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Nucleophilic Substitution Reaction of Aromatic Chlorides with Cyclic Tertiary Amines under High Pressure

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The reaction of *p*-chloronitrobenzene with *N*-methylpyrrolidine under high pressure gave demethylation product and ring opening products through quaternary ammonium chloride intermediate formed by the S_NAr reaction. On the other hand, the reactions with *N*-methylpiperidine and *N*-methylmorpholine gave only demethylation products. The reactions of *o*-chloronitrobenzene and 2,4-dichloronitrobenzene with above amines gave similar results.

Nucleophilic substitution reaction of aromatic halides with amines is usually reluctant in comparison with the corresponding reaction of aliphatic halides,[1] and is reported to be effectively accelerated by high pressure.[2] Because of the lower nucleophilicity of tertiary amine than that of primary and secondary amines, the title reaction has been recognized to be difficult to proceed under ordinary pressure. To the best of our knowledge, only a few papers have been reported on the S_NAr reaction of aromatic halide with tertiary amines.[3] Recent works of Matsumoto *et al.* on the reaction of heteroaromatic halides with acyclic tertiary amines under high pressure focusing on the selectivity of demethylation and dealkylation of quaternary ammonium halide intermediates[3] prompted us to report our results. Here we wish to report the S_NAr reactions of aromatic chlorides with cyclic tertiary amines such as *N*-methylpyrrolidine, *N*-methylpiperidine, and *N*-methylmorpholine in order to confirm the structural effect on the selectivity between ring opening and demethylation of the quaternary ammonium chloride formed as an intermediate of the initial S_NAr reaction.

The reaction of *p*-chloronitrobenzene (**1**) with *N*-methylpyrrolidine under high pressure (0.6 GPa, 50 °C, 20 h, in tetrahydrofuran) gave *p*-pyrrolidinonitrobenzene (**3a**), *N*-methyl-*N*-(4-chlorobutyl)-*p*-nitroaniline (**4a**), and *N*-(5-(*p*-nitrophenyl)-5-azahexyl)-*N*-methylpyrrolidinium chloride (**5a**) in 18, 7.8 and 28% yields, respectively, together with the recovered **1** (46%) (Table 1, run 1). *N*-Methylpiperidine (**2b**) and *N*-methylmorpholine (**2c**) gave the corresponding *p*-piperidino- (**3b**) and *p*-morpholinonitrobenzenes (**3c**) as the sole products in low

yields. Under the forced reaction conditions (0.75 GPa, 80 °C) *N*-methylpyrrolidine gave the products **3a** and **5a** in moderate yields without affording **4a** (Table 1, run 4). The reactions with **2b** and **2c** are also accelerated under these reaction conditions.

The fact that the ring opening products were formed only in the reaction of *N*-methylpyrrolidine seems to be attributed to the ring strain of the pyrrolidine ring system in comparison to those of piperidine and morpholine.

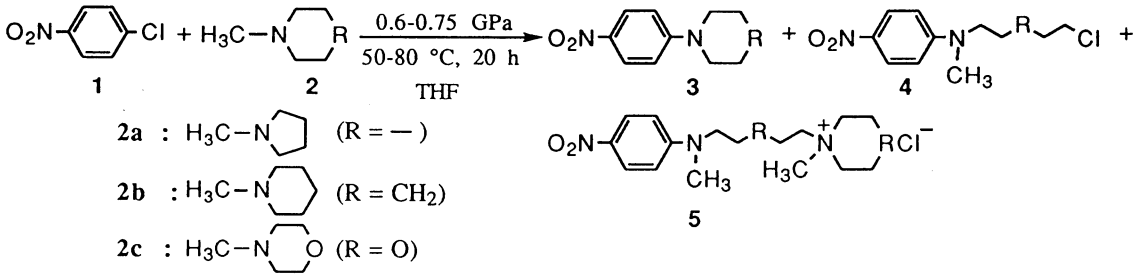
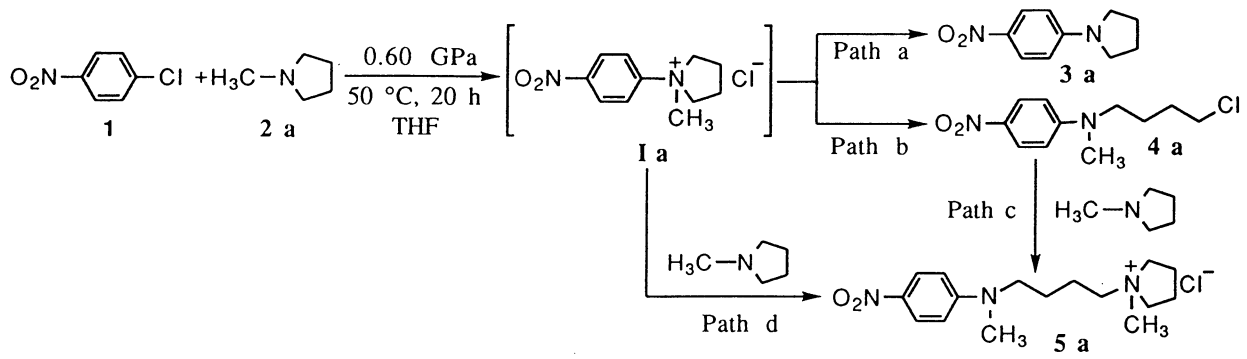


Table 1. Yields[a] of the Reaction Products of **1** with Amines[b]

Run	Amine	Pressure	Temp	Yield/%				Recovered
		GPa	℃	3	4	5	Total	1/%
1	*N*-Methylpyrrolidine	0.60	50	18.0	7.8	28.3	54.1	45.9
2	*N*-Methylpiperidine	0.60	50	6.4	0	0	6.4	91.0
3	*N*-Methylmorpholine	0.60	50	0.3	0	0	0.3	96.5
4	*N*-Methylpyrrolidine	0.75	80	35.0	0	60.1	95.1	4.9
5	*N*-Methylpiperidine	0.75	80	52.9	0	0	52.9	44.0
6[c]	*N*-Methylmorpholine	0.75	80	14.8	0	0	14.8	81.9

a) Isolated yield by medium pressure column chromatography.
b) Reaction conditions: 1.0 mmol of **1** and 4.0 mmol of amines, 20 h, in THF (5 ml).
c) Reaction time is 40 h.

The formation of **3a, 4a, 5a** is explained by the initial formation of a quaternary ammonium chloride intermediate (**Ia**) through S_NAr reaction, which would give **3a** by the demethylation (path a), and **4a** by the ring opening (path b) followed by the attack of **2a** to give **5a** (path c). There is a possibility of an alternative path to yield **5a** through the direct attack of **2a** on **Ia** (path d) as shown in Scheme 1.



Scheme 1.

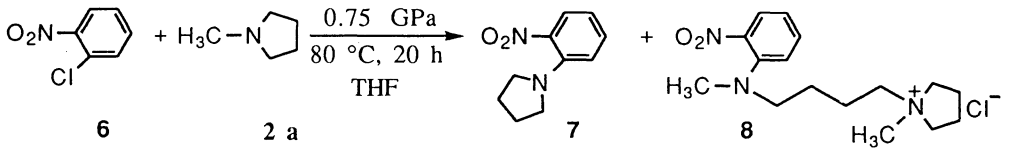
In order to ascertain this mechanism the effect of the concentration of *N*-methylpyrrolidine (**2a**) on the product ratio was investigated (Table 2). The increase of **2a** from 1.0 to 10.0 mmol caused the increase in the yield of **5a** with the decrease in the yield of **4a**. This is explained by the acceleration of the reaction of *N*-substituted butyl chloride (**4a**) with **2a** to give **5a** (path c). The decrease of the ratio of ring opening products to demethylation product, (**4a**+**5a**)/**3a**, from 3.4 to 1.3 was also observed. The possible explanations for the effect of the concentration of **2a** are as follows; (a) path d does not play an important role in the formation of **5a**, (b) *N*-methylpyrrolidine accelerates the demethylation process of **1a** to give **3a** (path a). The study to clarify the role of **2a** in path a is now in progress.[4)]

Table 2. Yields[a)] of the Reaction Products of **1** with **2a**[b)]

Run	Amine	Yield/%				Recovered	(4a+5a) / 3a
	mmol	3a	4a	5a	Total	1/%	
1	1	7.7	11.3	14.9	33.9	66.1	3.4
2	4	18.0	7.8	28.3	54.1	45.9	2.0
3	6	30.8	4.5	42.1	77.4	22.6	1.5
4	10	37.0	0.7	48.0	85.7	14.3	1.3

a) Isolated yield by medium pressure column chromatography.
b) Reaction conditions: 1.0 mmol of **1**, 0.60 GPa, 50 °C, 20 h, in THF (5 ml).

When *o*-chloronitrobenzene (**6**) was treated with 4.0 molar amounts of *N*-methylpyrrolidine (**2a**) under high pressure (0.75 GPa, 80 °C, 20 h, in THF), demethylation product **7** and quaternary ammonium chloride **8** were obtained in 8.2 and 24.5% yields, respectively. The ratio of the ring opening product to the demethylation product (**8**/**7**) was 3.0, which is larger than the corresponding value observed in the reaction of *p*-chloronitrobenzene with **2a** (1.7; Table 1, run 4). This indicates that the substituents on the ortho position to the pyrrolidinium intermediate also affect the selectivity of the reaction to increase the ring opening product.



6 **2a** **7** **8**

The reactions of 2,4-dichloronitrobenzene (**9**) with *N*-methyl substituted cyclic tertiary amines gave the corresponding products of demethylation and ring opening initiated by the S_NAr reaction at para and ortho positions to nitro group. However, the yield of the products from ortho-substitution is very low (Table 3, run 1). The reaction of *N*-methylpiperidine gave only demethylation product (**10b**) through para-substitution (runs 2 and 5). Although *N*-methylmorpholine (**2c**) did not react with **9** at the pressure of 0.60 GPa, it gave demethylation product **10c** in moderate yield at the forced reaction conditions (run 6).

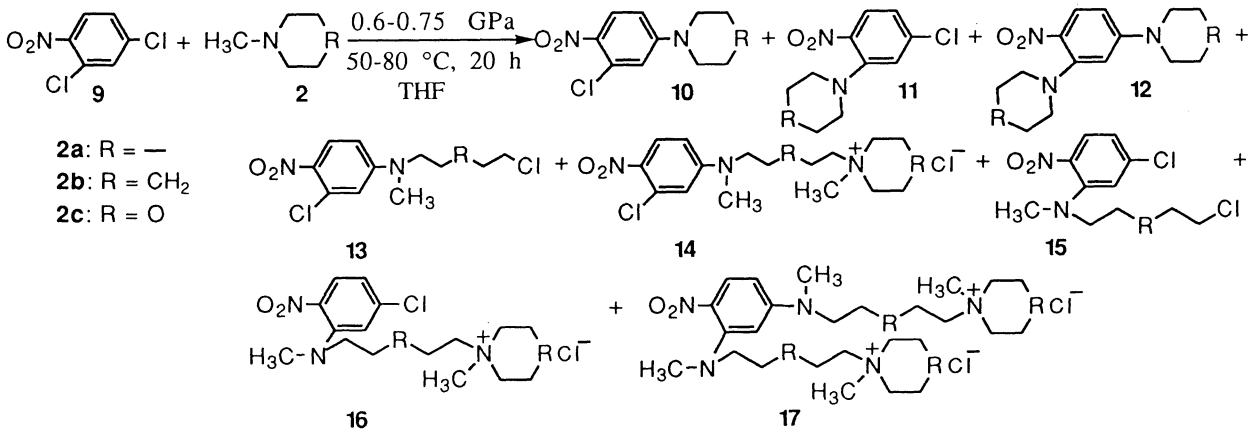


Table 3. Yields[a] of the Reaction products of **9** with Amines[b]

Run	2	Pressure	Temp	Yield/%									Recovered
		GPa	℃	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	Total	**9**/%
1	**2a**	0.60	50	27.5	1.4	0	26.5	29.5	0.8	1.6	0	87.3	11.1
2	**2b**	0.60	50	48.6	0	0	0	0	0	0	0	48.6	47.7
3	**2c**	0.60	50	0	0	0	0	0	0	0	0	0	100
4	**2a**	0.75	80	32.8	1.3	0.3	0	60.2	0	1.1	3.2	98.9	0
5	**2b**	0.75	80	91.9	0	0	0	0	0	0	0	91.9	7.1
6	**2c**	0.75	80	34.7	0	0	0	0	0	0	0	34.7	60.5

a) Isolated yield by medium pressure column chromatography.
b) Reaction conditions: 1.0 mmol of **9** and 4.0 mmol of amines, 20 h, in THF (5 ml).

References

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2) T. Ibata, Y. Isogami, and J. Toyoda, *Chem. Lett.*, **1987**, 1187; T. Ibata, Y. Isogami, and J. Toyoda, *Bull. Chem. Soc. Jpn.*, **64**, 42 (1991); T. Ibata and X-Z. Zou, *High Pressure Research*, **11**, 81 (1992); K. Matsumoto, T. Uchida, T. Okamoto, and S. Hashimoto, *Chem. Express*, **2**, 551 (1987); K. Matsumoto, H. Minatogawa, M. Munakata, M. Toda, and H. Tsukube, *Tetrahedron Lett.*, **31**, 3923 (1990).
3) K. Matsumoto, M. Toda, and S. Hashimoto, *Chem. Lett.*, **1991**, 1283; K. Matsumoto, S. Hashimoto, and S. Otani, *J. Chem. Soc., Chem. Commun.*, **1991**, 306.
4) In the formation of demethylation product **3** there is a possibility of a process through the direct reaction of a Meisenheimer type complex with *N*-methylpyrrolidine as suggested by one of referees. To confirm the mechanism of the demethylation we are planning experiments such as comparing the behavior of quaternary ammonium chloride **Ia** prepared by the methylation of **3a** with the results described in this paper.

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