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Synthesis of α-aryl nitriles through $B(C_6F_5)_3$-catalyzed direct cyanation of α-aryl alcohols and thiols

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ABSTRACT

Various α-aryl nitriles have been prepared in excellent yield from the corresponding α-aryl alcohols employing 3 mol % of $B(C_6F_5)_3$ (**1**) as Lewis acid catalyst and $(CH_3)_3SiCN$ (TMSCN) as cyanide source. Cyano transfer from TMSCN to alcohol proceeds within short reaction time at rt. α-Aryl thiols also produce corresponding nitriles in good to excellent yield at reflux condition.

1. Introduction

Nitriles are valuable intermediates that can be transformed to a variety of biologically important substances such as oxazoles,[1] thiazoles,[2] triazoles,[3] oxadiazoles,[4] and tetrazoles.[5] α-Arylnitriles are potentially valuable precursors for the synthesis of well known drugs such as verapamil,[6] indoprofen,[7] cicloprofen, and naproxen.[8] Direct substitutions of the hydroxyl group in alcohols by various nucleophiles such as allyl-, alkynyl-, and propargylsilanes,[9] 1,3-dicarbonyl compounds,[10] amides[11] or amines,[12] and so on[13] using the Lewis acid catalysts have aroused much research interest. In these reactions, the hydroxyl groups in alcohols can be directly substituted by the desired nucleophiles without the need for prior transformation into the groups that have good leaving potentials. Aryl nitriles are usually synthesized from aryl halides using stoichiometric amount of copper(I) cyanide, which has been known for over 80 years.[14] Nitriles are also prepared by dehydration of amides and aldoximes,[15] acylations of silyl ketene imines,[16] hydrocyanation of olefins,[17] and displacement of aryl triflates.[18] Microwave-assisted preparation of aryl nitriles has been reported too.[19] Recently palladium catalyzed cyanation of aryl and heteroaryl chlorides has appeared in the literature.[20]

The conversion of an alcohol into the corresponding nitrile is a fundamental synthetic process for carbon chain elongation. It is usually performed through prior conversion of hydroxyl group to halides and sulfonates. However, there are only a few reports on the direct cyanation of alcohols into nitriles in one-pot procedure.[21] Reagent system composed of TMSCN and $InBr_3$ in CH_2Cl_2 was reported as a convenient and efficient system for cyanation of secondary alcohols.[22]

While various Lewis acids are employed in modern organic synthesis, boron based reagents still remain prominent as a result of their high Lewis acid strength and ready availability. The strong organometallic Lewis acid, $B(C_6F_5)_3$ **1**, has emerged in recent years as a viable alternative to BF_3.[23] Owing to its uniqueness and commercial availability, its applications in organic synthesis are growing and have been reviewed.[24]

The first commercial application of **1** was introduced as the cocatalyst in metallocene mediated olefin polymerization.[25] The functional group transformation by **1** was initially undertaken by Ishihara et al. for aldol type reaction.[26] Recently, the applications of **1** are found in hydrosilation of alcohols,[27a] enones,[27b] carbonyl groups,[27c] and imines, [27d] stereoselective transformation of epoxides,[27e] tritylation of alcohols,[27f] allylstannation of aromatic alehydes,[27g] allylation of secondary benzyl acetates,[27h] Ferrier azaglycosylation with sulfonamides and carbamate,[27i] reduction of carbonyl group to methylene,[27j] cleavage of aryl and alkyl ether with hydrosilanes,[27k,l] aziridines' ring opening,[27m] and hydrogenation of imines.[27n]

2. Results and discussion

We have developed several catalytic methods for the oxidation of alcohols[28] and cyanosilylation of carbonyl compounds.[29] Herein

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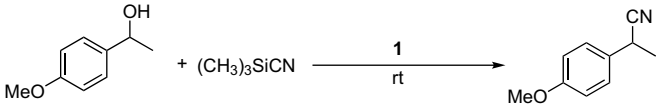
we report **1** as a simple and effective catalyst for the direct cyanation of α-aryl alcohols with TMSCN at rt. This can be the first example of borane catalyzed cyanation of alcohols.

To obtain the optimized reaction conditions, we have chosen the reaction of 4-methoxy-α-methylbenzyl alcohol with TMSCN in the presence of $B(C_6F_5)_3$ as Lewis acid catalyst. First we examined the solvent suitability for this reaction. The data in Table 1 indicate that CH_3CN is the most appropriate solvent (entries 1–9). CH_2Cl_2 also acts as a good solvent for this system with little longer reaction time (entry 7). The solvent-free reaction gave only good yield of the corresponding nitrile (entry 10). To determine the effect of catalytic loading for improving the yield, we have performed the reaction with 1–20 mol % of $B(C_6F_5)_3$ in CH_3CN. We have found that the reaction proceeds to give 94% yield with 3 mol % of the catalyst (entry 4). TMSCN and *n*-Bu_4NCN were also tested for the cyanation reaction as cyanide source. In terms of yield and reaction time, TMSCN gave the best results (entry 4). We have therefore chosen entry 4 (Table 1) as the optimum reaction condition for cyanation of α-aryl alcohols.

Having established the standard conditions, the scope of this protocol was examined for various α-aryl alcohols (Table 2). *sec*-1-Phenylethanol (entry 1) and its *para*-substituted derivatives (entries 2–6) are efficiently converted to corresponding α-aryl nitriles in relatively short reaction time. It is worthwhile to note that the recently reported $InBr_3$ catalyzed protocol[22] is not amenable to *sec*-1-phenylethanol for cyanation reaction. Our system, however, gives excellent yield for the same substrate. *ortho*-Di substituted α-aryl alcohol underwent smooth cyanation and gave moderate yield (entry 7). The change of phenyl to naphthyl group (entries 8 and 9) hardly influences the reactivity and also the yield. Benzhydrol underwent smooth cyanation and gave an excellent yield (entry 10). The reactions of benzhydrols having chlorine and fluorine atoms at *para*-position gave the corresponding α-aryl nitriles in high yields (entries 11 and 12). Furthermore, sterically hindered triphenylmethanol, which is known to be a difficult substrate for cyanation reaction, gave excellent yield in short reaction time (entry 13). This may indicate that steric hindrance is no longer important for the cyanation. It should be noted that alcohol having additional methylene group in the side chain was also proved as good substrate for cyanation reaction (entry 14). Good yields were obtained for *ortho*-methoxy substituted 1-phenylpropanol

Table 1
Direct cyanation of 4-methoxy-α-methylbenzyl alcohol under various reaction conditions[a]



Entry	Catalyst loading (mol %)	Solvent	Time (min)	Yield[b]
1	20	CH_3CN	30	96
2	10	CH_3CN	30	96
3	5	CH_3CN	60	95
4	3	CH_3CN	55	94
5	2	CH_3CN	90	95
6	1	CH_3CN	180	90
7	3	CH_2Cl_2	70	93
8	3	CH_3Cl	180	40
9	3	THF	240	50
10	3	No solvent	120	75
11	3	CH_3CN	120	50[c]

[a] Reagent and condition: 1.0 mmol of 4-methoxy-α-methylbenzyl alcohol, 1.0 mmol of TMSCN.
[b] Isolated yield.
[c] *n*-Bu_4NCN (5.0 mmol) was used as cyanide source.

Table 2
$B(C_6F_5)_3$-catalyzed direct cyanation of α-aryl alcohols with TMSCN at rt[a]

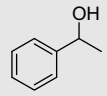
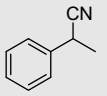
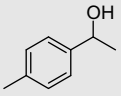
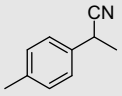
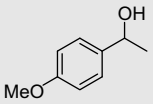
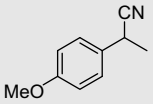
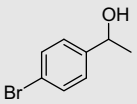
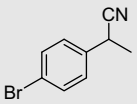
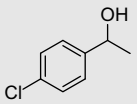
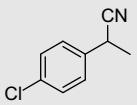
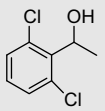
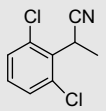
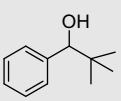
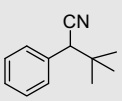
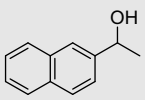
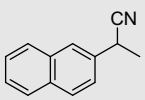
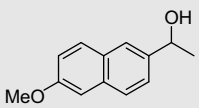
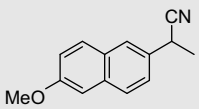
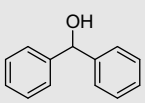
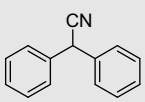
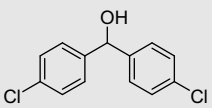
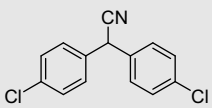
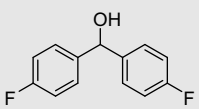
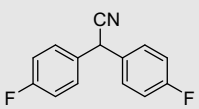
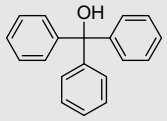
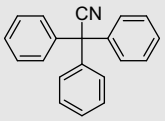
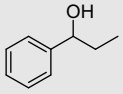
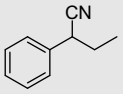
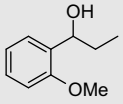
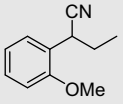
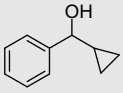
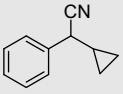
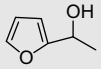
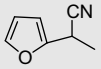
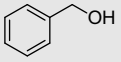
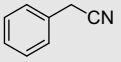
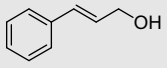
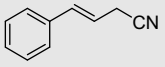
Entry	Substrate	Time (min)	Product	Yield[b]
1	 **(1a)**	60	 **(1b)**	90
2	 **(2a)**	60	 **(2b)**	90
3	 **(3a)**	55	 **(3b)**	94
4	 **(4a)**	70	 **(4b)**	90
5	 **(5a)**	60	 **(5b)**	89
6	 **(6a)**	70	 **(6b)**	85
7	 **(7a)**	60	 **(7b)**	92
8	 **(8a)**	60	 **(8b)**	90
9	 **(9a)**	60	 **(9b)**	92
10	 **(10a)**	60	 **(10b)**	93
11	 **(11a)**	60	 **(11b)**	91
12	 **(12a)**	60	 **(12b)**	90

Table 2 (*continued*)

Entry	Substrate	Time (min)	Product	Yield[b]
13	 **(13a)**	70	 **(13b)**	93
14	 **(14a)**	60	 **(14b)**	85
15	 **(15a)**	70	 **(15b)**	80
16	 **(16a)**	60	 **(16b)**	80
17	 **(17a)**	120	 **(17b)**	60
18	 **(18a)**	120	 **(18b)**	55
19	 **(19a)**	140	 **(19b)**	40
20	 **(20a)**	180	 **(20b)**	Trace
21	 **(21a)**	180	 **(21b)**	Trace

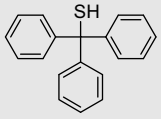
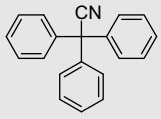
[a] Reagent and condition: α-aryl alcohol (1.00 mmol), TMSCN (1 mmol), 3 mol % of $B(C_6F_5)_3$.
[b] Isolated yield.

and α-cyclobenzyl alcohol (entries 15 and 16). Poor yields were obtained for heterocyclic and aliphatic α-aryl alcohols (entries 17–19). Cyanation products were not obtained for benzyl alcohol and cinnamyl alcohol under the present reaction conditions. The present system requires only 3 mol % of catalyst. It is worthwhile to note that the present protocol for cyanation reaction proceed efficiently at rt without any additives.

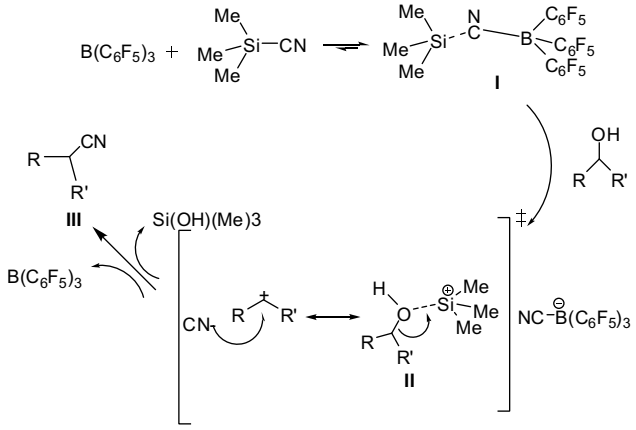
We also examined commercially available secondary and tertiary thiols for direct cyanation reaction. The results are summarized in Table 3. Thiols gave poor yields under optimized condition used for the alcohols. But increase of catalytic loading and temperature gives a good to moderate yields for the thiols (entries 1 and 2).

$B(C_6F_5)_3$-catalyzed cyanosilylation reaction may follow the catalytic pathway as shown in Scheme 1. Abstraction of cyanide anion from the silane by **1** in the presence of the alcohol substrate can lead to the formation of silyloxonium/cyanoborate ion pair (**II**), which may collapse to the product.

Table 3
$B(C_6F_5)_3$-catalyzed direct cyanation of α-aryl thiols with TMSCN at rt and reflux temperature[a]

Entry	Substrate	Time (min)	Catalyst loading (mol %)	Product	Yield[b]
1		60 120	3 10		40[c] 72[d]
2		60 120	3 10		30[c] 65[d]

[a] Reagent and condition: 1.0 mmol of thiol, 1.0 mmol of TMSCN.
[b] Isolated yield.
[c] Reaction at rt.
[d] Reaction at reflux condition.



Scheme 1. Proposed reaction pathway.

3. Conclusion

In summary, we have developed a very simple, efficient one-step method for the synthesis α-aryl nitriles from corresponding α-aryl alcohols. The significant features of this method include operational simplicity, low catalytic loading, moisture tolerant organometallic Lewis acid catalyst, and no need of any additives. Mild reaction condition, high yields of the products, and ease in handling of reagents make this method more convenient for direct cyanation of α-aryl alcohol into α-aryl nitriles.

4. Experimental section

4.1. General

4.1.1. Instrumentation

In all the cases the ^1H NMR spectra were recorded with Varian Gemini 200 or 400 MHz instrument. Chemical shifts are reported in parts per million in $CDCl_3$ with tetramethylsilane as the internal standard. ^{13}C NMR data were collected on Varian Gemini 200 or 400 MHz instrument (50 or 100 MHz). Compounds are identified by HRMS (EI) with Jeol DMX 303. Infrared (IR) spectra were obtained by 370 FT-IR spectrometer.

4.2. Experimental procedure

4.2.1. General procedure for cyanation of α-aryl alcohols/thiols

To a stirred solution of alcohol/thiol (1 mmol) and $B(C_6F_5)_3$ (3 mol %) in CH_3CN (1 ml) TMSCN (1 mmol) was added dropwise. The resulting solution was stirred continuously at rt for the time

indicated in Table 2/Table 3. The reaction mixture was purified by silica gel flash chromatography by using EtOAc–hexanes (1:9) mixture as the eluent.

4.2.2. Characterization data

*4.2.2.1. 2-Phenylpropanenitrile (**1b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.32–7.40 (m, 5H), 3.91 (q, J=10.81 Hz, H), 1.64 (d, J=3.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 136.9, 129.0, 127.9, 126.6, 121.5, 31.1, 21.36; IR (νC≡N) 2237 cm^{-1}. HRMS m/z calcd for C_9H_9N $[M+H]^+$ 131.0735, found 131.0731.

*4.2.2.2. 2-p-Tolylpropanenitrile **(2b)**.* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.10–7.23 (m, 4H), 4.19 (q, J=7.3 Hz, H), 2.34 (s, 3H), 1.34 (d, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.2, 135.9, 129.1, 126.2, 121.2, 30.9, 21.2, 20.6; IR (νC≡N) 2220 cm^{-1}. HRMS m/z calcd for $C_{10}H_{11}N$ $[M+H]^+$ 145.0891, found 145.0893.

*4.2.2.3. 2-(4-Methoxyphenyl)propanenitrile (**3b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.0 Hz, 2H), 4.18 (q, J=4.7 Hz, 1H), 4.14 (s, 3H), 1.94 (d, J=4.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.2, 129.1, 127.8, 121.9, 114.4, 55.3, 36.4, 21.36; IR (νC≡N) 2233 cm^{-1}. HRMS m/z calcd for $C_{10}H_{11}NO$ $[M+H]^+$ 161.0841, found 161.0844.

*4.2.2.4. 2-(4-Bromophenyl) propanenitrile (**4b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J=7.8 Hz, 2H), 7.14 (d, J=7.8 Hz, 2H), 4.16 (q, J=4.9 Hz, 1H), 1.34 (d, J=5.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.8, 131.6, 131.3, 127.9, 127.8, 121.2, 24.5; IR (νC≡N) 2230 cm^{-1}. HRMS m/z calcd for C_9H_8BrN $[M+H]^+$ 208.9840, found 208.9844.

*4.2.2.5. 2-(4-Chlorophenyl) propanenitrile (**5b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, J=7.4 Hz, 2H), 6.98 (d, J=7.4 Hz, 2H), 4.11 (q, J=4.7 Hz, 1H), 1.31 (d, J=5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.6, 130.3, 131.1, 125.8, 125.3, 120.6, 24.1; HRMS m/z calcd for C_9H_8ClN $[M+H]^+$ 165.0345, found 165.0341.

*4.2.2.6. 2-(2,6-Dichlorophenyl)-propionitrile (**6b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.90–7.11 (m, 3H), 4.43 (q, J=5.7 Hz, 1H), 1.30 (d, J=5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.6, 127.8, 127.1, 124.1, 115.3, 44.2, 25.3; HRMS m/z calcd for $C_9H_7Cl_2N$ $[M+H]^+$ 198.9956, found 165.9951.

*4.2.2.7. 3,3-Dimethyl-2-phenylbutanenitrile (**7b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.28–7.29 (m, 5H), 4.29 (s, 1H), 0.89 (9H, s); ^{13}C NMR ($CDCl_3$) δ 135.8, 131.9, 131.0, 129.6, 126.3, 121.3, 36.0, 27.3; IR (νC≡N) 2227 cm^{-1}. HRMS m/z calcd for $C_{12}H_{15}N$ $[M+H]^+$ 173.1204, found 173.1208.

*4.2.2.8. 2-(Naphthalen-2-yl)propanenitrile (**8b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.82–7.90 (m, 3H), 7.67 (s, 1H), 7.49–7.53 (m, 3H), 4.47 (q, J=7.1 Hz, 1H), 1.50 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 135.6, 133.2, 131.1, 129.3, 128.9, 127.6, 126.8, 125.6, 125.1, 121.5, 31.3, 21.8; IR (νC≡N) 2220 cm^{-1}. HRMS m/z calcd for $C_{15}H_{11}N$ $[M+H]^+$ 205.0891, found 205.0897.

*4.2.2.9. 2-(6-Methoxynaphthalen-2-yl)propanenitrile (**9b**).* Pale yellow solid; mp 72–73 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (t, J=8.0 Hz, 3H), 7.33–7.41 (m, 1H), 7.12–7.26 (m, 2H), 4.07 (q, J=7.1 Hz, 1H), 3.92 (s, 3H), 1.71 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 157.9, 133.9, 131.9, 129.2, 128.6, 127.8, 125.2, 124.8, 121.7, 119.4, 105.5, 55.2, 31.0, 21.3; IR (νC≡N) 2227 cm^{-1}. HRMS m/z calcd for $C_{16}H_{13}NO$ $[M+H]^+$ 235.0997, found 235.0996.

*4.2.2.10. 2,2-Diphenylacetonitrile (**10b**).* Pale yellow solid; mp 73–74 °C; ^{1}H NMR ($CDCl_3$) δ 6.99–7.14 (m, 10H), 5.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 136.3, 129.3, 128.4, 128.1, 120.2, 42.6; IR (νC≡N) 2230 cm^{-1}. HRMS m/z calcd for $C_{14}H_{11}N$ $[M+H]^+$ 193.0891, found 193.0891.

*4.2.2.11. 2,2-Bis(4-chlorophenyl)acetonitrile (**11b**).* Yellow solid; mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 7.15–7.34 (m, 8H), 5.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 139.7, 133.7, 129.8, 129.1, 121.3, 43.9; IR (νC≡N) 2235 cm^{-1}. HRMS m/z calcd for $C_{14}H_9Cl_2N$ $[M+H]^+$ 261.0112, found 261.0090.

*4.2.2.12. 2,2-Bis(4-fluorophenyl)acetonitrile (**12b**).* Colorless oil; ^{1}H NMR ($CDCl_3$,) δ 7.48–7.55 (m, 4H), 7.21–7.34(m, 4H), 5.56 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 161.4, 135.4, 132.7, 121.8, 117.8, 44.1; IR (νC≡N) 2239 cm^{-1}. HRMS m/z calcd for $C_{14}H_9F_2N$ $[M+H]^+$ 229.0703, found 229.0703.

*4.2.2.13. 2,2,2-Triphenylacetonitrile (**13b**).* White solid; mp 129–130; ^{1}H NMR ($CDCl_3$) δ 7.21–7.41 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 140.1, 128.8, 128.6, 128.1, 123.4, 57.3; IR (νC≡N) 2240 cm^{-1}. HRMS m/z calcd for $C_{20}H_{15}N$ $[M+H]^+$ 269.1204, found 269.1200.

*4.2.2.14. 2-Phenylbutanenitrile (**14b**).* Colorless oil; ^{1}H NMR ($CDCl_3$,) δ 7.33–7.41 (m, 5H), 3.77 (t, J=7.2 Hz, 1H), 1.93–2.00 (m, 2H), 1.10 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 135.7, 129.0, 128.0, 127.3, 120.8, 38.84, 29.2, 11.4. HRMS m/z calcd for $C_{10}H_{11}N$ $[M+H]^+$ 145.0891, found 145.0889.

*4.2.2.15. 2-(2-Methoxyphenyl)butanenitrile (**15b**).* Colorless oil; ^{1}H NMR ($CDCl_3$,) δ 6.60–7.20 (m, 4H), 4.10 (t, J=7.0 Hz, 1H), 3.72 (s, 3H), 1.79–1.94 (m, 2H), 0.75–0.85 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.0, 133.1, 129.2, 126.4, 123.2, 120.4, 114.3, 56.3, 29.3, 27.1, 11.6; HRMS m/z calcd for $C_{11}H_{13}NO$ $[M+H]^+$ 175.0997, found 175.0989.

*4.2.2.16. 2-Cyclopropyl-2-phenylacetonitrile (**16b**).* Colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.05–7.29 (m, 5H), 3.38 (d, J=7.2 Hz, 1H), 0.41–0.46 (m, 4H), 0.59–0.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.8, 129.0, 128.3, 127.3, 120.1, 39.1, 12.5, 4.2; HRMS m/z calcd for $C_{11}H_{11}N$ $[M+H]^+$ 157.0891, found 157.0898.

*4.2.2.17. 2-Furan-2-yl-propionitrile (**17b**).* Colorless oil; ^{1}H NMR ($CDCl_3$,) δ 6.05–7.29 (m, 3H), 4.38 (q, J=7.2 Hz, 1H), 1.80(d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.8, 139.0, 115.41, 109.8, 103.6, 30.6, 11.3; HRMS m/z calcd for C_7H_7NO $[M+H]^+$ 121.0528, found 121.0532.

*4.2.2.18. 2-Methyl-but-3-ynenitrile (**18b**).* Colorless oil; ^{1}H NMR ($CDCl_3$,) δ 4.1 (q, J=7.2 Hz, 1H), 2.17 (s, 1H), 1.82(d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 118.4, 85.3, 65.2, 24.5, 13.5; HRMS m/z calcd for C_5H_5N $[M+H]^+$ 79.0422, found 79.0426.

*4.2.2.19. 3-Dimethylamino-2-methyl-propionitrile (**19b**).* Colorless oil; ^{1}H NMR ($CDCl_3$,) δ 3.7 (q, J=7.1 Hz, 1H), 2.85–3.05 (m, 2H), 2.07 (s, 6H), 1.52 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 120.4, 55.3, 39.2, 25.5, 15.5. HRMS m/z calcd for $C_6H_{12}N_2$ $[M+H]^+$ 112.1000, found 112.1006.

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