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Cost-Effective and Scalable Synthesis of 4-Bromo-1,2-dimethyl-1*H*-imidazole: A Key Building Block for Bioactive Molecules

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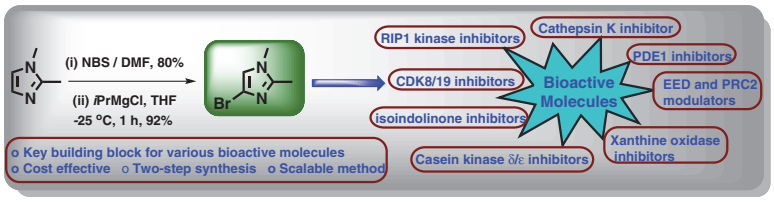

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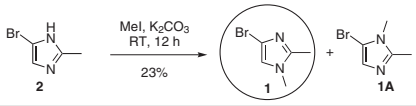
Abstract A cost-effective, scalable, high-yielding, and commercially viable synthesis of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**), an important building block to construct various bioactive molecules has been established. The main feature of this method includes the selection of appropriate starting material 1,2-dimethyl-1*H*-imidazole in which the existing issue of regioisomer formation is circumvented and the selective debromination is accomplished by using isopropyl magnesium chloride.

Key words bromination, debromination, imidazole derivative, cost-effective, scalable

4-Bromo-1,2-dimethyl-1*H*-imidazole (**1**) (Figure 1) has been identified as a promising key building block for the construction of various active pharmaceutical ingredients (APIs).[1] The structural motif of **1** has been utilized in several diversified bioactive compounds such as cathepsin K inhibitor,[1a] xanthine oxidase inhibitors,[1b] EED and PRC2 modulators,[1c] PDE1 inhibitors,[1d] casein kinase δ/ε inhibitors,[1e] CDK8/19 inhibitors,[1f] isoindolinone inhibitors,[1g] RIP1 kinase inhibitors,[1h] mGlu4 receptor positive allosteric modulators,[1i] and TGFb inhibitors,[1j] as illustrated in Figure 1.

As part of a medicinal chemistry effort focused on the identification of a casein kinase δ/ε inhibitor for anticancer therapy,[1e] compound **V** was identified and progressed into development; this necessitated a robust and scalable synthesis to produce larger quantities for further clinical evaluation. The reported first-generation synthesis[1e] to make **V** was revisited and it was found that the main issue would be sourcing the large quantity of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**). As reliability on commercial sources for larger quantities remained challenging, an in-house effort to develop a robust route to synthesize **1** was critical. One of the options of synthesizing **1** was described by Efremov *et al.*[1c] and Nichols *et al.*[2] involves methylating 5-bromo-2-methyl-1*H*-imidazole (**2**) (Scheme 1), resulting in a mixture of two regioisomers 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**) and 5-bromo-1,2-dimethyl-1*H*-imidazole (**1A**), which were separated by preparative-TLC to afford the desired **1** in 23% yield. It was a big challenge to prepare larger quantities of **1** using this methodology; thus, an alternate approach was required.



Scheme 1 Reported synthesis of **1**

First-Generation Synthesis of V

The first-generation synthesis of **V**, given in Scheme 2,[1e] started with Suzuki–Miyaura coupling of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**) and 4-fluorophenylboronic acid to afford **3** in 60% yield. Bromination of **3** using NBS in MeOH gave **4** in 80% yield, and subsequent Suzuki–Miyaura coupling with the in-house synthesized boronate **5** resulted in **6** in 40% yield. Deacetylation of **6** using HCl afforded the amine in quantitative yield, which was taken for the amidation with 3-fluoro-pyridine-4-carboxylic acid to give the desired API **V** in 40% yield.

Alternate Approaches for Imidazole Intermediate 3

Alternative approaches involved the construction of the imidazole ring of **3** from the corresponding bromoketone **7**, followed by methylation and bromination, as shown in

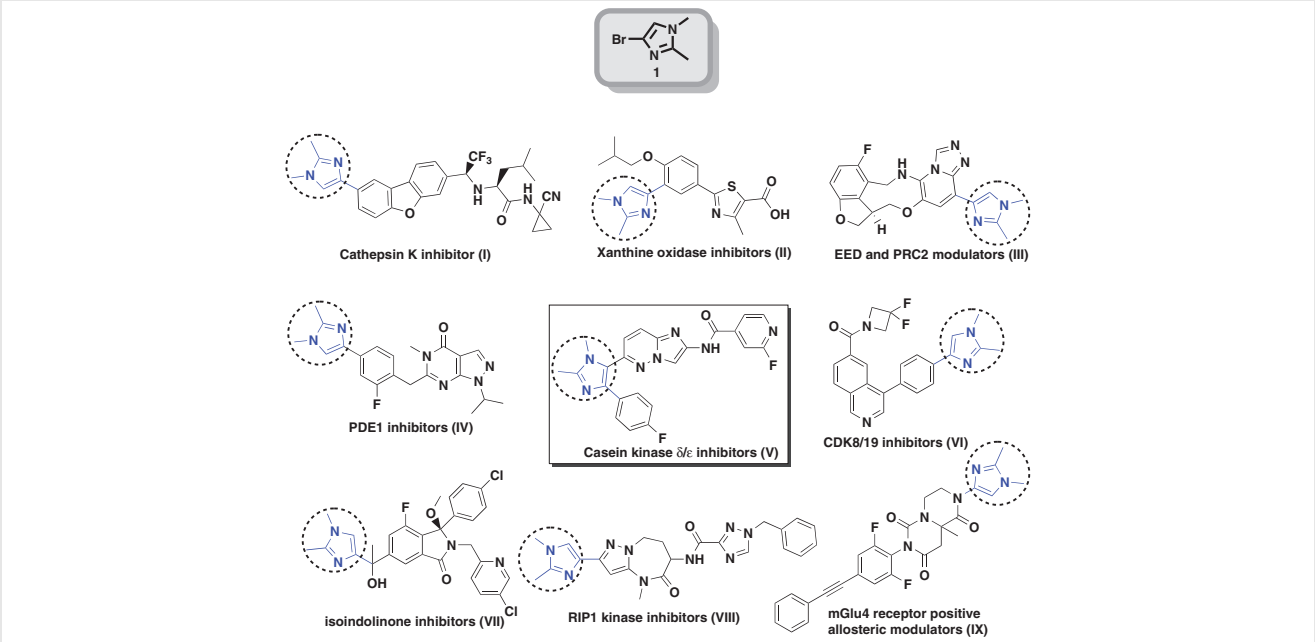
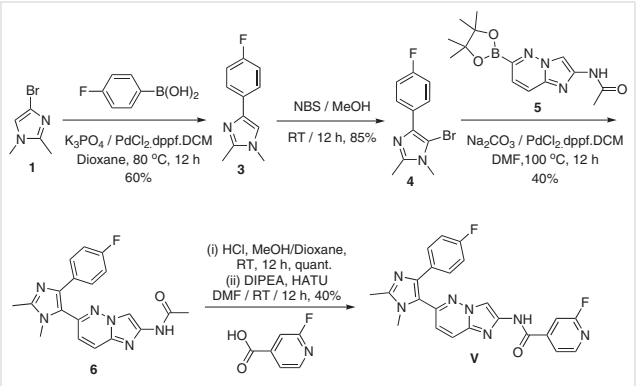
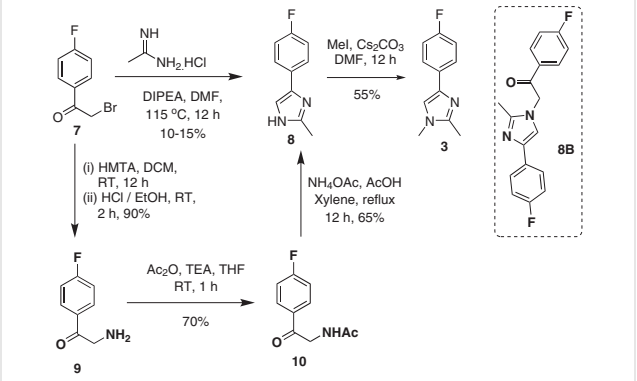


Figure 1 Structure of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**) and selected examples of bioactive compounds with **1** as a building block



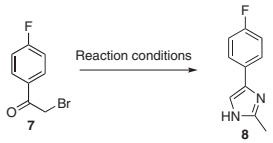
Scheme 2 First-generation synthesis of the desired API **V**[1e]



Scheme 3 Alternate attempts for the synthesis of intermediate **3**

Scheme 3. Initial efforts to obtain **8** by reaction of 2-bromo-1-(4-fluorophenyl)ethan-1-one (**7**) with acetamidine HCl salt in the presence of different bases and solvents resulted exclusively in the formation of either **8B** or a mixture of **8** and **8B**.[3] Model reaction using 3 equivalents of DIPEA at 50 °C resulted in 12–25% yield of undesired **8B** instead of the desired product **8**. It was found that as soon as compound **8** was formed, it further reacted with **7** to afford *N*-alkylated undesired product **8B**. A similar observation of the formation of *N*-alkylated intermediate **8B** in a greater ratio was reported earlier.[4] Increasing the temperature from 50 to 100 °C did not help to get the desired product (Table 1, entry 2). Further, changing the solvent from DMF to CH_3CN, and screening of other bases such as potassium carbonate or sodium hydroxide, did not give the desired product **8** (entries 3–5). As we could not obtain the desired product **8** in a single step, we followed the stepwise approach based on the earlier reports,[5,1e] as shown in Scheme 3. 4-Fluorophenacyl bromide **7** was converted into its corresponding amine **9** using hexamethylenetetramine in 90% yield, which was further acetylated using acetic anhydride and triethylamine to give **10**, with 70% yield. The acetylated compound **10** was reacted with NH_4OAc to give the desired imidazole intermediate **8** in 65% yield. The reaction of **8** with MeI in the presence of Cs_2CO_3 at room temperature for 12 h resulted in the desired 4-(4-fluorophenyl)-1,2-dimethyl-1*H*-imidazole (**3**) in 55% yield, along with minor quantities of its regioisomer. Though the approach was successful in making compound **3** and could afford the desired API **V** following the first-generation scheme, due to the longer sequence and challenges in separating the regioisomer at intermedi-

Table 1 Attempts to Synthesize Compound **8**



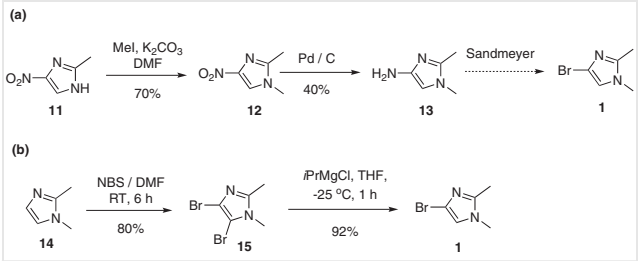
Entry	Reaction conditions[a]	**8**/**8B** (%)[b]
1	acetamidine (1.2 equiv), DIPEA (3 equiv), DMF, 50 °C, 12 h	0/12
2	acetamidine (1.2 equiv), DIPEA (3 equiv), DMF, 100 °C, 12 h	4/30
3	acetamidine (1.2 equiv), DIPEA (3 equiv), MeCN, 80 °C, 12 h	0/24
4	acetamidine (1.2 equiv), K_2CO_3 (3 equiv), DMF, 100 °C, 12 h	10/32
5	acetamidine (1.2 equiv), NaOH (3 equiv), DMF, 100 °C, 12 h	0/18

[a] All the reactions were carried out with a 2 mmol scale with solvent (2 mL).
[b] ^{1}H NMR conversions.

ate **3**, we realized that it was not worth pursuing the approach shown Scheme 3 to make the required intermediate **3**.

Scalable Synthesis of 4-Bromo-1,2-dimethyl-1*H*-imidazole (1)

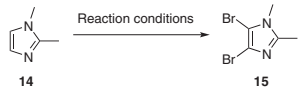
Based on literature precedence, the team came up with two different routes to synthesize compound **1** (Scheme 4). According to Scheme 4a, methylation of **11** followed by reduction of the nitro group to amine intermediate **13**, and Sandmeyer's deaminative bromination afforded **1**. The alternative route (Scheme 4b) commenced from commercially available 1,2-dimethyl-1*H*-imidazole **14**.



Scheme 4 (a) First alternate synthesis of **1** (b) Final optimized scheme for the synthesis of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**).

N-Methylation was performed on 2-methyl-4-nitro-1*H*-imidazole by following a reported protocol with methyl iodide and potassium carbonate (Scheme 4a) to give **12** in 70% yield.[5] Reduction of nitro to amine by hydrogenation with Pd/C or iron powder yielded **13** in poor yields.[6] Moreover, the conversion of amine **13** into the corresponding bromide *via* Sandmeyer reaction was not successful. For these reasons, Scheme 4a was abandoned. Based on our hypothesis, we started exploring the synthesis of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**15**) starting from commercially available 1,2-dimethyl-1*H*-imidazole (**14**). Bromination of **14** was performed with NBS by following a reported procedure,[7] and optimization of the reported conditions gave better yields of **15** (Table 2). Here different solvents such as MeCN, DMF, and toluene were screened, and DMF was found to be a better solvent for this transformation (entries 1, 4, and 7). Interestingly, the time interval of the reaction also played a crucial role in achieving good yields (entries 4–6) of about 80%. Notably, the NBS-DMF system has associated safety concerns during scale up.[8]

Table 2 Optimization of Dibromination



Entry	Reaction conditions[a]	Yield (%)[b]
1	NBS (2 equiv), MeCN, r.t., 3 h	48
2	NBS (2.5 equiv), MeCN, 50 °C, 3 h	65
3	NBS (2.5 equiv), MeCN, 50 °C, 12 h	63
4[7f]	NBS (2 equiv), DMF, r.t., 3 h	70
5	NBS (2.5 equiv), DMF, r.t., 6h	80
6	NBS (2 equiv), DMF, r.t., 12 h	75
7	NBS (2 equiv), toluene, r.t., 12 h	54

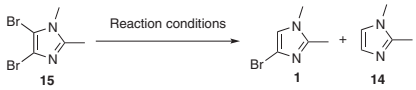
[a] All the reactions were carried out with 2 mmol **14** and solvent (2 mL).
[b] ^{1}H NMR conversion.

Optimization of Selective Debromination

Upon successful synthesis of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**15**), we turned our attention towards the selective debromination of **15**. Based on the literature,[9] an investigation was started to find suitable conditions for the selective debromination (Table 3). The reaction of **15** with tetramethylammonium fluoride (TMAF)[9a] in DMSO at 100 °C resulted in the formation small amounts of the desired product (entry 1). In the same line, the reaction of **15** with 3 equivalents of NaI and 5 equivalents of TMSCl in acetonitrile as a solvent at 80 °C resulted in 33% yield of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**) and 66% yield of unreacted **15** (entry 2). The same reaction with NaI in the presence of Na_2SO_3 failed to give the desired product (entry 3).[9c] Further, the reductive halogenation of **15** with sodium borohydride ($NaBH_4$)[9d] at 80 °C did not produce the desired product (entry 4). Consequently, we focused on selective bromine exchange with organometallic reagent followed by quenching with the proton source.[10] As planned, the reaction of **15** with 1.2 equivalents of *n*-butyl lithium in THF as solvent at –60 °C produced **1** in 78% yield (entry 5). When isopropyl magnesium chloride was used instead of *n*-BuLi, the formation of **1** improved to 83%, with 12% starting material (entry 6).[11] Increasing the number of equivalents of

isopropyl magnesium chloride from 1 to 1.2 resulted in complete consumption of starting material and 87% yield of the desired product **1** (entry 7).

Table 3 Optimization of the Debromination



Entry	Reaction conditions[a]	**1**/**14** (%)[b]
1	**15**, TMAF (2 equiv), DMSO (0.1 M), 100 °C	5/84
2	**15**, NaI (3 equiv), TMSCl (5 equiv), MeCN (0.1 M), 80 °C	33/66
3	**15**, NaI (0.1 equiv), Na_2SO_3 (2 equiv), MeCN (0.1 M), 25 °C	NR
4	**15**, $NaBH_4$ (2 equiv), MeCN (0.1 M), 80 °C	NR
5	**15**, *n*-BuLi (1.2 equiv), THF (0.1 M), –60 °C	78/0
6	**15**, *i*PrMgCl (1 equiv), THF (0.1 M), 25 °C	83/12
7	**15**, *i*PrMgCl (1.2 equiv), THF (0.1 M), 25 °C	87/0
8	**15**, *i*PrMgCl (1.2 equiv), THF (0.1 M), 0 °C	90/0
9	**15**, *i*PrMgCl (1.2 equiv), THF (0.1M), –25 °C	95 (92)[c]/0
10	**15**, *i*PrMgCl (1.2 equiv), THF (0.1 M), –78 °C	94/0
11	**15**, *i*PrMgCl (1.2 equiv), toluene (0.1 M), r.t.	85/0
12	**15**, *i*PrMgCl (1.2 equiv), Et_2O (0.1 M), r.t.	87/0

[a] All the reactions were carried out with 2 mmol of **15** and solvent (2 mL)
[b] Based on ^{1}HNMR conversion. NR – no reaction.
[c] Isolated yield in parentheses.

When a series of control experiments were conducted to examine the effect of reaction temperature, the reaction at 0 °C under standard conditions produced 90% yield of the desired product (entry 8). Additionally, decreasing the temperature from 0 to –25 °C, improved the yield from 90 to 95%; however, a further decrease in temperature to –78 °C showed no significant improvement in the yield of **1** (Table 3, entries 8–10). Solvent screening studies revealed that both toluene and Et_2O are efficient solvents for the reaction but gave slightly lower yields (entries 11 and 12). Under these optimized conditions, a scaled-up reaction was performed on a 100 g to 1 Kg scale and the isolated yield was ca. 92%.

In conclusion, we developed a cost-effective, two-step, scalable synthesis of 4-bromo-1,2-dimethyl-1*H*-imidazole (**1**), which is an important building block for synthesizing various APIs of biological interest. Following the new route, ca. 1 kg of **1** was synthesized consistently. The developed synthetic route uses the less expensive raw material 1,2-dimethyl-1*H*-imidazole and provided **1** with an overall yield of 74%.

All starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. All reactions were performed under a nitrogen atmosphere unless otherwise specified. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} pre-coated plates and visualized with a UV lamp. All ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR spectra were recorded with a Bruker 400 MHz spectrometer, and chemical shifts are reported in ppm using TMS or the residual solvent peak as reference. High-resolution mass spectra (HRMS) were recorded with a Thermo Scientific LTQ XL Orbitrap velos using direct infusion modes. LC-MS analyses were conducted with an Agilent 6140 quadrupole LCMS instrument using C18 columns.

Synthesis of 4,5-Dibromo-1,2-dimethyl-1*H*-imidazole (15)

To a stirred solution of 1,2-dimethyl-1*H*-imidazole (500 g, 5.2 mol, 1 equiv) in DMF (5 L) in a 30 L reactor, *N*-bromosuccinimide (2.314 Kg, 13 mol, 2.5 equiv) was added slowly at room temperature and the reaction mixture was stirred at room temperature for another 6 h. Upon completion of the reaction (monitored by LCMS and TLC), the reaction was quenched with sodium thiosulfate solution and the mixture was extracted with EtOAc (3 × 1 L). The organic layers were combined and dried over sodium sulfate, followed by concentration to obtain the crude product. The desired product was purified by ISCO column chromatography to afford **15**.

Yield: 1.055 Kg (80%); pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.54 (s, 3 H).

The physical and spectral properties of this compound were consistent with those reported.[7f]

Synthesis of 4-Bromo-1,2-dimethyl-1*H*-imidazole (1)

To a stirred solution of 4,5-dibromo-1,2-dimethyl-1*H*-imidazole (**15**) (1.0 Kg, 3.94 mol, 1 equiv) in THF (0.1 M, 10 L) in a 30 L reactor, a solution of isopropyl magnesium chloride in THF (2 M, 2.16 L, 4.33 mol, 1.1 equiv) was added slowly dropwise at –25 °C over a period of 1 hour. The reaction mixture was then stirred at –25 °C for an additional 1 h. Upon completion of the reaction, as monitored by LCMS, the reaction was quenched with saturated ammonium chloride solution and the mixture was extracted with EtOAc (3 × 2 L). The organic layers were combined and concentrated to obtain the crude product, which was triturated with a mixture of CH_2Cl_2 and petroleum ether (1:10) to give **1**.

Yield: 635 g (92%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.24 (s, 3 H), 3.51 (s, 3 H), 7.13 (s, 1 H).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 12.2, 32.5, 111.2, 119.6, 144.9.

The physical and spectral properties of this compound were consistent with those reported.[1c,2] The structure was further confirmed by 2D-NOESY NMR analysis; see the Supporting Information for full spectral details.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2176-1585.

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