An Efficient Synthesis of *N*-Cyclopropylanilines by a Smiles Rearrangement

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Abstract: Treatment of 2-chloro-*N*-cyclopropylacetamide with phenols gave the corresponding 2-aryloxy-*N*-cyclopropylacetamides, which on treatment with a base gave the corresponding *N*-cyclopropylanilines.

Key words: rearrangements, amines, cyclopropanes

The discovery of fluoroquinoline antibacterials was a major breakthrough in curtailing bacterial infections. Ciprofloxacin (**1**) is an example of a blockbuster drug of this class (Figure 1). The cyclopropyl group at its N-1 position is critical for its activity. Among the many methods available for synthesizing such compounds, their preparation from *N*-cyclopropylanilines **2** has created a great deal of interest from process scientists.[1] *N*-Cyclopropylanilines can be used in detecting nitrogen-centered radicals,[2] and they also exhibit a range of biological activities.[3–7] 1,2,3-Trisubstituted cyclopropanes were conceived as peptidomimetics,[8] and they have been found to be active compounds.

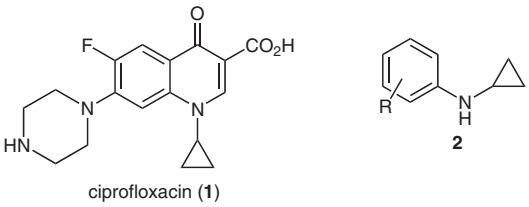

Figure 1 Structures of ciprofloxacin and *N*-cyclopropylanilines

N-Aliphatic cyclopropylamines can often be prepared by nucleophilic substitution of a leaving group with an appropriate amino nitrogen atom. However, *N*-cyclopropylanilines are rarely prepared by this method because of the poor reactivity of cyclopropyl halides towards nucleophiles.[9] Indirect methods have therefore been developed to prepare *N*-cyclopropylanilines.[10]

The first and most widely used method begins with the conversion of [(1-ethoxycyclopropyl)oxy](trimethyl)silane (**3**) into 1-bromo-1-ethoxycyclopropane (**4**), which subsequently reacts with an aromatic amine to generate the cyclopropyl hemiaminal ether **5** (Scheme 1).[11] Reduction of this intermediate then gives the desired amine **6**.

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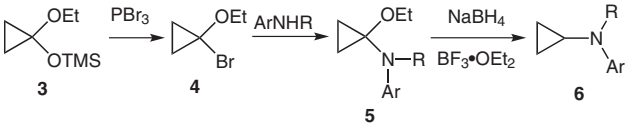
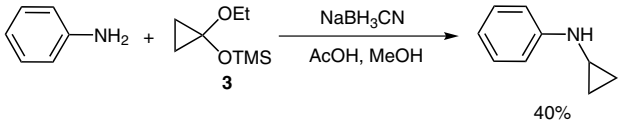


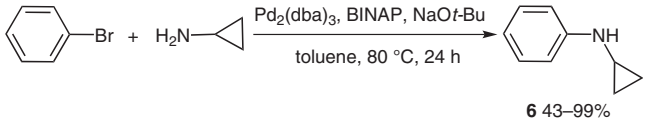
Scheme 1 Preparation of *N*-cyclopropylanilines

An improved one-step version of the reductive amination with siloxane **3** results in cyclopropanation of aromatic amines, as exemplified in Scheme 2, but yields are low.[12]



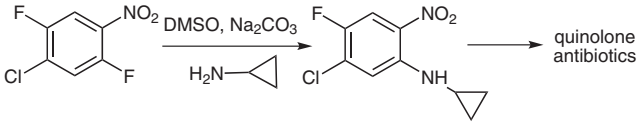
Scheme 2 One-step reductive amination

Cui and co-workers made effective use of Buchwald–Hartwig procedures for the synthesis of *N*-cyclopropylanilines **6** in moderate-to-good yields, as exemplified in Scheme 3.[2]



Scheme 3 Palladium-catalyzed arylation of a cyclopropylamine

The pharmaceutical industry has also developed several methods for this synthesis.[1] The method developed by Caludio and co-workers[1b] (Scheme 4) is worth mentioning, although it suffers the limitation of requiring the presence of a strong electron-withdrawing group in the position adjacent to the leaving group.



Scheme 4 Direct cyclopropanation

When we attempted to scale up the synthesis of silane **3**, even to 100–200 g, we found that it was difficult to maintain the same yields. We therefore devised a different strategy for the synthesis of *N*-cyclopropylanilines that is both scalable and reproducible. In this approach, we used the Smiles rearrangement to prepare *N*-cyclopropylanilines **6** (Scheme 5).

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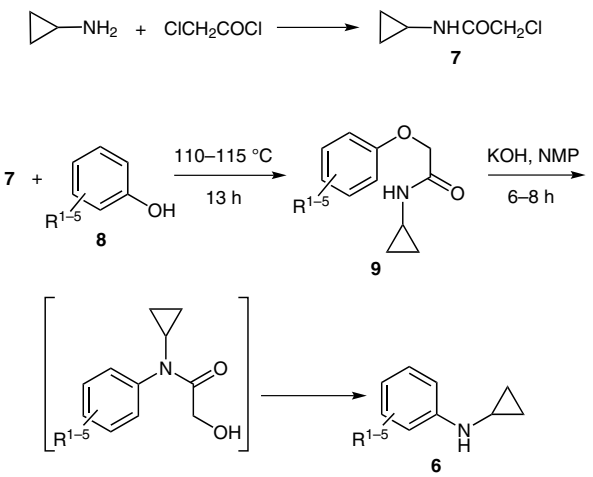


Scheme 5 The Smiles rearrangement method

Substituted phenols **8** reacted with 2-chloro-*N*-cyclopropylacetamide (**7**)[13] under basic conditions to give good yields of the corresponding ethers **9**. All these ethers were well characterized from their spectral data. Under basic conditions, the ethers **9** rearranged to form the corresponding *N*-cyclopropylanilines **6** in good yields (Table 1).

Table 1 Synthesis of Ethers **9** and *N*-Cyclopropylanilines **6**

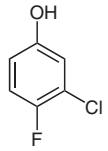
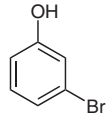
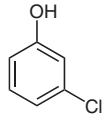
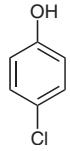
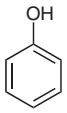
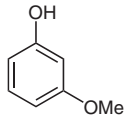
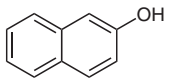
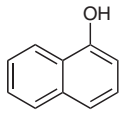
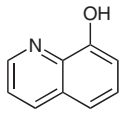
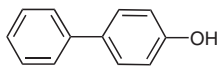
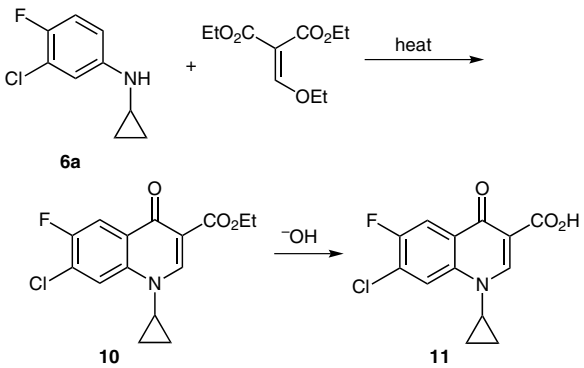
Entry	Phenol	Yield[a] (%) of **9**	Yield (%) of **6**
1	 **8a**	96	73[11a]
2	 **8b**	94	76[11a]
3	 **8c**	81	71
4	 **8d**	88	62[2]

Table 1 Synthesis of Ethers **9** and *N*-Cyclopropylanilines **6** (continued)

Entry	Phenol	Yield[a] (%) of **9**	Yield (%) of **6**
5	 **8e**	78	72[2]
6	 **8f**	95	77[2]
7	 **8g**	82	77[11a]
8	 **8h**	83	56[11a]
9	 **8i**	–	30[b]
10	 **8j**	90	70[c]

[a] Yields calculated on the basis of the recovered starting phenol.
[b] Intermediate **9i** was not isolated, and product **6i** was obtained directly.
[c] 4-$PhC_6H_4NH_2$ (10%) was also isolated by HPLC.

The dihalo compound **6a** is a useful intermediate for preparing quinoline antibiotics. Most of the relevant patents[1a,c,e] report that this aniline reacts with diethyl ethoxymethylenemalonate to give a product that cyclizes to the ester **10**, which undergoes hydrolysis to give good yields of the quinolinecarboxylic acid **11** (ciprofloxacin Q-acid; Scheme 6).



Scheme 6 Preparation of ciprofloxacin Q-acid

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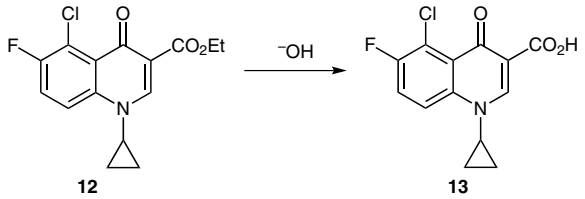
However, when we repeated this reaction with compound **6a**, we found that, together with **10**, the unwanted isomer **12** was also formed in 45% yield (HPLC), which none of the patents reported. We have characterized both the ester **12** and its parent acid **13** (Scheme 7).



Scheme 7 Hydrolysis of unwanted isomer **12**

In conclusion, we have developed a simple and reproducible method for the preparation of *N*-cyclopropylanilines from phenols through a Smiles rearrangement.

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded by using a Bruker 400 Spectrometer with TMS as internal standard. IR spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied BioSystems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240CHN elemental analyzer. Analytical TLC was conducted on E-Merck 60F254 aluminum-backed plates of silica gel (0.2 mm). Developed plates were visualized by using UV light or in an iodine chamber. HPLC was performed by using a Shimadzu 2010 instrument.

2-Chloro-*N*-cyclopropylacetamide (7)
Cyclopropylamine (100.0 g, 1.75 moles) was added to a stirred solution of K_2CO_3 (484.21 g, 3.5 moles) in DCE (1 L), and the mixture was cooled to 5–10 °C. $ClCH_2COCl$ (208.15 g, 1.84 moles) was added at 5–10 °C over 1 h. The mixture was maintained at 20–25 °C for 1 h then heated to 50 °C for 3 h. The solvent was evaporated under vacuum at 40 °C, and the residue was mixed with hexane (300 mL) at 20–25 °C. The product was isolated by filtration and washed with hexane to give a white solid; yield: 168 g (71%); mp 85.8–86.9 °C.

IR (KBr): 3273, 3066, 1650, 1552, 1250 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.52–0.59 (m, 2 H), 0.77–0.86 (m, 2 H), 2.71–2.78 (m, 1 H), 4.02 (s, 2 H), 6.63 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.20, 22.68, 42.33, 167.36.

2-(3-Chloro-4-fluorophenoxy)-*N*-cyclopropylacetamide (9a); Typical Procedure
3-Chloro-4-fluorophenol (**6a**; 21.94 g, 0.149 moles) and 2-chloro-*N*-cyclopropylacetamide (**7**; 8.0 g, 0.059 moles) were added to a stirred soln of K_2CO_3 (20.67 g, 0.149 moles) in toluene (200 mL) at 20–25 °C. The mixture was heated at 105–110 °C for 6–8 h then the solvent was then evaporated under vacuum at 50 °C. The residue was added to 10% aq NaOH (200 mL) at 20–25 °C and the mixture was stirred for 2 h at 20–25 °C. The precipitate was isolated by filtration and washed with H_2O to give an off-white solid; yield [based on recovered phenol **6a** (13.0 g)]: 14.0 g (96%); mp 85.9–87.2 °C.

IR (KBr): 3290, 3074, 1652, 1495, 1254, 1209, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.55–0.59 (m, 2 H), 0.82–0.87 (m, 2 H), 2.75–2.80 (m, 1 H), 4.41 (s, 2 H), 6.54 (s, 1 H), 6.74–6.78 (m, 1 H), 6.95–6.97 (q, 1 H), 7.06–7.10 (t, *J* = 8.76 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.38, 22.06, 68.00, 133.81, 116.63, 121.48, 152.28, 153.20, 154.70, 168.62.

ESI-MS: *m/z* = 244.2 [M + H]$^+$.

2-(3-Bromophenoxy)-*N*-cyclopropylacetamide (9b)
Yellow solid; yield: 19.0 g (94%); mp 83.6–85.5 °C.

IR (KBr): 3292, 3068, 1654, 1474, 1228, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.55–0.62 (m, 2 H), 0.77–0.86 (m, 2 H), 2.75–2.81 (m, 1 H), 4.44 (s, 2 H), 6.58 (s, 1 H), 6.81–6.84 (m, 1 H), 7.08 (s, 1 H), 7.14–7.22 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.40, 22.06, 67.34, 113.06, 118.29, 122.94, 125.20, 130.77, 157.67, 168.81.

ESI-MS: *m/z* = 270 [M + H]$^+$.

2-(3-Chlorophenoxy)-*N*-cyclopropylacetamide (9c)
Off-white solid; yield: 13.68 g (81%); mp 78.1–80.0 °C.

IR (KBr): 3292, 3072, 1655, 1478, 1230 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.57–0.63 (m, 2 H), 0.77–0.90 (m, 2 H), 2.75–2.81 (m, 1 H), 4.44 (s, 2 H), 6.58 (s, 1 H), 6.77–6.79 (dd, *J* = 2.16, 2.16 Hz, 1 H), 6.91–6.95 (t, *J* = 1.92 Hz, 1 H), 7.00–7.02 (d, *J* = 7.76 Hz, 1 H), 7.21–7.27 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.39, 22.05, 67.34, 112.59, 115.38, 122.28, 130.47, 135.10, 157.64, 168.84.

ESI-MS: *m/z* = 226.1 [M + H]$^+$.

2-(4-Chlorophenoxy)-*N*-cyclopropylacetamide (9d)
Off-white solid; yield: 30.0 g (88%); mp 76.6–78.2 °C.

IR (KBr): 3284, 1655, 1489, 1241, 824 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.54–0.58 (m, 2 H), 0.76–0.85 (m, 2 H), 2.74–2.80 (m, 1 H), 4.42 (s, 2 H), 6.59 (s, 1 H), 6.81–6.83 (d, *J* = 8.92 Hz, 2 H), 7.25–7.27 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.37, 22.04, 67.50, 115.82, 126.99, 129.55, 155.60, 169.00.

ESI-MS: *m/z* = 226.2 [M + H]$^+$.

***N*-Cyclopropyl-2-phenoxyacetamide (9e)**
White solid; yield: 8.0 g (78%); mp 68.7–70.0 °C.

IR (KBr): 3292, 3067, 1651, 1544, 1252, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.55–0.59 (m, 2 H), 0.80–0.85 (m, 2 H), 2.75–2.81 (m, 1 H), 4.46 (s, 2 H), 6.63 (s, 1 H), 6.89–6.91 (d, *J* = 8.12 Hz, 2 H), 7.00–7.04 (t, *J* = 7.36 Hz, 1 H), 7.24–7.33 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.38, 22.01, 67.25, 114.51, 122.02, 129.68, 157.02, 169.50.

ESI-MS: *m/z* = 192.3 [M + H]$^+$.

***N*-Cyclopropyl-2-(3-methoxyphenoxy)acetamide (9f)**
Colorless liquid; yield: 7.8 g (95%).

IR (neat): 3419, 3289, 3077, 3009, 1667, 1602, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.51–0.58 (m, 2 H), 0.70–0.79 (m, 2 H), 2.71–2.75 (m, 1 H), 3.73 (s, 3 H), 4.38 (s, 2 H), 6.42–6.44 (d, *J* = 8.44 Hz, 2 H), 6.51–6.53 (d, *J* = 7.83 Hz, 1 H), 6.69 (s, 1 H), 7.13–7.17 (t, *J* = 8.08 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.32, 22.01, 55.17, 67.26, 101.17, 106.46, 107.45, 130.10, 158.22, 160.82, 169.40.

ESI-MS: *m/z* = 222.1 [M + H]$^+$.

***N*-Cyclopropyl-2-(2-naphthyloxy)acetamide (9g)**
Off-white solid; yield: 14.8 g (82%); mp 114.7–117.1 °C.

IR (KBr): 3354, 1654, 1542, 1367, 1212, 1054, 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.59–0.64 (m, 2 H), 0.78–0.86 (m, 2 H), 2.79–2.82 (m, 1 H), 4.59 (s, 2 H), 6.68 (s, 1 H), 7.13–7.17 (m, 2 H), 7.36–7.40 (t, *J* = 7.36 Hz, 1 H), 7.45–7.49 (t, *J* = 7.43 Hz, 1 H), 7.73–7.80 (m, 3 H).

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.42, 22.08, 67.30, 107.47, 117.92, 124.29, 126.68, 126.80, 127.56, 129.36, 129.80, 134.15, 154.86, 169.40.

ESI-MS: *m/z* = 242.3 $[M + H]^+$.

***N*-Cyclopropyl-2-(1-naphthyloxy)acetamide (9h)**
Off-white solid; yield: 14.9 g (83%); mp 121.3–122.4 °C.

IR (KBr): 3305, 1669, 1651, 1536, 1268, 793 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56–0.59 (m, 2 H), 0.83–0.86 (m, 2 H), 2.80–2.83 (m, 1 H), 4.68 (s, 2 H), 6.68 (s, 1 H), 6.79–6.81 (d, *J* = 7.51 Hz, 1 H), 7.36–7.41 (m, 1 H), 7.50–7.54 (m, 3 H), 7.83–7.85 (m, 1 H), 8.15–8.17 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.55, 22.11, 67.79, 105.65, 121.09, 121.78, 125.02, 125.64, 125.67, 126.62, 127.75, 134.50, 152.77, 169.59.

ESI-MS: *m/z* = 242.3 $[M + H]^+$.

2-(Biphenyl-4-yloxy)-*N*-cyclopropylacetamide (9j)
Off-white solid; yield: 18.0 g (90%); mp 146.1–148.2 °C.

IR (KBr): 3261, 1662, 1651, 1645, 825, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.57–0.61 (m, 2 H), 0.79–0.86 (m, 2 H), 2.78–2.82 (m, 1 H), 4.49 (s, 2 H), 6.74 (s, 1 H), 6.95–6.97 (d, *J* = 8.54 Hz, 2 H), 7.30–7.33 (t, *J* = 7.24 Hz, 1 H), 7.42–7.46 (t, *J* = 8.31 Hz, 2 H), 7.52–7.54 (d, *J* = 8.11 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.41, 22.09, 67.41, 114.86, 126.66, 126.91, 128.32, 128.70, 135.15, 140.19, 156.56, 169.53.

ESI-MS: *m/z* = 268.1 $[M + H]^+$.

3-Chloro-*N*-cyclopropyl-4-fluoroaniline (6a); Typical Procedure
Acetamide **7a** (14.0 g, 0.057 moles) was added to a stirred soln of KOH (6.43 g, 0.114 moles) and NMP (70 mL) in toluene (280 mL) at 20–25 °C. The mixture was heated to 120–130 °C for 12 h then cooled to 40–45 °C. H_2O (200 mL) was added with stirring. The layers were separated and the aqueous layer was extracted with toluene (100 mL). The organic layers were combined, washed with H_2O (2 × 200 mL), and concentrated to give a yellow liquid; yield: 7.84 g (73%).

IR (neat): 3412, 3090, 2965, 1504, 1364, 1226, 1050, 806 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48–0.51 (m, 2 H), 0.68–0.76 (m, 2 H), 2.35–2.40 (m, 1 H), 4.11 (s, 1 H), 6.54–6.58 (m, 1 H), 6.79–6.81 (dd, *J* = 2.59, 2.55 Hz, 1 H), 6.91–6.96 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.29, 25.35, 112.17, 133.82, 116.42, 120.89, 145.48, 152.23.

ESI-MS: *m/z* = 186.1 $[M + H]^+$.

3-Bromo-*N*-cyclopropylaniline (6b)
Brown liquid; yield: 6.0 g (76%).

IR (neat): 3418, 3091, 2986, 1548, 820 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.49–0.53 (m, 2 H), 0.70–0.77 (m, 2 H), 2.38–2.43 (m, 1 H), 4.21 (s, 1 H), 6.64–6.67 (dd, *J* = 1.54, 1.45 Hz, 1 H), 6.83–6.88 (d, *J* = 7.48 Hz, 1 H), 6.94–6.94 (d, *J* = 1.69 Hz, 1 H), 7.00–7.04 (t, *J* = 7.99 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.33, 24.91, 111.85, 115.50, 120.31, 123.04, 130.22, 149.90.

ESI-MS: *m/z* = 213.1 $[M + H]^+$.

3-Chloro-*N*-cyclopropylaniline (6c)
Yellow liquid; yield: 4.0 g (71%).

IR (neat): 3405, 2972, 1600, 1495, 1364, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.51–0.54 (m, 2 H), 0.71–0.78 (m, 2 H), 2.39–2.44 (m, 1 H), 4.22 (s, 1 H), 6.61–6.63 (dd, *J* = 1.65, 1.61 Hz, 1 H), 6.68–6.72 (dd, *J* = 2.11, 1.03 Hz, 1 H), 6.800–6.809 (t, *J* = 1.69 Hz, 1 H), 7.07–7.11 (t, *J* = 7.99 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.38, 24.94, 111.45, 112.62, 117.43, 129.92, 134.78, 149.75.

ESI-MS: *m/z* = 168.0 $[M + H]^+$.

Anal. Calcd for $C_9H_{10}ClN$: C, 64.48; H, 6.01; N, 8.36. Found: C, 64.32; H, 6.12; N, 8.32.

4-Chloro-*N*-cyclopropylaniline (6c)
Yellow liquid; yield: 4.6 g (62%).

IR (neat): 3404, 1600, 1496, 817 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48–0.52 (m, 2 H), 0.71–0.75 (m, 2 H), 2.38–2.4 (m, 1 H), 4.12 (s, 1 H), 6.69–6.72 (d, *J* = 8.71 Hz, 2 H), 7.12–7.14 (d, *J* = 8.72 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.35, 25.19, 114.11, 122.16, 128.81, 147.15.

ESI-MS: *m/z* = 168.1 $[M + H]^+$.

***N*-Cyclopropylaniline (6e)**
Colorless liquid; yield: 4.5 g (72%).

IR (neat): 3391, 3087, 3009, 1603, 1504, 1020, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.53 (m, 2 H), 0.70–0.76 (m, 2 H), 2.42–2.45 (m, 1 H), 4.17 (s, 1 H), 6.74–6.82 (m, 3 H), 7.19–7.23 (t, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.30, 25.15, 113.07, 117.64, 129.02, 148.60.

ESI-MS: *m/z* = 134.2 $[M + H]^+$.

***N*-Cyclopropyl-3-methoxyaniline (6f)**
Colorless liquid; yield: 4.5 g (77%).

IR (neat): 3389, 3002, 1603, 1155, 1048, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.52–0.56 (m, 2 H), 0.72–0.77 (m, 2 H), 2.42–2.47 (m, 1 H), 3.78 (s, 3 H), 4.21 (s, 1 H), 6.33–6.35 (t, *J* = 4.59 Hz, 1 H), 6.40–6.42 (d, *J* = 7.25 Hz, 2 H), 7.10–7.14 (t, *J* = 7.96 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.33, 25.13, 54.98, 99.07, 102.65, 106.30, 129.74, 150.07, 160.66.

ESI-MS: *m/z* = 164.1 $[M + H]^+$.

Cyclopropyl(2-naphthyl)amine (6g)
White solid; yield: 14.5 g (77%); mp 52.4–53.4 °C.

IR (KBr): 3374, 2955, 1625, 1361, 826, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64–0.67 (m, 2 H), 0.86–0.90 (m, 2 H), 2.57–2.62 (m, 1 H), 4.32 (s, 1 H), 6.97–6.99 (dd, *J* = 1.92, 1.92 Hz, 1 H), 7.242–7.245 (d, *J* = 1.1 Hz, 1 H), 7.32–7.36 (t, *J* = 7.44 Hz, 1 H), 7.49–7.53 (t, *J* = 7.49 Hz, 1 H), 7.73–7.75 (d, *J* = 8.74 Hz, 1 H), 7.79–7.82 (t, *J* = 6.74 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.48, 25.33, 105.60, 117.69, 122.04, 126.10, 126.27, 127.70, 127.80, 128.78, 135.19, 146.38.

ESI-MS: *m/z* = 184.2 $[M + H]^+$.

Cyclopropyl(1-naphthyl)amine (6h)
White solid; yield: 6.3 g (56%); mp 50.1–51.4 °C (Lit.[2] 36–37 °C).

IR (KBr): 3391, 1575, 1518, 1284, 766 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.651–0.656 (m, 2 H), 0.85–0.91 (m, 2 H), 2.58–2.59 (m, 1 H), 4.87 (s, 1 H), 7.04–7.08 (d, *J* = 7.46 Hz, 1 H), 7.23–7.29 (m, 1 H), 7.35–7.47 (m, 3 H), 7.72–7.81 (d, *J* = 7.78 Hz, 1 H), 7.79–7.81 (d, *J* = 7.64 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.47, 25.41, 105.74, 117.69, 119.62, 123.10, 124.58, 125.55, 126.52, 128.58, 134.12, 143.78.

ESI-MS: *m/z* = 184.2 $[M + H]^+$.

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_N_-Cyclopropylquinolin-8-amine (6i)
Note: In this example, the acetamido **9i** was not isolated, but was converted directly into **6i**.

Yellow liquid; yield: 1.6 g (30%).

IR (neat): 3397, 3038, 2961, 1575, 1519, 1478, 1380, 817, 790, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.68–0.79 (m, 2 H), 0.81–0.88 (m, 2 H), 2.55–2.58 (m, 1 H), 6.39 (s, 1 H), 7.09–7.11 (d, *J* = 7.92 Hz, 2 H), 7.24–7.44 (m, 2 H), 8.05–8.07 (t, *J* = 4.24 Hz, 1 H), 8.69–8.70 (t, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.09, 24.57, 106.18, 114.38, 121.22, 127.63, 128.42, 135.91, 137.89, 145.18, 146.83.

ESI-MS: *m/z* = 185.2 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.31; H, 6.62; N, 15.24.

Biphenyl-4-yl(cyclopropyl)amine (6j)
Off-white solid; yield: 9.7 g (70%); mp 42.4–44.0 °C.

IR (KBr): 3406, 2981, 1612, 1489, 822, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.55–0.57 (m, 2 H), 0.72–0.79 (m, 2 H), 2.46–2.50 (m, 1 H), 4.25 (s, 1 H), 6.86–6.88 (d, *J* = 8.38 Hz, 2 H), 7.25–7.28 (t, *J* = 7.31 Hz, 1 H), 7.38–7.42 (t, *J* = 7.64 Hz, 2 H), 7.45–7.47 (d, *J* = 8.38 Hz, 2 H), 7.54–7.56 (d, *J* = 7.54 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.41, 25.19, 123.34, 125.99, 126.29, 127.76, 128.57, 130.62, 141.29, 148.05.

ESI-MS: *m/z* = 210.0 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.16; H, 7.26; N, 6.75.

Biphenyl-4-ylamine (Byproduct of Synthesis of 6j)
[CAS Reg. No. 92-67-1]

White solid; yield: 1.08 g (10%); mp 53.6–54.9 °C.

IR (KBr): 3423, 3391, 3294, 3197, 3030, 1487, 1258, 831, 762, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 2 H), 6.76–6.78 (d, *J* = 8.44 Hz, 2 H), 7.26–7.30 (t, *J* = 7.91 Hz, 1 H), 7.39–7.44 (m, 4 H), 7.54–7.56 (d, *J* = 7.58 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.37, 126.25, 126.37, 127.97, 128.67, 131.45, 141.13, 145.87.

ESI-MS: *m/z* = 170.0 $[M + H]^+$.

_N_-(3-Chloro-4-fluorophenyl)-_N_-cyclopropylacetamide (_N_-Acetyl 6a)[1b]
White solid; yield: 0.5 g (80%); mp 53.4–54.8 °C (Lit.[1b] 50–52 °C).

IR (KBr): 3095, 3015, 1660, 1501, 1377, 1325, 1235, 843, 818, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.49 (m, 2 H), 0.85 (m, 2 H), 2.11 (br s, 3 H), 3.02 (m, 1 H), 6.99 (s, 1 H), 7.07–7.11 (t, *J* = 8.35 Hz, 1 H), 7.17–7.18 (d, *J* = 4.85 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.15, 23.17, 31.45, 116.39, 120.86, 126.97, 129.36, 138.67, 138.71, 172.35.

ESI-MS: *m/z* = 228.1 $[M + H]^+$.

_N_-Cyclopropyl-_N_-quinolin-8-ylacetamide (_N_-Acetyl 6i)
White solid; yield: 0.6 g (80%); mp 110.4–115.8 °C.

IR (KBr): 3060, 3011, 1663, 1593, 1573, 1426, 1383, 797 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.53 (m, 2 H), 0.87 (m, 2 H), 1.67 (s, 3 H), 3.40 (m, 1 H), 7.44–7.45 (d, *J* = 6.56 Hz, 2 H), 7.53–7.57 (t, *J* = 7.64 Hz, 1 H), 7.81–7.83 (d, *J* = 7.76 Hz, 1 H), 8.17–8.19 (d, *J* = 8.12 Hz, 1 H), 8.94 (s, 1 H).

ESI-MS: *m/z* = 227.2 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{14}NO_2$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.52; H, 6.23; N, 12.35.

Ethyl 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (10) and Ethyl 5-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (12)
A mixture of diethyl {[(3-chloro-4-fluorophenyl)(cyclopropyl)amino]methylene}malonate (5.0 g, 0.014 moles) and PPA (20 g) was stirred for 2 h at 70–80 °C. The mixture was cooled and then chilled H_2O (100 mL) was added. The resulting mixture was stirred for 1 h at 20–25 °C. The product was collected by filtration, washed with H_2O (20 mL), and purified by column chromatography to give the desired product **10** together with its 5-chloro isomer **12** as an unwanted byproduct.

10
Yield: 2.27 (52%); mp 220.1–221.9 °C.

IR (KBr): 2999, 1726, 1614, 1479, 1330, 1034.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (m, 2 H), 1.36–1.42 (m, 5 H), 3.44–3.46 (m, 1 H), 4.36–4.42 (q, 2 H), 7.99–8.00 (d, *j* = 5.72 Hz, 1 H), 8.19–8.21 (d, *j* = 8.96 Hz, 1 H), 8.57 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.15, 14.29, 34.63, 61.77, 110.71, 113.63, 118.81, 126.73, 137.07, 148.71, 154.30, 156.79, 165.12, 172.64.

12
White solid, yield: 1.87 g (43%); mp 251.2–252.8 °C.

IR (KBr): 2988, 1726, 1624, 1609, 1474, 1301, 1241, 814 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.14 (m, 2 H), 1.24–1.42 (m, 5 H), 3.40–3.46 (m, 1 H), 4.36–4.41 (q, 2 H), 7.45–7.49 (t, *J* = 8.62 Hz, 1 H), 7.86–7.89 (dd, *J* = 4.36, 4.36 Hz, 1 H), 8.50 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.20, 19.09, 39.96, 65.28, 116.46, 121.29, 121.38, 124.46, 124.71, 130.19, 143.70, 152.26, 159.13, 169.35.

ESI-MS: *m/z* = 310.2 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{13}ClFNO_3$: C, 58.17; H, 4.23; N, 4.52. Found: C, 58.28; H, 4.21; N, 4.59.

5-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (13)
A mixture of ester **12** (350 mg, 0.0011 moles), EtOH (0.3 mL), and 2 M aq NaOH (10 mL) was refluxed with stirring for 2 h. The mixture was cooled and then acidified with 50% aq HCl (10 mL). The resulting product was collected by filtration and washed with H_2O (10 mL) to give a white solid; yield: 200 mg (63%); mp 276.82–279.66 °C.

IR (KBr): 3445, 3119, 3064, 1724, 1614, 1455, 1435, 1219, 821 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.31 (m, 4 H), 3.82 (s, 1 H), 8.04–8.08 (t, *J* = 9.00 Hz, 1 H), 8.33–8.37 (dd, *J* = 4.32, 4.36 Hz, 1 H), 8.73 (s, 1 H), 14.87 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 8.32, 37.14, 108.66, 119.73, 122.29, 123.03, 140.25, 148.97, 154.81, 157.25, 165.25, 178.28.

ESI-MS: *m/z* = 282.0 $[M + H]^+$.

Anal. Calcd for $C_{13}H_9ClFNO_3$: C, 55.43; H, 3.22; N, 4.97. Found: C, 55.38; H, 3.18; N, 4.85

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