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## An Improved Synthesis of DL-Histidine<sup>1)</sup>

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Histidine is an important amino acid for protein and a number of synthetic methods have been studied.<sup>2)</sup> Of these, a method using hydroxymethylimidazole (1) as an intermediate, which is easily obtained by a condensation reaction of dihydroxyacetone with formalin and ammonia,<sup>3)</sup> has figured prominently. For example, condensation reaction of diethyl acetamidomalonate (DAM) with chloromethylimidazole,<sup>4)</sup> which is obtained by chlorination of (1),<sup>5)</sup> has been frequently employed. However, these methods would not be practical because of the low yields.

In our studies on the syntheses of amino acids, we found that O-acyl group of hydroxymethylimidazole is a useful leaving group for the introduction of the imidazole skeleton. In this paper, we wish to report an improved synthesis of DL-histidine using acyloxy-methylimidazole (3) as shown in Fig. 1.

The compound (3), especially 1-tosyl-4-(or 5)-acetoxy-methylimidazole (3a) is easily prepared by a reaction of N-tosyl imidazole compound (2), which was prepared from hydroxymethylimidazole (1) with *p*-toluenesul-

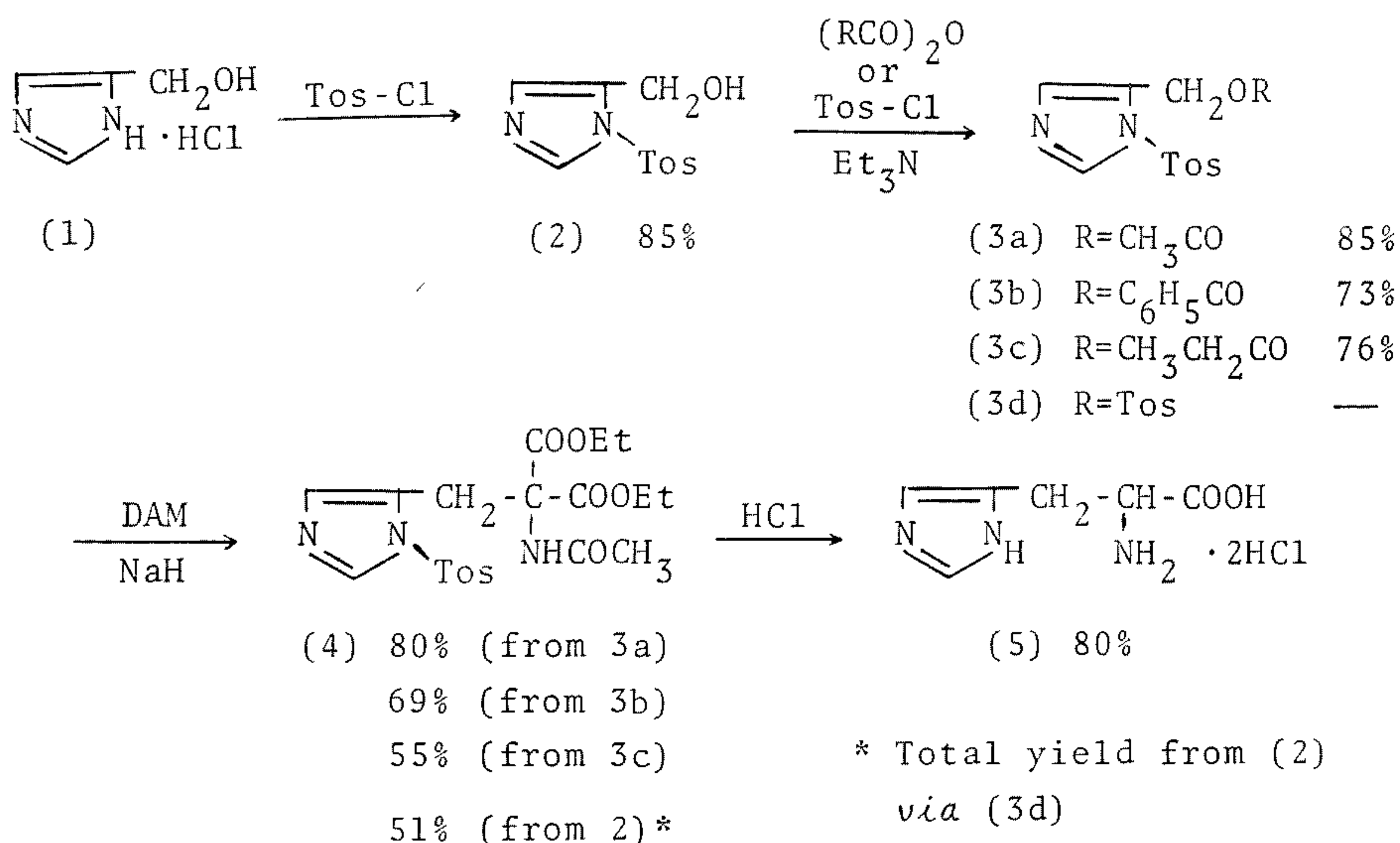
fonyl chloride (Tos-Cl), with acetic anhydride in the presence of triethylamine in chloroform in 85% yield. The compound (3a) was reacted with DAM in the presence of sodium hydride in dimethylformamide (DMF) and the coupling product (4) was obtained in 80% yield as colorless needles. Furthermore, the diester compound (4) was converted to DL-histidine by hydrolysis accompanied by decarboxylation according to the usual method.<sup>4)</sup> The resulting DL-histidine dihydrochloride (5) was homogeneous by paper partition chromatography (PPC) and electrophoresis (EP) criteria and possessed the physicochemical properties of an authentic specimen.

We have also studied the reaction of (2) with various acylating reagents other than acetic anhydride, *e.g.*, benzoic anhydride and propionic anhydride. In these results, the acylation proceeded in 73% and 76% yields, respectively. Furthermore, the coupling reactions of the compounds (3b and 3c) with DAM also proceeded in 69% and 55% yields, respectively. On the other hand, ditosyl compound (3d) which was prepared by reaction of (2) with Tos-Cl was not isolated in this step because of the unstability, and subsequently reacted with DAM. As a result, compound (4) was obtained in 51% total yield from (2).

Thus, it should be noted that the acetoxy group is used as a leaving group in practical synthesis as well as in enzymatic reaction.<sup>6)</sup>

### EXPERIMENTAL<sup>7)</sup>

*1-Tosyl-4 (or 5)-hydroxymethylimidazole (2).* To a solution of Na<sub>2</sub>CO<sub>3</sub> (8.4 g, 0.08 mole) dissolved in water (40 ml) was gradually added (1) (2.69 g, 0.02 mole) at 0~5°C with stirring. Subsequently, Tos-Cl (4.56 g,



\* Total yield from (2)  
via (3d)

FIG. 1.



0.024 mole) dissolved in AcOEt (30 ml) was dropwise added to the above mixture for a period of 1 hr at 20~30°C with vigorous stirring. After stirring was continued for 5 hr at the same temperature, the separated organic layer was washed with dil. NaHCO<sub>3</sub>, treated with activated charcoal, dried over MgSO<sub>4</sub> and then evaporated *in vacuo*. The obtainable crystals were recrystallized from AcOEt (10 ml) to afford (2) (4.3 g), yield 85%, mp 107~108.5°C. *Anal.* Found: C, 52.23; H, 4.77; N, 11.09; S, 12.91. Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S: C, 52.36; H, 4.79; N, 11.10; S, 12.70%.

*1-Tosyl-4 (or 5)-acetoxymethylimidazole (3a).* To a solution of (2) (2.52 g, 0.01 mole) dissolved in CHCl<sub>3</sub> (10 ml) was dropwise added triethylamine (2.02 g, 0.02 mole) at 20~30°C with stirring and followed by addition of acetic anhydride (1.33 g, 0.013 mole) for a period of 2 hr. After stirring was continued for 5 hr, the solvent was removed under reduced pressure and the resulting residue was extracted with AcOEt (30 ml). The extract was washed with dil. NaHCO<sub>3</sub> and water, treated with activated charcoal, dried over MgSO<sub>4</sub> and then evaporated *in vacuo*. The obtainable residue was dissolved in AcOEt (3 ml) and the solution was allowed to stand overnight. The precipitate was collected by filtration to obtain (3a) (2.51 g), yield 85%, mp 109~110°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3150 (CH), 1740 (C=O), 1600 (C=N, C=C). NMR (in CDCl<sub>3</sub>)  $\delta$ : 7.30~8.00 (6H, m, aromatic H and imidazole H), 5.00 (2H, s, CH<sub>2</sub>), 2.50 (3H, s, CH<sub>3</sub> of tosyl), 2.06 (3H, s, COCH<sub>3</sub>). *Anal.* Found: C, 53.37; H, 4.99; N, 9.82; S, 10.62. Calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S: C, 53.04; H, 4.79; N, 9.51; S, 10.89%.

*1-Tosyl-4 (or 5)-benzoxymethylimidazole (3b).* This compound was prepared in a similar way described above using benzoic anhydride in 73% yield, mp 114~116°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3140 (CH), 1720 (C=O), 1595 (C=N, C=C). NMR (in CDCl<sub>3</sub>)  $\delta$ : 7.25~8.10 (11H, m, aromatic H and imidazole H), 5.25 (2H, s, CH<sub>2</sub>), 2.43 (3H, s, CH<sub>3</sub> of tosyl). *Anal.* Found: C, 60.84; H, 4.56; N, 7.97; S, 8.87. Calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: C, 60.66; H, 4.53; N, 7.86; S, 9.00%.

*1-Tosyl-4 (or 5)-propioxymethylimidazole (3c).* This compound was prepared in a similar way described above using propionic anhydride in 76% yield, mp 67~68.5°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3140 (CH), 1725 (C=O), 1590 (C=N, C=C). NMR (in CDCl<sub>3</sub>)  $\delta$ : 7.26~7.96 (6H, m, aromatic H and imidazole H), 5.00 (2H, s, CH<sub>2</sub>-O), 2.35 (2H, q, CH<sub>2</sub>-C), 2.43 (3H, s, CH<sub>3</sub> of tosyl), 1.10 (3H, t, C-CH<sub>3</sub>). *Anal.* Found: C, 54.70; H, 5.27; N, 9.20; S, 10.07. Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S: C, 54.53; H, 5.23; N, 9.09; S, 10.40%.

*1-Tosyl-imidazole-4 (or 5)-methyl p-toluenesulfonate (3d).* To a solution of (2) (1.26 g, 0.005 mole) dissolved in CHCl<sub>3</sub> (4 ml) triethylamine (4.04 g, 0.04 mole) at

20~25°C was dropwise added with stirring. Subsequently, Tos-Cl (1.52 g, 0.008 mole) in CHCl<sub>3</sub> (3 ml) was gradually added to the mixture below 15°C. After stirring was continued for 40 min at room temperature, the reaction mixture without isolation of the ditosyl product (3d) was used for further experiments.

*Synthesis of DL-histidine dihydrochloride (5).* A typical example is as follows; DAM (1.08 g, 0.005 mole) dissolved in DMF (5 ml) was dropwise added to a suspension of sodium hydride (64% in oil, 0.19 g) in DMF (5 ml) at 0~5°C and stirring was continued for 1 hr at the same temperature. Subsequently, the mixture was gradually added to a solution of (3a) (1.47 g, 0.05 mole) dissolved in DMF (5 ml) under cooling on an ice bath and stirring was continued for 2 hr at room temperature. After the reaction was over, the mixture was neutralized with AcOH under ice cooling. Then, AcOEt (30 ml), Et<sub>2</sub>O (30 ml) and dil. NaHCO<sub>3</sub> (30 ml) were added to the mixture. The separated organic layer was washed with water, dried over MgSO<sub>4</sub> and evaporated *in vacuo*. The obtainable crystals were recrystallized from EtOH to give ethyl  $\alpha$ -ethoxycarbonyl- $\alpha$ -acetyl-amino- $\beta$ -(1-tosylimidazole-4 (or 5))-propionate (4) (1.80 g), yield 80%, mp 125~127°C. IR  $\nu_{\text{max}}^{\text{Nujol}}$  cm<sup>-1</sup>: 3400 (NH), 3100 (CH), 1735 (COOEt), 1670 (NHCO), 1595 (C=N, C=C). NMR (in CDCl<sub>3</sub>)  $\delta$ : 7.00~7.90 (6H, m, aromatic H and imidazole H), 6.70 (1H, broad, NH), 4.25 (2H  $\times$  2, q, CH<sub>2</sub>-C), 3.56 (2H, s, CH<sub>2</sub>), 2.45 (3H, s, COCH<sub>3</sub>), 1.90 (3H, s, CH<sub>3</sub> of tosyl), 1.25 (3H  $\times$  2, t, C-CH<sub>3</sub>). *Anal.* Found: C, 53.01; H, 5.56; N, 9.25; S, 6.65. Calcd. for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>7</sub>S: C, 53.20; H, 5.58; N, 9.30; S, 7.10%.

After a mixture of (4) (4.51 g, 0.01 mole) and conc. HCl (50 ml) was heated at 105~110°C for 6 hr under stirring, the solution which was decolorized with activated charcoal, was concentrated to dryness under reduced pressure. The resulting residue was recrystallized from a mixture of conc. HCl and iso-PrOH to obtain DL-histidine dihydrochloride (5) (1.82 g) in 80% yield, mp 224~228°C (dec.) (Lit<sup>4)</sup> 231~235°C (dec.)).

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  - 7) Melting points were uncorrected and measured by the use of the Yamato melting point apparatus.
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IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20A highresolution NMR spectrometer with tetramethylsilane as an internal standard.