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An efficient synthesis of cyanoarenes and cyanoheteroarenes via lithiation followed by electrophilic cyanation

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Abstract—A one-pot procedure for the conversion of mono-substituted arenes and heteroarenes into the *ortho*-cyano derivatives was achieved through directed lithiation followed by electrophilic cyanation with phenyl cyanate. This reaction method proved to be applicable to halogen–lithium exchanged intermediates, so especially useful for the synthesis of benzonitriles. The scope of the reaction sequence was explored using a number of substrates.

1. Introduction

The synthesis of aromatic nitriles is of continuing interest due to the versatile and useful intermediates for the various classes of compounds. In particular, the cyano aromatics bearing an *ortho*-substituent are expected highly to be utilized for the buildup of heteroaromatics, e.g. 2-aminoarenecarbonitriles to fused pyrimidines.[1] The introduction of cyano group at the position adjacent to *sec*-amino or hydroxyl substituents on benzene has been accomplished by treatment with BCl_3 followed by CCl_3CN.[2] This synthetic method is, however, limited in the application to further substituted arenes. On the other hand, an aromatic carbon adjacent to a heteroatom-containing functional group undergoes metalation with organolithium,[3] so that the *ortho*-lithiation methodology would be a powerful tool for the current target-directed synthesis. In this paper, we describe an efficient synthesis of *ortho*-cyanobenzenes and -cyanoheteroarenes through directed lithiation and following electrophilic cyanation.[4]

2. Result and discussion

The nitriles are usually prepared by the nucleophilic attack of a cyanide ion (CN^-) on an electrophilic carbon, although several reagents proved to behave like cyano cation (CN^+) equivalents on treatment with a carbanion. These include $(CN)_2$,[5] ClCN,[6] tosyl cyanide,[7–9] phenyl cyanate,[10] 2-chlorobenzyl thiocyanate,[11] pentachlorobenzonitrile,[12] 1-cyanobenzotriazole[13,14] and 1-cyanoimidazole.[15] For safety and accessibility of reagent, the utilization of phenyl cyanate (PhOCN) which is easily prepared from phenol and BrCN[10,16] was first examined.

N,*N*-Diisopropylbenzamide (**1a**) was lithiated by adding *t*-butyllithium below −70°C,[17] and the resulting 2-lithiobenzamide **2a** was immediately treated with neat phenyl cyanate at this temperature (Scheme 1). The reaction mixture was stirred below −70°C for 30 min and then allowed to warm to 0°C during 2 h. After workup the desired 2-cyano product **3a** was obtained in 98% yield (Table 1, entry 4). The shorter reaction time or quenching below −70°C resulted in a significant decrease in the yield of **3a** (entries 1–3). The direct addition of neat phenyl cyanate via a syringe was practically convenient, but it sometimes suffered when the needle clogged with the frozen reagent by injection through a chilled septum cap. A solution of phenyl cyanate in THF was employed to avoid this drawback, when the nitrile **3a** formed with a slight decrease in the yield (entry 5). The use of 4-nitrophenyl cyanate[18] and 1-cyanoimidazole[15] instead of phenyl cyanate under comparable conditions also afforded the cyanobenzamide **3a** although in lower yields (entries 6 and 7). An attempt using commercially available CCl_3CN, pentafluorobenzonitrile or dimethylcyanamide instead of phenyl cyanate failed, and the starting material **1a** was fully recovered in the case with CCl_3CN (entry 8).

The further benzenes **1b-e** bearing a directed metalation group (DMG) were similarly subjected to the one-pot lithiation/cyanation sequence (Scheme 1, Table 2), in which each lithiation was performed according to the procedure in literatures.[17,19,20] The electrophilic cyanation proceeded compatibly with using either neat phenyl cyanate (odd

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Keywords: lithiation; electrophilic cyanation; phenyl cyanate; cyano arenes.

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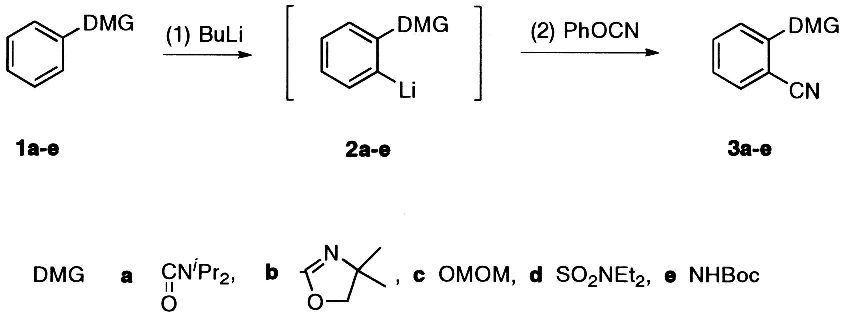


Scheme 1.

Table 1. Cyanation of 2-lithiobenzamide **2a**

Entry	Reagent[a]	Conditions	Conversion (%)	Yield of **3a**[b] (%)
1	PhOCN (n)	<-70°C/30 min	64	40
2	PhOCN (n)	<-70°C/1 h	100	62
3	PhOCN (n)	<-70°C/15 min to 0°C/1 h	100	67
4	PhOCN (n)	<-70°C/30 min to 0°C/2 h	100	98
5	PhOCN (s)	<-70°C/30 min to 0°C/2 h	90	86
6	4-Nitro-PhOCN (s)	<-70°C/30 min to 0°C/2 h	79	23
7	1-Cyanoimidazole (s)	<-70°C/30 min to 0°C/2 h	71	52
8	CCl_3CN (n)	<-70°C/30 min to 0°C/2 h	0	0

The lithio compound **2a** was formed by treating with *t*-BuLi (1.1 equiv.) in THF (10 mL/1.0 mmol of **1a**) below -70°C for 1 h.

[a] Cyanation reagent was added with neat (n) or solution in THF (s).

[b] Isolated yields of pure material after silica gel chromatography.

Table 2. Synthesis of cyanobenzenes **3**

Entry	Substrate	Lithiation conditions[a]	PhOCN used[b]	Conversion (%)	Product	Yield[c] (%)
1	**1b**	^{t}BuLi/ether (3 mL)/<-70°C/1 h	n	92	**3b**	73
2	**1b**	^{t}BuLi/ether (3 mL)/<-70°C/1 h	s	85	**3b**	72
3	**1c**	^{t}BuLi/ether (3 mL)/0°C/1 h	n	94	**3c**	78
4	**1c**	^{t}BuLi/ether (3 mL)/0°C/1 h	s	97	**3c**	76
5	**1d**	^{n}BuLi/THF (2 mL)/0°C/30 min	n	84	**3d**	64
6	**1d**	^{n}BuLi/THF (2 mL)/0°C/30 min	s	83	**3d**	70
7	**1e**	^{t}BuLi[d]/ether (3 mL)/-10°C/3 h	n	90	**3e**	68[e]
8	**1e**	^{t}BuLi[d]/ether (3 mL)/-10°C/3 h	s	89	**3e**	68[e]

[a] Lithiation was performed by treatment of the substrate (1.0 mmol) in THF or diethyl ether, which are shown together with the requisite volume, with BuLi (1.1 mmol unless otherwise noted).

[b] PhOCN was added with neat (n) or solution in THF or ether (s).

[c] Isolated yields of pure material after silica gel chromatography unless otherwise noted.

[d] BuLi (2.2 mmol) used.

[e] Isolated yields of pure material after silica gel chromatography and successive HPLC.

entries) or its solution (even entries). Therefore, the latter addition procedure was employed for all subsequent cyanation reactions. In contrast to such a successful substitution to nitriles, the cyanation of *N*,*N*-diethyl-2-lithiobenzylamine[17,21] was problematic leading to the formation of many undesirable products.

A number of heteroaromatic compounds were in turn subjected to the electrophilic cyanation after lithiating with butyllithium[22–24] (Schemes 2 and 3). Furan[25] and thiophene-2-carboxylic derivatives **4** gave good yields of the corresponding 3-cyano compounds **5** (Table 3, entries 1 and 3). The lithiation/cyanation of *N*-Boc-aminoheteroarenes **4b**, **7b** and **9** was efficiently realized (entries 2, 6, and 7). Conversely, the reactions of **4d**, **7a** and **11** were somewhat distressed with the formation of some byproducts, giving the modest yields of cyano compounds (entries 4, 5, and 8). The lithiation of *N*-Boc-amine **11** was sluggish at -20°C for 3 h compared to the other isomers **7b** and **9** (entries 6 and 7 vs. 8), hence the metalation was carried out at 0°C resulting in an unexpectedly appreciable decrease in the yield of the desired product **12**, albeit in promotion of lithiation (entry 9). It is worthy of note that the cyanation of *N*-Boc-amines **4b** and **4d** led to the exclusive formation of 5-cyano products **6** unlike that of the carboxylic derivatives **4a** and **4c**. The regioselectivity can be rationalized by preferable lithiation α to sulfur of thiophene nucleus over *ortho*-lithiation induced by the Boc-amino substituent probably because of the weaker directing ability than carboxylic functionalities. Another notable regiochemistry is the cyanation of *N*-Boc-3-aminopyridine **9** (entry 7), which afforded only the 4-cyano derivative **12**, not 2-cyano isomer.[26]

Halogen–lithium exchange is a different way of forming

Table 3. Synthesis of cyanoheteroarenes

Entry	Substrate	Lithiation conditions[a]	Conversion (%)	Product	Yield[b] (%)
1	**4a**	^{n}BuLi/THF (3 mL)/<−70°C/2 h	85	**5a**	74
2	**4b**	^{t}BuLi[c]/THF (3 mL)/−20°C/1 h[d]	89	**6b**	71
3	**4c**	^{n}BuLi/ether (10 mL)/0°C/30 min[d]	85	**5c**	80[e]
4	**4d**	^{t}BuLi[c]/THF (3 mL)/−20°C/1 h[d]	94	**6d**	48
5	**7a**	^{n}BuLi[c]/THF (3 mL)/0°C/3 h	81	**8a**	43[f]
6	**7b**	^{t}BuLi[c]/THF (3 mL)/−20°C/3 h[d]	95	**8b**	77
7	**9**	^{t}BuLi[c]/THF (3 mL)/−20°C/3 h[d]	100	**10**	73
8	**11**	^{t}BuLi[c]/THF (3 mL)/−20°C/3 h[d]	36	**12**	31
9	**11**	^{t}BuLi[c]/THF (3 mL)/0°C/3 h[d]	83	**12**	25

[a] Lithiation was performed by treatment of the substrate (1.0 mmol) in THF or diethyl ether, which are shown together with the requisite volume, with BuLi (1.1 mmol unless otherwise noted).

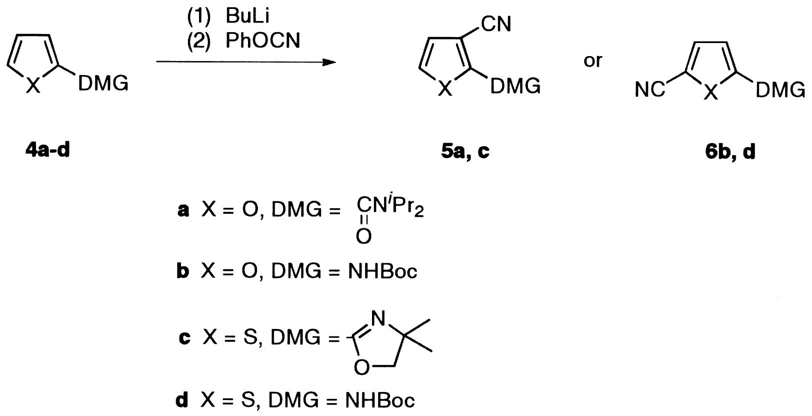
[b] Isolated yields of pure material after silica gel chromatography unless otherwise noted.

[c] BuLi (2.2 mmol) used.

[d] After addition of BuLi below −70°C, the mixture was stirred for 15 min at that temperature and then subjected to the given conditions.

[e] An 85% yield of **5c** was obtained using neat PhOCN. The product was isolated in pure form by HPLC.

[f] A 47% yield of **8a** was obtained when neat PhOCN was used.



Scheme 2.

organolithiums, which were also cyanated under identical conditions (Scheme 4). For example, bromobenzenes **13** were converted into the corresponding benzonitriles **14** in excellent yields (Table 4, entries 1 and 2). However, bromopyridines **15** and **17** gave low yields of cyanopyridines (entries 3 and 4) in spite of allowing clean lithiation using inverse addition of the halides to ethereal butyllithium. These bromopyridines were earlier shown to afford a variety of products in 54–98% yields by lithiation/electrophilic substitution.[27–30] It is conceivable that phenyl cyanate reacts slower with the lithiated intermediates than when commonly using electrophiles such as aldehydes, ketones or alkyl formate. In other words, the majority of highly reactive organolithio species decomposes or produces undesired materials prior to coupling with cyano cation. The failure of cyanation in *N*,*N*-diethylbenzylamine can be likewise explained.

Another synthesis of aryl and heteroaryl nitriles was recently developed through halogen–magnesium exchange, which involves reaction of tosyl cyanide with organomagnesiums which were formed by treatment of aromatic iodides with isopropylmagnesium bromide or diisopropylmagnesium.[31–34]

In summary, a general and convenient route to cyanoarenes and cyanoheteroarenes has been devised using *ortho*-metalation or halogen–metal exchange protocol. This approach should be seen as a wide utility in the synthesis of fused heteroaromatic compounds.

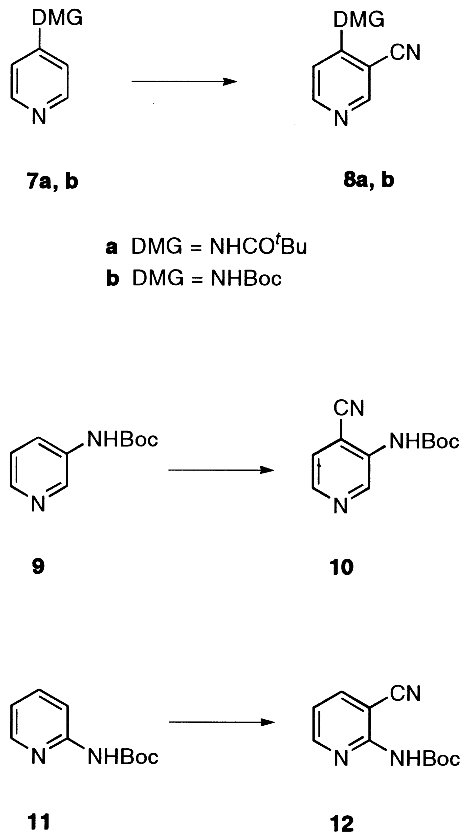
Table 4. Cyanation of bromoaromatics

Entry	Substrate	Lithiation conditions[a]	Conversion (%)	Product	Yield[b] (%)
1	**13a**	^{n}BuLi/THF (3 mL)/<−70°C/1 h	100	**14a**	82
2	**13b**	^{n}BuLi/THF (5 mL)/<−70°C/1 h	100	**14b**	88
3	**15**	^{n}BuLi[c]/ether (3 mL)/0°C/10 min	100	**16**	31
4	**17**	^{n}BuLi[c]/ether (3 mL)/<−70°C/10 min	100	**18**	30

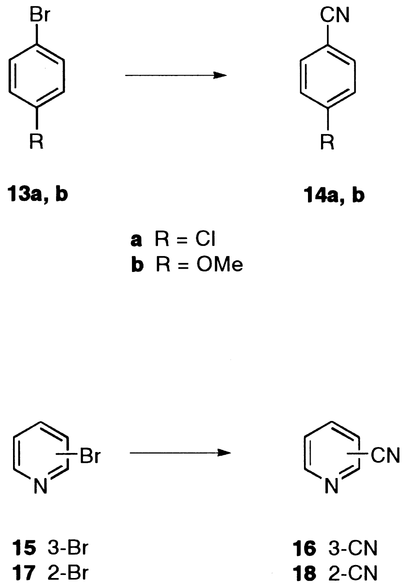
[a] Lithiation was performed by treatment of the substrate (1.0 mmol) in THF or diethyl ether, which are shown together with the requisite volume, with BuLi (1.2 mmol).

[b] Isolated yields of pure material after silica gel chromatography.

[c] Inverse addition: bromopyridines were added to BuLi.



Scheme 3.



Scheme 4.

3. Experimental

THF and ether were distilled from sodium/benzophenone. The concentration of commercial *n*-butyllithium (1.56–1.58 M in hexane) and *t*-butyllithium (1.40–1.60 M in pentane) was determined by using 4-biphenylmethanol as reagent-indicator.[35] Melting points were determined with a Büchi capillary apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer Spectrum One. The NMR spectra were obtained on a Brucker Avance 400 (400 MHz ^{1}H, 100.6 MHz ^{13}C) instrument with solutions in deuteriochloroform using tetramethylsilane as the internal standard.

3.1. General procedure for lithiation/cyanation

Butyllithium was added dropwise to a solution of substrate (1.0 mmol) in dry THF or ether under argon. The amount of butyllithium, the requisite volume of solvent and the temperature during addition are summarized in Tables 1–4. The reaction mixture was stirred under the conditions given in the above tables and then cooled below −70°C if the lithiation was required at higher temperatures than −70°C. Phenyl cyanate (1.2 equiv.) was added, and the mixture was stirred below −70°C for 30 min and then warmed to 0°C during 2 h. After quenching with 0.5 M aqueous sodium hydroxide (20 mL), the mixture was extracted with dichloromethane or ethyl acetate (3×20 mL). The combined extracts were washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel and/or HPLC (10 μm silica gel, 2.2×30 cm).

3.1.1. *N*,*N*-Diisopropyl-2-cyanobenzamide (3a). Colorless prisms (hexane), mp 107–108°C, bp 175°C/2 mm Hg (Kugelrohr); ^{1}H NMR δ 1.60 (d, 6H, J=6.2 Hz, CH_3), 3.59 (septet, 2H, J=6.7 Hz, CH), 7.34 (ddd, 1H, J=7.7, 1.2, 0.6 Hz, H-6), 7.45 (td, 1H, J=7.7, 1.2 Hz, H-4), 7.62 (td, 1H, J=7.7, 1.3 Hz, H-5), 7.68 (ddd, 1H, J=7.8, 1.3, 0.6 Hz, H-3); ^{13}C NMR δ 20.3 (0.5C, CH_3), 20.8 (0.5C, CH_3), 46.3 (0.5C, CH), 51.5 (0.5C, CH), 109.2 (C-2), 116.9 ($C\equiv N$), 125.9 (C-6), 128.6 (C-4), 132.9 (C-3), 133.0 (C-5), 142.6 (C-1), 166.9 ($C{=}O$); IR (KBr) ν_{max} 2226 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.72; H, 7.73: N, 12.03.

3.1.2. 2-(4′,4′-Dimethyl-2′-oxazolinyl)benzonitrile (3b). Bp 140°C/2 mm Hg (Kugelrohr), mp 57°C; ^{1}H NMR δ 1.42 (s, 6H, CH_3), 4.20 (s, 2H, H-5′), 7.56 (td, 1H, J=7.7, 1.3 Hz, H-5), 7.63 (td, 1H, J=7.7, 1.3 Hz, H-4), 7.76 (dd, 1H, J=7.6, 1.0 Hz, H-6), 8.04 (dd, 1H, J=7.9, 0.8 Hz, H-3); ^{13}C NMR δ 28.3 (CH_3), 68.3 (C-4′), 79.8 (C-5′), 111.8 (C-1), 117.7 ($C\equiv N$), 130.2 (C-3), 130.7 (C-2), 131.0 (C-5), 132.3 (C-4), 134.4 (C-6), 159.7 (C-2′); IR (neat) ν_{max} 2229 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.09; H, 6.02: N, 14.00.

3.1.3. 2-(Methoxymethyl)oxybenzonitrile (3c). Bp 77–78°C/0.04 mm Hg; ^{1}H NMR δ 3.53 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 7.06 (td, 1H, J=7.6, 0.9 Hz, H-5), 7.23 (d, 1H, J=8.4 Hz, H-3), 7.52 (ddd, 1H, J=8.5, 7.5, 1.7 Hz, H-4), 7.57 (dd, 1H, J=7.7, 1.7 Hz, H-6); ^{13}C NMR δ 56.5 (CH_3), 94.8 (CH_2), 102.9 (C-1), 114.9 (C-3), 116.3 ($C\equiv N$), 121.9 (C-5), 133.6 (C-6), 134.3 (C-4), 159.1 (C-2); IR (neat) ν_{max} 2229 cm^{-1} (CN). Anal. calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.27; H, 5.58; N, 8.54.

3.1.4. *N*,*N*-Diethyl-2-cyanobenzenesulfamide (3d). Bp 180°C/2 mm Hg (Kugelrohr), mp 53–54°C; ^{1}H NMR δ 1.17 (t, 6H, J=7.1 Hz, CH_3), 3.43 (q, 4H, J=7.1 Hz, CH_2), 7.67 (td, 1H, J=7.6, 1.3 Hz, H-4), 7.74 (td, 1H, J=7.7, 1.4 Hz, H-5), 7.86 (dd, 1H, J=7.6, 1.3 Hz, H-3), 8.12 (dd, 1H, J=7.6, 1.3 Hz, H-6); ^{13}C NMR δ 13.7 (CH_3), 41.6 (CH_2), 110.4 (C-2), 116.3 ($C\equiv N$), 130.1 (C-6), 132.3 (C-4), 132.8 (C-5), 135.5 (C-3), 143.6 (C-1); IR (KBr) ν_{max} 2226 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.76. Found: C, 55.54; H, 5.94: N, 11.62.

3.1.5. *N*-(*t*-Butoxycarbonyl)-2-aminobenzonitrile (3e). Colorless needles (hexane), mp 72–75°C, bp 165°C/2 mm Hg (Kugelrohr); ^{1}H NMR δ 1.54 (s, 0.91×9H, CH_3), 1.58 (s, 0.09×9H, CH_3), 7.03 (br s, 1H, NH), 7.08 (td, 1H, J=7.7, 0.9 Hz, H-5), 7.53 (dd, 1H, J=7.8, 1.3 Hz, H-6), 7.55 (td, 1H, J=7.8, 1.3 Hz, H-4), 8.23 (dd, 1H, J=7.6, 0.9 Hz, H-3); ^{13}C NMR δ 27.8 (0.09C, CH_3), 28.2 (0.91C, CH_3), 81.9 (0.91C, $C-CH_3$), 86.6 (0.09C, $C-CH_3$), 100.7 (C-1), 116.5 ($C\equiv N$), 119.2 (C-3), 122.7 (C-5), 132.3 (C-6), 134.1 (C-4), 141.4 (C-2), 151.9 ($C=O$); IR (KBr) ν_{max} 2218 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.05; H, 6.47: N, 12.83.

3.1.6. *N*,*N*-Diisopropyl-3-cyanofuran-2-carboxamide (5a). Colorless needles (hexane), mp 62–63°C, bp 170°C/2 mm Hg (Kugelrohr); ^{1}H NMR δ 1.40 (br s, 12H, CH_3), 3.80 (br s, 2H, CH), 6.67 (d, 1H, J=1.9 Hz, H-4), 7.44 (d, 1H, J=1.9 Hz, H-5); ^{13}C NMR δ 24.7 (CH_3), 48.8 (CH), 99.1 (C-3), 112.6 ($C\equiv N$), 112.8 (C-4), 142.8 (C-5), 155.6 (C-2), 157.3 ($C=O$); IR (KBr) ν_{max} 2238 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.43; H, 7.36: N, 12.68.

3.1.7. 2-(4′,4′-Dimethyl-2′-oxazolinyl)thiophene-3-carbonitrile (5c). Colorless prisms (hexane), mp 64°C, bp 140°C/2 mm Hg (Kugelrohr); ^{1}H NMR δ 1.40 (s, 6H, CH_3), 4.21 (s, 2H, H-5′), 7.30 (d, 1H, J=5.2 Hz, H-4), 7.48 (d, 1H, J=5.2 Hz, H-5); ^{13}C NMR δ 28.2 (CH_3), 68.4 (C-4′), 80.3 (C-5′), 111.4 (C-3), 114.2 ($C\equiv N$), 129.7 (C-5), 130.7 (C-4), 138.6 (C-2), 155.7 (C-2′); IR (KBr) ν_{max} 2234 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.04; H, 4.80: N, 13.37.

3.1.8. *N*-(*t*-Butoxycarbonyl)-5-aminofuran-2-carbonitrile (6b). Colorless needles (hexane), mp 139–139.5°C; ^{1}H NMR δ 1.52 (s, 9H, CH_3), 6.20 (d, 1H, J=3.4 Hz, H-4), 7.19 (br s, 1H, NH), 7.08 (d, 1H, J=3.4 Hz, H-3); ^{13}C NMR δ 28.1 (CH_3), 82.8 ($C-CH_3$), 93.6 (C-2), 112.0 (C-4), 118.3 ($C\equiv N$), 125.2 (C-3), 155.2, 155.3 (C-5 and $C=O$); IR (KBr) ν_{max} 2234 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.71; H, 5.69: N, 13.45.

3.1.9. *N*-(*t*-Butoxycarbonyl)-5-aminothiophene-2-carbonitrile (6d). Colorless tiny needles (hexane), mp 127°C; ^{1}H NMR δ 1.53 (s, 9H, CH_3), 6.43 (d, 1H, J=3.8 Hz, H-4), 7.37 (d, 1H, J=3.8 Hz, H-3), 7.56 (br s, 1H, NH); ^{13}C NMR δ 28.2 (CH_3), 83.0 ($C-CH_3$), 99.6 (C-2), 109.2 (C-4), 115.3 ($C\equiv N$), 136.0 (C-3), 146.8 (C-5), 151.9 ($C=O$); IR (KBr) ν_{max} 2203 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.82; H, 5.40: N, 12.11.

3.1.10. 4-(*N*-Pivaloylamino)pyridine-3-carbonitrile (8a). Colorless needles (hexane), mp 84.5–85°C; bp 130°C/2 mm Hg (Kugelrohr); ^{1}H NMR δ 1.37 (s, 9H, CH_3), 8.07 (br s, 1H, NH), 8.48 (d, 1H, J=5.9 Hz, H-5), 8.67 (d, 1H, J=5.9 Hz, H-6), 8.74 (s, 1H, H-2); ^{13}C NMR δ 27.7 (CH_3), 41.0 ($C-CH_3$), 98.7 (C-3), 113.7 (C-5), 114.8 ($C\equiv N$), 147.4 (C-4), 153.1 (C-2), 154.8 (C-6), 177.7 ($C=O$); IR (KBr) ν_{max} 2224 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 64.93; H, 6.45: N, 20.71.

3.1.11. *N*-(*t*-Butoxycarbonyl)-4-aminopyridine-3-carbonitrile (8b). Light tan needles (hexane), mp 128°C; ^{1}H NMR δ 1.55 (s, 9H, CH_3), 7.24 (br s, 1H, NH), 8.25 (d, 1H, J=6.0 Hz, H-5), 8.61 (d, 1H, J=6.0 Hz, H-6), 8.69 (s, 1H, H-2); ^{13}C NMR δ 28.1 (CH_3), 83.4 ($C-CH_3$), 97.4 (C-3), 111.9 (C-2), 114.6 ($C\equiv N$), 147.8 (C-4), 150.8 ($C=O$), 153.0 (C-5), 153.9 (C-6); IR (KBr) ν_{max} 2234 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.50; H, 6.04: N, 19.14.

3.1.12. *N*-(*t*-Butoxycarbonyl)-3-aminopyridine-4-carbonitrile (10). Light tan oil which decomposed during Kugelrohr distillation at 160°C (0.3 mm Hg); ^{1}H NMR δ 1.56 (s, 9H, CH_3), 7.07 (br s, 1H, NH), 7.42 (d, 1H, J=4.7 Hz, H-5), 8.43 (d, 1H, J=4.7 Hz, H-6), 9.54 (s, 1H, H-2); ^{13}C NMR δ 28.1 (CH_3), 82.8 ($C-CH_3$), 108.2 (C-3), 114.3 ($C\equiv N$), 124.3 (C-5), 136.2 (C-3), 142.5 (C-2), 143.6 (C-6), 151.4 ($C=O$); IR (KBr) ν_{max} 2234 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.21; H, 6.25: N, 18.82.

3.1.13. *N*-(*t*-Butoxycarbonyl)-2-aminopyridine-3-carbonitrile (12). Colorless needles (hexane/EtOAc 2:1), mp 160.5–161°C; ^{1}H NMR δ 1.56 (s, 9H, CH_3), 7.15 (dd, 1H, J=7.8, 4.9 Hz, H-5), 7.88 (br s, 1H, NH), 7.96 (dd, 1H, J=7.8, 1.9 Hz, H-4), 8.61 (dd, 1H, J=4.9, 1.9 Hz, H-6); ^{13}C NMR δ 28.1 (CH_3), 82.6 ($C-CH_3$), 101.0 (C-3), 115.4 ($C\equiv N$), 118.9 (C-5), 142.3 (C-4), 151.1 ($C=O$), 152.1 (C-6), 152.7 (C-2); IR (KBr) ν_{max} 2232 cm^{-1} ($C\equiv N$). Anal. calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.23; H, 5.94: N, 19.10.

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