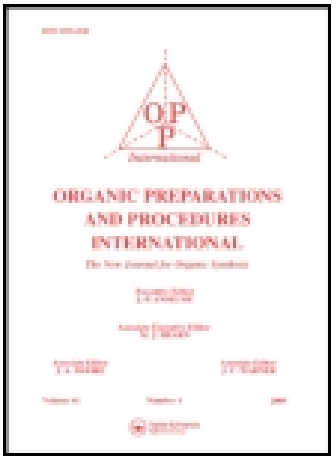

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A Practical Synthesis of 7-(3-Chloropropoxy)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile, a Key Intermediate to Bosutinib

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A Practical Synthesis of 7-(3-Chloropropoxy)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile, a Key Intermediate to Bosutinib

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Bosutinib (**5**, SKI-606) marketed as *bosulif*® is an ATP-competitive Bcr-Abl tyrosine-kinase inhibitor with an additional inhibitory effect on SRc family kinases (including Src, Lyn and Hck) for use in the treatment of cancer.[1, 2] *Bosulif*® has received approval of the United States FDA and EU European Medicines Agency in 2012 and 2013 respectively for the treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance, or intolerance to previous therapy.[3–5] A couple of preparations of **5** on a multi-gram scale have been reported.[6–12] However, a practical synthetic process is still needed because commonly used method (*Scheme 1*) is based on Gould-Jacobs methodology[13] involving thermal cyclization **3** at 250 ≡C for 4 h in Dowtherm A to obtain the key intermediate 7-fluoro-6-methoxy-4-oxo-1,4-dihydroquinoli- ne-3-carbonitrile (**4**).[6,7] Although this route is short, the high reaction temperature required to convert **3** to **4** leads to the formation of tars and resins with attendant difficulty in the purify- cation and lower yield of **4** from **3** (40%). Furthermore, Dowtherm A is a high boiling solvent difficult to recover, harmful to environment and may also cause allergic reaction to people handling it.

Withbroe *et al.*[8] developed a streamlined process for the synthesis and isolation of bosutinib monohydrate (**5**, *Scheme 2*). A three-component coupling reaction of **6** with cyanoacetamide **7** and triethyl orthoformate led to **8** as a mixture of *cis/trans* isomers. Cyclization of **8** using $POCl_3$ in sulfolane provided the core structure of **5**. Yin *et al*[11, 12] also reported a new synthesis of **5** (*Scheme 3*), which started with esterification of the material vanillic acid (**9**), followed by alkylation, nitration, reduction to give the methyl 2-amino- benzoate **10**. Condensation of **10** with 3,3-diethoxypropanenitrile in TFA followed by cyclization of **11** with NaOH in ethanol gave7-(3-chloropropoxy)-6-methoxy-4-oxo- 1,4-dihydroquinoline-3-carbonitrile (**12**) in 40.6% overall yield from **9**. Bosutinib was eventually obtained in 16.7% yield from **9** after chlorination and two consecutive aminations.

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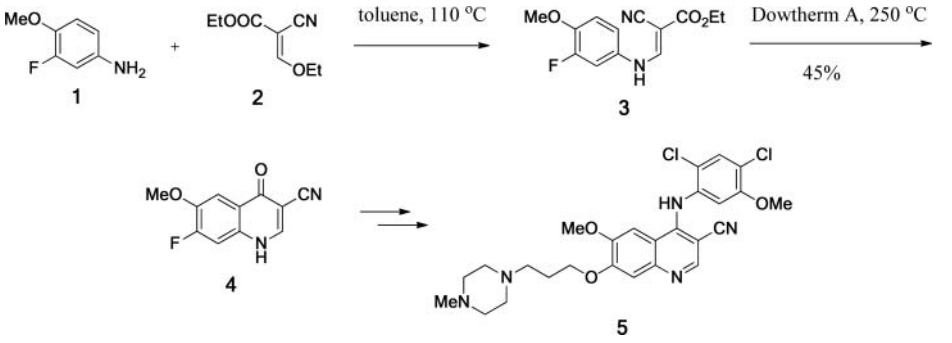
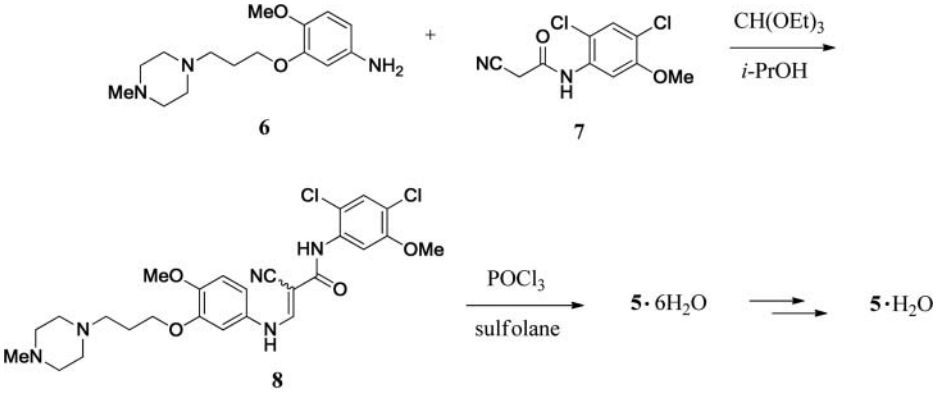
[§]Y.M. and X.T. have contributed equally to this work.



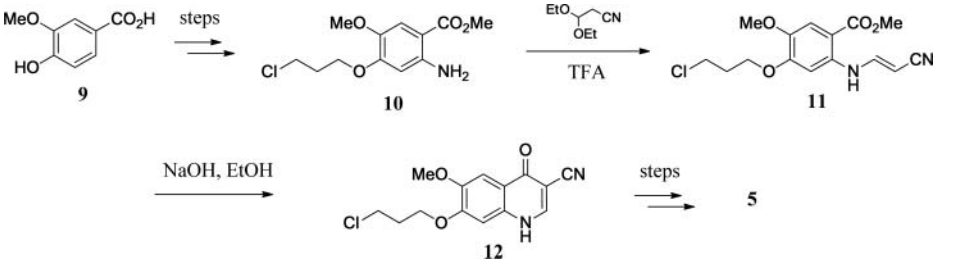
Scheme 1

In order to devise a practical and commercial preparation of **5**, a new and practical route involving a reductive cyclization of 2-(*o*-nitrobenzoyl)-3-(dimethylamino)acrylonitrile **(20)** with hydrogen and Raney Ni was developed to give key intermediate **12**, as shown in *Scheme 4*. Treatment of methyl vanillate (**13**) with 1-bromo-3-chloropropane gave **14** in 91% yield. Nitration of **14** carried out in HNO_3/AcOH, led to compound **15** in 81% yield. Hydrolysis of **15** under basic conditions (92% yield) followed by consecutive reactions with oxalyl chloride (the use of thionyl chloride requires reflux and gave a colored product) and ethyl cyanoacetate, provided **18**, purified by recrystallization from hexane/EtOAc in 79% yield from **16**. Treatment of **18** in 1:9 aqueous DMSO led to **19** in 82% yield after recrystallization from hexane/EtOAc. Condensation of **19** with DMF-DMA at room temperature gave compound **20** in 78% yield. The final reductive cyclization was carried out by catalytic hydrogenation of **20** over Raney Ni/THF at room temperature. A similar reductive cyclization had also be utilized by us during the synthesis of *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide as the key intermediate for the preparation of *neratinib*.[13–17] The crude **12** was purified by digestion in 50% EtOH/EtOAc to give the compound with 71% overall yield and 98.6% purity (HPLC).

In summary, we have developed a new and practical synthetic route of bosutinib intermediate **12** on a hectogram scale from commercially available methyl vanillate (**13**) as the starting material in eight simple steps including alkylation, ester hydrolysis, nitration, decarboxylation, and reductive cyclization to give the final product **12** in 24.3% yield and 98.6% purity (HPLC).



Scheme 2



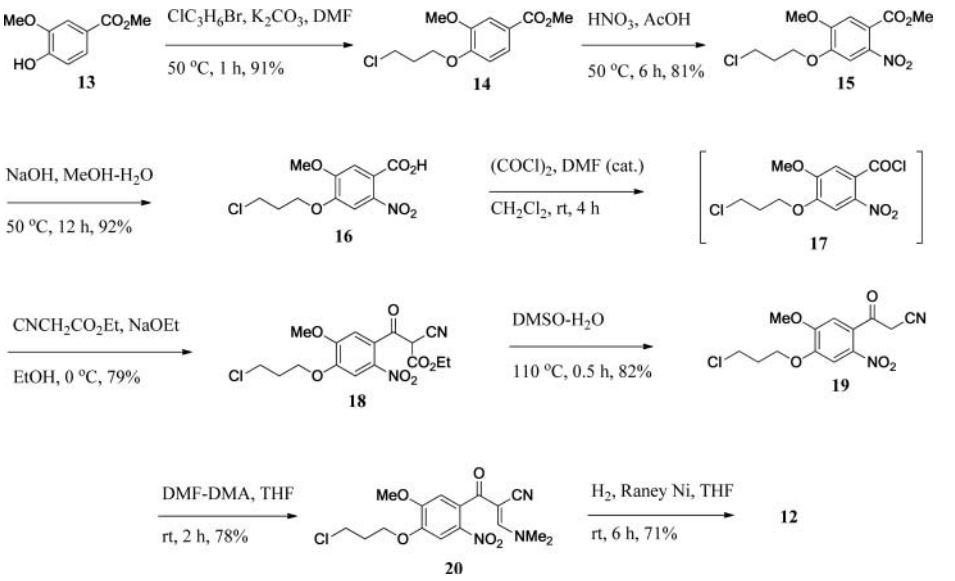
Scheme 3

Experimental Section

All commercially available materials and solvents were used as received without any further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. 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 data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds were based on the areas of HPLC UV. Although compounds **12**,[11,12,18,19] **14**,[11,12] **15**,[11,12] and **16**[20] are mentioned in the literatures, they were not fully characterized and no mps were reported.

Methyl 4-(3-Chloropropoxy)-3-methoxybenzoate (14)

1-Bromo-3-chloropropane (404 g, 2.57 mol) was added dropwise to a stirred mixture of methyl vanillate (**13**, 360 g, 1.98 mol) and potassium carbonate (415 g, 3.0 mol) in DMF (1.8 kg) at 60 ≡C. The reaction mixture was stirred at this temperature for another 1 h then cooled to room temperature, and poured slowly into ice-water (8 kg) while stirring



Scheme 4

constantly. The solid formed was collected, washed with cold water (0.8 kg × 2), and dried at 60 ≡C for 4 h. The white product was digested by stirring and heating with 2:1 hexane/EtOAc (1 kg) at 60 ≡C for 2 h then cooled to room temperature. The resulting solid was collected and washed with 1:1 hexane/EtOAc (300 g × 2), dried at 50 ≡C for 4 h to afford **14** (466 g, 91%) as a white solid, mp 106.5−107 °C. ^{1}H NMR ($CDCl_3$): δ 2.29−2.35 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.78 (t, $J = 6.4$ Hz, 2 H, $ClCH_2CH_2CH_2O$), 3.90 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.23 (t, $J = 6.0$ Hz, 2 H, $ClCH_2CH_2CH_2O$), 6.91 (d, $J = 8.4$ Hz, 1 H, Ar*H*), 7.55 (d, $J = 2.0$ Hz, 1 H, Ar*H*), 7.67 (dd, $J = 2.0$, 8.4 Hz, 1 H, Ar*H*). MS-ESI (*m*/*z*): 281.0 $(M+Na)^+$.

Anal. Calcd for $C_{12}H_{15}ClO_4$: C, 55.71; H, 5.84; Found: C, 55.93; H, 5.80.

Methyl 4-(3-Chloropropoxy)-5-methoxy-2-nitrobenzoate (15)

A stirred suspension of **14** (317 g, 1.23 mol), 65% HNO_3 (179 g, 1.85 mol) and AcOH (1.5 kg) was stirred at 40–50 ≡C for 6 h to form a white milky mixture which was poured slowly into ice water (5 kg) over 20 min and stirred at the ambient temperature for another 2 h. The resulting white solid was collected and washed with H_2O (300 g × 3) and dried at 60 ≡C for 5 h. The crude product was recrystallized from 1:1 hexane/EtOAc (0.7 kg) to afford **15** (302 g, 81%) as a white solid, mp 101.5−104.2 °C. ^{1}H NMR ($CDCl_3$): δ 2.30−2.36 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.78 (t, $J = 6.0$ Hz, 2 H, $ClCH_2CH_2CH_2O$), 3.91 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.25 (t, $J = 6.0$ Hz, 2 H, $ClCH_2CH_2CH_2O$), 7.08 (s, 1 H, Ar*H*), 7.49 (s, 1 H, Ar*H*). MS-ESI (*m*/*z*): 326.0 $(M+Na)^+$.

Anal. Calcd for $C_{12}H_{14}ClNO_6$: C, 47.46; H, 4.65; N, 4.61; Found: C, 47.58; H, 4.60; N, 4.65.

4-(3-Chloropropoxy)-5-methoxy-2-nitrobenzoic Acid (16)

A mixture of **15** (470 g, 1.55 mol), NaOH (80 g, 2.0 mol) in MeOH (2 kg) and H_2O (2 kg) was stirred at 50–60 ≡C for 12 h to form a colorless solution. It was cooled to room temperature and conc. H_2SO_4 was added slowly into the reaction solution to pH 2–3. The white suspension was stirred at the ambient temperature for 1 h. The resulting solid was collected and washed with H_2O (0.5 kg × 3) and MeOH (0.3 kg × 1), dried at 50 ≡C for 5 h to give **16** (352 g, 92%) as a white solid, mp 134.6−135.6 °C. ^{1}H NMR (DMSO-d_6): δ 2.17−2.24 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.78 (t, $J = 6.0$ Hz, 2 H, $ClCH_2CH_2CH_2O$), 3.92 (s, 3 H, OCH_3), 4.23 (t, $J = 6.0$ Hz, 2 H, $ClCH_2CH_2CH_2O$), 7.30 (s, 1 H, Ar*H*), 7.62 (s, 1 H, Ar*H*), 13.52 (br s, 1 H, COO*H*). ^{13}C NMR (DMSO-d_6): δ 31.88, 42.17, 56.96, 66.59, 108.77, 111.97, 121.93, 141.89, 149.62, 152.43, 166.61. MS-ESI (*m*/*z*): 312.0 $(M+Na)^+$.

Anal. Calcd for $C_{11}H_{12}ClNO_6$: C, 45.61; H, 4.18; N, 4.84; Found: C, 45.78; H, 4.22; N, 4.80.

Ethyl 3-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-2-cyano-3-oxopropanoate (18)

Oxalyl chloride (190 g, 1.5 mol) and DMF (7.3 g, 0.1 mol) were added consecutively to a mixture of **16** (290 g, 1.0 mol) in CH_2Cl_2 (2 kg) at room temperature and the mixture was stirred for 4 h to give a homogeneous solution. Removal of the volatiles left 4-(3-

chloropropoxy)-5-methoxy-2-nitrobenzoyl chloride (**17**) as a light brown oil (315 g, 102.2%).

A suspension of NaOEt (95 g, 1.4 mol) in anhydrous EtOH (0.8 kg) was stirred at 40–50 ≡C for 1 h; then $CNCH_2CO_2Et$ (170 g, 1.5 mol) was added to the solution. The resulting white suspension was heated to reflux for another 0.5 h and then cooled to –5 ≡C in an ice-salt bath and treated dropwise with a solution of the above **17** (315 g, 1.0 mol) in THF (0.8 kg) over 2 h, keeping the reaction temperature below 0 ≡C. The reaction mixture was then added to chilled water (6 kg), stirred and acidified to pH 2–3 with H_2SO_4. The resulting solid was collected, washed with H_2O (400 g × 3), and dried at 50 ≡C for 5 h to give crude **18**, which was recrystallized from 3:1 hexane/EtOAc (1 kg) to afford **18** (304 g, 79%) as an off-white solid, mp 85.2−88.2 °C. ^{1}H NMR ($CDCl_3$): δ 0.99 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 2.20−2.26 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.80 (t, J = 6.4 Hz, 2 H, $ClCH_2CH_2CH_2O$), 3.87 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 3.89 (s, 3 H, OCH_3), 4.26 (t, J = 6.0 Hz, 2 H, $ClCH_2CH_2CH_2O$), 7.09 (s, 1 H, Ar*H*), 7.78 (s, 1 H, Ar*H*), 10.35 (br s, 1 H, O*H*, enolization). ^{13}C NMR ($CDCl_3$): δ 14.32, 31.96, 42.20, 57.17, 60.00, 66.49, 80.85, 108.70, 111.86, 117.23, 127.75, 138.58, 148.34, 154.24, 164.17, 181.77. MS-ESI (*m*/*z*): 407.1 $(M+Na)^+$.

Anal. Calcd for $C_{16}H_{17}ClN_2O_7$: C, 49.94; H, 4.45; N, 7.28; Found: C, 49.78; H, 4.49; N, 7.20.

3-(4-(3-Chloropropoxy)-5-methoxy-2-nitrophenyl)-3-oxopropanenitrile (19)

A mixture of **18** (300 g, 0.78 mol), DMSO (900 g) and H_2O (100 g) was stirred at 100–110 ≡C for 30 min. Then the brown solution was cooled to around 50 ≡C, poured into chilled water (4 kg), and stirred for 1 h. The resulting precipitate was collected, washed with H_2O (300 g × 3) and 50% EtOH/H_2O (200 g × 1), dried at 60 ≡C for 4 h to give a brown solid, which was recrystallized from 1:1 hexane/EtOAc (0.8 kg) to afford **19** (200 g, 82%) as light-tan solid, mp 149.5−151.9 °C. ^{1}H NMR (DMSO-d_6): δ 2.19−2.26 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.79 (t, J = 6.8 Hz, 2 H, $ClCH_2CH_2CH_2O$), 3.94 (s, 3 H, OCH_3), 4.27 (t, J = 6.0 Hz, 2 H, $ClCH_2CH_2CH_2O$), 4.52 (s, 2 H, CH_2CN), 7.32 (s, 1 H, Ar*H*), 7.76 (s, 1 H, Ar*H*). ^{13}C NMR (DMSO-d_6): δ 31.75, 33.02, 42.06, 57.18, 66.57, 108.71, 110.67, 115.47, 128.97, 138.73, 149.41, 154.21, 191.71. MS-ESI (*m*/*z*): 335.0 $(M+Na)^+$.

Anal. Calcd for $C_{13}H_{13}ClN_2O_5$: C, 49.93; H, 4.19; N, 8.96; Found: C, 49.68; H, 4.15; N, 8.89.

2-(4-(3-Chloropropoxy)-5-methoxy-2-nitrobenzoyl)-3-(dimethylamino)acrylonitrile (20)

To a stirred suspension of **19** (131 g, 0.42 mol) in THF (0.5 kg) was added DMF-DMA (65.7 g, 0.55 mol). The mixture was stirred at room temperature for 2 h to give a light-yellow suspension. Hexane (0.5 kg) was added and the mixture was stirred at room temperature for 1 h, then cooled to around 10 ≡C in an ice-water bath. The resulting solid was collected, washed with 50% hexane /THF (100 g × 2), and dried at 40 ≡C to give a yellow solid **20** (127 g, 82%), mp 145.5 °C (dec.). ^{1}H NMR (DMSO-d_6): δ 2.19−2.26 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.33 (br s, 6 H, NC_2H_6), 3.80 (t, J = 6.4 Hz, 2 H, $ClCH_2CH_2CH_2O$), 3.92 (s, 3 H, OCH_3), 4.25 (t, J = 6.0 Hz, 2 H, $ClCH_2CH_2CH_2O$), 7.02 (s, 1 H, Ar*H*), 7.72 (s, 1 H, Ar*H*). ^{13}C NMR (DMSO-d_6): δ 31.93, 42.08, 47.96, 57.17,

66.21, 71.55, 99.10, 92.87, 108.67, 111.02, 138.73, 148.22, 148.33, 154.20, 181.06. MS-ESI (*m/z*): 390.1 $(M+Na)^+$.

Anal. Calcd for $C_{16}H_{18}ClN_3O_5$: C, 52.25; H, 4.93; N, 11.43; Found: C, 52.01; H, 4.99; N, 11.55.

7-(3-Chloropropoxy)-6-methoxy-4-oxo-1,4-dihydroquinoline-3-carbonitrile (12)

Compound **20** (184 g, 0.50 mol) and Raney Ni (wet, 30 g) were added to THF (2 kg), and stirred for 6 h at room temperature under a hydrogen atmosphere (balloon) to form a brown solution which was then filtered through a pad of Celite, the filter cake was washed by THF (150 g × 2). The combined filtrate was concentrated to give the product **12** as a brown solid, which was digested with 1:1 EtOH/EtOAc (250 g) at 60 ≡C for 2 h then cooled to room temperature, the resulting solid was collected and washed with 1:1 EtOH/EtOAc (50 g × 2), dried at 60 ≡C for 4 h to afford **12** (104 g, 71%) as an off-white solid, mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 2.23−2.30 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.80−3.85 (m, 2 H, $ClCH_2CH_2CH_2O$), 3.88 (s, 3 H, OCH_3), 4.17−4.21 (m, 2 H, $ClCH_2CH_2CH_2O$), 7.07 (s, 1 H, Ar*H*), 7.46 (s, 1 H, Ar*H*), 8.59 (s, 1 H, Py*H*), 12.50 (br s, 1 H, O*H*, enolization). ^{13}C NMR (DMSO-d_6): δ 31.77, 42.23, 56.27, 65.89, 93.21, 101.54, 104.93, 117.62, 119.73, 135.18, 145.33, 148.54, 153.17, 173.77. MS-ESI (*m/z*): 315.1 $(M+Na)^+$.

Anal. Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.44; H, 4.48; N, 9.57; Found: C, 57.58; H, 4.44; N, 9.52. HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 280 nm; Flow rate: 0.8 mL/min; Temperature: rt; Injection load: 2 μL; Solvent: acetonitrile; Run time: 5 min; Mobile phase: acetonitrile/water = 80/20, t_R: 0.490 min, purity: 98.6%.

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