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Efficient Synthesis of 1-Substituted-5-Hydroxymethylimidazole Derivatives: Clean Oxidative Cleavage of 2-Mercapto Group[1]

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Abstract:

1-Substituted-5-hydroxymethylimidazoles were prepared through green desulfurization of their 2-mercapto derivatives by the treatment of 30% hydrogen peroxide in the presence of a catalytic amount of transition metal catalysts.

Recently we have published the discovery of a series of 1,5-disubstituted imidazole derivatives as potent and selective farnesyl transferase inhibitors.[2] For the proper supply of this class of compounds in reasonable quantity, it is a prerequisite to establish a scalable route towards 1-substituted-5-hydroxymethylimidazoles.

In the literature various procedures are known for the preparation of 1-substituted-5-hydroxymethylimidazoles, which are via oxidative desulfurization[3] of 1-substituted-2-mercapto-5-hydroxymethylimidazole, selective alkylation of 4-hydroxymethylimidazole,[4] and less commonly, via the reduction[5] of 5-substituted-1-carboxylates. Among these methods, the last two routes are not viable for the large-scale preparation due to the lack of bulk availablility of 4-hydroxymethylimidazole and because of lengthy steps, respectively. Accordingly we have chosen the oxidative desulfurization route of readily available 1-substituted-2-mercapto-5-hydroxymethylimidazole under the known conditions, employing nitrite/nitric acid or fuming nitric acid (Scheme 1). However, we found that the reaction conditions were quite exothermic and accompanied by a vigorous evolution of a stoichiometric amount of nitrous oxide gas to render the reaction improper for a large-scale preparation in terms of safety and environmental concerns.[6] Recently, an improved procedure[7] using hydrogen peroxide in acidic medium[8] has been reported by Merck process chemists. However the method is still complicated with the use of excess hydrogen peroxide (7−8 equiv) and organic acid as reaction medium, which inevitably calls for the subsequent quench of excess hydrogen peroxide by a reducing agent and for neutralization of the organic acid by the excess of base in the workup procedure. In this report we would like to disclose safe and clean desulfurization conditions of 2-mercapto-5-hydroxymethylimidazole derivatives.

It was speculated that the reaction mechanism of the nitrite/nitric acid method would involve a sequence of reactions, oxidation of the mercapto group of 2-mercaptoimidazole to a sulfinic or sulfonic acid group through oxygen transfer from nitrogen to sulfur and subsequent elimination of these groups to afford imidazole. This assumption led us to test various thiol- or sulfide-oxidizing reagents for desulfurization.

The starting materials, 2-mercapto-imidazole derivatives (**2a**−**f**) were prepared according to literature precedents.[2a] For oxidative desulfurization, we have employed a tungstic acid/hydrogen peroxide system based on the literature precedents[9] which demonstrated clean and efficient oxidation of sulfide groups to sulfone derivatives. As expected, desulfurization of 2-mercapto imidazole derivatives proceeded smoothly in methanol or ethanol with slow addition of 30% hydrogen peroxide (3.0−3.5 equiv) in the presence of catalytic amounts of tungstic acid (Table 1). In general 1 mol % of catalyst was employed, but the amount could be reduced to 0.1 mol % with comparable results. It is also worth mentioning that there was neither hydroxyl group oxidation[10] of the 5-hydroxymethyl fragment of **2a**−**f** nor epoxidation[11] of the double bond of **2e**. After all the starting material was consumed, the reaction mixture was neutralized with aqueous base, and the formed solid was filtered to give the product. In most cases, the purity of the products was >95% by HPLC analysis.

Other transition metal catalysts were also tested. Vanadyl sulfate[12] showed almost the same reactivity of tungstic acid. Vanadium oxide[13] and methyltrioxorhenium[14] revealed slightly

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Scheme 1

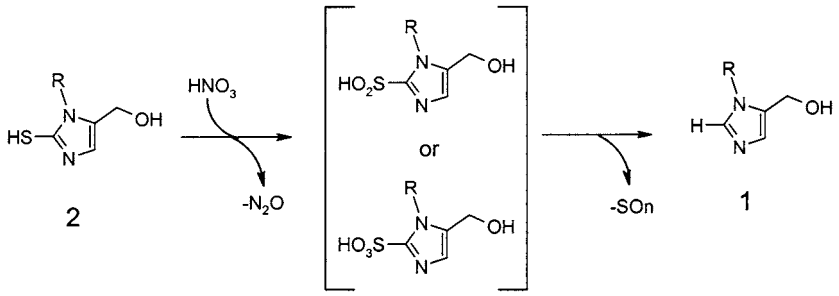
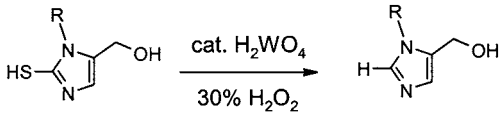


Table 1. **Desulfurization of 2a−f**



2a-f **1a-f**

reactant	R	yield (%)
2a	piperonyl	64
2b	*p*-bromobenzyl	82
2c	3-ethoxypropyl	90
2d	*p*-fluorophenylethyl	83
2e	allyl	76
2f	Et	68

decreased turnover, which required 2−3 mol % catalyst loading for the complete conversion of the reaction.

During the course of the desulfurization reaction, the pH of the reaction mixture became acidic and about 2 mol equiv of sodium hydroxide was required to neutralize the reaction mixture at the end of reaction. This observation gives us a clue that the thiol group should be eliminated as SO_2 or SO_3,[15] which reacts with water to form sulfinic or sulfuric acid. A clear evidence for the assumption is obtained from the desulfurization of 1-piperonyl-2-mercapto-5-hydroxymethylimidazole (**2a**). In the course of the reaction of **2a** with catalytic tungstic acid/hydrogen peroxide, an intermediate having molecular weight larger by 80 (═SO_3) than that of the desired imidazole **1a** was detected by HPLC/MS analysis and finally isolated[16] and confirmed to be **2a**−**2** on the basis of spectral analysis. Since this intermediate was not converted to **1a** under prolonged exposure to the same desulfurization reaction conditions, it is clear that the sulfinic acid intermediate **2a**−**1** forms the desired product with the exclusion of sulfur dioxide, which is rapidly oxidized by hydrogen peroxide and reacted with water to form sulfuric acid via sulfur trioxide, and as a minor pathway, further oxidation yielded the side product, sulfonic acid **2a**−**2**. Thus, a minimum of 3 equiv of hydrogen peroxide is required for the complete conversion of the reaction (Scheme 2).

In conclusion we have developed an efficient and clean desulfurization process of 2-meracapto-5-hydroxymethylimidazole derivatives, which is safer[17] and environmentally more benign than the known methods.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. NMR was performed on a Bruker 400 MHz and JEOL 500 MHz spectrometer. HPLC was performed on a Hewlett-Packard 1100 system and Waters 490E detector and 616 pump system.

[1-(1,3-Benzodioxol-5-ylmethyl)-2-sulfanyl-1*H*-imidazol-5-yl]-methanol (2a). To a stirred mixture of piperonylamine hydrochloride (15.56 kg, 82.93 mol), dihydroxyacetone dimer (7.67 kg, 42.6 mol), KSCN (12.42 kg, 127.8 mol) in 2-propanol (70.7 kg) was added acetic acid (16.37 kg, 272.65 mol) at 25 °C. The mixture was stirred for 48 h at 25−30 °C and was heated at 85 °C for 1 h. The mixture was cooled to 20−25 °C, and water (17 kg) was added. After the mixture stirred for 30 min, the solid was filtered, and the filter cake was washed with water (60 kg). The filter cake was dried with nitrogen purge to give **2a** as a light yellow solid (24.64 kg). Karl-Fisher analysis showed 7% water content. HPLC analysis[18] showed 99.1% purity (PAR).

[1-(1,3-Benzodioxol-5-ylmethyl)-1*H*-imidazol-5-yl]methanol (1a). To a stirred mixture of **2a** (20.6 kg on anhydrous base, 77.94 mol) and a catalytic amount of tungstic acid (19.5 g, 0.001 equiv, 78 mmol) in ethanol (46 kg) and water (56

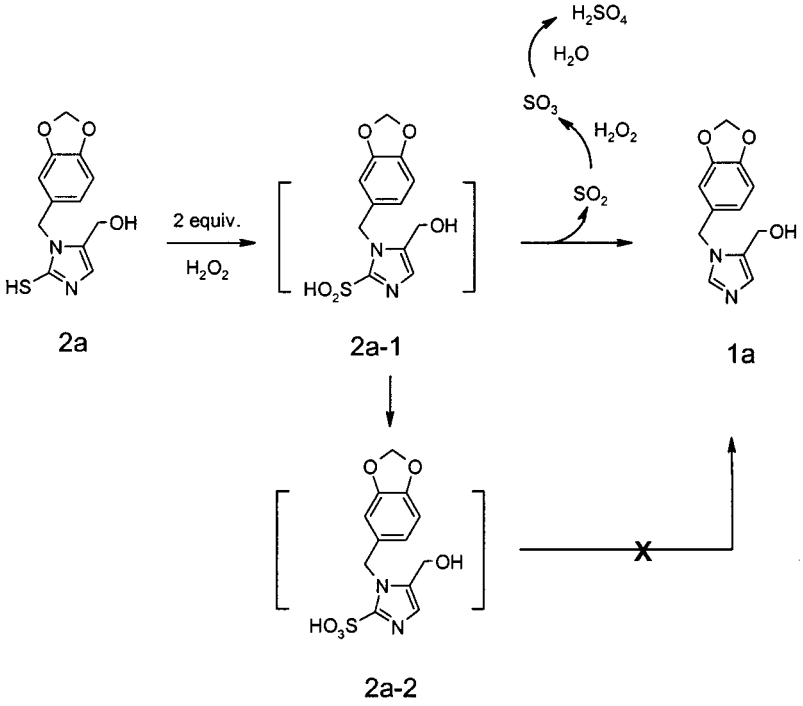
(15) On the mechanism of oxidation of 2-mercaptoimidazole by nitric acid, the authors commented as follows: "since the sulfur appears as sulfuric acid, the oxidation would probably produce the sulfonic acid, which is hydrolyzed": Fieser, L. F.; Fieser, F. *Reagent for Organic Synthesis*; Wiley: New York, 1967; p 734.

(16) The filtrate of the reaction mixture was acidified by concentrated hydrochloric acid to pH 1, and the formed solid was filtered to give the product **2a**−**2**. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.48 (1H, s), 6.94 (1H, s), 6.90 (1H, d, J = 8.3 Hz), 6.85 (1H, d, J = 8.3 Hz), 6.01 (2H, s), 5.60 (2H, s), 4.29 (2H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 148.1, 148.0, 147.7, 135.9, 128.3, 122.0, 117.1, 108.8, 108.5, 101.8, 53.4, 49.1; MS (FAB) *m*/*z* 311 ([M − H]$^-$).

(17) (a) For the considerations for the safe use of hydrogen peroxide, see: Jones, C. W. *Applications of Hydrogen Peroxide and Derivatives*: Royal Society of Chemistry: Cambridge, UK, 1999; pp 21−35. (b) According to calorimetric analysis of the reaction of **2a**, the addition of hydrogen peroxide is a highly exothermic reaction which can be controlled by the addition rate of hydrogen peroxide. There is no induction period for the initiation of the reaction. Total heat output is 580.53 kJ/mol with respect to **2a**, and adiabatic temperature rise is 46 °C (C_p = 3120 J/kg K). (c) The level of hydrogen peroxide was carefully monitored in the course of the reaction using titanium sulfate colorimetric analysis (For the reference, see: Satterfield, C. N.; Bonnell, A. H. *Anal. Chem.* **1955**, *27*, 1174.). Immediately after the completion of addition, about 1% (wt/wt) of hydrogen peroxide was detected. In 10 h at 45 °C after neutralization with sodium hydroxide, a negligible amount of hydrogen peroxide (about 0.001%) was observed. Although this level of hydrogen peroxide is well below the detonable limit, it is safer to quench the reaction mixture with reducing reagent before *partial* distillation of ethanol. Quenching with sodium hydrogen sulfite before distillation did not change the profile of the reaction to give comparable results.

(18) Analysis conditions are as follows: Capcellpack C-18 (4.6 cm × 250 cm) with 1.2 mL/min flow rate of a solution of H_2O:acetonitrile:trifluoroacetic acid = 80:20:0.1 at 270 nm.

Scheme 2



kg) was added dropwise 30% hydrogen peroxide (32.2 kg, 290 mol) over 2 h, maintaining the reaction temperature in the range of 40−80 °C. To the mixture was added 6 N aqueous NaOH solution (26.3 kg, 144.9 mol) to adjust the pH of the reaction mixture to ∼11, the mixture was stirred for 6−12 h at 45 °C, and about two-thirds of the ethanol was distilled under vacuum. The formed solid was filtered and washed with water to afford **1a** (11.5 kg, 64%). HPLC analysis showed 96.6% purity (PAR). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.67 (1H, s), 6.87 (1H, d, J = 7.8 Hz), 6.81 (1H, s), 6.79 (1H, d, J = 1.8 Hz), 6.70 (1H, dd, J = 7.8 and 1.8 Hz), 5.99 (2H, s), 5.11 (2H, s), 4.35 (2H, s); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 148.1, 147.5, 138.1, 132.9, 130.6, 124.8, 121.7, 108.8, 108.6, 101.7, 53.2, 48.6.

Following the same procedure, compounds (**1b**), (**1c**), and (**1d**) were prepared in the specified yield as shown in Table 1.

[1-(4-Bromobenzyl)-1*H*-imidazol-5-yl]methanol (1b): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (1H, s), 7.54 (2H, dd, J_1 = 6.4 Hz, J_2 = 1.8 Hz), 7.12 (2H, dd, J_1 = 6.4 Hz, J_2 = 1.8 Hz), 6.83 (1H, s), 5.21 (2H, s), 5.12 (1H, s, OH), 4.32 (2H, d, J = 3.25 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 139.0, 137.7, 132.1, 129.8, 128.08, 121.2, 113.8, 53.3, 47.5.

[1-(3-Ethoxypropyl)-1*H*-imidazol-5-yl]methanol (1c): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (1H, s), 6.79 (1H, s), 4.42 (2H, s), 4.02 (2H, t, J = 7.1 Hz), 3.39 (2H, q, J = 7.0 Hz), 3.30 (2H, t, J = 6.2 Hz), 1.94 (2H, m), 1.11 (3H, t, J = 6.9 Hz).; ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.4, 132.2, 127.4, 67.0, 65.9, 53.1, 42.0, 31.1, 15.6.

[1-(4-Fluorophenylethyl)-1*H*-imidazol-5-yl]methanol (1d): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40 (1H, s), 7.20−7.09 (4H, m), 6.74 (1H, s), 5.09 (1H, t, J = 5.1), 4.38 (2H, d, J = 5.1), 4.17 (2H, t, J = 7.3), 3.03 (2H, t, J = 7.3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.5, 131.9, 131.2, 131.1, 127.7, 115.7, 115.5, 53.2, 46.1, 36.4.

Compounds (**1e**) and (**1f**) were obtained from extraction with *n*-butanol after the neutralization step and subsequent concentration.

[1-Allyl-1*H*-imidazol-5-yl]methanol (1e): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (1H, s), 6.79 (1H, s), 6.00 (1H, ddd, J_1 = 16.95 Hz, J_2 = 10 Hz, J_3 = 5.5 Hz), 6.15 (1H, dd, J_1 = 10 Hz, J_2 = 1.35 Hz), 4.98 (1H, dd, J_1 = 16.95 Hz, J_2 = 1.35 Hz), 4.64 (2H, dd, J_1 = 5.5 Hz, J_2 = 1.35 Hz), 4.39 (2H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.5, 135.2, 132.2, 127.7, 117.4, 60.9, 47.1.

[1-Ethyl-1*H*-imidazol-5-yl]methanol (1f): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (1H, s), 6.76 (1H, s), 4.43 (2H, s), 4.36 (2H, s), 3.99 (2H, q, J = 7.3 Hz), 1.33 (3H, t, J = 7.3 Hz); ^{13}C NMR(125 MHz, DMSO-d_6) δ 137.8, 131.9, 127.7, 60.9, 53.2, 16.9.

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