[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF PURDUE UNIVERSITY]

Reduction of Aryl Halides by Lithium Dialkylamides

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The formation of anisole from the reactions of various lithium dialkylamides with *o*-bromoanisole was investigated. It was established that the dialkylamide ion is concomitantly oxidized as the aryl halide is reduced. Thus lithium benzylmethylamide when treated with *o*-bromoanisole was oxidized to 2,5-diphenylpyrazine; lithium dibenzylamide to 2,3,5,6-tetraphenylpyrazine; and lithium *bis*-(*p*-methoxybenzyl)amide to 2,3,5,6-tetra-(*p*-methoxyphenyl)pyrazine.

That the initial oxidation product might be an imine was demonstrated when lithium benzylmethylamide reacted with N-benzilidinemethylamine to give 2,5-diphenylpyrazine. Also lithium dibenzylamide when treated with N-benzilidinebenzylamine gave 2,3,5,6-tetraphenylpyrazine.

A possible reaction mechanism which is consistent with these findings is presented.

Gilman and co-workers[1] observed that in the reactions of lithium diethylamide with *o*-iodoanisole and with 1-chloronaphthalene, anisole (22%) and naphthalene (8.5%) were formed. They examined the possibility that halogen-metal interconversion was occurring, but were unable to isolate 1-naphthoic acid by carbonating the reaction mixture from 1-bromonaphthalene and lithium diethylamide. We have observed similar reductions in the reactions of lithium dimethylamide with *o*-bromoanisole, 2-bromo-3-methylanisole, 2-bromo-4-methylanisole, and 2-bromo-6-methylanisole.[2]

The reactions of aryl halides with lithium dialkylamides in ether and with sodium amide in ammonia seem very similar, except that reduction products have not been observed in the latter system. It appeared that reduction was due, therefore, to some difference either in the amide, solvent, or reaction temperature. Since considerably less reduction was observed in the reaction of *o*-chloroanisole with lithium dimethylamide,[3] electronegativity of the halogen must also be an important factor. In order to gain some insight into the nature of this reduction, the reaction of *o*-bromoanisole with several lithium dialkylamides was investigated.

The first possibility examined was that lithium hydride was formed, either by decomposition of the amide ion, or by its reaction with the solvent, and that possibly reduction of the bromoanisole was occurring *via* this reagent. Since lithium hydride has very limited solubility in ether, the reduction of *o*-bromoanisole by lithium aluminum hydride was studied. The latter is a considerably more soluble reagent than is lithium hydride. Only a 5% yield of anisole was realized after the same reaction time as that employed in the dialkylamide displacements. Since this yield was in no way comparable to that normally observed, despite the use of a much more soluble hydride, it was concluded that reduction by hydride ion was not the principal mode of formation of the anisole.

The solvent seemingly was not a factor in these reductions, since anisole was formed in the reactions utilizing ethyl ether, dimethylamine, or excess *o*-bromoanisole as solvent. The lower yield of reduction product when *o*-bromoanisole was used as solvent did not appear significant, since the amide was not very soluble in this medium. By a process of elimination it was concluded that the anisole was arising by some type of oxidation-reduction process involving the dialkylamide ion and the aryl halide. Unfortunately no oxidation products of the dialkylamide ion had previously been reported. We thus undertook an investigation of a series of reactions between dialkylamides and *o*-bromoanisole to see whether such oxidation products could be isolated. Also in this way we hoped to gain an insight as to how the nature of the substituents attached to the nitrogen affected the reduction.

From the reactions of lithium diphenylamide and lithium methylanilide with *o*-bromoanisole, nothing other than starting materials could be isolated. These amides were evidently too weakly basic to allow either substitution or reduction to occur.

Lithium benzylanilide reacted with *o*-bromoanisole to give a 20% yield of anisole. This was the only compound which could be identified other than starting material. The low recovery of amine compared to the amount of *o*-bromoanisole used, and the isolation of other ill-defined basic materials, suggested that perhaps the amide had been oxidized.

Lithium piperidide reacted with *o*-bromoanisole to give a 15% yield of anisole and a 21% yield of 1-(*m*-methoxyphenyl)piperidine. A large amount of red tar formed on acid hydrolysis which was thought to be some polymer of an unsaturated piperidine. The reaction was repeated and nitrobenzene was added before acidification in the hope that any unsaturated piperidine would be oxidized to pyridine. No pyridine could be isolated and the tar was obtained again.

The reaction of lithium benzylmethylamide with *o*-bromoanisole gave a 13% yield of anisole and a 26% yield of N-benzyl-N-methyl-*m*-anisidine.

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[1] Gilman, Crounse, Massie, Benkeser, and Spatz, *J. Am. Chem. Soc.*, **67**, 2106 (1945).

[2] Benkeser and DeBoer, *J. Org. Chem.*, **21**, 365 (1956).

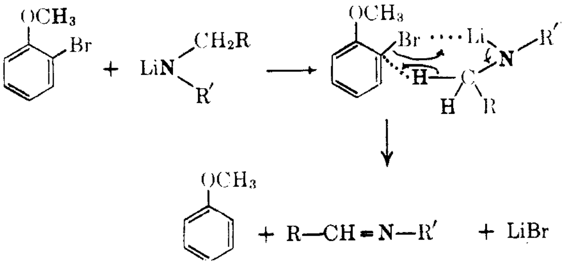
[3] Benkeser and Schroll, to be published.

There were no other definite liquid amine fractions, but the black solid from the pot residue gave a small amount of 2,5-diphenylpyrazine on vacuum sublimation.

Lithium dibenzylamide and *o*-bromoanisole gave a 36% yield of anisole, an 8% yield of N,N-dibenzyl-*m*-anisidine, and a 28% yield of 2,3,5,6-tetraphenylpyrazine. Similarly, lithium, N,N-*bis*-(*p*-methoxybenzyl)amide and *o*-bromoanisole gave a 12% yield of anisole, an 11% yield of N,N-*bis*-(*p*-methoxybenzyl)-*m*-anisidine and a 6% yield of 2,3,5,6-tetra-(*p*-methoxyphenyl)pyrazine.

The isolation of pyrazines in these reactions showed definitely that the amides were oxidized during the reactions presumably as the *o*-bromoanisole was reduced. The formation of pyrazines as oxidation products indicated a complex oxidative mechanism. It seemed likely that the oxidation products of these reactions were traceable to the basic tars which invariably accompany these cases. Thus, with low molecular weight amides, oxidation probably leads to complex basic polymers.

A mechanism consistent with the facts as we now know them is shown below. This involves an initial coordination with the halogen, formation of a *quasi* six-membered ring and an electron shift.



It will be noted that such a mechanism *requires* the presence of *alpha* hydrogens on the amide for reduction to occur. The fact that lithium diphenylamide did not cause reduction is some positive evidence in this connection. The mechanism also indicates that the reduction process is not contingent on any cine[4] substitution reaction and must be considered an independent reaction. In partial substantiation of this view it will be noted that lithium benzylanilide reacted with *o*-bromoanisole to form anisole in 20% yield, but no cine substitution product could be detected. Finally, the mechanism would predict the formation of an imine, which in itself should be isolable, or else act as a precursor of the pyrazine derivatives which were actually obtained.

The reaction products were examined carefully for the presence of imines, but none were detected. In order to determine whether this type of compound would be stable under the conditions of the experiment, the reactions of lithium benzylmethylamide with N-benzilidinemethylamine and lithium dibenzylamide with N-benzilidinebenzylamine were carried out.

The former case gave a small amount of 2,5-diphenylpyrazine. The recovery of methylbenzylamine was 91%, but none of the imine was recovered. No other definite products were isolated. Similarly, N-benzilidinebenzylamine gave a 20% yield of 2,3,5,6-tetraphenylpyrazine. The recovery of dibenzylamine was 78%, but none of the imine or any other definite product could be isolated.

The fact that neither of the imines could be recovered from the reaction mixtures established that, if an imine were formed during the reduction, it would not be stable. Isolation of the identical pyrazines which were obtained in the corresponding reactions with *o*-bromoanisole demonstrated that these could conceivably be formed initially as the mechanism indicates, but under the conditions of the reaction were transformed ultimately to pyrazine derivatives.

EXPERIMENTAL[5]

Reduction of o-bromoanisole with lithium aluminum hydride. A solution of 18.7 g. (0.1 mole) of *o*-bromoanisole in 30 ml. of ether was added dropwise to a solution of 1.14 g. (0.03 mole) of lithium aluminum hydride in 50 ml. of ether. The mixture was refluxed for ten hours. This gave 0.5 g. (5%) of anisole and 17.8 g. (95%) of recovered *o*-bromoanisole.

Lithium dimethylamide and o-bromoanisole in ether. Lithium dimethylamide was prepared by condensation of excess dimethylamine into an ether solution of 0.15 mole of *n*-butyllithium. The solvent and excess amine were removed by a water aspirator with the aid of gentle heating with warm water. To the dry solid was added 100 ml. of anhydrous ether and 28.05 g. (0.15 mole) of *o*-bromoanisole. The mixture was refluxed with stirring for ten hours and then was hydrolyzed with 100 ml. of water. This gave: 2.5 g. (16%) of anisole, 7.4 g. (26%) of *o*-bromoanisole, 7.6 g. (34%) of N,N-dimethyl-*m*-anisidine, and 1.7 g. of higher-boiling basic material, which gave the trinitrobenzene derivative of N,N,N′,N′-tetramethyl-*m*-phenylenediamine.[2]

Lithium dimethylamide and o-bromoanisole in dimethylamine. Lithium dimethylamide was prepared from 0.6 mole of *n*-butyllithium. All of the solvent and excess amine were removed with an aspirator and gentle heating with warm water. Then, about 500 ml. of dimethylamine was condensed in the flask followed by the dropwise addition of 93.5 g. (0.5 mole) of *o*-bromoanisole. The mixture was allowed to reflux with stirring for 15½ hours at which time most of the amine was removed with an aspirator. The mixture was hydrolyzed with 500 ml. of water. This gave 7.0 g. (13%) of anisole, 29.0 g. (31%) of recovered *o*-bromoanisole, 26.5 g. (35%) of N,N-dimethyl-*m*-anisidine, and 2.7 g. of higher-boiling basic material. There was also obtained 4.7 g. of a tar which could not be distilled.

Lithium dimethylamide and o-bromoanisole in excess o-bromoanisole as solvent. Lithium dimethylamide was prepared from 0.2 mole of *n*-butyllithium. The excess amine and ether were removed. Then, 100 g. of *o*-bromoanisole was added. The mixture initially became very hot and then gradually cooled after two hours. Stirring was continued for an additional 20 hours and the mixture was hydrolyzed with water. This gave 1.8 g. (8%) of anisole, 70.0 g. of recovered

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(4) Cine substitution is a term introduced by Bunnett [*Chem. Revs*, **49**, 382 (1951)] to indicate abnormal substitution.

(5) All melting points are uncorrected.

o-bromoanisole, 14.1 g. (47%) of N,N-dimethyl-*m*-anisidine, and 1.4 g. of higher-boiling basic material.

Lithium diphenylamide and o-bromoanisole. Lithium diphenylamide was prepared by dropwise addition of 0.55 mole of *n*-butyllithium to a solution of 104 g. (0.6 mole) of diphenylamine in 300 ml. of ether. A solution of 93.5 g. (0.5 mole) of *o*-bromoanisole in 150 ml. of ether was added and the mixture was refluxed with stirring for 20 hours. Then it was hydrolyzed with water. The only products isolated were 91% of recovered *o*-bromoanisole and 89% of recovered diphenylamine.

Lithium methylanilide and o-bromoanisole. To 31.8 g. (0.3 mole) of methylaniline in 50 ml. of ether was added 0.25 mole of *n*-butyllithium in 135 ml. of ether. After stirring for one-half hour, 46.75 g. (0.25 mole) of *o*-bromoanisole was added and the mixture was refluxed with stirring for 20 hours. The mixture was hydrolyzed with 100 ml. of water. Nothing other than 43.1 g. (92%) of *o*-bromoanisole and 27.3 g. (86%) of methylaniline was isolated.

Lithium benzylanilide and o-bromoanisole. Lithium benzylanilide was prepared by addition of 0.45 mole of *n*-butyllithium in 300 ml. of ether to 81 g. (0.49 mole) of benzylaniline[6] in 100 ml. of ether. After stirring one-half hour, 69.2 g. (0.37 mole) of *o*-bromoanisole was added and the mixture was refluxed with stirring for 21 hours. The mixture was hydrolyzed with 250 ml. of 1:3 hydrochloric acid. The solid obtained gave 47.6 g. (59%) of benzylaniline after neutralization and distillation. From the filtrate there was isolated 7.9 g. (20%) of anisole, 49.5 g. (72%) of *o*-bromoanisole, and an additional 8.9 g. (11%) of benzylaniline. There were higher-boiling basic materials, but these gave no distinct fractions.

N-Methylbenzylamine. This was prepared following the directions of Holmes and Ingold;[7] b.p. 73° (20 mm.), n_D^{20} 1.5222.

Lithium benzylmethylamide and o-bromoanisole. To 36.0 g. (0.3 mole) of methylbenzylamine in 50 ml. of ether was added 0.25 mole of *n*-butyllithium. To this was added 46.75 g. (0.25 mole) of *o*-bromoanisole and the mixture was refluxed with stirring for 19 hours. The mixture was hydrolyzed with 200 ml. of water. The products isolated were 3.4 g. (13%) of anisole, 17.1 g. (48%) of methylbenzylamine, 25.2 g. (56%) of *o*-bromoanisole, and 14.7 g. (26%) of N-benzyl-N-methyl-*m*-anisidine; b.p. 151–155° (2.5 mm.), n_D^{20} 1.5977.

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.25; H, 7.50. Found: C, 79.11; H, 7.15.

There were higher-boiling basic materials, but no distinct fractions. The pot residue gave a dark brown solid which could not be purified by recrystallization, but which gave a small amount of 2,5-diphenylpyrazine on vacuum sublimation. This was identified by mixture melting point with an authentic sample prepared by the directions of Tutin.[8]

Lithium dibenzylamide and o-bromoanisole. To a solution of 92.0 g. (0.467 mole) of dibenzylamine in 100 ml. of ether was added 0.4 mole of *n*-butyllithium. To the suspension of the amide was added 75.0 g. (0.4 mole) of *o*-bromoanisole and the mixture was refluxed with stirring for 20 hours. Then it was hydrolyzed with 250 ml. of water. The products isolated were 15.4 g. (36%) of anisole, 34.8 g. (46%) of *o*-bromoanisole, 57.0 g. (62%) of dibenzylamine, and 10.2 g. (8%) of N,N-dibenzyl-*m*-anisidine; b.p. 190–215° (1 mm.), m.p. 56°.

Anal. Calc'd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.68. Found: C, 83.01; H, 7.04; N, 4.80.

A *picrate* of this material melted at 169.5–170° and did not depress the melting point of an authentic sample.

Anal. Calc'd for $C_{27}H_{24}N_4O_8$: C, 60.91; H, 4.54; N, 10.52. Found: C, 61.01; H, 4.66; N, 11.00.

The pot residue solidified to an orange glass. Digestion with ethanol gave 21.4 g. (28%) of a light yellow solid identified as 2,3,5,6-tetraphenylpyrazine by a mixture melting point with an authentic sample prepared by the directions of Davidson and co-workers.[9]

Anal. Calc'd for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Found: C, 87.21; H, 5.23; N, 7.46.

N,N-dibenzyl-m-anisidine. A mixture of 15.5 g. (0.126 mole) of *m*-anisidine, 32.8 g. (0.26 mole) of benzyl chloride, 10.5 g. (0.13 mole) of potassium carbonate, and 100 ml. of water was refluxed overnight. The dark oil obtained on cooling gave 6.8 g. of the desired product after several crystallizations from ethanol-acetone; m.p. 56°. A *picrate* melted 169–170°.

p-Methoxybenzylamine. Following the general directions of Amundsen and Nelson[10] anisonitrile was reduced to *p*-methoxybenzylamine. From 27 g. (0.71 mole) of lithium aluminum hydride and 100 g. (0.71 mole) of anisonitrile was obtained 65 g. (67%) of the amine.

N,N-bis-(p-methoxybenzyl)amine. The procedure employed was that used by Phillips[11] for the preparation of dibenzylamine. From 65 g. (0.475 mole) of *p*-methoxybenzylamine and 65 g. (0.475 mole) of anisaldehyde was obtained 65.0 g. (53%) of the amine, b.p. 192° (3 mm.), m.p. 32–33°.[12]

Lithium N,N-bis-(p-methoxybenzyl)amide and o-bromoanisole. To 64.25 g. (0.25 mole) of N,N-*bis*-(*p*-methoxybenzyl)-amine in 100 ml. of ether was added dropwise 0.2 mole of *n*-butyllithium. After one-half hour, 37.4 g. (0.2 mole) of *o*-bromoanisole was added. The mixture was refluxed with stirring for 20 hours before hydrolysis with 100 ml. of water. Distillation gave 2.6 g. (12%) of anisole, 23.7 g. (63%) of *o*-bromoanisole, 48.1 g. (75%) of N,N-*bis*(-*p*-methoxybenzyl)amine, and 9.1 g. (11%) of N,N-*bis*-(*p*-methoxybenzyl)-*m*-anisidine; b.p. 235–245° (1 mm.) m.p. 65–66° from ethanol.

Anal. Calc'd for $C_{23}H_{25}NO_3$: C, 76.04; H, 6.93; N, 3.85. Found: C, 76.16; H, 7.24; N, 4.16.

The pot residue was dissolved in benzene, filtered, and ethanol was added. This gave 3.2 g. (6%) of 2,3,5,6-tetra-(*p*-methoxyphenyl)pyrazine which was identified by mixture melting point with an authentic sample prepared from anisoin[13] and ammonium acetate following the directions of Davison[9] for the preparation of amarone. This melted 267.5–269°.[14]

Lithium piperidide and o-bromoanisole. Lithium piperidide was prepared from 0.45 mole of *n*-butyllithium and 52.5 g. (0.62 mole) of piperidine in 350 ml. of ether. After stirring one-half hour, 93.5 g. (0.5 mole) of *o*-bromoanisole was added. The mixture was refluxed with stirring for 19 hours before hydrolysis with 250 ml. of 1:3 hydrochloric acid. When the solution became acidic, a large amount of red tar separated. The products isolated were 7.1 g. (15%) of anisole, 31.2 g. (33%) of *o*-bromoanisole, 4.7 g. (9%) of piperidine, and 18.1 g. (21%) of 1-(*m*-methoxyphenyl)-piperidine; b.p. 116° (3 mm.), n_D^{20} 1.5611. A *picrate* melted at 157–158°.

Anal. Calc'd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.51; H, 9.03.

Anal. Calc'd for $C_{18}H_{20}N_4O_8$: C, 51.42; H, 4.80; N, 13.33. Found: C, 51.60; H, 4.88; N, 13.28.

High-boiling, basic materials were obtained as well as considerable amounts of tar.

N-Benzilidinemethylamine. This was prepared following

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[6] *Org. Syntheses*, Coll. Vol. I, 2nd Ed., 102 (1941).

[7] Holmes and Ingold, *J. Chem. Soc.*, **127**, 1800 (1925).

[8] Tutin, *J. Chem. Soc.*, **97**, 2495 (1910).

[9] Davidson, Weiss, and Jelling, *J. Org. Chem.*, **2**, 328 (1937).

[10] Amundsen and Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

[11] Phillips, *J. Soc. Chem. Ind.* (*London*), **66**, 325 (1947).

[12] Takeo Ueda, *J. Pharm. Soc. Japan*, **58**, 156 (1938); [*Chem. Abstr.*, **32**, 4149 (1938)].

[13] Dewar and Read, *J. Soc. Chem. Ind.* (*London*), **55**, 347T (1936).

[14] Novelli, *Anales asoc. quim. argentina*, **27**, 161 (1939); [*Chem. Abstr.*, **34**, 1660 (1940)].

the directions of Cromwell, Babson, and Harris;[15] b.p. 41–42° (3 mm.), n_D^{20} 1.5526.

Reaction of lithium benzylmethylamide with N-benzylidinemethylamine. Lithium benzylmethylamide was prepared from 13.3 g. (0.12 mole) of methylbenzylamine and 0.1 mole of *n*-butyllithium. To this suspension of amide was added 11.9 g. (0.1 mole) of N-benzilidinemethylamine. The mixture was refluxed with stirring for 20 hours before hydrolysis with 100 ml. of water. This gave on distillation 12.1 g. (91%) of methylbenzylamine and 1.8 g. of basic material which boiled over a wide range. The pot residue yielded a dark brown solid which gave some 2,5-diphenylpyrazine on vacuum sublimation.

N-Benzilidinebenzylamine. This was prepared from benzylamine and benzaldehyde in ethanol-water; b.p. 135–136° (2.5 mm.), $n_D^{17.5}$ 1.6012.[16]

Reaction of lithium dibenzylamide with N-benzilidinebenzylamine. Lithium dibenzylamide was prepared from 19.7 g. (0.1 mole) of dibenzylamine and 0.08 mole of *n*-butyllithium in 150 ml. of ether. To this was added 19.5 g. (0.1 mole) of N-benzilidinebenzylamine. The mixture was refluxed with stirring for 20 hours before hydrolysis with water. The only products identified were 18.1 g. (78%) of dibenzylamine hydrochloride and 3.8 g. (20%) of 2,3,5,6-tetraphenylpyrazine.

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(15) Cromwell, Babson, and Harris, *J. Am. Chem. Soc.*, **65**, 312 (1943).

(16) Mignonac, *Ann. chim.*, [11], **2**, 225 (1934); [*Chem. Abstr.*, **29**, 1074 (1935)].