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Nitro Group Substitution Reaction of 2,3,5,6-Tetrachloronitrobenzene with Primary and Secondary Amines under High Pressure

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Abstract: The ratio of substitutions of nitro group and chlorine atom is affected by the bulkiness of amines in the aromatic nucleophilic substitution of 2,3,5,6-tetrachloronitrobenzene with various primary and secondary amines under high pressure of 0.6 GPa.

Aromatic nucleophilic substitution (SNAr) reaction has been studied extensively in these four decades from the mechanistic and synthetic interests.[1)] In the kinetic studies of the SNAr reaction, the nucleofugicity of nitro group is shown to be approximately 200 times stronger than that of chlorine atom,[2)] and nitro group is recognized as a good leaving group.[3)] However, the SNAr reaction of mono-, di-, and trichloronitrobenzenes with amines under high pressure gave only substitution products of chlorine atom on ortho and para positions to nitro group without affording any nitro group substitution product.[4,5)] Therefore, we studied the leaving ability of nitro group and chlorine atom in the SNAr reaction of 2,3,5,6-tetrachloronitrobenzene (**1**) with primary and secondary amines under high pressure.

The reaction of **1** with an equimolar amount of morpholine in the presence of 5.0 molar excess of triethylamine under high pressure (0.6 GPa, 50 °C, 20 h, in THF) gave nitro group substitution product (**3a**, 1.6% yield), ortho-mono-substitution product (**4a**, 30.2% yield) and meta-mono-substitution product (**5a**, 6.7% yield) together with recovered **1** (58.6%). Piperidine gave similar products (**3b**, **4b**, and **5b**) in higher yields than the case of morpholine, reflecting the reactivity of these amines.[4,5)] The reaction of pyrrolidine with **1** gave nitro group substitution product **3c** in high yield (38%) besides mono-substitution products **4c** and **5c** and ortho-ortho-disubstitution product **6c** (0.6% yield). Diethylamine gave only an ortho-mono substitution product **4d** in 7.1% yield, showing the low reactivity of diethylamine in comparison to the cyclic secondary amines described above. Aniline gave no product under the similar reaction conditions and **1** was recovered quantitatively. On the contrary, aliphatic primary amines such as benzylamine and butylamines react with **1** readily to give nitro group and chlorine atom substitution products (Table 1, runs f-j). The high yields of the nitro group substitution products **3** were observed in these reactions except the reaction with t-butylamine. Especially, n-butylamine gave **3g** in 82.8% yield. Although all butylamines used in these reactions have similar basicity (pKb=3.36-3.51), the total yield of the products differs very much (19.7-98.5%). The ratio (3/(total yield)) also changes widely from 0.84 (n-butylamine) to 0.37 (t-butylamine). These results can be explained by the steric effect as shown below.

Substitution reactions of nitro group and chlorine atom are assumed to proceed through the Meisenheimer type intermediates[6] A, B, and C, which give products 3, 4, and 5, respectively. Steric hindrance seems to suppress the formation of these intermediates, which consequently reduces the yields of the products. These steric hindrances are suggested to be larger in the intermediate A than in B and C by the CPK model inspection of the intermediates. The difference in the selectivity of morpholine and piperidine (3/(total yield)=0.042 and 0.060) and pyrrolidine (3/(total yield)= 0.426) can also be explained by the similar steric effect.

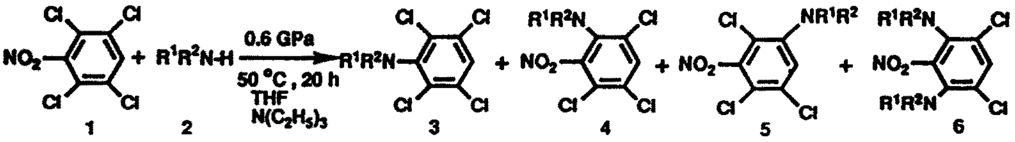
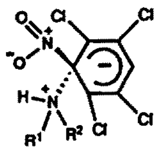


Table 1. Yields of the Reaction of 2, 3, 5, 6-Tetrachloronitrobenzene (1) with Amines

Run	Amine	Yield (%)				Total Yield (%)	Recovered 1 (%)	Ratio 3/total yield
		3	4	5	6			
a	Morpholine	1.6	30.2	6.7	0	38.5	58.6	0.042
b	Piperidine	5.3	72.2	10.4	0	87.9	8.1	0.060
c	Pyrrolidine	38.0	42.1	8.6	0.6	89.3	1.9	0.426
d	Diethylamine	0	7.1	0	0	7.1	87.1	0
e	Aniline	0	0	0	0	0	100	----
f	Benzylamine	64.7	14.3	0	0	79.0	8.0	0.819
g	Butylamine	82.8	15.7	0	0	98.5	1.1	0.841
h	iso-Butylamine	48.2	17.7	3.4	0.9	70.2	14.4	0.687
i	sec-Butylamine	40.3	19.1	6.6	1.7	67.7	16.1	0.595
j	t-Butylamine	7.3	12.4	0	0	19.7	74.2	0.371



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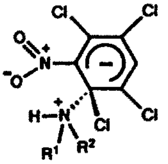

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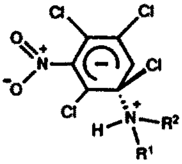

C

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