NUCLEOPHILIC SUBSTITUTION REACTION OF *p*-CHLORONITROBENZENE WITH *N*-SUBSTITUTED CYCLIC AMINES UNDER HIGH PRESSURE

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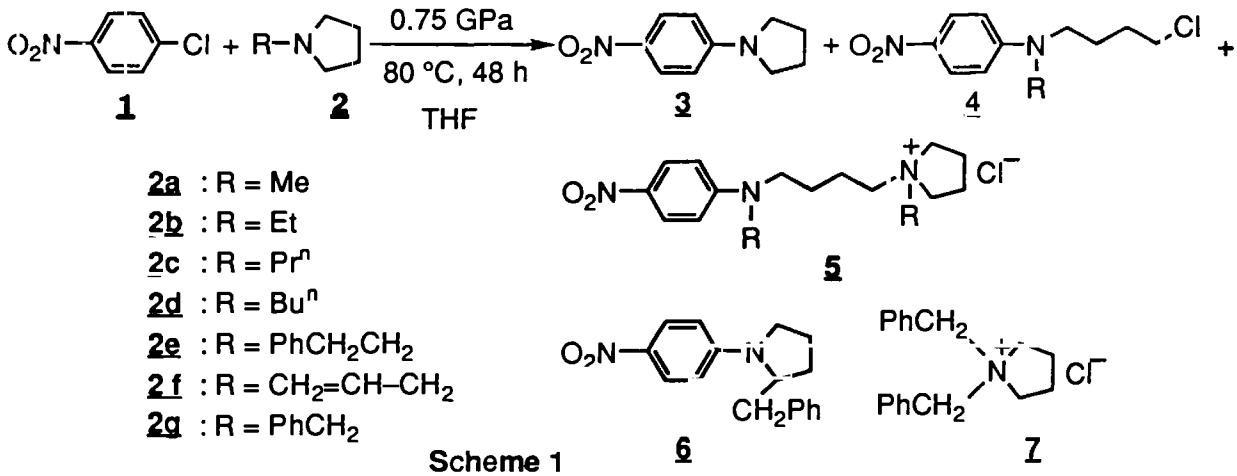
Abstract : SNAr reaction of *p*-chloronitrobenzene with *N*-substituted pyrrolidines under high pressure gave *p*-pyrrolidinonitrobenzene and ring opening products depending on the electronic and steric factor of *N*-substituents. The reactions with *N*-ethylaziridine and *N*-ethylazetidine gave ring opening products without affording deethylation product.

Nucleophilic substitution of aromatic halides with amines is not facile in comparison with the reaction of aliphatic halides (1), and is limited to halides having strong electron-withdrawing substituents with amines of strong nucleophilicity. In our previous papers, we have reported that SNAr reactions of aromatic halides with primary and secondary amines are effectively accelerated under high pressure (2). Because of low reactivity of tertiary amines due to in comparison with primary and secondary amines, the title reaction has been recognized to be difficult to proceed under ordinary pressure. The reaction of 2-chlorobenzothiazole with *N*-methylpyrrolidine under high pressure has been reported to give demethylation product in high yield without affording any ring opening product (3). According to our previous paper, the SNAr reactions of mono- and dichloronitrobenzenes with *N*-methylpyrrolidine under high pressure gave demethylation products and ring opening products through quaternary ammonium chloride intermediates (4). On the other hand, the reactions with *N*-methylpiperidine and *N*-methylmorpholine gave only demethylation products (4). Therefore, we studied the SNAr reactions of *p*-chloronitrobenzene **1** with various *N*-substituted pyrrolidines under high pressure of 0.75 GPa in order to clarify the steric and electronic effects of *N*-substituents of pyrrolidines on selectivity of dealkylation and ring opening processes. The effect of ring strain on the selectivity was also studied in the reaction of **1** with *N*-ethylaziridine and *N*-ethylazetidine.

The reaction of *p*-chloronitrobenzene **1** with 4.0 molar amount of *N*-methylpyrrolidine **2a** under high pressure (0.75 GPa, 80 °C, 48 h, in THF) gave demethylation product **3** and 1:2–product **5a** through pyrrolidine ring opening in 36.7 and 62.4% yields, respectively (Table 1, run 1).



Scheme 1

Table 1. Yields[a] of the Reaction of 1 with *N*-Substituted Pyrrolidines[b]

Run	R	Yield/%				(4 + 5) / Total	Recovered 1
		3	4	5	Total		%
1	Me	36.7	0	62.4	99.1	0.63	0
2	Et	3.8	4.5	62.2	70.5	0.95	27.8
3	Pr^n	1.9	2.7	56.8	61.4	0.97	36.5
4	Bu^n	1.6	2.4	49.0	53.0	0.97	45.3
5	$PhCH_2CH_2$	1.4	1.7	39.1	42.2	0.97	56.8
6	$CH_2=CH-CH_2$	29.7	1.0	16.5	47.2	0.37	52.1
7	$PhCH_2$	8.1	0	0	17.6[c]	0	80.5

a) Isolated yield by medium pressure column chromatography.

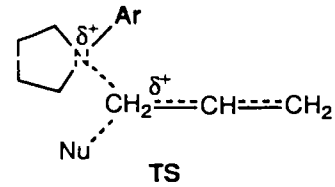
b) Reaction conditions: 1.0 mmol of 1 and 4.0 mmol of amine, in THF (5 ml).

c) Compounds 6 and 7 were obtained in 9.5% and 9.2% yields, respectively.

The ratio of ring opening products to total yield of the products was 0.63. *N*-Ethylpyrrolidine 2b gave deethylation product 3 in low yield together with ring opening products 4b and 5b. The total yield of the reaction of 2b is lower than the case of 2a. The obvious increase of the ratio of ring opening products to total yield was observed (0.95). The reactions of 1 with *N*-propylpyrrolidine 2c, *N*-butylpyrrolidine 2d, and *N*-phenethylpyrrolidine 2e also gave similar results affording dealkylation product 3 and, ring opening products 4 and 5 (Table 1, runs 3-5).

On the contrary, the reaction of *N*-allylpyrrolidine 2f increased the deallylation product 3 decreasing the yields of 4f and 5f. Consequently, the ratio decreased to 0.37 (Table 1, run 6). Because *N*-allyl-, and *N*-propylpyrrolidines have similar

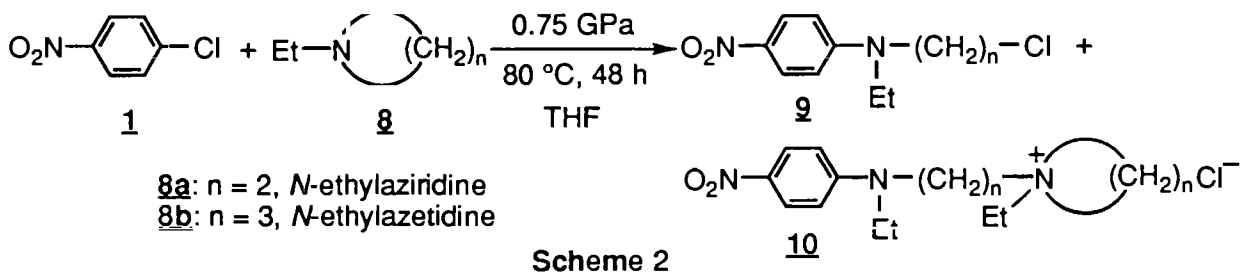
bulkiness, the difference in the ratio may be attributed to the electronic effect of the *N*-substituents. In the transition state of deallylation the positive charge on quaternary ammonium nitrogen delocalized to allyl group as shown in Formula TS, which accelerates the deallylation.



TS

The reaction of *N*-benzylpyrrolidine **2g** with **1** gave a debenzylation product **3** (8.1% yield) and an unexpected product **6** (5) (9.5% yield) along with *N*,*N*-dibenzylpyrrolidinium chloride **7** (6) (9.2% yield) without the formation of ring opening product. The preference of the debenzylation to ring opening is also explained by the similar electronic effect as the reaction of **2f**. Product **6** was presumably formed via Stevens rearrangement of ylide intermediate which would be formed by the deprotonation of *N*-benzyl-(*p*-nitrophenyl)-pyrrolidinium chloride from a methylene group adjacent to ammonium nitrogen of pyrrolidine ring, followed by the migration of benzyl group. High pressure assumed to accelerate the rearrangement, because the Stevens rearrangement is usually limited to the reaction catalyzed by strong base such as sodamide under the ordinary pressure (7). The product **7** correlates with the debenzylation process of the quaternary ammonium ion intermediate. *N*-Phenyl- and *N*-(*p*-methoxphenyl)pyrrolidines failed to react with **1** under the same reaction conditions.

We also studied the reactions of **1** with tertiary amines of three- and four-membered ring in order to investigate the effect of ring size on the ring opening process of the quaternary ammonium salt intermediate (Table 2).



Scheme 2

Table 2. Yields[a] of the Reaction of **1** with *N*-Ethylaziridine and *N*-Ethylazetidine[b]

Run	Amine	Yield/%			Recovered **1**
		9	**10**	Total	%
1	*N*-ethylaziridine	20.6	28.4	49.0	50.3
2	*N*-ethylazetidine	0.5	81.2	81.7	15.4

a) Isolated yield by medium pressure column chromatography.

b) Reaction conditions: 1.0 mmol of **1** and 4.0 mmol of amine, in THF (5 ml).

The reaction of 1 with *N*-ethylaziridine 8a gave the ring opening products 9a and 10a exclusively (49% total yield) without affording any deethylation product. The reaction of *N*-ethylazetidine 8b also gave similar results.

In conclusion, the SNAr reactions studied here proceeds in a similar manner as those of the von Braun reaction of tertiary amines with cyanogen bromide, and the chemical behaviors of the quaternary ammonium ion intermediates formed in the initial step of these two reactions are quite similar (8). The bulkiness of the *N*-substituents seems to suppress the initial step to form the quaternary ammonium salt intermediate. The nucleophilic attacks of chloride ion and tertiary amine on the alkyl group or a methylene carbon of pyrrolidine ring of the intermediate give the dealkylation and ring opening products, respectively. The increase of bulkiness of *N*-substituent of the tertiary amine increases ring opening products by the nucleophilic attack on methylene carbon. Aziridine and azetidine ring systems are highly strained and unstable than the pyrrolidine ring, and then the ring opening reactions are prone to be easier in these systems than the pyrrolidine system.

Further investigation on the reaction of 1 with tertiary amines of other *N*-substituted cyclic system is now in progress.

References and Notes

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(5) Structure of 6 was determined by CHN and spectroscopic measurements including H–H and C–H COSY

(6) 7: Colorless crystal (from ethanol); mp: >250 °C; IR (KBr) 1676, 1452, 1206, 1135, 839, 801, 757, 722, and 705 cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 2.08 (4H, m, CH_2), 3.54 (4H, m, N^+CH_2), 4.60 (4H, s, N^+CH_2Ph), 7.47–7.60 (10H, m, PhH); ^{13}C NMR (67.8 MHz, CD_3OD) δ 23.04 (t, CH_2), 55.65 (t, NCH_2), 60.46 (t, NCH_2), 130.10 (s, Ph), 131.33 (d, Ph), 132.71 (d, Ph), 135.08 (d, Ph)

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Received February 25, 1995