[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Lithium Aluminum Hydride Reduction of Grignard–Nitrile Adducts to Primary Amines

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The preparation of five disubstituted carbinamines by the lithium aluminum hydride reduction of Grignard–nitrile adducts is described. Optimum yields of amine are obtained using 1.2 moles of lithium aluminum hydride per mole of the complex. N-(1-Phenylpropyl)-1-phenylpropylidenimine was prepared from 1-phenylpropylideniminomagnesium bromide and 1-phenylpropylamine followed by mild basic decomposition. Incomplete reduction of 1-phenylpropylideniminomagnesium bromide with lithium aluminum hydride followed by mild basic decomposition yields the same imine.

In the course of preparing a number of disubstituted carbinamines for pharmacological testing, it was observed that addition compounds, formed by the reaction of Grignard reagents with nitriles, may be reduced directly to the corresponding amines by the use of lithium aluminum hydride.[1] The use of

$$RMgX + R'CN \longrightarrow R{-}\overset{\overset{NMgX}{\|}}{C}{-}R' \xrightarrow{LiAlH_4} R{-}\overset{\overset{NH_2}{|}}{CH}{-}R'$$

this procedure eliminated the steps necessary for the conversion of the intermediate ketones to the amines.

The reduction of benzalaniline to benzylaniline requires one mole of lithium aluminum hydride per four moles of aldimine.[2] In the ethyl ether solution the reduction of one mole of nitrile to the primary amine requires one mole of lithium aluminum hydride.[3] In order to determine the optimum quantity of lithium aluminum hydride for reduction of the Grignard–nitrile addition compounds, the preparation of 1-phenylpropylamine was studied.

The reaction of phenylmagnesium bromide with propionitrile has been reported to yield 83% of propiophenone.[4] When the reaction mixture from 1.2 moles of phenylmagnesium bromide and 1 mole of propionitrile was reduced with 1.2 moles of lithium aluminum hydride, 80% of 1-phenylpropylamine was isolated. However, a reduction with 0.4 mole of lithium aluminum hydride yielded 51% of N-(1-phenylpropyl)-1-phenylpropylidenimine (I) as

$$\begin{array}{l} C_6H_5{-}CH{-}C_2H_5 \\ \quad\quad | \\ \quad\quad N \qquad\qquad I \\ \quad\quad \| \\ C_6H_5{-}C{-}C_2H_5 \end{array}$$

the main product and 8% of 1-phenylpropylamine. An intermediate quantity, 0.8 mole of lithium aluminum hydride, yielded 62% of 1-phenylpropylamine and only 10% of the impure imine I.

The imine I was hydrolyzed using dilute hydrochloric acid to 1-phenylpropylamine and propiophenone. Hydrogenation of I over platinum oxide catalyst required one mole of hydrogen. Two optical forms of di-(1-phenylpropyl)-amine were isolated.

It was not possible to prepare the imine I from propiophenone and 1-phenylpropylamine in benzene solution using sodium hydride or triethylamine catalysts. However, the addition of 1-phenylpropylamine to 1-phenylpropylideniminomagnesium bromide followed by hydrolysis as in the reduction procedure yielded 74% of I.

The influence of structure on the reactions of Grignard reagents with nitriles has been studied.[4] In cases where the reaction gave good yields of ketones, reduction of the intermediate complexes with lithium aluminum hydride gave good yields of the amines. Reduction of the complexes from phenyl and benzylmagnesium bromides with propionitrile, yielded 80% of 1-phenylpropylamine and 71% of 2-amino-1-phenylbutane. 1-Phenylhexylamine was formed in 54% yield from the reduction of the 1-phenylhexylideniminomagnesium bromide.

Only 23% of 3-aminopentane was obtained by reduction of 3-pentylideniminomagnesium bromide. In the last example, addition of the Grignard reagent to the nitrile group is apparently not the major pathway of the reaction.

One diamine, 4-diethylamino-1-phenylbutylamine, was prepared in 62% yield by reduction of the complex from phenylmagnesium bromide and 4-diethylaminobutyronitrile.

Experimental[5]

1-Phenylpropylamine. Method A.—Phenylmagnesium bromide was prepared from 47.3 g. (0.30 mole) of bromobenzene, 7.2 g. (0.30 mole) of magnesium and 300 ml. of ether. The Grignard solution was stirred during the dropwise addition of 13.8 g. (0.25 mole) of propionitrile and then the reaction mixture was refluxed two hours. A slurry of 11.4 g. (0.30 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran was added slowly to the reaction mixture. It was refluxed 18 hours and then decomposed, with cooling, by the careful addition of 12 ml. of water, 9 ml. of 20% sodium hydroxide and finally 42 ml. of water. The solid was collected on a filter and washed with ether. The combined filtrate was dried over magnesium sulfate and distilled. The 1-phenylpropylamine boiled at 78–80° (7.0 mm.), $n^{25}D$ 1.5186, weight 27.1 g. (80%).

In another run, an acid extraction was employed to separate the base. After the decomposition of the reaction with water and base, the organic layer was added to 200 ml. of dilute hydrochloric acid and concentrated *in vacuo* to 75 ml. The amine was liberated with 50% sodium hydroxide and dried in ether solution over magnesium sulfate. The product boiled at 78–79° (7.0 mm.), $n^{25}D$ 1.5185, weight 26.5 g. (78%).

Method B.—The procedure was that used in A except that 3.8 g. (0.1 mole) of lithium aluminum hydride was used in the reduction. The crude 1-phenylpropylamine boiled at 85–87° (10 mm.), weight 2.8 g. (8%). N-(1-Phenylpropyl)-1-phenylpropylidenimine boiled at 156–157° (3.4 mm.), weight 15.8 g. (51%).

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.00; H, 8.42; N, 5.58. Found: C, 85.86; H, 8.18; N, 5.83.

(1) After this work was complete, D. J. Cram reported the lithium aluminum hydride reduction of 1-methyl-2-phenylpropylideniminomagnesium iodide to the corresponding amine, Abs. of the 13th Nat. Org. Sym. of the Am. Chem. Soc. (1953).

(2) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3738 (1948).

(3) L. H. Amundsen and L. S. Nelson, *ibid.*, **73**, 242 (1951).

(4) C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **15**, 359 (1950).

(5) Melting points and boiling points are uncorrected.

Method C.—The procedure was that used in A except that 7.6 g. (0.2 mole) of lithium aluminum hydride was used. The 1-phenylpropylamine boiled at 84–85° (10 mm.), $n^{25}D$ 1.5182, weight 19.5 g. (62%). The crude imine boiled at 100–150° (2.8 mm.), weight 3.2 g. (10%).

2-Amino-1-phenylbutane.—The procedure was that used in method A for 1-phenylpropylamine except that benzylmagnesium chloride prepared from 38 g. (0.3 mole) of benzyl chloride, 19 g. (0.8 mole) of magnesium and 300 ml. of ether was used in place of phenylmagnesium bromide. The product boiled at 96–97° (9.5 mm.), $n^{25}D$ 1.5130, weight 26.2 g. (71%).

1-Amino-2-phenylbutane is reported[6] to boil at 106° (15 mm.), $n^{20}D$ 1.5142.

1-Phenylhexylamine.—The procedure was that used in method A for 1-phenylpropylamine except that 24.3 g. (0.25 mole) of *n*-capronitrile was substituted for the propionitrile. The product boiled at 82–83° (0.90 mm.), $n^{25}D$ 1.5070, weight 23.6 g. (54%).

Anal. Calcd. for $C_{12}H_{19}N$: N, 7.90. Found: N, 7.76.

3-Aminopentane.—The procedure was essentially that used in method A for 1-phenylpropylamine. Ethylmagnesium bromide was prepared from 32.7 g. (0.30 mole) of ethyl bromide, 7.2 g. (0.3 mole) of magnesium and 300 ml. of ether. After the reaction mixture was decomposed with water and base, the organic phase was added to 200 ml. of dilute hydrochloric acid and concentrated *in vacuo* to 75 ml. The amine was liberated with 50% sodium hydroxide and dried in ether solution over magnesium sulfate. The product boiled at 87° at ordinary pressure, $n^{25}D$ 1.4030, weight 4.8 g. (23%). The hydrochloride was prepared in ether and recrystallized twice from methanol–ethyl acetate, m.p. 215–216°, weight 4.8 g.

The amine is reported[7] to boil at 90° and its hydrochloride[8] to melt at 215–216°.

4-Diethylamino-1-phenylbutylamine.—The procedure was that used in method B for 1-phenylpropylamine except that 28 g. (0.20 mole) of 4-diethylaminobutyronitrile was used in place of propionitrile. The product boiled at 115–116° (0.80 mm.), $n^{25}D$ 1.5081, weight 27.5 g. (62%).

Anal. Calcd. for $C_{14}H_{24}N_2$: N, 12.71. Found: N, 12.95.

The amine is reported[9] to boil at 116–118° (1 mm.).

N-(1-Phenylpropyl)-1-phenylpropylidenimine.—A reaction mixture containing 26.8 g. (0.2 mole) of propiophenone, 26.8 g. (0.2 mole) of 1-phenylpropylamine, 4.8 g. (0.2 mole) of sodium hydride and 150 ml. of benzene was refluxed overnight without the formation of water in the water separator. No imine was isolated by distillation. Another run using 6 ml. of triethylamine was unsuccessful.

1-Phenylpropylideniminomagnesium bromide was prepared as described in method A. Then 33.8 g. (0.25 mole) of 1-phenylpropylamine was added dropwise. The reaction mixture was refluxed with stirring for three hours and then decomposed by addition of 4 ml. of water, 3 ml. of 20% sodium hydroxide and finally 24 ml. of water. After stirring for two hours at room temperature, the ether solution was decanted and dried over magnesium sulfate. The product distilled at 125–126° (0.60 mm.), $n^{25}D$ 1.5552, weight 46.0 g. (74%).

Hydrolysis of N-(1-Phenylpropyl)-1-phenylpropylidenimine.—A reaction mixture containing 7.0 g. of the imine in 100 ml. of dilute hydrochloric acid was refluxed for one hour. The insoluble oil was dissolved in ether. The ether was distilled and the 2,4-dinitrophenylhydrazone of the residual oil was prepared. After three recrystallizations from ethyl acetate, the product melted at 188–189°, weight 2.0 g. There was no depression in the mixed melting point with an authentic sample of propiophenone 2,4-dinitrophenylhydrazone.[10] The acid aqueous phase was concentrated to dryness *in vacuo* and the 1-phenylpropylamine hydrochloride[11] recrystallized from methanol–ethyl acetate solution, m.p. 193–194°, weight 3.6 g.

Hydrogenation of N-(1-Phenylpropyl)-1-phenylpropylidenimine.—The imine, 10.0 g. (0.04 mole), was reduced in 200 ml. of ethanol using 200 mg. of platinum oxide catalyst. The reduction required 0.04 mole of hydrogen. The catalyst was collected on a filter and the filtrate concentrated *in vacuo*. The residual oil was dissolved in ether and the hydrochloride prepared using anhydrous hydrogen chloride. Two optical forms of di-(1-phenylpropyl)-amine hydrochloride were separated by fractional crystallization from methanol–ethyl acetate. The α-form, after five recrystallizations, melted at 252–253°, weight 0.8 g.

Anal. Calcd. for $C_{18}H_{23}N\cdot HCl$: C, 74.58; H, 8.36; N, 4.83; Cl, 12.23. Found: C, 74.70; H, 8.47; N, 5.05; Cl, 12.41.

The more soluble β-form, after five recrystallizations, melted at 242–243°, weight 2.7 g. A mixed melting point was 215–217°.

Anal. Calcd. for $C_{18}H_{23}N\cdot HCl$: C, 74.58; H, 8.36; N, 4.83; Cl, 12.23. Found: C, 74.23; H, 8.49; N, 5.09; Cl, 12.40.

(6) N. Kornblum and D. C. Iffland, THIS JOURNAL, **71**, 2137 (1949).
(7) M. A. Mailhe, *Bull. soc. chim., France*, [4] **15**, 327 (1914).
(8) W. A. Noyes, *Am. Chem. J.*, **15**, 539 (1893).
(9) W. J. Humphlett, M. J. Weiss and C. R. Hauser, THIS JOURNAL, **70**, 4020 (1948).
(10) T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 2607 (1932).
(11) P. Billon, *Ann. chim.*, **7**, 314 (1927).

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Ketimines. VI. o-Tolyl Alkyl Ketimines[1]

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Seven ketimines have been prepared by the action of Grignard reagents on *o*-tolunitrile. Each imine was hydrolyzed to the corresponding ketone. With the exception of *s*-butyl *o*-tolyl ketimine, the imines reduced readily to the corresponding primary amines. Polarographic half wave potentials of the imines and ketones in absolute alcohol were obtained.

Most of the work reported in earlier papers[2–6] of this series has been devoted to the determination of factors which contribute to the stability of a ketimine toward hydrolysis. It was noted that *o*-tolyl *t*-butyl ketimine is stable while the *o*-tolyl isopropyl ketimine hydrolyzes readily.[2] In later papers isopropyl 1-methyl-3-isopropyl-cyclopentyl ketimine[5] and *o*-tolyl 1,1-diphenylethyl ketimine[6] were shown to be stable. These findings have prompted further interest in the *o*-tolyl ketimines and the alkyl series was prepared to determine the reactivity compared to the *o*-tolyl isopropyl and *t*-butyl ketimines which have been reported.

It was found that the time needed for the addition of Grignard reagent to nitrile is considerably less than previously considered necessary. In the synthesis of the isoamyl ketimine, for example, 44-hour refluxing gave a yield of 55% while a

(1) From a thesis submitted in partial fulfillment of the requirements for the Ph.D. at the University of Oklahoma.
(2) P. L. Pickard, *et al.*, THIS JOURNAL, **72**, 876 (1950).
(3) *Ibid.*, **72**, 5017 (1950). (5) *Ibid.*, **74**, 4607 (1952).
(4) *Ibid.*, **73**, 42 (1951). (6) *Ibid.*, **75**, 2148 (1953).