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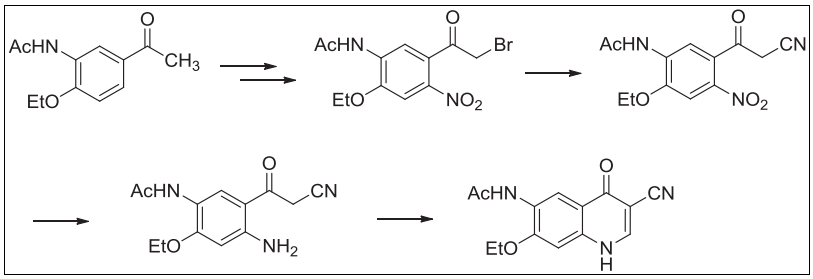

New and practical synthetic route of *N*-(3-cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (**1**) is described, through the cyclization of 2-aminophenyl-ethanone (**12**) with *N*,*N*-dimethylformamide dimethylacetal. The overall yield of **1** obtained from this process is 46% (five steps) with a purity of >99% (HPLC).

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INTRODUCTION

4-Hydroxyquinolines (equal to 4-oxo-1,4-dihydroquinolines) are the key synthetic precursors for anticancer [1], antimalarial [2], antidiabetic [3], antiviral [4] agents, and reversible (H^+/K^+) ATPase inhibitors [5]. *N*-(3-Cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (**1**) (Fig. 1) was developed as an important intermediate for the preparation of EKB-569 (**2**) and neratinib (**3**), which were developed as irreversible inhibitors of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER-2) kinases [6–8].

The earlier work to prepare **1** (Scheme 1) [9] was based on Gould–Jacobs methodology [10] and involved the reaction of 4-acetamido-3-ethoxyaniline (**5**) with ethyl 2-cyano-3-ethoxyacrylate to afford ethyl cyanopropenoate (**6**). Thermal cyclization of **6** at 260°C in Dowtherm A for 15–20 h then yielded *N*-(3-cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (**1**).

This route was straightforward, but the high temperature required for cyclization of **6** to **1** on a kilogram scale proved to be a disadvantage. The main problem was that prolonged exposure of **6** to high temperature led to extensive decomposition with significant tar formation. This led to difficulties in purification, which dramatically reduced the yield to 35–45%.

RESULTS AND DISCUSSION

When searching for a new synthetic route to produce **1** [11], we noted that Atkins [12] and Tois [13] had prepared 3-butyryl-8-methoxy-4-hydroxyquinoline and 6,7-substituted-4-hydroxyquinolines, respectively, via formation of the nitroenamine intermediates by condensation of *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) with the corresponding starting materials *o*-nitrophenylethanones.

Such approaches enlightened our direction, and we designed a new route to obtain 3-cyano-4-hydroxyquinoline (**1**) (Scheme 2). Starting from 4-hydroxy-3-nitrophenylethanone (**7**), phenylethanone (**8**) was prepared by using the method described by Wissner [14]. Nitration of **8** to **9** was conducted in good yield by using fuming nitric acid–nitromethane system [15]. Other conditions, such as KNO_3-H_2SO_4 [16], or 65% HNO_3 [17] gave inferior yields for this transformation. Compound **9** was then treated with 1 equiv of bromine in dichloromethane to give **10** [18], and followed by 1.1 equiv of sodium cyanide in DMSO at RT to afford **11** in 81% yield over two steps [19]. The nitro compound **11** was reduced by using Fe-HCl or Zn-AcOH system to give the aniline (**12**), which was then condensed with DMF-DMA in DME to provide the final product **1** (70% from **11**) [20]. DMF-DMA could be replaced by trimethyl orthoformate or triethyl orthoformate, but this required the reaction to be performed at 90–100°C for 4–6 h.

In conclusion, a new route of making *N*-(3-cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl)acetamide (**1**) was developed to simplify the process, improve the yield, and make it cost-effective. The key step is the cyclization reaction of the 2-aminophenyl-ethanone (**12**) with DMF-DMA. The overall yield of **1** obtained from this process was 46% (five steps) with HPLC purity >99%.

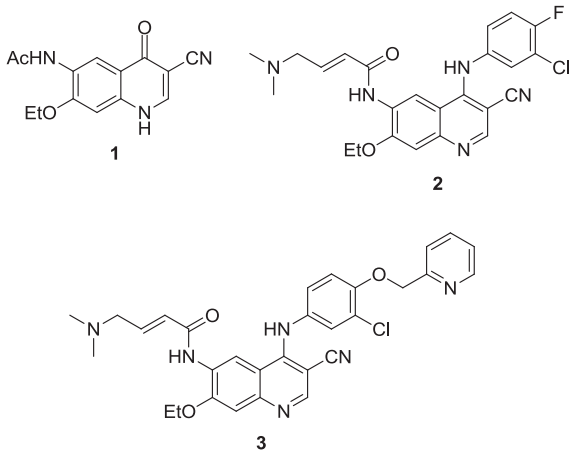


Figure 1. Chemical structures of **1**, EKB-569 (**2**), and HKI-272 (**3**).

EXPERIMENTAL

All commercially available materials and solvents were used as received without any further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Gemini-300 spectrometer (EquipNet, Inc., Hong Kong, China) using TMS as an internal standard. The mass spectra were obtained from a Finnigan MAT-95/711 spectrometer (Thermo Fisher Scientific Inc. Barrington, IL). Melting points were measured on a Buchi-510 melting point apparatus and were uncorrected. The HPLC results were generated using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump Waters Corporation (Shanghai), China.

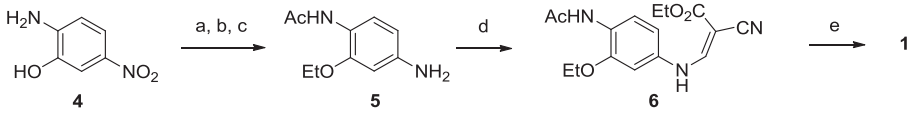
5-Acetamido-4-ethoxy-2-nitrophenylethanone (9). 3-Acetamido-4-ethoxyphenyl-ethanone (**8**) was prepared from 4-hydroxy-3-nitrophenyl-ethanone (**7**) using Wissner's method [14] to give a light orange solid in 78% (three steps), purity 99.08% (HPLC), mp 96–97°C. ^{1}H-NMR ($CDCl_3$, δ): 1.48 (t, 3H, J = 7.2 Hz), 2.23 (s, 3H), 2.57 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 6.90 (d, 1H, J = 8.7 Hz), 7.72 (dd, 1H, J = 8.7 Hz, 1.8 Hz), 7.75 (br s, 1H), 8.99 (d, 1H, J = 1.8 Hz). ^{13}C-NMR ($CDCl_3$, δ): 14.63, 24.94, 26.53, 64.51, 110.19, 120.38, 124.36, 127.25, 130.13, 150.53, 168.33, 197.26. 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.

Fuming HNO_3 (23.0 mL, 0.5 mol) was added to a stirred solution of **8** (45.0 g, 0.2 mol) in CH_3NO_2 (900 mL). The reaction mixture was stirred at 25–35°C for 4 h. The resulting solution was washed with H_2O, saturated $NaHCO_3$, respectively, dried (Na_2SO_4), and concentrated to give a dark brown solid. Recrystallization from EtOAc to petroleum ether yielded **9** (44.2 g, 82%) as a sand-like solid, purity 97.04% (HPLC), mp 78–80°C. ^{1}H-NMR ($CDCl_3$, δ): 1.52 (t, 3H, J = 7.2 Hz), 2.25 (s, 3H), 2.52 (s, 3H), 4.23 (q, 2H, J = 7.2 Hz), 7.53 (s, 1H), 7.96 (br s, 1H), 8.52 (s, 1H). ^{13}C-NMR ($CDCl_3$, δ): 14.42, 25.04, 30.28, 65.44, 106.25, 116.26, 132.07, 133.09, 139.90, 146.79, 168.66, 199.83. ESI–MS (*m/z*) 265.1 (M – H), 267.0 (M + H).

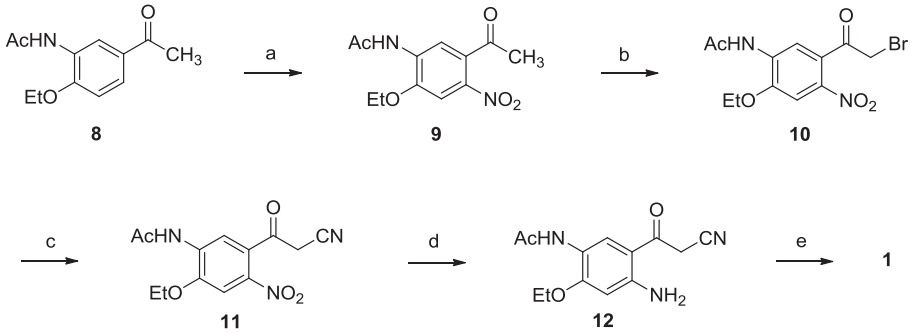
1-(5-Acetamido-4-ethoxy-2-nitrophenyl)-2-bromoethanone (10). Br_2 (5.0 mL, 0.1 mol) was added to a stirred solution of **9** (26.6 g, 0.1 mol) in CH_2Cl_2 (500 mL). The reaction mixture was stirred at 15–30°C for 4 h. The resulting solution was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to give **10** (33.1 g, 96%) as a pale yellow solid, mp 104–106°C. ^{1}H-NMR ($CDCl_3$, δ): 1.55 (t, 3H, J = 7.2 Hz), 2.26 (s, 3H), 4.27 (q, 2H, J = 7.2 Hz), 4.30 (s, 3H), 7.64 (s, 1H), 7.88 (br s, 1H), 8.59 (s, 1H). ^{13}C-NMR ($CDCl_3$, δ): 14.42, 25.07, 34.53, 65.60, 106.15, 117.36, 128.80, 133.59, 139.74, 147.26, 168.65, 193.79. ESI–MS (*m/z*) 344.9 (M + H), 368.9 (M + Na).

5-Acetamido-4-ethoxy-2-nitrobenzoylacetonitrile (11). A solution of **10** (10.4 g, 0.03 mol) in DMSO (30 mL) and EtOH

Scheme 1. Reagents and conditions: (a) AcOH, Ac_2O, 60°C; (b) C_2H_5Br, K_2CO_3, DMF, 60°C; (c) H_2, Pd-C, THF, 71% (three steps); (d) ethyl 2-cyano-3-ethoxyacrylate, toluene, 90°C, 16 h, 90%; and (e) Dowtherm A, 260°C, 20 h, 35–45%.



Scheme 2. Reagents and conditions: (a) fuming HNO_3, CH_3NO_2, 82%; (b) Br_2, CH_2Cl_2, 96%; (c) NaCN, DMSO-H_2O, 85%; (d) Fe, HCl, DME-EtOH, 70–80°C, 79%; and (e) DMF-DMA, RT, DME, 88%.



(30 mL) was cooled in an ice-water bath, then treated dropwise with NaCN (1.6 g, 0.033 mol) in H_2O (20 mL) over 1 h. The mixture was stirred for another 4 h at 20–30°C. The resulting solution was diluted with H_2O (200 mL) and filtered, and the filtrate was acidified with 2*M* HCl to pH = 2–3. The resulting solid was collected via suction filtration, washed with H_2O, and dried under reduced pressure to give **11** (7.4 g, 85%) as a pale yellow solid, purity 96.23% (HPLC), mp 171–175°C (dec.). ^{1}H-NMR ($CDCl_3$, δ): 1.56 (t, 3H, *J* = 5.4 Hz), 2.28 (s, 3H), 3.86 (s, 2H), 4.28 (q, 2H, *J* = 5.4 Hz), 7.88 (s, 1H), 8.01 (br s, 1H), 8.58 (s, 1H). ^{13}C-NMR (DMSO-d_6, δ): 14.10, 24.20, 32.28, 65.40, 107.41, 115.26, 118.47, 126.94, 133.35, 140.49, 149.24, 169.69, 191.32. ESI–MS (*m*/*z*) 290 (M − H), 292.0 (M + H), 314.0 (M + Na).

5-Acetamido-2-amino-4-ethoxybenzoylacetonitrile (12). To a mixture of **11** (29.0 g, 0.1 mol) and iron powder (28.0 g, 0.5 mol) in DME (600 mL) and EtOH (100 mL) was added 2*M* HCl (50 mL, 0.1 mol). The resulting suspension was stirred at 70–80°C for 5 h. The hot reaction mixture was filtered through celite pad; the filtrate was concentrated to ~ 100 mL and diluted with H_2O (500 mL). The resulting product was filtered, washed with H_2O, and dried under reduced pressure to afford **12** (20.6 g, 79%) as a brown solid, purity 96.62% (HPLC), mp 213–216°C (dec.). ^{1}H-NMR (DMSO-d_6, δ): 1.35 (t, 3H, *J* = 6.6 Hz), 2.00 (s, 3H), 4.04 (q, 2H, *J* = 6.6 Hz), 4.43 (s, 2H), 6.35 (s, 1H), 7.32 (br s, 2H), 7.78 (s, 1H), 8.85 (s, 1H). ^{13}C-NMR (DMSO-d_6, δ): 14.27, 23.29, 29.89, 63.76, 97.89, 107.41, 116.36, 126.69, 151.54, 157.02, 168.35, 187.57. EIMS (*m*/*z*) 261 (M − H).

***N*-(3-Cyano-7-ethoxy-4-oxo-1,4-dihydroquinolin-6-yl) acetamide (1)**. To a stirred suspension of **12** (13.0 g, 0.05 mol) in DME (250 mL) was added DMF-DMA (8.0 mL, 0.06 mol), and the mixture was stirred at 15–30°C for 1 h. The resulting solid was collected via suction filtration, washed with EtOAc, and dried under reduced pressure to give the product **1** (11.9 g, 88%) as a pale brown solid, purity 99.07% (HPLC) via slurring in EtOH-EtOAc, mp >300°C. ^{1}H-NMR (DMSO-d_6, δ): 1.45 (t, 3H, *J* = 6.6 Hz), 2.14 (s, 3H), 4.20 (q, 2H, *J* = 6.6 Hz), 7.05 (s, 1H), 8.59 (d, 1H, *J* = 6.3 Hz), 8.70 (s, 1H), 9.18 (s, 1H), 12.52 (d, 1H, *J* = 6.3 Hz). ^{13}C-NMR (DMSO-d_6, δ): 14.13, 23.98, 64.62, 92.97, 99.75, 116.32, 117.04, 118.67, 126.54, 136.55, 145.42, 152.86, 168.68, 173.49. ESI–MS (*m*/*z*) 270.2 (M − H), 272.2 (M + H). 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; Concentration: 0.5 mg/mL; Run time: 60 min; Mobile phase A: H_2O (0.1% H_3PO_4); Mobile phase B: MeCN; Gradient program: time (min): 0, 5, 45, 50; % of mobile phase A: 95, 95, 5, 5; % of mobile phase B: 5, 5, 95, 95, t_R: 18.0 min.

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