

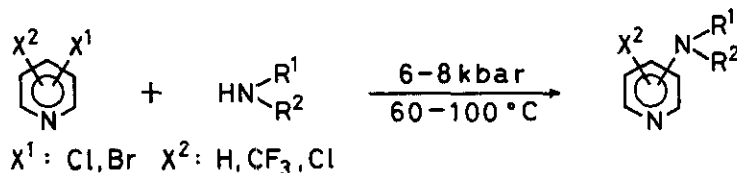
## AMINOLYSIS OF HALOGENOPYRIDINES AT HIGH PRESSURES

Shiro Hashimoto <sup>a)</sup>, Shinichi Otani <sup>a)</sup>, Tadashi Okamoto <sup>b)</sup>, and  
Kiyoshi Matsumoto <sup>a)</sup>\*

College of Liberal Arts and Science <sup>a)</sup>, Kyoto University, Kyoto  
606, Japan, and Institute for Chemical Research <sup>b)</sup>, Kyoto  
University, Uji 611, Japan

**Abstract**—The transformation of some halogenopyridines to  
the corresponding aminopyridines has been realized in  
moderate to excellent yields at high pressures of 6~8 kbar.

Although nucleophilic aromatic substitution ( $S_NAr$ ) reactions are not generally facile, halogenopyridines and halogenodiazines undergo  $S_NAr$  reactions more readily than halogenobenzenes as a consequence of their  $\pi$ -deficient nature.<sup>1</sup> Particularly, nucleophilic substitution of 2- and 4-halogeno heterocycles is an extremely important method for the introduction of a wide range of functional groups such as oxygen, nitrogen, carbon, and sulfur substituents. However, aminolysis of halogenopyridines usually requires considerably severe reaction conditions, e.g. higher temperatures than 150°C and often the presence of catalysts such as acids, zinc(II) chloride, and copper(II) sulfate. Highly negative activation volumes are reported for the  $S_NAr$  reactions promoted by secondary amines, amounting ca.  $-70 \text{ cm}^3/\text{mol}$  in certain cases.<sup>2</sup> In spite of these facts, the high pressure technique has not been applied to this type of reaction for synthetic purposes,<sup>3,4</sup> though a wealth of kinetic data for such substitution is available.<sup>5</sup>










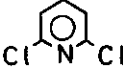

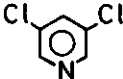


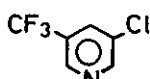


We now report that representative chloropyridines (and 3-bromopyridine) undergo  $S_NAr$  reaction with primary and secondary amines without Lewis acid catalyst at moderate temperatures when performed at high pressures of 6~8 kbar which are now readily attainable in a considerably large scale.<sup>6</sup> The selected results are

summarized in Table 1.<sup>7</sup> As is expected, 4-chloro- and 2-chloropyridines were considerably reactive towards amines (especially to secondary amines, entries 1~4), though they are known to be less reactive ( $10^2 \sim 10$  times) than are halogenonitrobenzenes.<sup>5a</sup> Reactivity differences between the 2- and 4-chloropyridines are relatively small, a factor of only  $10^{5a}$ , being in accordance with the results in Table 1. In contrast, "unreactive" 3-chloropyridine was almost inert to "reactive" pyrrolidine even under high pressures (entries 5 and 6). This is not unexpected since 3-chloropyridine is  $10^4$  times less reactive than 2-chloropyridine and therefore ca.  $10^5$  less so than 4-chloropyridine. Replacement of chlorine with bromine increased the yield upto 71% in the reaction with pyrrolidine at 6 kbar and 100°C (entry 7); the relative reactivities with respect to  $S_NAr$  reaction increase in the order  $Cl \leq Br \leq I \leq F$ .<sup>1</sup> The process is slightly facilitated by an additional electron-withdrawing group  $\beta$  to the chlorine. For example, 3,5-dichloropyridine underwent aminolysis quantitatively with pyrrolidine at 6 kbar and 100°C (entry 10), though the procedure was not so effective towards less reactive amines such as piperidine and butylamine. Analogous results were obtained in the reactions of 3-chloro-5-trifluoromethylpyridine with amines (entries 13, 14, and 15). This finding may be practically significant since some amino(trifluoromethyl)aromatics have been of interest as bio-related materials like pesticides.<sup>8</sup> Finally, 2,6-dichloropyridine reacted with pyrrolidine and piperidine producing, in addition to 2-chloro-6-pyrrolidino- and 2-chloro-6-piperidinopyridines (3% and 89% yield), 2,6-bis(pyrrolidino)- and 2,6-bis(piperidino)pyridines in 97% and 11% yields, respectively. The formation of these 2,6-bisaminopyridines is intriguing since this type of compounds has been employed as metal chelating agents.<sup>9</sup> In conclusion,  $S_NAr$  reactions seem to become more practical when carried out at high pressures.

#### ACKNOWLEDGEMENT

We are grateful to Ishihara Sangyo Kaisha, Ltd. for supply of 3-chloro-5-trifluoromethylpyridine. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture (Nos. 61840017 and 62430007).

Table 1 Aminolysis of halogenopyridines<sup>a)</sup>

Entry	Halide	Amine	Pressure (kbar)	Temp (°C)	Time (d)	Yield (%)	Mp (°C)
1			8	60	4	90 <sup>b)</sup>	78-79
2	∕	n-BuNH <sub>2</sub>	7	60	1	61	58-59
3			8	60	4	72 <sup>c)</sup>	oil
4	∕	n-BuNH <sub>2</sub>	6	80	1	31 <sup>d)</sup>	38-39
5			8	60	6	0	
6	∕	∕	6	100	4	10	oil
7		∕	6	100	4	71	∕
8		∕	8	80	3	3 <sup>e)</sup>	68
9	∕		8	60	4	89 <sup>f)</sup>	oil
10			6	100	3	100	78-79
11	∕		8	60	4	23	oil
12	∕	n-BuNH <sub>2</sub>	8	60	4	2	oil
13			8	100	3	100	63-64
14	∕		8	100	3	94	oil
15	∕	n-BuNH <sub>2</sub>	8	80	3	20	oil

a) Reaction conditions were not optimized. b) 33% Yield at 1 bar and 80°C for 24 h. c) 5% Yield at 1 bar and 80°C for 24 h. d) No reaction at 1 bar and 80°C. e) 40 mmol of Pyrrolidine was used. 2,6-Bis(pyrrolidino)pyridine was also isolated in 97% yield. f) 30 mmol of Piperidine was employed. In addition to the monoamino compound, 11% yield of 2,6-bis(piperidino)pyridine was obtained.

REFERENCES

1. (a) A. R. Katritzky and C. W. Rees Eds., "Comprehensive Heterocyclic Chemistry", Pergamon Press, Oxford, 1984, Vol. 2, pp. 59-61, 360-362; Vol.3, pp. 25-28, 98-104, 175-176; (b) K. Matsumoto, "Yukihanno III, Heterokankagobutsu", K. Maruyama Ed., Maruzen, Tokyo, 1983, pp. 64-73 and references cited in these reviews.
2. K. R. Brower, J. Am. Chem. Soc., 1959, 81, 3504.
3. K. Matsumoto, A. Sera, and T. Uchida, Synthesis, 1985, 1.
4. During the course of our investigation on this subject, Professor Ibata kindly informed us of their results on  $S_N Ar$  reactions of halogenonitrobenzenes under high pressure: T. Ibata, Y. Isogami, and J. Toyoda, Chem. Lett., 1987, 1187.
5. For example, (a) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, Amsterdam, 1968, pp. 234-289; (b) G. Illuminati, Adv. Heterocycl. Chem., 1964, 3, 285; (c) R. H. Shepherd and J. L. Fedrick, Adv. Heterocycl. Chem., 1965, 4, 145; (d) R. A. Abramovitch and J. G. Saha, Adv. Heterocycl. Chem., 1966, 6, 274.
6. N. S. Isaacs and A. V. George. Chem. Brit., 1987, 47: this review emphasizes that commercial exploitation is to be expected in the future.
7. All new compounds gave correct CHN analyses and were in accord with  $^1H$ - and  $^{13}C$ -NMR spectra. Procedure: a mixture of the halide (5 mmol) and the amine (20 mmol) is diluted with tetrahydrofuran in an 8 ml Teflon<sup>®</sup> capsule, that is stored at the stated pressures and temperatures for the stated days (Table 1). After removal of the solvent and amine, the residue is treated with flash chromatography on silica gel with benzene and benzene/ethyl acetate. For a description of the high pressure equipment employed in this study, see ref. 3.
8. T. Haga, K. Fujikawa, T. Koyanagi, T. Nakajima, and K. Hayashi, Heterocycles, 1984, 22, 117 and references cited.
9. E.g. D. E. C. Corbridge and E. G. Cox, J. Chem. Soc., 1956, 594.

Received, 26th September, 1987