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A NOVEL ROUTE FOR C-N COUPLING REACTION: ALTERNATIVE SYNTHESIS OF 2-N-BENZYLAMINOQUINOLINE-3-CARBONITRILE IN AQUEOUS MEDIA

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Abstract

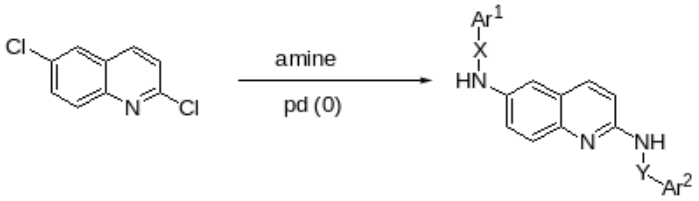
The present work relates to a process for C-N Coupling which can be used in a variety of chemical reactions. Work provides a process for C-N coupling between aryl halide and aliphatic amines also a low-cost process for C-N Coupling. It is to develop a process for C-N coupling that explores Buchwald-Hartwig amination reaction. Process may use for making N-alkylaminoquinoline which has industrial applications as a ligand.

Keywords: N-alkylaminoquinoline; Ligand; Buchwald-Hartwig amination reaction; C-N Coupling.

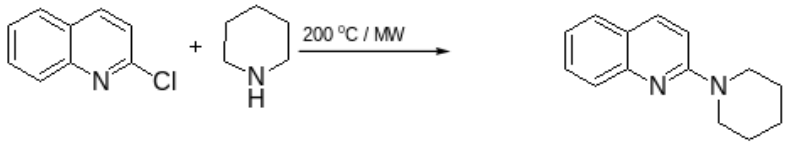
1. INTRODUCTION

Nitrogen containing compounds are of great importance because of their interesting and diverse biological activities. The construction of the C–N bond is of significant importance as it opens avenues for the introduction of nitrogen in organic molecules. Beside advancements, still the C–N bond coupling is still a major challenge for organic chemists. Because it involve harsh reaction conditions or the use of expensive catalysts in many cases. Thus, it is a challenge to develop alternative, milder and cheaper processes for the construction of C–N bonds.

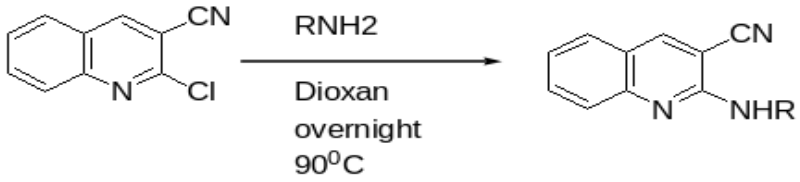
WO 2008037626 discloses that the C-N coupling reaction occurred by treating the 2, 6-dichloroquinoline with amine and palladium as catalyst under harsh reaction condition.[1] Product yield reported as only 67%.



The C-N coupling process as described by Melissa Miller *et al*, requires high temperature.[2]

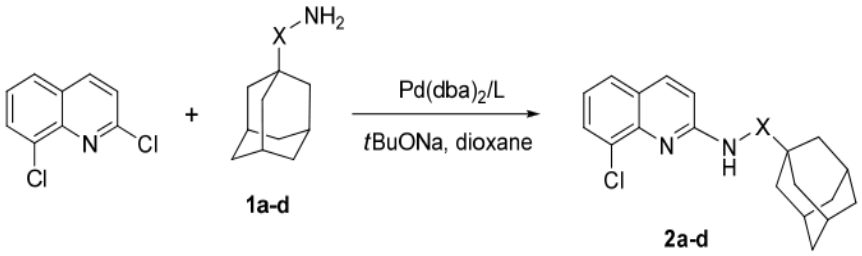


Another C-N coupling, comprising the amination of 2-chloroquinoline-3-carbonitrile along with primary amine has been optimized at longer reaction time.



A C-N coupling beginning with 6-Bromo, 2-chloroquinoline and secondary amine requires catalyst and harsh reaction condition as disclosed by Jessica A. Smith et al.[4]

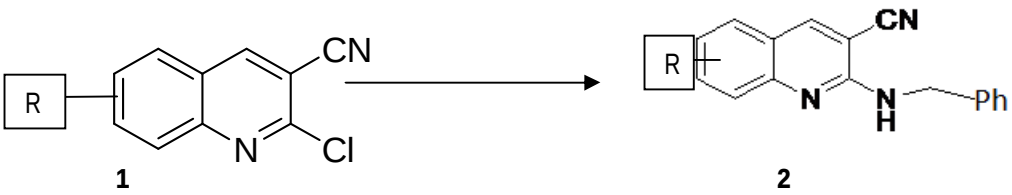
Synthesis, beginning from bulkier amine, catalyst and 2, 8-dichloroquinoline for C-N coupling has been described by Anton S. Abel et al.[5]. Drawback associated with this process is use of expensive bulkier amine which causes steric hindrance. Steric hindrances lower the rate of reaction and also lower the yield of product.



In view of aforementioned drawbacks, there is a need to develop a new process for C-N bond formation.

2. MATERIAL AND METHODS

C-N Coupling reaction is optimized with 2-chloroquinoline-3-carbonitrile 1 (1.0 equiv), aryl / heteroaryl amine (3.0 equiv) and 3 ml water. at 25°C. The scheme of the reaction is as shown below.



Reagent: NH_2CH_2Ph / H_20
Condition: 25 ^0C
R = H, Me, MeO, Et, Cl, Br

Following amines and quinolines were used to optimize the reaction.

S. No	Amines	Quinolines
1	Benzyl	6Me
2	Methyl	6MeO
3	Ethyl	7Me
4	n-Butyl	7MeO
5	Cyclohexyl	8Me
6	Isopropyl	8Et
7	N,N-Dimethyl	6Br
8	Piperidine	7Cl
9	Morpholine	
10	Aniline	

C-N Coupling reaction performed at room temperature. With the help of open capillary tube and using Buchi Melting-point apparatus the melting point of formed product is detected and are found that more accurate.

The structure of synthesizes product was characterized spectral analysis for example NMR, IR and etc. FTIR spectrophotometers VARIAN 3300 are used for IR detection. JEOL spectrometer is used for 1 H (300 MHz) and 13C (75 MHz). Frequency used is of AL 300 MHz TMS (tetramethylsilane) was used as internal reference for both 1H and 13C detection. CDCl3/DMSO both are used to operate the NMR analysis.

Carbon, Nitrogen and Hydrogen percentage and Mass analyses was performed on CHN Analyzer Model CE-400. Thermo LCQ Advantage Max (ESI and APCI) Ion Trap (LCeMS/MS). All these instruments are available with from Department of Chemistry, IIT, Delhi.

Thin-layer chromatography (TLC) was used to moniter the reaction. TLC plate that used are made up of glass coated with silica gel. Mixture of polar and non-polar solvent was used as eluent.

UV chamber with UV lamp were used to visualize the spots.

Formed crude product was purified via column chromatography. Silica gel (60-120 mesh) Qualigen's was used for column chromatography.

3. RESULTS AND DISCUSSION

Initially we have optimized reaction between 2-chloroquinoline-3- carbonitrile 1a and benzyl amine. Benzyl amine (3 equiv) with 2-chloroquinoline-3- carbonitrile in water optimized at 25 ^{0}C for 3 h.

The reaction proceeded through SNAr smoothly. Amino group of benzylamine displace chlorine atom of substrate and leads to the desired product **2a** in good yields, Scheme 1.

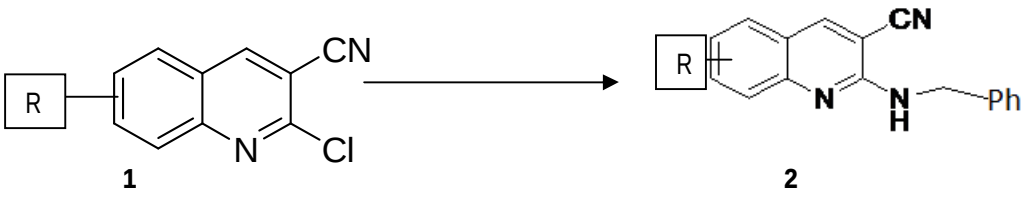
The above mentioned C-N Coupling reaction initially optimized with various solvents such as EtOH, DMF, MeOH, CH_3CN. It observed that product using ethanol as solvent obtained in quantitative yield (Table 1, entries 1-4).

Amongs various solvents, fortunately the reaction with aqueous methyl amine using ethanol as solvent under similar reaction condition proceeded very fast and overall reaction completed only in 10 min. Yield of formed product was quantitative yield (entry 5).

This result prompts us further to reoptimized reaction under similar reaction condition in water. On optimization it observed that reactions completed only in 55 min. Product yield are found to be 82% (entry 6).

On lower the molar ratio of benzyl amine (Using 2 equiv) not leads to complete reaction even after 24 h (entry 7).

Further, it is to be noted that without solvent C-N Coupling reaction resulted in incomplete conversion of reactant into product (entry 8).



Reagent: NH_2CH_2Ph / H_20
Condition: 25 ^0C
R = H, Me, MeO, Et, Cl, Br

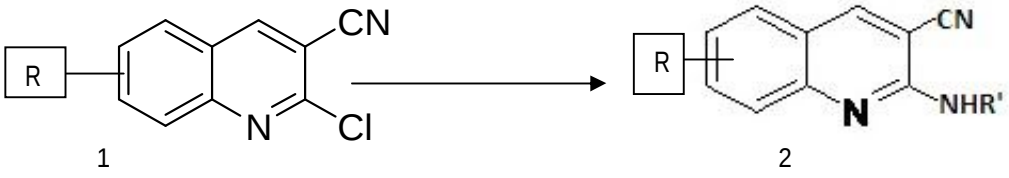
Scheme 1: C-N coupling between **2-choloroquinoline-3-carbonitrile (1a) and benzylamine**

Table 1: Optimization reaction conditions with different solvent on C-N coupling between 2-choloroquinoline-3-carbonitrile (1a) and benzylamine[a]

Entry	Solvent	Time (h)	Yield of 2a[b] (%)
1	EtOH	3.0	90.2
2	MeOH	3.5	60.3
3	CH3CN	5.0	75.4
4	DMF	3.5	55
5[c]	H2O	5 (min)	92
6	H2O	50	82
7[d]	H2O	24	35

a 2-Choloroquinoline-3-carbonitrile (1 mmol), benzyl amine (3.0 mmol), solvent(1 ml / mmol), 25 ^0C.
b Isolated yields.
c 2-Choloroquinoline-3-carbonitrile (1 mmol), benzyl amine (3.0 mmol), water(1 ml / mmol), 25^0C.
d Using 2 equiv of benzylamine.

In next step, reaction further examined using water as solvent with other amines under similar reaction. With primary and secondary amines it observed that coupling reactions proceeded smoothly. The results are discussed in Table 2 (entries 1-9).



Reagent: NH_2CH_2Ph / H_20
Condition: 25 ^0C

Table 2: C-N Coupling between 2-choloroquinoline/pyridine-3-carbonitriles and different alkyl/aryl amines in water

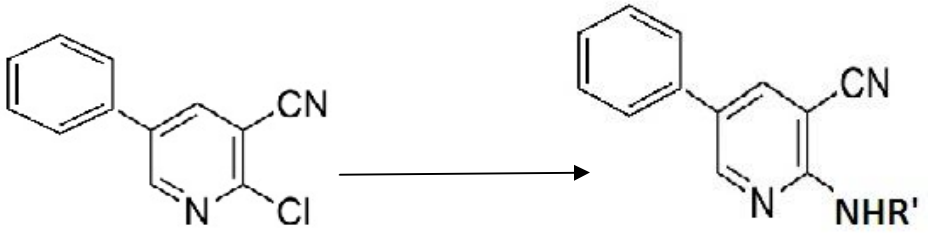
Entry	R	R'	Product	Time	Yiels(%)
1	H	Benzyl	2a	50	82
2	H	Methyl	2ab	5	92
3	H	Ethyl	2ac	20	80
4	H	n-Butyl	2ad	90	75
5	H	Cyclohexyl	2ae	25	79
6	H	Isopropyl	2af	30	82
7	H	N,N-Dimethyl	2ag	25	78
8	H	Piperidine	2ah	40	92
9	H	Morpholine	2ai	35	90
10	H	Aniline	SM	40h	00
11	6Me	Benzyl	2b	50	82
12	6MeO	Benzyl	2c	65	88
13	7Me	Benzyl	2d	57	80
14	7MeO	Benzyl	2e	70	85
15	8Me	Benzyl	2f	50	84
16	8Et	Benzyl	2g	48	88
17	6Br	Benzyl	2h	40	82
18	7Cl	Benzyl	2i	45	80
19	3	Benzyl	4a	60	85
20	3	Methyl	4b	10	80
21	3	n-Butyl	4c	95	78
22	3	N,N-Dimethyl	4d	30	72
23	3	Morpholine	4e	20	85

Amines with lengthy alkyl chain do not alter the yield of desired product (entries 2-4). Alternatively, under similar reaction conditions amines with branched alkyl chain increase the yield of the products. Difference in result arises due to inductive effect which is associated with alkyl groups (entries 5 and 6). In discussing secondary amines aliphatic open chain (entry 7), and cyclic secondary amines, it seems that cyclic enhance the yields significantly (entries 8 and 9).

While aromatic amine does not react at all even at higher temperature (entry 10). Further C-N Coupling reactions also examined using different 2-chloroquinoline-3-carbonitrile derivatives (1b-i) under similar reaction condition. Results are mentioned in Table 2 (entries 11-18).

In 2-chloroquinoline-3-carbonitrile when electron withdrawing groups present at benzene ring increase the reaction rate while alternatively electron donating groups in contrast decrease the rate of the reaction. Along with quinoline derivative we have also examined same reaction under similar reaction condition with pyridine (Scheme 2). Thus, 2-chloro-5-phenylpyridin-3-carbonitrile (3) with different amines primary/secondary, aliphatic/aromatic provided desired amino pyridines 4ae in good yields.

The results are summarized in Table 2 (entries 19-23).



3 **4**

Reagent: NH_2CH_2Ph / H_20
Condition: 25 ^0C

Scheme 2: Synthesis of 2-aminosubstituted pyridine-3-carbonitrile (4a) from 2-choloropyridine-3-carbonitrile (3).

3. CONCLUSIONS

In conclusion, a noval route for C-N Coupling between 2- chloroquinoline-3-carbonitriles and different amines in aqueous media is to be discovered. The reaction proceeded via simple SNAr reaction.

4. EXPERIMENTAL SECTION

4.1. General procedure for synthesis of 2-N-Benzylaminoquinoline-3- carbonitriles (2)

2-Chloroquinoline-3-carbonitrile (1 eq.) was treated with benzylamine (3 eq.) in presence of water (3ml) at room temperature. The reaction proceeded after 15 min as monitored by thin layer chromatography (TLC) and completed after 3 hrs checked by same techniques. After completion of reaction, the reaction mixture was poured into ice-cold water. As a result a yellow-green precipitate of 2-N-Benzylaminoquinoline-3-carbonitrile appeared which was filtered out and washed out 2-3 times by pure water. After drying 2-N-Benzylaminoquinoline-3-carbonitrile, the spectral analysis was carried out to confirm the product. 2-N-Benzylaminoquinoline-3-carbonitrile hence obtained further undergoes purification by column chromatography and is obtained in quantitative yield.

4.1.1. 2-Benzylaminoquinoline-3-carbonitrile (2a). mp 118 _C; 1H NMR (300 MHz, CDCl3): d¼4.81 (d, J¼5.2 Hz, 2H), 5.52 (s, 1H, D2O exchangeable), 7.34-7.43 (m, 3H), 7.62-7.731(m, 6H), 8.22 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼45.9, 95.3, 116.4, 121.5, 123.6, 126.7, 127.7, 128.7, 128.7, 128.8, 132.4, 138.3, 143.1, 149.2, 153.4; IR (KBr): 2217 (CN), 3382 (NH) Anal. Calcd for C17H13N3: C, 78.74; H, 5.05; N, 16.20%. Found: C, 78.62; H,5.00; N, 16.20%.

4.1.2. 2-Methylaminoquinoline-3-carbonitrile (2ab). mp 120 ^0C (d); 1 H NMR (300 MHz, CDCl3): d¼3.16 (d, J¼4.1 Hz, 3H), 5.81 (s, 1H, D2O exchangeable), 7.59-7.75 (m, 4H), 8.21 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼48.1, 95.8, 116.6, 121.1, 123.1, 126.2, 128.2, 132.7, 143.5, 149.8, 154.8; IR (KBr): 2222 (CN), 3385 (NH). Anal. Calcd for C11H9N3 C, 72.11; H, 4.95; N, 22.94%. Found: C, 72.08; H, 4.95; N, 21.32%.

4.2.3. 2-Ethylaminoquinoline-3-carbonitrile (2ac). mp 60-63 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼1.33 (t, J¼7.3 Hz, 3H), 3.66 (q, J¼7.1 Hz, 2H), 5.17 (br s, 1H, D2O exchangeable), 7.54-7.64 (m, 4H), 8.18 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼14.3, 36.6, 95.3, 116.4, 121.2, 123.3, 126.4, 128.1, 132.6, 143.9, 149.9, 153.3; IR (KBr): 2223 (CN), 3399 (NH). Anal. Calcd for C12H11N3 C, 73.06; H, 5.62; N, 21.31%. Found: C, 73.06; H, 5.65; N, 21.34%.

4.2.4. 2-n-Butylaminoquinoline-3-carbonitrile (2ad). mp: 191 ^{0}C (decomp.); 1 H NMR (300 MHz, CDCl3): d¼0.98 (t, J¼7.2 Hz, 3H), 1.42-1.55 (m, 1H), 1.63-1.75 (m, 2H), 3.63 (m, 2H); 5.21 (br s, 1H, D2O exchangeable), 7.55-7.71 (m, 4H), 8.20 (s, 1H); 13C NMR (75 MHz, CDCl3): d 13.9, 20.7, 31.8, 41.9, 95.4, 116.8, 121.4, 123.2, 126.9, 128.2, 132.8, 143.9, 149.6, 153.8; IR (KBr): 2217 (CN), 3369 (NH). Anal. Calcd for C14H15N3 C, 74.64; H, 6.71; N, 18.65%. Found: C, 74.66; H, 5.61; N, 18.63%.

4.2.5. 2-Cyclohexylaminoquinoline-3-carbonitrile (2ae). mp: 131 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼1.24-1.32 (m, 4H), 1.65-1.84 (m, 4H), 2.12-2.16 (m, 2H), 4.14-4.24 (m, 1H), 5.08 (br s, 1H, D2O exchangeable), 7.56-7.69 (m, 4H), 8.19 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼13.9, 20.2, 31.4, 41.3, 95.3, 116.8, 120.8, 123.1, 126.2, 128.9, 132.9, 143.5, 149.7, 153.9; IR (KBr): 2219 (CN), 3405 (NH). Anal. Calcd for C16H17N3 C, 74.92; H, 6.37; N, 17.71%. Found: C, 74.92; H, 6.38; N, 17.74%.

4.2.6. 2-Isopropylaminoquinoline-3-carbonitrile (2af). mp: 111-113 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼1.31 (d, J¼6.3 Hz, 6H), 4.45-4.56 (m, 1H), 5.02 (s, 1H, D2O exchangeable), 7.52-7.71 (m, 3H); 7.95 (t, J¼7.8 Hz, 1H), 8.19 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼22.7, 42.9, 95.4, 116.6, 120.8, 123.2, 126.9, 128.4, 132.8, 143.6, 149.9, 153.3; IR (KBr): 2229 (CN), 3448 (NH). Anal. Calcd for C13H13N3 C, 73.91; H, 6.20; N, 19.89%. Found: C, 73.88; H, 6.18; N, 19.89%.

4.2.7. 2-Dimethylaminoquinoline-3-carbonitrile (2ag). mp 191 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼3.34 (s, 6H), 7.61-7.72 (m, 4H), 8.31(s, 1H); 13C NMR (75 MHz, CDCl3): d¼40.7, 96.4, 118.6, 121.5, 123.7, 126.8, 127.7, 132.5, 146.9, 148.5, 156.8; IR (KBr): 2222 (CN), 3383 (NH). Anal. Calcd for C12H11N3 C, 73.07; H, 5.62; N, 21.30%. Found: C, 72.08; H, 5.61; N, 21.27%.

4.2.8. 2-Piperidine-1-yl-quinoline-3-carbonitrile (2ah). mp 171 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼1.68-1.79 (m, 6H), 3.67 (t, J¼4.8 Hz, 4H), 7.35 (t, J¼7.4 Hz, 1H); 7.65-7.77 (m, 3H), 8.32 (s, 1H); 13C NMR (75 MHz, CDCl3): d 24.6, 25.8, 50.2, 99.4, 117.9, 122.1, 124.4, 127.6, 127.7, 132.4, 146.1, 148.9, 158.7; IR (KBr): 2232 (CN), 3422 (NH). Anal. Calcd for C15H15N3: C, 75.92; H, 6.37; N, 17.71%. Found: C, 74.91; H, 6.37; N, 17.71%.

4.2.9. 2-Morpholine-4-yl-quinoline-3-carbonitrile (2ai). mp 81 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼3.71 (t, J¼4.5 Hz, 4H), 3.92 (t, J¼4.8 Hz, 4H), 7.41 (t, J¼6.9 Hz, 1H), 7.66--7.82 (m, 3H), 8.39 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼49.3, 66.9, 99.1, 117.7, 122.3, 125.2, 127.7, 127.8, 132.5, 146.3, 148.4, 157.9; IR (KBr): 2217 (CN). Anal. Calcd for C14H13N3O: C, 70.28; H, 5.48; N, 17.56%. Found: C, 70.21; H, 5.46; N, 17.58%.

4.2.10. 2-Benzylamino-6-methyl-quinoline-3-carbonitrile (2b). mp 1356 ^{0}C (decomp.); 1 H NMR (300 MHz, CDCl3): d¼2.44 (s, 3H), 4.82 (d, J¼5.7 Hz, 2H), 5.43 (s, 1H, D2O exchangeable), 7.27-7.43 (m, 5H), 7.53 (d, J¼9.3 Hz, 1H), 7.63-7.66 (m, 2H), 8.18 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼21.1, 45.6, 95.9, 116.3, 121.4, 126.5, 126.3, 127.7, 127.5, 128.5, 133.9, 135.4, 138.6, 143.5, 147.7, 153.9; IR (KBr): 2217 (CN), 3339 (NH). Anal. Calcd for C18H15N3: C, 79.10; H, 5.53; N, 15.37%. Found: C, 78.91; H, 5.42; N, 15.19%.

4.2.11. 2-Benzylamino-6-methoxy-quinoline-3-carbonitrile (2c). mp 122 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼3.88 (s, 3H), 4.78 (d, J¼5.4 Hz, 2H), 5.38 (s, 1H, D2O exchangeable), 6.92 (s, 1H), 7.24-7.42 (m, 6H), 7.65 (d, J¼9.3 Hz, 1H), 8.13 (s,1H); 13C NMR (75 MHz, CDCl3): d¼45.3, 55.4, 95.5,105.8,116.7, 121.8, 125.2, 127.3, 128.1, 128.2, 128.8, 138.6, 142.9, 145.`1, 152.9, 157.; IR (KBr): 2224 (CN), 3379 (NH). Anal. Calcd for C18H15N3O: C, 74.72; H, 5.23; N, 14.52%. Found: C, 74.66; H, 5.07; N, 14.49%.

4.2.12. 2-Benzylamino-7-methyl-quinoline-3-carbonitrile (2d). mp 121-124 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼2.48 (s, 3H), 4.82 (d, J¼5.4 Hz, 2H), 5.48 (br s, 1H, D2O exchangeable), 7.12 (d, J¼7.5 Hz,1H), 7.22-7.55 (m, 7H), 8.19 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼22.1, 45.1, 94.2, 116.8, 120.2, 125.8,126.5,127.8,127.9,127.4,128.5,138.9,143.3,143.3,149.5,153.8; IR (KBr): 2215 (CN), 3428 (NH). Anal. Calcd for C18H15N3: C, 79.10; H, 5.53; N, 15.37%. Found: C, 79.03; H, 5.48; N, 15.36%.

4.2.13. 2-Benzylamino-7-methoxy-quinoline-3-carbonitrile (2e). mp 121 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼3.92 (s, 3H), 4.72 (d, J¼5.4 Hz, 2H), 5.37 (br s, 1H, D2O exchangeable), 6.95 (s, 1H), 7.14 (s, 1H), 7.24-7.42 (m, 2H), 7.52-7.53 (m, 1H), 7.63 (d, J¼9.3 Hz, IH), 7.97 (d, J¼9.3 Hz, 1H), 8.17 (s, 1H), 8.46 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼42.6, 55.3, 97.3, 105.8, 112.2, 116.9, 117.7, 123.4, 126.8, 127.3, 128.1, 128.2, 138.2, 143.9, 148.7, 152.2; IR (KBr): 2217 (CN), 3391 (NH). Anal. Calcd for C18H15N3: C, 74.72; H, 5.23; N, 14.52%. Found: C, 74.71; H, 5.18; N, 14.43%.

4.2.14. 2-Benzylamino-8-methyl-quinoline-3-carbonitrile (2f). mp 122 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼2.61 (s, 3H), 4.82 (d, J¼5.7 Hz, 2H), 5.63 (br s, 1H, D2O exchangeable), 7.14 (t, J¼7.5 Hz,1H), 7.26-7.36 (m, 2H), 7.42-7.51(m, 5H), 8.21 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼17.1, 45.2, 95.1, 116.3, 121.1, 123.1, 125.2, 127.5, 127.8, 128.4, 132.7, 134.5, 138.2, 144.1, 148.2, 152.8; IR (KBr): 2221 (CN), 3452 (NH). Anal. Calcd for C18H15N3: C, 79.10; H, 5.53; N, 15.37%. Found: C, 78.98; H, 5.45; N, 15.18%.

4.2.15. 2-Benzylamino-8-ethyl-quinoline-3-carbonitrile (2g). mp 118-120 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼1.24 (t, J¼7.4 Hz, 3H), 3.05 (q, J¼7.6 Hz, 2H), 4.86 (d, J¼5.6 Hz, 1H), 5.67 (s, 1H, D2O exchangeable), 7.17-7.37 (m, 3H), 7.47-7.57 (m, 5H), 8.24 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼14.4, 24.6, 45.7, 95.4, 116.9, 121.4, 123.4, 125.5, 127.6, 127.4, 128.5, 131.6, 138.7, 140.5, 144.3, 147.8, 152.9; IR (KBr): 2225 (CN), 3445 (NH). Anal. Calcd for C19H17N3: C, 79.41; H, 5.96; N, 14.62%. Found: C, 79.35; H, 5.55; N, 14.64%.

4.2.16. 2-Benzylamino-6-bromoquinoline-3-carbonitrile (2h). mp: 161 ^{0}C (decomp.); 1 H NMR (300 MHz, CDCl3): d¼4.81 (d, J¼5.4 Hz, 2H), 5.52 (br s, 1H, D2O exchangeable), 7.32-7.42 (m, 3H), 7.52-7.74 (m, 5H), 8.24 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼45.5, 95.5, 116.4, 119.6, 124.3, 127.4, 128.5, 128.6, 128.7, 128.8, 131.6, 138.5, 143.7, 149.9, 154.2; IR (KBr): 2217 (CN), 3372 (NH). Anal. Calcd for C17H12BrN3: C, 60.37; H, 3.58; N, 12.43%. Found: C, 60.31; H, 3.58; N, 12.41%.

4.2.17. 2-Benzylamino-7-chloroquinoline-3-carbonitrile (2i). mp: 141 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼4.81 (d, J¼5.4 Hz, 2H), 5.51 (br s, 1H, D2O exchangeable), 7.21-7.41 (m, 4H), 7.49-7.63 (m, 4H), 8.21 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼43.8, 94.1, 116.7, 119.2, 125.3, 126.3, 127.2, 128.3, 138.3, 143.7, 143.3, 149.5, 153.8; IR (KBr): 2211 (CN), 3391 (NH). Anal. Calcd for C17H12ClN3: C, 69.51; H, 4.12; N, 14.30%. Found: C, 69.51; H, 4.12; N, 14.25%.

4.2.18. 2-Benzylamino-5-phenyl-pyridine-3-carbonitrile (4a). mp: 131 ^{0}C (decomp.); 1 H NMR (300 MHz, CDCl3): d¼4.72 (d, J¼5.4 Hz, 2H), 5.52 (br s, 1H, D2O exchangeable), 7.32-7.34 (m, 4H), 7.43-7.45 (m, 4H), 7.88 (s, 1H), 8.56 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼40.4, 45.5, 91.5, 116.7,

126.4, 127.4, 128.9, 129.4, 136.8, 138.1, 139.3, 142.2, 150.1, 151.3, 157.1; IR (KBr): 2212 (CN), 3362 (NH). Anal. Calcd for C19H15N3: C, 79.98; H, 5.30; N, 14.73%. Found: C, 79.91; H, 5.29; N, 14.71%.

4.2.19. 2-Methylamino-5-phenyl-pyridine-3-carbonitrile (4b). mp: 119 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼ 3.12 (d, J¼4.8 Hz, 3H), 5.22 (br s,1H, D2O exchangeable), 7.43-7.45 (m, 5H), 7.85 (s, 1H), 8.56 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼41.6, 91.7, 117.6, 125.8, 125.7, 126.5, 127.4, 129.4, 136.5, 139.3, 151.4, 157.7; IR (KBr): 2219 (CN), 3362 (NH). Anal. Calcd for C13H11N3: C, 74.62; H, 5.30; N, 20.08%. Found: C, 74.62; H, 5.18; N, 19.94%.

4.2.20. 2-Butylamino-5-phenyl-pyridine-3-carbonitrile (4c). mp: 83 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼0.94-1.03 (m, 3H), 1.43-1.44 (m, 2H), 1.64-1.66 (m, 2H), 3.53-3.59 (m, 2H), 5.19 (br s, 1H, D2O exchangeable), 7.33-7.43 (m, 5H), 7.83 (s,1H), 8.53 (s,1H); 13C NMR (75 MHz, CDCl3): d¼13.3, 20.4, 31.4, 41.5, 91.5, 116.5, 125.6, 126.6, 127.3, 129.3, 136.3, 139.8, 151.3, 157.9; IR (KBr): 2217 (CN), 3361 (NH). Anal. Calcd for C16H17N3: C, 76.46; H, 6.82; N, 16.72%. Found: C, 76.40; H, 6.79; N, 16.58%.

4.2.21. 2-Dimethylamino-5-phenyl-pyridine-3-carbonitrile (4d). mp: 122 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼3.32 (s, 6H), 7.32-7.48 (m, 5H), 7.94 (s, 1H), 8.54 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼40.5, 90.6, 119.5, 125.4, 126.4, 127.4, 129.3, 136.4, 142.4, 150.4, 158.8; IR (KBr): 2214 (CN), 336 (NH). Anal. Calcd for C14H13N3: C, 75.31; H, 5.87; N, 18.82%. Found: C, 75.12; H, 5.81; N, 18.72%.

4.2.22. 2-Morpholin-4-yl-5-phenyl-pyridine-3-carbonitrile (4e) mp: 108 ^{0}C; 1 H NMR (300 MHz, CDCl3): d¼3.79 (d, J¼4.5 Hz, 4H), 3.88 (d, J¼4.8 Hz, 4H), 7.41-7.46 (m, 5H), 7.97 (s, 1H), 8.52 (s, 1H); 13C NMR (75 MHz, CDCl3): d¼48.9, 66.2, 94.2, 117.1, 126.1, 127.6, 127.8, 129.3, 135.7, 141.8, 150.2, 159.2; IR (KBr): 2222 (CN), 3361 (NH). Anal. Calcd for C16H15N3O: C, 72.43; H, 5.70; N, 15.84%. Found: C, 72.31; H, 5.69; N, 15.79%.

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