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# Expedient synthesis of substituted imidazoles from nitriles

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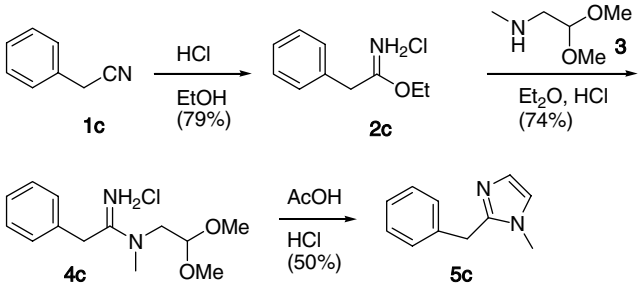
**Abstract**—Expedient and practical new methodology for the synthesis of substituted imidazoles was developed to provide a rapid access to a variety of 2-substituted, 1,2-disubstituted and 1,2,4-trisubstituted imidazoles by the direct CuCl-mediated reaction of nitriles with α-amino acetals in an intermolecular as well as intramolecular fashion.


## 1. Introduction

Imidazoles are common scaffolds in many compounds of significant biological activity[1] and have attracted the attention of synthetic chemists for over a century.[2] Recently, we needed rapid access to a variety 1,2-disubstituted imidazoles to support pre-clinical activities in one of our therapeutic areas. Despite their apparent simplicity, a survey of the literature procedures revealed a lack of general methodologies for the expedient synthesis of these types of heterocycles. Elegant methods employing TosMic[3] derivatives were not suitable for the preparation of imidazoles with the required substitution pattern. At first glance, the classic method reported by Lawson[4] for the formation of 1,2-disubstituted imidazoles from imidate salts and α-amino acetals appeared well suited for this purpose, and the synthesis of imidazole **5c**[5] from imidate hydrochloride **2c**[6] and α-amino acetal **3** using such methodology is illustrated in Scheme 1. However, after synthesizing a number of 1,2-disubstituted imidazoles in this manner, it became obvious the above protocol suffered from a number of limitations: for example, synthesis of the required imidazoles took two to three steps from commercially available nitriles (**1**), formation of the imidate salts (**2**) often required prolonged reaction times (up to weeks), the yields of the imidate salts varied widely and these intermediates were hygroscopic and prone to decomposition.




**Scheme 1.** Synthesis of imidazole **5** from imidate **2**.[5]

Since the reaction of imidates (**2**) and α-amino acetal **3** give rise to amidine intermediates such as **4**, we reasoned it should be possible to arrive at the amidine intermediates directly from the corresponding nitriles (**1**) and α-amine-acetals like **3** avoiding the formation of imidate salts like **2** and the problems associated with them. Moreover, we intended to carry out the cyclization to imidazoles **5** without isolation of the intermediate amidines (**4**). The relatively mild Cu(I)-induced addition of amines to nitriles reported by Capdevielle and co-workers[7] seemed promising for the synthesis of the required amidines (**4**), even though the amines previously used for this transformation lacked functionality such as the acetal present in **3**. Satisfyingly, after minimal optimization of the reaction conditions we were able to obtain good to fair yields of the desired imidazoles. Best results

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were obtained when the Cu(I)-promoted formation of the amidine intermediates was carried out in the absence of solvent followed by cyclization with TFA or HCl in MeOH. The cyclization could be done after removing the Cu salts from the mixture (Method A) or more conveniently in a 'one-pot' procedure in which the Cu salts are removed after cyclization (Method B). This approach gave us quick access to the required imidazoles, and even when the yield of the reaction was moderate in some cases, the reaction mixtures were virtually free of organic side-products facilitating the isolation of the products.

The results from our expedient synthesis of imidazoles from nitriles and α-amino acetals are summarized in Table 1. The reaction conditions that afforded the best yields varied slightly for the different substrates investigated; in some cases the 'one-pot' procedure gave better results, but in other cases it was advantageous to remove the copper salts at the amidine stage. Similarly, HCl was the acid of choice in some instances while TFA worked better for the cyclization of other amidine intermediates. Regardless of the specific reaction conditions, a variety of 1,2-disubstituted imidazoles were prepared by the intermolecular as well as the intramolecular reaction of nitriles and α-amino acetals. Good results were obtained upon the reaction of fluoroacetonitrile (**1a**) or cyclopropropanecarbonitrile (**1b**) with (methylamino)-acetaldehyde dimethyl acetal (**3a**) (entries 1 and 2). The yield decreased with bulkier nitriles (entries 3–5) such as benzyl cyanide (**1c**) and benzonitrile (**1e**), or when nitriles with short aliphatic chains such as propionitrile (**1f**) or butyronitrile (**1g**) were employed (entry 6). The presence of electron-withdrawing groups on the starting nitrile was beneficial to the reaction, as it can be seen by the higher yield of **5d** (entry 4)[8] compared with **5e** (entry 5).[9] The synthesis of imidazoles with substituents at the 2-position other than methyl was also demonstrated by the synthesis of 2-substituted imidazole **5h** from primary amine **3b** (entry 7) and the synthesis of *N*-benzyl imidazole **5i** from **1a** and **3c** (entry 8). Our protocol also worked well for the intramolecular version of the reaction (entries 9 and 10) to afford bicyclic imidazoles **5j**[10,11] and **5k**.[10,11] The formation of **5j** is noteworthy because a non-copper catalyzed, two step approach to this compound was reported to take over four weeks to give **5j** in 11% yield.[12] Finally, the synthesis of 1,2,4-trisubstituted imidazoles was demonstrated, albeit in modest yield, by the synthesis of **5l** (entry 11).

In conclusion, to support pre-clinical activities in one of our therapeutic areas we developed methodology for the synthesis of substituted imidazoles that provides the desired targets in a more expedient way and in higher yield than previously reported approaches. Our protocol provides practical and rapid access to a variety of 2-substituted, 1,2-disubstituted and 1,2,4-trisubstituted imidazoles by the direct CuCl-mediated reaction of nitriles with α-amino acetals in an intermolecular as well as intramolecular fashion. Our methodology is complimentary to existing approaches to imidazoles and should prove a valuable addition to the existing 'toolbox' available for the synthesis of these heterocycles.

## 2. Experimental section

### 2.1. General methods

Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer. Shifts are reported in ppm relative to tetramethylsilane; coupling constants (*J*) are reported in Hertz, and refer to apparent peak multiplicities, and may not necessarily be true coupling constants. The commercially available starting materials were used as received without further purification and all solvents were dried by standard methods prior to use. All melting points are recorded using a Fisher–Johns melting point apparatus and are uncorrected.

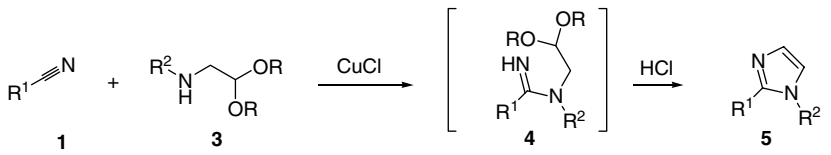
**2.1.1. Method A.** (Methylamino)acetaldehyde dimethyl acetal **3a** (2.0 mL, 15.56 mmol) was charged into a round-bottomed flask followed by benzyl cyanide **1c** (2.25 mL, 19.45 mmol) and CuCl (1.93 g, 19.45 mmol). The mixture was then stirred at 85 °C for 12 h. The mixture was allowed to reach ambient temperature and a 3:1 mixture of MTBE/THF (12 mL) was charged. The resulting mixture was placed over an ice bath and 50% aq NaOH (3.2 g) was added keeping the temperature below 20 °C. The mixture was stirred for 5 min and filtered over a Celite pad. The solids were rinsed with MTBE/THF 3:1 (2 × 15 ml). The combined organic portions were concentrated under reduced pressure and taken up in neat TFA (5 mL). The mixture was heated to 75 °C for 1 h, cooled to ambient temperature and concentrated to afford **5c** (67% yield by GC assay).

**2.1.2. Method B.** (Methylamino)acetaldehyde dimethyl acetal **3a** (2.0 mL, 15.56 mmol) was charged into a round-bottomed flask followed by fluoroacetonitrile **1a** (1.08 mL, 19.45 mmol) and CuCl (1.93 g, 19.45 mmol). The mixture was then stirred at 85 °C for 8 h. The mixture was allowed to reach ambient temperature and methanol (12 mL) was charged followed by conc. HCl (3.24 mL). The resulting mixture was refluxed for 4 h and concentrated under reduced pressure to remove MeOH. The mixture was placed over an ice bath and 50% aq NaOH (5.0 g) was added keeping the temperature below 20 °C. MTBE (30 mL) was added, the mixture was stirred for 5 min and decanted. The solids were rinsed with MTBE (2 × 15 mL). The combined organic portion was dried ($Na_2SO_4$) and concentrated under reduced pressure to afford 1.89 g (90% purity by HPLC) of **5a**.

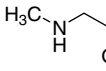
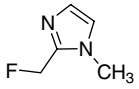
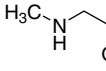
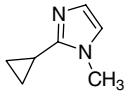
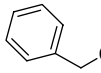
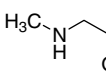
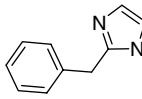
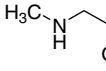
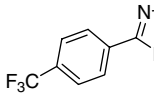
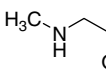
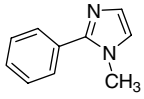
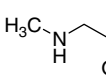
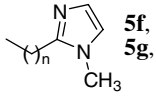
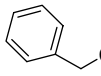
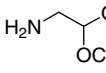
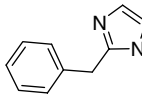
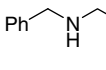
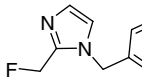
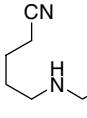
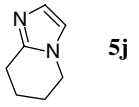
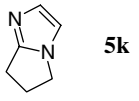
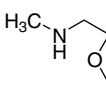
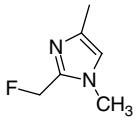
**2.1.3. 2-Fluoromethyl-1-methyl-1*H*-imidazole (5a).** Imidazole **5a** was obtained in 96% yield using the experimental procedure B. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.75 (s, 3H), 5.43 (d, $^2J_{F-H} = 52$ Hz, 2H), 6.95 (s, 1H), 7.04 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 32.2, 75.1 (d, $J = 164$ Hz), 122.5, 127.4, 142.2; HRMS calcd for 115.0671 ($MH^+$), found 115.0679.

**2.1.4. 2-Cyclopropyl-1-methyl-1*H*-imidazole (5b).** Imidazole **5b** was obtained in 79% yield using the procedure B. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.91–1.01 (m, 4H), 1.74–1.81 (m, 1H), 3.67 (s, 3H), 6.77 (d, $J = 1.0$ Hz,

**Table 1.** Direct synthesis of imidazoles from nitriles and α-amino acetals




1 3 4 5

| Entry | Nitrile | α-Amine-acetal | Imidazole | Yield |
|---|---|---|---|---|
| 1 |  **1a** |  **3a** |  **5a** | 96%[a,c] |
| 2 |  **1b** |  **3a** |  **5b** | 79%[a,c] |
| 3 |  **1c** |  **3a** |  **5c** | 67%[b] |
| 4 |  **1d** |  **3a** |  **5d** | 68%[b] |
| 5 |  **1e** |  **3a** |  **5e** | 47%[a] |
| 6 |  **1f**, n = 1 **1g**, n = 2 |  **3a** |  **5f**, n = 1 **5g**, n = 2 | 32%[a,b] |
| 7 |  **1c** |  **3b** |  **5h** | 58%[b] |
| 8 |  **1a** |  **3c** |  **5i** | 53%[b] |
| 9 |  **1h** | — |  **5j** | 85%[b] |
| 10 |  **1i** | — |  **5k** | 54%[b] |
| 11 |  **1a** |  **3d** |  **5l** | 32%[b] |

[a] HCl was used.
[b] TFA was used.
[c] One-pot (HCl).

1H), 6.85 (d, $J = 1.0$ Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 6.36, 6.67, 32.1, 120.1, 126.4, 149.3; HRMS calcd for $C_7H_{11}N_2$ ($MH^+$) 123.0916, found 123.0921.

**2.1.5. 2-Benzyl-1-methyl-1*H*-imidazole (5c).** Imidazole **5c** was obtained in 67% yield by following procedure A. The spectral data are consistent with the reported literature values.[5]

**2.1.6. 1-Methyl-2-(4-trifluoromethyl-phenyl)-1*H*-imidazole (5d).** Imidazole **5d** was obtained in 68% using procedure A. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.89 (s,

3H), 7.78–8.04 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 35.4, 121.2, 122.4, 125.1, 125.9, 128.1, 130.3, 130.9, 131.2. HRMS $C_{11}H_9F_3N_2$ calcd for $C_{11}H_{10}F_3N_2$ ($MH^+$) 227.20, found 227.08.

**2.1.7. 1-Methyl-2-phenyl-1*H*-imidazole (5e).** Imidazole **5e** was obtained in 47% yield by following the experimental procedure B using HCl/MeOH for the cyclization of the amidine intermediate. The spectral data are consistent with the reported literature values.[9]

**2.1.8. 2-Ethyl-1-methyl-1*H*-imidazole (5f).** Imidazole **5f** was obtained in 32% yield using either procedure A or B. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33 (t, $J = 7.6$ Hz, 3H), 2.69 (q, $J = 7.6$ Hz, 2H) 3.57 (s, 3H), 6.69 (d, $J = 0.8$ Hz, 1H) 6.92 (d, $J = 0.8$ Hz, 1H); HRMS calcd for $C_6H_{11}N_2$ ($MH^+$) 111.0916, found 111.0922.

**2.1.9. 1-Methyl-2-propyl-1*H*-imidazole (5g).** Imidazole **5g** was obtained in 32% yield using the procedure A or B. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.95 (t, $J = 7.4$ Hz, 3H), 1.73 (sextuplet, $J = 7.4$ Hz, 2H), 2.59 (t, $J = 7.4$ Hz, 2H), 3.52 (s, 3H), 6.73 (s, 1H), 6.87 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 13.8, 21.1, 28.5, 32.4, 120.1, 126.7, 148.4. HRMS calcd for $C_7H_{13}N_2$ ($MH^+$) 125.1073, found 125.1079.

**2.1.10. 2-Benzyl-1*H*-imidazole (5h).** Imidazole **5h** was obtained in 58% yield by following the experimental procedure A. The spectral data are consistent with the literature values.[13]

**2.1.11. 1-Benzyl-2-fluoromethyl-1*H*-imidazole (5i).** Imidazole **5i** was obtained in 53% yield by following the procedure A. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.21 (s, 2H), 5.39 (d, $^2J_{F-H} = 48$ Hz, 2H), 6.97 (br s, 1H), 7.10 (br s, 1H), 7.13–7.15 (m, 2H), 7.31–7.38 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 49.8, 75.8 (d, $J = 164$ Hz) 122.2 (br), 126.9, 128.1, 128.4, 128.8, 135.6, 142.9 (br); HRMS calcd for $C_{11}H_{12}N_2F$ 191.0979 ($MH^+$), found 191.0990.

**2.1.12. 5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyridine (5j).** Imidazole **5j** was obtained in 85% yield by following the experimental procedure A. The analytical data are consistent with the literature values.[11]

**2.1.13. 6,7-Dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (5k).** Imidazole **5k** was obtained in 54% yield by following the procedure A. The analytical data are consistent with the literature values.[11]

**2.1.14. 2-Fluoromethyl-1,4-dimethyl-1*H*-imidazole (5l).** Imidazole **5l** was obtained in 32% yield by following the procedure A. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.30 (s, 3H), 3.85 (s, 3H), 5.62 (s, 1H), 5.74 (s, 1H), 7.12 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 9.6, 34.6, 70.3, 72.0, 121.1, 130.1, 138.8, 139.0; HRMS calcd for $C_6H_{10}N_2F$ (M+H) 129.0822, found 129.0830.

## References and notes


1. For recent reviews see: (a) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. *Mini-Rev. Med. Chem.* **2005**, *5*, 319; (b) Jin, Z. *Nat. Prod. Reports* **2003**, *6*, 584; (c) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, UK, 1996; Vol. 3, p 77.
2. For recent reviews see: (a) Murry, J. A. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 945; (b) Hoffman, H.; Lindel, T. *Synthesis* **2003**, *12*, 1753; (c) Dolensky, B.; Nam, G.; Deng, W.-P.; Narayanan, J.; Fan, J.; Kirk, K. L. *J. Fluorine Chem.* **2004**, *125*, 501.
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