Notes

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Catalytic Reactions of Pyridines. V.[1] Alkylation of α-, β-, and γ-Picolines with Alcohols catalyzed by Ammonium Halides

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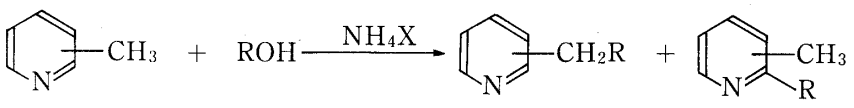
A new method was found for the homogeneous liquid-phase alkylation of α-, β-, and γ-picolines with either methanol or ethanol. Addition of a catalytic amount of an ammonium halide to a mixture of a picoline and an alcohol resulted in a great increase in the yields of both side-chain- and α-alkylated derivatives of the starting picoline when the reaction was carried out at 320—335°C in an atmosphere of nitrogen. The higher the reaction temperature, the greater the yields of side-chain alkylated derivatives became. In practice, this alkylation gave 2-ethylpyridine and 2,6-lutidine from α-picoline with methanol, 3-ethylpyridine and 2,5-lutidine from β-picoline with methanol, 4-ethylpyridine and 2,4-lutidine from γ-picoline with methanol, 2-propylpyridine and 2-ethyl-6-methylpyridine from α-picoline with ethanol, 2-ethyl-5-methylpyridine from β-picoline with ethanol, and 4-propylpyridine and 2-ethyl-4-methylpyridine from γ-picoline with ethanol.

Keywords——alkylation; catalyst; ammonium halide; α-picoline; β-picoline; γ-picoline; ethylpyridine; propylpyridine; methanol; ethanol

The pyridine ring is well-known to be less reactive than most other aromatic rings to substitution. Therefore, relatively few papers have appeared on the catalytic substitution of aromatic compounds containing pyridine rings. As regards the direct alkylation of pyridines, the side-chain alkylation of 2- and 4-alkylpyridines with olefins in the presence of alkali metals,[2–5] and the ring methylation of pyridine with methanol in the presence of acetic acid, chloroacetic acid, or trichloroacetic acid[6] were investigated in some detail in the liquid phase. Later, we reported the heterogeneous vapor-phase alkylation of pyridines with alcohols over some cation exchanged zeolites: the formation of 2-alkyl and 2,6-dialkyl derivatives of the starting pyridines over Ni^{2+} exchanged zeolites at 350°C,[7] and the formation of side-chain alkylated derivatives of the starting pyridines over Na^+, K^+, Rb^+, or Cs^+ exchanged zeolites at 450°C.[1] Moreover, we discovered a unique alkylation of pyridines, *i.e.*, the γ-ray-induced homogeneous liquid–phase mono-methylation of either pyridine or γ-picoline with methanol in the presence of nickel nitrate.[8] On the other hand, we also reported the homogeneous liquid–phase *N*-alkylation of aniline, α-pyrrolidone, α-piperidone, formamide, or acetanide with alcohols in the presence of a small amount of an ammonium halide catalyst.[9]

A new method was found for the homogeneous liquid–phase alkylation of picolines with alcohols. As shown in Chart 1, the presence of a catalytic amount of an ammonium halide was found to promote both the side-chain and ring alkylation of α-, β-, and γ-picolines with either methanol or ethanol at 320—335°C in an atmosphere of nitrogen. In contrast to earlier reports,[1–8] ammonium halides can promote both the side-chain and ring alkylation



R=Me, Et

Chart 1

of picolines at the same time. Thus, the object of the present work was to explore the influence of reaction conditions, such as temperature, the duration of heating, and the composition of the starting solution, on the activities of ammonium halide catalysts.

Experimental

Materials——α-Picoline, β-picoline, γ-picoline, lutidines, ethylpyridines, ethylmethylpyridines, and propylpyridines, having a purity of over 99%, were commercial products, and were used after being distilled and confirmed to be gas chromatographically pure. Other chemical reagents were of commercial GR grade and were used without further purification.

Procedure——A rotating stainless steel autoclave[10] of 100 ml capacity was charged with 16.0 g of an alcohol, 10.0 g of a picoline, and 1.0 g of an ammonium halide, sealed, flushed out with nitrogen, and then heated at 280—335°C[11] with stirring. The duration of heating was usually 2 h for methylation, 5 h for ethylation, and 12 h for other alkylations.

Analysis——The reaction mixture was analyzed by gas chromatography using a 3 mm × 2 m stainless steel column with 30% Silicon DC 550 (80—100 mesh). The carrier gas was H_2 and the analysis temperature was 140°C. Reaction products were separated by distillation under reduced pressure, and each component was identified by comparing its boiling point, UV spectrum, IR spectrum, and relative retention time in gas chromatography with those of an authentic sample. The yield of alkylpyridine produced was calculated as follows:

$$\text{yield} = \frac{\text{mol of alkylpyridine produced}}{\text{mol of picoline supplied}} \times 100\,(\text{mol \%})$$

Results and Discussion

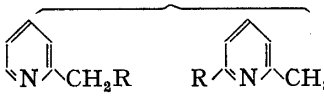
Alkylation of Picolines

The results of the homogeneous liquid-phase alkylation of α-, β-, and γ-picolines with alcohols in the presence of 1.0 g of an ammonium halide are summarized in Tables I, II, and III, respectively. As far as the methylation of picolines with methanol is concerned, picolines are not reactive with methanol even on heating for 2 h at 335°C in the absence of an ammonium halide. In contrast, the addition of only 1.0 g of NH_4Cl results in a large increase in the yields of the corresponding ethylpyridines and lutidines containing an α-methyl group on heating for 2 h at 320°C. In contrast to the results of heterogeneous vapor-phase side-chain alkylation of picolines over alkali cation exchanged zeolites,[1] the formation of vinylpyridines and the thermal decomposition of the pyridine ring were not observed. No derivatives of picolines other than the ethylpyridines and lutidines shown in Tables I—III were ultimately obtained. The yields of ethylpyridines and lutidines increased with increase in the reaction temperature and in the duration of heating. A higher temperature was found to be advantageous for higher selectivities to ethylpyridines and for larger conversions of picolines. In the methylation of γ-picoline, for instance, ring alkylation occurs mainly at temperatures below 320°C, but side-chain alkylation increases with reaction temperature and becomes predominant at 335°C. The catalytic activity of NH_4Br is almost identical with that of NH_4Cl, but the activities of NH_4F and NH_4I were found to be rather small. Furthermore, the yields of ethylpyridines also showed a tendency to increase with increase either in the amount of ammonium halide catalyst or in the fraction of methanol in the starting solution. For example, when 0.5, 1.0, 2.0, or 3.0 g of NH_4Cl was added to a mixture of 10.0 g of α-picoline and 16.0 g of methanol and the whole was heated for 2 h at 320°C in an atmosphere of nitrogen, the yield of 2-ethylpyridine was 9.4, 11.0, 11.9, or 12.3%, respectively. Next, when 8.0, 16.0, 24.0, or 32.0 g of methanol was added to the reaction system of 10.0 g of α-picoline and 1.0 g of NH_4Cl and the mixture was heated for 2 h at 320°C in an autoclave, the yield of 2-ethylpyridine was 8.0, 11.0, 12.8, or 14.7%, respectively.

As regards the ethylation of picolines with ethanol, as can also be seen from Tables I—III, picolines were unreactive with ethanol even on heating for 5 h at 335°C in the absence of an

ammonium halide, whereas the presence of 1.0 g of NH_4Cl promoted the reaction and gave considerable amounts of propylpyridines and ethylmethylpyridines containing a 2-ethyl group on heating for 5 h at 320°C. Exceptionally, only 2-ethyl-5-methylpyridine was formed from β-picoline due to the instability of 3-propylpyridine at elevated temperature. In general, increased yields of propylpyridines were obtained when the reaction temperature, the duration of heating, the amount of ammonium halide, and the fraction of methanol in a starting solution were increased.

Table I. Results of the Alkylation of α-Picoline with Alcohols in the Presence of 1.0 g of an Ammonium Halide

ROH	NH_4X	Temperature (°C)	Heating duration (h)	Yield (%) 	
CH_3OH	None	335	2	0.0	0.0
	NH_4F	320	2	2.3	0.5
	NH_4Cl	280	2	0.1	0.1
		300	2	1.2	0.7
		310	2	3.1	0.8
		320	0.5	4.7	0.5
		320	1	7.7	0.5
		320	2	11.0	1.1
		320	5	17.2	1.6
		320	12	19.5	1.7
		335	2	13.0	0.8
		335	5	22.6	1.4
		335	12	28.1	1.8
	NH_4Br	300	2	1.2	0.7
		320	2	8.3	1.3
		335	2	12.4	0.9
	NH_4I	320	2	3.0	0.6
C_2H_5OH	None	335	5	0.0	0.0
	NH_4Cl	320	5	1.3	3.0
		335	5	6.6	1.9
		335	12	8.7	2.6
	NH_4Br	335	5	6.8	1.9

When a mixture of 10.0 g of α- or γ-picoline, 16.0 g of propyl alcohol, and 1.0 g of NH_4Cl was heated for 12 h at 320°C, 0.8% 2-propylpyridine or 1.6% 4-propylpyridine, respectively, was generated. Contrary to expectation, butylpyridines and methylpropylpyridines were not produced. However, 3-propylpyridine was not produced from β-picoline. Next, when isopropyl alcohol, butyl alcohol, *sec*-butyl alcohol, or *tert*-butyl alcohol was used as an alcohol, and was heated with both a picoline and NH_4Cl for more than 12 h, no reaction with respect to the picoline took place even at 335°C.

Considerations on Reaction Mechanism

The liquid–phase side-chain alkylation of pyridines has been reported to take place in the presence of basic catalysts.[2–5] In contrast, the ring alkylation of pyridines occurred in the presence of acidic catalysts.[6] Next, ammonium halide is known to sublime at temperatures higher than 300°C and to decompose into ammonia and hydrogen halide.[12] The most important role of ammonia seems to be as a basic catalyst for the side-chain alkylation of picolines, while that of hydrogen halide seems to be as an acidic catalyst for the ring alkylation of picolines.

Table II. Results of the Alkylation of β-Picoline with Alcohols in the Presence of 1.0 g of an Ammonium Halide

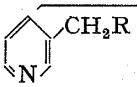
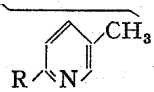
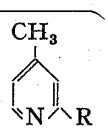
ROH	NH_4X	Temperature (°C)	Heating duration (h)	Yield (%) 	Yield (%) 
CH_3OH	None	335	2	0.0	0.0
	NH_4F	320	2	0.5	1.1
	NH_4Cl	280	2	0.0	0.1
		300	2	0.2	1.0
		310	2	0.8	2.2
		320	0.5	1.4	2.4
		320	1	2.0	3.7
		320	2	3.0	6.1
		320	5	4.3	8.8
		320	12	4.8	10.1
		335	2	7.0	3.2
		335	5	12.4	5.7
		335	12	16.4	7.8
	NH_4Br	300	2	0.1	0.8
		320	2	3.0	6.2
		335	2	7.4	3.2
	NH_4I	320	2	0.6	1.3
C_2H_5OH	None	335	5	0.0	0.0
	NH_4Cl	320	5	0.0	2.6
		335	5	0.0	3.1
	NH_4Br	335	5	0.0	3.1

Table III. Results of the Alkylation of γ-Picoline with Alcohols in the Presence of 1.0 g of an Ammonium Halide

ROH	NH_4X	Temperature (°C)	Heating duration (h)	Yield (%) 	Yield (%) 
CH_3OH	None	335	2	0.0	0.0
	NH_4F	320	2	1.0	2.4
	NH_4Cl	280	2	0.0	0.2
		300	2	0.4	1.8
		310	2	1.3	3.0
		320	0.5	1.9	3.6
		320	1	2.8	5.6
		320	2	4.5	9.0
		320	5	6.7	13.3
		320	12	7.4	15.2
		335	2	11.0	3.9
		335	5	19.3	6.9
		335	12	25.5	9.5
	NH_4Br	300	2	0.4	1.5
		320	2	4.4	9.0
		335	2	10.2	3.9
	NH_4I	320	2	1.5	3.3
C_2H_5OH	None	335	5	0.0	0.0
	NH_4Cl	320	5	2.2	2.6
		335	5	6.4	2.5
		335	12	8.3	3.1
	NH_4Br	335	5	6.5	2.3

A possible mechanism for the ring methylation of, for example, α-picoline with methanol in the presence of NH_4Cl is illustrated in Chart 2. The ring methylation is supposed to begin with the coordination of HCl, formed by the decomposition of NH_4Cl, to the nitrogen atom of α-picoline, forming 2-methylpyridinium chloride. This pyridinium salt is then methylated with methanol at elevated temperature, forming 1,2-dimethylpyridinium chloride. Generally speaking, *N*-alkylpyridinium halides have been reported to rearrange into 2- and 4-alkylpyridinium halides at about 300°C.[13] In a similar manner, 1,2-dimethylpyridinium chloride produced here may rearrange into 2,6-dimethylpyridinium chloride. Finally, 2,6-dimethylpyridinium chloride may decompose into 2,6-lutidine and NH_4Cl upon cooling to room temperature.

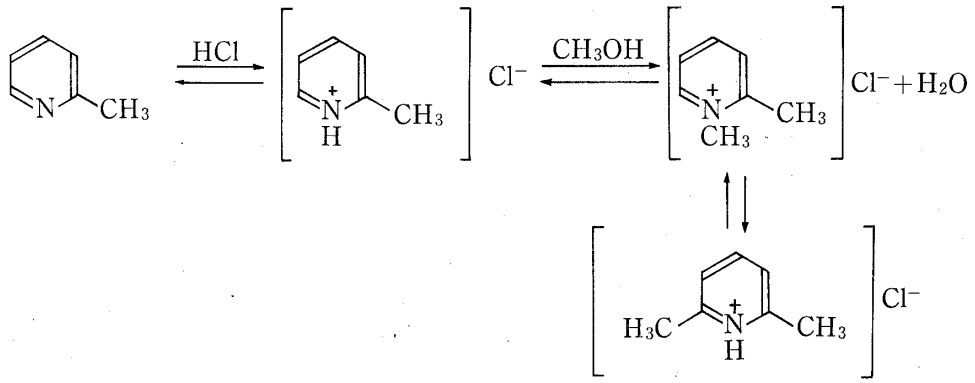


Chart 2

The homogeneous liquid–phase side-chain alkylation of aromatic hydrocarbons[14] or picolines[4] with olefins in the presence of sodium metal has been reported to have the characteristics of a chain reaction. Therefore, our side-chain alkylation of picolines in the presence of an ammonium halide may proceed by a mechanism similar to the one proposed for the side-chain alkylation of picolines with olefins catalyzed by sodium metal.[4] A possible mechanism for the side-chain methylation of α-picoline with methanol in the presence of NH_4Cl is shown in Chart 3. In step 1 in Chart 3, the chain initiator, ammonia, produced by the decomposition of NH_4Cl, abstracts a proton from α-picoline to form a picolyl carbanion. In step 2, a pyridylethyl carbanion is produced through condensation between the picolyl carbanion and methanol. Next, the pyridylethyl carbanion thus formed can react with the picoline, as indicated in step 3. As the temperature is lowered, ammonia combines again with hydrogen chloride. Then the equilibrium in step 1 is gradually shifted to the left, and finally the reaction stops.

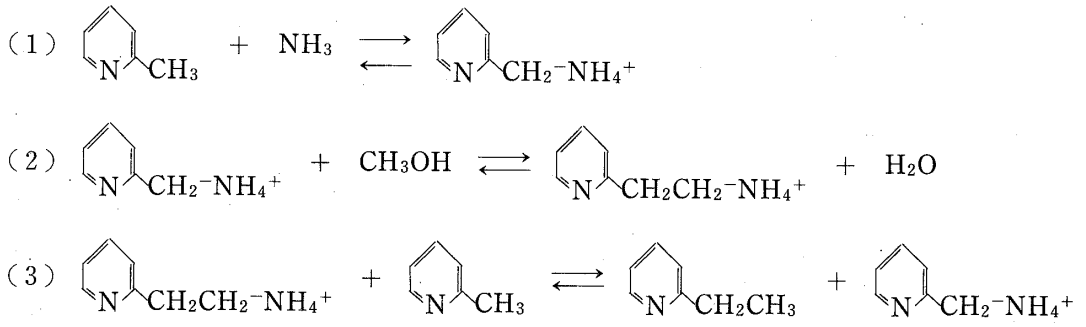


Chart 3

A striking characteristic of the catalytic reactions of picolines described above is the cooccurrence of both the ring and side-chain alkylation. As described above, an ammonium halide is transformed into an equimolar mixture of hydrogen halide and ammonia at elevated

temperature, but reverts to the ammonium halide upon cooling to room temperature. Therefore, the presence of an ammonium halide does not disturb the separation of alkylpyridines from the reaction mixture by distillation.

References and Notes

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8) H. Kashiwagi and S. Enomoto, *Chem. Pharm. Bull.*, **30**, 1 (1982).
9) H. Kashiwagi and S. Enomoto, *Nippon Kagaku Kaishi*, **1980**, 279.
10) Ammonium halides are known to be corrosive at elevated temperature. However, we had to use an autoclave, because a temperature much higher than the boiling points of picolines and alcohols was required for the reaction and the pressure during the reaction sometimes rose above 100 atm. In practice, the amounts of metals dissolved from the autoclave were found to be very small per reaction, and the components of stainless steel (Fe, Cr, and Ni) did not show catalytic activity.
11) It would be interesting to examine these reactions at temperatures higher than 335°C. However, the reaction could not be run safely at a temperature higher than 335°C, because the expected pressure exceeded the safety limit of the autoclave.
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