[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

THE FORMATION OF PRIMARY AMINES FROM GRIGNARD REAGENTS AND MONOCHLORO-AMINE

BY GEORGE H. COLEMAN AND C. R. HAUSER[1]

RECEIVED DECEMBER 19, 1927 PUBLISHED APRIL 5, 1928

Comparatively few reactions of Grignard reagents with halogen compounds in which the halogen atom is attached to nitrogen have been studied. Oddo[2] prepared nitrosobenzene from nitrosyl chloride (NOCl) and phenylmagnesium bromide. Zuskine[3] has reported, however, that nitroxyl chloride (NO_2Cl) does not form nitro compounds with either phenylmagnesium bromide or ethylmagnesium bromide. Strecker[4] isolated only ammonium salts from the reaction mixtures of nitrogen trichloride with phenylmagnesium bromide and ethylmagnesium bromide. Buylla[5] failed in an attempt to prepare triethylamine by the action of iododiethylamine on ethylmagnesium bromide, the iododiethylamine being recovered almost quantitatively. Grignard[6] and his co-workers have studied the reactions of cyanogen chloride, bromide and iodide with a variety of organomagnesium halides. With cyanogen chloride the principal product is in many cases the nitrile. In such reactions the authors regard the cyanogen chloride as reacting in that form in which the chlorine is attached to carbon ($Cl—C\equiv N$). With cyanogen bromide and iodide the principal product is the corresponding halogen derivative instead of the nitrile. The halogen atoms are here regarded as being attached to nitrogen ($I—N\equiv C$ or $I—N=C<$).

The present investigation was carried out to determine the possibility of preparing primary amines directly from Grignard reagents and monochloro-amine. The results thus far obtained show that primary amines and ammonia are formed. In this reaction a variation in the yields of the products obtained with chlorides, bromides and iodides has also been observed. If the Grignard reagent be represented by RMgX, then for the same radical R, the yield of amine is greatest when X is chlorine and least when X is iodine. When X is bromine the yield of amine lies between the other two. The results with twenty-three Grignard reagents thus far used are given in Table I. It is apparent that the yield of ammonia increases as the yield of amine decreases.

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[1] This communication is an abstract of the thesis submitted by C. R. Hauser in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the State University of Iowa.

[2] Oddo, *Gazz. chim. ital.*, **39**, I, 659 (1909).

[3] Zuskine, *Bull. soc. chim.*, **37**, 187 (1925).

[4] Strecker, *Ber.*, **43**, 1131 (1910).

[5] Buylla, *Rev. real. acad. cien.* (*Madrid*), **9**, 635–653, 718–734 (1910).

[6] (a) Grignard, Bellet and Courtot, *Ann. chim.*, [9] **12**, 364 (1919); (b) Grignard and Perrichon, *ibid.*, [10] **5**, 5 (1926).

TABLE I

PERCENTAGE YIELDS OF AMINES AND AMMONIA FROM MONOCHLORO-AMINE AND GRIGNARD REAGENTS

	X = Cl % yields		X = Br % yields		X = I % yields	
Reagent	RNH_2	NH_3	RNH_2	NH_3	RNH_2	NH_3
CH_3MgX	..	..	26.3	68.4	7.6	87.5
C_2H_5MgX	57.2	39.6	27.7	65.7	16.2	81.4
n-C_3H_7MgX	58.2	36.9	27.0	63.8	13.9	69.8
n-C_4H_9MgX	58.9	38.5	27.2	65.2	15.3	84.7
Iso-$C_5H_{11}MgX$	55.2	41.2	26.8	71.7	10.9	83.9
C_6H_5MgX	26.7	68.0	14.5	83.9	0.8	95.6
$C_6H_5CH_2MgX$	85.0	3.7	54.7	38.7	49.4	45.8
$C_6H_5C_2H_4MgX$	74.0	18.4	42.3	52.6	15.0	73.7

The Grignard reagents were prepared in the usual manner in ether solution and, since in each reaction with monochloro-amine an excess of the Grignard reagent was used, the variation in the yields with chlorides, bromides and iodides must have been caused by the different halogens present in the reagent.

The monochloro-amine was prepared in ether solution by a modification of the method described by Marckwald and Wille.[7] These authors found that monochloro-amine distributes itself between water and ether in the ratio of approximately one to one. The solubility of monochloro-amine in other common organic solvents is less than this.

The reaction of monochloro-amine with the Grignard reagent is rapid even at 0°, and the penetrating odor of monochloro-amine quickly disappears. The following reactions are suggested for the formation of the amines and ammonia.

$$RMgX + NH_2Cl = RNH_2 + MgXCl \qquad (1)$$
$$RMgX + NH_2Cl = RCl + MgXNH_2 \qquad (2)$$

With the Grignard reagents of the lower alkyl halides the corresponding hydrocarbon gas was evolved, as would be expected due to the secondary reaction of the excess Grignard reagent with the products.

Since, as indicated in Table I, nearly all of the monochloro-amine is accounted for in the formation of ammonia and the amine, the above reactions are the principal ones occurring. With benzylmagnesium chloride the largest yield of amine was obtained, and with phenylmagnesium iodide the lowest yield of amine with the production of the largest yield of ammonia. If the formation of ammonia is due to reaction (2), then we should expect the formation of the corresponding chloride. Thus, with phenylmagnesium iodide, in which, as mentioned, the yield of ammonia was greatest, an equivalent amount of chlorobenzene was to be expected. In this reaction chlorobenzene was isolated from the reaction products.

No indication of the presence of secondary or tertiary amines was found.

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[7] Marckwald and Wille, *Ber.*, **56**, 1319 (1923).

The products obtained as the hydrochlorides were analyzed and derivatives prepared.

This work is being continued with other chloro-amines.

Experimental

Preparation of Monochloro-amine.—A solution of 200 cc. of sodium hypochlorite, made from 2 *N* sodium hydroxide and the calculated amount of chlorine (the solution remained alkaline after the addition of the chlorine), was mixed with 200 cc. of *N* ammonium hydroxide containing pieces of ice. The monochloro-amine was either extracted with ether directly or, when a more concentrated solution was desired, the mixture was distilled at 30–40° under a pressure of 15–25 mm. until about 100 cc. of distillate had collected in the receiver. A spiral condenser surrounded by ice water was used and the receiver was immersed in a freezing mixture of either ice and salt, or carbon dioxide snow and alcohol. When the latter freezing mixture was used, about 80 cc. of ether placed in the receiver retained much of the monochloro-amine which would otherwise have been lost. The ether solution was poured off, the ice melted and the solution extracted three times with ether. About 80 cc. was used for each extraction. The ether extracts were poured together and dried with calcium chloride for a few minutes, keeping the container immersed in a freezing mixture. The dry ether solutions prepared by this method contained over 100 mg. moles of monochloro-amine. Other drying agents were used but calcium chloride seemed to be very satisfactory if the drying was carried out as specified above. An analysis of the solution before and after drying showed little change in the concentration of monochloro-amine.

Analysis of the Monochloro-amine Solution.—The analysis of the monochloro-amine solution for nitrogen was carried out by adding 5 cc. of the ether solution to 15 cc. of cold concentrated hydrochloric acid contained in a small flask. When the reaction was complete the ether was removed by gentle heating and the ammonia determined by the addition of excess alkali and distillation into standard acid.

The analysis for chlorine was carried out by adding 5 cc. of the solution to an excess of sodium sulfite solution. After the completion of the reaction the ether was removed by means of a separatory funnel and the excess sulfite oxidized with potassium permanganate after acidifying with nitric acid. The chlorine content was then determined by the Volhard method.

In some cases the weight of the sample was used instead of the volume. The results of a large number of determinations showed that the ratio of nitrogen to chlorine was 1:1. The ether solutions of monochloro-amine were always colorless, thus also indicating the absence of appreciable amounts of either chlorine or nitrogen trichloride.

Reaction of Monochloro-amine with the Grignard Reagents

The reactions of monochloro-amine with the Grignard reagents were carried out by adding, slowly and with shaking, the cold, dry ether solution of monochloro-amine to the Grignard reagent, which was cooled to 0° or below. As soon as the ether solution of monochloro-amine came in contact with the Grignard reagent a precipitate formed, leaving at the end a more or less gelatinous mass. In the reactions with organomagnesium iodides a brown coloration always appeared immediately upon the addition of the monochloro-amine solution. After the completion of the reaction, the flask containing the mixture was connected to a condenser with an adapter at the lower end dipping under dilute hydrochloric acid. The excess Grignard reagent was then decomposed by the addition of water through a dropping funnel, and the basic mixture either treated directly with steam, or first brought into solution with acid, and then made alkaline and steam distilled until no more basic substance passed over. The ether and aqueous layers of the distillate were shaken together and, after separating, the hydrochloric acid solution was evaporated to dryness on a water-bath. After drying thoroughly in a vacuum desiccator, the amine hydrochloride was dissolved in *n*-butyl alcohol and the undissolved ammonium chloride filtered off. The amine hydrochloride was obtained by evaporating the alcohol on a water-bath.

The purity of the hydrochlorides was determined by analysis and the amines were identified by preparing derivatives and taking mixed melting points with known compounds.

Phenylmagnesium Iodide[8] with Monochloro-amine.—A solution of 120 mg. moles of monochloro-amine in 300 cc. of ether was added to excess of the Grignard reagent products: $C_6H_5NH_2HCl$, 0.13 g.; NH_4Cl, 6.13. g.

The ether layer of the distillate was dried with calcium chloride and fractionated. About 4 g. of chlorobenzene, several grams of benzene, iodobenzene and a residue of diphenyl were obtained. The 4 g. of chlorobenzene is only about a third of that which would theoretically be present according to equation (2) but the pure product completely freed from the other fractions, which were much larger, does not represent all of this compound present in the reaction mixture.

Preparation of Phenylethyl Iodide.[9]—A solution of 200 g. of sodium iodide in 100 cc. of acetone was mixed with 137 g. of phenylethyl chloride. After boiling for four hours, about three-fourths of the acetone was distilled off and the remaining liquid poured into twice its volume of cold water. The oil was separated and washed successively with sodium bisulfite solution, water, sodium carbonate solution and again with water. It was then dried with calcium chloride and fractionated *in vacuo*. There was a rather large low boiling fraction. The fraction boiling at 125–128° at 18–20 mm. was analyzed and used in the preparation of the Grignard reagent.

Anal. (Parr bomb). Subs., 0.1757, 0.2927: 7.44, 12.37 cc. of 0.1010 N $AgNO_3$. Calcd. for C_8H_9I: I, 54.71. Found: 54.27, 54.17.

Phenylethyl iodide has been prepared by Heidelberger;[10] the boiling point, however, did not indicate a pure product.

Preparation of Benzyl Iodide.[11]—A solution of 100 g. of sodium iodide in 500 cc. of acetone was mixed with 63 g. of benzyl chloride and refluxed for one hour. The mixture was poured into 1500 cc. of water and the oil separated and placed in an ice-salt bath until it solidified. By recrystallizing from alcohol a yield of 38 g. of benzyl iodide (m. p. 24°) was obtained.

Summary

Monochloro-amine reacts with Grignard reagents to form primary amines and ammonia. The yields of amines are greatest with organomagnesium chlorides, less with bromides and least with iodides.

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[8] Since the yield of ammonia was greatest in this reaction and chlorobenzene was isolated from the reaction products, the details are here given.

[9] Most of the reagents used are readily obtainable. The two described here are somewhat less common.

[10] Heidelberger, *J. Biol. Chem.*, 21, 466 (1915).

[11] Kumpf, *Ann.*, **224**, 126 (1884).