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Synthesis of tri- and tetrasubstituted imidazoles

Daniel V. Paone [a,*], Anthony W. Shaw [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 4, West Point, PA 19486, USA

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ABSTRACT

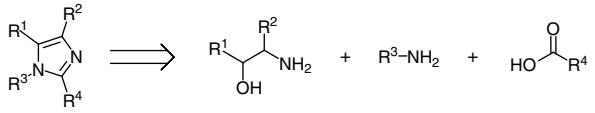
A reliable sequence that allows for regiospecific incorporation of four alkyl substituents on an imidazole ring has been developed. This procedure involves the addition of a substituted amino alcohol to a thioamide and subsequent oxidation with PDC. Unlike many imidazole syntheses, acid-sensitive functionality is tolerated given the mild conditions.

Imidazoles are commonly utilized substructures within the pharmaceutical industry, as these heterocycles impart unique physical and biological properties to compounds of interest.[1] Within the context of a recent medicinal chemistry program, we identified a promising 1,2-dialkyl imidazole template, which prompted us to more fully investigate structure–activity relationships in this new lead series. This required preparation of analogs with various substituents at the 4- and 5-positions, resulting in tri- and tetrasubstituted imidazoles.

To enable higher throughput of target compounds, it was necessary to carry out the imidazole ring formation in the presence of an *N*-Boc group—a commonly employed amine protective group that is easily removed under acidic conditions. Additionally, we found that only alkyl substitution of the imidazole was tolerated, and this presented further challenges toward the synthesis of these compounds.[2]

There are several known methods for the preparation of polysubstituted imidazoles. Two of the more common approaches include introduction of a substituted amine to a dicarbonyl substructure,[3] and acid-catalyzed cyclization of a masked aldehyde or ketone onto an amidine.[4] Use of these conditions requires protic or Lewis acid conditions to effect deprotection of the carbonyl group, which is not compatible with acid-sensitive functionality. Further, the amino acetal or ketal subunits themselves often require several synthetic steps to prepare.

We developed an efficient and mild sequence toward tri- and tetraalkyl-substituted imidazoles, which could be performed on late-stage intermediates. Importantly, imidazole formation proceeded cleanly and without loss of the *N*-Boc group. We proceeded to explore the generality of this approach and envisioned tetrasubstituted imidazoles arising from three fragments (Scheme 1). Amide bond formation would allow incorporation of the first two substituents (R^3 and R^4), and the remaining two substituents (R^1 and R^2) could be introduced via an amino alcohol to yield tetrasubstituted imidazoles after oxidation and cyclization.



Scheme 1. Imidazole retrosynthesis.

The sequence begins with EDC coupling of 3-phenylpropan-1-amine (**1**) and 3-(4-fluorophenyl)propanoic acid (**2**) to give the amide in high yield (Scheme 2).[5] Treatment with Lawesson's reagent[6] furnishes corresponding thioamide **3**, which upon condensation with a substituted vicinal amino alcohol (**4**) with mercury(II) chloride assistance gives rapid formation of the intermediate amidine (**5**), typically within 10 min at ambient temperature. Filtration of this mixture followed by addition of pyridinium dichromate (PDC) directly to the filtrate and heating at 60 °C for 2 h affords cyclized imidazole products (**6**) in good yields after aqueous workup[7] and purification by silica gel chromatography.[8] Of note is the absence of either an aqueous workup or purification of the amidine intermediate. Though generally useful as a means of preparing tri- and tetraalkyl-substituted imidazoles, this protocol is particularly efficient when investigating variations of R^1 and/or R^2, as analogs can be prepared in two steps from thioamide starting material with a single workup and purification.

* Corresponding author. Tel.: +1 215 993 2269; fax: +1 215 652 7310.
E-mail address: daniel_paone@merck.com (D. V. Paone).

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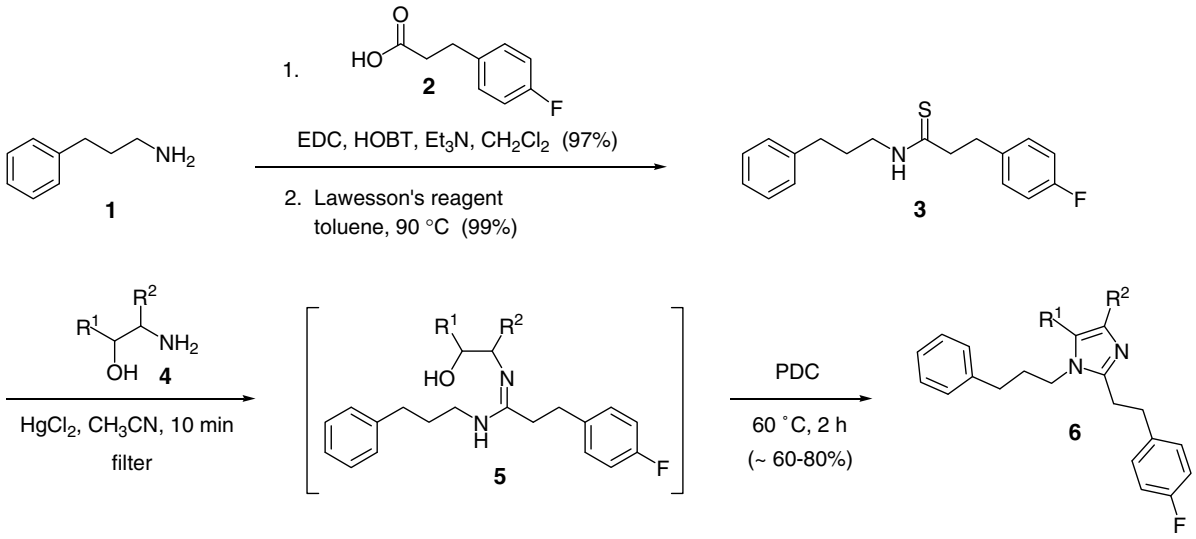
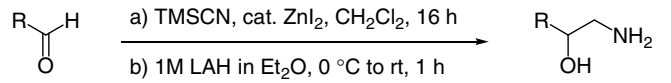
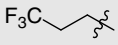
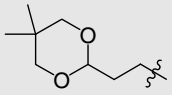


Scheme 2. Synthesis of substituted imidazoles.

Table 1
Synthesis of substituted amino alcohols

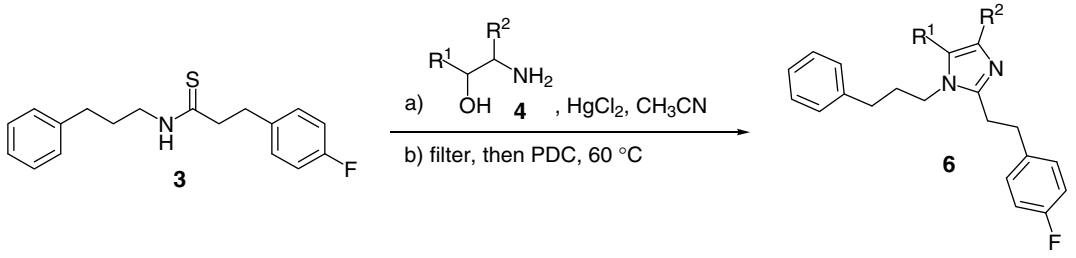


Entry	R	Yield (%)
1		81
2		87
3		91
4		92
5		75

Substituted amino alcohols (**4**), where R^1 = H (Scheme 2), are readily available from reduction of the corresponding amino acids, and several derivatives are also commercially available. For the less common trisubstituted isomer, where R^2 = H, we utilize a one-pot, two-step protocol starting with aliphatic aldehydes (Table 1).[9] Treatment with trimethylsilyl cyanide affords the silyl-protected cyanohydrins, which are then reduced with lithium aluminum hydride. The amino alcohols obtained after filtration are of sufficient purity for subsequent transformations.

Isolated yields of several analogs of substituted imidazole **6** are shown in Table 2.[10] 1,2,5-Trialkyl-substituted derivatives (entries 1–7) were synthesized from amino alcohols prepared using the sequence described in Table 1. Branched, fluorinated, and oxygenated alkyl substituents are tolerated (entries 1–6),[11] as is the acid-sensitive acetal functional group (entry 7). This methodology is compatible with aryl substituted amino alcohols as well, giving the 5-aryl-substituted imidazole (entry 8). Generation of the 1,2,4-trialkyl-substituted isomers proceeds in a similar manner (entries 9–11) though yields are generally lower. Again aryl substitution is tolerated (entry 12).

Table 2
Formation of differentially substituted imidazoles: variation of R^1 and R^2



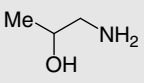
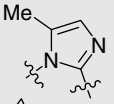
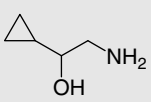
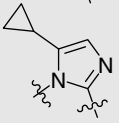
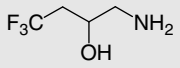
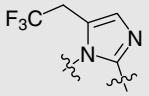
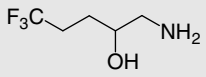
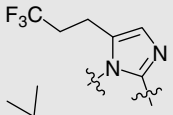
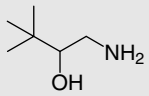
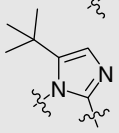
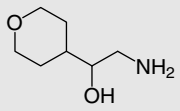
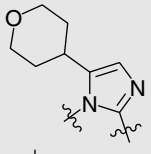
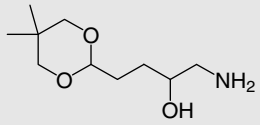
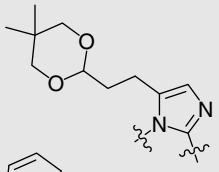
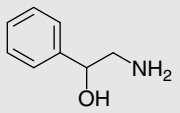
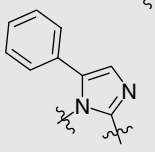
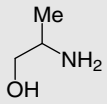
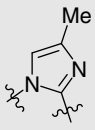
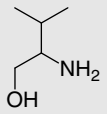
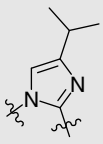
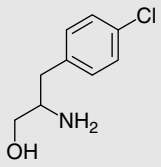
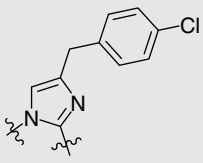
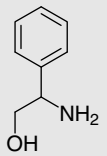
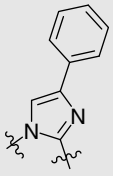
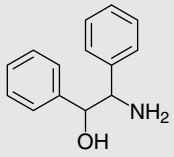
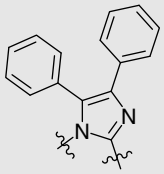
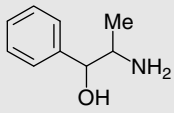
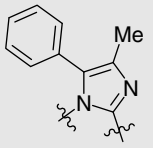
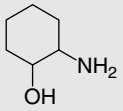
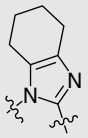
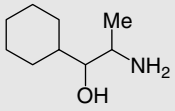
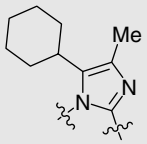
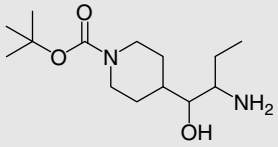
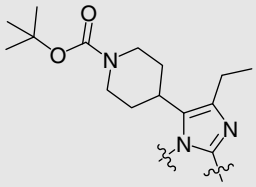
Entry	Amino alcohol	Imidazole product	Yield[b] (%)
1			68
2			72

Table 2 (*continued*)

Entry	Amino alcohol	Imidazole product	Yield[b] (%)
3[a]			63
4			69
5			71
6			72
7			64
8			75
9			60
10			66
11			60
12			50
13			68
14			87

(*continued on next page*)

Table 2 (*continued*)

Entry	Amino alcohol	Imidazole product	Yield[b] (%)
15			68
16			70
17			62

[a] HCl salt of the amino alcohol was used with equimolar amounts of triethylamine.
[b] Isolated yield after column chromatography.

1,2,4,5-Tetrasubstituted imidazoles containing either one or two aryl substituents (entries 13–14) were prepared in good yield. The cyclohexane-fused analog in entry 15 represents an interesting approach to partially saturated benzimidazoles,[12] and the utility of this methodology is highlighted by the successful preparation of differentially substituted tetraalkyl imidazoles (entries 16–17). The cyclohexyl analog in entry 16 was synthesized from the corresponding disubstituted amino alcohol[13] in 70% yield from thioamide **3**. Further, tolerance of the *N*-Boc-protected piperidine moiety in entry 17 demonstrates the mildness of this protocol.

In summary, we have optimized a two-step procedure for the synthesis of tri- and tetraalkyl-substituted imidazoles starting from readily available thioamides. This sequence proceeds under mild conditions enabling preparation of compounds containing acid-sensitive functionality. Additionally, aryl substitution at both the 4- and 5-positions is tolerated. Finally, facile preparation of the required substituted amino alcohols for use in preparation of 1,2,5-trisubstituted imidazoles was described.

Acknowledgments

The authors thank Drs. Christopher S. Burgey and Shaun R. Stauffer for reviewing this Letter, and Hongbo Qi for the preparation of the amino alcohol in entry 17 of Table 2.

References and notes

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2. With certain methods, the presence of enolizable hydrogens in carbonyl precursors can often preclude imidazole formation altogether, thus requiring the use of aryl substituents at specific positions; see Refs. 2 and 3.
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5. The differentiated alkyl-tethered aryl chain 1- and 2-substituents were chosen for ease of UV detection and purification.
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7. The aqueous workup of the PDC reaction is greatly facilitated by first quenching with a reducing agent such as sodium sulfite, then adjusting the mixture to mildly acidic pH (~5). This allows for complete dissolution of chromium salts and separation of two homogeneous layers.
8. Major byproducts of the sequence include reversion back to the amide precursor of **3** and oxazoline formation resulting from nucleophilic attack of the hydroxyl group prior to oxidation.
9. *Typical procedure for the synthesis of substituted aminomethyl alcohols* (Table 1, *entry 3*): Trimethylsilyl cyanide (920 mg, 9.28 mmol) was added dropwise to a solution of 2,2-dimethylpropanal (400 mg, 4.64 mmol) and zinc iodide (15 mg, 0.046 mmol) in dichloromethane (10 mL) at 0 °C, and the solution was allowed to warm to ambient temperature. After 16 h the solution was recooled to 0 °C, lithium aluminum hydride (1.0 M in ether; 11.6 mL, 11.6 mmol) was added, and the solution was allowed to warm to ambient temperature. After 1 h the mixture was cooled to 0 °C and treated successively with water (0.44 mL), 15% aqueous sodium hydroxide (0.44 mL), and water (1.32 mL). After stirring for 30 min, the mixture was filtered and washed with dichloromethane. The filtrate was dried with sodium sulfate, filtered, and concentrated to give 1-amino-3,3-dimethyl-butan-2-ol (496 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.14 (dd, J = 10.3, 2.9 Hz, 1H), 2.92 (dd, J = 12.2, 2.7 Hz, 1H), 2.47 (dd, J = 12.2 Hz, 10.3 Hz, 1H), 0.91 (s, 9H).
10. *Typical procedure for the synthesis of substituted imidazoles* (Table 2, *entry 5*): To a solution of 3-(4-fluorophenyl)-*N*-(3-phenylpropyl)propanethioamide (50.0 mg, 0.17 mmol) and 1-amino-3,3-dimethyl-butan-2-ol (38.9 mg, 0.33 mmol) in acetonitrile (1.7 mL) was added mercury(II) chloride (90.1 mg, 0.33 mmol). After 10 min the mixture was filtered and washed with a total of 6 mL acetonitrile. Pyridinium dichromate (312 mg, 0.83 mmol) was added to the filtrate and the mixture was heated to 60 °C. After 2 h the mixture was allowed to cool to ambient temperature and quenched with saturated aqueous sodium sulfite (4 mL) and water (4 mL). The mixture was adjusted to pH 5 with concentrated hydrochloric acid (1 mL), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate, filtered and concentrated.

Purification by silica gel chromatography (dichloromethane→4% methanol/dichloromethane with 1% ammonium hydroxide) gave 5-(1,1-dimethylethyl)-2-[2-(4-fluorophenyl)ethyl]-1-(3-phenylpropyl)-1 H-imidazole (43.0 mg, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.28 (m, 2H), 7.24–7.21 (m, 1H), 7.16–7.14 (m, 2H), 7.00–6.98 (m, 2H), 6.95–6.90 (m, 2H), 6.67 (s, 1H), 3.69–3.66 (m, 2H), 3.03 (t, J = 8.6 Hz, 2H), 2.74–2.71 (m, 2H), 2.65 (t, J = 7.1 Hz, 2H), 1.95–1.89 (m, 2H), 1.26 (s, 9H). HPLC R_t = 2.56 min (100% purity). HRMS calcd for $C_{24}H_{29}N_2F$ [M+H]: 365.2388; found 365.2390.

11. For the trifluoroethyl analog in entry 3 of Table 2, the HCl salt of the amino alcohol was used along with equimolar triethylamine, and the yields were comparable to those when the free base was used.
12. The corresponding cyclopentane-fused imidazole was not obtained under the standard conditions, presumably due to increased ring strain versus the 6,5-fused system.
13. The amino alcohol in entry 16 was obtained from hydrogenation of the commercially available aryl derivative.