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Zhizhen Barbara Zheng [a], Alan Xiangdong Wang [a], Paul Scola [a] & Stanley D'Andrea [a]
[a] Bristol-Myers Squibb, Discovery Chemistry, Pharmaceutical Research Institute, Wallingford, Connecticut, USA
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Improved Synthesis of 1-Chloro-6-methoxy-isoquinolin-3-ol and Its Derivatives

Zhizhen Barbara Zheng, Alan Xiangdong Wang, Paul Scola, and Stanley D'Andrea
Bristol-Myers Squibb, Discovery Chemistry, Pharmaceutical Research Institute, Wallingford, Connecticut, USA

Abstract: A convenient and efficient synthetic route to 1-chloro-6-methoxy-isoquinolin-3-ol and its derivatives is reported. This new method involves carboxylation of 4-methoxy-2-methylbenzonitrile, subsequent conversion of the resulting 2-cyano-5-methoxy-phenylacetic acid to its acid chloride, and acid-promoted cyclization of the 2-cyano-5-methoxy-phenyl-acetyl chloride. This procedure offers a better overall yield than the previously reported route and is also less hazardous and more reproducible.

Keywords: Carboxylation, cyclization, 1-chloro-6-methoxy-isoquinolin-3-ol, 4-methoxy-2-methylbenzonitrile

INTRODUCTION

A recent research project in our laboratory required a convenient synthesis of 1-chloro-6-methoxy-isoquinolin-3-ol. A literature search revealed that there was just one reported route to this compound and its desmethoxy derivative.[1,2] This synthetic route requires five steps and provides an overall yield of about 5.3% (Scheme 1). These steps include (1) carboxylation of 3-methyl-4-nitroanisole **1** using diethyl oxalate in the presence of sodium methoxide to give 5-methoxy-2-nitrophenylacetic acid **2**, (2) reduction of the nitro group with hydrogen in the presence

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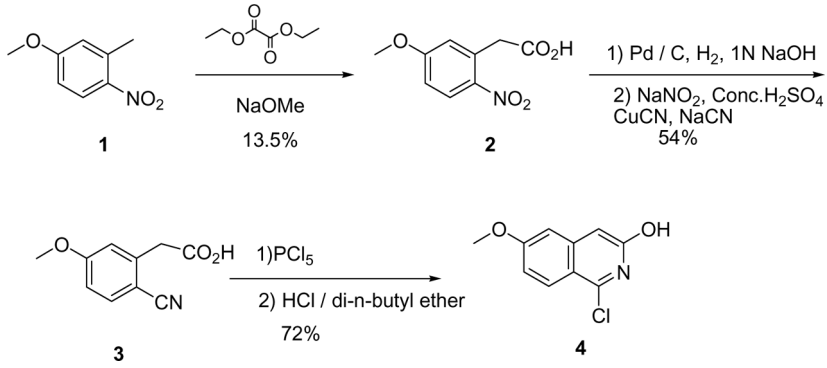
Address correspondence to Zhizhen Barbara Zheng, Bristol-Myers Squibb, Discovery Chemistry, Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492, USA. E-mail: zhizhen.zheng@bms.com

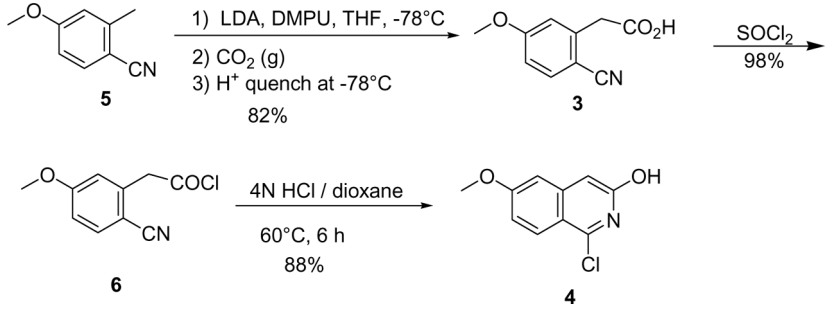


Scheme 1. Previously published route to **4**.

of 10% palladium/carbon to form 2-amino-5-methoxyphenylacetic acid, (3) Sandmeyer reaction of 2-amino-5-methoxyphenylacetic acid to give 2-cyano-5-methoxyphenylacetic acid **3**, (4) conversion of 2-cyano-5-methoxyphenylacetic acid to 2-cyano-5-methoxyphenylacetyl chloride by treatment with phosphorus pentachloride, and (5) hydrogen chloride–induced cyclization of 2-cyano-5-methoxyphenylacetyl chloride to form 1-chloro-6-methoxy-isoquinolin-3-ol **4**.

RESULTS AND DISCUSSION

In our hands, the Sandmeyer reaction was not very reproducible, which added to the difficulties in relying on this lengthy five-step procedure. We report here a short, efficient synthesis of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (Scheme 2) and its subsequent use in the preparation of isoquinolin-3-ol ethers.



Scheme 2. Improved route to 1-chloro-6-methoxy-isoquinolin-3-ol **4**.

We avoided the potentially problematic Sandmeyer reaction by starting with 4-methoxy-2-methylbenzonitrile **5**, which has the requisite cyano group already in place. Deprotonation[3] of 4-methoxy-2-methylbenzonitrile **5** using 1.4:1 lithium diisopropylamide (LDA)–1,3-dimethyl-3,4,5,6-tetrahyde-2(1H)-pyrimidone (DMPU) in tetrahydrofuran (THF) proceeded smoothly at −78 °C. The benzylic anion was treated with carbon dioxide to generate the desired acid **3**. [Acylation of the 4-methoxy-2-methylbenzonitrile anion with other electrophiles such as methyl chloroformate gave a mixture of mono and dicarboxylation products (4:1 mono–dicarboxylation)]. Pure **3** was easily isolated in 82% yield by precipitating it from an acidic aqueous solution. Because the benzylic protons in **3** were considered to be more acidic than the corresponding position in the starting material **5**, 2.4 eq. of LDA was used in the reaction to prevent quenching of the anion of **5** by **3**. We also noticed that an aqueous quench of this reaction needs to be performed at −78 °C to avoid obtaining both the mono- and dicarboxylated products. However, the dicarboxylated product can be easily converted to the desired monocarboxylated product **3** by treatment with trifluoroacetic acid (TFA) at room temperature for 10–20 min.[4] Thus, 2-cyano-5-methoxyphenylacetic acid **3** was prepared in a single step in 82% yield without the need for chromatographic purification. This synthesis of **3** is more efficient and reproducible than the Sandmeyer route discussed previously.[1] It is also safer because it avoids the use of toxic cyanide salts and potentially explosive diazonium compounds. Cyano-5-methoxyphenylacetyl chloride **6** was obtained by treatment of **3** with thionyl chloride. The acid chloride is then cyclized with commercially available 4 M hydrogen chloride in dioxane at 60 °C to form 1-chloro-6-methoxy-isoquinolin-3-ol, a process that presumably involves the intermediacy of the benzimidoyl chloride.[1] This procedure is more convenient than the literature conditions[2] in which **6** was dissolved in the highly peroxidizabledi-n-butyl ether prior to treatment with hydrogen chloride gas. The improved three-step synthesis of 1-chloro-6-methoxy-isoquinolin-3-ol **4** is straightforward and efficient with an overall yield of 70%.

We were also interested in alkylating and arylating 1-chloro-6-methoxy-isoquinolin-3-ol. Therefore, 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) was treated with potassium carbonate and various electrophiles (RX) in DMF to yield the alkylated products[5] (Scheme 3). The alkylation conditions and yields are summarized in Table 1. Both primary and second alkyl halides react with compound **4** to provide the ethers in good yield.

Alkylation of compound **4** with primary halides required shorter reaction time than the secondary halides. Benzylation was best carried out patiently at room temperature using benzyl bromide.

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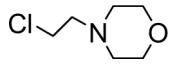
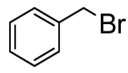
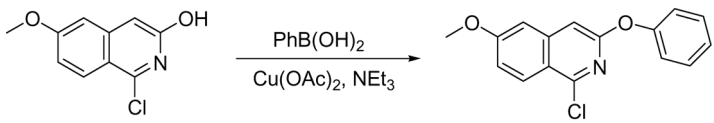
Scheme 3. Alkylation of 1-chloro-6-methoxy-isoquinolin-3-ol **4**.

Table 1. Alkylation of phenol **4**

Compound	RX	Temperature (°C)	Time (hours)	Yield (%)
7	MeI	80	3	77
8	EtI	80	3	83
9		80	3	66
10		80	3	65
11		80	5	71
12		80	6	79
13		Rt	2 days	87

The arylation of 1-chloro-6-methoxy-isoquinolin-3-ol was accomplished in modest yield by a copper-promoted cross-coupling reaction with phenylboronic acid as depicted in Scheme 4.[6]

In conclusion, we have developed an improved three-step synthesis of 1-chloro-6-methoxy-isoquinolin-3-ol that offers a better overall yield than the previously reported procedure.[1,2] In addition, we have shown



4 14

Scheme 4. Arylation of 1-chloro-6-methoxy-isoquinolin-3-ol **4**.

that alkylation and arylation of 1-chloro-6-methoxy-isoquinolin-3-ol **4** yields a variety of isoquinolin-3-ol ethers.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker 300 or 500 megahertz (MHz) spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2). All liquid chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-vis detector, and mass spectrometry (MS) data were determined with a Micromass Platform for LC in electrospray mode (ES+). Melting points were recorded on a EZ-Melt automated melting-point apparatus by Stanford Research Systems.

(2-Cyano-5-methoxy-phenyl)-acetic Acid (3)

A mixture of LDA (2.0 M in heptane/THF/ethyl benzene, 122.40 mL, 244.80 mmol) in 300 mL of THF was cooled to –78 °C, and 21.60 mL of DMPU [1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone] was added slowly. The reaction was stirred for 5 min. A solution of 4-methoxy-2-methyl-benzonitrile (15.00 g, 102.0 mmol) in 20 mL of THF was added, and the mixture was maintained at –78 °C for 2 h to form a deep red solution. Carbon dioxide gas was introduced into the reaction mixture at –78 °C until complete decolorization occurred and the red solution had turned nearly colorless. Water (100 mL) was added at –78 °C, and the reaction mixture was warmed to rt. The reaction mixture was extracted with 200 mL of ether, and the separated aqueous phase was adjusted to pH 1 with 6 M HCl. A white solid precipitated from the acidic aqueous solution and was collected by filtration, washed with H_2O, and dried in vacuo to give 16 g of **3** as an off-white solid (82%); mp = 213.1–214.5 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 3.83 (s, 2H), 3.86 (s, 3H), 6.99 (m, 2H), 7.64 (d, $J = 8.42$ Hz, 1H). HRMS calcd. for $[C_{10}H_9ClNO_3 + 1]^+$: 192.0661; found: 192.0669.

(2-Cyano-5-methoxy-phenyl)-acetyl Chloride (6)

Ten mL of $SOCl_2$ was added to a mixture of (2-cyano-5-methoxyphenyl) acetic acid (**3**) (1.77 g, 9.26 mmol) in 10 mL of CH_2Cl_2. The mixture was stirred at rt for 3 h and then placed in a refrigerator for 2 days before

concentrating in vacuo to yield 1.90 g (98%) of the acid chloride **6,** an orange oil. This material was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (m, 3H), 4.35 (s, 2H), 6.92 (m, 2H), 7.63 (d, $J = 8.78$ Hz, 1H).

1-Chloro-6-methoxy-isoquinolin-3-ol (4)

First Procedure

A mixture of (2-cyano-5-methoxyphenyl)acetyl chloride (**6**) (18.00 g, 86.12 mmol) in 200 mL of 4 N HCl/dioxane was heated at 60 °C for 6 h. The reaction mixture was cooled to rt and concentrated in vacuo to afford a brown solid, which was recrystallized from EtOH to provide 10.00 g (56%) of pure **4** as an off-white solid (an additional 6.01 g of impure **4** was recovered from the mother liquors); mp = 203.2–205.5 °C, lit.[2] mp = 211 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 3.98 (s, 3H), 6.94 (s, 1H), 7.14 (m, 2H), 8.10 (d, $J = 9.16$ Hz, 1H). HRMS calcd. for $[C_{10}H_8ClNO_2 + 1]^+$: 210.0322; found: 210.0331.

Alternate Procedure

A solution of 2-(2-cyano-5-methoxyphenyl)acetyl chloride (**6**) (6.40 g, 30.62 mmol) in 4 M HCl/1,4-dioxane (100 mL) was heated in a sealed vessel at 60 °C with stirring overnight. After cooling to rt, the solids were collected by filtration, and the filter cake washed thoroughly with EtOAc. The solid was dried in vacuo to provide 6.14 g (96%) of **4** as a fine, pale yellow powder.

General Procedure for Alkylation of 4

Preparation of 1-Chloro-3,6-dimethoxyisoquinoline (**7**)

Methyl iodide (607 μL, 0.95 mmol) and K_2CO_3 (0.13 g, 0.95 mmol) were added to a mixture of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (0.10 g, 0.48 mmol) in 3 mL of DMF. The mixture was heated at 80 °C for 3 h, cooled to rt, and concentrated in vacuo to afford a brown solid. The crude product was purified by flash chromatography eluting with 10% EtOAc/hexane to isolate 82 mg (77%) of **7** as a white solid; mp = 135.1–136.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.80 (s, 1H), 6.89 (d, $J = 2.56$ Hz, 1H), 7.03 (dd, $J = 9.15$, 2.56 Hz, 1H), 8.06 (d, $J = 9.51$ Hz, 1H). HRMS calcd. for $[C_{11}H_{10}ClNO_2 + 1]^+$: 224.0478; found: 224.0488.

1-Chloro-3-ethoxy-6-methoxyisoquinoline (8)

Compound **8** was prepared in a manner similar to that described previously to provide 188 mg (83%) of **8** as a tan solid, mp = 89.0–90.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (t, $J = 7.02$ Hz, 3H), 3.92 (m, 3H), 4.36 (q, $J = 7.02$ Hz, 2H), 6.79 (s, 1H), 6.89 (d, $J = 2.44$ Hz, 1H), 7.03 (dd, $J = 9.46$, 2.44 Hz, 1H), 8.06 (d, $J = 9.16$ Hz, 1H). HRMS calcd. for $[C_{12}H_{12}ClNO_2 + 1]^+$: 238.0635; found: 238.0623.

1-Chloro-6-methoxy-3-propoxy-isoquinoline (9)

n-Propyl iodide (160 mg, 0.95 mmol) and K_2CO_3 (132 mg, 0.95 mmol) were added to a mixture of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (100 mg, 0.48 mmol) in 2 mL of DMF. The mixture was heated at 80 °C for 2 h, cooled to rt, and concentrated in vacuo to obtain a brown solid. The crude product was purified by flash chromatography, eluting with 10% EtOAc/hexane to isolate 80 mg (66%) of **9** as a colorless oil, which was solidified as a white solid on standing at rt; mp = 45.1–45.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, $J = 7.32$ Hz, 3H), 1.84 (m, 2H), 3.91 (s, 3H), 4.25 (t, $J = 6.77$ Hz, 2H), 6.80 (s, 1H), 6.89 (d, $J = 2.56$ Hz, 1H), 7.03 (dd, $J = 9.15$, 2.56 Hz, 1H), 8.06 (d, $J = 9.51$ Hz, 1H). HRMS calcd for $[C_{13}H_{14}ClNO_2 + 1]^+$: 252.0791; found: 252.0794.

4-(2-(1-Chloro-6-methoxyisoquinolin-3-yloxy)ethyl)morpholine (10)

4-(2-Chloroethyl)morpholine hydrochloride (222 mg, 1.49 mmol) and K_2CO_3 (414 mg, 3.00 mmol) were added to a mixture of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (209 mg, 1.00 mmol) in 3 mL of DMF. The mixture was heated at 80 °C for 3 h, cooled to rt, and concentrated in vacuo to obtain a brown solid. The crude product was then purified by flash chromatography eluting with 10% methanol in ethyl acetate to isolate 210 mg (65%) of **10** as a white solid; mp = 73.2–73.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (m, 4H), 2.81 (t, $J = 5.65$ Hz, 2H), 3.69-3.75 (m, 4H), 3.91 (s, 3H), 4.48 (t, $J = 5.80$ Hz, 2H), 6.84 (s, 1H), 6.88 (d, $J = 2.14$ Hz, 1H), 7.04 (dd, $J = 9.31$, 2.29 Hz, 1H), 8.05 (d, $J = 9.46$ Hz, 1H). HRMS calcd. for $[C_{16}H_{94}ClNO_2 + 1]^+$: 323.1162; found: 323.1172.

1-Chloro-3-isopropoxy-6-methoxy-isoquinoline (11)

Compound **11** was prepared from 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (100 mg, 0.48 mmol), isopropyl iodide (138 mg, 0.95 mmol), and

K_2CO_3 (132 mg, 0.95 mmol) in DMF as described in the general procedure to give 85 mg (70%) of **11** as a yellow solid; mp = 78.0–78.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.38 (s, 3H), 3.91 (s, 3H), 5.24 (m, 1H), 6.77 (s, 1H), 6.86 (d, $J = 2.20$ Hz, 1H), 7.02 (dd, $J = 9.15$, 2.56 Hz, 1H), 8.04 (d, $J = 9.15$ Hz, 1H). HRMS calcd. for $[C_{13}H_{14}ClNO_2 + 1]^+$: 252.0791; found: 252.0788.

1-Chloro-3-(cyclopentyloxy)-6-methoxyisoquinoline (12)

Cyclopentyl iodide (215 mg, 1.10 mmol) and K_2CO_3 (264 mg, 1.91 mmol) were added to a mixture of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (209 mg, 1.00 mmol) in 2 mL of DMF. The mixture was heated at 80 °C for 6 h, cooled to rt, and concentrated in vacuo to obtain a brown solid. The crude product was then purified by flash chromatography, eluting with 10% ethyl acetate in hexane to isolate 220 mg (79%) of **12** as a white solid; mp = 86.0–87.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58–1.70 (m, 2H), 1.78–1.92 (m, 4H), 1.92–2.04 (m, 2H), 3.91 (s, 3H), 5.22–5.35 (m, 1H), 6.75 (s, 1H), 6.88 (d, $J = 2.14$ Hz, 1H), 7.03 (dd, $J = 9.31$, 2.29 Hz, 1H), 8.05 (d, $J = 9.16$ Hz, 1H). HRMS calcd. for $[C_{15}H_{16}ClNO_2 + 1]^+$: 278.0948; found: 278.0954.

3-Benzyloxy-1-chloro-6-methoxy-isoquinoline (13)

Benzyl bromide (87 mg, 0.50 mmol) and K_2CO_3 (87 mg, 0.63 mmol) were added to a mixture of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (97 mg, 0.46 mmol) in 3 mL of DMF. The mixture was stirred at rt for 2 days, and then concentrated in vacuo to obtain a brown solid. The crude product was then purified by flash chromatography, eluting with 5% ethyl acetate in hexane to isolate 120 mg (87%) of **13** as a white solid; mp = 116.8–117.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 5.42 (s, 2H), 6.88 (d, $J = 2.56$ Hz, 2H), 7.04 (dd, $J = 9.33$, 2.38 Hz, 1H), 7.34 (m, 3H), 7.49 (d, $J = 6.59$ Hz, 2H), 8.07 (d, $J = 9.15$ Hz, 1H). HRMS calcd. for $[C_{17}H_{14}ClNO_2 + 1]^+$: 300.0791; found: 300.0797.

1-Chloro-6-methoxy-3-phenoxy-isoquinoline (14)

Phenylboronic acid (580 mg, 4.75 mmol), Et_3N (480 mg, 4.75 mmol), and copper acetate (440 mg, 2.43 mmol) were added to a mixture of 1-chloro-6-methoxy-isoquinolin-3-ol (**4**) (500 mg, 2.39 mmol) in 10 mL of CH_2Cl_2.. The mixture was stirred at rt for 18 h. It was then concentrated

in vacuo to obtain a brown-green solid. This crude product was purified by flash chromatography, eluting with 10% EtOAc/hexane to isolate 50 mg (7.3%) of **14** as a white solid; mp = 124.1–125.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.81 (s, 1H), 6.90 (d, $J = 2.44$ Hz, 1H), 7.13 (m, 3H), 7.21 (t, $J = 7.48$ Hz, 1H), 7.41 (t, $J = 7.93$ Hz, 2H), 8.13 (d, $J = 9.16$ Hz, 1H). HRMS calcd. for $[C_{16}H_{12}ClNO_2 + 1]^+$: 286.0635; found: 286.0629.

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