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Technical Notes

Efficient Multikilogram Synthesis of 5-Bromo-2-cyclopropyl-1-methyl-1*H*-imidazole

Rogelio P. Frutos,* Sonia Rodríguez, Nitinchandra Patel, Joe Johnson, Anjan Saha, Dhileepkumar Krishnamurthy, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877-0368, U.S.A.

Abstract:

Herein we describe the optimization and application of a copper(I) chloride-mediated protocol for the multikilogram synthesis of 5-bromo-2-cyclopropyl-1-methyl-1*H*-imidazole hydrochloride (1), a key building block used in the preparation of several biologically active small molecules.

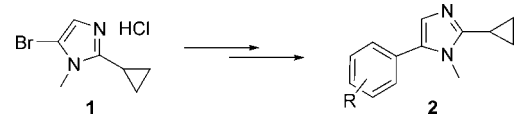
Introduction

Substituted imidazoles are important building blocks commonly found in natural products as well as in active pharmaceutical ingredients.[1] Although deceptively simple in structure, practical, regioselective, economical, and scalable synthetic routes to these heterocycles remain scarce[2] or, depending on the particular imidazole substitution pattern, virtually nonexistent. The need to attain rapid access to a number of these compounds to support preclinical activities in one of our therapeutic areas prompted us to develop an expedient CuCl-mediated synthesis of imidazoles with varied substitution patterns from nitriles and α-amino acetals.[3] Herein we describe the optimization and application of our CuCl-mediated protocol for the multikilogram synthesis of 5-bromo-2-cyclopropyl-1-methyl-1*H*-imidazole hydrochloride (**1**), a key building block used in the preparation of several small molecules with potential therapeutic value (Scheme 1).[4]

Results and Discussion

Most of the general methods reported for the synthesis of 1,2-disubstituted imidazoles such as **1** from acyclic precursors rely on imidates generated upon the treatment of nitriles with strong protic or Lewis acids[2e] or from the treatment of amides with Meerwein salts[5] (Scheme 2). To the imidate precursors an appropriate N-alkyl or N-aryl amine acetal is added to give amidines that give the desired imidazoles upon cyclization. Careful evaluation of these methods revealed several issues that rendered them far from ideal for the economical, safe and efficient multi-kilogram synthesis of **1**. Among the detrimental attributes observed were the long reaction time for the synthesis and crystallization of imidate hydrochloride **4**, the relatively high cost of the trialkyloxonium fluoroborate (Meerwein salts) for the formation of **8**, the hygroscopic nature and the tendency of both **4** and **8** to decompose upon storage, and the low recovery of **6** after an aqueous workup.

Scheme 1. **Use of 1 as a building block**



To circumvent the above complications resulting from the synthesis and handling of amidines such as **4** and **8**, an expedient CuCl-promoted protocol for the synthesis of an assortment of substituted imidazoles was developed,[3] and the methodology was successfully applied to the synthesis of **6**. Accordingly, **6** was synthesized in one pot upon treating a mixture of aminoacetal **5** and cyclopropanecarbonitrile **3** with CuCl, followed by addition of HCl in methanol (Scheme 3). Nevertheless, further refinements were needed to make the procedure suitable for scale-up. First among the issues that needed attention prior to the implementation of our protocol in fixed equipment was an effective way to remove copper. Initial experiments indicated that removal of copper salts at the amidine (**9**) stage rather than at the imidazole (**6**) stage resulted in a much easier filtration and a modest increase in yield. Different solvents were also investigated (MTBE, THF, IPAc, MeOH, etc.) during workup, and IPAc was found to be a good solvent to improve filtration. Attempts to remove the copper salts by extraction into aqueous ammonia resulted in very poor yields, due to the high water solubility of **6** and **9**. Higher yields were obtained by addition of 50% aqueous NaOH to the reaction mixture upon formation of **9** followed by filtration. Nevertheless, the filtration turned out to be very slow and laborious due to the viscosity of the mixture, and it did not improve significantly with the use of

* To whom correspondence should be addressed. E-mail: rfrutos@rdg.boehringer-ingelheim.com.

(1) (a) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. *Mini-Rev. Med. Chem.* **2005**, *5*, 319. (b) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196 and references cited therein. (c) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, U.K., 1996; Vol. 3, p 77.

(2) (a) Murry, J. A. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 945. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. (c) Dolensky, B.; Nam, G.; Deng, W.-P.; Narayanan, J.; Fan, J.; Kirk, K. L. *J. Fluorine Chem.* **2004**, *125*, 501. (d) Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153. (e) Lawson, A. *J. Chem. Soc.* **1957**, 4225.

(3) Frutos, R. P.; Gallou, I.; Reeves, D.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2005**, *46*, 8369.

(4) Cogan, D.; Hao, M.-H.; Kamhi, V. M.; Miller, C. A.; Netherton, M. R.; Swinamer, A. D. Patent WO 2005090333 A1, 2005.

(5) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1988**, *44*, 7063 and references cited therein.

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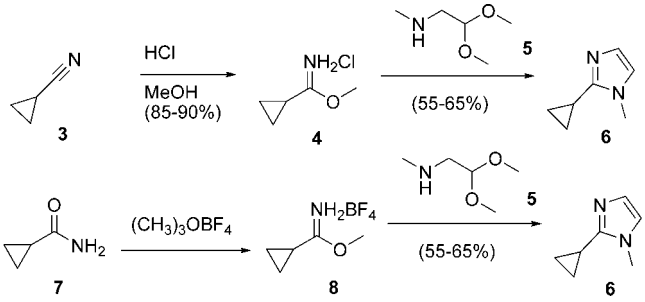
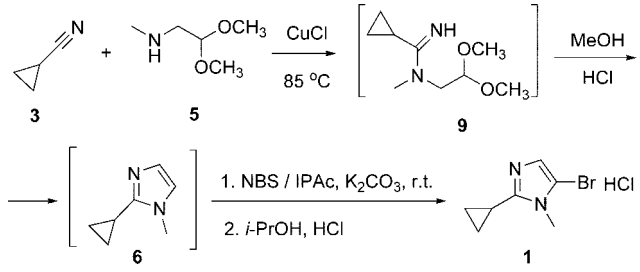
Scheme 2. **Established methods for the synthesis of 1,2-disubstituted imidazoles**



Scheme 3. **New process for the synthesis of 1**



filtering agents such as Celite or cellulose filter aid. A major improvement came about by addition of thioacetamide to the crude reaction mixture containing **9** followed by a filtration through a pad of Celite. Under these conditions the filtration was significantly faster, due to the reduced viscosity of the copper complex that presumably forms upon addition of thioacetamide.

Isolation of imidazole **6** was not practical for scale-up due to its high solubility in water, low molecular weight, and volatility, which reduced the yield upon isolation. Instead, a solution of crude **6** was directly submitted to bromination conditions. Both THF and IPAc could be used as solvent, although the latter was chosen on the basis of the ease of transition between the imidazole formation step and the bromination. Optimization of the concentration was required in order to minimize bis-brominated byproducts.[6] In this way, the synthesis of **1** from **6** was straightforward and regioselective and the undesired regioisomer of **1** that would result from bromination at C-4 of the imidazole was not observed. The side product resulting from bis-bromination was observed in small amounts (approximately 1–2%), and the major impurities were dimers (5–6%) that most likely result from dimerization of **1** catalyzed by residual copper left over from the previous step. The progress of the reaction and impurity profile of the product were monitored by HPLC. After completion of the reaction, the bromoimidazole was isolated and purified as the hydrochloride salt to provide a stable, easy to handle solid with a good impurity profile.

The above optimization efforts allowed for the successful synthesis of multikilogram quantities of **1** in fixed equipment at the pilot plant. Accordingly, the synthesis could be carried out safely and conveniently in a 50 L or larger reactor by heating a mixture of (methylamino)acetaldehyde dimethyl acetal **5** and cyclopropane carbonitrile **3** to ca. 85–87 °C in the presence of CuCl to form amidine **9**. After treatment with thioacetamide to facilitate filtration of copper salts, **9** was cyclized using concentrated HCl at reflux, affording imidazole **6**. A solvent switch to IPAc followed by treatment with NBS and potassium carbonate gave rise to **1** in 48% isolated yield after salt formation using 5–6 M HCl in IPA.

(6) It was determined that the optimum concentration for the bromination reaction was 25 mL/g of imidazole **6**, since higher concentrations resulted in higher levels of bis-bromination (approximately 7–8%).

Conclusion

In summary, we have described the optimization and application of an expedient and efficient CuCl-promoted protocol for the synthesis of substituted imidazoles.[3] The introduction of thioacetamide as complexating agent facilitated the filtration of the copper salts, which otherwise was very sluggish on a large scale. Imidazole **6** was converted into bromide **1**, which was isolated and purified by formation of the corresponding hydrochloride salt. The development of this process has enabled us to generate 5-bromo-2-cyclopropyl-1-methyl-1*H*-imidazole hydrochloride (**1**) in sufficient amounts for further synthetic steps towards biologically active small molecules.

Experimental Section

General Considerations. Reagents were used as purchased without further purification. NMR spectra were recorded on a Bruker 400 MHz spectrometer. The chemical shift data are reported in units of δ (ppm) downfield from tetramethylsilane, which was used as an internal standard; coupling constants (J) are reported in hertz and refer to apparent peak multiplicities. GC analysis was performed on an Agilent 6890N series using a Restek RTX-5 amine column: 70 °C for 2 min, 25 °C/min to 250 °C, hold at 250 °C for 3 min. HPLC analysis was performed on an Agilent 1100 series using a Cadenza CD-C18 column, flow rate 1 mL/min, with a UV detection at 220 nm: mobile phase 10% acetonitrile in water (20 nM KPF_6, 0.1% H_3PO_4) for 2 min, to 60% acetonitrile in water in 8 min, and then back to 95% acetonitrile in water in 10 min.

Preparation of 5-Bromo-2-cyclopropyl-1-methyl-1*H*-imidazole Hydrochloride (1). To a solution of **5** (3.06 kg, 25.7 mol) and **3** (2.58 kg, 38.5 mol) was added CuCl (3.18 kg, 32.1 mol) in five portions over a period of 30 min, while the temperature was maintained between 0 and 20 °C. The reaction mixture was stirred at 87 °C for 22 h. After the mixture was cooled to 50 °C, MeOH (5.24 kg) was added and the mixture was further cooled to 0–5 °C with vigorous stirring. Thioacetamide (2.43 kg, 32.1 mol) was added in five portions over a period of 30 min while the temperature was maintained between 0 and 25 °C, and the mixture was stirred for an additional 1 h at 45 °C. The mixture was filtered through a pad of Celite that was then rinsed with MeOH (5.3 L). The filtrate was cooled to −5 °C, and 12 M HCl (4.6 L) was added slowly over a 20 min period, with the temperature maintained below 20 °C. The resulting mixture was heated to reflux and stirred for 3 h. The mixture was distilled under reduced pressure, IPAc was added, and distillation was continued to remove residual MeOH. The mixture was dissolved in IPAc (1.15 L), cooled to 0 °C, and basified to pH 11–12 by the addition of 40% aqueous NaOH (7.72 kg), with the temperature being kept below 20 °C. After

it was stirred for an additional 30 min at ambient temperature, the mixture was filtered through a pad of Celite, the bed being rinsed with IPAc (4 L) and water (1.1 L). The aqueous layer was extracted with IPAc (2 × 3.7 L), and the organic layers were combined.

The combined organic stream (1.97 kg in 15 kg solution) and K_2CO_3 (513 g) was diluted with IPAc (25.26 kg). A Karl Fisher titration was carried out on the above solution to ensure the water content was below 2%. After the solution was cooled to 5 °C, NBS (3.10 kg) was added in six portions over 5–15 at approximately 30 min intervals. After it was stirred for 10 min after the last addition, the reaction mixture was quenched with a 20% aqueous solution of K_2CO_3 (10.61 kg) and stirred overnight. The organic layer was washed three more times with 20% aqueous K_2CO_3 (8.9, 6.5, and 7.2 kg). The organic layer was distilled under vacuum at 30 °C. IPAc (4.84 kg) was added, and the distillation was continued until the IPAc content was less than 8% by weight. The crude material was dissolved in IPA (1.7 kg), cooled to 0 °C, and treated with a 5–6 M solution of HCl in IPA (1.1 equiv of HCl) over 2 h, the temperature being kept below 15 °C. The reaction mixture was stirred at 22 °C for 3 h and filtered. The solid was rinsed with IPA (1.1 kg) and dried under vacuum at 50 °C to afford 2.9 kg (48% from **5**) of **1** as an off-white solid. ^{1}H NMR (400 MHz, methanol-d_4): δ 7.60 (s, 1H), 3.87 (s, 3H), 2.29 (dt, J = 8.0, 4.8 Hz, 1H), 1.6–1.28 (m, 2H), 1.18–1.11 (m, 2H). ^{13}C NMR (100 MHz, methanol-d_4): δ 151.1, 119.6, 109.0, 33.8, 7.7, 7.3; HRMS: m/z calcd for $C_7H_{10}BrN_2$ 201.0021 (MH+), found 201.0027.

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Supporting Information Available

^{1}H and ^{13}C NMR spectra are available for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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