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EXPEDIENT *N*-ARYLATION FOR THE SYNTHESIS OF 2-ARYLAMINO-3-CYANOPYRIDINES USING IONIC COPPER(I) COMPLEX AS A CATALYST

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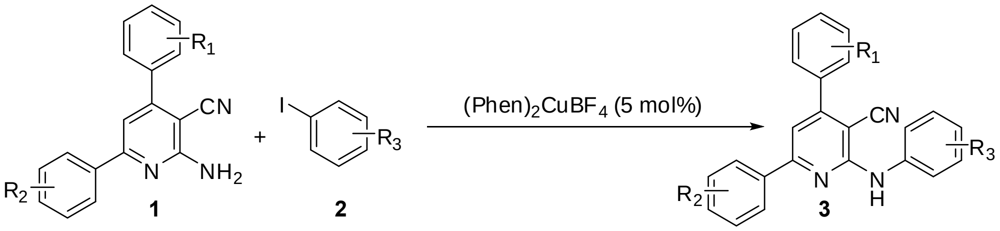
Abstract — The *N*-arylation of 2-amino-3-cyanopyridines is firstly described by using ionic copper(I) complex $(Phen)_2Cu^+BF_4^-$ (phen = 1,10-phenanthroline) as an efficient catalyst. The synthetic protocol can be applied to synthesize a wide range of 2-arylamino-3-cyanopyridine products in good to excellent isolated yields. The resulted products are potentially building blocks for further preparation of biologically interesting products or useful ligands for metal catalysis.

INTRODUCTION

2-Arylamino-3-cyanopyridines constitute significant important structural units found in numerous bioactive products,[1] pigments[2] and functional materials.[3] Additionally, such a class of compounds can serve as synthetically interesting building blocks for preparation of bioactive heterocycles[4] or nitrogen-containing ligands for metal catalysis.[5] Generally, 2-arylamino-3-cyanopyridines can be prepared by multicomponent reactions.[6] In spite of these elegant contributions, to the best of our knowledge, copper-catalyzed *N*-arylation (or so-called Ullmann-type coupling) of 2-amino-3-cyanopyridines with aryl halides has not been performed yet, such a strategy can provide an alternative pathway for the synthesis of 2-arylamino-3-cyanopyridines. However, the challenging points for such a transformation are associated with the steric hindrance of *ortho*-cyano group on pyridine skeleton, or the nitrogen atoms in substrates may competitively occupy the coordination sites of copper catalysts that could decrease the catalyst activity.[7]

Owing to the economic attractiveness and excellent functional tolerance of copper catalysis, copper is considered as a desired alternative for toxic or expensive transition-metal catalysts (i.e. palladium, rhodium) in some aspects.[8] Notably, the application of copper-catalyzed Ullmann-type coupling reactions has regained considerable attention during the past decade since the breakthrough was achieved by the group of Buchwald and others.[9] Generally, the related catalytic systems were formed by in situ generation of active copper species in the presence of suitable copper precursors and ligands. However, the development of efficient and well-defined copper complexes as the catalysts for C-N coupling reactions still remains an interesting and demanding goal.

Drawing from the significant importance of 2-arylamino-3-cyanopyridines and our continuous interest in developing efficient methodologies for the synthesis of pyridine-based products[10] and finding their applications in organometallic chemistry,[11] we became interested in establishing a copper-catalyzed *N*-arylation of 2-amino-3-cyanopyridines. Herein, we present our new protocol for realizing such a goal by using ionic copper(I) complex $(Phen)_2Cu^+BF_4^-$ as an efficient catalyst without introduction of additional ligands (Scheme 1).

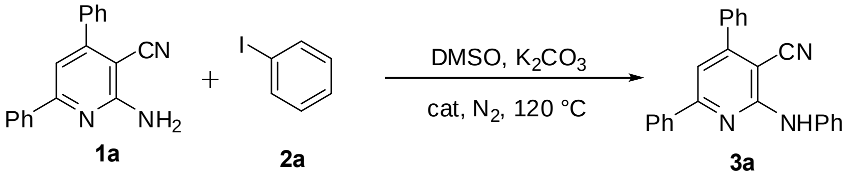


Scheme 1. *N*-Arylation of 2-amino-3-cyano-pyridines using ionic copper(I) complex as a catalyst

RESULTS AND DISCUSSION

In order to determine an efficient catalytic system, our investigation was initiated by using a CuI/L-proline system which was developed by Ma and co-workers,[12] and the synthesis of 2-*N*-arylated product **3a** from 2-amino-4,6-diphenylnicotinonitrile **1a** and iodobenzene **2a** was chosen as a model reaction and conducted at 120 °C for 24 hours to evaluate the influence of different solvents on the reaction efficiency. Among the solvents tested (Table 1, entries 1-4), DMSO showed the best reactivity and resulted in **3a** in 48% yield. Under the same reaction conditions, CuI in combination with 1,10-phenanthroline improved the product yield to 66% (Table 1, entry 5). However, the absence of 1,10-phenanthroline resulted in a low yield (Table 1, entry 6), which indicates that the nitrogen-ligand is essential to promote such an arylation reaction. Subsequently, a variety of copper(I) and copper(II) catalyst precursors in combination with 1,10-phenanthroline were explored for the model reaction (Table 1, entries 7-10). The obtained results showed that $(MeCN)_4CuBF_4$ exhibited excellent activity in the formation of product **3a** while 10 mol% of catalyst was used (Table 1, entry 10).

Table 1. Screening catalytic system for the synthesis of 3a[a]



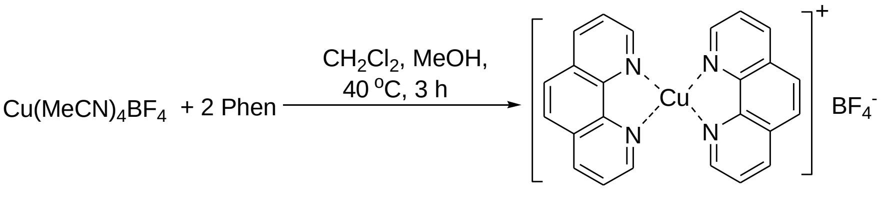
Entry	Catalyst/Ligand	Base	Solvent	Yield% of **3a**[b]
1	CuI/L-proline	K_2CO_3	toluene	<10
2	CuI/L-proline	K_2CO_3	dioxane	12
3	CuI/L-proline	K_2CO_3	DMF	36
4	CuI/L-Proline	K_2CO_3	DMSO	48
5	CuI/Phen	K_2CO_3	DMSO	66
6	CuI/-	K_2CO_3	DMSO	38
7	$Cu(OAc)_2$/Phen	K_2CO_3	DMSO	42
8	$Cu(OTf)_2$/Phen	K_2CO_3	DMSO	40
9	CuCl/Phen	K_2CO_3	DMSO	69
10	$Cu(MeCN)_4BF_4$/ Phen	K_2CO_3	DMSO	(78, 72, 50)[c]
11	complex **A**	K_2CO_3	DMSO	(80, 80, 58)[c]
12	complex **A**[d]	NaOH	DMSO	52
13	complex **A**[d]	NEt_3	DMSO	21
14	complex **A**[d]	Cs_2CO_3	DMSO	78

[a] Reaction conditions: unless otherwise stated, the mixture of **1a** (0.5 mmol, 135 mg), **2a** (0.5 mmol, 102 mg), base (1 mmol), solvent (1 mL), catalyst (10 mol%) and ligand (20 mol%) were stirred under N_2 atmosphere in a schlenk tube at 120 °C for 24 h.

[b] Isolated yields.

[c] Yields are with respect to 10 mol%, 5 mol% and 1 mol% of catalyst used, respectively.

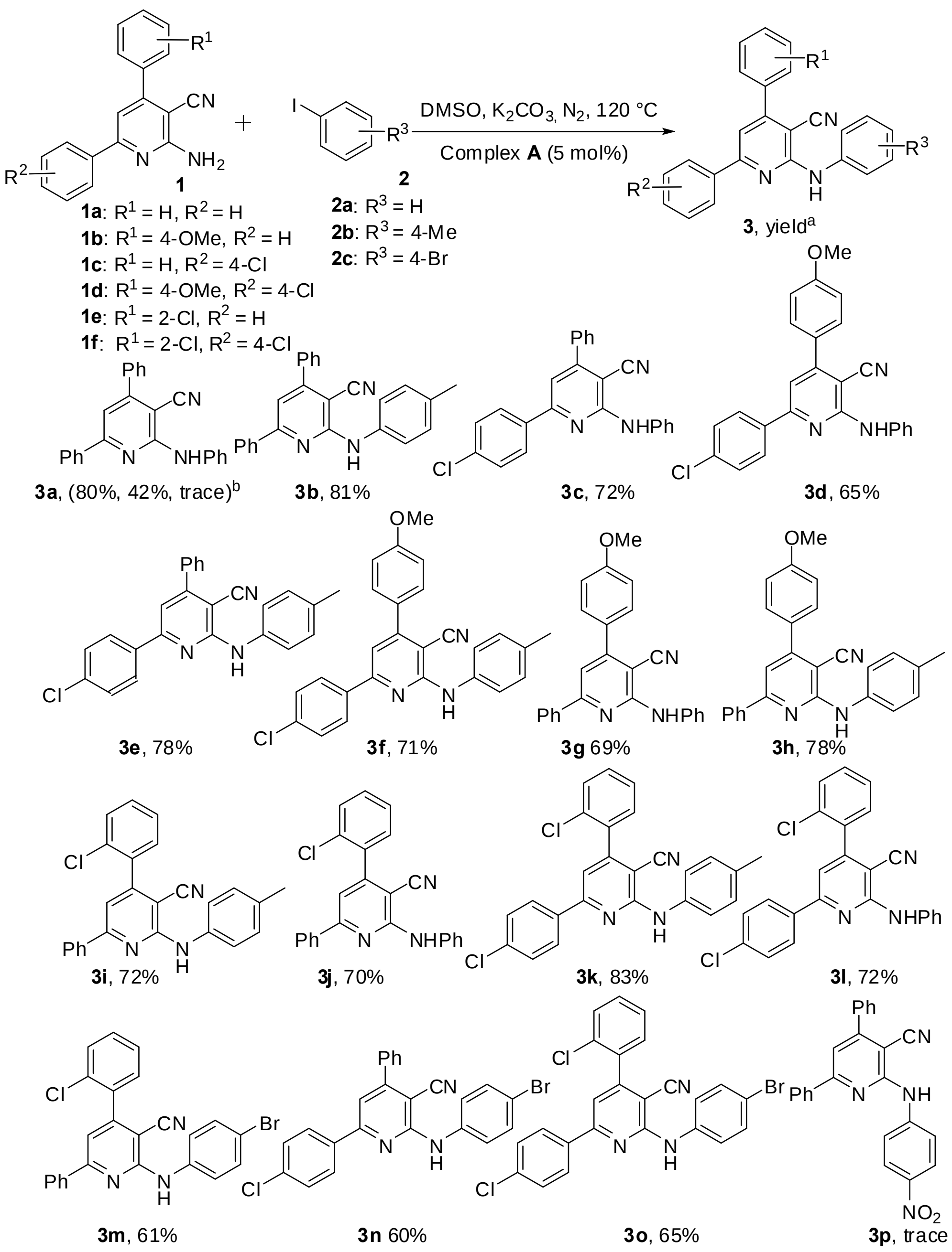
[d] Catalyst loading: 5 mol%.



Complex **A**: $(Phen)_2Cu^+BF_4^-$, 80%

Scheme 2. Synthesis of ionic copper(I) complex **A**

With the above-mentioned effective catalytic system in hand, we then tried to obtain a copper catalyst that can catalyze the *N*-arylation of 2-amino-3-cyanopyridines in an efficient manner. Ionic copper(I) complex featuring two bidentate ligand (phen = 1,10-phenanthroline) was prepared according to reported protocols (Scheme 2).[13] And further investigations showed that only 5 mol% of this complex were sufficient to result in a desired product yield without introduction of additional ligands (Table 1, entries 11). The results clearly indicates that $(Phen)_2Cu^+BF_4^-$ has better catalytic activity than that of $(MeCN)_4Cu^+BF_4^-$ in combination with 1,10-phenanthroline. The presence of $(Phen)_2Cu^+BF_4^-$ also other inorganic and organic bases can be used, although the product yields were relatively lower (Table 1, entries 12-14). Thus, the use of 5 mol% of $(Phen)_2Cu^+BF_4^-$ (complex **A**), 2 equivalent of K_2CO_3 in DMSO and at 120 °C was chosen as the optimal conditions for our *N*-arylation.



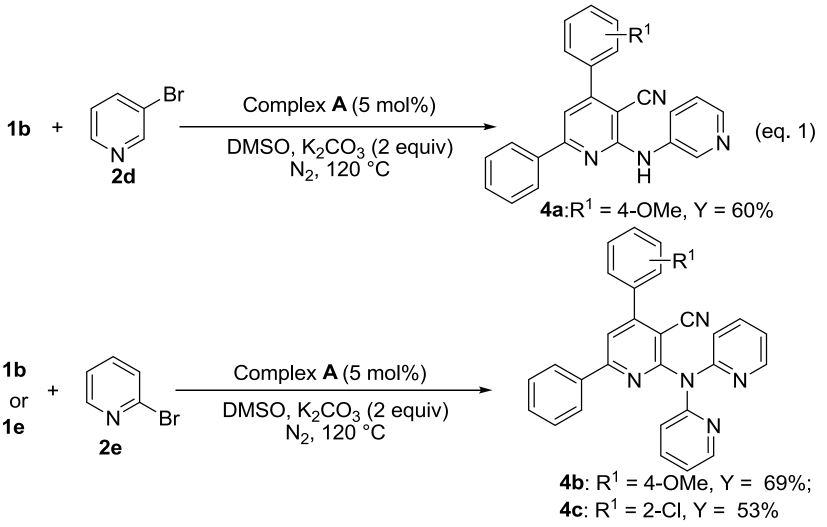
Scheme 3.[c] *N*-Arylation of 2-amino-3-cyanopyridines with aryl halides

[a] Isolated yields are with respect to substrate **1** used.

[b] Yields are with respect to iodobenzene, bromobenzene and chlorobenzene used, respectively.

[c] Reaction conditions: the mixture of **1** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (1 mmol), DMSO (1 mL) and complex **A** (0.025 mmol) were stirred at 120 °C for 24 h under N_2 atmosphere in schlenk tube.

Subsequently, we examined the scope of this ionic copper(I) complex-catalyzed protocol by using a variety combination of 2-amino-3-cyanopyridines **1** with aryl halides **2**. As shown in Scheme 3, aryl iodides were proven to be effective coupling partners, while aryl bromide and aryl chloride have low reactivity in the formation of expected products (Scheme 3, see **3a**). So we then focused on the *N*-arylation reactions by using different aryl iodide reagents. All the reactions proceeded smoothly and resulted in desired products in good to excellent yields (Scheme 3, **3a**-**3o**). The electronic properties of different aryl substituents on the pyridine skeleton have little influence on the formation of 2-*N*-arylated products. However, the substituents on the aryl iodides have significant influence on the product yields. Specifically, electron-rich aryl iodides favored the formation of 2-*N*-arylated products and gave relatively higher product yields (Scheme 3, compared **3a**-**3l** with **3m**-**3p**). While aryl iodide bearing a strong electron-withdrawing group (i. e. 1-iodo-4-nitrobenzene) gave only a trace amount of expected product (Scheme 3, see **3p**). The appeared phenomenon is in marked contrast to most Ullmann coupling systems reported. It might be attributed to the reductive elimination step can significantly influence the product formation in the catalytic cycle,[14] and the discoveries will benefit the design of novel and efficient copper catalysts for C-N coupling reactions of electron-rich halogenated substrates.



Scheme 4. *N*-Arylation by using pyridyl haldes as coupling partner

Furthermore, our protocol was tested by applying 3-bromopyridine **2d** and 2-bromopyridine **2e** as the coupling partners. As described in Scheme 4, the reaction of **1b** and **2d** resulted in expected *mono*-arylated product **4a** in 60% yields (Scheme 2, eq. 1). Interestingly, diarylated product **4b** and **4c** were obtained exclusively even using equimolar of 2-bromopyridine **2e** with **1b** or **1c**. The *N*-diarylation can be explained as the mono-arylated product arising from **2e** can serve as a tridentate ligand by replacing 1,10-phenanthroline ligand in complex **A**, and forming an active species that favor a second

N-arylation. Notably, the diarylated products may serve as potentially valuable ligands for metal catalysis,[5] metal-based photosensitiser,[15] and etc.

In conclusion, the ***N***-arylation of 2-amino-3-cyano-pyridines was firstly established by using ionic copper(I) complex $(Phen)_2Cu^+BF_4^-$ as an efficient catalyst. This copper-catalyzed intermolecular Ullmann-type coupling reaction can be applied for the synthesis of a wide range of 2-arylamino-3-cyano-pyridine products in good to excellent isolated yields. Diarylated products can also be obtained while 2-bromopyridine was employed as a coupling reagent. We are convinced this synthetic protocol is of general interest for preparation of 2-arylamino-3-cyano-pyridines and pyridine-based ligands.

EXPERIMENTAL

All the obtained products (except **3a**, **3d** and **3f**, all other products are new ones) were characterized by melting points (mp), ^{1}H-NMR, ^{13}C-NMR, Low-resolution mass spectra (LRMS), and infrared spectra (IR). Melting points were measured on an Electrothemal SGW-X4 microscopy digital melting point apparatus and are uncorrected; IR spectra were recorded on a FTLA2000 spectrometer; ^{1}H-NMR spectra were obtained on Bruker-400. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br); MS was measured on ZMD-4000 spectrometer; TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm; All the reagents were purchased from commercial sources (Alfa, Acros, Aldrich), and used without further purification.

Typical procedure for synthesis of polyfunctional 4,6-diphenyl-2-(phenylamino)nicotinonitrile (3a).

2-Amino-4,6-diphenylnicotinonitrile **1a** (0.5 mmol, 135 mg), iodobenzene **2a** (0.5 mmol, 102 mg), K_2CO_3 (1 mmol, 138 mg) and $(Phen)_2Cu^+BF_4^-$ (0.025 mmol, 13.7 mg) were added in a Schlenk tube, then 1 mL DMSO was added successively under N_2 atmosphere, the resulting mixture was stirred at 120 °C for 24 hours, after cooling to room temperature, the reaction mixture was filtered, then it was purified by preparative TLC on silica, eluting with petroleum ether: EtOAc (10: 1) to provide desired products **3a**.

Synthesis of complex $(Phen)_2Cu^+BF_4^-$

Complex $(Phen)_2Cu^+BF_4^-$ was synthesized following a similar procedure reported in the literature.[13] To a 25 mL Schlenk tube was added $(MeCN)_4CuBF_4$ (0.2 mmol, 62.0 mg), Phen (0.4 mmol, 79.2 mg), then 5 mL methanol and 2 mL CH_2Cl_2 were added successively under N_2 atmosphere, the resulting mixture was stirred at 40 °C for 3 h. After the evaporation of solvent, the product was obtained as black brown powder.

Yield: 80%; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.94-8.18 (m, 8H), 8.67-8.93 (m, 8H); IR (KBr, cm^{-1}): ν_{max} = 1625, 1591, 1522, 1427, 1066, 842, 722.

Analytical Data of all obtained compounds

(1) 4,6-Diphenyl-2-(phenylamino)nicotinonitrile (3a)

Yield: 80%; yellow solid; mp 215-217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (t, *J* = 7.2 Hz, 1H), 7.37 (br, 1H), 7.36 (s, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.50-7.52 (m, 3H), 7.55-7.60 (m, 3H), 7.68-7.70 (m, 2H), 7.79 (d, *J* = 7.6 Hz, 2H), 8.09-8.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.99, 156.61, 155.49, 139.01, 137.95, 137.05, 130.36, 129.95, 129.04, 128.98, 128.89, 128.26, 127.48, 123.61, 120.67, 117.09, 111.54, 90.10; IR (KBr, cm^{-1}): ν_{max} = 3335, 2215, 1602, 1582, 1548, 1497, 1446, 1376, 1260, 1098, 1025, 802, 732, 684; MS (EI, m/z): 347 $[M]^+$.

(2) 4,6-Diphenyl-2-(p-tolylamino)nicotinonitrile (3b)

Yield: 81%; yellow solid; mp 195-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.24 (s, 2H), 7.26 (br, 1H), 7.33 (s, 1H), 7.49-7.58 (m, 6H), 7.64-7.70 (m, 4H), 8.08-8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.97, 156.75, 155.43, 138.01, 137.12, 136.37, 133.27, 130.31, 129.90, 129.47, 129.01, 128.85, 128.25, 127.48, 120.89, 117.18, 111.22, 89.81, 20.91; IR (KBr, cm^{-1}): ν_{max} = 3329, 2928, 2215, 1608, 1577, 1550, 1513, 1524, 1492, 1458, 1408, 1256, 814, 757, 699; MS (EI, m/z): 361 $[M]^+$.

(3) 6-(4-Chlorophenyl)-4-phenyl-2-(phenylamino)nicotinonitrile (3c)

Yield: 72%; yellow solid; mp 207-209 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 7.2 Hz, 1H), 7.32 (s, 1H), 7.42-7.49 (m, 4H), 7.57-7.60 (m, 3H), 7.67-7.69 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 8.02-8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.69, 156.69, 155.74, 138.81, 136.87, 136.58, 136.33, 130.06, 129.13, 129.08, 129.00, 128.72, 128.22, 123.84, 120.84, 116.90, 111.29, 90.38; IR (KBr, cm^{-1}): ν_{max} = 3328, 2214, 1614, 1584, 1541, 1498, 1432, 1375, 1094, 1164, 1129, 835, 766, 698; MS (EI, m/z): 382 $[M]^+$.

(4) 6-(4-Chlorophenyl)-4-(4-methoxyphenyl)-2-(phenylamino)nicotinonitrile (3d)

Yield: 65%; yellow solid; mp 217-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.25 (s, 2H), 7.29 (br, 1H), 7.38 (s, 1H), 7.46-7.49 (m, 2H), 7.65 (t, *J* = 8.4 Hz, 2H), 7.73-7.78 (m, 4H), 8.00-8.04 (m, 2H); IR (KBr, cm^{-1}): ν_{max} = 3332, 2949, 2217, 1608, 1580, 1541, 1513, 1491, 1434, 1370, 1030, 826, 756, 693; MS (EI, m/z): 412 $[M]^+$.

(5) 6-(4-Chlorophenyl)-4-phenyl-2-(p-tolylamino)nicotinonitrile (3e)

Yield: 78%; yellow solid; mp 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.23 (s, 2H), 7.25

(s, 1H), 7.45-7.49 (m, 2H), 7.55-7.62 (m, 5H), 7.66-7.69 (m, 2H), 8.00-8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.69, 156.75, 155.63, 136.96, 136.50, 136.41, 136.18, 133.52, 130.00, 129.50, 129.07, 129.05, 128.71, 128.21, 121.07, 117.00, 110.96, 90.08, 20.92; IR (KBr, cm^{-1}): ν_{max} = 3328, 2945, 2216, 1610, 1580, 1546, 1513, 1490, 1449, 1410, 1397, 1364, 1253, 1091, 1013, 824, 762, 699; MS (EI, m/z): 396 $[M]^+$.

(6) 6-(4-Chlorophenyl)-4-(4-methoxyphenyl)-2-(p-tolylamino)nicotinonitrile (3f)

Yield: 71%; yellow solid; mp 218-220 °C; IR (KBr, cm^{-1}): ν_{max} = 3324, 2921, 2217, 1609, 1580, 1546, 1511, 1491, 1448, 1418, 1368, 1255, 1092, 1029, 820, 790; MS (EI, m/z): 426 $[M]^+$.

(7) 4-(4-Methoxyphenyl)-6-phenyl-2-(phenylamino)nicotinonitrile (3g)

Yield: 71%; yellow solid; mp 189-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.07-7.11 (m, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.34 (s, 1H), 7.40-7.46 (m, 2H), 7.50-7.54 (m, 3H), 7.65-7.68 (m, 2H), 7.78 (dd, *J* = 8.8 Hz, 2H), 8.08-8.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.09, 158.83, 156.69, 155.07, 139.09, 138.07, 130.27, 129.71, 128.96, 128.86, 127.45, 125.68, 123.51, 120.61, 117.44, 114.48, 111.32, 89.79, 55.47; IR (KBr, cm^{-1}): ν_{max} = 3309, 2919, 2215, 1605, 1572, 1536, 1511, 1497, 1459, 1446, 1424, 1374, 1298, 1255, 1234, 1180, 1038, 832, 763, 732, 694; MS (EI, m/z): 377 $[M]^+$.

(8) 4-(4-Methoxyphenyl)-6-phenyl-2-(p-tolylamino)nicotinonitrile (3h)

Yield: 78%; yellow solid; mp 229-231 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.92 (s, 3H), 7.07-7.11 (m, 2H), 7.22 (br, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 1H), 7.48-7.53 (m, 3H), 7.64-7.67 (m, 4H), 8.07-8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.04, 158.82, 156.84, 155.03, 138.12, 136.45, 133.16, 130.20, 129.70, 129.45, 129.35, 128.82, 127.44, 120.84, 117.53, 114.45, 111.01, 89.49, 55.46, 20.90; IR (KBr, cm^{-1}): ν_{max} = 3321, 2923, 2216, 1608, 1574, 1534, 1496, 1458, 1419, 1350, 1263, 1164, 1029, 829, 757, 696; MS (EI, m/z): 391 $[M]^+$.

(9) 4-(2-Chlorophenyl)-6-phenyl-2-(p-tolylamino)nicotinonitrile (3i)

Yield: 72%; yellow solid; mp 187-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.12 (br, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H), 7.43-7.52 (m, 6H), 7.58-7.61 (m, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 8.07-8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.86, 156.20, 153.27, 137.85, 136.24, 136.02, 133.36, 132.38, 130.75, 130.39, 130.31, 129.50, 128.86, 127.52, 127.18, 120.88, 116.25, 112.09, 91.53, 20.92; IR (KBr, cm^{-1}): ν_{max} = 3341, 2949, 2215, 1602, 1578, 1547, 1474, 1456, 1431, 1406, 1374, 1252, 1233, 1053, 963, 813, 755, 697; MS (EI, m/z): 396 $[M]^+$.

(10) 4-(2-Chlorophenyl)-6-phenyl-2-(phenylamino)nicotinonitrile (3j)

Yield: 75%; yellow solid; mp 167-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (t, *J* = 7.2 Hz, 1H), 7.22 (br, 1H), 7.28 (s, 1H), 7.40-7.50 (m, 8H), 7.56-7.58 (m, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 8.05-8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.88, 156.06, 153.33, 138.90, 137.80, 135.96, 132.39, 130.81, 130.46, 130.39, 130.33, 129.00, 128.91, 127.54, 127.21, 123.70, 120.67, 116.16, 112.41, 91.85; IR (KBr, cm^{-1}): ν_{max} = 3347, 2211, 1602, 1579, 1541, 1497, 1445, 1420, 1376, 1253, 1175, 1053, 1029, 961, 856, 761, 694; MS (EI, m/z): 382 $[M]^+$.

(11) 4-(2-Chlorophenyl)-6-(4-chlorophenyl)-2-(p-tolylamino)nicotinonitrile (3k)

Yield: 83%; yellow solid; mp 205-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.18 (br, 1H), 7.23 (s, 1H), 7.22-7.27 (d, *J* = 8.4 Hz, 2H), 7.43-7.48 (m, 5H), 7.58-7.62 (m, 3H), 8.00 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.59, 156.21, 153.47, 136.59, 136.27, 136.05, 135.85, 133.62, 132.34, 130.85, 130.34, 129.52, 129.09, 128.76, 127.23, 121.07, 116.09, 111.83, 91.82, 20.93; IR (KBr, cm^{-1}): ν_{max} = 3349, 2939, 2212, 1604, 1573, 1548, 1486, 1456, 1433, 1407, 1376, 1164, 1034, 961, 849, 757, 698; MS (EI, m/z): 430 $[M]^+$.

(12) 4-(2-Chlorophenyl)-6-(4-chlorophenyl)-2-(phenylamino)nicotinonitrile (3l)

Yield: 72%; yellow solid; mp 200-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.4 Hz, 1H), 7.24 (br, 1H), 7.26 (s, 1H), 7.42-7.50 (m, 7H), 7.59-7.61 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 8.01 (dd, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.61, 156.05, 153.52, 138.70, 136.67, 136.21, 135.77, 132.34, 130.90, 130.35, 129.14, 129.02, 128.77, 127.25, 123.90, 120.81, 115.99, 112.16, 92.12; IR (KBr, cm^{-1}): ν_{max} = 3341, 2221, 1611, 1576, 1542, 1507, 1497, 1474, 1457, 1435, 1385, 1363, 1252, 1092, 1012, 961, 828, 757, 745, 691; MS (EI, m/z): 416 $[M]^+$.

(13) 2-(4-Bromophenylamino)-4-(2-chlorophenyl)-6-phenylnicotinonitrile (3m)

Yield: 61%; yellow solid; mp 201-203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (br, 1H), 7.33 (s, 1H), 7.42-7.49 (m, 3H), 7.50-7.57 (m, 5H), 7.59-7.61 (m, 1H), 7.68 (dd, *J* = 6.8 Hz, 2H), 8.05-8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.90, 155.72, 153.43, 137.99, 137.62, 135.79, 132.35, 131.92, 130.89, 130.60, 130.36, 128.98, 127.49, 127.24, 122.23, 116.12, 116.00, 112.80, 92.09; IR (KBr, cm^{-1}): ν_{max} = 3342, 2211, 1600, 1574, 1548, 1524, 1489, 1456, 1428, 1397, 1366, 1253, 1073, 1050, 1015, 961, 855, 811, 759, 703; MS (EI, m/z): 461 $[M]^+$.

(14) 2-(4-Bromophenylamino)-6-(4-chlorophenyl)-4-phenylnicotinonitrile (3n)

Yield: 60%; yellow solid; mp 237-240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06-7.10 (m, 3H), 7.42 (dd, *J* = 8.8 Hz, 2H), 7.50 (s, 1H), 7.51-7.59 (m, 6H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.75, 155.77, 153.00, 137.88, 136.91, 132.65, 131.94, 130.16, 129.23, 129.01, 128.51, 127.28, 127.09, 122.38, 118.43, 114.9, 111.67, 92.71; IR (KBr, cm^{-1}): ν_{max} = 3341, 2212, 1602, 1573, 1543, 1522, 1487, 1455, 1428, 1396, 1356, 1254, 1078, 1052, 1016, 961, 855, 813, 761, 702; MS (EI, m/z): 461 $[M]^+$.

(15) 2-(4-Bromophenylamino)-4-(2-chlorophenyl)-6-(4-chlorophenyl)nicotinonitrile (3o)

Yield: 65%; yellow solid; mp 197-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (dd, *J* = 6.8 Hz, 1H), 7.21 (br, 1H), 7.40-7.44 (m, 2H), 7.45-7.50 (m, 4H), 7.55 (dd, *J* = 6.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.64, 155.72, 153.61, 137.79, 136.84, 136.04, 135.61, 132.65, 131.97, 130.98, 130.39, 129.22, 128.72, 127.28, 127.18, 122.36, 116.37, 115.82, 111.57, 92.38; IR (KBr, cm^{-1}): ν_{max} = 3343, 2922, 2209, 1596, 1577, 1546, 1488, 1401, 1367, 1256, 1093, 1071, 1012, 830, 809, 759, 735; MS (EI, m/z): 495 $[M]^+$.

(16) 4-(4-Methoxyphenyl)-6-phenyl-2-(pyridin-3-ylamino)nicotinonitrile (4a)

Yield: 60%; yellow solid; mp 211-213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.25 (br, 1H), 7.37 (m, 1H), 7.40 (s, 1H), 7.51-7.54 (m, 3H), 7.67 (d, *J* = 8.8 Hz, 2H), 8.06-8.08 (m, 2H), 8.20-8.22 (m, 1H), 8.41 (d, *J* = 4.4 Hz, 1H), 9.03 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.22, 158.96, 156.35, 155.26, 142.40, 137.77, 135.92, 132.44, 130.50, 130.11, 129.74, 128.98, 127.43, 124.16, 123.48, 115.66, 114.54, 112.11, 90.22, 55.48; IR (KBr, cm^{-1}): ν_{max} = 3297, 2923, 2215, 1605, 1570, 1536, 1513, 1483, 1457, 1422, 1403, 1372, 1264, 1235, 1185, 1026, 832, 765, 695; MS (EI, m/z): 378 $[M]^+$.

(17) 2-(Dipyridin-2-ylamino)-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (4b)

Yield: 69%; yellow solid; mp 171-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.08-7.11 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.37-7.39 (m, 3H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.64 (s, 1H), 7.68-7.70 (m, 2H), 7.83-7.85 (m, 2H), 7.19 (dd, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.90, 157.18, 155.72, 153.43, 148.67, 137.99, 135.79, 131.92, 130.89, 130.60, 130.36, 128.98, 127.49, 127.24, 122.23, 116.12, 116.00, 112.80, 92.09, 55.43; IR (KBr, cm^{-1}): ν_{max} = 2929, 2853, 2221, 1608, 1586, 1532, 1513, 1468, 1429, 1375, 1278, 1255, 1180, 1029, 835, 770, 741, 693; MS (EI, m/z): 455 $[M]^+$.

(18) 4-(2-Chlorophenyl)-2-(dipyridin-2-ylamino)-6-phenylnicotinonitrile (4c)

Yield: 53%; yellow solid; mp 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.39-7.47 (m, 6H), 7.54-7.57 (m, 1H), 7.63 (s, 1H), 7.71-7.75 (m, 2H), 7.71 (dd, *J* = 8.0 Hz, 2H), 8.45 (dd, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.19, 157.92, 155.98, 153.04, 147.69, 136.92, 136.10, 134.58, 131.59, 129.78, 129.66, 129.31, 129.20, 127.71, 126.37, 126.12, 119.10, 117.83, 116.32, 113.84, 102.69; IR (KBr, cm^{-1}): ν_{max} = 3056, 2963, 2854, 2225, 1577, 1538, 1469, 1430, 1376, 1312, 1240, 1150, 1056, 995, 891, 769, 738, 696; MS (EI, m/z): 460 $[M]^+$.

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