Synthesis of 4(5)-Hydroxymethylimidazoles by Hydroxymethylation and Decarboxylation of Imidazole-4(5)-carboxylic Acids

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4(5)-Hydroxymethylimidazoles were prepared by hydroxymethylation and decarboxylation of imidazole-4(5)-carboxylic acid esters. The reaction was simply carried out with aqueous formaldehyde solution in the presence of base.

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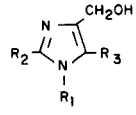
Recent studies have shown that certain 4(5)-hydroxymethylimidazoles are key intermediates for the preparation of a gastric acid secretion inhibitor of the H_2-antagonist type [1-6], one of which is known generically as cimetidine and has been therapeutically used in the treatment of peptic ulcer [2]. In connection with these findings, we were interested in developing a simple synthetic method of 4(5)-hydroxymethylimidazoles **1a-d**.



1a, $R_1 = R_2 = R_3 = H$,
b, $R_1 = R_2 = H$, $R_3 = CH_3$
c, $R_1 = R_2 = H$, $R_3 = C_6H_5$
d, $R_1 = R_3 = CH_3$, $R_2 = H$

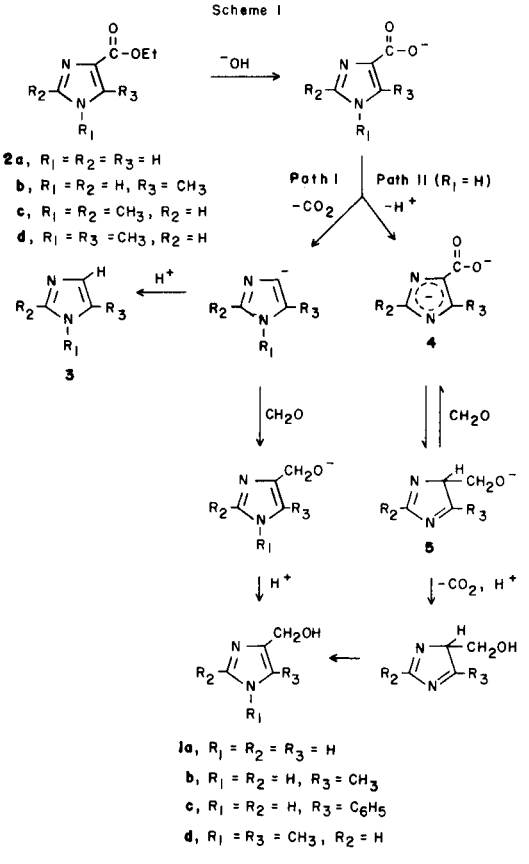
The 4(5)-hydroxymethylimidazoles have been prepared by a variety of known methods [6-16]. However, the known methods have certain inherent disadvantages for large scale preparation. For instance, the reduction of imidazolecarboxylic acid esters to the corresponding hydroxymethylimidazoles involves the use of expensive and hazardous reducing agents in a substantially anhydrous environment [6,11-13]. The hydroxymethylation of an imidazole was also frustrated by low yields, the need for the application of high pressure and the difficult separation of the product from the reaction mixture [7-10].

In the present study, we would like to report a simple method for preparation of the 4(5)-hydroxymethylimidazoles **1a-d** based on the hydroxymethylation and decarboxylation of imidazole-4(5)-carboxylic acids or its ester **2a-d**. When the imidazole-4(5)-carboxylic acids or esters **2a-d** were reacted with aqueous formaldehyde solution (~37%) in the presence of an alkali metal hydroxide, the 4(5)-hydroxymethylimidazoles **1a-d** were obtained in good yield (50~70%). The best yields in this reaction were obtained when the reaction temperature was in the range of 90~100%. The use of non-aqueous systems with paraformaldehyde was unsuccessful. Carboxylic acids of the imidazoles **2a-d** as starting material gave the same results.

The mechanism proposed suggests that the reaction could proceed through either path I or II or by both pathways as shown in Scheme I. Under the reaction conditions, the 1*H*-imidazoles **2a-c** having no substituent on the nitrogen atom are assumed to form an anion intermediate **4** which is stabilized by a carboxyl group, and the anion allows the hydroxymethylation to take place at the carbon atom attached to the carboxyl group and subsequent decarboxylation occurs to give the products.

The reaction with the *N*-methylated imidazole **2d**, which can not form the anion intermediate **4**, necessitated a higher reaction temperature and an approximately three times longer reaction time in order to achieve yields comparable to that of the unsubstituted imidazoles **2a-c**, and the imidazole **3** formed by decarboxylation of the starting

Scheme I



2a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$, $R_3 = CH_3$
c, $R_1 = R_2 = CH_3$, $R_2 = H$
d, $R_1 = R_3 = CH_3$, $R_2 = H$

3

4

5

1a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = H$, $R_3 = CH_3$
c, $R_1 = R_2 = H$, $R_3 = C_6H_5$
d, $R_1 = R_3 = CH_3$, $R_2 = H$

imidazole was obtained in considerable amount. These findings suggest that the reaction with 1*H*-imidazoles **2a-c** favors following Path I while the *N*-substituted imidazole **2d** prefers Path II.

EXPERIMENTAL [20]

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Infrared spectra were recorded on a Beckmann 12 spectrophotometer or a Perkin-Elmer 735B spectrophotometer and pmr spectra on a Varian EM 360A spectrometer using tetramethylsilane as an internal standard. Microanalyses were performed by Kaist, Seoul, Korea.

4(5)-Hydroxymethylimidazole (**1a**).

A mixture of 4(5)-carbethoxylimidazole **2a** [17] (1.4 g, 0.01 mole) and potassium hydroxide (1.12 g, 0.02 mole) in water (8 ml) was heated to reflux for 30 minutes. To the reaction mixture was then added ~37% aqueous formaldehyde (4 ml). The mixture was heated at 80-90° for 3 hours and then concentrated *in vacuo*. The residue was extracted with ethyl acetate. The extract was concentrated to give a powdered solid (0.6 g, 61%), mp 89-90° (lit [14] mp 91-92°).

4(5)-Methyl-5(4)-hydroxymethylimidazole (**1b**).

To a suspension of 1.54 g (0.01 mole) of 4(5)-carbethoxy-5(4)-methylimidazole [18] in water (10 ml) was added 1.0 g of sodium hydroxide. The mixture was heated to reflux for 30 minutes. To the resultant mixture was added 4 ml of ~37% aqueous formaldehyde solution, and the mixture was refluxed for 2 hours. After completion of the reaction, the solvent was evaporated *in vacuo* and the remaining residue was extracted by refluxing with ethyl acetate. The extract was concentrated to obtain 0.76 g (68%) of the product, mp 137-138° (lit [7] mp 138°).

4(5)-Carbethoxy-5(4)-phenylimidazole (**2c**).

A mixture of formamide (16 ml, 0.4 mole), formic acid (11 ml, 0.3 mole) and 57 g (0.9 mole) of ammonium formate was heated to 135 ±5°, and 68 g (0.3 mole) of ethyl α-chlorobenzoylacetate was slowly added in the course of 2 hours while maintaining the reaction temperature at 135 ±5°. After the completion of the addition of the chloride, the reaction mixture was heated for an additional 3 hours at 135 ±5°. The reaction mixture was cooled to room temperature, and 100 ml of water was added with vigorous stirring. The resultant solid was filtered and washed with water. The solid was recrystallized with methanol and active charcoal to obtain 24 g (37%) of pale yellow crystals, mp 223-226°; ir (potassium bromide): 3450 (s), cm^{-1}, 1710 (s); nmr (trifluoroacetic acid): δ 1.3 (t, 3, CH_3), 4.5 (q, 2, $-CH_2-$), 7.6 (m, 5, phenyl ring protons), 8.8 (s, 1, imidazole ring proton).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.56; N, 12.93. Found: C, 66.48; H, 5.68; N, 13.06.

4(5)-Hydroxymethyl-5(4)-phenylimidazole (**1c**).

To a suspension of 2.16 g (0.01 mole) of 4(5)-carbethoxy-5(4)-phenylimidazole **2c** in 10 ml of water was added 0.8 g (0.02 mole) of sodium hydroxide. The mixture was heated to reflux for 20 minutes. To this mixture was added 4 ml of ~37% aqueous formaldehyde solution, and the resultant mixture was heated at 60-65° for 8 hours with stirring. The reaction mixture was cooled and the resltant solid was collected by filtration, washed with water and recrystallized from ethyl acetate to give 1.2 g (69%) of the pure product, mp 175-176°, HCl salt mp 185-186°; ir (potassium bromide): 3400-2600 (broad), 1460 (s), 1000 (s), 760, 700 (m); nmr (trifluoroacetic acid): δ 5.1 (s, 2, $-CH_2-$), 7.55 (m, 5, phenyl ring protons), 8.1 (s, 1, imidazole ring proton).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.75; N, 16.09. Found: C, 68.78; H, 5.83; N, 16.12.

1,4-Dimethyl-5-hydroxymethylimidazole (**1d**).

A mixture of 5-carbethoxy-1,4-dimethylimidazole **2d** [19] (3.36 g, 0.02 mole) and sodium hydroxide (1.03 g, 0.024 mole) in 15 ml of water was refluxed for 30 minutes. To the resultant solution was added 5 ml of ~37% aqueous formaldehyde solution, and heated to reflux for 18 hours. The solvent was evaporated under vacuum and the residue was extracted with acetone by refluxing. The acetone extract was concentrated, and the resultant residue was recrystallized with ethyl acetate to give 1.4 g (55.6%) of white solid, mp 122-124° (lit [8] mp 126-127°).

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