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Nucleophilic Substitution of Aromatic Halides with Amines under High Pressure

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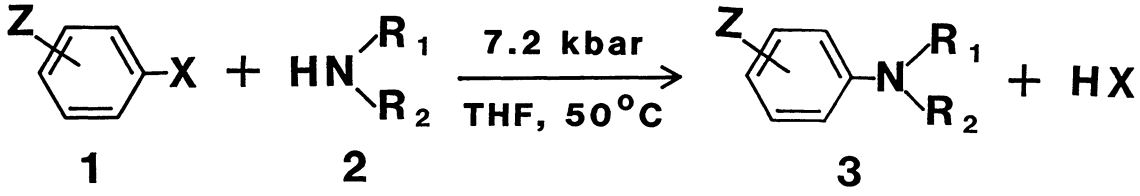
The reaction of aromatic chlorides, bromides and iodides with various primary or secondary amines in a tetrahydrofuran solution under high pressure of 6-12 kbar gave the corresponding secondary and tertiary aromatic amines. The yields of the products depend on the bulkiness of amines used. 1,4-Diazabicyclo[2.2.2]octane and quinuclidine gave N-aryl quarternary ammonium halides in high yields in contrast to the low reactivity of acyclic tertiary amines.

Nucleophilic substitution of aromatic halides has been generally recognized to be difficult to proceed under ordinary pressure and to be limited to some fluorides or chlorides having a strongly electron-attracting group such as nitro group at para or ortho position.[1] These aromatic nucleophilic substitution reactions are confirmed to proceed through the Meisenheimer type dipolar intermediate,[2] and expected to be accelerated under high pressure.[3] However, to the best of our knowledge, no nucleophilic substitution of aromatic halides under high pressure has been reported from the synthetic point of view.[3,4] The authors wish to report here the high pressure acceleration of the nucleophilic substitution of aromatic halides with various primary, secondary, and tertiary amines.



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The high pressure reactions were carried out in a Teflon capsule using a Hikari Kouatsu high pressure reaction apparatus.[3] When p-nitrochlorobenzene (1.0 mmol) was treated with excess propylamine (10 mmol) in a freshly distilled tetrahydrofuran (THF) solution (3.0 ml) at 50 °C under 7.2 kbar for 20 h, N-propyl-p-nitroaniline (3a) was obtained as yellow crystals in 93% yield [mp 68.0-68.5 °C; NMR ($CDCl_3$) δ 1.02 (t, J=7.5 HZ, 3H, CH_3), 1.69 (sex, J=7.5 Hz, 2H, CH_2), 3.16 (broad dt, 2H, CH_2), 4.63 (broad s, 1H, NH), 6.49 and 8.04 ppm (ABq, J=9.2 Hz, 4H, arom-H)] along with propylamine hydrochloride. The reaction did not proceed at 80 °C under ordinary pressure.

The reactions of p-nitrochlorobenzene with other primary or secondary amines under high pressure of 6.0-9.0 kbar also gave the corresponding secondary or tertiary p-nitroanilines as shown in Table 1.[5] The yields of the reactions are affected strongly by the bulkiness of amines. For example, isopropylamine gave N-isopropyl-p-nitroaniline (3b) only in 26% yield under the same reaction condition in spite of the close basicity to propylamine (pKa 10.63 and 10.53 respectively). A similar trend was also observed in the reaction of four butyl amines (Table 1, runs c-f). Very low yield (2%) of 3f is ascribed to the bulkiness of tert-butyl group.

Cyclohexylamine gave N-cyclohexyl-p-nitroaniline (3h) in 18% yield. Aromatic primary amines showed reactivity lower than aliphatic ones because of their low basicity. Even p-anisidine gave p-nitro-p'-methoxydiphenylamine (3i) in only 2% yield.

Secondary amines exhibited smaller reactivity than the corresponding primary amines (compare runs a with k, b with l, and c with m). However, cyclic secondary amines such as morpholine, piperidine, and pyrrolidine showed extremely higher reactivity than acyclic secondary amines such as diethylamine and dipropylamine. These differences in reactivity may be attributed to both basicity and bulkiness of amines. o-Nitrochlorobenzene also showed high reactivity toward pyrrolidine (run q). However, m-nitrochlorobenzene was shown to have much less reactivity (run r). p-Nitrobromobenzene and p-nitroiodobenzene reacted with pyrrolidine to give 3a in high yields.

p-Cyanochlorobenzene and p-chloroacetophenone gave the corresponding N-aryl-pyrrolidines in moderate yields (runs s and t). These results indicate that 9 kbar is not enough to accelerate the reactions of these halides.[6]

Table 1. Reaction of aromatic halides with primary and secondary amines under high pressure[a)]

Run	Aromatic halide		Amine	Pressure	Reaction	Product[b)]	Mp	Yield[c)]
	Z	X	2	kbar	time/h	3	θ_m/°C	%
a	p-NO_2	Cl	$PrNH_2$	7.2	20	3a	68-69	93 (0)
b	"	"	$^iPrNH_2$	7.2	20	3b	68-69	26 (0)
c	"	"	$BuNH_2$	7.2	20	3c	60-61	76 (0)
d	"	"	$^iBuNH_2$	7.2	20	3d	76-77	61 (0)
e	"	"	$^{sec}BuNH_2$	7.2	20	3e	oil	13 (0)
f	"	"	$^tBuNH_2$	7.2	20	3f	oil	2 (0)
g	"	"	$HexNH_2$	7.2	20	3g	67-68	65 (0)
h	"	"	c-$C_6H_{11}NH_2$	7.2	20	3h	104-105	18 (0)
i	"	"	p-$AnisNH_2$	7.2	50	3i	158-159	2 (0)
j	"	"	Et_2NH	7.2	20	3j	77-78	39 (0)
k	"	"	Pr_2NH	7.2	20	3k	62-63	24 (0)
l	"	"	$^iPr_2NH$	7.2	50	3l	-	0 (0)
m	"	"	Bu_2NH	7.2	20	3m	oil	15 (0)
n	"	"		6.0	20	3n	158-159	100 (3)
o	"	"		6.0	20	3o	108-109	100 (22)
p	"	"		6.0	20	3p	178-179	100 (92)
q	o-NO_2	Cl	"	6.0	20	3q	oil	100 (85)
r	m-NO_2	Cl	"	9.0	50	3r	96-98	2 (0)
s	p-CN	Cl	"	6.0	20	3s	90-91	34 (0)
t	p-CH_3CO	Cl	"	7.2	20	3t	135-136	18 (0)
u	p-NO_2	Br	"	12.0	20	3p	"	100 (51)
v	p-NO_2	I	"	12.0	20	3p	"	100 (14)

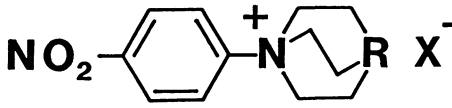
a) All reactions listed were carried out in THF at 50 °C for 20 h.
b) Products were separated by the preparative medium-pressure liquid chromatography on silica gel and characterized on the basis of NMR and IR spectra.
c) Yields in parentheses refer to reactions under 1 atm at 80 °C.

The reactions of 3a with propylamine and morpholine were dramatically accelerated at 6 kbar. Pyrrolidine was more reactive and 6 kbar was enough for completion of the reaction (Table 2).

Table 2. Pressure effect on the yields of the reaction of p-nitrochlorobenzene with propylamine, morpholine, and pyrrolidine[a)]

Pressure	Propylamine		Morpholine		Pyrrolidine	
/kbar	3a/%	1/%[b)]	3n/%	1/%[b)]	3p/%	1/%[b)]
1/1000	0	100	0	100	16.7	81
1.0	0.6	96	0.5	96	43.2	56
2.0	1.7	96	1.4	94	63.5	35
4.0	4.4	94	13.0	81	90.6	5
6.0	28.3	70	36.5	61	100	0
8.0	42.8	53	88.9	10	-	-
10.0	81.1	17	99.7	0	-	-

a) The reactions were carried out in THF at 50 °C for 2 h.
b) Percentage of recovered 1.



4 : R = N ; X = Cl, Br, I
5 : R = CH ; X = Cl

Although triethylamine did not react with p-nitrochlorobenzene even at 12 kbar, 1,4-diazabicyclo[2.2.2]octane reacted with p-nitrohalobenzenes to give the corresponding ammonium halides (4) in quantitative yields (6 kbar, 50 °C, 20 h). Quinuclidine also gave ammonium chloride (5) in quantitative yield in the reaction with p-nitrochlorobenzene.

References

1) J. F. Bunnett and R. E. Zahler, Chem. Revs., 49, 273 (1951).
2) J. F. Bunnett, Quart. Rev. (London), 12, 1 (1958); J. Sauer and R. Huisgen, Angew. Chem., 72, 294 (1960); S. Ross, Progr. Phys. Org. Chem., 1, 31 (1963)
3) K. Matsumoto, A. Sera, and T. Uchida, Synthesis, 1985, 1.
4) K. Matsumoto, private communication; We thank him for showing us his unpublished results on the nucleophilic substitution of aromatic halides.
5) All reaction products were characterized on the basis of analytical and spectral data.
6) Optimization of the reaction conditions was not carried out.

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