Facile Synthesis of 2,6-Diaryl-4-Secondary Aminonicotinonitriles and Highly Substituted Unsymmetrical 2,2′-Bipyridines

Sidhanath V. Bhosale,* Umesh D. Patil, Mohan B. Kalyankar, Santosh V. Nalage, Vijay S. Patil, and Kamlesh R. Desale

Department of Organic Chemistry, North Maharashtra University, Jalgaon 425001, India
*E-mail: sidhanath2003@yahoo.co.in

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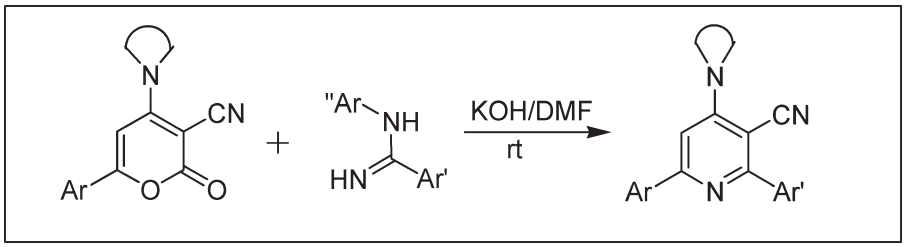

The ring transformation of *2H*-pyran-2-one by *N*-aryl amidine in the presence of KOH in DMF at room temperature resulted in a facile synthesis of the 2,6-diaryl-4-secondary aminonicotinonitrile and highly substituted unsymmetrical 2,2′-bipyridines in moderate yield.

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INTRODUCTION

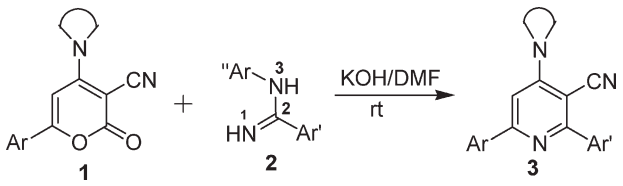
2*H*-pyran-2-ones are extensively used for the synthesis of a wide variety of heterocyclic compounds via ring transformation [1]. Ram and coworkers applied this strategy for the synthesis of various organic compounds like pyrimidine, fused heterocycles, congested benzene [1j], and pyridine [2]. The pyridine ring is one of the fundamental heterocycle present in many biologically active natural products. The compounds containing pyridine ring possess a broad range of biological activities [3]. Kawamura et al. have synthesized 4-substituted 2,6-diphenyl pyridines and reported there bleaching herbicidal activity [3b]. It was also found that 2-(*p*-aminobenzamido) pyridines exhibit a powerful inhibiting effect on gastric ulcers in rats [3g]. The pyridines 2,2′-bi- and 2,2′,2″-ter-pyridine were used as metal chelating legends with various substituents [4a]. Similarly, pyridine derivatives are of growing relevance in material science and supramolecular chemistry [4b]. Therefore, there is a continuous interest to develop the new synthetic methods for pyridines and their derivatives. Classical routes to pyridine preparation are Hantzsch [5], Chichibabin [6], Petrenko-Kritschenko and Zoneff [7], Krohnke [8], and Guareschi-Thorpe [9] condensation reactions. The condensation of 1,5-diketone with ammonia followed by nitric acid oxidation is a common approach for the synthesis of pyridines [10]. The reaction of dienamine and ketone in the presence of Vilsmeier type 1-substituted-1,2,3-benzotriazole reagent results in the formation of nicotinonitriles [11]. The construction of unsymmetrically substituted pyridines was achieved by the reaction of 1,3-dicarbonyl compounds and 3-aminoenones or nitriles [12]. Saikai et al. reported indium trichloride catalyzed synthesis of tetrasubstituted pyridines [13]. Penieres et al. have synthesized pyridine by using microwave irradiated Hantzsch reaction [14]. A transition metal mediated 6-endo-dig cyclization of *N*-propargylamine derivative was carried out by Abbiati et al. to generate a pyridine ring [15]. Combinatorial approach also has been used for the synthesis of pyridine derivatives [16]. 2,4,6-trisubstituted pyridine derivatives were prepared from aroylketene dithioacetal by Potts et al. [17]. Recently, Ram and coworkers [18] have described the use of 2*H*-pyran-2-one for the synthesis of substituted pyridines, prompted us to carry out the synthesis of novel pyridines.

RESULT AND DISCUSSION

We investigated that compound **3** in moderate yield can be constructed from 2H-pyran-2-one **1** and the *N*-aryl amidine **2** via a ring transformation reaction using KOH in DMF at room temperature (Scheme 1).

Pyridine **3** isolated in this study could arise by nucleophilic attack of amidine N-1 at C-6 position of 2*H*-pyran-2-one. The intermediate **4** formed is unstable and it undergoes cyclization with a retro [2 + 2] process to yield **3a–i** with the loss of carbon dioxide. In the event of ring transformation of 2*H*-pyran-2-one **1** (Scheme 2) with *N*-aryl amidine **2**, the N-1 takes part in the reaction as a nucleophile rather than N-3. It might be due to the lone pair electrons on N-3 are delocalized over the

Scheme 1. Preparation of 2,6-diaryl-4-secondary aminonicotinonitriles **3** from 2*H*-pyran-2-one **1** and *N*-aryl amidine **2**.



benzene nucleus by orbital overlap with the π-orbital of the aromatic ring; therefore, they are less available for nucleophilic attack.

To generalize our strategy, we examined this method for the reaction of 2*H*-pyran-2-one **1** with *N*-heteroaryl amidine **6** in the presence of KOH/DMF catalytic system (Scheme 3). The reaction of 2*H*-pyran-2-one with *N*-heteroaryl amidine furnished the corresponding 2,6-disubstituted nicotinonitrile **3** in the poor yields (Table 1). The structure of the newly synthesized compounds was confirmed by spectroscopic data. It was observed that there is no improvement of yield even after 48 h also. The plausible mechanistic pathway is shown in Scheme 4.

In 2H-pyran-2-one **1**, three electrophilic centers are present C-3, C-4, and C-6, in which C-6 is more electrophilic in nature due to presence of an electron withdrawing group (—CN) at C-3 position of the ring system. The synthesis of 2,6-diaryl nicotonitrile involves the nucleophilic attack by more basic N-1 of amidine **6** at C-6 of *2H*-pyran-2-one. The attack of amidine N-1 leads to form unstable intermediate **7** followed by ring closure and a retro [2 + 2] process with the elimination of carbon dioxide to form 2,6-diaryl nicotonitrile **3**. It is noteworthy that the pyridine ring nitrogen of amidine does not involve in ring transformation reaction. The structures of compounds **3a–i** (Table 2) were determined based on the spectroscopic data and elemental analysis. Thus, in both cases (Schemes 1 and 3), the 2,6-diaryl nicotonitriles were formed exclusively without any side product.

Finally, we used our strategy to synthesize highly substituted unsymmetrical 2,2-bipyridines (Scheme 5) in presence of powdered KOH and DMF at room temperature. The results show that the yield of obtained bipyridine was moderate (Table 2). We believe that the reaction proceeds with the same mechanistic pathway as depicted in Scheme 2.

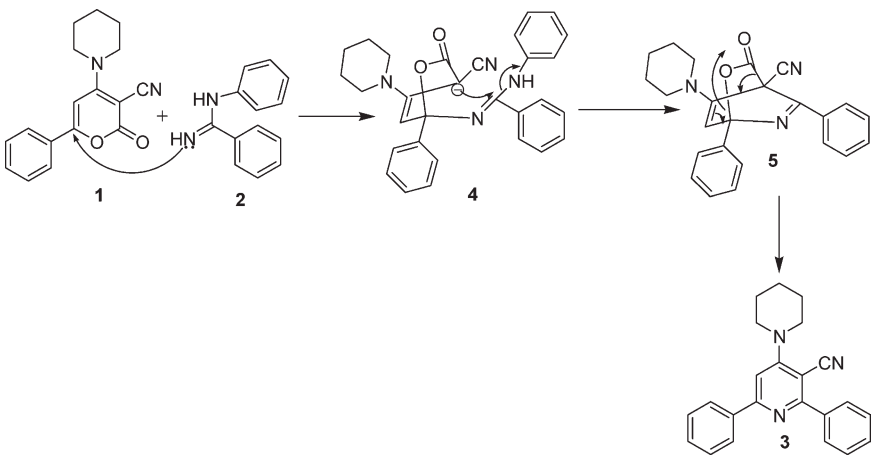
CONCLUSIONS

In summary, this study demonstrates that the ring system proposed for nicotonitrile is correct with the substitution pattern. An additional finding is that the ring transformation of 2*H*-pyran-2-one by *N*-pyridyl amidine provides useful information for construction of the nicotonitrile ring system with 2,6-diaryl substituent. Furthermore, we synthesized highly substituted unsymmetrical bipyridine using this method. Further studies on the applications of this method for the synthesis of nicotonitrile with the 2,6-heteryl substituent are underway.

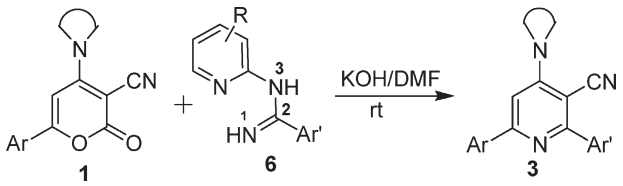
EXPERIMENTAL

General procedures. Melting points were determined in open capillaries and are uncorrected. Progress of the reaction was monitored by TLC (visualization was effected by exposure to UV light). Commercial reagents were used without purification. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. Mass spectra were recorded under ESI mode, on Thermo Finnigan (model-LCQ Advantage MAX) mass spectrometer. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker Spectrometers, operating at 300 MHz and 75 MHz for ^{1}H NMR and ^{13}C NMR, respectively, and shifts are given in ppm downfield from TMS as an internal standard.

Scheme 2. The plausible mechanism [18] for the formation of substituted compounds **3**.



Scheme 3. Reaction between 2*H*-pyran-2-one **1** and *N*-heteroaryl amidine **6** for synthesis of 2,6-disubstituted nicotinonitrile.



Elemental analysis was carried out on Thermo Quest microanalysis instrument, Whitehouse, NJ.

General experimental procedure for the synthesis of 3a–l. The mixture of 2H-pyran-2-one-3-carbonitrile (1.0 mmol), *N*-phenyl/heteroaryl benzamidine (1.0 mmol) and powdered KOH (2.0 mmol) in 5 mL DMF was stirred for 5–6 h at room temperature. The reaction was monitored by TLC. After completion of the reaction, excess DMF was removed under reduced pressure. Then the residue was poured into crushed ice with vigorous stirring. The aqueous solution was neutralized with 10% HCl, the precipitate obtained was filtered, and the obtained residue was purified by column chromatography on silica gel 60–120 by eluting 5% ethyl acetate:hexane.

2,6-Diphenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3a). White solid, IR (KBr): 2209 (C≡N), 1568 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.73 (d, *J* = 5.7 Hz, 2H, CH_2), 1.83 (d, *J* = 3.3 Hz, 4H, $2CH_2$), 3.54 (t, *J* = 9.9 Hz, 4H, $2CH_2N$), 6.91 (s, 1H, CH), 7.5 (m, 5H, ArH), 7.84 (d, *J* = 4.7 Hz, 2H, ArH), 8.05 (t, *J* = 9.5 Hz, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.2, 26.1, 52.1, 96.4, 106.7, 118.7, 124.4, 125.3, 127.6, 128.5, 128.9, 129.6, 130.1, 138.9, 159.8, 162.9, 164.2. MS (ESI, 70 eV) *m/z* (%) = 340 (100) $[M^+]$, 341(27) $[(M+H)^+]$. Anal. Calcd. for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.42; H, 6.20; N, 12.38.

6-(4-Bromophenyl)-2-phenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3b). White solid, IR (KBr): 2212 (C≡N), 1568 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.72 (d, 2H, CH_2), 1.8 (d, *J* = 5 Hz, 4H, $2CH_2$), 3.54 (t, *J* = 10.6 Hz, 4H, $2CH_2N$), 7.12 (s, 1H, CH), 7.51 (m, 3H, ArH), 7.59 (s,

Scheme 4. The plausible mechanism [18] for the formation of substituted 2,6-disubstituted nicotinonitrile.

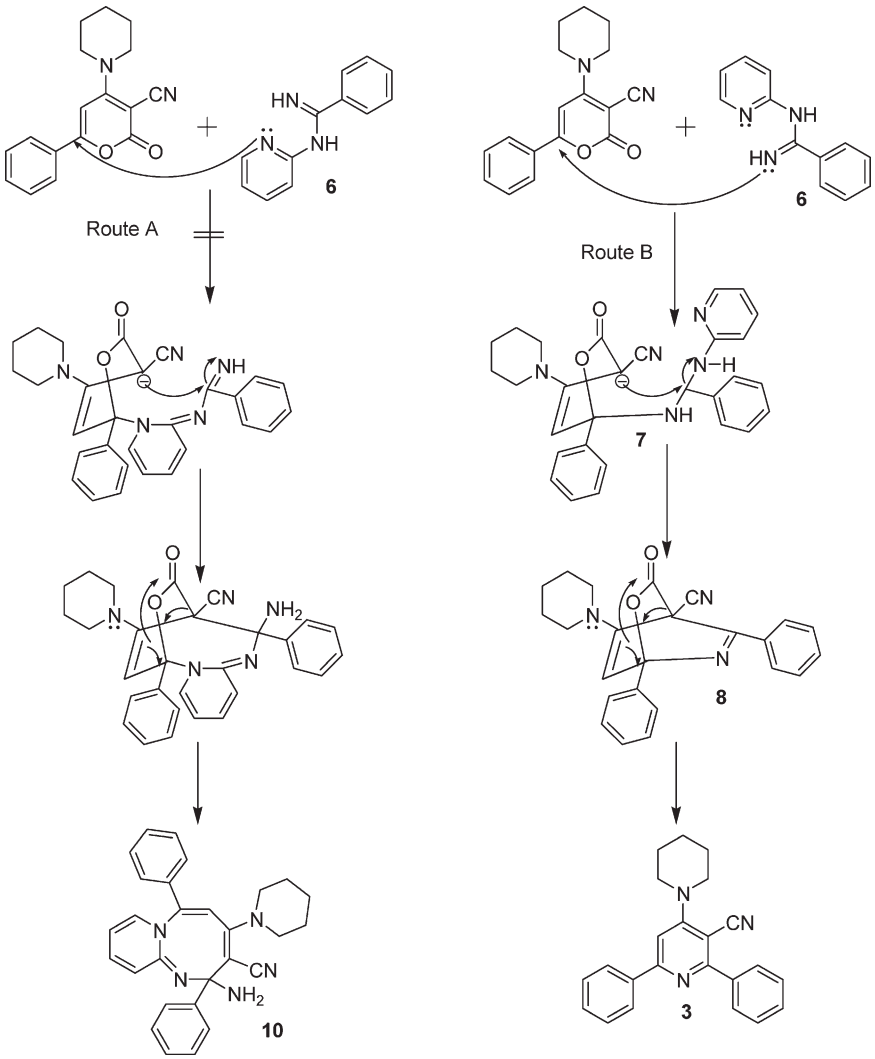


Table 1

Preparation of 2,6-diaryl-4-secondary aminonicotinonitriles **3**[a] from 2*H*-pyran-2-one **1** and *N*-aryl amidine **2**[b].

Entry	Ar		Ar′	Ar″	Yields[c] (%)	m.p.
3a	C_6H_5	Piperidine	C_6H_5	4-F-C_6H_4	48%	160°C
3a	C_6H_5	Piperidine	C_6H_5	C_6H_5	48%	161°C
3b	4-Br-C_6H_4	Piperidine	C_6H_5	C_6H_5	48%	173°C
3b	4-Br-C_6H_4	Piperidine	C_6H_5	4-F-C_6H_4	42%	173°C
3c	4-Br-C_6H_4	Morpholine	C_6H_5	4-F-C_6H_4	46%	172°C
3c	4-Br-C_6H_4	Morpholine	C_6H_5	C_6H_5	44%	172°C
3d	4-Cl-C_6H_4	Morpholine	C_6H_5	4-F-C_6H_4	39%	198°C

[a] All products were characterized by using I.R., ^{1}H, ^{13}C NMR, mass spectroscopy, and elemental analysis.
[b] 2H-pyran-2-one **1** (1.0 mmol), *N*-aryl amidine **2** (1.0 mmol), KOH (2.0 mmol), and DMF (5 mL), room temperature.
[c] Isolated yield.

1H, ArH), 7.62 (s, 1H, ArH), 7.93 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.2, 26.1, 52.0, 96.8, 106.4, 118.6, 124.7, 128.6, 129.2, 129.6, 130.1, 132.1, 137.7, 138.7, 158.5, 162.9, 163.9. MS (ESI, 70 eV) *m/z* (%) = 418 (100) [M^+], 420 (92) [$(M+2H)^+$]. Anal. Calcd. for $C_{23}H_{20}BrN_3$: C, 66.04; H, 4.82; N, 10.04. Found: C, 66.01; H, 4.77; N, 10.08.

6-(4-Bromophenyl)-4-(morpholin-4-yl)-2-phenylpyridine-3-carbonitrile (3c). White solid, IR (KBr): 2210 (C≡N), 1582 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.55 (q, *J* = 13.5 Hz, 4H, $2CH_2N$), 3.94 (q, *J* = 14 Hz, 4H, $2CH_2O$), 6.73 (s, 1H, CH), 7.51 (q, *J* = 9.9 Hz, 3H, ArH), 7.59 (s, 1H, ArH), 7.63 (s, 1H, ArH), 7.92 (m, 3H, ArH), 7.97 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 50.9, 66.8, 97.3, 106.3, 118.2, 125.1, 128.6, 129.2, 129.5, 130.3, 132.2, 137.3, 138.3, 159.1, 162.6, 164.2. MS (ESI, 70 eV) *m/z* (%) = 420 (28%) [M^+], 422 (12%) [$(M+2H)^+$], 393 (8). Anal. Calcd. for $C_{22}H_{18}BrN_3O$: C, 62.87; H, 4.32; N, 10.00. Found: C, 62.82; H, 4.37; N, 10.11.

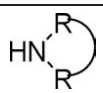
6-(4-Chlorophenyl)-4-(morpholin-4-yl)-2-phenylpyridine-3-carbonitrile (3d). White solid, IR (KBr): 2216 (C≡N), 1583 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.54 (q, *J* = 14.1 Hz, 4H, $2CH_2N$), 3.94 (q, *J* = 13.9 Hz, 4H, $2CH_2O$), 7.14 (s, 1H, CH), 7.51 (m, 5H, ArH), 7.89 (m, 2H, ArH), 8.00 (s, 1H, ArH), 8.04 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 50.9, 66.8, 97.2, 106.3, 118.2, 128.6, 128.9, 129.3, 129.5, 130.3, 136.7, 136.9, 138.3, 159.0, 162.7, 164.2. MS (ESI, 70 eV) *m/z* (%): 376 (100) [M^+], 378 (33) [$(M+2H)^+$]. Anal. Calcd. for $C_{22}H_{18}ClN_3O$: C, 70.30; H, 4.83; N, 11.18. Found: C, 70.34; H, 4.94; N, 11.23.

2,6-Bis(4-bromophenyl)-4-(piperidin-1-yl)pyridine-3-carbonitrile (3e). White solid, IR (KBr): 2214 (C≡N), 1580 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.79 (m, 6H, $3CH_2$), 3.53 (t, *J* = 15 Hz, 4H, $2CH_2N$), 7.12 (s, 1H, CH), 7.62 (m, 4H, ArH), 7.77 (d, *J* = 4.7 Hz, 1H, ArH), 7.81 (d, *J* = 3 Hz, 1H, ArH), 7.89 (d, *J* = 3 Hz, 1H, ArH), 7.93 (s, 1H, ArH). MS (ESI, 70 eV) *m/z* (%) = 497.8 (25) [M^+], 499 (12) [$(M+2H)^+$]. Anal. Calcd. for $C_{23}H_{19}Br_2N_3$: C, 55.56; H, 3.85; N, 8.45. Found: C, 55.59; H, 3.81; N, 8.48.

6-(4-Chlorophenyl)-2-phenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3f). White solid, IR (KBr): 2214 (C≡N), 1568 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.73 (d, *J* = 532 Hz, 2H, CH_2), 1.82 (d, *J* = 5.0 Hz, 4H, $2CH_2$), 3.55

Table 2

Reaction conditions with yields and m.p. for products[a] **3**.

Entry	Ar		Ar′	R	Yields[b] (%)	m.p.
3a	C_6H_5	Piperidine	C_6H_5	H	13%	160°C
3b	4-Br-C_6H_4	Piperidine	C_6H_5	H	26%	173°C
3c	4-Br-C_6H_4	Morpholine	C_6H_5	H	24%	172°C
3d	4-Cl-C_6H_4	Morpholine	C_6H_5	H	24%	198°C
3e	4-Br-C_6H_4	Piperidine	4-Br-C_6H_4	H	22%	168°C
3f	4-Cl-C_6H_4	Piperidine	C_6H_5	H	16%	172°C
3g	4-Cl-C_6H_4	Pyrolidine	C_6H_5	H	19%	156°C
3g	4-Cl-C_6H_4	Pyrolidine	C_6H_5	4-Br	22%	156°C
3h	4-CH_3O-C_6H_4	Piperidine	C_6H_5	H	38%	166°C
3i	4-Cl-C_6H_4	Pyrolidine	4-Br-C_6H_4	H	44%	122°C

[a] All products were characterized by using I.R., ^{1}H, ^{13}C NMR, mass spectroscopy, and elemental analysis.
[b] Isolated yield.

Table 3

Reaction conditions with yields and m.p. for products[a] **3**.

Entry	Ar	HNRR	Ar″	Yields[b] (%)	m.p.
3j	4-Br-C_6H_4	Pyrolidine	4-Br-C_6H_4	43%	206–208°C
3k	4-Cl-C_6H_4	Morpholine	4-Br-C_6H_4	48%	164–166°C
3l	C_6H_5	Morpholine	3,4-Cl-C_6H_3	52%	152–154°C

[a] All products were characterized by using I.R., ^{1}H, ^{13}C NMR, mass spectroscopy, and elemental analysis.
[b] Isolated yield.

(t, J = 10.6 Hz, 4H, $2CH_2N$), 7.13 (s, 1H, CH), 7.44 (m, 5H, ArH), 7.93 (q, J = 9.68 Hz, 2H, ArH), 8.00 (s, 1H, ArH), 8.03 (s, 1H, ArH). MS (ESI, 70 eV) m/z (%) = 374 (100) [M^+], 376 (35) [$(M+H)^+$]. Anal. Calcd. for $C_{23}H_{20}ClN_3$: C, 73.89; H, 5.39; N, 11.24. Found: C, 73.97; H, 5.35; N, 11.36.

6-(4-Chlorophenyl)-2-phenyl-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (3g). White solid, IR (KBr): 2199 (C≡N), 1590 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ 2.09 (m, 4H, $2CH_2$), 3.81 (t, J = 13.2 Hz, 4H, $2CH_2N$), 6.85 (s, 1H, CH), 7.48 (m, 5H, ArH), 7.86 (q, J = 9.6 Hz, 2H, ArH), 7.98 (d, J = 8.66 Hz, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.9, 50.5, 96.1, 106.5, 118.6, 128.4, 128.6, 129.0, 129.6, 129.8, 135.9, 137.5, 139.3, 158.6, 162.8, 163.1. MS (ESI, 70 eV) m/z (%) = 360 (100) [M^+], 362 (32) [$(M+2H)^+$]. Anal. Calcd. for $C_{22}H_{18}ClN_3$: C, 73.43; H, 5.04; N, 11.68. Found: C, 73.42; H, 5.04; N, 11.03.

6-(4-Methoxyphenyl)-2-phenyl-4-(piperidin-1-yl)pyridine-3-carbonitrile (3h). White solid, IR (KBr): 2209 (C≡N), 1607 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 1.72 (d, J = 5.1 Hz, 2H, CH_2), 1.83 (d, J = 4.6 Hz, 4H, $2CH_2$), 3.52 (t, J = 10.5 Hz, 4H, $2CH_2N$), 3.88 (s, 3H, CH_3O), 6.98 (s, 1H, CH), 7.01 (s, 1H, ArH), 7.12 (s, 1H, ArH), 7.50 (m, 3H, ArH), 7.94 (q, J = 9.6 Hz, 2H, ArH), 8.04 (s, 1H, ArH), 8.06 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.3, 25.1, 52.1, 55.6, 95.9, 105.7, 114.3, 124.7, 124.9, 129.1, 131.2, 131.8, 131.8, 132.2, 137.5, 159.4, 161.5, 163.0. MS (ESI, 70 eV) m/z (%) = 370 (100) [M^+], 371 (32) [$(M+2H)^+$]. Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.06; H, 6.29; N, 11.34.

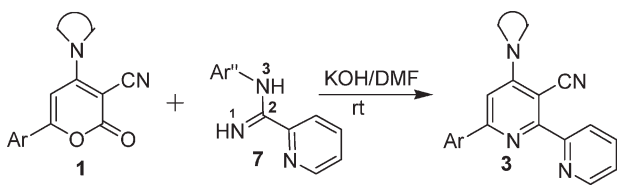
2-(4-Bromophenyl)-6-(4-chlorophenyl)-4-(pyrrolidin-1-yl) pyridine-3-carbonitrile (3i). White solid, IR (KBr): 2115 (C≡N), 1590 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 2.08 (brs, 4H), 3.79 (brs, 4H), 6.84 (s, 1H), 7.43 (s, 2H), 7.63 (s, 2H), 7.73 (s, 2H), 7.96 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.2, 50.1, 88.5, 103.6, 119.5, 123.2, 128.6, 128.9, 131.1, 131.3, 134.3, 134.6, 136.7, 138.1, 155.1, 155.4, 162.7. MS (ESI, 70 eV) m/z (%) = 438 [M^+, 43%], 440 [$(M+2H)^+$, 55%]. Anal. Calcd. for $C_{22}H_{17}BrClN_3$: C 60.22; H 3.91; N 9.58. Found: C, 60.42; H, 3.83; N, 9.42.

6-(4-Bromophenyl)-2-(pyridine-2-yl)-4-(pyrrolidin-1-yl)pyridine-3-carbonitrile (3j). Yellowish red solid, IR (KBr): 2190 (C≡N), 1566 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 2.07 (bs, 4H, CH_2), 3.82 (bs, 4H, $2NCH_2$), 6.91 (s, 1H, CH), 7.39 (s, 1H, ArH), 7.59 (s, 2H, ArH), 7.91 (bs, 3H, ArH), 8.02 (bs, 1H, ArH), 8.77 (bs, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.7, 50.4, 94.4, 103.9, 116.4, 123.9, 124.3, 128.8, 131.8, 136.7, 137.6, 146.7, 148.7, 158.3. MS (ESI, 70 eV) m/z (%) = 405 (100) [M^+]. Anal. Calcd. for $C_{21}H_{17}BrN_4$: C, 62.23; H, 4.23; N, 13.82. Found: C, 62.43; H, 4.364; N, 13.87.

6-(4-Chlorophenyl)-4-morpholino-2-(pyridine-2-yl)pyridine-3-carbonitrile (3k). Yellowish red solid, IR (KBr): 2225 (C≡N), 1566 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.55–3.58 (t, 4H, $2NCH_2$), 3.94–3.97 (t, 4H, $2OCH_2$), 7.21 (s, 1H, CH), 7.41–7.49 (m, 3H, ArH), 7.85–7.91 (m, 1H, ArH), 8.02–8.05 (q, 2H, ArH), 8.17–8.19 (d, J = 7.8 Hz, 1H, ArH), 8.78–8.79 (dd, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 50.8, 66.6, 97.4, 107.3, 117.5, 123.7, 124.8, 128.8, 129.2, 136.7, 148.8, 155.4, 158.3, 162.8. MS (ESI, 70 eV) m/z (%) = 377 [M^+, 100%], 379 [$(M+2H)^+$, 35%]. Anal. Calcd. for $C_{21}H_{17}ClN_4O$: C, 66.93; H, 4.55; N, 14.87. Found: C, 66.83; H, 4.64; N, 14.94.

4-Morpholino-6-phenyl-2-(pyridin-2-yl)pyridine-3-carbonitrile (3l). Yellowish red solid, IR (KBr): 2215 (C≡N), 1574, 1538 (C=N) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) δ = 3.55–3.58 (t, 4H, $2NCH_2$), 3.94–3.97 (t, 4H, $2OCH_2$), 7.25 (s, 1H, CH), 7.40–7.51 (m, 4H, ArH), 7.85–7.91 (m, 1H, ArH), 8.07–8.09 (t, 2H, ArH), 8.20–8.23 (d, J = 7.8 Hz, 1H, ArH), 8.77–8.79 (d, J = 4.2 Hz, 1H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 50.7, 66.6, 97.3, 107.5, 117.6, 123.7, 124.7, 127.4, 128.8, 130.2, 136.8, 138.1, 148.6, 155.5, 159.5, 161.3, 162.7, 165.3. MS (ESI, 70 eV) m/z (%) = 343 [$(M+H)^+$, 78%]. Anal. Calcd. for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.88; H, 5.42; N, 16.44.

Scheme 5. Synthesis of highly substituted unsymmetrical bipyridine.



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