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A NEW AND CONVENIENT SYNTHETIC METHOD FOR 4-AMINOQUINOLINE-3-CARBONITRILE AND ITS DERIVATIVES

Amer H. Tarawneh*

Department of Chemistry, Tafila Technical University, P.O. Box 179, Tafila, Jordan, E-mail: amer.tarawneh@ttu.edu.jo

Abstract – A convenient approach is described for the general synthesis of 4-aminoquinoline-3-carbonitrile scaffolds. A series of substituted anthranilonitriles bearing electron-donating and-withdrawing groups on the arene react with 3-bromopropanenitrile and *t*-BuOK in anhydrous DMF at ca. 24 °C. A wide variety of bases have been used to optimize selective mono-*N*-alkylation. The best conditions lead to the corresponding 2-(cyanoethylamino)benzonitriles in moderate or good yields. Thorpe–Ziegler cyclization of the *N*-unprotected 2-(cyanoethylamino)benzonitrile analogs with *t*-BuLi in THF at -78 °C gives 4-amino, 4-amino-6-methyl, 4-amino-7-methyl, and 4-amino-6-fluoro-quinoline-3-carbonitriles in moderate yields. Owing to their vicinal amino and cyano functional groups that can function as enaminonitrile moieties, 4-aminoquinoline-3-carbonitriles are attractive building blocks frequently used in ring construction.

INTRODUCTION

Quinoline is the parent compound of a huge family of naturally occurring and/or biologically active heterocycles. Recently, the quinolone scaffold has attracted enormous attention from chemists as well as biologists due to its use in medicinal chemistry and as part of many drugs and bioactive substances.[1,2] Hydroxychloroquine is utilized to treat or prevent malaria;[3] moxifloxacin is used to treat a number of bacterial infections including acute bacterial sinusitis, urinary tract infections, and chronic prostatitis,[4] cryptolepine and camptothecin act as anticancer agents;[5,6] tacrine has been shown to act as a potent acetylcholinesterase inhibitor and as a result has been approved for the treatment of Alzheimer's disease marketed under the trade name Cognex (Figure.1).[7] Many of these bioactive compounds such as hydroxychloroquine, levofloxacin, moxifloxacin, cryptolepine, camptothecin, and tacrine are polynuclear heterocyclic compounds (PHCs). Not surprisingly, suitably substituted quinolines that can function as

starting materials for accessing PHCs are important in the search for new small molecule drugs.[8-15]

Owing to their vicinal amino and cyano functional groups that can function as enaminonitrile moieties, substituted 4-aminoquinoline-3-carbonitriles are attractive building blocks (or synthetic scaffolds). Because enaminonitriles are frequently used in ring construction,[16-18] their presence strongly suggests that 4-aminoquinoline-3-carbonitriles could be used to build larger polycyclic systems (PHCs).

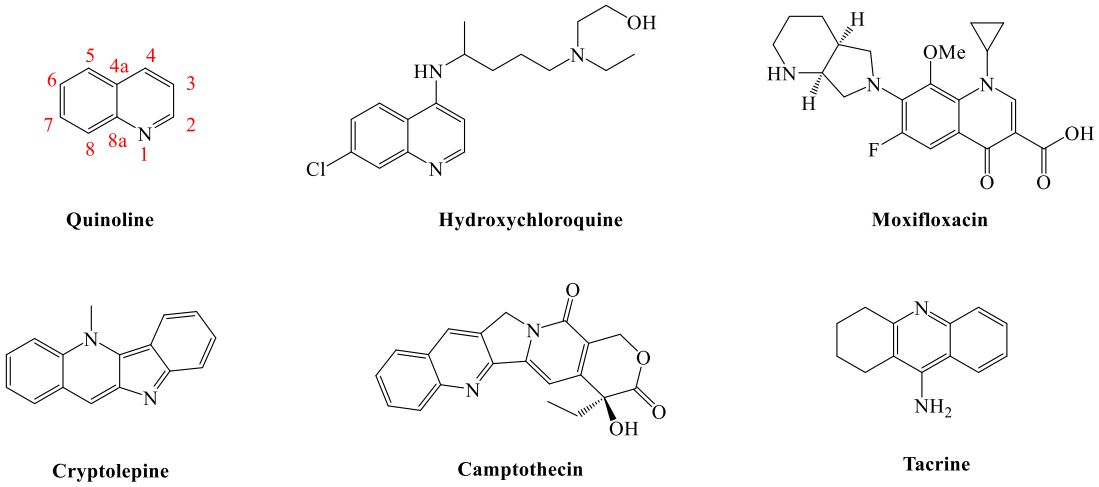


Figure 1. Quinoline with IUPAC numbering indicated in RED and some bioactive quinoline containing compounds

In recent decades, very little research has been conducted focusing on 4-aminoquinoline-3-carbonitriles besides research efforts that led to the synthesis of the corresponding 2-(trifluoromethyl)quinoline derivatives and quinolines via the intramolecular Friedel-Crafts reaction.[19-22] Worthy of note is that significantly more cyclization chemistry has been described for the isomeric 2-aminoquinoline-3-carbonitriles,[16,17] which has led to a number of patented biologically active compounds.[23,24]

We recently developed a new route to 4-aminoquinoline-3-carbonitriles starting by cyanoethylation of 2-aminobenzonitrile to afford 2-((2-cyanoethyl)amino)benzonitrile, which can then be cyclized via base-assisted Thorpe-Ziegler cyclization to finally yield 4-aminoquinoline-3-carbonitriles. In present work, we decided to investigate whether this method could be employed for the synthesis of 4-aminoquinoline-3-carbonitriles with varying substituents on the arene moiety.

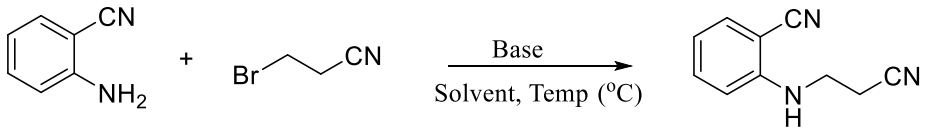
RESULTS AND DI SCUSSION

CYANOETHYLATION:

Our initial attempt at direct cyanoethylation of anthranilonitrile **1a** began by investigating the effects of different organic and inorganic bases for efficient mono-*N*-alkylation conditions (Table 1). First, we

applied a highly chemoselective *N*-alkylation method to the primary amine by using deep eutectic solvent (DES).[24,25] Probing mixtures of choline chloride with urea produces eutectics (DES) and results in high chemoselectivity with poor conversion (Table 1, entry 1). Increasing the reaction temperature slightly improved the yield of coupling (Table 1, entry 2). In our trial to improve the performance of the DES condition, the reaction was conducted with added alkali base (entries 7 & 8), but unfortunately there was no enhancement of yield. Recently, utilizing cesium carbonate and cesium hydroxide was reported to be the most effective method in improving chemoselectivity in mono-*N*-alkylation.[26-28] A similar result to that with DES was obtained when the reaction was carried out in the presence of an equivalent of these bases (entries 3 & 4). Of the various alkali hydroxides tested, potassium *tert*-butoxide was the most successful base (Table 1, entry 10), producing the greatest yield of mono-*N*-alkylation. When other bases were used, the formation of **3a** was diminished (entries 5 & 6).

Table 1. Optimization of the reaction conditions for the synthesis of secondary *N*-arylamine **3a**



1a **2** **3a**

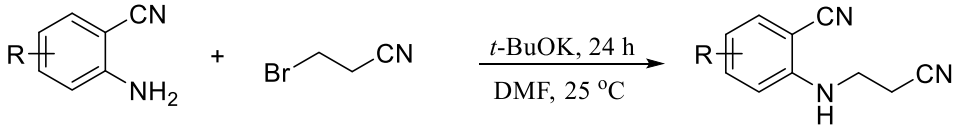
Entry	Base	Solvent	Time [h]	Temp [°C]	Yield [%][a]
1	DES		70	rt	12
2	DES		70	60	14
3	CsOH, H_2O	DMF, 4Å MS	24	rt	24
4	Cs_2CO_3	DMF	24	rt	10
5	K_2CO_3	DMF	24	rt	n.p[b]
6	NaOH	DMF	24	rt	n.p[b]
7	DES, NaOH		24	rt	22
8	DES, Cs_2CO_3		24	rt	18
9	$BmimPF_6$	DMF	24	rt	n.p[b]
10	*t*-BuOK	DMF	6	rt	75

[a] Based on the isolated product after silica gel chromatography. [b] n.p: no product is shown by TLC

As delineated in Table 2, mono-*N*-alkylaminobenzonitrile **3a** was produced with good yield using 2 equivalents of 2-aminobenzonitrile **1a**, 1.2 equivalent of 3-bromopropanenitrile 2, potassium *tert*-butoxide, anhydrous *N*,*N*-dimethylformamide (DMF) as solvent and a 24 h reaction time (Table 2, entry 1). This condition for *N*-alkylation was applied to aminobenzonitriles **1a-g** bearing

electron-donating or -withdrawing groups at the 4 or 5 positions to provide the corresponding C4 or C5-substituted 2-(2-cyanoethylamino)benzonitrile **3a-g** in moderate to good yields (entries 2–9).

Table 2. Mono-*N*-alkylation of anthranilonitriles with alkyl halides **2**. [a] Reaction conditions: **1a-g** (2 equiv.), **2** (1.2 equiv.), *t*-BuOK (1.2 equiv.), DMF (4.0 mL). [b] The ^{1}H NMR analysis of the crude reaction indicated no formation of the tertiary amine.



1a-g **2** **3a-g**

Entry	R		Yield [%]
1	H	**3a**	75
2	4-Me	**3b**	70
3	5-Me	**3c**	67
4	4-Cl	**3d**	60
5	5-Cl	**3e**	62
6	5-F	**3f**	64
7	5-Br	**3g**	65

Molecular electrostatic potential (MEP) maps have been constructed using DFT calculation for all optimized geometries. The MEP is a plot of calculated electrostatic potentials mapped onto an electron density surface. Since MEP surfaces provide charge distributions of molecules, they can be very useful in predicting reactivity sites of electrophilic or nucleophilic attacks. Additionally, they can illustrate the size and shape of molecules and how they interact and influence each other. Figure 2 depicts the colored electrostatic potential maps corresponding to the contour of 0.002 a.u. isodensity surface, along with a color scale showing the positive (blue), negative (red) and near-zero (green) electrostatic potentials. An electron-rich nucleophile baring negative potential will be attracted to electrophiles enclosed by regions of positive potential. In Rxn.1, the region with the most negative potential is mainly located around the NH_2 group of aniline (-155.8 KJ/mol) with a calculated exposed area of 7.619 Å2, while the region with the least negative potential is located around the CH_2- moiety in 2-bromoacetonitrile (+178.9 KJ/mol) with an exposed area of 13.412 Å2. The CN group in *o*-cyanoaniline (rxn.2), however, has a dual effect on the reactivity of the NH_2 group; electronically reducing the electrostatic potential to -111.4 KJ/mol and sterically decreasing the exposed area to 7.225 Å2. Additionally, the calculated electrostatic potential value for the CH_2- moiety in 3-bromopropanenitrile is +134.8 KJ/mol with a considerably reduced exposed area of 10.573 Å2.

These findings clearly imply that the NH_2 group in aniline is more favored to undergo nucleophilic

substitution reaction than in *o*-cyanoaniline. Furthermore, we can conclude that the reactive site in 2-bromoacetonitrile is more prone to nucleophilic attack than in 3-bromopropanenitrile. These finding explain the high yield of mono-*N*-alkylation as illustrated in Table 2.

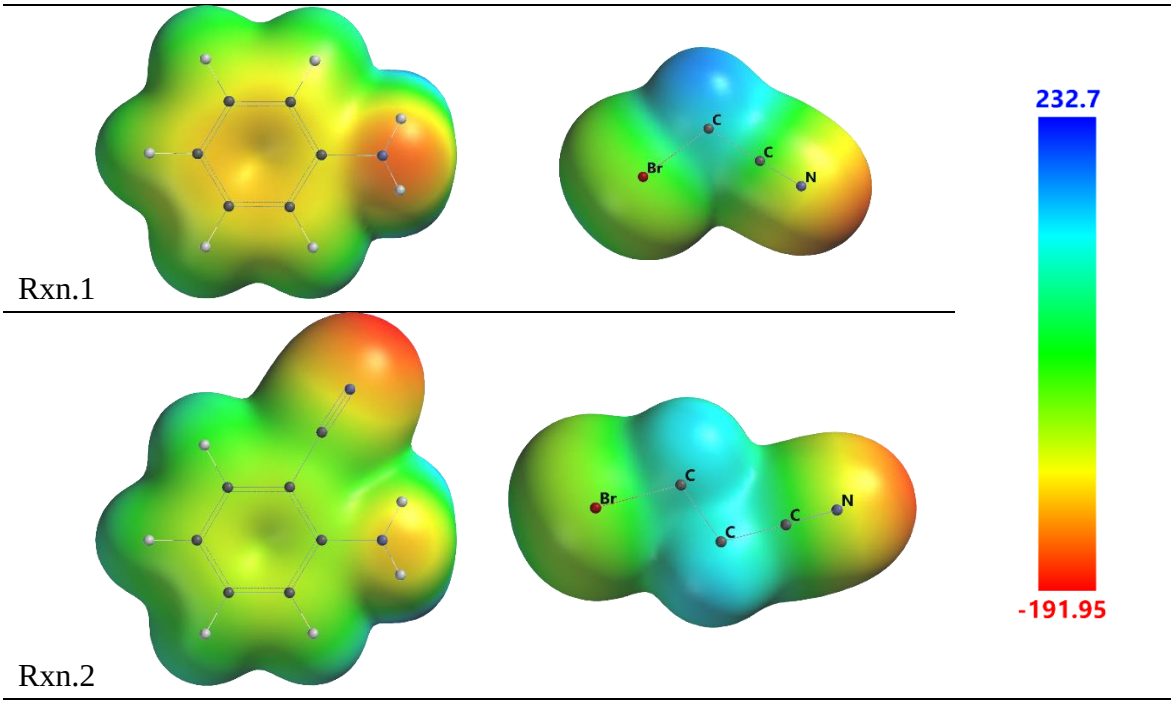


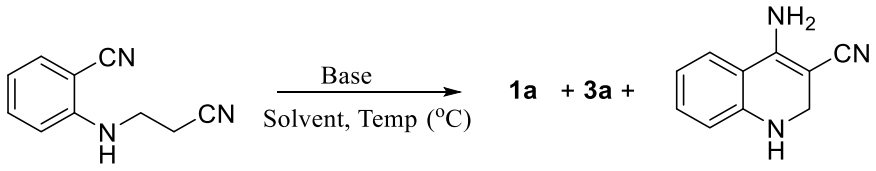
Figure 2. Electrostatic potential maps for species involved in mono-*N*-alkylation reactions

THORPE-ZIEGLER CYCLIZATION:

Thorpe-Ziegler dinitrile cyclization is one of the first powerful methods of generating 5- to 33-membered rings.[29] Intramolecular dinitrile cyclization provides a rapid route to generate a 6-member ring, often occurring during the formation of the dinitrile precursor.[30,31] Mechanistically, exposure of a dinitrile to a base generates an intermediate nitrile-substituted carbanion that attacks the neutral nitrile to generate medium-sized rings.[30,31] Our attempt to optimize the conditions for the cyclization of 2-(2-cyanoethylamino)benzonitriles **3a-g** into 4-amino-1,2-dihydroquinoline-3-carbonitriles using a variety of bases (2 equiv K_2CO_3, Cs_2CO_3, NaOH, *t*-BuOK, KH, and NaH) in THF at room temperature gave no reaction. Additionally, attempts at ring closure using K_2CO_3 (1 equiv) in EtOH at 140 °C (autoclave) for 1 h only gave recovery of the starting materials, while *t*-BuOK (1 equiv) in EtOH at 140 °C led to *N*-dealkylation (Table 3, entry 10). The ring closure of 2-(2-cyanoethylamino)benzonitriles **3a**, **3b** and **3c** to afford 4-amino-1,2-dihydroquinoline-3-carbonitrile **4a-c** worked well in THF and with organolithium reagents (entries 11-13). After isolation of product **4a**, it was rapidly oxidized by air to the quinoline form **5a**. This phenomenon has been reported in many previous studies.[32,33] Upon further optimization, it was found that the reaction mixture could be diluted with DCM to afford the

aromatized/oxidized subsequent product **5a** in an 60% isolated yield over two steps.

Table 3. Optimization of the reaction conditions of Thorpe-Ziegler cyclization



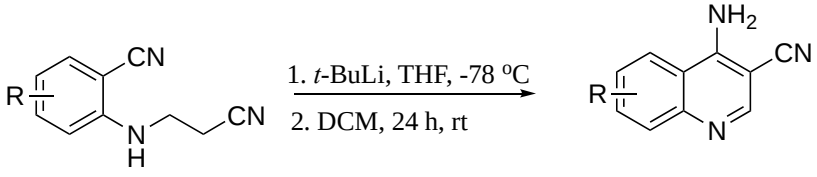
3a **4a**

Entry	Base	Solvent	Temp	Observed		
				1a	**3a**	**4a**
1	K_2CO_3	THF	rt	+[a]	+[b]	-
2	*t*-BuOK	THF	rt	-	+	-
3	NaOH	THF	rt	-	+	-
4	Cs_2CO_3	THF	rt	-	+	-
5	NaH	THF	rt	-	+	-
6	KH	THF	rt	-	+	-
7	K_2CO_3	EtOH	60	-	+	-
8	K_2CO_3	EtOH	140	-	+	-
9	*t*-BuOK	EtOH	60	-	+	-
10	*t*-BuOK	EtOH	140	+	-	-
11	*n*-BuLi	THF	-78	-	-	+
12	*s*-BuLi	THF	-78	-	-	+
13	*t*-BuLi	THF	-78	-	-	+

[a] + detected, [b] - not detected

Thorpe–Ziegler cyclization of the *N*-unprotected 2-(2-cyanoethylamino)benzonitriles **3a**-**c** and **3f** with *t*-BuLi in THF at -78 °C gives 4-amino, 4-amino-7-methyl, 4-amino-6-methyl, and 4-amino-6-fluoro-quinoline-3-carbonitriles **5a**–**c** and **5f** in moderate yields (Table 4). However, **3d**, **3e** and **3g** failed to afford the quinoline product under these conditions.

Table 4. Reaction conditions and percent yield for Thorpe–Ziegler cyclization of the *N*-unprotected 2-(2-cyanoethylamino)benzonitriles



3a-c,f **5a-c,f**

Entry	R(**3a-c**,**f**)		Yield [%]
1	H	**5a**	80

2	4-Me	**5b**	75
3	5-Me	**5c**	76
4	5-F	**5f**	72

CONCLUSION

A new transformation of anthranilonitriles into 4-aminoquinoline-3-carbonitrile has been discovered. 4-Aminoquinoline-3-carbonitrile supporting different substituents on the arene were prepared from anthranilonitriles via the *N*-unprotected Thorpe–Ziegler cyclisation of the 2-(2-cyanoethylamino)benzonitriles **3a**–**c**,**f** in two steps in best overall yields of 60, 53, 51 and 46%, respectively.

EXPERIMENTAL

General information: All chemicals used in this presented work were purchased from Sigma-Aldrich and were used as received. Thin-layer chromatography plates (Macherey-Nagel GmbH POLYGRAM SIL G/UV254, 40×80 mm, 0.20 mm silica gel 60). Ultra Violet Fluorescence Analysis Cabinet was used to visualize the colorless spots. Melting points (uncorrected) were determined on the Electrothermal IA6304 Melting Point apparatus in open capillary tubes.^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance NEO 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C). All experiments were carried out at room temperature (25 °C), if not noted otherwise. Spectra were plotted with MestReNova V.6.0.2. Quantitative elemental analyses were performed on Vario Micro Tube (Elementar Analysensysteme GmbH Hanau).

General Procedure for the *t*-BuOK-Promoted Synthesis of *N*-Alkylanthranilonitrile 3a–g. A mixture of *t*-BuOK (1.0 equiv.) and corresponding anthranilonitrile **1a-g** (2.0 equiv.) in anhydrous DMF (4.0 mL) was stirred at 25 °C for 30 min. To this white suspension was added the alkyl halide **2** (1.0 equiv.) in one portion, and the resulting reaction mixture was stirred for 24 h. Then, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The crude mixture was diluted with EtOAc (25 mL). The organic layer was separated and rinsed with H_2O (3 × 10.0 mL). The organic layer was washed with brine (2 × 10.0 mL), dried with anhydrous sodium sulfate, filtered and concentrated under vacuum to give the crude product. Column chromatography on silica gel of this material afforded pure 2-(cyanoethylamino)benzonitrile **3a**–**g**.

Preparation of 2-((cyanoethyl)amino)benzonitrile 3a: 266 mg (2.3 mmol) of **1a**, 154 mg (1.15 mmol, 95 µL) of 3-bromopropanenitrile, 130 mg (1.15 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF were mixed and stirred for 24 h. Silica gel, hexane/EtOAc (8:2) to get 146 mg (75%) of white solid. Rf = 0.18 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 1H), 6.76 (td, *J* = 7.7, 0.7 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 3.63 (dd, *J* = 8.3, 5.5 Hz, 1H), 2.68 (t, *J* = 6.9 Hz, 1H). ^{13}C

NMR (151 MHz, $CDCl_3$) δ 148.82, 134.58, 133.35, 117.97, 117.67, 117.54, 110.46, 96.92, 39.30, 18.18. Anal. Calcd. for $C_{10}H_9N_3$ (171.20): C 70.16; H 5.30; N 24.54; found: C 70.66; H 5.38, N 24.42.

Preparation of 2-((2-cyanoethyl)amino)-4-methylbenzonitrile 3b: 200 mg (1.5 mmol) of **1b**, 100 mg (0.75 mmol, 63 µL) of 3-bromopropanenitrile, 85 mg (0.75 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF were mixed and stirred for 24 h. Silica gel, hexane/EtOAc (8:2) to get 97 mg (70%) of white solid. Rf = 0.26 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 6.48 (s, 1H), 3.63 (t, *J* = 7.0 Hz, 1H), 2.68 (t, *J* = 7.0 Hz, 1H), 2.35 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.71, 145.75, 133.13, 119.37, 117.80, 117.56, 111.01, 94.30, 39.38, 22.53, 18.27. HRMS (cation) *m/z* calcd. for $[M+Na]^+$ 208.0845. Found 208.0844.

Preparation of 2-((2-cyanoethyl)amino)-5-methylbenzonitrile 3c: 200 mg (1.5 mmol) of **1c**, 100 mg (0.75 mmol, 63 µL) of 3-bromopropanenitrile, 85 mg (0.75 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF for were mixed and stirred 24 h. Silica gel, hexane/EtOAc (8:2) to get 91.8 mg (67%) of white solid. Rf = 0.28 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.26 – 7.24 (m, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 3.61 (t, *J* = 6.9 Hz, 1H), 2.66 (t, *J* = 6.9 Hz, 1H), 2.24 (s, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ 146.76, 146.73, 135.49, 133.11, 127.59, 127.57, 117.71, 117.67, 110.76, 96.90, 39.56, 20.06, 18.25. Anal. Calcd for $C_{11}H_{11}N_3$ (185.23): C 71.33; H 5.99; N 22.69. Found: C 71.81; H 6.03, N 22.69.

Preparation of 4-chloro-2-((2-cyanoethyl)amino)benzonitrile 3d: 200 mg (1.3 mmol) of **1d**, 87 mg (0.65 mmol, 55 µL) of 3-bromopropanenitrile, 75 mg (0.65 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF for were mixed and stirred 24 h. Silica gel, hexane/EtOAc (8:2) to get 81.3 mg (60%) of light brown solid. Rf = 0.35 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 1.4 Hz, 1H), 6.72 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.67 (t, *J* = 5.9 Hz, 1H), 3.50 (q, *J* = 6.5 Hz, 1H), 2.77 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 150.77, 139.87, 135.01, 119.32, 117.22, 116.56, 111.02, 93.77, 38.26. Anal. Calcd for $C_{10}H_8ClN_3$ (205.64): C 58.41; H 3.92; N 20.43. Found: C 58.64; H 3.93, N 20.33.

Preparation of 5-chloro-2-((2-cyanoethyl)amino)benzonitrile 3e: 200 mg (1.3 mmol) of **1e**, 87 mg (0.65 mmol, 55 µL) of 3-bromopropanenitrile, 75 mg (0.65 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF were mixed and stirred for 24 h. Silica gel, hexane/EtOAc (8:2) to get 83.5 mg (62%) of light brown solid. Rf = 0.35 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 4.5, 2.4 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 6.65 (t, *J* = 6.6 Hz, 1H), 3.62 (t, *J* = 6.8 Hz, 1H), 2.68 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.48, 134.78, 132.41, 122.70, 117.34, 116.24, 111.86, 98.12, 39.53, 18.28. Anal. Calcd for $C_{10}H_8ClN_3$ (205.64): C 58.41; H 3.92; N 20.43. Found: C 58.57; H 3.98, N 20.10.

Preparation of 2-((2-cyanoethyl)amino)-5-fluorobenzonitrile 3f: 200 mg (1.47 mmol) of **1f**, 1.408 g (0.73 mmol, 62 µL) of 3-bromopropanenitrile, 82 mg (0.73 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF were mixed and stirred for 24 h. Silica gel, hexane/EtOAc (8:2) to get 88.3 mg (64%) of light brown solid. Rf = 0.30 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (ddd, *J* = 9.1, 7.9, 3.0 Hz, 1H), 7.16 (dd, *J* = 7.7, 3.0 Hz, 1H), 6.66 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.61 (t, *J* = 6.8 Hz, 1H), 2.68 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.31, 153.72, 145.76, 122.44, 122.29, 119.21, 119.05, 117.48, 116.40, 116.39, 112.02, 111.97, 97.20, 97.14, 39.84, 18.33. HRMS (cation) *m/z* calcd. for $[M+Na]^+$ 212.0594. Found 212.0597

Preparation of 5-bromo-2-((2-cyanoethyl)amino)benzonitrile 3g: 200 mg (1.0 mmol) of **1g**, 67 mg (0.50 mmol, 42 µL) of 3-bromopropanenitrile, 56 mg (0.50 mmol) of potassium *tert*-butoxide and 4.0 mL of anhydrous DMF for were mixed and stirred 24 h. Silica gel, hexane/EtOAc (8:2) to get 81.5 mg (65%) of brown solid. Rf = 0.35 hexane/EtOAc (8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 8.9, 2.2 Hz, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 3.61 (t, *J* = 6.8 Hz, 1H), 2.68 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.92, 137.51, 135.22, 117.44, 116.18, 112.18, 108.92, 98.52, 39.39, 18.20. Anal. Calcd for $C_{10}H_8BrN_3$ (250.10): C 48.02; H 3.22; N 16.80. Found: C 48.39; H 3,32, N 16.71.

General Procedure for the Thorpe-Ziegler Cyclization 5a-d. 2-(Cyanoethylamino)benzonitrile (**3a**) (240 mg, 1.40 mmol) in anhydrous THF (6 mL) under nitrogen was cooled to -78 °C while stirring. *tert*-Butyllithium (1.6 M solution in pentane, 1.75 mL, 2.8 mmol) was added dropwise via syringe and the reaction left to stir and warm up to room temperature over 8 h. Sat. aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The organic layer was separated and dried and the solvent was evaporated in vacuum. Dilution in 3 mL CH_2Cl_2 (DCM) yielded 24 h later a white precipitate characterized as the title compound **5a** (191 mg, 80% yield).

Preparation of 4-aminoquinoline-3-carbonitrile 5a: 240 mg (1.4 mmol) **3a**, 1.75 mL (2.6 mmol) *t*-BuLi in 6 mL anhydrous THF were mixed and stirred at -78 °C and allowed to warm up to room temperature during an 8 h period. After quenching the reaction mixture and work up as descripted above, the reaction was diluted in 5 mL DCM and left over night to obtain **5a**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.78 – 7.74 (m, 1H), 7.55 – 7.51 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.77, 151.42, 148.51, 131.86, 129.27, 125.74, 122.95, 117.66, 116.96, 84.63. Anal. Calcd for $C_{10}H_7N_3$ (169.19): C 70.99; H 4.17; N 24.84. Found: C 71.23; H 4.58, N 25.33.

Preparation of 4-amino-7-methylquinoline-3-carbonitrile 5b: 240 mg (1.3 mmol) **3b**, 1.63 mL (2.6 mmol) *t*-BuLi in 6 mL anhydrous THF were mixed and stirred at -78 °C and allowed to warm up to room temperature during an 8 h period. After quenching the reaction mixture and work up as descripted above, the reaction was diluted in 5 mL DCM and left over night to obtain **5b**. ^{1}H NMR (600 MHz, DMS-d_6) δ 8.46 (s, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.61 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 2.47 (s, 1H). ^{13}C NMR (151

MHz, DMSO-d_6) δ 151.23, 128.20, 127.32, 122.51, 20.94. HRMS (cation) *m/z* calcd. for $[M+H]^+$ 184.0869. Found 184.0867.

Preparation of 4-amino-6-methylquinoline-3-carbonitrile 5c: 240 mg (1.3 mmol) **3c**, 1.63 mL (2.6 mmol) *t*-BuLi in 6 mL anhydrous THF were mixed and stirred at -78 °C and allowed to warm up to room temperature during an 8 h period. After quenching the reaction mixture and work up as descripted above, the reaction was diluted in 5 mL DCM and left over night to obtain **5c**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.18 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.7 Hz, 1H), 2.46 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.30, 150.50, 146.88, 135.31, 133.59, 129.05, 121.97, 117.75, 116.76, 84.54, 21.16. Anal. Calcd for $C_{11}H_9N_3$ (183.21): C 72.11; H 4.95; N 22.94. Found: C 71.81; H 5.04, N 22.54.

Preparation of 4-amino-6-fluoroquinoline-3-carbonitrile 5f: 240 mg (1.3 mmol) **3f**, 1.63 mL (2.6 mmol) *t*-BuLi in 6 mL anhydrous THF were mixed and stirred at -78 °C and allowed to warm up to room temperature during an 8 h period. After quenching the reaction mixture and work up as descripted above, the reaction was diluted in 5 mL DCM and left over night to obtain **5f**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.30 – 8.25 (m, 1H), 7.94 (d, *J* = 8.3 Hz, 3H), 7.73 (dd, *J* = 11.7, 5.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 160.24, 158.62, 154.39, 150.93, 145.70, 132.15, 132.09, 121.31, 121.14, 117.70, 117.64, 117.43, 107.44, 107.28, 84.94. HRMS (cation) *m/z* calcd. for $[M+H]^+$ 188.0619. Found 188.0620.

Preparation of 4-amino-1,2-dihydroquinoline-3-carbonitrile 4a: 240 mg (1.4 mmol) **3a**, 1.75 mL (2.6 mmol) *t*-BuLi in 6 mL anhydrous THF were mixed and stirred at -78 °C and allowed to warm up to room temperature during an 8 h period. After quenching the reaction mixture and work up as described above. Silica gel, DCM/EtOAc (85:15) to get 25 mg (10%) of light brown solid. Rf = 0.35 hexane/EtOAc (8:2). Since most of the cyclized products with a 1,4-dihydroquinoline moiety were relatively unstable and gradually decomposed during isolation, the very low yield was obtained. The issue was well reported.[30,31] ^{1}H NMR (600 MHz, CD_3CN) δ 7.26 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.14 – 7.09 (m, 1H), 6.69 – 6.64 (m, 1H), 6.60 (dd, *J* = 8.1, 0.8 Hz, 1H), 3.90 (s, 2H). ^{13}C NMR (151 MHz, CD_3CN) δ 152.41, 149.01, 132.52, 123.98, 120.17, 116.01, 115.42, 41.81.

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