[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE REACTION OF GRIGNARD REAGENTS WITH OXIMES. II. THE ACTION OF ARYL GRIGNARD REAGENTS WITH MIXED KETOXIMES

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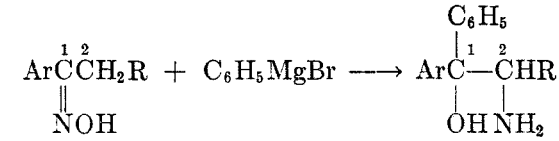
In an earlier paper from this Laboratory (1), it was shown that phenylmagnesium bromide reacts at elevated temperatures (no reaction takes place at ordinary temperatures) with mixed ketoximes to yield, not the hydroxylamines which would be formed by the addition of the Grignard reagent to the carbon-nitrogen double bond, but rather beta-amino alcohols. In this reaction a rearrangement of nitrogen from carbon atom 1 to carbon atom 2 has occurred.



In the earlier paper the reaction of phenylmagnesium bromide with the oximes of acetophenone, propiophenone, methyl *p*-tolyl ketone, and *p*-chloroacetophenone was described. It seemed of interest to extend this reaction to other mixed ketoximes, and especially to other aryl Grignard reagents; the results of this study are recorded in the present paper.

When acetophenone oxime was treated with *p*-tolylmagnesium bromide, α-naphthylmagnesium bromide, and *p*-anisylmagnesium bromide by the technique used previously, the corresponding amino alcohols were obtained. Amino alcohols were also obtained from propiophenone oxime and *p*-tolylmagnesium bromide, from *p*-phenylacetophenone oxime and phenylmagnesium bromide, and from butyrophenone oxime and phenylmagnesium bromide; the structures of these amino alcohols were established by comparison with authentic samples made by different methods; the data are recorded in Table I. Several attempts were made to prepare 1-phenyl-1-*p*-anisyl-2-aminoethanol from phenylmagnesium bromide and the oxime of *p*-methoxyacetophenone, but only tars were obtained.

In the case of the 1-phenyl-1-*p*-tolyl-2-amino propanol (from *p*-tolylmagnesium bromide and propiophenone oxime) two diastereoisomers are possible; only one of these was obtained, and it corresponded to the isomer prepared by Tiffeneau (2), from isonitrosopropiophenone and *p*-tolylmagnesium bromide.

EXPERIMENTAL

Preparation of materials. Most of the chemicals were obtained from the Eastman Kodak Co. and were purified by distillation. *p*-Phenylacetophenone (3), and *p*-methoxyacetophenone (4), were made by the Friedel-Crafts reaction; *p*-bromotoluene was prepared from *p*-toluidine (5), and *p*-bromoanisole was made by the bromination of anisole (6).

The ketoximes were prepared as follows. To 0.5 mole of ketone in 300 cc. of 95% alcohol was added a solution of 56 g. of hydroxylamine hydrochloride in 80 cc. of water; 157 g. of 50% aqueous potassium hydroxide solution was then added, and the mixture was refluxed for two hours. The cooled solution was poured into several volumes of ice and water, and then acidified with hydrochloric acid. The precipitated oxime was washed well with water, and was then dried *in vacuo* over calcium chloride and then over phosphorus pentoxide. The yields varied from 80–90%; the oximes had the following melting points; acetophenone, 59°; propiophenone, 53–55°; *p*-phenylacetophenone, 184–186°; butyrophenone, 50°.

Reaction of aryl Grignard reagents with ketoximes. Since these reactions were all carried out in the same general way, only a typical run will be described in detail.

The Grignard reagent was prepared from 6 g. of magnesium turnings, 125 cc. of dry ether, and a slight excess of aryl halide.[1] When all the magnesium had dissolved, ether was distilled off by heating the reaction flask in an oil-bath. When the bath temperature reached 150–155° the characteristic color change described previously (1), occurred, and the distillation was stopped. Usually about 60 cc. of ether was recovered in the distillation. Thirty cubic centimeters of dry toluene was added to the concentrated Grignard reagent, and a solution of 0.05 mole of oxime in about 30 cc. of dry toluene was added dropwise while the oil-bath temperature was kept at 150°. Usually a vigorous reaction occurred, and the addition required 30–40 minutes. When all the oxime solution had been added, the mixture was heated and stirred for 15–30 minutes more, and was then allowed to cool. It was hydrolyzed by pouring onto ice and hydrochloric acid. Usually the acid mixture was extracted three times with ether to remove non-basic impurities, and these extracts were discarded. Sometimes, especially with the naphthyl and diphenylamino alcohols, the sparingly soluble hydrochloride separated at the ether-water interface, and was removed by filtration. The acid aqueous layer was then made strongly basic with ammonium hydroxide, and was again extracted three times with ether. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed. The solid residue was purified by recrystallization from alcohol or an alcohol-water mixture. The yields of amino alcohols so obtained varied from 40–75%.

The amino alcohols were converted to their hydrochlorides by adding a solution of dry hydrogen chloride in anhydrous ether to a solution of the amino alcohol in anhydrous ether, care being taken to avoid an excess of hydrogen chloride. The solid so formed was recrystallized from absolute alcohol and ether.

The amino alcohol benzamides were made from 1-g. quantities of the amino alcohols by the Schotten-Baumann procedure.

Comparisons of the amino alcohols and their derivatives with authentic samples are shown in Table I.

Synthesis of amino alcohols for comparison. 1-Phenyl-1-*p*-tolyl-2-aminoethanol (8), 1-phenyl-1-α-naphthyl-2-aminoethanol (9), and 1-phenyl-1-*p*-anisyl-2-aminoethanol (10) were prepared by the action of the appropriate Grignard reagent on phenacylamine hydrochloride (11). 1-Phenyl-1-*p*-tolyl-2-aminopropanol was made from *p*-tolylmagnesium bromide and alpha-aminopropiophenone hydrochloride (2). The amino alcohol so obtained melted higher (m.p. 74–75°) than the product reported by Tiffeneau (2), (m.p. 69–70°).

1-Phenyl-1-*p*-biphenyl-2-aminoethanol, which has not been reported before, was prepared as follows: α-Bromo-*p*-phenylacetophenone, prepared by the method of Drake and Bronitsky (3), was converted to alpha-amino-*p*-phenylacetophenone hydrochloride in the following way. A solution of 52 g. of the bromo ketone in 200 cc. of chloroform was treated with a solution of 33.3 g. of hexamethylenetetramine in 150 cc. of hot chloroform. The reaction mixture was allowed to stand for 24 hours, and the solid product was then collected. It was suspended in a mixture of 55 cc. of concentrated hydrochloric acid and 450 cc. of

[1] For the preparation of α-naphthylmagnesium bromide the procedure of Gilman and co-workers (7) was used.

95% alcohol, and this mixture was allowed to stand for several days. The precipitated solid was collected and recrystallized from hot water acidulated with hydrochloric acid. The amino ketone so obtained charred on heating, but showed no definite melting point. Nine and one-half grams of this amino ketone hydrochloride was added gradually to a solution of phenylmagnesium bromide prepared from 5 g. of magnesium, 33 g. of bromobenzene and 94 cc. of dry ether. After addition was complete, the reaction mixture was refluxed for four hours and then was hydrolyzed with ice and ammonium chloride, and extracted with ether. The solid remaining on evaporation of the ether was recrystallized from an alcohol-water mixture.

TABLE I

COMPARISON OF AMINO ALCOHOLS FROM OXIMES WITH AUTHENTIC SAMPLES

AMINO ALCOHOL	SOURCE	M.P. °C FREE BASE	M.P. °C HYDRO-CHLORIDE	M.P. °C BENZAMIDE
1-Phenyl-1-*p*-tolyl-2-aminoethanol	Acetophenone oxime and C_7H_7MgBr	103–104	183–184	142–143
	Phenacylamine and C_7H_7MgBr	104–105	183–184	142–143
	Mixture	104	183–184	142–143
1-Phenyl-1-naphthyl-2-aminoethanol	Acetophenone oxime and $C_{10}H_7MgBr$	159–160	232–234	193–194
	Phenacylamine and $C_{10}H_7MgBr$	158	236–238	192–193
	Mixture	159	236–237	193
1-Phenyl-1-*p*-anisyl-2-aminoethanol	Acetophenone oxime and $MeOC_6H_4MgBr$	132.5–133	162–163	
	Phenacylamine and $MeOC_6H_4MgBr$	134	164–165	
	Mixture	133–134	163–164	
1-Phenyl-1-biphenyl-2-aminoethanol	*p*-Phenylacetophenone oxime and C_6H_5MgBr	86–88	220–222	193–195
	Amino-*p*-phenylacetophenone and C_6H_5MgBr	85–87	222–224	192–194
	Mixture	86–88	220–223	192–194
1-Phenyl-1-*p*-tolyl-2-aminopropanol	Propiophenone oxime and C_7H_7MgBr	72–73	237–238	195–196
	Aminopropiophenone and C_7H_7MgBr	74–75	239	195–195.5
	Mixture	73–74	239	195
1,1-Diphenyl-2-aminobutanol	Butyrophenone oxime and C_6H_5MgBr	77–78	259	209–211
	Aminobutyric ester and C_6H_5MgBr	76.5–77	258	208–210
	Mixture	77–78	258	208–210

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.05; H, 6.62; N, 4.84.
Found: C, 83.12; H, 6.74; N, 4.69.

The benzamide of the amino alcohol was prepared; it was obtained as a white crystalline powder after recrystallization; it melted at 193–195°.

Anal. Calc'd for $C_{27}H_{23}NO_2$: N, 3.57. Found: N, 3.32.

1,1-Diphenyl-2-aminobutanol was prepared from ethyl α-aminobutyrate and phenylmagnesium bromide. Alpha-aminobutyric acid was obtained in 63% yield from alpha-bromobutyric acid (12), and was converted to the ester hydrochloride in the usual way.

Thirty-three grams of the ester hydrochloride (m.p. 141°) was added during the course of one hour to 1.25 moles of phenylmagnesium bromide, and the mixture was refluxed for one hour. It was hydrolyzed with ice, the basic solution was extracted several times with ether, and the extracts were dried over anhydrous magnesium sulfate. The solid obtained on evaporation of the ether was recrystallized from an alcohol-water mixture. The yield of recrystallized material was 33 g. or 62%.

Anal. Calc'd for $C_{16}H_{19}NO$: C, 79.65; H, 7.89; N, 5.81.
Found: C, 79.50; H, 8.05; N, 5.88.

The benzamide, prepared in the usual way, melted at 209–210° after recrystallization from alcohol.

Anal. Calc'd for $C_{24}H_{23}NO_2$: N, 3.92. Found: N, 3.89.

SUMMARY

Several aryl Grignard reagents have been shown to react with the oximes of aryl alkyl ketones to yield β-amino alcohols. Two new amino alcohols, 1-phenyl-1-*p*-biphenyl-2-aminoethanol, and 1,1-diphenyl-2-aminobutanol have been described.

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