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STUDIES OF PYRAZINES. II[1]. SYNTHETIC STUDY OF HYDROXYPYRAZINE

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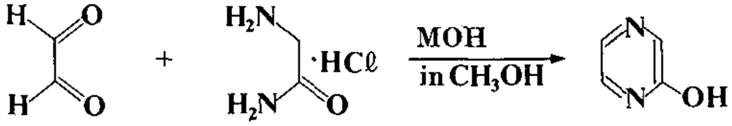
The effects of a reaction temperature and an alkali-addition velocity on the yield of hydroxypyrazine in the condensation of glycine amide hydrochloride with glyoxal, were discussed. The lower the reaction temperature, the higher was the yield of hydroxypyrazine, unless the reaction mixture was solidified. The effect of the alkali-addition velocity on the yield of the product was like that of pH on the rate of Shiff-base formation reaction, which shows a maximum value.

In the course of our investigation of physical and chemical properties of pyrazines, we have shown that alkoxypyrazines were thermally decomposed to give hydroxypyrazine and alkenes and that alkylthiopyrazines to give dipyrazinyl sulfide and alkenes[1]. Jones had devised a direct synthtic method of hydroxypyrazines from an α-aminoacid amide and an α,β-dicarbonyl compound[2]. However, the method was forced to be modified by Karmas and Spoerri because of the difficulty of the preparation of α-aminoacid amides[3]. They employed α-aminoacid amide hydrochlorides instead of the free amides, and obtained good yields. On the other hand, the condensation reaction of glycine nitrile with glyoxal to give hydroxypyrazine has been reported by Hultquist[4], but it appears to give a poor yield and a low purity[5]. In both reactions, both the yields and the purities of the products should be significantly affected by experimental conditions (e.g. a reaction temperature, a molar ratio, a reaction period, etc.), which have not been discussed in their reports.

In this paper, we wish to report our findings on the various kinds of experimental conditions to affect the yield of hydroxypyrazine (1) in the Karmas-Spoerri's method[3]. The condensation of glycine amide Hydrochloride (2) (0.2 mol) with glyoxal (3) (0.24 mol) was performed in the presence of alkali-metal hydroxide (0.5 mol) at a low temperature as shown in Eq. 1. The reaction is expected to proceed by a two-step mechanism involving a calvinolamine intermediate, which is often observed in a Shiff-base formation reaction including pH dependence. In order to confirm the above, an effect of an alkali-addition velocity, v



(3) (2) (1)

M = Alkali metal

(1)

(mmol/min), on the yield of 1 was examined. Sodium hydroxide was employed as an alkali catalizer[6]. When v was changed from 5.68 to 10.20 mmol/min at -30 ∿ -40°, the yield of 1 isolated from the first crop shows a maximum value of 61.5% at the v value of 8.3 mmol/min as shown in Fig. 1. The behavior of the yield suggests that the reaction shows the same pH dependence of the reaction rate as a Shiff-base formation reaction of an amide with a carbonyl compound does[7]. If the sodium hydroxide solution is added too rappidly, the dehydration reaction of the carbinolamine intermediate will be suppresed. Consequently, the amount of 1 produced after a definite reaction time (1 h at -30 ∿ -40° and 4 h at room temperature) is decreased. The slow-addition velocity also decreases the yield of 1 because the carbinolamine formation rate is slow in an acidic medium. However a more detailed discussion must be done, of course, in a kinetic study.

Moreover, the reaction of glycine amide hydrochloride 2 with glyoxal 3 (Eq. 1) is expected to proceed competitively with a hydrolysis reaction of 2 (Eq. 2)[8]. For that reason, the yield of

$$(2) + H_2O \xrightarrow{OH^-} H_2NCH_2COO^- + NH_4Cl + H^+ \qquad (2)$$

1 should be also affected by the reaction temperature. When the sodium hydroxide solution is added at a rate of 8.3 ∿ 9.1 mmol/min at various temperature, the yield of 1 decreases with the rise in the reaction temperature (Fig. 2). When the reaction was carried out at -30° (the Karmas-Spoerri's condition[3]), only thirty-three percent of the theoretical amount of 1 was isolated from the first crop. While the reaction was carried out at a temperature lower than the above, both the isolated and the uv yield increased (61.4% isolated yield obtained from the reaction at -55°). Thus the lower the temperature, the higher was the yield, unless the reaction mixture was solidified. It was solidified at the temperature lower than -60°. The yield of 1 at the temperature lower than -55° shows some scatter and constriction because of

the solidification. These temperature dependences of the yield yield may be attributable to the fact that the hydrolysis rates of glycine amide to glycine are smaller than the condensation rates at such low temperatures (Eqs. 1 and 2)[5,8].

As a result, hydroxypyrazine **1** is more effectively obtained at -50 ∿ -55° by adding a sodium hydroxide solution at an addition velocity of 8.0 ∿ 8.6 mmol/min.

In a typical procedure, a solution of glycine amide hydrochloride (22.2 g, 0.2 mol) and water (40 ml) in methanol (400 ml) was stirred at -30 ∿ -40° while a 40% glyoxal solution (34.8 g, 0.24 mol) was added rapidly. The mixture was then cooled at a constant temperature lower than -30°, and 12.5 M sodium hydroxide standard solution (0.5 mol) was added at a definite rate through a burette. After an additional stirring period of 1 h at this temperature, the mixture was allowed to rise to room temperature with stirring for 4 h. Then it was treated by the same way as before[3]. The crude product was recrystallized from ethanol after decolorization with activated carbon. The results are illustrated in Figs. 1 and 2. Mp 185° (lit.[3] 188 ∿ 190°), uv (H_2O): $\lambda_{max} = 220$ ($\varepsilon = 10100$), 318 nm (550), ir (KBr): $\nu_{max} = 3160$, 3090, 1650,1615 cm^{-1}, nmr (D_2O): $\delta = 8.15$ (s, 1H, 3-H), 7.03 (m, 2H, 5- and 6-H), mass spectrum: m/e = 96(M^+), 68, 41.

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2. R. G. Jones, *J. Am. Chem. Soc.*, 1949, **71**, 781.

3. G. Karmas and Spoerri, *J. Am. Chem. Soc.*, 1952, **74**, 1580.

4. M. E. Huletquist, U.S. 2,805,223(1957); *Chem. Abstr.*, 1958, **52**, 2935i.

5. A condensation of glycine nitrile sulfate (15.4 g, 0.0992 mol) with glyoxal (0.157 mol) in concentrated sodium hydroxide was performed at -10° by a method of Huletquist[4] to give **1** with a low yield and a low purity (17%, mp ca. 153°, lit.[4] mp 185 ∿ 188°, yield was not reported). The low yield may by because of the hydrolysis reaction of glycine nitrile to glycine. An evolution of gaseous ammonia was found during the reaction. On the other hand, the condensation reaction of glycine nitrile sulfate (0.1 mol) with glyoxal (0.12 mol) under the same conditions as ones reported in this paper gave also less satisfactory results (mp 170°, yield 16%).

6. Sodium hydroxide gave a more favourable result than the others, potassium and lithium hydroxides.

7. R. L. Reeves, 'The Chemistry of the Carbonyl Group,' edit. by S. Patai, Interscience Publishers, London, 1966, p. 608; and references cited therein.

8. The rate constants of hydrolysis of glycine amide at 25 ∿ 35° have been investigated by Conley and Martin[9], and that of the condensation of glycine amide with pyridoxal in methanol at 25° by Matsushima[10]. From these data, a relative rate of the reactions (hydrolysis/condensation) was estimated to be about 10^{-2} at 25°.

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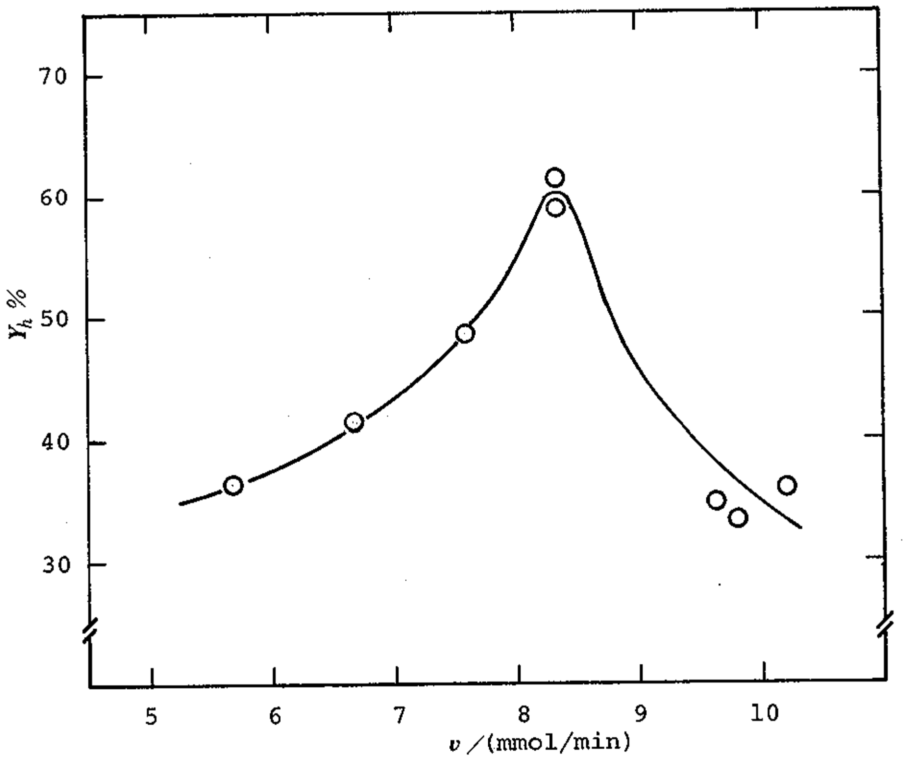

FIG. 1. A plot of the alkali-addition velocity v *vs.* the isolated yield Y_h of **1** at -30 ∿ -40°.

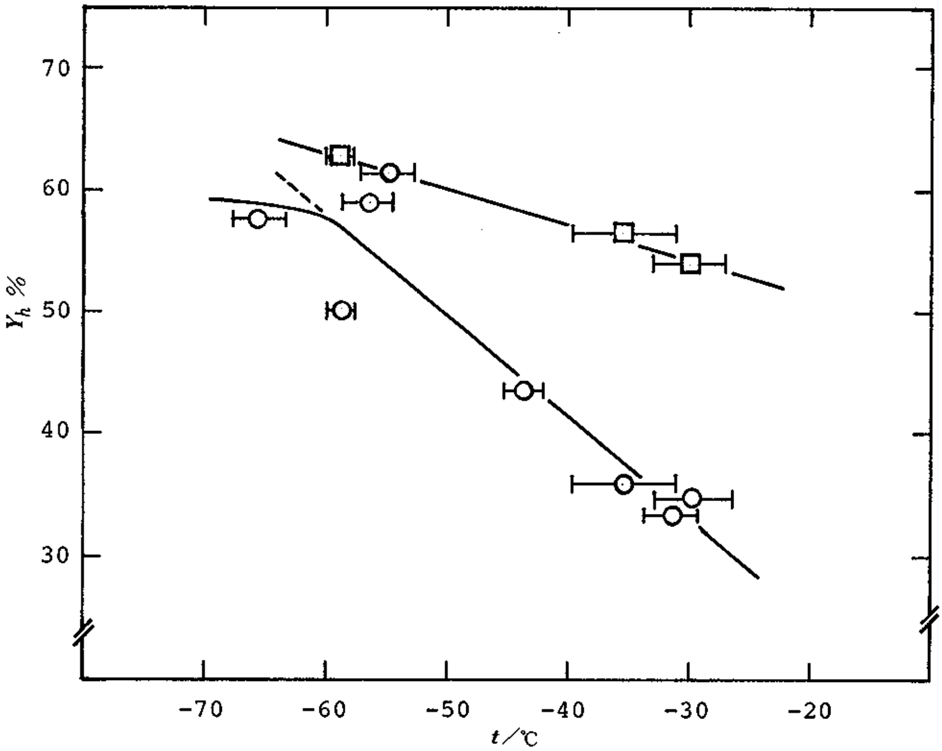

FIG. 2. Temperature dependence of the yield, Y_h, for hydroxypyrazine 1.

—○—: isolated yield; —□—: uv yield; alkali-addition velocity v = 8.3 ∿ 9.1 mmol/min.

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