Preparation of DL-Alanine by the Reaction of (±)-2-Chloropropionic Acid with Aqueous Ammonia under Pressure[1)]

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Synopsis. The effects of experimental conditions (molar ratio of reactants, concentration, temperature, and pressure) on the yield of DL-alanine produced by the reaction of (±)-2-chloropropionic acid with aqueous ammonia have been studied. Molar ratio of NH_3: $CH_3CHClCO_2H$ (*ca.* 10:1) much lower than that reported in the literature (68:1) can give a comparable yield (*ca.* 78%) by the reaction under pressure at 70 °C for 5 h, a much shorter time than that reported in the literature (over 96 h). Addition of ammonium carbonate does not increase the yield against the literature.[16)]

There are a number of methods for the chemical synthesis of 2-amino acids, *e.g.*, Strecker reaction with aldehyde–HCN–NH_3,[2-4)] Bücherer method[5)] using hydantoin with the components analogous to the Strecker's, and also ammonolysis of 2-halo acids with aqueous ammonia.[6-16)] The ammonolysis of 2-halo acids uses a large excess of ammonia (*e. g.*, NH_3: halo acid=60:1) at room temperature to avoid by-products, 2,2′-iminodipropionic and 2,2′,2″-nitrilotripropionic acid.

$$CH_3CHClCO_2H + NH_3 \longrightarrow \underset{\text{alanine}}{CH_3CH(NH_2)CO_2H}$$

$$+ \underset{\substack{\text{2,2′-iminodipropionic acid}\\(\text{Im})}}{[CH_3\dot{C}H(CO_2H)]_2NH} + \underset{\text{2,2′,2″-nitrilotripropionic acid}}{[CH_3\dot{C}H(CO_2H)]_3N}$$

However, this large excess of ammonia and a very long reaction time, *e. g.*, 4 d, are inconvenient, whereas the reaction at higher temperature in an open vessel gave a very poor yield because of the volatilization of ammonia. Hence we wished to shorten the reaction time and lower the molar ratio of (NH_3) : (halo acid), and we examined the effects of the molar ratio, reaction time, pressure, and temperature on the yield of DL-alanine produced by the reaction of (±)-2-chloropropionic acid with NH_3.

A few reports[6-16)] are available on this type of synthesis of 2-amino acid, but the reports discussing the effects of reaction conditions in detail are rare[10,16)] The present report is the summary of our data on the effect of several reaction parameters, especially pressure, on the yield of DL-alanine formed by the reaction of (±)-2-chloropropionic acid with aqueous saturated ammonia.

Results and Discussion

Effect of Temperature. A mixture of (±)-2-chloropropionic acid and 14.5 M (1 M=1 mol dm^{-3}) ammonia in a molar ratio of 10:1 was allowed to react in a sealed tube at various temperatures of 0—130 °C for 5 h, and the yield was measured by NMR. The results are shown in Fig. 1.

The optimum temperature was in a range of 50—70 °C; hence the increase of yield with progress of the reaction was recorded at 50, 60, and 70 °C. The results are shown in Fig. 2, which indicates that the optimum temperature is 70 °C, where a 78% yield based on (±)-2-chloropropionic acid is attained in 5 h reaction.

Effect of the Molar Ratio of Reactants. The ammonolysis was conducted with various ratios of $[NH_3]_0/[CH_3CHClCO_2H]_0$: 5/1, 10/1, 20/1, and 30/1.

The reaction with the molar ratio of 5:1 gave an appreciable amount of 2,2′-iminodipropionic acid (Im), while virtually no Im was found in the reaction with the ratio of 10:1. Consequently, we employed the ratio of 10:1 for most of the ammonolysis study. The higher ratio such as 68:1, which had been recommended in the literature[10,11)] gave really somewhat better yields, but the isolation of the product became troublesome due to dilution.

Effect of Initial Concentration of Ammonia. In order

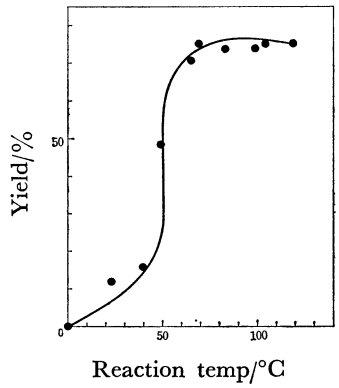

Fig. 1. Effect of the reaction temperature on the yield of DL-alanine formed by the reaction of (±)-2-chloropropionic acid with aqueous ammonia at 0—120 °C for 5 h with $[NH_3]_0$: $[ClCH(CH_3)CO_2H]_0$ =10:1.

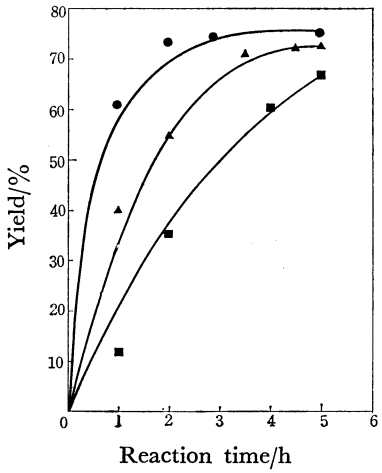

Fig. 2. Conversion curves for the formation of DL-alanine at various temperatures with $[NH_3]_0$:$[CH_3CHClCO_2H]_0$=10:1.
■: 50 °C, ▲: 60 °C, ●: 70 °C.

Table 1. Effect of initial concentration of NH_3 on the yield (%) of DL-alanine at various initial ratios of $[NH_3]_0/[CH_3CHClCO_2H]_0$

$\frac{[NH_3]_0}{[CH_3CHClCO_2H]_0}$	5	10	20	30
$[NH_3]_0=14.5$ M, yield/%	60.5	75.7	84.4	89.7
$[NH_3]_0=22.2$ M, yield/%	66.2	75.1	84.0	89.6

to find the effect of increasing concentration of ammonia, 22.8 M aqueous ammonia was prepared by passing gaseous NH_3 into the ice-cooled aqueous 14.5 M ammonia.

The effect of an increase in initial concentration of ammonia on the yield of DL-alanine at various initial molar ratios of reactants is shown in Table 1. The data in Table 1 show that the supersaturated solution of NH_3 cannot give a higher yield.

Effect of Agitation, Pressure and Addition of Ammonium Carbonate. Since there was no appreciable difference between the reaction in an autoclave and that in a sealed tube, the effect of agitation seems to be small. When the reaction was conducted at over 100 °C in an autoclave (*e. g.*, 130—140 °C at 17—19 atm), the yields of the by-products, Im, and DL-lactic acid, tended to increase.

Addition of ammonium carbonate was reported to give a better yield of DL-alanine,[16] but in our hands its addition reduced the yield to 37% accompanied by a rather high yield of DL-lactic acid.

Isolation of DL-*Alanine.* The NMR analysis of DL-alanine was checked by its isolation. The isolation was done by evaporation, addition of methanol and filtration. The decrease of alanine yield in the isolation and purification processes was *ca.* 32% in comparison with the yield based on the NMR analysis, whereas the yield of purified alanine which contained *ca.* 0.8 wt% NH_4Cl and no iminodipropionic acid, was 46%. The large loss of alanine in the purification process is due to a high solubility of alanine similar to that of NH_4Cl in aqueous solution. The analogous yield (43—46%) was reported in the reaction of 68 fold excess ammonia with chloropropionic acid carried out at room temperature for 96 h.[10,11] Although a better isolation yield may be obtained for bromopropionic acid due to small solubility of NH_4Br in methanol,[10] we did not attempt to use it because of its high cost.

Experimental

General. NMR spectra were measured on a 60 MHz Hitachi R-24B NMR spectrometer at 25 °C using dimethyl sulfoxide as an internal standard. Melting points were measured by a Yanagimoto micro melting point apparatus and uncorrected.

Materials. (±)-2-Chloropropionic acid (bp: 182.0—182.5 °C) was of guaranteed grade and used without further purification. Aqueous ammonia of 28% (14.5 M) was titrated by standard 0.1 M HCl. DL-Lactic acid with bp 130.0—134.0 °C (25 Torr), and DMSO with bp 81.0—83.5 °C (23 Torr) were of first-grade commercial products. 2,2′-Iminodipropionic acid was prepared according to the literature.[17] D_2O used was 99.8% pure.

Apparatus. Two sorts of apparatus were used for ammonolysis; one is a 1.5 mm thick sealed tube of 150 ml (38 mm×200 mm) capacity dipped in a polyethylene glycol (PEG) thermostat; the other is a stainless steel autoclave made by Taiatsu Glass Ind. Co., TEM-D 300 type, of 250 ml capacity with a mechanical stirrer, which is dipped in a PEG thermostat.

Typical Procedure. A mixture of (±)-2-chloropropionic acid (0.07 mol, 3.4 g) and 14.5 M aqueous ammonia (50 ml, 0.73 mol) was placed in a sealed tube or an autoclave and heated in a PEG bath. The internal temperature was maintained in a range of ±3 °C.

Thus far, the yield of alanine was measured by isolating it by addition of methanol after completion of the reaction,[8–11] and evaporation of water, but poor solubility of accompanying NH_4Cl in methanol rendered the estimation of the yield rather inaccurate; hence the NMR measurement of the formed DL-alanine solution was employed for estimation of the yield as described below.

Identification and Estimation of Products. Aliquots (each 1 ml) of the reaction mixture were pipetted out, and each sample was added with DMSO as an internal standard, diluted with D_2O, and the NMR peak assigned to methyl proton of DL-alanine (δ: 1.43 d) was measured. The working curve was prepared with an aqueous 14.5 M ammonia solutions of given concentrations of DL-alanine at pH 10—11 containing NH_4Cl (2.0 g). Contaminated DL-lactic acid, (±)-2-chloropropionic acid, and 2,2′-iminodipropionic acid were also characterized and estimated analogously by using their characteristic NMR peaks, δ 1.40, 1.65, and 1.54 d, respectively.

Besides estimation of the yield by NMR analysis DL-alanine was isolated from the reaction mixture. The reaction of (±)-2-chloropropionic acid (0.07 mol) with 14.5 M aqueous ammonia (50 ml, 0.73 mol) was conducted at 70 °C for 5 h in an autoclave. Then the solution was concentrated under a reduced pressure to 10 ml, added with methanol (100 ml), and the product was filtered. The filtered mass weighing 4.6 g (60%) contained 18% NH_4Cl, and it was purified by reprecipitation from water (20 ml) with methanol (100 ml) and then standing the mixture overnight in a refrigerator. The filtered pure DL-alanine (2.9 g) contained 0.8 wt% NH_4Cl, and the yield was 46%.

References

1) Contribution No. 277.
2) A. Strecker, *Justus Liebigs Ann. Chem.*, **75**, 27 (1850).
3) D. T. Mowry, *Chem. Rev.*, **42**, 236 (1948).
4) Y. Ogata and A. Kawasaki, *J. Chem. Soc., B*, **1971**, 325.
5) H. T. Bücherer and W. Steiner, *J. Prakt. Chem.*, **140**, 291 (1934).
6) K. Kraut, *Ber.*, **23**, 2577 (1890).
7) G. R. Robertson, *J. Am. Chem. Soc.*, **49**, 2889 (1927).
8) J. M. Orten and R. M. Hill, *J. Am. Chem. Soc.*, **53**, 2797 (1931).
9) J. M. Orten and R. M. Hill, *Org. Synth.*, Coll. Vol. I, 300 (1941).
10) W. C. Tobie and G. B. Ayres, *J. Am. Chem. Soc.*, **59**, 950 (1937).
11) W. C. Tobie and G. B. Ayres, *Org. Synth.*, Coll. Vol. I, 23 (1941).
12) C. S. Marvel, *Org. Synth.*, Coll. Vol. III, 495 (1955).
13) C. S. Marvel, *Org. Synth.*, Coll. Vol. III, 523 (1955).
14) H. E. Carter and H. D. West, *Org. Synth.*, Coll. Vol. III, 774 (1955).
15) C. S. Marvel, *Org. Synth.*, Coll. Vol. III, 848 (1955).
16) N. D. Cheronis and H. Spitzmueller, *J. Org. Chem.*, **6**, 349 (1941).
17) G. Studnikoff, *Ber.*, **40**, 1014 (1907).