[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CONNECTICUT]

Reduction of Nitriles to Primary Amines with Lithium Aluminum Hydride[1]

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The usefulness of lithium aluminum hydride as a reagent for the reduction of nitriles to primary amines has recently been indicated.[3a,b] The main objective of this work was to develop a widely-applicable preparatory procedure based on extensive studies of optimum experimental conditions. Most of the experimental work was done on caprylonitrile, but the final procedure was applied successfully to several other nitriles.

Zaugg and Horrom[4] claim that the reduction of 1 mole of a nitrile requires only 0.5 mole of lithium aluminum hydride, and Nystrom and Brown[2] also presumably were under the impression that this was the combining ratio and that the following equation written by them correctly represented the course of the reaction.

$$2RCN + LiAlH_4 = (RCH_2N)_2LiAl$$

In the present work, however, evidence was obtained to show that the reduction, in ethyl ether solution, of 1 mole of a nitrile actually requires 1 mole of lithium aluminum hydride.

Experimental Results and Discussion

Materials.—Caprylonitrile (octanenitrile) and caprinitrile (decanenitrile) were technical grade products of Armour and Company. All other nitriles were the white label grade of Eastman Kodak Company. All nitriles were purified by fractional distillation. The lithium aluminum hydride was the product of Metal Hydrides, Inc. Commercial anhydrous ethyl ether further dried over sodium was used.

Ratio of Reactants.—Table I summarizes the data obtained when the reduction of caprylonitrile was carried out with different molar ratios of lithium aluminum hydride. These reactions, as well as those furnishing the data presented in the following sections, were carried out with 0.1–0.2 mole of caprylonitrile following essentially the experimental procedure given under General Procedure.

TABLE I

Moles of $LiAlH_4$ per mole of $C_7H_{15}CN$	0.49	0.56	0.58	0.63	0.69
Max. poss. % yield on hydride H used	69	79	72	85	89
Moles of $LiAlH_4$ per mole of $C_7H_{15}CN$	0.72	0.75	0.78	1.00	
Max. poss. % yield on hydride H used	89	92	96	100	

In obtaining the data given in Table I, hydrolysis was not carried out. Aliquots of the reaction mixtures were withdrawn and tested using essentially the same apparatus as that described by Krynitsky, Johnson and Carhart[5] for determining the concentration of lithium aluminum hydride in solution. In this way, the amount of unreacted hydride hydrogen in the reaction mixtures was determined. The amount of hydride hydrogen that was consumed was then found by difference. Table I shows the yield of amine that would have been obtained if all of the hydride hydrogen which was consumed had gone to reduce the nitrile. It does not necessarily follow that these percentages represent the yield of amine produced. Anything that would react with the hydride, such as moisture in the reaction mixture, would cause the percentages in Table I to be higher than the yield of the amine. It must be emphasized, however, that these data represent the highest possible yields of amine. It may be concluded, therefore, that the reduction of 1 mole of caprylonitrile requires *at least* approximately 1 mole of lithium aluminum hydride rather than 0.5 mole as might be inferred from previously published reports.[3,4]

It was then necessary to determine whether 1 mole of lithium aluminum hydride were *enough* to reduce 1 mole of caprylonitrile. This was accomplished by carrying out a reduction with this ratio of reactants, continuing through the hydrolysis step, and isolating the octylamine. When this was done, yields of approximately 90% were obtained as indicated under General Procedure. This probably represents a virtually quantitative yield since when a sample of octylamine, instead of caprylonitrile, was put through the entire process, 88% was recovered. To demonstrate further that this molar ratio was sufficient, reductions were carried out with greater amounts of lithium aluminum hydride with no increase in the yield.

This 1:1 molar ratio of reactants is in sharp contrast to the combining ratio of 2 moles of *o*-tolunitrile to 1 mole of hydride which Nystrom and Brown[3] determined by application of the Gilman–Schulze color test.

Application of this color test to the reduction of benzonitrile, which was presumed to be analogous to *o*-tolunitrile, substantiated the results of these workers. However, application of this color test to the reduction of caprylonitrile indicated a combining ratio of 1 mole of nitrile to 1 mole of hydride.

From this it might be concluded that the reduction of benzonitrile or *o*-tolunitrile requires only half of the amount of hydride needed for the reduction of caprylonitrile. To test this hypothesis, reductions of benzonitrile were carried out with dif-

TABLE II

Moles of $LiAlH_4$ per mole of C_6H_5CN	0.50	0.75	0.78	1.00
Max. poss. % yield based on hydride H used	55	70	75	97

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(3) (a) Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 (1947); (b) Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

(4) Zaugg and Horrom, *Anal. Chem.*, **20**, 1026 (1948).

(5) Krynitsky, Johnson and Carhart, *ibid.*, **20**, 311 (1948).

ferent molar ratios of hydride to nitrile with the results shown in Table II.

Here, as with the data in Table I, it may be concluded that complete reduction of benzonitrile requires at least a 1:1 molar ratio of reactants. When only 0.5 mole of hydride per mole of nitrile is used, not nearly enough hydride hydrogen is consumed to reduce all of the nitrile.

Therefore, we have concluded that the Gilman–Schulze color test is not suitable for following the course of the reduction since, in the present work, it has been shown to give different results with two nitriles that behave similarly toward lithium aluminum hydride.

Since 1 mole of lithium aluminum hydride is required to reduce 1 mole of nitrile, it would seem evident that 0.5 mole could reduce only 0.5 mole of nitrile. Nevertheless, the first entry in Table I indicates that, when 0.5 mole of hydride was used per mole of nitrile, enough hydride was consumed to reduce 0.69 mole of nitrile. This must mean that with a 0.5 molar ratio of hydride to nitrile either more than half of the hydride hydrogen is available for the reduction of the nitrile or some of the hydride hydrogen was consumed in another way.

It has already been pointed out that moisture in the reaction mixture might explain this abnormal consumption of hydride. It is practically certain, however, that neither water nor any other contaminant capable of reacting with the hydride was present in the reaction mixture in any appreciable amount. We suspected, therefore, that part of the hydride was consumed by some substance which arose from the unreduced nitrile. Since Grignard reagents can cause nitriles to dimerize,[6] it occurred to us that the addition product of lithium aluminum hydride and a nitrile might have a similar effect. The α-hydrogen ionized during this dimerization might be expected to consume some of the hydride.

The infrared absorption spectrum of the reaction mixture from a 0.5 molar ratio of hydride to caprylonitrile was measured. It was not inconsistent with the theory that the dimer of caprylonitrile might be present. In addition to the absorption band at about 2245 cm.$^{-1}$ arising from the cyano group of caprylonitrile, there was an absorption band at about 2175 cm.$^{-1}$ which might well be characteristic of the cyano group in the dimer.

Time of Reaction.—Following the General Procedure up to the hydrolysis step, reaction mixtures were obtained which showed no difference in the amount of hydride consumed when they were refluxed for periods varying from 10 minutes to 72 hours.

Temperature of Reaction.—Reductions were carried out at 0°, 25° and 35° which yielded respectively 77, 75 and 78% octylamine, isolated by distillation. The procedure for these reductions differed from the General Procedure only in that more sodium hydroxide was used in the hydrolysis step. There is no significance to the fact that the yields listed in this and the following section are lower than those reported elsewhere in this paper. These particular experiments were carried out before the conditions of the hydrolysis had been perfected. The important fact here is that there are no significant differences in the yields within either of the two groups. It is concluded that the reduction can be carried out equally satisfactorily at any convenient temperature between 0° and the reflux temperature of ethyl ether. This is approximately the maximum temperature range that could be encountered in carrying out the reduction in ethyl ether using ice-bath cooling.

Dilution of Reactants.—In order to test the effect of concentration, reductions were carried out using the four possible combinations of two concentrations of each reactant: caprylonitrile, 0.35 and 4.37 molar; lithium aluminum hydride, 0.25 and 0.62 molar. The yields of octylamine, isolated by distillation, did not differ significantly (77–81%). Thus reasonable variations in the concentration of reactants appear not to affect the yield. Other experiments, however, have indicated that the subsequent hydrolysis is more smoothly and easily carried out if the average concentration of the two reactants is no greater than approximately 1 molar. It is considerably more convenient, when the nitrile is added to the hydride, as it ordinarily should be to avoid dimerization, to use about nine-tenths of the ether to dissolve the hydride and the remainder to dissolve the nitrile.

Conditions of Hydrolysis.—After the reaction between a nitrile and lithium aluminum hydride has taken place, some type of basic hydrolysis is preferable if the amine is wanted in the free state. Most basic hydrolyses have been carried out with a large volume of sodium hydroxide solution. This produces a voluminous, gelatinous precipitate which ensnares some of the product. Nystrom and Brown[3] surmounted this difficulty by using aqueous sodium potassium tartrate to form a soluble aluminum complex. In our hands this method was not entirely satisfactory because clear mixtures were not obtained.

In an attempt to avoid this difficulty in another way, a large excess of sodium hydroxide was added to convert the aluminum hydroxide to water-soluble sodium aluminate. This produced an emulsified rather than a clear aqueous layer. On standing, however, the aqueous layer cleared but scum floating at the interface prevented a clean separation.

Work was then directed toward determining the minimum amount of sodium hydroxide required in the hydrolysis. As a result of this study, a procedure was evolved in which basic hydrolysis was used in such a way that no aqueous layer was present after the hydrolysis. The inorganic residue which resulted was in a granular, dry form from which the ether solution of the product was easily decanted.

General Procedure.—To a cooled (ice-bath) solution of 3.8 g. (0.10 mole) of lithium aluminum hydride in 200 ml. of anhydrous ethyl ether was slowly added 12.5 g. (0.10 mole) of caprylonitrile dissolved in 20 ml. of anhydrous ethyl ether. With continued cooling and vigorous stirring 4 ml. of water, 3 ml. of 20% sodium hydroxide, and 14 ml. of water were added in succession. The ether solution was decanted from the white, granular inorganic residue. This residue was washed twice with ether and the ether portions

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[6] Gilman, "Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 661.

were all combined. The ether was distilled off and the product was distilled at 53–54° at 6 mm. to yield 11.5–11.9 g. (89–92%) of octylamine.

Applicability and By-products.—The General Procedure was successfully applied also to caprinitrile, benzonitrile, *p*-chlorobenzonitrile and butyronitrile with the following respective yields of the corresponding primary amines: 92, 83, 81 and 57%. The low yield of butylamine was probably the result of volatilization of the product when the ether was boiled off through an air condenser, since the vapors emerging instantly turned red litmus paper blue.

In view of the reported reduction of alkyl halides to hydrocarbons,[7] it is worth noting that the reduction of *p*-chlorobenzonitrile gave a good yield of *p*-chlorobenzylamine which, from its boiling range, appeared to be completely free of benzylamine.

It appears likely, however, that complicating side reactions can be expected when this procedure is used for the reduction of nitriles whose α-hydrogen atoms are doubly activated. Phenylacetonitrile, in contrast to all other nitriles worked with, gave a reaction mixture which quickly turned a very dark green when exposed to the atmosphere.

Several of our products were carefully examined before distillation for the presence of secondary amines using the nickel chloride–carbon disulfide test.[8] The results completely substantiated the report[3] that secondary amines are not produced.

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Summary

1. A procedure, arising from extensive investigations of the reaction conditions, has been described for the reduction of caprylonitrile to octylamine with lithium aluminum hydride. This procedure appears to be widely applicable to other nitriles.

2. In contrast to inferences which may be drawn from the work of others, it has been suggested that only half the hydrogen of lithium aluminum hydride is available for the reduction of the cyano group, when the reaction is carried out below 35°.

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[7] Johnson, Blizzard and Carhart, THIS JOURNAL, **70**, 3664 (1948).

[8] Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd ed., 1948, p. 111.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

Stereochemistry of 1,4-Addition. I. The Chlorination of Butadiene[1]

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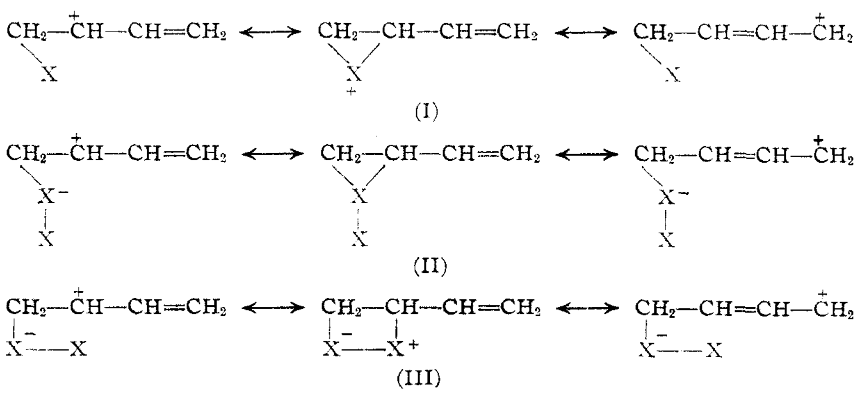
Addition of halogens to conjugated systems is commonly regarded as a two-stage process[2,3]: electrophilic attack by halogen[4] or halonium ion,[5] followed by nucleophilic attack by halide ion. This view is consistent with the observed kinetics and stereochemistry of halogen additions to isolated double bonds, as well as with the proportions of 1,2- and 1,4-adducts in halogen additions to conjugated double bonds.


(I)

(II)

(III)

In the transition state, according to this approach, the attacking reagent coördinates with one of the terminal double bonds, as illustrated by selected contributing structures (I), (II) and (III).[4] These hybrids will be referred to as terminal.

It is conceivable, on the other hand, that electrophilic attack might occur with the attacking reagent disposed centrally and symmetrically with respect to, and coplanar with, the diene molecule. Such possible transition state hybrids, which will be referred to as frontal, are illustrated by selected contributing structures (IV),[3] (V) and (VI).[6]

The frontal transition states all have the *cis*-2-butenoid structure; stereochemically related, although mechanistically not strictly comparable, transition states are involved in the *cis*-reduction of butadiene,[7] the Diels–Alder synthesis,[8] iron

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[1] Presented before the Division of Organic Chemistry, 118th American Chemical Society Meeting, Chicago, Illinois, September 6, 1950.

[2] de la Mare, Hughes and Ingold, *J. Chem. Soc.*, 17 (1948).

[3] de la Mare, *Quart. Revs.* (*London*), **3**, 126 (1949).

[4] Waters, Caverhill and Robertson, *J. Chem. Soc.*, 1168 (1947).

[5] Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937).

[6] Eyring, Sherman and Kimball (*J. Chem. Phys.*, **1**, 586 (1933)) have proposed a related transition state. Their calculations indicate that one-stage, 1,4-addition is energetically feasible.

[7] Ziegler, *et al.*, *Ann.*, **528**, 101 (1937).

[8] Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, New York, N. Y., 1949, p. 150.