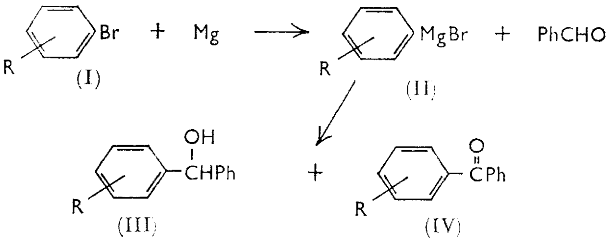
Formation of Grignard Reagents from 3-Bromo-*NN*-dimethylbenzylamine and 4-Bromo-*NN*-diethylbenzylamine and their Reactions with Benzaldehyde

By James H. Short

3-Bromo-*NN*-dimethylbenzylamine and 4-bromo-*NN*-diethylbenzylamine failed to react with magnesium in ether in accordance with reports in the literature for similar compounds, but the Grignard reagents were easily obtained using tetrahydrofuran as the solvent. Reaction with benzaldehyde produced the expected alcohols; and, unexpectedly, the corresponding ketones were also obtained. By appropriate modification of the experimental procedure, either alcohol or ketone could be obtained exclusively.

Jones and Hauser[1] and Mehta and Strelitz[2] have investigated the reaction of bromobenzylamines (I) with magnesium in ether and found that the *ortho* isomers formed Grignard reagents while the *meta* and *para* isomers failed to react with magnesium.



a; R = $3\text{-}Me_2NCH_2$; b; R = $4\text{-}Et_2NCH_2$

Some years ago attempts were made in these laboratories to obtain the Grignard reagent from 2-diethylaminoethyl 4-bromophenyl ether[3] (I; R = $4\text{-}Et_2NCH_2CH_2O$). The latter could not be induced to react with magnesium in ether, but when tetrahydrofuran was used as the reaction medium, the Grignard reagent formed smoothly in high yield.

The use of tetrahydrofuran, in place of ether, therefore, seemed indicated as a possible method for obtaining the Grignard reagents (IIa and IIb) of the type which Jones and Hauser[1] and Mehta and Strelitz[2] failed to obtain.

For this purpose, 3-bromo-*NN*-dimethylbenzylamine (Ia) and 4-bromo-*NN*-diethylbenzylamine (Ib) were prepared from the corresponding bromobenzyl bromides and appropriate amines. In tetrahydrofuran both were smoothly converted to the corresponding Grignard reagents and the latter were caused to react with benzaldehyde.

The expected products were 3-dimethylaminomethylbenzhydrol (IIIa) and 4-diethylaminomethylbenzhydrol (IIIb). The infrared (i.r.) spectra of the products obtained confirmed the presence, in each case, of hydroxyl groups, but, surprisingly, significant carbonyl absorption

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[1] F. N. Jones and C. R. Hauser, *J. Org. Chem.*, 1962, **27**, 701.

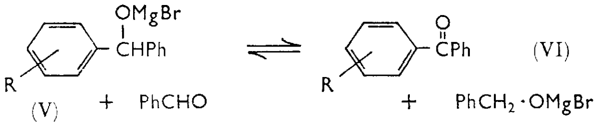
[2] N. B. Mehta and J. Z. Strelitz, *J. Org. Chem.*, 1962, **27**, 4412.

[3] J. H. Short, U. Biermacher, D. A. Dunnigan, G. F. Lambert, D. L. Martin, C. W. Nordeen, and H. B. Wright, *J. Med. Chem.*, 1965, **8**, 223.

was present in the spectra of the products of both reactions. That the carbonyl-bearing compounds were 3-dimethylaminomethylbenzophenone (IVa) and 4-diethylaminomethylbenzophenone (IVb) was confirmed by nuclear magnetic resonance (n.m.r.) spectroscopy. The methyl and methylene groups gave rise to twice the expected number of peaks. For example the methyl group of IVa was a doublet instead of a singlet, whilst the methyl group of IVb consisted of a sextet instead of the expected triplet. The methine and hydroxyl protons, on the other hand, gave rise to the expected singlets. The peaks due to the alcohols absorbed at 4—8 c./sec. upfield in relation to the corresponding ketone peaks. The integration curves could be used to approximate the relative percentages of the two components, and it was found, in various runs, that the alcohol–ketone ratio varied from 1 : 2 to 3 : 1.

The formation of ketones by this procedure seemed surprising, but is not without precedent. Marshall[4] found that when phenylmagnesium bromide is treated with two equivalents of benzaldehyde, the main products are benzophenone and benzyl alcohol. He also obtained about a 60% yield of acetophenone from the same Grignard reagent and acetaldehyde. A similar reaction was observed by Meisenheimer[5] who identified propiophenone, obtained when ethylmagnesium bromide was treated with an excess of benzaldehyde. Shankland and Gomberg,[6] and Palfray, Metayer, and Panouse,[7] have also commented on this reaction.

The reactions were repeated, but using two equivalents of benzaldehyde. In both cases the products isolated were the ketones (IVa and IVb), as determined by their n.m.r. and i.r. spectra. The alcohols (IIIa and IIIb) were obtained exclusively when the temperature was maintained at 0° during the addition of the benzaldehyde and the subsequent hydrolysis with ammonium chloride solution; absence of the corresponding ketones was evident from the n.m.r. and i.r. spectra of the products. The results obtained from the n.m.r. spectra of the four compounds are given in the Table. Clearly this type of reaction is a variation of the Oppenauer oxidation procedure,[8] and may be represented as shown.



(V) (VI)

N.m.r. results [a]

	CH_3	CH_2	CH_2	OH	CH
(IIIa)	126	—	201	294	344
(IIIb)	52	138 [c]	212	201	345
	60	145			
	67	152			
		160			
(IVa)	134	—	209	—	—
(IVb)	56 [b]	144 [c]	220	—	—
	63	151			
	70	158			
		165			

[a] All spectra were determined with a Varian Associates A-60 spectrometer in $CDCl_3$ solution. Proton signals are expressed in c./sec. downfield from internal tetramethylsilane. [b] Triplet. [c] Quartet.

In the typical Oppenauer oxidation the equivalent of compound (V) is formed from the alcohol to be oxidised and aluminium isopropoxide or aluminium *t*-butoxide, and the hydrogen acceptor (oxidising agent) is usually a ketone such as acetone or cyclohexanone. An equilibrium is reached, and the reaction is forced in the desired direction by use of a large excess of the oxidising agent, or by removal of the product. In the two cases described here, only ketone is isolated, even though both compound (V) and benzaldehyde are present in approximately the same concentration, and the product is not removed. The fact that only compound (IV), and no (III), is present after hydrolysis must be due to the much greater oxidising power of benzaldehyde compared to that of compound (IV).

EXPERIMENTAL

3-*Bromo*-NN-*dimethylbenzylamine* (Ia).—The reaction between dimethylamine and *m*-bromobenzyl bromide was carried out in the manner described by Eliel, Ferdinand, and Herrmann.[9] The amine, a colourless oil, distilled at 101—102°/5 mm., 126—127°/28 mm., and had n_D^{25} 1·5408. The yield was 80%. Beard, Van Eanam, and Hauser[10] observed b. p. 105—108°/9·8 mm. and n_D^{25} 1·5388.

4-*Bromo*-NN-*diethylbenzylamine* (Ib).—The reaction between diethylamine and *p*-bromobenzyl bromide was effected in the manner described above. The yield of *amine*, a colourless oil, was 85%, and it had b. p. 124—125°/8 mm., 151—153°/27 mm., n_D^{25} 1·5318 (Found: C, 54·75; H, 6·4; N, 5·9. $C_{11}H_{16}BrN$ requires C, 54·55; H, 6·65; N, 5·8%).

3-*Dimethylaminomethylbenzhydrol* (IIIa).—A 500 ml. three-neck flask was fitted with a reflux condenser, stirrer and dropping funnel. The condenser and dropping funnel were protected by calcium chloride tubes. No other special precautions were taken. In the flask were placed 1·2 g. (0·05 mole) of magnesium turnings, 10·7 g. (0·05 mole) of 3-bromo-*NN*-dimethylbenzylamine, and 50 ml. of dry tetrahydrofuran. The reaction mixture was stirred and heated under reflux until the reaction started, when the source of heat was removed until the exothermic reaction ceased. Heating was then continued under reflux for 1 hr., when nearly all the magnesium had been consumed. Addition of 50 ml. of dry tetrahydrofuran was necessary to keep the Grignard reagent in solution when it was cooled to 0° in an ice–salt bath. A solution of 5·3 g. (0·05 mole) of benzaldehyde in 50 ml. of dry tetrahydrofuran was added

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[4] J. Marshall, *J. Chem. Soc.*, 1914, **105**, 527; *ibid.*, 1915, **107**, 509.

[5] J. Meisenheimer, *Annalen*, 1926, **446**, 76.

[6] R. V. Shankland and M. Gomberg, *J. Amer. Chem. Soc.*, 1930, **52**, 4973.

[7] L. Palfray, M. Metayer, and J. Panouse, *Bull. Soc. chim. France*, 1947, 766.

[8] The Oppenauer method of oxidation has been reviewed by T. Bersin in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, 1948, p. 125; and by C. Djerassi in R. Adams, *Organic Reactions*, vol. VI, John Wiley and Sons, Inc., New York, 1951, p. 207.

[9] E. L. Eliel, T. N. Ferdinand, and M. C. Herrmann, *J. Org. Chem.*, 1954, **19**, 1693.

[10] W. Q. Beard, jun., D. N. Van Eanam, and C. R. Hauser, *J. Org. Chem.*, 1961, **26**, 2315.

from the dropping funnel during 2 hr. with the temperature maintained below 0°. Hydrolysis was effected by the dropwise addition of 100 ml. of 20% ammonium chloride solution. The two layers were separated, and the aqueous layer was extracted with 50 ml. of tetrahydrofuran. The organic layer was extracted twice with 50 ml. of 10% sodium carbonate solution, and dried over Drierite. Distillation gave, after removal of low-boiling forerun, 7·0 g. (58%) of light yellow, viscous oil, b. p. 138—139°/0·3 mm., n_D^{25} 1·5738. The product afforded a white solid on standing, and, after recrystallisation from aqueous ethanol, gave the *carbinol*, which melted at 74—76° (Found: C, 79·8; H, 8·25; N, 6·05; O, 6·85. $C_{16}H_{19}NO$ requires C, 79·65; H, 7·95; N, 5·8; O, 6·65%). It has an absorption peak in the infrared region at 3585 cm.$^{-1}$, but none in the 1650 cm.$^{-1}$ region.

4-*Diethylaminomethylbenzhydrol* (IIIb).—The Grignard reagent was prepared, as described above, from 12·1 g. (0·05 mole) of 4-bromo-*NN*-diethylbenzylamine and 1·2 g. (0·05 mole) of magnesium turnings; caused to react with 5·3 g. (0·05 mole) of benzaldehyde, and hydrolysed. The yield of *carbinol*, a light yellow viscous oil, b. p. 154—156°/0·1 mm., n_D^{25} 1·5612, was 6·6 g. (49%) (Found: C, 80·0; H, 8·6; N, 5·4; O, 6·4. $C_{18}H_{23}NO$ requires C, 80·25; H, 8·6; N, 5·2; O, 5·95%). The product has an absorption peak in the infrared region at 3590 cm.$^{-1}$, but none in the 1650 cm.$^{-1}$ region.

3-*Dimethylaminomethylbenzophenone* (IVa).—The Grignard reagent was prepared in the usual manner from 10·7 g. (0·05 mole) of 3-bromo-*NN*-dimethylbenzylamine and 1·2 g. (0·05 mole) of magnesium turnings in 50 ml. of dry tetrahydrofuran. A solution of 10·6 g. (0·1 mole) of benzaldehyde* in 50 ml. of dry tetrahydrofuran was added dropwise, and the resulting solution was heated under reflux for 2 hr. Hydrolysis was effected with 100 ml. of 20% ammonium chloride solution. The aqueous layer was extracted with 50 ml. of tetrahydrofuran, and the organic layer was then extracted twice with 50 ml. portions of 2N-hydrochloric acid. The aqueous layer was chilled, and made alkaline with 50% sodium hydroxide solution. The free base was taken up in ether, dried over Drierite, and distilled. Low-boiling forerun was removed and the *ketone* distilled at 136—137°/0·3 mm., 126—127°/0·15 mm., n_D^{25} 1·5790. The light yellow oil weighed 7·0 g. (59%) (Found: C, 80·3; H, 7·3; N, 5·75; O, 6·8. $C_{16}H_{17}NO$ requires C, 80·3; H, 7·15; N, 5·85; O, 6·7%). It has an absorption peak in the infrared region at 1645 cm.$^{-1}$, but none in the 3600 cm.$^{-1}$ region.

4-*Diethylaminomethylbenzophenone* (IVb).—The Grignard reagent was formed in the usual manner from 12·1 g. (0·05 mole) of 4-bromo-*NN*-diethylbenzylamine and 1·2 g. (0·05 mole) of magnesium turnings. The Grignard reagent was treated with 10·6 g. (0·1 mole) of benzaldehyde,* and the mixture was worked up in the manner described above for 3-dimethylaminomethylbenzophenone. The yield of *ketone*, a light yellow oil, b. p. 143—144°/0·15 mm., n_D^{25} 1·5696, was 8·9 g. (66%) (Found: C, 81·1; H, 8·05; N, 5·35; O, 6·0. $C_{18}H_{21}NO$ requires C, 80·85; H, 7·9; N, 5·25; O, 6·0%). It has an absorption peak in the infrared region at 1660 cm.$^{-1}$, but none in the 3600 cm.$^{-1}$ region.

The course of the reaction in the absence of oxygen was determined by a run under nitrogen; the same product was obtained, in about the same yield.

The microanalyses were provided by Mr. Orville Kolsto, the infrared spectra by Mr. William Washburn, and the n.m.r. spectra by Dr. Richard Mattoon.

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[5/906 *Received, August* 20*th*, 1965]

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* The early experiments, in which mixtures of ketones and alcohols were obtained, were carried out as described here, but using only one equivalent of benzaldehyde.