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Preparation of Trifluoromethylated (Arylaminomethylene)malononitriles Suitable for Synthesis of 4-Amino-2-(trifluoromethyl) quinoline Derivatives by Intramolecular Friedel–Crafts Reaction

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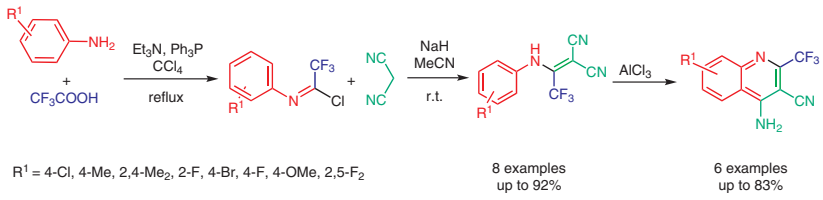

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Abstract An approach for the synthesis of 4-amino-2-(trifluoromethyl)quinolines via the intramolecular Friedel–Crafts reaction of 2-(1-(arylamino)-2,2,2-trifluoroethylidene)malononitrile derivatives is reported. This simple protocol provides a wide variety of 4-amino-2-(trifluoromethyl)quinolines in good to excellent yields, without any purification. Furthermore, the 2-(1-(arylamino)-2,2,2-trifluoroethylidene) malononitrile derivatives used in this project have been synthesized by the reaction of *N*-aryl-2,2,2-trifluoroacetimidoyl chlorides and malononitrile at ambient temperature and under microwave irradiation in excellent yields, for the first time.

Key words 4-amino-2-(trifluoromethyl)quinolones, intramolecular Friedel–Crafts reaction, trifluoromethylated (arylaminomethylene)malononitriles, trifluoroacetimidoyl chlorides, trifluoromethylated compounds

Quinolines are one of the most important classes of organic compounds for chemists, as well as biologists, because they are potent, broad-spectrum antibacterial agents and have a favorable pharmacokinetic profile.[1] Quinoline derivatives have been found useful in diverse applications including pharmaceuticals and are available as drugs today. For example, they are used as antimalarial drugs (quinine, quinidine, chloroquine, mefloquine, amodiaquine, primaquine).[2,3]

Ciprofloxacin, levofloxacin, gatifloxacin, and norfloxacin are some known fluoroquinolone antibiotic drugs that have been successfully synthesized and widely used in the clinic. Due to its steric and electronic properties, fluorine can alter the physical and chemical properties of molecules, such as bioavailability, lipophilicity, and metabolic stability, which play a crucial role in drugs, functional materials, and reagents.[4] In order to synthesize compounds with applications in agrochemistry, the pharmaceutical industry, and materials science,[5,6] the direct incorporation of a polyfluoroalkyl group, especially trifluoromethyl moieties, into organic molecules is very important. The progress in the field of fluorination of organic compounds has been summarized in numerous review articles.[7]

The most widely applicable routes for the direct introduction of a trifluoromethyl group can be mainly divided into two categories: one involves C–F bond formation via substitution of a functional group by fluoride, such as the Swarts reaction.[8] The scope of the Swarts reaction is limited to robust functional groups due to the harsh reaction conditions. The second category involves C–C bond formation using commercially available trifluoromethyl-substituted compounds.[9] This category can be further divided into three classes, namely radical, electrophilic, and nucleophilic trifluoromethylations, that have been summarized in many review articles.[6b,10] The synthesis of the required reagents also involves the use of highly expensive iodide precursors. Furthermore, nucleophilic trifluoromethylation reactions still suffer from the limited availability of inexpensive and low-molecular-weight trifluoromethyl sources.

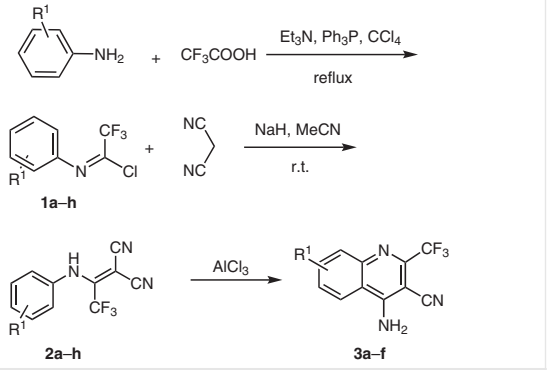
Still, the development of efficient methods for the late-stage trifluoromethylation of organic molecules is of high interest for synthetic and large-scale industrial applications. For example, the use of trifluoroacetic acid and its anhydride (TFAA) in trifluoromethylation reactions was recently reported.[11] Also, in recent times, diverse methods for the preparation of fluoroalkylated heterocycles, based on exploration of fluorinated 1,3-dipoles such as nitrones,[12a] nitrile imines,[12b] and nitrile oxides,[12c] have been reported.

In addition to the above-mentioned methods, commercially available, trifluoromethyl-containing starting materials can be used for the synthesis of trifluoromethylated compounds. They should contain potential functional groups usable for further reactions in order to achieve molecular modification. On this basis, trifluoroacetimidoyl chlorides are unique reagents for the synthesis of trifluoro-

methylated compounds due to following advantages: easy synthesis with high yields, relatively stable upon storage, and containing highly potential functional groups.[13] Trifluoroacetimidoyl chlorides were described for the first time in 1994 and were applied in the electrochemically performed synthesis of 2-(trifluoromethyl)-3*H*-indole derivatives.[14]

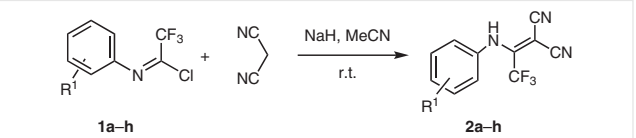
In recent decades, research efforts on trifluoroacetimidoyl chlorides have led to the synthesis of different trifluoromethylated heterocycles.[15–17] Earlier, we have reported the synthesis of trifluoromethylated tetrazoles and pyrroles by using trifluoroacetimidoyl chlorides. As an extension of our results,[18,19] we decided to investigate whether this method could be employed for the synthesis of trifluoromethylated quinolines. Uneyama's group in Japan have shown the utility of trifluoroacetimidoyl chlorides in the synthesis of 1-unsubstituted 2-trifluoromethylated quinolones.[20] Also recently, the synthesis of fluorinated compounds via the Friedel–Crafts reaction was reported.[21]

In this project, at first, we synthesized the 2-(1-(arylamino)-2,2,2-trifluoroethylidene)malononitrile derivatives **2a–h** by the reaction of trifluoroacetimidoyl chlorides **1** with malononitrile in the presence of sodium hydride (Table 1). Then, compounds **2** were subjected to cyclization with $AlCl_3$ under solvent-free conditions to obtain 4-amino-2-(trifluoromethyl)quinolines **3a–f** (Table 2), in good to excellent yields. This simple, two-step procedure shows the use of anilines and trifluoroacetimidoyl chlorides as building blocks for the construction of trifluoromethylated heterocycles (Scheme 1).



Scheme 1 Synthesis of 4-amino-2-(trifluoromethyl)quinoline derivatives

N-Aryl-2,2,2-trifluoroacetimidoyl chlorides **1a–h** were reacted with malononitrile in acetonitrile and in the presence of sodium hydride at ambient temperature, which produced the corresponding 2-(1-(arylamino)-2,2,2-trifluoroethylidene)malononitrile derivatives **2a–h** in high yields (Scheme 2).



Scheme 2 Synthesis of 2-(1-(arylamino)-2,2,2-trifluoroethylidene)-malononitrile derivatives **2a–h**

In order to reduce reaction time and enhance the yields, we also sought to carry out the reaction under microwave irradiation. As shown in Table 1, it was found that this method could reduce reaction times, and also gave higher product yields and a more convenient operation. A wide range of substrates, and both electron-withdrawing and electron-releasing substituents, could be accommodated without significant differences in reaction time or yield (Table 1). The pure products can be obtained simply by washing with *n*-hexane, without use of the traditional purifications by chromatography or recrystallization. The structure of products **2** was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, mass spectrometry, elemental analysis, and X-ray crystal structure analysis. For some derivatives, the NH proton was not observed in the ^{1}H NMR spectrum due to the tautomeric equilibrium of NH–C=C.

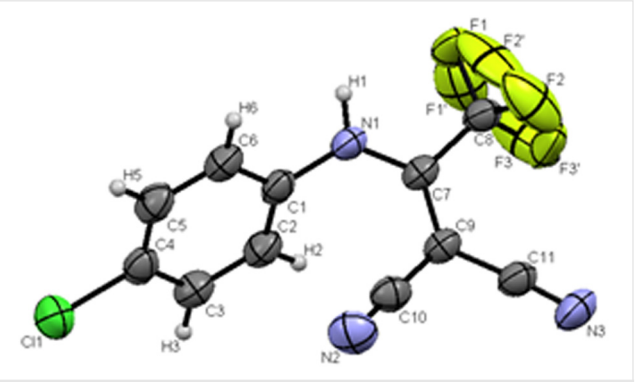
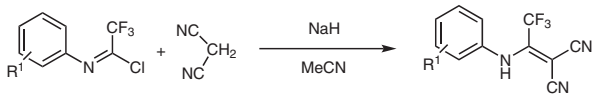


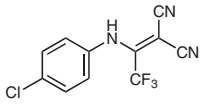
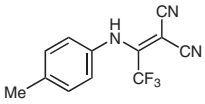
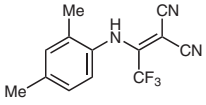
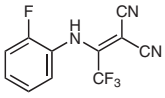
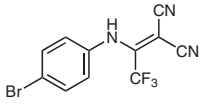
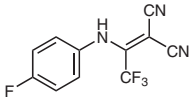
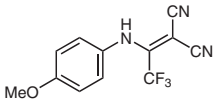
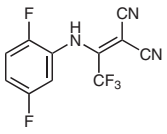
Figure 1 X-ray crystal structure of **2a**

In a continuation of this work, we investigated the intramolecular Friedel–Crafts cyclization reaction for the synthesis of 4-amino-2-(trifluoromethyl)quinoline derivatives. In a typical procedure, 2-{1-[(4-chlorophenyl)amino]-2,2,2-trifluoroethylidene}malononitrile (**2a**) and $AlCl_3$, under solvent-free conditions, was heated at 140 °C for 2 hours; then, the mixture was cooled and poured into ice–water. The crude product was collected by filtration, washed with water, and dried to give **3a** in 95% yield (Scheme 3).

The substrate scope for the cyclization step was then investigated, and the results are summarized in Table 2. We tested derivative **2b** with an electron-donating methyl group and also derivatives with electron-withdrawing groups such

Table 1 Synthesis of 2-(1-(Arylamino)-2,2,2-trifluoroethylidene)malononitrile Derivatives **2a–h**

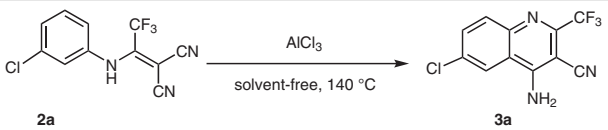


R^1	Product		At room temperature		Under microwave conditions		Melting point (°C)
			Time (h)	Isolated yield (%)	Microwave irradiation time (min)	Isolated yield (%)	
4-Cl	**2a**		16	84	30	95	190–192
4-Me	**2b**		16	78	30	92	144–145
2,4-Me_2	**2c**		16	76	30	90	115–116
2-F	**2d**		16	78	30	95	135–136
4-Br	**2e**		16	69	30	94	177–180
4-F	**2f**		16	68	30	97	160–162
4-OMe	**2g**		16	71	30	96	143–146 (142–143)[14]
2,5-F_2	**2h**		16	75	30	93	121–123

X-ray crystallographic analysis revealed the structure of compound **2a** as depicted in Figure 1.[22]

as the chloro and fluoro group. The reaction of these substrates afforded the final products in good to high yields.

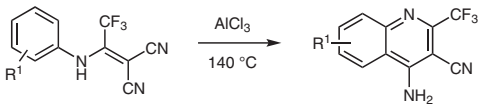
The structure of compounds **3** was deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **3a** showed a broad singlet signal for NH_2 at 8.49 ppm, and two doublet signals at 8.68 and 7.99 ppm and a multiplet signal at 7.95–7.92 ppm for aromatic protons. The decoupled ^{13}C NMR spectrum of **3a** showed 11

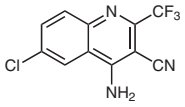
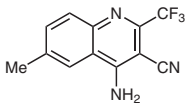
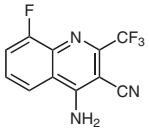
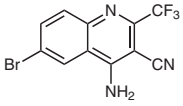
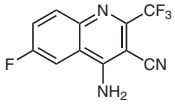
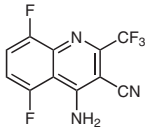


2a 3a

Scheme 3 Synthesis of 4-amino-6-chloro-2-(trifluoromethyl)quinoline-3-carbonitrile (**3a**)

Table 2 Synthesis of 4-Amino-2-(trifluoromethyl)quinoline Derivatives **3a–f**[a]



R^1	Product		Isolated yield (%)	Melting point (°C)
4-Cl	**3a**		95	226–229
4-Me	**3b**		93	195–197
2-F	**3c**		96	290
4-Br	**3d**		91	201–204
4-F	**3e**		95	168–170
2,5-F_2	**3f**		83	158–160

[a] The R^1 substituent numbering refers to the starting material **2**.

distinct resonances, in agreement with the proposed structure. The IR spectrum of **3a** displayed characteristic CN and NH_2 vibrations at 2218 and 3365 cm^{-1}, respectively.

A possible mechanism for this two-step reaction is proposed in Scheme 4.

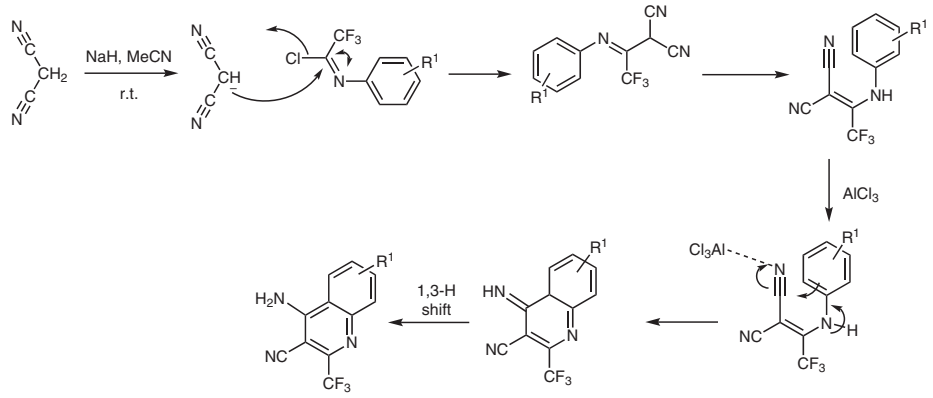
In conclusion, we have successfully designed and synthesized a new series of quinoline derivatives which contain a trifluoromethyl group at the 2-position in good to excellent yields via the intramolecular Friedel–Crafts reaction of 2-(1-(arylamino)-2,2,2-trifluoroethylidene)malononitrile derivatives. These intermediates were synthesized from *N*-aryl-2,2,2-trifluoroacetimidoyl chlorides and malononitrile in excellent yields. This method constitutes a facile, easy workup, and inexpensive route to obtain 4-amino-2-(trifluoromethyl)quinolines which are of great importance in medicinal chemistry.

All chemicals and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Melting points were determined with a Barnstead electrothermal and are uncorrected. IR spectra were obtained on a Mattson-1000 FT-IR spectrophotometer. Peaks are reported in wavenumbers (cm^{-1}). NMR spectra were recorded on a Bruker DRX-400 Avance (^1H: 400 MHz, ^{13}C: 100 MHz, ^{19}F: 375 MHz) or a Varian (^1H: 500 MHz, ^{13}C: 125 MHz) NMR spectrometer. Chemical shifts for ^1H and ^{13}C NMR are reported in parts per million from TMS as an internal standard and for ^{19}F NMR in parts per million from $CFCl_3$ as an internal standard, in DMSO-d_6 as a solvent. GC-EIMS analyses were carried out by using a Hewlett-Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV.

2-[1-(Arylamino)-2,2,2-trifluoroethylidene]malononitrile Derivatives 2a–h; General Procedures

A: At Room Temperature

A mixture of a trifluoroacetimidoyl chloride **1** (1 mmol), malononitrile (1 mmol), NaH (1 mmol), and acetonitrile (5 mL) was stirred at room temperature for 16 h; after completion of the reaction, as indicated by TLC, the reaction mixture was filtered. After removal of the



Scheme 4 Possible mechanism for the synthesis of 4-amino-2-(trifluoromethyl)quinolines

solvent under reduced pressure, if necessary the crude product was purified by washing with *n*-hexane.

B: Under Microwave Conditions

A mixture of trifluoroacetimidoyl chloride (1 mmol), malononitrile (1 mmol), NaH (1 mmol), and acetonitrile (3 mL) was irradiated in a microwave oven at 400 W for 30 min; after completion of the reaction, as indicated by TLC, the reaction mixture was filtered. After removal of the solvent under reduced pressure, if necessary the crude product was purified by washing with *n*-hexane.

2-{1-[(4-Chlorophenyl)amino]-2,2,2-trifluoroethylidene}malononitrile (2a)

Prepared according to General Procedure A and B; yield: 257 mg (95%); mp 190–192 °C.

IR (KBr): 3225, 2231, 2225 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.25 (s, 1 H, NH), 7.51 (d, *J* = 6.0 Hz, 2 H), 7.43 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.91 (q, *J* = 32 Hz, C–CF_3), 134.74, 133.51, 129.38, 128.47, 119.46 (q, *J* = 278 Hz, CF_3).

^{19}F NMR (375 MHz, DMSO-d_6): δ = –65.63.

GC-EIMS: *m*/*z* (%) = 273 (34), 272 (15), 271 (100) [M^+], 175 (16), 11 (24).

Anal. Calcd for $C_{11}H_5ClF_3N_3$: C, 48.64; H, 1.86; N, 15.47. Found: C, 48.54; H, 1.73; N, 15.55.

2-[2,2,2-Trifluoro-1-(p-tolylamino)ethylidene]malononitrile (2b)

Prepared according to General Procedure A and B; yield: 230 mg (92%); mp 144–145 °C.

IR (KBr): 3233, 2222, 2216 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.31 (s, 1 H, NH), 7.26–7.21 (m, 4 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 138.07, 129.77, 125.87, 116.02, 114.83, 21.12.

^{19}F NMR (375 MHz, DMSO-d_6): δ = –66.28.

GC-EIMS: *m*/*z* (%) = 252 (15), 251 (100) [M^+], 232 (11), 231 (57), 230 (11), 155 (17).

Anal. Calcd for $C_{12}H_8F_3N_3$: C, 57.37; H, 3.21; N, 16.73. Found: C, 57.24; H, 3.32; N, 16.54.

2-{1-[(2,4-Dimethylphenyl)amino]-2,2,2-trifluoroethylidene}malononitrile (2c)

Prepared according to General Procedure A and B; yield: 238 mg (90%); mp 115–116 °C.

IR (KBr): 3438, 2210, 2198 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.79 (s, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 6.42 (d, *J* = 7.7 Hz, 1 H), 2.16 (s, 3 H, Me), 1.92 (s, 3 H, Me).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 131.02, 130.29, 127.34, 126.41, 120.68, 119.59, 20.91, 17.57.

^{19}F NMR (375 MHz, DMSO-d_6): δ = –68.08.

GC-EIMS: *m*/*z* (%) = 266 (16), 265 (100) [M^+], 264 (14), 200 (39), 196 (31), 131 (18).

Anal. Calcd for $C_{13}H_{10}F_3N_3$: C, 58.87; H, 3.80; N, 15.84. Found: C, 58.67; H, 3.85; N, 15.78.

2-{2,2,2-Trifluoro-1-[(2-fluorophenyl)amino]ethylidene}malononitrile (2d)

Prepared according to General Procedure A and B; yield: 242 mg (95%); mp 135–136 °C.

IR (KBr): 3216, 2230, 2227 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.51–7.44 (m, 2 H), 7.39 (t, *J* = 9 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.32 (d, *J* = 252 Hz, C–F), 154.22 (q, *J* = 35 Hz, C–CF_3), 131.72, 125.48, 125.45, 119.49 (q, *J* = 279 Hz, CF_3), 116.54, 113.86, 111.79.

Anal. Calcd for $C_{11}H_5F_4N_3$: C, 51.78; H, 1.98; N, 16.47. Found: C, 51.67; H, 1.92; N, 16.34.

2-{1-[(4-Bromophenyl)amino]-2,2,2-trifluoroethylidene}malononitrile (2e)

Prepared according to General Procedure A and B; yield: 297 mg (94%); mp 177–180 °C.

IR (KBr): 3228, 2229, 2216 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.65 (d, *J* = 10 Hz, 2 H), 7.37 (d, *J* = 10 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 153.7 (q, *J* = 36 Hz, C–CF_3), 135.64, 132.86, 132.39, 128.64, 121.82, 119.59 (q, *J* = 278 Hz, CF_3).

Anal. Calcd for $C_{11}H_5BrF_3N_3$: C, 41.80; H, 1.59; N, 13.29. Found: C, 41.75; H, 1.56; N, 13.16.

2-{2,2,2-Trifluoro-1-[(4-fluorophenyl)amino]ethylidene}malononitrile (2f)

Prepared according to General Procedure A and B; yield: 247 mg (97%); mp 160–162 °C.

IR (KBr): 3225, 2231, 2216 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 7.34 (dd, *J* = 5, 8 Hz, 2 H), 7.24 (t, *J* = 9 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.66 (d, *J* = 242 Hz, C–F), 153.92 (q, *J* = 32 Hz, C–CF_3), 134.71 (d, *J* = 88 Hz), 128.01, 119.80 (q, *J* = 278 Hz, CF_3), 116.13 (d, *J* = 22 Hz), 114.90, 114.59.

Anal. Calcd for $C_{11}H_5F_4N_3$: C, 51.78; H, 1.98; N, 16.47. Found: C, 51.68; H, 1.93; N, 16.42.

2-{2,2,2-Trifluoro-1-[(4-methoxyphenyl)amino]ethylidene}malononitrile (2g)

Prepared according to General Procedure A and B; yield: 256 mg (96%); mp 143–146 °C (Lit.[14] 142–143 °C).

IR (KBr): 3225, 2226, 2217 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 11.33 (br s, 1 H, NH), 7.34 (d, *J* = 9 Hz, 2 H), 7.00 (d, *J* = 9 Hz, 2 H), 3.79 (s, 3 H, OMe).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.02, 154.34 (q, *J* = 32 Hz, C–CF_3), 128.41, 128.13, 123.14, 119.60 (q, *J* = 278 Hz, CF_3), 114.62, 55.89.

Anal. Calcd for $C_{12}H_8F_3N_3O$: C, 53.94; H, 3.02; N, 15.73. Found: C, 53.87; H, 2.95; N, 15.75.

2-{1-[(2,5-Difluorophenyl)amino]-2,2,2-trifluoroethylidene}malononitrile (2h)

Prepared according to General Procedure A and B; yield: 253 mg (93%); mp 121–123 °C.

IR (KBr): 3227, 2207, 2203 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.80 (br s, 1 H, NH), 7.11–7.06 (m, 1 H), 6.81–6.77 (m, 1 H), 6.52–6.47 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.73, 158.69 (d, J = 237 Hz, C–F), 149.32 (d, J = 233 Hz, C–F), 144.46 (q, J = 35 Hz, C–CF_3), 140.94, 131.94, 129.26, 116.79 (q, J = 273 Hz, CF_3), 109.99, 106.52.

Anal. Calcd for $C_{11}H_4F_5N_3$: C, 48.37; H, 1.48; N, 15.38. Found: C: 48.16, H: 1.39, N: 15.45%.

4-Amino-2-(trifluoromethyl)quinoline Derivatives 3a–f; General Procedure

A mixture of a 2-[1-(arylamino)-2,2,2-trifluoroethylidene]malononitrile **2** (1 mmol) and $AlCl_3$ (4 mmol) was heated at 140 °C for 2 h, then cooled and poured into ice–water. The crude product was collected by filtration, washed with water, and dried under vacuum at room temperature to yield the pure product.

4-Amino-6-chloro-2-(trifluoromethyl)quinoline-3-carbonitrile (3a)

Yield: 257 mg (95%); mp 226–229 °C.

IR (KBr): 3365, 3255, 2218 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.68 (d, ^4J = 2.4 Hz, 1 H), 8.49 (br s, 2 H, NH_2), 7.99 (d, J = 8 Hz, 1 H), 7.95–7.92 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.93, 147.21 (q, J = 43 Hz, C–CF_3), 144.80, 133.67, 133.07, 132.25, 122.92, 121.10 (q, J = 274 Hz, CF_3), 118.63, 114.52, 81.12 (CN).

Anal. Calcd for $C_{11}H_5ClF_3N_3$: C, 48.64; H, 1.86; N, 15.47. Found: C, 48.53; H, 1.78; N, 15.45.

4-Amino-6-methyl-2-(trifluoromethyl)quinoline-3-carbonitrile (3b)

Yield: 233 mg (93%); mp 195–197 °C.

IR (KBr): 3474, 3372, 2209 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (s, 1 H), 8.14 (br s, 2 H, NH_2), 7.88–7.72 (m, 2 H), 2.5 (s, 3 H, overlap with DMSO).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.06, 157.20, 154.25, 146.00 (q, J = 32 Hz, C–CF_3), 142.95, 138.39, 135.15, 130.21, 122.56, 116.24 (q, J = 243 Hz, CF_3), 79.98 (CN), 21.71 (Me).

Anal. Calcd for $C_{12}H_8F_3N_3$: C, 57.37; H, 3.21; N, 16.73. Found: C, 57.25; H, 3.19; N, 16.67.

4-Amino-8-fluoro-2-(trifluoromethyl)quinoline-3-carbonitrile (3c)

Yield: 244 mg (96%); mp 290 °C.

IR (KBr): 3444, 3370, 2222 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.55 (br s, 2 H, NH_2), 8.33 (d, J = 8 Hz, 1 H), 7.81–7.68 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.01 (d, J = 253 Hz, C–F), 157.47, 147.18 (q, J = 43 Hz, C–CF_3), 136.24, 128.64, 121.10 (q, J = 275 Hz, CF_3), 119.54, 119.50, 118.17, 114.58, 81.31 (CN).

Anal. Calcd for $C_{11}H_5F_4N_3$: C, 51.78; H, 1.98; N, 16.47. Found: C, 51.73; H, 1.94; N, 16.23.

4-Amino-6-bromo-2-(trifluoromethyl)quinoline-3-carbonitrile (3d)

Yield: 287 mg (91%); mp 201–204 °C.

IR (KBr): 3370, 3243, 2217 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.79 (d, J = 4 Hz, 1 H), 8.28 (br s, 2 H, NH_2), 7.99 (dd, J = 4, 8 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.74, 155.57, 148.66, 143.64, 136.48, 132.57, 126.02, 121.58, 118.63, 115.35, 80.96 (CN).

Anal. Calcd for $C_{11}H_5BrF_3N_3$: C, 41.80; H, 1.59; N, 13.29. Found: C, 41.68; H, 1.95; N, 13.52.

4-Amino-6-fluoro-2-(trifluoromethyl)quinoline-3-carbonitrile (3e)

Yield: 242 mg (95%); mp 168–170 °C.

IR (KBr): 3362, 3257, 2221 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.34–8.30 (m, 1 H), 8.20 (br s, 2 H, NH_2), 8.01–7.97 (m, 1 H), 7.79–7.74 (m, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.34 (q, J = 67 Hz), 161.13 (d, J = 245 Hz, C–F), 157.31, 146.45 (q, J = 32 Hz, C–CF_3), 143.38, 133.30 (d, J = 8 Hz), 121.18 (q, J = 275 Hz, CF_3), 118.73, 114.62, 108.27 (d, J = 25 Hz), 80.67 (CN).

Anal. Calcd for $C_{11}H_5F_4N_3$: C, 51.78; H, 1.98; N, 16.47. Found: C, 51.69; H, 1.95; N, 16.52.

4-Amino-5,8-difluoro-2-(trifluoromethyl)quinoline-3-carbonitrile (3f)

Yield: 226 mg (83%); mp 158–160 °C.

IR (KBr): 3443, 3331, 2208 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.00–6.96 (m, 1 H), 6.56 (dd, J = 11.2, 7.5 Hz, 1 H), 5.35 (br s, 2 H, NH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.43, 156.10 (d, J = 240 Hz, C–F), 147.01 (d, J = 232 Hz, C–F), 137.75 (q, J = 35 Hz, C–CF_3), 121.15 (q, J = 270 Hz, CF_3), 117.11, 116.94, 109.06, 102.66, 102.47, 83.55 (CN).

Anal. Calcd for $C_{11}H_4F_5N_3$: C, 48.37; H, 1.48; N, 15.38. Found: C, 48.25; H, 1.38; N, 15.29.

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Supporting Information

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(22) CCDC 1048265 (**2a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures; structural parameters for **2a**: $C_{11}H_5ClF_3N_3$, M_r = 271.63, monoclinic system, space group $P2_1$, a = 7.5522(15) Å, b = 5.2370(10) Å, c = 14.730(3) Å, V = 564.29(19) Å^3, Z = 2.