Selective Preparation of 2,3-Epoxypropanamide and Its Facile Conversion to 2,3-Dihydroxypropanamide with Acidic Resins

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(Received April 18, 1989)

In the equimolar reaction of acrylonitrile with hydrogen peroxide to 2,3-epoxypropanamide (glycidamide), the selectivity and the yield of the epoxide were improved by adding aq. NaOH solution continuously at a constant rate. The conventional literature procedure, by controlled pH from 7.0 to 7.5, resulted in an unfavorable decomposition of hydrogen peroxide. 2,3-Epoxypropanamide could be easily converted to 2,3-dihydroxypropanamide (glyceramide) by a catalytic amount of commercially available acidic resins.

In 1961, Payne and his colleague reported the alkaline epoxidation of acrylonitrile (**1**) with hydrogen peroxide (**2**) to 2,3-epoxypropanamide (**3**), which was hydrated to 2,3-dihydroxypropanamide (**4**) with formic acid.[1] The epoxide (**3**) is a useful intermediate for resins, plant protective and preservative agents, and dyes. An aqueous solution of **4** is equivalent to commercial glyceric acid (65—70% in water). Many articles[2] and patents[3,4] related to the preparation and the properties of **3** have been reported. Payne emphasized that the solution pH should be controlled from 7.3 to 7.5 to obtain **3** in high yield.[1] The succeeding patents[4] also supported his conclusion: that the pH was controlled from 7.0 to 7.5, and improved mainly in the concentration of **2** and the removal of the peroxides. However, an excess of **2** to **1** was sometimes mentioned in those reports,[3,4] where the selectivity of **3** based on **2** must be relatively poor. In the conversion of **3** to **4**, formic acid, which is difficult to remove from the reaction solution, was employed as a catalyst, as mentioned in the literature.[1] If hydration might have occurred with acidic resins, the removal of the acid can be very easy.

Herein, we describe in detail the effect of the pH and the continuous supply of an alkaline solution on the epoxidation of **1** with **2**. The conversion of **3** to **4** with various organic acids and acidic ion-exchange resins is also described.

Experimental

Apparatus and Procedure. Epoxidation of Acrylonitrile (1) to 2,3-Epoxypropanamide (3). To a three-neck, flat-bottom flask equipped with a dropping funnel or a microtube pump (MP-101, Tokyo Rika Kikai), a condenser and a standard electrode connected to pH meter (M-5 pH meter, Hitachi-Horiba) were charged with a known amount of *acrylonitrile (**1**) and hydrogen peroxide (**2**) (0.2 mol respectively, unless otherwise stated)* in water (total volume of the reaction solution, 100 cm^3) at 35 or 45 °C. The solution was magnetically stirred while a known concentration of aq. NaOH was added through a dropping funnel or a microtube pump. After a given reaction period, hydrogen peroxide (**2**) and 2,3-epoxypropanamide (**3**) were analyzed by means of iodometric titration for **2**[5] and titration for oxirane oxygen of **3**,[6] respectively. Furthermore, in order to analyze the other organic species, after the treatment of the reaction solution with 5% palladium carbon to decompose the excess peroxide,[1] and after evaporation of the solution at 50 °C in vacuo, the residue was analyzed with NMR in a DMSO-d_6 solution (Hitachi R-24 spectrometer at 60 MHz); chemical shifts are expressed in the unit δ.

Hydration of 2,3-Epoxypropanamide (3) to 2,3-Dihydroxypropanamide (4). An aqueous solution (30 cm^3) of 18.0 mmol of 2,3-epoxypropanamide (**3**) containing 2.37 mmol of formic acid, acetic acid, carboxylated resin (Amberlite IRC-50, 10 mequiv/g, Rohm and Haas Co.), or sulfonated resin (Amberlyst 15, 4.9 mequiv/g, Rohm and Haas Co.) was allowed to warm at 80 °C. Monitoring of the epoxide (**3**) and 2,3-dihydroxypropanamide (**4**) was carried out with the oxirane titration[6] and the glycol cleavage by periodic acid,[7] respectively.

Materials. Preparation of 2,3-Epoxypropanamide (3). After observing the epoxidation behavior of acrylonitrile (**1**) to 2,3-epoxypropanamide (**3**), the reaction mixture was treated overnight with 5% palladium carbon. After removing the catalyst, the mixture was concentrated at 50 °C in vacuo. To the residue, acetone was added and an insoluble hygroscopic salt was removed by filtration. The solvent was evaporated and the residue was distillated under reduced pressure (bp 90 °C/1.8 mmHg, lit of **3**,[1] 72—73 °/0.2 mmHg 1 mmHg≈133.322 Pa). By using dilute alkali (e.g., 0.2 M NaOH) (1 M=1 mol dm^{-3}) in the epoxidation of acrylonitrile (**1**), acrylamide (**5**) was detected in this fraction; however, upon using 6 M NaOH, the amide (**5**) was not detected with NMR (see Results and Discussion).

2,3-Epoxypropanamide (**3**): ^{1}H NMR (DMSO-d_6) δ= 2.65—3.15 (2H, m), 3.39 (1H, dd, *J*=5, 3 Hz), and 5.7—7.0 (2H, br m). IR (KBr) 3300, 1660, 1320, 895, and 790 cm^{-1}.

Preparation of 2,3-Dihydroxypropanamide (4). Procedure A. After observing of the hydration behavior of 2,3-epoxypropanamide (**3**) to 2,3-dihydroxypropanamide (**4**) (in the case of the acidic resin, the resin was filtered off), the reaction mixture was evaporated in vacuo at 80 °C. The residue was purified by recrystallization from methanol to give pure diol (**4**).

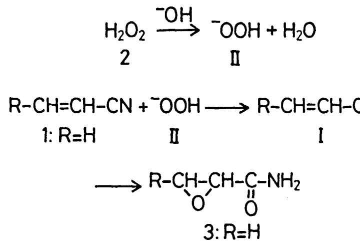
Procedure B from Glyceric Acid. Commercial glyceric acid (Tokyo Kasei Co., 65—70% in water: the purity was checked by acidmetry; 67.1%; 10.02 g, 63.4 mmol) was dissolved in a mixture of benzene and methanol (1/1 by volume). Water was removed by azeotropic distillation. Benzene was also removed by azeotrope with methanol.8) To this solution, 14% boron trifluoride methanol complex (Wako Co., 96 cm^3, 198 mmol) was added and refluxed for 1 h. The solution was then cooled to room temperature and poly(4-vinylpyridine) (Aldrich, 7.6 mequiv/g: 40.03 g, 304 mequiv) was added to the solution in order to remove the Lewis acid. After the solution was stirred for 15 min, the polymer was filtered off and the filtrate was evaporated. The residue was distilled in vacuo to give methyl glycerate (**6**) (5.77 g, 75.7%). To the methanol solution of **6**, NH_3 gas was bubbled until a spot of **6** in TLC (silica gel 60 GF_{254} (Merck); R_f=0.75 with AcOEt) disappeared. The solution was evaporated in vacuo to give 2,3-dihydroxypropanamide (**4**), almost quantitatively. The diol (**4**) was purified with silica-gel column chromatography (Wakogel C-300 (Wako)) with MeOH-AcOEt (1 : 1) and recrystallization from methanol.

2,3-Dihydroxypropanamide (4): Mp 85—87 °C (lit,1) 89—90 °C); Found: C, 34.05; H, 6.58; N, 13.11%. Calcd for $C_3H_7NO_3$: C, 34.29; H, 6.71; N, 13.33%. ^{1}H NMR (CD_3OD) δ=3.68 (2H, m), 4.00 (1H, m). IR (KBr) 3200 and 1640 cm^{-1}.

Methyl Glycerate (6): Bp 92—94 °C/2.1 mmHg (lit,9) 67—69 °C/0.1 mmHg); Found: C, 40.07; H, 6.85%. Calcd for $C_4H_8O_4$: C, 40.00; H 6.71%. ^{1}H NMR (CD_3OD) δ=3.75 (3H,s), 3.76 (2H, d, J=4 Hz), 4.13 (1H, t, J=4 Hz). IR (KBr) 3400 and 1740 cm^{-1}.

Results and Discussion

Epoxidation of 1 to 3. The Effect of pH. Under a weakly alkaline condition, the reaction of α,β-unsaturated nitrile with hydrogen peroxide forms a peroxycarboximidic acid intermediate (**I**) to give epoxyamide (Scheme 1).1)



Scheme 1.

In the epoxidation of **1** to **3**, Payne emphasized it was necessary to keep the pH between 7.3 and 7.5 in order to produce **3** in high yield.1) Indeed, the perhydroxyl anion (**II**) from **2** is generated with alkali.9) However, an excess of alkali may decompose **2** and polymerize **3**. Thus, the optimum for the yield and selectivity must depend on the concentration of the additive alkaline solution, but not on the pH of the reaction solution.

As shown in Fig. 1, without alkali at 35 °C,1,10) practically no reaction was observed in the attempted epoxidation. However, according to Payne's procedure, using 1 M NaOH to control the pH from 7.0 to 7.5 at 35 °C,1) the reaction occurred quickly to give a 38% yield of **3** after 5.2 h, while the selectivity of **3** based on **2** in charge was 45%. In this case, during the initial stage of the reaction, **2** quickly decomposed along with the generation of molecular oxygen. Epoxidation after 2 h was slow due to a lack of **2**. Thus, under this condition, alkali is used both for the generation of **II** from **2** and its decomposition. By controlling pH from 6.0 to 6.5 with 0.5 M NaOH at 35 °C, the consumption of **2** was rather slow and the selectivity of **3** was improved to 63% at 5 h. However, the yield of **3** was scarcely increased (35% at 5 h). These results show that maintaining the pH at an acidic condition can not increase the yield of **3**, while the selectivity can not be improved under a basic condition.

The Effect of Continuous Supply of Aqueous Alkali with Various Concentrations. From the above results, it seemed likely that the yield and the selectivity of **3** might be improved with a continuous addition of an alkaline solution of the appropriate concentration to the reaction solution, instead of the above Payne's procedure. Figure 2 compares the epoxidation behavior for both added 0.2 M and 6 M NaOH at

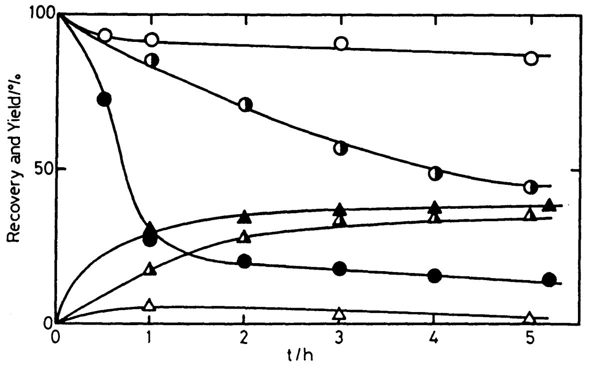


Fig. 1. The effect of pH on the reaction of **1** with **2** at 35 °C.
○: Recovery of **2**. △: Yield of **3**. Open symbols: without alkali. Half-filled symbols: pH at 6.0—6.5. Filled symbols: pH at 7.0—7.5.

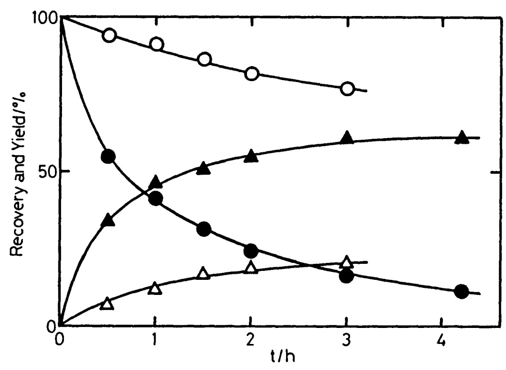


Fig. 2. The effect of concentration of alkali supplying at 1.0 ml h^{-1} on the reaction of **1** with **2** at 45 °C.
○: Recovery of **2**. △: Yield of **3**. Open symbols: addition of 0.2 M NaOH. Filled symbols: addition of 6 M NaOH.

a constant rate of 1.0 ml h^{-1} with a micro-tube pump at 45 °C.[10] In the case of 0.2 M NaOH, the pH was varied between 5.98 and 5.50, and the reaction proceeded very slowly (the yield of **3** was 20% at 3 h), while the selectivity was up to 87% after 3 h. In the case of 6 M NaOH, the pH was varied from 6.34 to 8.51 with the proceeding of the reaction and the yield of **3** increased up to 61% with a relatively poor selectivity of 73% after 3 h. The yield and the selectivity were remarkably improved compared with those of Payne's procedure. During the initial stage, at a reaction time within 1 h, where the concentration of alkali in the reaction solution was low and the pH was less than 6.9, the reaction occurred very quickly with high selectivity. After 1 h, the reaction became slow with lower selectivity and the observed pH was more than 7.0. Therefore, after 1 h, the decomposition of **2** should have occurred prior to epoxidation. Furthermore, in such a strongly alkaline condition (e.g. pH>8), a polymerization of **3** may also be possible (see below).

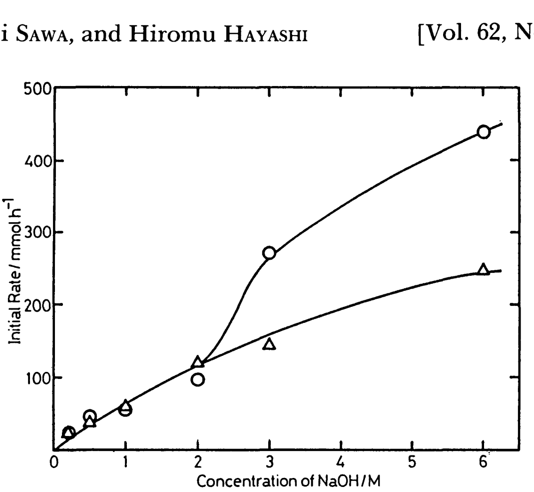


Fig. 4. The effect of concentration of alkali on initial rate of the reaction of **1** with **2** at 45 °C.
○: Initial rate of decomposition of **2**. △: Initial rate of formation of **3**.

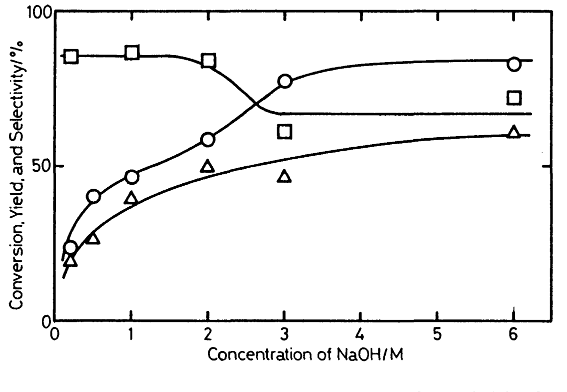


Fig. 3. The behavior of conversion of **2**, yield of **3**, and the selectivity of **3** based on **2** with concentration of alkali in the reaction of **1** with **2** at 45 °C.
○: Conversion of **2**. △: Yield of **3**. □: Selectivity.

In Fig. 3, the effects of the concentration of the alkaline solution on the yield of **3**, the conversion of **2**, and the selectivity at 3 h are shown. At a lower concentration (less than 2 M NaOH), the selectivity was relatively good, but the yield was less than 50%. At a higher concentration (more than 3 M NaOH), the yield was better than 50%, but the selectivity was relatively poor. In the present procedure, the yield and the selectivity should depend on both the initial rate of formation of **3** and that of consumption of **2**. As shown in Fig. 4, at a lower concentration (less than 2 M NaOH), the initial rates of formation and consumption overlapped on a single curve to form **3** in high selectivity, while the decrease in the selectivity of **3** was observed at a higher concentration (more than 3 M NaOH) where the rate of consumption of **3** exceeded that of the formation of **2**. The present results show that our improved procedure given above favorably contributes to avoiding the decomposition of **2** with alkali, and results in increasing both the yield and selectivity of **3**.

The Effect of the Molar Ratio of 1 to 2. According to Payne's procedure,[3] the yield of **3** was affected with a molar ratio of **1** to **2**. This should be related to the decreasing of the selectivity due to the decomposition of **2** with an excess of alkali to maintain the pH. In our procedure, the effect of the alkali must be the most critical factor. We examined the effect of the molar ratio of **1** to **2**. To the solution of a known ratio of **1** and **2** (**1**/**2**=0.1 mol/0.2 mol, 0.2 mol/0.2 mol, or 0.2 mol/0.1 mol, respectively), 0.5 M NaOH was added at 0.9 ml h^{-1}. As shown in Fig. 5, the rate of the forma-

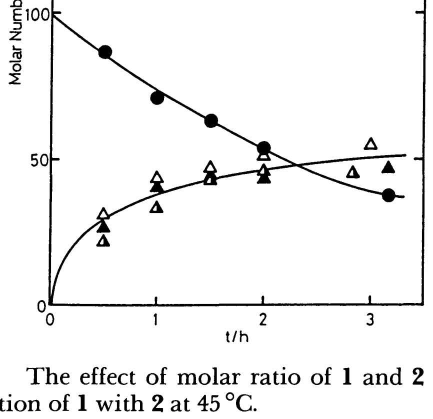
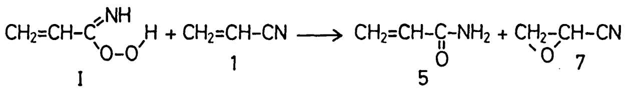


Fig. 5. The effect of molar ratio of **1** and **2** on the reaction of **1** with **2** at 45 °C.
○: Recovered **2**. △: Formed **3**. Open symbols: **1**/**2**=1/1. Half-filled symbols: **1**/**2**=2/1. Filled symbols: **1**/**2**=1/2.

tion of **3** and that of the consumption of **2** are equal in each case. In this case, an excess of alkali did not exist in the reaction mixture and the selective epoxidation to **3** proceeded. It seemed that the rate of formation of **3** and the selectivity were not affected with a molar ratio of **1** and **2** in our procedure.

Formation of 3 via 5. Payne reported that **4** and **5** were given as by-products in the present epoxidation.[1,3] It was apparent that **4** was formed through the hydration of **3**. With our NMR analysis, although the formation of **4** was observed, the reaction mixture had to stand at room temperature for several days. We also detected **5** with NMR in the case of 0.2 M NaOH, where **5** disappeared with time, as shown in Table 1. However, **5** was not detected for a concentration of the alkali higher than 6 M NaOH.

The **5** must be formed by an intermolecular nucleophilic attack of the active intermediate **I** to **1** (Scheme 2).

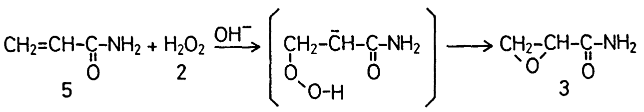


Scheme 2.

2,3-Epoxypropanenitrile (**7**), formed together with **5**, must be reactive to give **3**, successively. The disappearance in 0.2 M NaOH and no formation of **5** in 6 M NaOH could not refer to the oxidation of **5** with **I**. In the oxidation of **5** with **I**, **3** and **5** are formed. Therefore, **5** does not decrease at all with time. Generally, an olefin conjugated with ketons may be oxygenated directly with **2** under the alkaline condition to give an epoxide.[11] In the present case, **5** must be epoxidized directly with **2** to give **3** (Scheme 3).

Table 1. The Behavior of **5** in the Reaction of **1** and **2** with 0.2 M NaOH

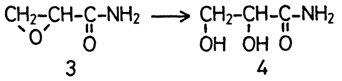
t/min	15	45	75	105	150
3/mmol	7	21	23	24	30
5/mmol	8	8	7	3	3



Scheme 3.

In the reaction with 6 M NaOH, the signals for a polymer of **3** or other organic species scarcely appeared in the NMR spectra.

Hydration of 3 to 4. Payne gave **4** by the hydration of **3** with a catalytic amount of formic acid (1/4 equiv) at 75 °C for 5 h (Scheme 4).



Scheme 4.

A comparison of the hydration at 80 °C with a small amount (ca. 1/10 equiv) of formic acid and acetic acid is shown in Fig. 6.

Obviously, acetic acid was as effective as the stronger acid, formic acid, for the hydration of **3** to afford **4** with the selectivity more than 85%. However, removal of organic acids from the aqueous solution is very difficult to decrease the yield during purification with distillation.[1] By employing acidic resins as a catalyst, the expected product **4** could be separated by simple filtration, and the yield of **4** would be increased. Hydration occurred smoothly on a carboxylated resin (Fig. 6), but it was relatively slow and the selectivity of **4** decreased to less than 74%, presumably due to trapping of the substrate on the resin. In order to increase the yield of **4**, a strongly acidic

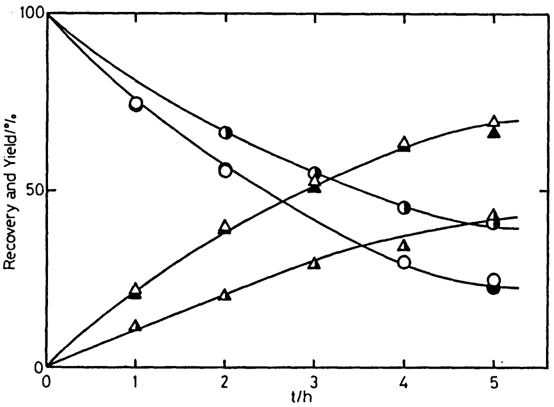


Fig. 6. The comparison of the hydration of **3** to **4** with some acids at 80 °C.
○: Recovery of **3**, △: Yield of **4**. Open symbols: formic acid. Filled symbols: acetic acid. Half-filled symols: Amberlite IRC-50.

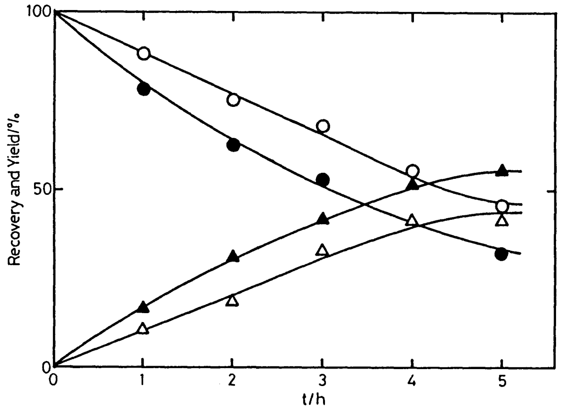


Fig. 7. The comparison of the hydration of **3** to **4** with acidic resins at 80 °C.
○: Recovery of **3**, △: Yield of **4**. Open symbols: Amberlite IRC-50. Filled symbols: Amberlyst 15.

sulfonated resin was effectively used (comparable to formic acid, as shown in Fig. 7).

In conclusion, for the preparation of **3** more selectively than the known procedure, a continuous supply of an alkaline solution was a very effective procedure. The hydration of **3** to **4** proceeded smoothly with acidic resins.

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7) V. C. Mehlenbacher, "Organic Analysis," ed by J. Mitchell, Jr., I. M. Kolthoff, E. S. Proskauer, and A. Weissberger, Interscience Publishers, New York (1953), Vol. 1, p. 41: This quantitative analysis is available to α-glycols, α-hydroxy ketones, α-diketones, and α-oxo aldehydes. But it is not always quantitative; e.g. **4**; 100%,[1] glyceric acid; 67%, methyl glycerate; 91%, 2,3-dihydroxy-3-phenylpropanoic acid; 100%, tartaric acid; 100%, methyl tartarate; 5%, ethyl tartarate; 1%, oxalic acid; 50%, pyruvic acid; 11%, methyl pyruvate; 0%, pyruvamide; 2%, hydroxy acetone; 62%, diethylene glycol; 1%, and propylene glycol; 100% (reacting with periodic acid for 2 h at room temperature).

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