

that mechanism of the Wurtz-Fittig reaction which postulates the intermediate formation of organometallic compounds.

AMES, IOWA

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The Grignard Reaction in the Synthesis of Ketones. III. The Preparation and Characterization of a Series of Mono- and Dichlorodesoxybenzoin

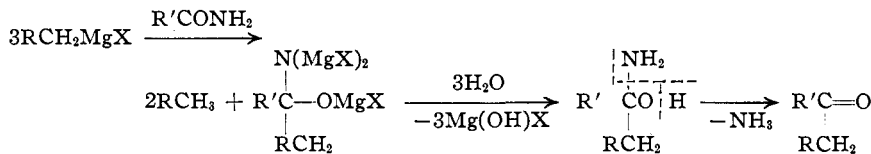
BY SANFORD S. JENKINS

In previous work,¹ which was contained in Article I of this series, the Grignard reaction was applied to the synthesis of a number of desoxybenzoin. The method, which consists in the reaction of primary benzamides with benzylmagnesium halides, was found to be entirely satisfactory when three to four equivalents of the Grignard reagent with one equivalent of the amide were heated for sufficiently long periods of time. In Article II² the preparation of a series of eight mono and di ortho and para chlorodesoxy ketones was set forth.

The purpose of the present article is to describe the synthesis of the remaining members (the meta chloro derivatives) of this series (see Table I).

In order to confirm further the assigned structures, the method previously adopted^{1,2} was employed in the present work. The compounds were oximated and, under the conditions of the experiments, all of the ketones produced single oximes, which, when rearranged in the Beckmann manner, gave anilides whose structures were established by comparison with anilides of known configuration. The oximes were all of the *anti* benzyl type.

Since the maximum yields of ketones were always obtained when at least three equivalents of the Grignard reagents to one equivalent of the amides were employed it appears that the reaction should be represented as

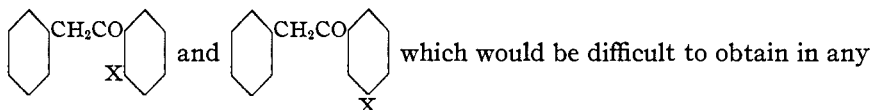


Before this explanation of the reaction can be definitely accepted, however, further confirmatory evidence must be obtained. This question is being studied at present and will be discussed in a future report.

The Grignard method of preparing ketones should be of value in work of structure dealing with compounds of the desoxy class and especially in the synthesis of the ortho and meta substituted phenyl types such as

(1) Jenkins, *THIS JOURNAL*, **55**, 703 (1933).

(2) Jenkins and Richardson, *ibid.*, **55**, 1618 (1933).



Experimental

Preparation of *m*-Chlorobenzyl Bromide.—This bromide was conveniently prepared by brominating *m*-chlorotoluene in carbon tetrachloride solution at 60–80°, employing a 500-watt tungsten lamp as the source of the light energy. The bromine in molecular proportion was dissolved in the same solvent and slowly added from a dropping funnel (one hour). After distilling off the solvent the impure halide was fractionated under reduced pressure employing a 60-cm. column; properties: colorless liquid, when freshly distilled, on standing it turns yellow. Like its isomers it is a powerful lachrymator. The substance when cooled strongly solidifies to a mass of long, white, flat needles which melt at 15–15.5° (corr.); b. p. 103–105° (8 mm.), d_{25}^{25} 1.5652. *Anal.* Calcd. for C₇H₆-ClBr: Br, 38.93. Found: Br, 39.24. Yield, based on reacted *m*-chlorotoluene, 55%.

Preparation of the Benzyl Phenyl Ketones.—These ketones were all prepared according to the method which was described in the preceding papers^{1,2} by refluxing the Grignard reagent made from 0.10 mole of the benzyl halides and 0.025 mole of the respective amides (Table I), in an atmosphere of hydrogen, for forty-eight hours.

TABLE I
YIELDS, CONSTANTS AND ANALYTICAL DATA OF THE KETONES

Grignard reagent	Amide	Letter	Ketone	Yield, %
<i>m</i> -ClC ₆ H ₄ CH ₂ MgBr	C ₆ H ₅ CONH ₂	A	<i>m</i> -ClC ₆ H ₄ CH ₂ COC ₆ H ₅	42
C ₆ H ₅ CH ₂ MgCl	<i>m</i> -ClC ₆ H ₄ CONH ₂	B ¹	C ₆ H ₅ CH ₂ COC ₆ H ₄ Cl- <i>m</i>	65
<i>m</i> -ClC ₆ H ₄ CH ₂ MgBr	<i>m</i> -ClC ₆ H ₄ CONH ₂	C	<i>m</i> -ClC ₆ H ₄ CH ₂ COC ₆ H ₄ Cl- <i>m</i>	79
<i>m</i> -ClC ₆ H ₄ CH ₂ MgBr	<i>o</i> -ClC ₆ H ₄ CONH ₂	D	<i>m</i> -ClC ₆ H ₄ CH ₂ COC ₆ H ₄ Cl- <i>o</i>	78
<i>m</i> -ClC ₆ H ₄ CH ₂ MgBr	<i>p</i> -ClC ₆ H ₄ CONH ₂	E	<i>m</i> -ClC ₆ H ₄ CH ₂ COC ₆ H ₄ Cl- <i>p</i>	60
<i>o</i> -ClC ₆ H ₄ CH ₂ MgBr	<i>m</i> -ClC ₆ H ₄ CONH ₂	F	<i>o</i> -ClC ₆ H ₄ CH ₂ COC ₆ H ₄ Cl- <i>m</i>	61
<i>p</i> -ClC ₆ H ₄ CH ₂ MgBr	<i>m</i> -ClC ₆ H ₄ CONH ₂	G	<i>p</i> -ClC ₆ H ₄ CH ₂ COC ₆ H ₄ Cl- <i>m</i>	85

Appearance	M. p., °C. (corr.)	Mol. wt.		Mol. Formula	Chlorine analyses, %	
		Calcd.	Found		Calcd.	Found
A Thin, brilliant, colorless plates	43	230.5	235	C ₁₄ H ₁₁ ClO	15.37	15.45
B White plates	62	230.5	238	C ₁₄ H ₁₁ ClO	15.37	15.58
C Short, white prisms	65	265	278	C ₁₄ H ₁₀ Cl ₂ O	26.76	26.90
D Faint yellow oil	B. p. 185–190/6 mm.	265	285	C ₁₄ H ₁₀ Cl ₂ O	26.76	26.98
E Thick, colorless prisms	75.5	265	272	C ₁₄ H ₁₀ Cl ₂ O	26.76	26.88
F Clusters, white spangles	71	265	279	C ₁₄ H ₁₀ Cl ₂ O	26.76	26.95
G Thin, colorless plates	74.5	265	269	C ₁₄ H ₁₀ Cl ₂ O	26.76	26.62

Ketone "B" was described in the first article¹ of this series. The molecular weights were determined by means of the Menzies-Wright method³ using benzene as the solvent. The Parr bomb method was employed throughout this work in the chlorine determinations. The melting points were taken with a thermometer which had been calibrated by the Bureau of Standards and they are correct to $\pm 0.5^\circ$. The ketones are fairly soluble in 95% alcohol and benzene, very soluble in ether and moderately soluble in ligroin (Skellysolve "C") and petroleum ether (b. p. 30–60°). They were purified by recrystallization from dilute alcohol. The yields tabulated are based on the amides employed and represent the substances after one crystallization.

(3) Menzies and Wright, THIS JOURNAL, 43, 2314 (1921).

TABLE II
CONSTANTS AND ANALYTICAL DATA OF THE OXIMES AND CORRESPONDING ANILIDES

Letter	Ketoximes	Appearance	M. p., °C. (corr.)		
A	<i>m</i> -Chlorobenzylphenyl-	Thick, white prisms	101-102		
B	Benzyl- <i>m</i> -chlorophenyl-	White needles	120		
C	<i>m</i> -Chlorobenzyl- <i>m</i> -chlorophenyl-	Long, white matted needles	103-104		
D	<i>m</i> -Chlorobenzyl- <i>o</i> -chlorophenyl-	Thick, white prisms	86-87		
E	<i>m</i> -Chlorobenzyl- <i>p</i> -chlorophenyl-	White needles	127-128		
F	<i>o</i> -Chlorobenzyl- <i>m</i> -chlorophenyl-	Short, white rhomboids	130.5-131.5		
G	<i>p</i> -Chlorobenzyl- <i>m</i> -chlorophenyl-	Long, glittering matted needles	100		
	Anilide	Appearance	M. p., °C. (corr.)		
A	<i>m</i> -Chlorophenylaceto-	Thin, white plates	130		
B	Phenylaceto- <i>m</i> -chloro-	White needles	95		
C	<i>m</i> -Chlorophenylaceto- <i>m</i> -chloro-	Long, white matted needles	120		
D	<i>m</i> -Chlorophenylaceto- <i>o</i> -chloro-	White needles	120		
E	<i>m</i> -Chlorophenylaceto- <i>p</i> -chloro-	Long, thin, colorless needles	150.5		
F	<i>o</i> -Chlorophenylaceto- <i>m</i> -chloro-	Long, white hair-like needles	154		
G	<i>p</i> -Chlorophenylaceto- <i>m</i> -chloro-	Thin, white glittering plates	137.5		
		Oximes	Anilides		
Mol. formula of oxime and anilide	Chlorine analyses, %		Chlorine analyses, %		
	Calcd.	Found	Calcd.	Found	
A	C ₁₄ H ₁₂ NCIO	14.46	14.32	14.46	14.70
B	C ₁₄ H ₁₂ NCIO	14.46	14.51	14.46	14.62
C	C ₁₄ H ₁₁ NCI ₂ O	25.30	25.53	25.30	25.48
D	C ₁₄ H ₁₁ NCI ₂ O	25.30	25.17	25.30	25.52
E	C ₁₄ H ₁₁ NCI ₂ O	25.30	25.12	25.30	25.38
F	C ₁₄ H ₁₁ NCI ₂ O	25.30	25.58	25.30	25.45
G	C ₁₄ H ₁₁ NCI ₂ O	25.30	25.40	25.30	25.18

The oximes, which were all of the *anti* benzyl type, were obtained in yields of 82 to 99% and when rearranged they formed the corresponding anilides in 64 to 80% yields.

Preparation of Oximes.—The oximes were prepared according to the method described in the preceding articles.^{1,2} The oxime from ketone D, however, could not be induced to crystallize in the usual manner. Accordingly, the following procedure was adopted. The solution was diluted with a large volume of water. After standing in a cool place for several days the oil settled out and the water was decanted. The oil was then washed several times with water and dried *in vacuo*. When crystals were seen to form a small amount of benzene was added—just enough to dissolve the oil without dissolving all of the crystals. Petroleum ether was then added until the solution became cloudy, after which the flask was corked and allowed to stand in a cool place until crystallization was complete.

Preparation of Anilides

1. **By Rearrangement of the Oximes.**—To 0.50 g. of the oxime dissolved in 15-20 cc. of anhydrous ether was added about a gram of powdered phosphorus pentachloride. The solution was shaken for ten minutes and poured into 100 cc. of cold water. The ether was evaporated by means of a stream of air after which the crude anilide was separated and recrystallized from dilute alcohol.

2. **By Synthesis from the Acid and Amine.**—The acid and amine (0.010 mole of each) were placed in a test-tube fitted with an air condenser and heated in an oil-bath for two hours at 180-190°. The anilide was then recrystallized from dilute alcohol.

The structures of the anilides as obtained by the rearrangement of the oximes (Method I) were established by mixed melting points with the authentic specimens.

Preparation of *m*-Chlorophenylacetic Acid.⁴ Grignard Reaction: This acid was readily obtained in yields of 65-75% by carbonating *m*-chlorobenzylmagnesium bromide. Prepared in the above manner it consists of thin colorless plates and melts at 77.5-78.5° (corr.). It is only very slightly soluble in water, soluble in all proportions in ether, quite soluble in alcohol and benzene and is best purified by recrystallization from commercial *n*-heptane (Skellysolve "C").

Anal. Calcd. for C₈H₇ClO₂: Cl, 20.79. Found: Cl, 20.64.

The *o*- and *p*-chlorophenylacetic acids employed in this work were prepared by the method of Mehner.⁵

Summary

The Grignard method of synthesizing desoxybenzoins, which was previously described, has been extended to include the preparation of *m*-chlorobenzyl phenyl, benzyl *m*-chlorophenyl, *m*-chlorobenzyl *m*-chlorophenyl, *m*-chlorobenzyl *o*-chlorophenyl, *m*-chlorobenzyl *p*-chlorophenyl, *o*-chlorobenzyl *m*-chlorophenyl and *p*-chlorobenzyl *m*-chlorophenyl ketones.

In no case was any evidence of an abnormal product obtained in these reactions. The oximes were rearranged by the Beckmann method and the structures of the resulting anilides were established. Under the conditions of the experiments all of the ketones produced single oximes which were of the *anti* benzyl type.

In the course of this work eighteen new compounds were prepared and characterized. Convenient methods of preparing *m*-chlorobenzyl bromide and *m*-chlorophenylacetic acid were described.

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(4) Cerecedo and Sherwin, *J. Biol. Chem.*, **58**, 215 (1923); Buck and Ide, *THIS JOURNAL*, **54**, 3309 (1932).

(5) Mehner, *J. prakt. Chem.*, **62**, 562 (1900).