A novel strategy for the synthesis of 2-amino-4,6-diarylnicotinonitrile

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Dedicated to the memory of Dr. Chaitanya G. Dave, an inspiring teacher, Formerly Head of Chemistry, St Xavier's College

Abstract

An efficient and novel strategy has been developed using liquid liquid phase transfer catalysis conditions for the synthesis of 2-amino-4,6-diarylnicotinonitrile and 5,7-diaryltetrazolo[1,5-a]pyridine-8-carbonitrile. The former was obtained either by two step process involving azidolysis of 2-chloro-4,6-diarylnicotinonitrile followed by chemoselective reduction of tetrazole moiety while facile one-pot procedure was conveniently carried out from corresponding 2-chloro-4,6-diarylnicotinonitrile.

Keywords: 2-Aminonicotinonitrile, tetrazolo[1,5-a]pyridine, chemoselective reduction, liquid-liquid phase transfer catalysis condition

Introduction

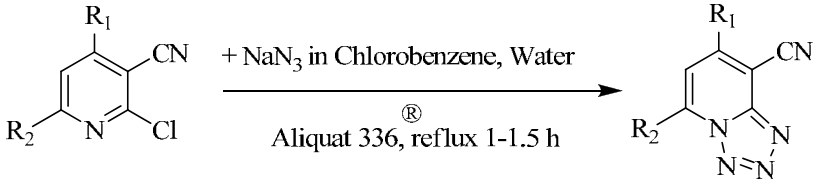
Synthetic compounds containing the pyridine scaffold exhibit interesting pharmacological properties.[1] As a consequence many efficient procedures have been reported in the literature for the synthesis of functionalized pyridines.[2] Among these, 2-aminopyridines are promising substituted pyridines which have been shown to be biologically active molecules.[3] Additionally, because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry.[4] Moreover 2-aminopyridines are also valuable synthetic precursor for the synthesis of fused nitrogen heterocycles[5] were as cyanopyridines with different alkyl and aryl groups were found to have antimicrobial,[6a] antihypertensive,[6b] cardiovascular,[6c] anti-inflammatory, analgesic, antipyretic properties[3e,6d] as well as IKK-β inhibitor properties.[6e] The preparation of the 2-amino-3-cyanopyridine derivatives has been reported in the literature from

corresponding 2-chloro derivatives[7], chalcones on treatment with ammonium acetate via Michael-type condensation,[8a] as well as via a one pot coupling reaction of four components[8b,c] acetophenone, benzaldehyde, malononitrile, and ammonium acetate in conventional heating or under microwave irradiation, various aliphatic aldehydes could also be used in the pyridine construction reaction using traditional and combinatorial chemistry approaches[9] and by other methods.[10] The 2-amino-3-cyanopyridines are also very versatile intermediates for the synthesis of nitrogen heterocycles.[11]

As part of our ongoing development of efficient protocols for the preparation of biologically active heterocyclic derivatives along with the versatility of the organic synthon[12], we herein report the synthesis of 2-amino-4,6-diarylnicotinonitrile **4**. The strategy includes either a two step process involving azidolysis of 2-chloro-4,6-diarylnicotinonitrile **2** yielding novel 5,7-diaryltetrazolo[1,5-a]pyridine-8-carbonitrile **3** followed by chemoselective reduction under phase-transfer catalysis conditions or an efficient one-pot synthesis achieved for the first time to form 2-chloro-4,6-diarylnicotinonitrile **2** via in situ generation of tetrazolopyridines.

Results and Discussion

Tetrazolo[1,5-a]pyridines are typically prepared by heating a 2-halopyridine and NaN_3 in a polar solvent[13], 2-hydrazinopyridines with sodium nitrite in acidic solution[14] or prepared directly from the *N*-oxides using toluenesulfonyl azide (TsN_3)[15] and diphenyl phosphorazidate (DPPA).[16]
We elected to examine the conversion of 2-chloro-4,6-diarylnicotininitrile **2** to tetrazolopyridines **3** with the goals of optimizing reaction conditions, determining substrate scope, and developing the process for multigram scale and hence liquid-liquid phase-transfer conditions employed for the first time using chlorobenzene and water as solvent and tricapryl-methylammonium chloride (Aliquat 336®) as catalyst (Scheme 1) Table 1.



2 **3**

Scheme 1

The reaction period for all these reactions was between 1-1.5 h. Phase transfer catalysis makes it possible to carry out azidolysis using sodium azide in a non polar solvent like chlorobenzene. The products are obtained in quantitative yield in most cases; moreover the solvent was also recoverable.

Table 1. Synthesis of 5,7-diaryltetrazolo[1,5-a]pyridine-8-carbonitrile **3a-j**

Entry	Compound	R^1	R^2	Time h.	Yield[a] (%)	Mp ^oC
1	**3a**	C_6H_5	C_6H_5	1. 5	75	182-83
2	**3b**	C_6H_5	4-CH_3 C_6H_4	1	78	127-28
3	**3c**	C_6H_5	4-$OCH_3C_6H_4$	1.5	71	190-91
4	**3d**	C_6H_5	4-ClC_6H_4	1	68	210-11
5	**3e**	4-CH_3 C_6H_4	C_6H_5	1.5	72	215-17
6	**3f**	4-$OCH_3C_6H_4$	C_6H_5	1.5	69	180-81
7	**3g**	4-$OCH_3C_6H_4$	4-CH_3 C_6H_4	1.5	70	212-13
8	**3h**	4-ClC_6H_4	C_6H_5	1	71	215-17
9	**3i**	4-ClC_6H_4	4-CH_3 C_6H_4	1.5	73	205-07
10	**3j**	4-ClC_6H_4	4-ClC_6H_4	1	74	218-19

[a]Isolated yields.

The same reaction was tried with different catalysts like tetrabutylammonium bromide (TBAB), benzyltriethylammonium chloride (TEBA), tributylbenzylammonium chloride, tetraethylammonium bromide and cetyltrimethylammonium chloride but none of these catalysts gave satisfactory results. Similar reaction conditions using toluene, 18-crown-6 and sodium azide, found to increase the reaction time by one to two hours.

Heterocyclic azides are known to spontaneously cyclize to give the fused tetrazole form or more generally exist as an equilibrium mixture and been described in the literature as a tautomerism, as an azidomethine-tetrazole (imideamide-tetrazole) equilibrium, as a 1,5-dipolar cyclization and as a valence isomerization.[15,17,18] This ambiguity was removed on the basis of X-ray crystallography. Absence of absorption around 2100 cm^{-1} in IR (KBr) suggestive of the formation of 5,7-diaryltetrazolo[1,5-a]pyridine-8-carbonitrile **3** and absence of azido group, which was further supported by X-ray crystallography.[19] (Figure 1)

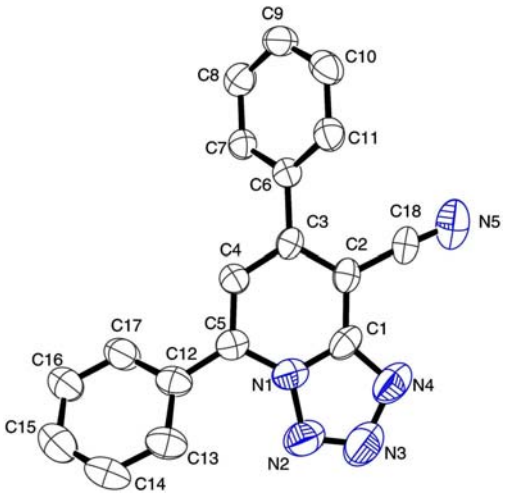
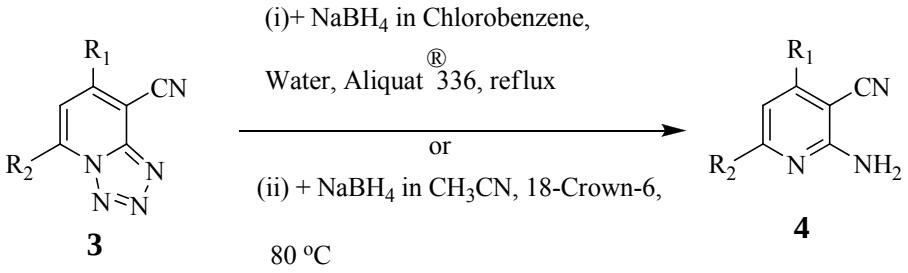


Figure 1. Ortep diagram of 5,7-dipheyltetrazolo[1,5-a]pyridine-8-carbonitrile[19] **3a**.

Azides and tetrazoles can be viewed as latent amino functionalities. While azides undergo chemoselective reduction by novel system[20], lithium aluminum hydride[21], or by catalytic hydrogenation[21a-d, 22] and numbers of other reagents[23] to yield amines, tetrazoles are highly resistant to reductions,[24] however several methods have been reported.[25] With respect to the literature methods, the PTC technique shows the novelty of using sodium borohydride as an efficient reducing agent for tetrazoles. It affords pure products in high yields and offers the advantages of permitting a one-pot conversion of 2-chloro-4,6-diarylnicotininitrile **2** into 2-amino-4,6-diarylnicotininitrile **4** with very simple operative conditions. Thus, in a modified procedure, two synthetic strategies based on PTC were adopted and evaluated for the reductive ring cleavage of tetrazolopyridines **3** keeping sodium borohydride as a reducing agent. In liquid-liquid phase-transfer conditions, tricapryl-methylammonium chloride (Aliquat 336®) was used as catalyst and chlorobenzene together with water (3:1) was preferred as solvent and in another strategy catalyst 18-crown-6 was used along with reducing agent and acetonitrile as solvent, longer time period as well as side reactions were evident (TLC). (Scheme 2) Table 2.



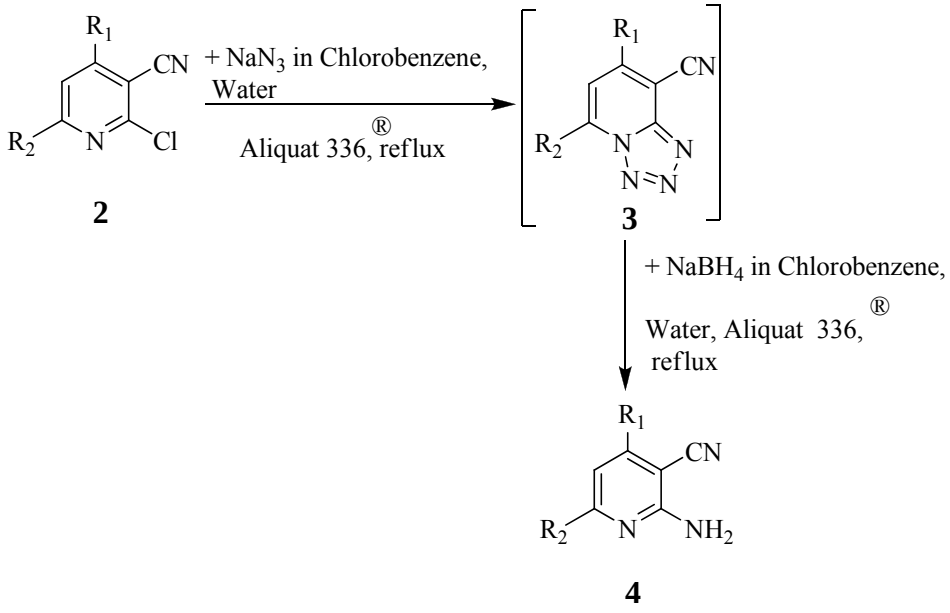
Scheme 2

One-pot synthesis of 2-amino-4,6-diarylnicotininitrile **4** was achieved efficiently using liquid-liquid PTC conditions, chlorobenzene and water as solvents and tricapryl-methylammonium chloride (Aliquat 336®) as catalyst, however, a higher mole % of catalyst was required. First reaction of **2** was carried out with sodium azide to form compound **3** (TLC). After completion of the reaction equivalent quantity of powdered sodium borohydride was added portion wise to the same reaction mixture in order to get the compound **4.** (Scheme 3)

Table 2. Synthesis of 2-amino-4,6-diarylnicotinonitrile **4a-j**

Entry	Compound	R_1	R_2	Time h. Method I	Time h. Method II	Yield[a,b] (%) Method I	Yield[a,b] (%) Method II	Mp °C Found/Lit
1	**4a**	C_6H_5	C_6H_5	1	2.5	75	70	187-88/ 186-87[7]
2	**4b**	C_6H_5	4-CH_3 C_6H_4	1.5	2.5	78	72	180-82
3	**4c**	C_6H_5	4-$OCH_3C_6H_4$	1.5	3	71	64	177-79
4	**4d**	C_6H_5	4-ClC_6H_4	1.5	2.5	68	59	240-41
5	**4e**	4-CH_3 C_6H_4	C_6H_5	1.5	3	72	63	175-76
6	**4f**	4-$OCH_3C_6H_4$	C_6H_5	1	2.5	69	61	184-85/ 180-82 [8b]
7	**4g**	4-$OCH_3C_6H_4$	4-CH_3 C_6H_4	1.5	3	70	62	166-66
8	**4h**	4-ClC_6H_4	C_6H_5	1	2.5	71	60	223-25
9	**4i**	4-ClC_6H_4	4-CH_3 C_6H_4	1	2.5	73	69	210-11
10	**4j**	4-ClC_6H_4	4-ClC_6H_4	1.5	2.5	74	65	228-29

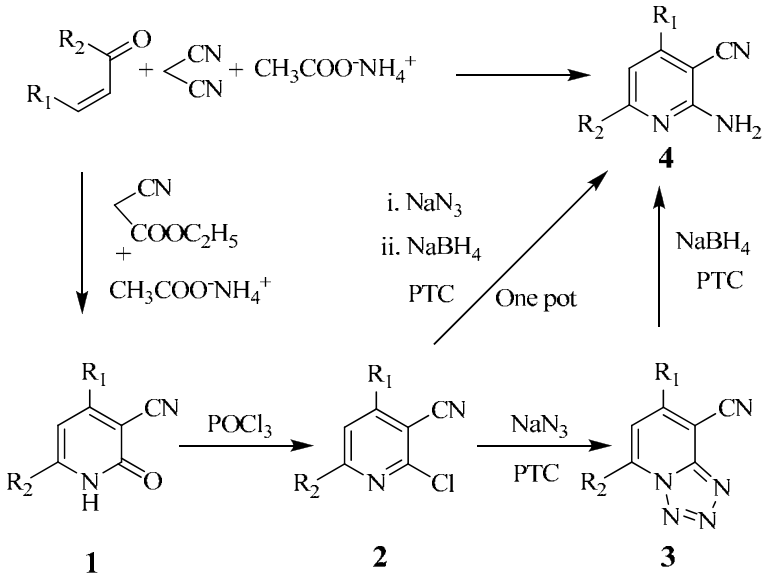
[a]overall yields for method I from compound **3** and for method II from compound **2**. [b]Isolated yields.



Scheme 3

An important accomplishment of this phase transfer catalyst assisted route for the synthesis of 2-amino-4,6-diarylnicotinonitrile **4** is, expensive chemical like malononitrile can be avoided.

2-amino-4,6-diarylnicotinonitrile **4** via formation of tetrazolo[1,5-a]pyridine **3**, employed 2-oxo-4,6-diaryl-1,2-dihydropyridine-3-carbonitrile **1** as starting material which can be synthesized by refluxing corresponding chalcones with ethyl cyanoacetate. (Scheme 4)



Scheme 4. Various routes for the synthesis of 2-amino-4,6-diarylnicotinonitrile **4**.

Conclusions

In summary we have described a two new strategy for the synthesis of 2-amino-4,6-diarylnicotinonitrile **4** which eventually gave liberty to replace expensive malononitrile. 5,7-diaryltetrazolo[1,5-a]pyridine-8-carbonitrile **3** were conveniently synthesized and transformed via chemoselective reduction to compound **4** for the first time using phase-transfer conditions. Novel one pot reaction was effectively achieved for 2-amino-4,6-diarylnicotinonitrile **4** from 2-chloro-4,6-diarylnicotinonitrile **2** without the need to work up for every step. The operational simplicity of this synthetic route will offer an attractive alternative to the conventional methods.

Experimental Section

General Procedures. Melting points were determined by electro thermal method in open capillary tube and are uncorrected. The IR spectra were recorded in cm^{-1} for KBr pellets on a Buck-500 spectrophotometer. The ^1H NMR spectra were recorded on a Varian 300 & 400 MHz spectrophotometer in $CDCl_3$, using TMS as internal standard and the chemical shifts are expressed in δ ppm. MS spectra were recorded on a JEOL/ SX-102 mass spectrophotometer

under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. The completion of reaction was checked by TLC using silica gel G and spots were exposed to iodine vapour.
2-Chloro-4,6-diarylnicotinonitrile was synthesized by refluxing 2-oxo-4,6-diaryl-1,2-dihydropyridine-3-carbonitrile **1** in phosphoryl trichloride.

Synthesis of 5,7-diaryltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3a-j). General procedure
To the well stirred solution of 2-chloro-4,6-diarylpyridine (**2**, 0.005 mole) and tricaprylmethylammonium chloride (Aliquat 336®) (0.0005 mole, 0.202 g) in chlorobenzene (20 mL) was added sodium azide (0.006 mole, 0.390 g) in water (5 mL). The reaction mixture was stirred under reflux for 1-1.5 h. The progress of the reaction was monitored by TLC. On completion, two phases were separated. The aqueous phase was extracted with chlorobenzene (15 mL) and combined organic layer was washed with water (10 × 2 ml) and dried over anhydrous Na_2SO_4. The solvent was recovered in vacuo and the oily residue obtained after distillation was treated with chilled methanol. The solid thus obtained was filtered, dried and crystallized from alcohol : chloroform (6:4 v/v) (Table 1).

5,7-Diphenyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3a). IR (KBr): ν = 3020, 2940, 2228, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51-8.14 (m, 11H, Ar-H); MS: m/z = 297 (M^+). Anal. Calcd for $C_{18}H_{11}N_5$ (297.31): C, 72.72; H, 3.73; N, 23.56; Found: C, 72.60; H, 3.98; N, 23.30 %.

7-Phenyl-5-p-tolyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3b). IR (KBr): ν = 3030, 2970, 2216, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 (s, 3H, CH_3), 7.48-8.02 (m, 10H, Ar-H); MS: m/z = 311 (M^+). Anal. Calcd for $C_{19}H_{13}N_5$ (311.34): C, 73.30; H, 4.21; N, 22.49; Found: C, 73.60; H, 4.11; N, 22.30 %.

5-(4-Methoxyphenyl)-7-phenyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3c). IR (KBr): ν = 3010, 2960, 2230, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 7.55-8.13 (m, 10H, Ar-H); MS: m/z = 327 (M^+). Anal. Calcd for $C_{19}H_{13}N_5O$ (327.34): C, 69.71; H, 4.00; N, 21.39; Found: C, 69.60; H, 4.11; N, 21.30 %.

5-(4-Chlorophenyl)-7-phenyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3d). IR (KBr): ν = 3030, 2990, 2230, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61-8.19 (m, 10H, Ar-H); MS: m/z = 331 (M^+). Anal. Calcd for $C_{18}H_{10}ClN_5$ (331.76): C, 65.17; H, 3.04; N, 21.11; Found: C, 65.01; H, 3.11; N, 21.30 %.

5-Phenyl-7-*p*-tolyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3e). IR (KBr): ν = 3010, 2990, 2226, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 3H, CH_3), 7.60-8.13 (m, 10H, Ar-H); MS: m/z = 311 (M^+). Anal. Calcd for $C_{19}H_{13}N_5$ (311.34): C, 73.30; H, 4.21; N, 22.49; Found: C, 73.17; H, 4.11; N, 22.33 %.

7-(4-Methoxyphenyl)-5-phenyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3f). IR (KBr): ν = 3020, 2980, 2224, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.99 (s, 3H, OCH_3), 7.50-8.11 (m, 10H, Ar-H); MS: m/z = 327 (M^+). Anal. Calcd for $C_{19}H_{13}N_5O$ (327.34): C, 69.71; H, 4.00; N, 21.39; Found: C, 69.80; H, 3.95; N, 21.45 %.

7-(4-Methoxyphenyl)-5-*p*-tolyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3g). IR (KBr): ν = 3030, 2990, 2230, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.84 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3) 7.59-8.09 (m, 9H, Ar-H); MS: m/z = 341 (M^+). Anal. Calcd for $C_{20}H_{15}N_5O$ (341.37): C, 70.37; H, 4.43; N, 20.52; Found: C, 70.17; H, 4.31; N, 20.35 %.

7-(4-Chlorophenyl)-5-phenyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3h). IR (KBr): ν = 3020, 2980, 2200, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.59-8.15 (m, 10H, Ar-H); MS: m/z = 331 (M^+). Anal. Calcd for $C_{18}H_{10}ClN_5$ (331.76): C, 65.17; H, 3.04; N, 21.11; Found: C, 65.27; H, 2.96; N, 21.18 %.

7-(4-Chlorophenyl)-5-*p*-tolyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (3i). IR (KBr): ν = 3020, 2980, 2230, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.83 (s, 3H, CH_3), 7.55-8.11 (m, 9H, Ar-H); MS: m/z = 345 (M^+). Anal. Calcd for $C_{19}H_{12}ClN_5$ (345.79): C, 66.00; H, 3.50; N, 20.25; Found: C, 66.08; H, 3.56; N, 20.18 %.

5,7-Bis(4-chlorophenyl)tetrazolo[1,5-*a*]pyridine-8-carbonitrile (3j). IR (KBr): ν = 3010, 2980, 2228, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56-8.13 (m, 9H, Ar-H); MS: m/z = 366 (M^+). Anal. Calcd for $C_{18}H_9Cl_2N_5$ (366.2): C, 59.04; H, 2.48; N, 19.12; Found: C, 59.18; H, 2.56; N, 19.18 %.

Synthesis of 2-amino-4,6-diarylpyridine (4a-j). General procedure

Method I liquid-liquid PTC conditions

A mixture of 5,7-diaryltetrazolo[1,5-*a*]pyridine-8-carbonitrile (**3**, 0.002 mole) and tricaprylmethylammonium chloride (Aliquat 336®) (0.0005 mole, 0.202 g), Chlorobenzene (15 mL) and water (5 mL) was stirred on in a flat bottom flask at 60 °C. Powdered sodium borohydride (0.008 mole, 0.302 g) was added to this reaction mixture portion wise cautiously over a period of 30 min. The reaction mixture was then refluxed for 1-1.5 h. On completion (TLC) the aqueous phase was separated. The aqueous phase was extracted with Chlorobenzene (15 mL) and combined organic layer was washed with water (10 × 2 mL) and dried over anhydrous Na_2SO_4. The solvent was recovered in vacuo, the content was treated with n-hexane and solid thus formed was filtered, washed with cold methanol, dried and crystallized from methanol : chloroform (7:3 v / v) (Table 2).

Method II One pot reaction

To the well stirred solution of 2-chloro-4,6-diarylpyridine (**2**, 0.005 mole) and tricaprylmethylammonium chloride (Aliquat 336®) (0.0008 mole, 0.323 g) in chlorobenzene (25 ml) was added sodium azide (0.006 mole, 0.390 g) in water (5 ml). The reaction mixture was stirred under reflux for 1-1.5 h. The progress of the reaction was monitored with TLC, after the formation tetrazolopyridine **3** powdered sodium borohydride (0.008 mole, 0.302g) was added cautiously over a period of 30 min to the same reaction mixture and was refluxed for 1-1.5 hour in order to get the corresponding 2-amino-4,6-diarylpyridine **4**. The workup affected according to method I (Table 2).

2-Amino-4,6-diphenylnicotinonitrile (4a).[7] IR (KBr): ν = 3460, 3320, 3010, 2995, 2200, 1638, 1576 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.35 (s, 2H, NH_2), 7.59-8.15 (m, 11H, Ar-H); MS: m/z = 271 (M^+). Anal. Calcd for $C_{18}H_{13}N_3$ (271.32): C, 79.68; H, 4.83; N, 15.49; Found: C, 79.88; H, 4.93; N, 15.28 %;

2-Amino-4-phenyl-6-*p*-tolylnicotinonitrile (4b). IR (KBr): ν = 3450, 3300, 3030, 2990, 2212, 1628, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.82 (s, 3H, CH_3) 5.33 (s, 2H, NH_2), 7.55-8.11 (m, 10H, Ar-H); MS: m/z = 285 (M^+). Anal. Calcd for $C_{19}H_{15}N_3$ (285.34): C, 79.98; H, 5.30; N, 14.73; Found: C, 79.68; H, 5.33; N, 14.68 %;

2-Amino-6-(4-methoxyphenyl)-4-phenylnicotinonitrile (4c). IR (KBr): ν = 3460, 3320, 3015, 2980, 2224, 1632, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3H, OCH_3), 5.30 (s, 2H, NH_2), 7.65-8.10 (m, 10H, Ar-H); MS: m/z = 301 (M^+). Anal. Calcd for $C_{19}H_{15}N_3O$ (301.34): C, 75.73; H, 5.02; N, 13.94; Found: C, 75.68; H, 5.33; N, 13.88 %.

2-Amino-6-(4-chlorophenyl)-4-phenylnicotinonitrile (4d). IR (KBr): ν = 3450, 3310, 3000, 2980, 2208, 1624, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.35 (s, 2H, NH_2), 7.68-8.11 (m, 10H, Ar-H); MS: m/z = 305 (M^+). Anal. Calcd for $C_{18}H_{12}ClN_3$ (305.76): C, 70.71; H, 3.96; N, 13.74; Found: C, 70.68; H, 3.90; N, 13.88 %.

2-Amino-6-phenyl-4-*p*-tolylnicotinonitrile (4e). IR (KBr): ν = 3470, 3320, 3010, 2990, 2212, 1636, 1576 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.82 (s, 3H, CH_3), 5.35 (s, 2H, NH_2), 7.60-8.10 (m, 10H, Ar-H); MS: m/z = 285 (M^+). Anal. Calcd for $C_{19}H_{15}N_3$ (285.34): C, 79.98; H, 5.30; N, 14.73; Found: C, 79.68; H, 5.40; N, 14.88 %.

2-Amino-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (4f).[8b] IR (KBr): ν = 3450, 3300, 3015, 2990, 2220, 1628, 1588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.99 (s, 3H, OCH_3), 5.31 (s, 2H, NH_2), 7.58-8.06 (m, 10H, Ar-H); MS: m/z = 301 (M^+). Anal. Calcd for $C_{19}H_{15}N_3O$ (301.34): C, 75.73; H, 5.02; N, 13.94; Found: C, 75.68; H, 5.33; N, 13.88 %.

2-Amino-4-(4-methoxyphenyl)-6-p-tolylnicotinonitrile (4g). IR (KBr): ν = 3465, 3300, 3010, 2980, 2216, 1620, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 5.32 (s, 2H, NH_2), 7.58-8.06 (m, 9H, Ar-H); MS: m/z = 315 (M^+). Anal. Calcd for $C_{20}H_{17}N_3O$ (315.37): C, 76.17; H, 5.43; N, 13.32; Found: C, 76.28; H, 5.33; N, 13.45 %.

2-Amino-4-(4-chlorophenyl)-6-phenylnicotinonitrile (4h). IR (KBr): ν = 3455, 3300, 3010, 2980, 2204, 1624, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.34 (s, 2H, NH_2), 7.67-8.14 (m, 10H, Ar-H); MS: m/z = 305 (M^+). Anal. Calcd for $C_{18}H_{12}ClN_3$ (305.76): C, 70.71; H, 3.96; N, 13.74; Found: C, 70.68; H, 3.90; N, 13.88 %.

2-Amino-4-(4-chlorophenyl)-6-*p*-tolylnicotinonitrile (4i). IR (KBr): ν = 3465, 3320, 3015, 2990, 2224, 1636, 1578 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.85 (s, 3H, CH_3), 5.32 (s, 2H, NH_2), 7.67-8.14 (m, 9H, Ar-H); MS: m/z = 319 (M^+). Anal. Calcd for $C_{19}H_{14}ClN_3$ (319.79): C, 71.36; H, 4.41; N, 13.14; Found: C, 71.38; H, 4.30; N, 13.40 %.

2-Amino-4,6-bis(4-chlorophenyl)nicotinonitrile (4j). IR (KBr): ν = 3470, 3330, 3020, 2995, 2216, 1624, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.32 (s, 2H, NH_2), 7.67-8.14 (m, 9H, Ar-H); MS: m/z = 340 (M^+). Anal. Calcd for $C_{18}H_{11}Cl_2N_3$ (340.21): C, 63.55; H, 3.26; N, 12.35; Found: C, 65.38; H, 3.30; N, 12.40 %.

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