[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

The Grignard Reaction in the Synthesis of Ketones. I. A New Method of Preparing Desoxybenzoins

BY SANFORD S. JENKINS

In order to facilitate certain studies, some of which have been published,[1a,b] dealing with desoxybenzoins a general method of synthesizing this interesting class of ketones was sought.

The object of this report is to describe a method that is more generally applicable than the usual ones and which appears to be entirely reliable in its indication of structure. Briefly, the method, which is an adaptation with certain improvements of that of Béis[2] for preparing aliphatic ketones, consists in condensing primary benzamides with benzylmagnesium halides. In order to obtain the maximum yields, however, there are two conditions to be observed: three to four equivalents of the halide to one of the amide must be used and long heating of the reactants is necessary.

In this manner benzyl phenyl, benzyl *m*-chlorophenyl, benzyl *p*-methoxyphenyl, *o*-chlorobenzyl *p*-methoxyphenyl and *p*-chlorobenzyl *p*-methoxyphenyl ketones were obtained in satisfactory yields.

Although rearrangements are known to take place when benzylmagnesium halides are condensed with certain substances,[3] no evidence of any abnormal product was obtained in this work. Where possible the products were compared directly with the desoxy ketones obtained in the reduction of the corresponding benzoins but since most of the latter compounds were either not available or have not been described, this procedure was supplemented by the Beckmann rearrangement of the ketoximes.[4] The structures of the resulting anilides were then established by comparison with authentic samples. When prepared according to the directions given below the oximes are all of the *anti*-benzyl type.

Experimental

Preparation of Ketones

Apparatus and Method.—A 500-cc. three-necked, round-bottomed flask is fitted with a mechanical stirring apparatus, a dropping funnel, and a condenser to which is attached a drying tube. A very satisfactory heater may be made by inserting an electric bulb in the apex of an inverted cone of asbestos paper the base of which is placed under the flask. When mounted on a single ringstand the apparatus is compact and convenient.

After placing the required amount of thin, bright magnesium turnings and a small crystal of iodine in the flask and connecting the various parts, the apparatus is swept out with dry hydrogen. A solution of the benzyl halide in 100 to 125 cc. of ether is

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[1] (a) Jenkins, THIS JOURNAL, **53**, 3115 (1931); (b) *ibid.*, **54**, 1155 (1932).

[2] Béis, *Compt. rend.*, **137**, 575 (1903).

[3] Austin and Johnson, THIS JOURNAL, **54**, 647 (1932).

[4] Günther, *Ann.*, **252**, 68 (1889).

TABLE I

PREPARATIONAL DATA AND CONSTANTS OF KETONES WITH MOLECULAR WEIGHTS AND ANALYSES

Amide	Grignard reagent	Letter	Ketone	Yield, %	M. P., °C. (corr.)	Mol. wt. (Rast) Calcd.	Mol. wt. (Rast) Found	Formula	Chlorine, % (Parr bomb) Calcd.	Chlorine, % (Parr bomb) Found
$C_6H_5CONH_2$	$C_6H_5CH_2MgCl$	A	$C_6H_5COCH_2C_6H_5$	77	57	...	...	......	...	...
m-$ClC_6H_4CONH_2$	$C_6H_5CH_2MgCl$	B	*m*-$ClC_6H_4COCH_2C_6H_5$	72	62	230.5	226	$C_{14}H_{11}ClO$	15.37	15.58
p-$CH_3OC_6H_4CONH_2$	$C_6H_5CH_2MgCl$	C	*p*-$CH_3OC_6H_4COCH_2C_6H_5$	74	77	226	228	......	...	...
p-$CH_3OC_6H_4CONH_2$	*o*-$ClC_4H_5CH_2MgBr$	D[5]	*p*-$CH_3OC_6H_4COCH_2C_6H_4Cl$-*o*	55	97.5	260.5	247	$C_{15}H_{13}ClO_2$	13.60	13.72
p-$CH_3OC_6H_4CONH_2$	*p*-$ClC_6H_4CH_2MgBr$	E	*p*-$CH_3OC_6H_4COCH_2C_6H_4Cl$-*p*	66	137.5	260.5	266	$C_{15}H_{13}ClO_2$	13.60	13.81

The reactants were employed in the ratio of 0.050 mole of amide to 0.20 mole of Grignard reagent and were heated for forty to forty-eight hours. Ketones A, B, and C were obtained as white plates, D as white cubes and E as white diamond-shaped plates.

The yields are based on the amides and represent material that was crystallized once from alcohol. Ketone B is soluble in ether and benzene, fairly soluble in 80% alcohol and may be conveniently crystallized from ligroin (Skelly Solve "C"). E is sparingly soluble in ether and alcohol and is best purified by crystallization from benzene-petroleum ether solution.

The amides were obtained in the usual manner from the corresponding acids. "Baker's C. P. Analysed" benzyl chloride and Eastman best grade of *o*- and *p*-chlorobenzyl bromides were used in this work.

Ketone A was found to be authentic by comparison with desoxybenzoin obtained in the reduction of benzoin. Ketone C proved to be identical with one of the reduction products of benzanisoin.[1b]

The molecular weights were obtained by means of the Rast method using borneol instead of camphor.

TABLE II

YIELDS, CONSTANTS AND ANALYTICAL DATA OF OXIMES AND ANILIDES

From ketone	Phenyl ketoxime, *Anti*	Yield, %	M. p., °C (corr.)	Formula	Chlorine, % (Parr bomb) Calcd.	Chlorine, % (Parr bomb) Found	Anilide	Yield, %	M. p., °C. (corr.)	Formula	Chlorine, % (Parr bomb) Calcd.	Chlorine, % (Parr bomb) Found
A	Benzyl-	90	98				Phenylacet-	60	117.5			
B	Benzyl-*m*-chloro-	92	120	$C_{14}H_{12}NClO$	14.47	14.41	Phenylacet-*m*-chloro-	65	95	$C_{14}H_{12}NClO$	14.47	14.57
C	Benzyl-*p*-methoxy-	95	118.5				Phenylacet-*p*-methoxy-	60	124			
D[5]	*o*-Chlorobenzyl-*p*-methoxy	93	99	$C_{15}H_{14}NClO_2$	12.86	12.93	*o*-Chlorophenylacet-*p*-methoxy[5]	60	166	$C_{15}H_{14}NClO_2$	12.86	12.92
E	*p*-Chlorobenzyl-*p*-methoxy	88	138.5	$C_{15}H_{14}NClO_2$	12.86	12.91	*p*-Chlorophenylacet-*p*-methoxy-	60	184	$C_{15}H_{14}NClO_2$	12.86	13.07

The oximes were all obtained as white needles. Anilides A and C crystallized as white plates, B and D as white needles while E consisted of white leaflets.

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(5) Buck and Ide, THIS JOURNAL, **53**, 1536 (1931).

placed in the dropping funnel and a small portion (10–15 cc.) added to the magnesium. The flask is now heated until the reaction is under way, after which the heat is cut off and the stirrer started. The solution is added at such a rate that gentle refluxing of the ether is maintained. After the addition the stirring is continued until the solution cools. The dropping funnel is now replaced by a cork and by means of a long-handled spatula the dry, finely-powdered amide is added in portions, the rate of addition being determined by the vigor of the reaction. The heat is now turned on and the solution allowed to reflux with occasional stirring for the required time.

The complexes were decomposed by pouring the solutions into 200 g. of a slush of ice and water containing 20 g. of sulfuric acid. After standing at room temperature for an hour the ether was separated. The water layer was heated on the hot-plate for half an hour, cooled and extracted with ether. In this way an additional portion of ketone was obtained. The ether extracts were then combined and steam distilled. On cooling the yellow residue solidified and was crystallized from alcohol.

Ketones C, D and E, not being very soluble in ether, usually separated in part when the complexes were hydrolyzed.

Preparation of Oximes.—The oximes were prepared by mixing 2.00 g. each of ketone and hydroxylamine hydrochloride, 3.20 g. of potassium acetate and 40 cc. of alcohol. After standing overnight at room temperature the mixture was heated on the water-bath under reflux for three hours. Hot water was then added until a clear solution was obtained and a faint opalescence appeared. The solution was then set aside in a cool place and after several hours the crystals were filtered. Further crops were obtained by adding cold water to the filtrates.

The oximes of ketones C and E were also prepared by using 20 cc. of pyridine instead of the alcohol and potassium acetate, with identical results.

Preparation of Anilides

1. By Rearrangement of the Oximes.—To 1.00 g. of oxime dissolved in 30 cc. of absolute ether about 1.50 g. of powdered phosphorus pentachloride was added portionwise. The solution was shaken and kept cold during the addition. After standing at room temperature for half an hour the mixture was poured into 100 cc. of cold water and the ether driven off by means of a stream of air. The crude anilide was then separated and washed with water.

2. By Synthesis from the Acids or Acid Chlorides and the Corresponding Anilines.—(a) Anilides A, B and C were prepared in the Schotten–Baumann manner by mixing phenylacetyl chloride and the corresponding anilines.

(b) Anilides D and E were obtained from *o*- and *p*-chlorophenylacetic acids[6] and *p*-anisidine by heating the mixture in an oil-bath at 180–200° for two hours.

The anilides as obtained by either method (1 or 2) were recrystallized from dilute alcohol until pure. Their identity was established by their mixed melting points and crystalline structures.

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Summary

A new method of synthesizing desoxybenzoins which appears to be of wide application has been described.

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[6] Mehner, *J. prakt. Chem.*, **62**, 554 (1900).

From the appropriate primary benzamides and benzylmagnesium halides benzyl phenyl, benzyl *m*-chlorophenyl, benzyl *p*-methoxyphenyl, *o*-chlorobenzyl *p*-methoxyphenyl and *p*-chlorobenzyl *p*-methoxyphenyl ketones have been obtained in satisfactory yields.

No evidence of rearrangements has been obtained in this type of Grignard reaction.

Six new compounds were prepared and characterized.

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Stereochemistry of Diphenyls. XXVII.[1] Comparison of the Racemization of 2,2′-Difluoro-6,6′-dicarboxydiphenyl and 2,2′-Dimethoxy-6,6′-dicarboxydiphenyl

BY W. M. STANLEY, EDWARD McMAHON[2] AND ROGER ADAMS

The methoxyl group has been shown in previous researches to have a smaller interference effect when substituted in the 2,2′,6,6′ positions than had at first been predicted. It was found impossible to resolve 2,2′-difluoro-6,6′-dimethoxy-3,3′-dicarboxydiphenyl[3] and the active 2-nitro-6-carboxy-2′-methoxydiphenyl was very readily racemized.[4] The relative interference value of the methoxyl was thus revised from 1.56, as at first estimated, to 1.45. The latter value would conform to all the facts thus far assembled in connection with various hydroxylated and methoxylated diphenyls; the interconversion of the *cis* to the *trans* isomers of di-(3-bromo-2,4,6-trimethylphenyl)2-5-dihydroxybenzoquinone[5] (interference on each side 0.135 Å.), the non-existence of two isomers in di-(2,4-dimethylphenyl)-2,5-dihydroxybenzoquinone[6] (interference on each side, −0.265 Å.) and in 2,2′6,6′-tetramethoxy-3,3′-dicarboxydiphenyl (interference on each side, 0.00 Å.).[7]

A more direct comparison of the methoxyl group and fluorine atom has now been made by the study of 2,2′-difluoro-6,6′-dicarboxydiphenyl (VI) and 2,2′-dimethoxy-6,6′-dicarboxydiphenyl. The two diastereoisomeric salts of each compound were isolated and from these the two active acids of each of the two diphenyls.

The active 2,2′-difluoro-6,6′-dicarboxydiphenyl was completely race-

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(1) For paper XXVI see Yuan and Adams, THIS JOURNAL, **54**, 4434 (1932).

(2) The experimental work on the fluorine derivatives was done by W. M. Stanley; that on the dimethoxy derivatives by Edward McMahon and was presented by him in a thesis for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

(3) Becker and Adams, THIS JOURNAL, **54**, 2973 (1932).

(4) Stoughton and Adams, *ibid.*, **54**, 4426 (1932).

(5) Shildneck and Adams, *ibid.*, **53**, 343, 5303 (1931).

(6) Unpublished results of G. C. Finger.

(7) Unpublished results of M. C. Cupery.