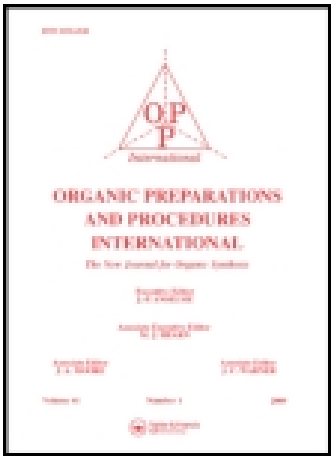

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New Synthesis of N-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide

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New Synthesis of *N*-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide

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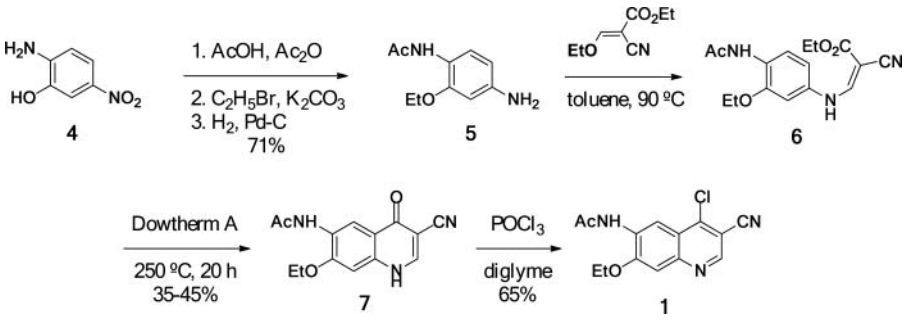
4-Chloroquinolines are key synthetic precursors for anticancer,[1] anti-malarial,[2] antidiabetic,[3] antiviral[4] agents and reversible (H^+/K^+) AT Phase inhibitors.[5] For example, *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (**1**) was developed as an important intermediate for the preparation of *pelitinib* (**2**) and *neratinib* (**3**) [*Fig. 1*], which act as irreversible inhibitors of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) kinases.[6–8]

Previous reports [9,10] described the preparation of **1** based on Gould-Jacobs methodology [11] using 2-amino-5-nitrophenol (**4**) as the starting material (*Scheme 1*). Treatment of **5** with ethyl (*E*)-2-cyano-3-ethoxypropenoate afforded the corresponding ethyl cyanopropenoate **6**. 3-Cyano-4-hydroxyquinoline (**7**) was obtained in ~ 40% yield through thermal cyclization at 250 °C for 20 h in Dowtherm A. After chlorination with $POCl_3$ in diglyme, **1** was produced in 65% yield. While this route was straightforward, the high temperature required for the cyclization of **6** to **7** on a kilogram scale proved to be disadvantageous because of the formation of tars and resins as well as low overall yield.



Scheme 1

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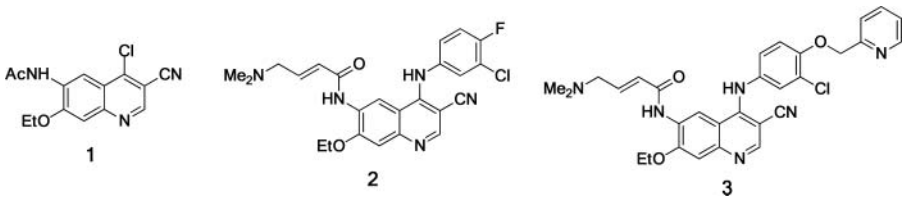
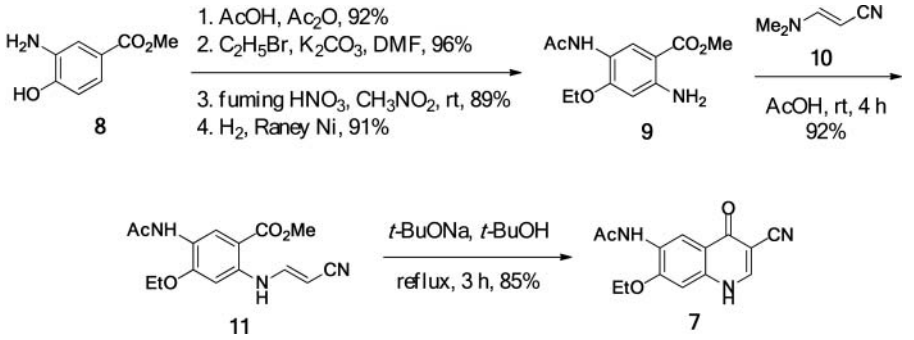
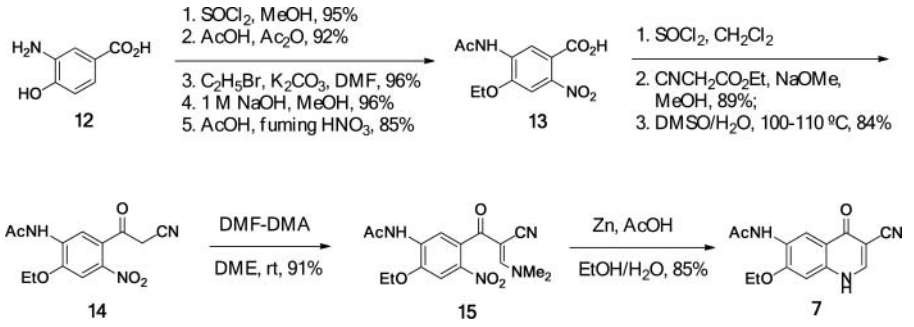


Fig. 1. Structures of **1**, pelitinib (**2**) and neratinib (**3**)

Recently, we developed new methods for the synthesis of **7**.[12–15] The key step in the first route (*Scheme 2*)[12,13] is the base-induced cyclization of *o*-[(2-cyanovinyl)amino]benzoate (**11**) using *t*-BuONa/*t*-BuOH to give **7** on a kilogram scale, in 51% yield over six steps (HPLC purity: 98.8%). In the second route (*Scheme 3*),[14,15] 3-(dimethylamino)-2-(2-nitrobenzoyl) acrylonitrile (**15**) was converted to **7** through a reductive cyclization method using a Zn/AcOH/EtOH. Since the solubility of compounds **15** and **7** are poor, operations with these compounds are not convenient and the overall yield of this reductive cyclization is about 30% over ten steps.

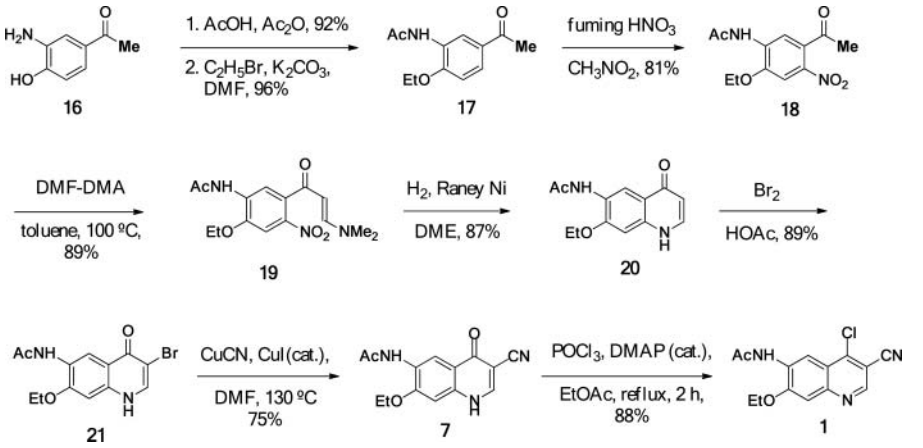


Scheme 2



Scheme 3

Herein, we report a new synthetic approach to compound **1** (*Scheme 4*) from 1-(3-amino-4-hydroxyphenyl)ethanone (**16**). Acetylation and ethylation of **16** afforded compound **17** in 88% yield.[6,7] Subsequent nitration was carried out in fuming HNO_3/CH_3NO_2



Scheme 4

[16] to give the resulting 1-(2-nitrophenyl)ethanone **18** in 81% isolated yield, which was then condensed with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) in toluene at 100°C to give the 3-(dimethylamino)-1-phenylprop-2-en-1-one **19** in 89% yield.[17,18] Reductive cyclization of **19** using Raney-Ni in DME furnished an 87% yield of quinolin-4(1*H*)-one **20**[19,20] which has better solubility than compound **7** in DME, THF, and CH_2Cl_2. 3-Bromoquinolin-4(1*H*)-one **21** was produced in 89% yield from **20** through bromination with Br_2/AcOH.[21] Displacement of Br using CuCN/CuI/DMF [22,23] affored 3-cyano-4-hydroxy quinoline **7**, which was purified by digestion in 50% EtOH/EtOAc to provide a 75% overall yield (HPLC purity: 99.1%). Finally, 4-chloro-3-cyanoquinoline **1** was obtained by reaction with $POCl_3$ in EtOAc, catalyzed by 5 mol% DMAP. Purification of **1** was carried out by washing with DMF and EtOAc at room temperature in 88% isolated yield (HPLC purity 98.9%).

In summary, we have developed a new synthetic route to 4-chloro-3-cyanoquinoline (**1**) on a hectogram scale. The key steps include the reductive cyclization process to produce the quinolin-4(1*H*)-one **20** from **19**, the bromination of **20** to give 3-bromoquinolin-4(1*H*)-one **21**, and substitution of the bromide at C3 by CN to give compound **7**. Final chlorination using $POCl_3$ in EtOAc provided product **1** in 32.5% yield over eight steps (HPLC purity 98.9%). Purification methods for **7** and **1** are also given.

Experimental Section

All chemicals and solvents are commercially available and were used as received without any further purification. ^{1}H NMR spectra were recorded on a Varian Gemini 300 spectrometer and ^{13}C NMR spectra were obtained from a Bruker AMX 400/600 at 400 MHz using TMS as an internal standard. Infrared spectra were recorded using a Thermo-Nicolet MAGNA-IR 750. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang WRS-1B melting point apparatus and are uncorrected. The HPLC results were generated using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. Although compounds **17** and **18** are mentioned in the literature,[13] they were not fully characterized and no mps were reported.

***N*-(5-Acetyl-2-ethoxyphenyl)acetamide (17).** To a stirred solution of 1-(3-amino- 4-hydroxyphenyl)ethanone **16** (200 g, 1.32 mol) in AcOH (760 mL) at 60 °C was added Ac_2O (148 mL, 1.57 mol) over 1 h, and the mixture was stirred at this temperature for 1 h. The mixture was poured into ice water (4 L) over 20 min and stirred. The resulting tan solid was collected and washed with water (500 mL × 2) and dried at 50 °C to give *N*-(5-acetyl-2- hydroxyphenyl)acetamide (235 g, 92%) as a white powder. This acetylated product was suspended with K_2CO_3 (250 g, 1.82 mol) in DMF (1.17 L) at 60 °C, C_2H_5Br (99 mL, 1.33 mol) was added over 1 h, and the mixture was stirred at this temperature for 1 h. The mixture was poured into ice water (5 L) and stirred for 30 min. The resulting grey solid was collected and washed with water (500 mL × 2) and dried at 50 °C to provide **17** (258 g, 96%) as a grey powder, which was used directly at the next step. An analytical sample of **17** was obtained by recrystallization from 1:1 hexane/EtOAc to afford an off-white solid, mp: 98–99 °C. ^{1}H NMR ($CDCl_3$): δ 1.48 (t, 3 H, $J = 7.2$ Hz), 2.23 (s, 3 H), 2.57 (s, 3 H), 4.18 (q, 2 H, $J = 7.2$ Hz), 6.90 (d, 1 H, $J = 8.7$ Hz), 7.72 (dd, 1 H, $J = 8.7$, 1.8 Hz), 7.75 (br s, 1 H), 8.99 (d, 1 H, $J = 1.8$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.6, 24.9, 26.5, 64.5, 110.2, 120.4, 124.4, 127.2, 130.1, 150.53, 168.3, 197.3. ESI-MS (*m/z*) 222.0 $(M+H)^+$, 244.1 $(M+Na)^+$, 260.0 $(M+K)^+$.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.86; N, 6.16.

***N*-(5-Acetyl-2-ethoxy-4-nitrophenyl)acetamide (18).** To a stirred solution of **17** (230 g, 1.04 mol) in CH_3NO_2 (3.1 L) was added fuming nitric acid (119 mL, 2.6 mol) to keep the reaction temperature below 30 °C. The resulting solution was stirred at 20–30 °C for another 4 h and diluted with chilled water (4 L) and stirred for 30 min. The organic layer was separated, washed with water (2 L × 2) and saturated $NaHCO_3$ (2 L × 2) respectively, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give the crude **18** as a brown solid, which was recrystallized from 1:1 hexane/EtOAc (1.4 L) to afford **18** (224 g, 81%) as a light-yellow solid, mp: 78–79 °C. ^{1}H NMR ($CDCl_3$): δ 1.52 (t, 3 H, $J = 7.2$ Hz), 2.25 (s, 3 H), 2.52 (s, 3 H), 4.23 (q, 2 H, $J = 7.2$ Hz), 7.53 (s, 1 H), 7.96 (br s, 1 H), 8.52 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.4, 25.0, 30.3, 65.4, 106.2, 116.3, 132.1, 133.1, 139.9, 146.8, 168.7, 199.8. ESI-MS (*m/z*) 265.1 $(M-H)^-$, 267.0 $(M + H)^+$.

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.25; H, 5.36; N, 10.46.

***N*-(5-(3-(Dimethylamino)acryloyl)-2-ethoxy-4-nitrophenyl)acetamide (19).** To a stirred suspension of **18** (200 g, 0.75 mol) in toluene (2.3 L) was added DMF-DMA (401 mL, 3.02 mol). The mixture was stirred at 90–100 °C for 24 h and then cooled to ~ 10 °C. The resulting yellow solid was collected, washed with cooled toluene (115 mL × 3), and dried under reduced pressure to give **19** (214 g, 89%) as a bright-yellow powder, which was used directly at the next step, mp: 174–175 °C. ^{1}H NMR (DMSO-d_6): δ 1.41 (t, 3 H, $J = 7.2$ Hz), 2.17 (s, 3 H), 2.83 (s, 3 H), 3.07 (s, 3 H), 4.24 (q, 2 H, $J = 7.2$ Hz), 5.18 (d, 1 H, $J = 12.9$ Hz), 7.58 (s, 1 H), 8.25 (s, 1 H), 9.42 (s, 1 H). MS-ESI (*m/z*): 322.1 $(M+H)^+$, 344.1 $(M+Na)^+$.

Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 56.19; H, 5.99; N, 12.99.

***N*-(7-Ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (20).** Compound **19** (180 g, 0.56 mol) and Raney-Ni (wet, 20 g) were added to DME (4.6 L), and stirred for 12 h at rt under 1 atm of hydrogen. A yellow solid was generated during the reaction. After the reaction was completed, around 3.5 L DME was recovered and the residue was dissolved into CH_2Cl_2 (3.8 L) to give a clear solution, which was then filtered through

celite pad, the filter cake was washed by CH_2Cl_2 (225 mL × 2). The combined filtrate was concentrated to give crude **20** as a tan solid, which was digested in 50% EtOH/EtOAc (532 mL), stirred and heated to reflux for 1 h. After cooling to rt, the resulting solid was collected, washed with 50% EtOH/EtOAc (70 mL × 3), dried at 50 °C to give **20** (119 g, 87%) as a faint yellow solid. An analytical sample of this solid was purified on a silica column using hexane/EtOAc (2:1) as the eluent to give **20** as an off-white solid. mp: 269–272 °C. ^{1}H NMR (DMSO-d_6): δ 1.44 (t, 3 H, $J = 6.9$ Hz), 2.12 (s, 3 H), 4.16 (q, 2 H, $J = 6.9$ Hz), 5.92 (d, 1 H, $J = 7.5$ Hz), 7.00 (br s, 1 H), 7.77 (d, 1 H, $J = 7.5$ Hz), 8.59 (s, 1 H), 9.06 (s, 1 H), 11.61 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 14.5, 23.4, 63.3, 91.6, 98.5, 111.8, 115.2, 126.0, 149.8, 152.64, 154.2, 168.1, 188.3. MS-EI (*m/z*): 247. IR (KBr): 3373, 3265, 1660, 1631, 1572.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.29; H, 5.79; N, 11.30.

***N*-(3-Bromo-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (21).** To a stirred suspension of **20** (105 g, 0.43 mol) in AcOH (1.9 L) was added dropwise of a solution of dry Br_2 (23.2 mL, 0.45 mol) in AcOH (190 mL) over 1 h, keeping the reaction temperature between 20–25 °C. A tan solid was generated immediately. The mixture was stirred at rt for another 1 h. The resulting solid was collected, washed with cooled EtOH (100 mL × 3), and dried under reduced pressure to give **21** (124 g, 89%) as a faint brown powder, which was used directly at the next step. An analytical sample of this solid was purified on a silica column using hexane/EtOAc (2:1) as the eluent to give **21** as an off-white solid, mp: 216 °C (dec.). ^{1}H NMR (DMSO-d_6): δ 1.45 (t, 3 H, $J = 6.9$ Hz), 2.13 (s, 3 H), 4.17 (q, 2 H, $J = 6.9$ Hz), 7.02 (s, 1 H), 8.34 (d, 1 H, $J = 5.7$ Hz), 8.68 (s, 1 H), 9.12 (s, 1 H), 12.01 (br s, 1 H). MS-EI (*m/z*): 324.

Anal. Calcd for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N, 8.62. Found: C, 48.19; H, 4.07; N, 8.58.

***N*-(3-Cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (7)**. Compound **21** (110 g, 0.34 mol), CuCN (60.9 g, 0.68 mol) and CuI (19.0 g, 0.1 mol) were suspended in DMF (742 mL) under nitrogen. The reaction mixture was stirred and heated to 130–140 °C for 6 h and then cooled to rt. The resulting mixture was filtered through a celite pad, the filter cake was washed with DMF (53 mL × 2). The combined filtrate was concentrated and ~ 525 mL DMF was recovered. The residue was added to 1 L water and stirred for 4 h at rt. The resulting white solid was collected, washed with water, and dried to give the crude product **7** (80 g), which was suspended in 50% EtOH/EtOAc (472 mL), stirred and heated to 70°C for 1 h. After cooled to rt, the resulting solid was collected, washed by 50% EtOH/EtOAc (36 mL × 2), and dried at 50°C to give the pure product **7** (69 g, 75%) as a pale solid, mp > 300 °C (*lit.*[7] > 250 °C). ^{1}H NMR (DMSO-d_6): δ 1.45 (t, 3 H, $J = 6.6$ Hz), 2.14 (s, 3 H), 4.20 (q, 2 H, $J = 6.6$ Hz), 7.05 (s, 1 H), 8.59 (d, 1 H, $J = 6.3$ Hz), 8.70 (s, 1 H), 9.18 (s, 1 H), 12.52 (d, 1 H, $J = 6.3$ Hz). ^{13}C NMR (DMSO-d_6): δ 14.1, 23.9, 64.6, 93.0, 99.7, 116.3, 117.0, 118.7, 126.5, 136.5, 145.4, 152.9, 168.7, 173.5. ESI-MS (*m/z*): 270.2 $(M–H)^-$, 272.2 $(M+H)^+$.

Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.89; H, 4.87; N, 15.56.

HPLC Conditions: Column: Phenomenex Prodigy ODS3, 150 mm × 4.6 mm × 5 μm; Detection: 230 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 5 μL; Solvent: DMF; Concentration: 0.5 mg/mL; Run time: 60 min; Mobile phase A: water (0.1% H_3PO_4); Mobile phase B: acetonitrile; Gradient program: time (min): 0, 5, 45, 50, 52, 60;% of mobile phase A: 95, 95, 5, 5, 95, 95;% of mobile phase B: 5, 5, 95, 95, 5, 5; t_R: 15.546 min; Purity: 99.1%.

***N*-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (1)**. Compound **7** (61 g, 0.22 mol) and DMAP (0.85 g, 5 mol%) were suspended in EtOAc (565 mL) and stirred at rt. $POCl_3$ (60 mL, 0.65 mol) was added slowly to the mixture over 1 h, and the reaction was heated to reflux for another 2 h to give a clear solution. After cooling to rt, the reaction solution was poured slowly into ice-water (900 mL) and stirred for 1 h. The resulting solid was collected, washed with water (80 mL × 2), and dried to give the crude product **1** (60 g), which was suspended in DMF (180 mL) and stirred at rt for 1 h. The solid was filtered, washed with EtOAc (39 mL × 3), and dried at 50 °C to give the pure product **1** (55 g, 88%) as a faint brown solid, mp: 255–258 °C (*lit.*[7] 250 °C). ^{1}H NMR (DMSO-d_6): δ 1.50 (t, 3 H, $J = 6.3$ Hz), 2.25 (s, 3 H), 4.40 (q, 2 H, $J = 6.3$ Hz), 7.60 (s, 1 H), 9.01 (s, 1 H), 9.17 (s, 1 H), 9.54 (s, 1 H). ESI-MS (*m/z*): 290.1 $(M+H)^+$.

Anal. Calcd for $C_{14}H_{12}ClN_3O_2$: C, 58.04; H, 4.17; N, 14.50. Found: C, 57.81; H, 4.07; N, 14.18.

IR (KBr): 3334, 2235, 1689, 1618. HPLC Conditions: Column: Phenomenex Prodigy ODS3, 150 mm × 4.6 mm × 5 μm; Detection: 230 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 5 μL; Solvent: DMF; Concentration: 0.5 mg/mL; Run time: 60 min; Mobile phase A: water/acetonitrile/H_3PO_4 = 950/50/0.5 (volume); Mobile phase B: water/acetonitrile/H_3PO_4 = 50/950/0.5 (volume); Gradient program: time (min): 0, 5, 45, 50, 52, 60;% of mobile phase A: 100, 100, 0, 0, 100, 100;% of mobile phase B: 0, 0, 100, 100, 0, 0; t_R: 26.018 min; Purity: 98.9%.

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