

[CONTRIBUTION OF THE RESEARCH LABORATORY OF THE DIAMOND ALKALI CO.]

Low Temperature Amination of Aromatic Polyhalides¹

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The reaction of metal amides with aromatic polyhalides in liquid ammonia was used for the preparation of halogenated aromatic amines. The position of the introduction of the amino group is in accord with the formation of the benzyne intermediate, and with the orienting influence of a substituent on the benzyne intermediate. The conditions for the amination of 1,2,4-trichlorobenzene were studied and it was found that lithium amide produces 3,4-dichloroaniline in 62% yield. The low-temperature amination reactions were demonstrated to serve as a method of separation and purification of mixtures of aromatic halides. When 1,2,4-tribromobenzene was treated with sodium amide in liquid ammonia, 1,3,5-tribromobenzene was one of the products.

The amination of aryl halides with metal amides in liquid ammonia was first reported by Bergstrom *et al.*² From halobenzenes they isolated aniline, as well as diphenyl- and triphenylamine. They also studied the order of ease of replacement of the halogen atom in phenyl dihalides of the type $p\text{-C}_6\text{H}_4\text{XY}$ without actually isolating any of the organic product(s). Such amination reactions were recently extended by Roberts *et al.*³ who also prepared substituted anilines from substituted monohalobenzenes. With the exception of the preparation of fluoroaniline from p -bromofluorobenzene³ (F is not replaced by NH_3 at -33°), the literature is void of reports of the preparation of haloaromatic amines by the low temperature amination of polyhalides. This paper deals with such reactions. The orienting influence of substituents in such aminations was studied as well as some reaction conditions for the preparation of certain amines in high yields.

The reactants, reaction conditions, and products are listed in Table I.

EXPERIMENTAL

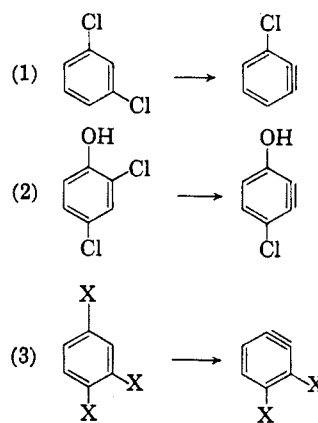
The halide in liquid ammonia was treated with the metal amide and the suspension stirred for a period of time as indicated in Table I. After evaporation of ammonia, the residue was treated with water and a representative sample analyzed for halide-ion concentration. The organic portion was taken into ether, and hydrogen chloride was passed through the dry ether solution. The precipitated amine hydrochloride was filtered and the amine liberated with base. The neutral and the amine portions were separated and distilled. The distillates were crystallized from appropriate solvents. No attempt was made to isolate the di- or triarylamines or the diamines formed in the reactions. The identity of the products was established by boiling points, melting points, conversion to solid N -acetyl and/or benzoyl derivatives, and by comparison of values listed in the literature. In cases of obvious discrepancies, at least two derivatives were made and the values compared with authentic samples.

DISCUSSION

Orientation in aminations of polyhalobenzenes. Roberts *et al.*⁴ established that the amination of halobenzenes in liquid ammonia involves an elimination-addition mechanism via a "benzyne" intermediate I. The acidities of the benzenoid hydrogens seem to be determined by the inductive effect of substituents.⁵ The formation of the benzyne intermediate by the elimination of hydrogen halide is thus a function of such acidities.³



In the present study the isolated haloanilines have the structure in accord with the addition of NH_2^- to the preferentially formed benzyne intermediate. Thus, in cases where more than one benzyne is possible, the predictions by Roberts³ were realized, the benzyne formed being those indicated in Equations (1)–(3). In the last case there should



be an equal possibility for the formation of but

no amine derived from such a benzyne was found. Because of ortho substituents, the other halides listed in Table I were capable of the formation of only one benzyne intermediate.

The direction of the addition of the NH_2^- to an asymmetrically substituted benzyne intermediate was predicted³ to take place so as to provide the most favorable location of the negative charge with respect to the inductive effect of the substituent on the benzyne. Because of the inductive

(1) Presented at the 134th National Meeting of the American Chemical Society, Chicago, September 1958.

(2) F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

(3) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenov, *J. Am. Chem. Soc.*, **78**, 611 (1956).

(4) J. D. Roberts, D. A. Semenov, H. E. Simmons, and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(5) G. E. Hall, R. Piccolini and J. D. Roberts, **77**, 4540 (1950).

TABLE I

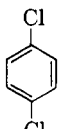
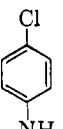
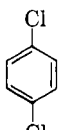
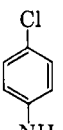
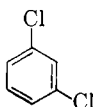
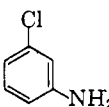
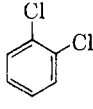
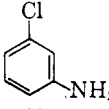
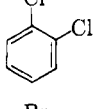
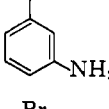
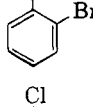
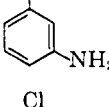
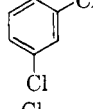
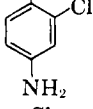
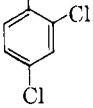
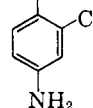
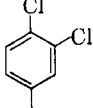
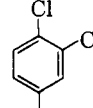
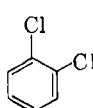
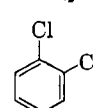
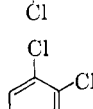
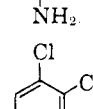
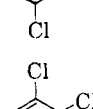
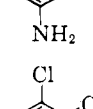
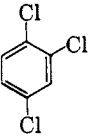
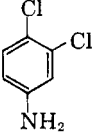
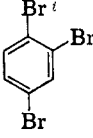
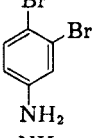
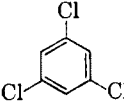
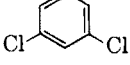
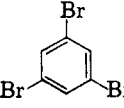
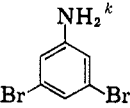
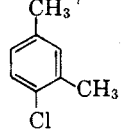
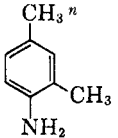
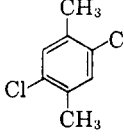
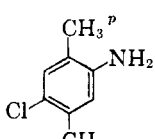
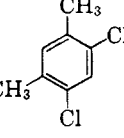
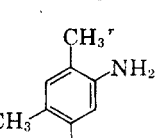
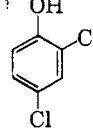
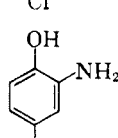
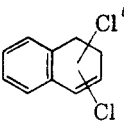
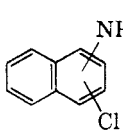
Experiment	Reactant	Mol.	MNH ₂	Mol.	Reaction Time, Hr.	% X ^w Found	Halide, % Recovered	Product	Yield	
									%	Total ^z Acctd. for
1		0.5	Na	0.6	18	73	8		14	22
2		0.5	Li	0.5	20	41	39		17	56
3		0.5	Na	0.75	19	65	48		28	76
4		0.5	Na	0.75	16	54	42		26 ^a	68
5		0.5	Li	0.75	5	36	51		18 ^e	69
6		0.03	Na	0.06	3	129	20 ^b		35 ^c	55
7		0.5	Na	1.1	22	127	10		27	37
8		0.5	Na ^d	0.5	5	50	52		20	72
9		0.5	Na ^d	1.5	5	146	5		25	30
10		0.5	Na ^e	1.0	8	98	24		37 ^f	61
11		0.5	Li	1.0 ^g	20	94	6		62 ^h	68
12		0.5	K	0.6	16	110	45		20	65

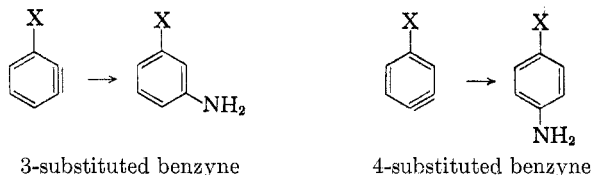
TABLE I (Continued)

Experiment	Reactant	Mol.	MNH ₂	Mol.	Reaction Time, Hr.	% X ^{-w} Found	Halide, % Recovered	Product	Yield	
									%	Total ^z Acctd. for
13		0.3	Ba	0.3	18	58	43		22	65
14		0.3	Na	0.6	18	86	33 ^j		24	57
15		0.5	Li	1.0	18	83	13		43	56
16		0.05	Na	0.1	3	100	20		45	65
17		0.4	Na	0.9	2	74	2 ^m		14	16
18		0.1	K ^o	0.2	16	100	34		55	89
19		0.8	Na	1.6	18	71	16		54	70
20		0.3	Li ^r	0.6	2	...	79		6	85
21		0.5	Na	0.7	18	52	61 ^u		21	82

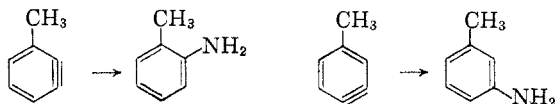
^a *o*-Chloroaniline was also present as evidenced by vapor chromatography. ^b Vapor chromatography showed it to be identical with starting halide. ^c No *m*-bromoaniline was found. ^d Room temperature and pressure. ^e Cooled to -50° . ^f When the reaction was cooled to -70° the yield was only 13%. ^g When 0.6 mole of LiNH₂ was used, the yield was 60%. ^h When the reaction was cooled to -50° the yield was 66%. ⁱ The halide was purchased from the Eastman Kodak Co. and melted at $40-43^{\circ}$. (Eastman Organic Chemicals, List No. 40, p. 193, P. 6466, lists m.p. of $33-38^{\circ}$.) The literature lists its m.p. $43-45^{\circ}$. A fractional crystallization from petroleum ether (b.p. $30-60^{\circ}$) gave six fractions melting in the range of $40-45^{\circ}$. Vapor chromatography showed only one band, and its infrared spectrum showed only traces of 1,3,5-tribromobenzene. ^j The neutral "recovered" fraction was 1,3,5-tribromobenzene, m.p. $121-122^{\circ}$. The structure was confirmed by elementary and spectroscopic analyses. Vapor chromatography showed the absence of the starting halide (1,2,4-tribromobenzene). ^k M.p. $59-60^{\circ}$. Anal. Calcd. for C₆H₃Br₂N: C, 28.7; H, 2.0. Found: C, 29.5; H, 2.3. *N*-acetyl derivative m.p. $230-231^{\circ}$ (lit. 231°). ^l The sample contained 0.1 mole of 2-chloro-*m*-xylene. ^m All of the 2,6-dimethylchlorobenzene was recovered. Spectroscopic analysis showed it to be 97% pure. ⁿ Since the mother liquor was not vapor chromatographed, the presence of 3,5-dimethylaniline is not excluded. ^o Using NaNH₂ the yield of amine was 47% (80% of Cl⁻ was found) and with LiNH₂ no amine was produced (2% of Cl⁻ was found). ^p The m.p. was $91-92^{\circ}$. The literature lists only the b.p. of the amine and the m.p. of 176°

for the *N*-acetyl derivative. Since the m.p. found was 182°, the structure of the amine was established by diazotization and conversion to 2,5-dichloro-*p*-xylene, m.p. 67–68°, reported m.p. 68–70°. The structure was also confirmed by diazotization and conversion to 2,4-dichloro-*m*-xylene, m.p. 67–68°. Using NaNH₂, only black tar was isolated. Commercial (Eastman Kodak Co.) dichloronaphthalene was used which was a mixture of 1,4:1,5:1,8 and 1,2 isomers of unknown ratio. The m.p. of this mixture was 43–45°. The m.p. was 66–67°. The reported m.p. for 1,4-dichloronaphthalene is 67–68°. From vapor phase chromatographic analysis this was the major component of the starting mixture. The chloronaphthylamines boiled at 123–126° at 2 mm. About 30% of this liquid crystallized, m.p. 88–91°, (*N*-acetyl derivative, m.p. 192–193°) and was identified as 1-amino-4-chloronaphthalene. The liquid portion formed a *N*-acetyl derivative, m.p. 142–145°. No definite product was isolated in attempts to replace the amino group with chlorine *via* the diazonium salt. Based on the amount of starting polyhalide. Higher amination products and/or tars by difference.

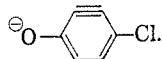
effect, Cl and Br are electron attracting groups and thus meta directing in a 3-substituted benzyne and para directing in a 4-substituted benzyne. On the other hand, the methyl



group is an electron donating group and ortho directing in a 3-substituted benzyne and meta directing in a 4-substituted benzyne.



In all of the cases studied, the amino group appeared in the predicted position. However, 4-chloro-*m*-xylene (Exp. 17) yielded 4-amino-*m*-xylene and there was no evidence that the equally predictable 5-amino-*m*-xylene was also formed. Similarly, 1,3,5-trichlorobenzene (Exp. 15) yielded 3,5-dichloroaniline and no 2,4-dichloroaniline was found. In the amination of 2,4-dichlorophenol (Exp. 20), the formation of 2-amino-4-chlorophenol indicates that the phenoxide ion is ortho directing in the formed benzyne intermediate,



In three cases the postulation of a benzyne intermediate best explains the experimental findings. The major product of amination of *o*-dichlorobenzene (Exp. 4) and *o*-dibromobenzene (Exp. 6) was *m*-chloroaniline and *m*-bromoaniline, respectively. The amination of a mixture of 4-chloro-*m*-xylene and 2-chloro-*m*-xylene (Exp. 17) yielded only the product from the isomer capable of formation of a benzyne intermediate. Since in most cases the amino group appeared in the position previously occupied by the halogen atom, we do not discount the possibility that direct substitution may have also taken place.^{6,7} Consequently the failure of 2-chloro-*m*-xylene to react might be explained by the shielding of the chlorine by the two methyl groups.

The rearrangement of 1,2,4-tribromobenzene to 1,3,5-tribromobenzene (Exp. 14) was unexpected. To test the possibility that other *o*-dibromo-substituted aromatic compounds are subject to such a rearrangement, *o*-dibromobenzene was treated with sodium amide in liquid ammonia (Exp. 6). However, there was no evidence for the presence of *m*-dibromobenzene in the recovered halide. At this time we are not able to propose a reasonable and consistent mechanism of reaction for this novel rearrangement.

(6) J. F. Bunnett and T. K. Brotherton, *J. Am. Chem. Soc.* **78**, 6265 (1956).

(7) F. Scardiglia and J. D. Roberts, *J. Org. Chem.*, **23**, 629 (1958).

The yields of amines. The conventional preparation of amines is a copper catalyzed high temperature amination or the reduction of nitro compounds. It was hoped that substituted aromatic amines could be prepared in satisfactory yields by low temperature amination. Of special interest were amines which cannot be conveniently secured by the conventional routes.

In the amination of polyhalides (Table I) the yields of primary amines depended on the extent of reaction. When amination did not proceed, the starting halide was recovered and there was no, or a low, concentration of halide ions. Furthermore, secondary reaction products could have been also responsible for low yields of primary amines. In such cases higher reaction products, di- or triarylamines, diamines, and tars were formed, and analyses showed a high concentration of halide ions.

The amination of 1,2,4-trichlorobenzene was studied in greater detail because of the ready availability of the halide from benzene hexachloride manufacture. The most active of the metal amides, potassium amide (Exp. 12), produced 3,4-dichloroaniline in only 20% yield. The chloride ion concentration was 110% (based on the molar quantity of the organic halide) indicative of more extensive amination. The least active lithium amide (Exp. 11) gave the highest yield (62%) of amine even in the presence of twice the molar ratio of amide to the halide. With sodium amide (Exp. 7 to 10) the yields were generally below that of LiNH₂. Some improvements were realized (Exp. 10) by conducting the experiments with sodium amide at –50° and a shorter reaction time. More of the starting halide was thus recovered and fewer chloride ions were found even at an amide-halide molar ratio of two. A high amide concentration (Exp. 9) produced a high chloride ion concentration, and little of the starting halide was recovered. On the other hand, an equimolar ratio of amide to halide (Exp. 8) decreased the chloride ion concentration and the yield of amine, but increased the amount of recovered halide, even with reaction at room temperature. Use of the sparingly soluble barium amide (Exp. 13) offered no advantage over the use of sodium amide.

The amination reactions of 2,5-dichloro-*p*-xylene (Exp. 18) clearly demonstrated that the yield depends on the activity of metal amide. No amination was observed when the relatively inactive lithium amide was used. Sodium amide produced the amine in 47% yield, and the yield was 55% when potassium amide was used. The produced chloride ion concentration also increased with the increase in the activity of the metal amide.

The low temperature amination provides a simple method for the purification of certain aromatic halides. The chlorination of naphthalene produces a mixture of dichloronaphthalenes which is difficult to separate. The amination is sufficiently selective to enable the recovery of pure 1,4-dichloronaphthalene (Exp. 21). Similarly, the monochlorination of *m*-xylene yields a mixture of 2- and 4-chloro-*m*-xylenes, b.p. 185–187 and 186–187°, respectively, which cannot be conveniently separated by distillation. From the amination reaction (Exp. 17), essentially pure 2-chloro-*m*-xylene was recovered.

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