

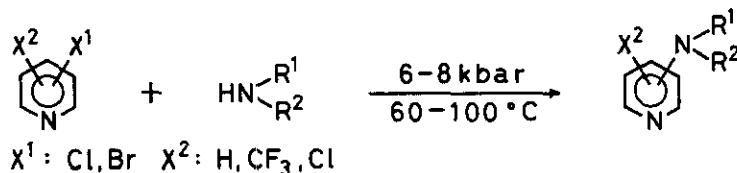
AMINOLYSIS OF HALOGENOPYRIDINES AT HIGH PRESSURES

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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 π -deficient nature.¹ 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 cm³/mol in certain cases.² In spite of these facts, the high pressure technique has not been applied to this type of reaction for synthetic purposes,^{3,4} though a wealth of kinetic data for such substitution is available.⁵



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.⁶ The selected results are

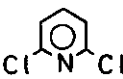
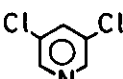
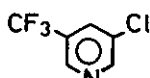
summarized in Table 1.⁷ As is expected, 4-chloro- and 2-chloropyridines were considerably reactive towards amines (especially to secondary amines, entries 1~4), though they are known to be less reactive ($10^2 \sim 10$ times) than are halogenonitrobenzenes.^{5a} Reactivity differences between the 2- 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 $Cl \leq Br \leq I \leq F$.¹ The process is slightly facilitated by an additional electron-withdrawing group β 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.⁸ 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.⁹

In conclusion, S_NAr reactions seem to become more practical when carried out at high pressures.

ACKNOWLEDGEMENT

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Table 1 Aminolysis of halogenopyridines^{a)}

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

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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[®] 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.
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