] = [159.1049693 (159.1047997)].

5-Phenylhexanenitrile

Yield = 63.1 %, IR (ν_{max}, film, cm^{-1}): 3024, 2960, 2928, 2872, 2244, 1600, 1492, 1452, 1024, 764, 700. ^{1}H-NMR ($CDCl_3$, δ): 7.14-7.33 (5H, m, Ar-*H*), 2.70 (1H, sex, -C*H*-, J = 7.0 Hz), 2.25 (2H, dt, -CH_2CN), 1.72 (2H, m, -CH_2CH_2CN), 1.53 (2H, m, -CHCH_2-), 1.26 (3H, d, -CH_3, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 17.16 (C-2), 22.38 (-CH_3), 23.57 (C-3), 37.10 (C-4), 39.44 (C-5), 119.65 (-CN), 126.27 (C-4′), 126.87 (C-3′, 5′), 128.54 (C-2′, 6′), 146.24 (C-1′). MS (*m/z*): 173 (M^+), 158, 117, 105 (100 %), 91, 77.

General method for the synthesis of nitriles by alkylation of phenylacetonitrile in presence of sodium amide:

To a solution of phenylacetonitrile (0.01 mol, 1.17 g) in dry ether (10 ml) was slowly added a suspension of sodium amide (0.011 mol, 0.42 g) in dry ether with stirring. The mixture was refluxed for one hour on an oil bath and then cooled thoroughly in

an ice bath. The alkyl halide (0.01 mol) was added drop wise with stirring. When the addition of alkyl halide was complete, the reaction mixture was allowed to warm up to room temperature and stirring continued until the reaction was complete (tlc). Water was added to the reaction mixture and the organic layer separated. The aqueous layer was extracted with ether (3 × 25 ml) and combined ether extracts were dried ($MgSO_4$). Purification of the product was carried out by column chromatography.

2-Phenylbutyronitrile

Yield = 43.0 %, b.p. = 105-107 °C (7 mm) {lit [21] 102-104 °C (7 mm)}, IR (ν_{max}, film, cm^{-1}): 3066, 3033, 2972, 2241, 1602, 1494, 1455, 760, 700. ^{1}H-NMR ($CDCl_3$, δ): 7.24-7.42 (5H, m, Ar-*H*), 3.72 (1H, t, -C*H*-, J = 7.0 Hz), 1.91 (2H, qu, -CH_2-, J = 7.0 Hz), 1.05 (3H, t, -CH_3, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 11.43 (-CH_3), 29.18 (-CH_2-), 38.82 (-CH-), 120.77 (-CN), 127.27 (C-3′, 5′), 127.98 (C-4′), 128.99 (C-2′, 6′), 135.76 (C-1′). MS (*m/z*): 145 (M^+), 130, 117 (100 %), 116, 90, 77. HR: M [found (calculated)] = [145.089146 (145.089149)].

α-Cyclohexylphenylacetonitrile

Yield = 49.5 %, IR (ν_{max}, film, cm^{-1}): 3062, 3034, 2935, 2856, 2233, 1600, 1494, 1455, 755, 700. ^{1}H-NMR ($CDCl_3$, δ): 7.24-7.44 (5H, m, Ar-*H*), 3.63 (1H, d, -C*H*-, J = 6.0 Hz), 1.54-1.92 (6H, b, cyclohexyl), 1.02-1.34 (8H, b, 5-cyclohexyl and 3 methyl protons). ^{13}C-NMR ($CDCl_3$, δ): 25.78, 25.83, 25.92 (C-3″, 4″, 5″), 29.54, 31.19 (C-2″, 6″), 42.73 (C-1″), 44.28 (-*C*HCN), 120.11 (-CN), 127.88 (C-4′), 127.96 (C-3′, 5′), 128.77 (C-2′, 6′), 134.70 (C-1′). MS (*m/z*): 199 (M^+), 166, 154, 140, 130, 117 (100 %), 116, 90, 77.

General method for synthesis of nitriles by phase transfer catalyzed alkylation:

Phenylacetonitrile (0.055 mol, 6.435g) and benzyltriethylammonium chloride (0.55 mmol, 0.125 g) were added into sodium hydroxide solution (20 ml, 50 %) in a three necked flask fitted with a dropping funnel, a reflux condenser and a thermometer. Stirring was begun and 0.05 moles of alkyl halide were added drop wise through the dropping funnel at such a rate that the temperature remains between 28 to 35 °C. If necessary, the flask may be cooled by means of a cold water bath. After the addition of alkyl halide, the stirring was continued for three hours and then the temperature was raised to 40-45 °C for an additional one hour. The reaction mixture was cooled in a cold-water bath and water (25 ml) was added followed by diethyl ether (25 ml). The layers were separated, and the aqueous phase extrac-ted with diethyl ether (2 × 20 ml). The organic layers were combined and washed successively with water (25 ml), aqueous dilute hydrochloric acid (25 ml) and again with water (25 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed by distillation under reduced pressure. The product was purified by column chromatography.

2-Phenylpentanenitrile

Yield = 76.0 %, IR (ν_{max}, film, cm^{-1}): 3063, 3033, 2962, 2240, 1602, 1495, 1455, 758, 700. ^{1}H-NMR ($CDCl_3$, δ): 7.25-7.45 (5H, m, Ar-*H*), 3.72 (1H, dd, -C*H*-), 1.81 (2H, m, -CHCH_2-), 1.45 (2H, m, -C$H_2$$CH_3$), 0.97 (3H, t, -C$H_3$, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 13.28 (-CH_3), 20.16 (C-4), 37.00 (C-2), 37.74 (C-3), 120.81 (-CN), 127.11 (C-3′, 5′), 127.83 (C-4′), 128.90 (C-2′, 6′), 135.94 (C-1′). MS (*m/z*): 159 (M^+), 144, 117 (100 %), 116, 90, 77.

3-Methyl-2-phenylbutyronitrile

Yield = 67.0 %, IR (ν_{max}, film, cm^{-1}): 3066, 3033, 2967, 2239, 1602, 1494, 1455, 740, 700. ^{1}H-NMR ($CDCl_3$, δ): 7.25-7.45 (5H, m, Ar-*H*), 3.67 (1H, d, -C*H*-, J = 6.5 Hz), 2.13 (1H, o, -C<u>H</u>(CH_3)$_2$, J = 6.5 Hz), 1.03 (3H, d, -CH_3, J = 5.0 Hz), 1.07 (3H, d, -CH_3, J = 5.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 18.78, 20.77 (2 X -CH_3), 33.76 (C-3), 45.05 (C-2), 119.86 (-CN), 127.85 (C-3′, 5′), 127.94 (C-4′), 128.80 (C-2′, 6′), 134.94 (C-1′). MS (*m/z*): 159 (M^+), 144, 117 (100 %), 116, 90, 77. HR: M [found (calculated)] = [159.1047383 (159.1047997)].

2-Phenylhexanenitrile

Yield = 73.0 %, IR (ν_{max}, film, cm^{-1}): 3066, 3033, 2959, 2241, 1602, 1495, 1455, 755, 699. ^{1}H-NMR ($CDCl_3$, δ): 7.27-7.40 (5H, m, Ar-*H*), 3.71 (1H, t, -C*H*-, J = 7.0 Hz), 1.84 (2H, m, -C*H*CH_2-), 1.43 (2H, m, -$CHCH_2$CH_2-), 1.31 (2H, m, -CH_2CH_3), 0.87 (3H, t, -CH_3, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 13.76 (-CH_3), 22.07 (C-5), 29.10 (C-4), 35.61 (C-3), 37.35 (C-2), 120.96 (-CN), 127.22 (C-3′, 5′), 127.95 (C-4′), 129.02 (C-2′, 6′), 136.09 (C-1). MS (m/z): 173 (M^+), 158, 130, 129, 117 (100 %), 116, 103, 90, 77. HR: M [found (calculated)] = [173.1204430 (173.1204499)].

2-Phenylheptanenitrile

Yield = 61.0 %, IR (ν_{max}, film, cm^{-1}): 3066, 3033, 2956, 2241, 1602, 1495, 1455, 756, 699. ^{1}H-NMR ($CDCl_3$, δ): 7.30-7.40 (5H, m, Ar-*H*), 3.70 (1H, dd, -C*H*-), 1.91 (2H, m, -CHCH_2-), 1.40 (2H, m, -CHCH$_2$CH_2-), 1.25 (4H, m, -CH_2CH_2CH$_3$), 0.83 (3H, t, -CH_3, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, δ): 13.93 (-CH_3), 22.34 (C-6), 26.69 (C-4), 31.09 (C-5), 35.87 (C-3), 37.37 (C-2), 120.94 (-CN), 127.21 (C-3′, 5′), 127.95 (C-4′), 129.01 (C-2′, 6′), 136.10 (C-1′). MS (*m/z*): 187 (M^+), 159, 158, 129, 117 (100%), 116, 90, 77. HR: M [found (calculated)] = [187.1361207 (187.1361092)].

Synthesis of 2-(2-methoxyphenyl)propionitrile using LDA as a base:

To diisopropylamine (2 mmol, 202 mg) in anhydrous THF (3 ml) at 0°C under argon atmosphere was added a solution (1.6 M) of *n*-butyllithium (2 mmol, 1.25 ml) in hexane. The solution was stirred for about half an hour at this temperature and then cooled to -78 °C. 2-Methoxyphenylacetonitrile (2 mmol, 294 mg) in THF (1.0 ml) was introduced and the solution was stirred for half an hour again. To this lithio-nitrile solution at -78 °C was added methyl iodide (2 mmol, 284 mg) in THF (1.0 ml). The reaction mixture was stirred for one hour at -78 °C, one hour at 0 °C and then one hour at room temperature when the reaction was complete. The reaction mixture was diluted with water, acidified with dilute hydrochloric acid and extracted with diethyl ether (3 × 25 ml). The combined extracts were washed with water and dried ($MgSO_4$). After filtration and evaporation of the solvent *in vacuo*, a yellow oil was obtained. The product was purified by column chromatography using petroleum ether and ethyl acetate (8:2) as eluents. Yield = 85.7 %, IR (ν_{max}, film, cm^{-1}): 2982, 2940, 2839, 2239, 1601, 1495, 1465, 1439, 1293, 1251, 1120, 1086, 1051, 1029, 756. ^{1}H-NMR ($CDCl_3$, δ): 7.23-7.45 (2H, m, Ar-*H*), 6.84-7.02 (2H, m, Ar-*H*), 4.24 (1H, q, -C*H*-, J = 7.2 Hz), 3.85 (3H, s, -OCH_3), 1.56 (3H, d, -CH_3, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, δ): 19.49 (-CH_3), 25.64 (-CH-), 55.45 (-OCH_3), 110.7 (C-3′), 120.96, (-CN), 125.36 (C-1′), 125.91 (C-5′), 127.54 (C-4′), 129.32 (C-6′), 156.03 (C-2′). MS (*m/z*): 161 (M^+), 146 (100 %), 135, 134, 133, 130, 107, 91, 90, 77.

Conclusions

The present study using different methods for the synthesis of nitriles suggests that although a number of direct methods are available for the synthesis of nitriles, they have their own limitations and that the most general method is still the indirect method (from ketones) of reduction, tosylation/ halogenation and cyanation. However, when applicable, the method of conversion of the ketones directly to nitriles by reaction with TosMIC has the advantage as it is a single step reaction and yields are also good. The method of condensation followed by reductive dehydration also gives a very good yield and has a clear advantage of introducing two carbon atoms in one step. In case of alkylations, the method using LDA as a base was found to be advantageous.

To the best of our knowledge three of the compounds, namely 2-(1-naphthyl)propionitrile, 3-(2, 4,6-trimethylphenyl)butyronitrile and 3-(2,4,6-trimethoxyphenyl)butyronitrile, have not been repor-ted in the literature so far.

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