The Grignard Reaction in the Synthesis of Ketones. IV. A New Method of Preparing Isomeric Unsymmetrical Benzoins

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In order to facilitate certain investigations[1] dealing with isomeric unsymmetrical benzoins, such as RCHOHCOR' and RCOCHOHR', a general method of synthesizing this interesting class of aromatic compounds was sought. The usual methods of preparation were found to be inadequate or at least unsatisfactory for this purpose. Thus the "Benzoin condensation," which may be shown as RCHO + R'CHO $\xrightarrow{[KCN]}$ RCHOHCOR', is restricted in its application because of the fact that many aromatic aldehydes do not undergo this condensation and furthermore where the reaction does take place usually only one isomer can be isolated. The Grignard method, in which mandelamides or cyanohydrins are treated with phenylmagnesium halides

R'CHOHCONH₂
    or $\xrightarrow{C_6H_5MgX}$ R'CH(OMgX)C(OMgX)-
R'CHOHC≡N

NHMgXC₆H₅ $\xrightarrow{H_2O}$ R'CHOHCOR, I
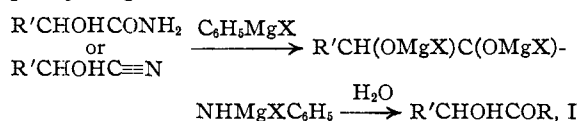
although very useful for purposes of identification, is tedious and generally does not give good yields.

The object of the present article is to describe a procedure which is easily carried out, gives excellent yields and appears to be of general application. The method is based on work which the author has already published[1a,2] at various times and depends on the fact that ketones of the type R'CH₂COR and RCH₂COR' (desoxybenzoins), in the presence of a source of light energy of sufficient intensity, can be converted readily into α-bromo derivatives such as R'CHBrCOR and RCHBr-COR' which in turn react with sodium alkoxides[3] to form the corresponding diacetals which themselves are easily hydrolyzed by cold, dilute mineral acids to the corresponding benzoins. The following scheme illustrates the course of these reactions.[3]

(1) Jenkins, THIS JOURNAL, (a) 55, 3048 (1933); (b) 53, 3115 (1931).

(2) Jenkins, ibid., (a) 55, 703, (b) 2896 (1933); (c) 54, 1155 (1932): Jenkins and Richardson, ibid., (d) 55, 1618, (e) 3874 (1933).

(3) Ward [J. Chem. Soc., 1541 (1929)] found that α-chlorobenzyl phenyl ketone reacts with sodium ethylate to form the corresponding diacetal, which readily undergoes hydrolysis in the presence of dilute hydrochloric acid and forms benzoin.
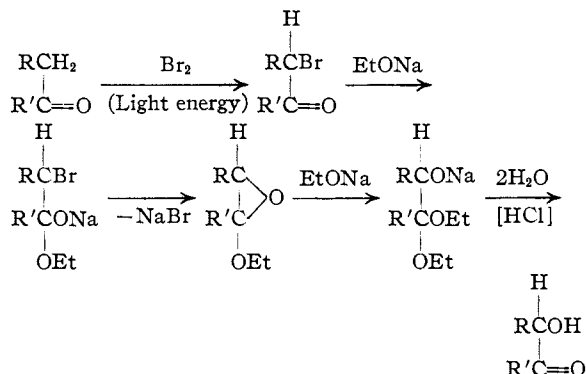
The benzylphenyl ketones (starting compounds) may be obtained by reducing unsymmetrical benzoins, where the latter are obtainable, with tin and hydrochloric acid, since it has been shown that this reaction[2c,e] usually produces both isomeric ketones. An application of the Grignard method,[2a,b,d] which has been described recently, is by far the most satisfactory, however, since it is very general in nature and usually gives excellent yields. The reactions may be shown as
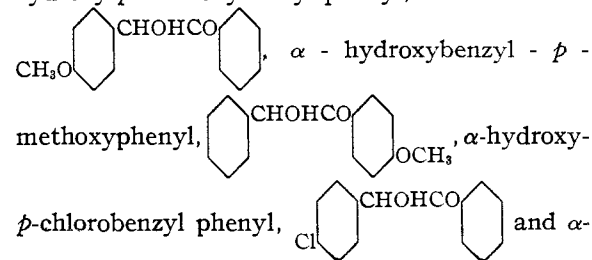
R'CONH₂ $\xrightarrow{3RCH_2MgX}$

R'C(OMgX)N(MgX)₂CH₂R $\xrightarrow{3H_2O}$ R'COCH₂R
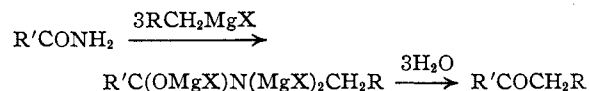
In a few cases where Grignard reagents of the type R'CH₂MgX cannot be prepared, one may employ an alternative method[2e] which can be shown as

R'CH₂CONH₂ $\xrightarrow{3RMgX}$

R'CH₂C(OMgX)N(MgX)₂R $\xrightarrow{3H_2O}$ R'CH₂COR
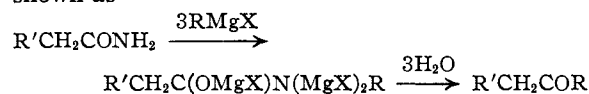
In general, however, phenylacetamides (latter reaction) do not give as good yields as do benzamides (former reaction).

Employing the procedure described above, the two pairs of isomeric unsymmetrical benzoins, α-hydroxy-p-methoxybenzyl phenyl,

, α - hydroxybenzyl - p - methoxyphenyl,

, α-hydroxy-p-chlorobenzyl phenyl,

and α-

hydroxybenzyl p-chlorophenyl, [structure: CHOHCO]
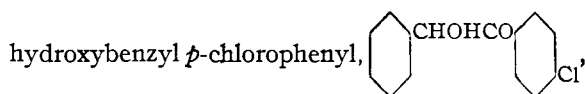
ketones have been synthesized in excellent yields. The p-chloro isomers, which have not heretofore been described, were shown to be authentic by comparison with specimens which were obtained by condensing the corresponding mandelamides and phenylmagnesium bromides according to reaction I illustrated above.

It is not necessary to isolate the desyl bromides, although they can be readily separated and purified, if desired. For analysis they are recrystallized and refluxed for a few minutes with alcoholic potassium hydroxide, the excess of which is titrated with a very dilute mineral acid of known strength employing methyl orange as the indicator (see experimental part).

Experimental Part

Preparation of p-Methoxybenzyl Phenyl Ketone

First Method.—This substance was obtained in a yield of 47% by reducing benzanisoin according to the method described in a previous paper.[2e]

Second Method.—The Grignard reagent from 15.70 g. of bromobenzene and 2.50 g. of magnesium turnings was prepared in the usual manner. To the ether solution of the phenylmagnesium bromide 4.13 g. of p-methoxyphenylacetamide[2e] was added and the mixture was then refluxed in an atmosphere of hydrogen for twenty hours. The solution was hydrolyzed with 10% ice cold sulfuric acid and worked up according to the technique[2a,d] which has been described previously. The ketone was obtained in a yield of 1.85 g. after one crystallization from alcohol which, based on the amide employed, was about 30%.

Preparation of Benzyl p-Methoxyphenyl Ketone

First Method.—This ketone was obtained in a yield of about 8% by reducing benzanisoin according to the method previously described.[2e]

Second Method.—This ketone was prepared in a much more satisfactory manner by means of the Grignard reaction, in which benzylmagnesium chloride (three equivalents) was condensed with p-methoxybenzamide (one equivalent) by means of the method and technique which have been described previously.[2a,b,d,e] Yields of 70–76% were obtained.

Preparation of the Isomeric p-Chlorodesoxybenzoins

Benzyl p-Chlorophenyl Ketone.—The Grignard reagent from 25.30 g. (0.20 mole) of benzyl chloride and 5.00 g. of magnesium turnings was prepared in the usual manner.[2d] To the ether solution 7.78 g. (0.050 mole) of p-chlorobenzamide was added, after which the mixture was refluxed for fifty-six hours in an atmosphere of hydrogen. After isolating the ketone in the usual manner[2a,b,d] it was recrystallized from ligroin (Skellysolve "C") and washed with petroleum ether (b. p. 30–60°) and was obtained in a yield of 77%.

p-Chlorobenzyl Phenyl Ketone.—This substance was obtained from p-chlorobenzylmagnesium bromide and benzamide by the method[2d] employed for its isomer in a yield of 70%.

Preparation of the α-Bromodesoxybenzoins.—The α-bromo derivatives were all obtained in the following manner. A solution of 0.010 mole of the desoxybenzoin in 20 to 40 cc. of warm carbon tetrachloride was prepared in a 150-cc. Pyrex flask. The flask was then exposed to the rays of a 500-watt tungsten lamp and 20 cc. of a solution containing 8.00 g. of bromine per 100 cc. of carbon tetrachloride was slowly added while the flask was shaken. Under these conditions the reaction was quite rapid, hydrogen bromide was liberated and the bromine color quickly disappeared. The major portion of the solvent was evaporated under reduced pressure and on cooling crystals began to form. Petroleum ether was added and on further cooling crystallization was soon complete. The solid was then separated and washed with a few cubic centimeters of cold petroleum ether. The yields were based on the product obtained at this stage (see Table I). Ordinarily the substance thus obtained was sufficiently pure for analysis. It may be further recrystallized from ligroin if desired. p-Methoxy-α-bromobenzyl phenyl ketone could not be further purified in a satisfactory manner since it appeared to decompose. The curious behavior of this substance is being studied further and will be discussed in a future report.

Analysis of the α-Bromo Derivatives.—The following method of analysis is convenient and gives good results. To a small amount (0.2000 to 0.3000 g.) of the substance is added an excess of a methyl alcoholic solution of potassium hydroxide. The solution is refluxed for about fifteen minutes in an all-glass apparatus. The excess of alkali is then determined by titration with 0.1000 normal hydrochloric acid employing methyl orange as the indicator.

Preparation of the Isomeric Benzoins

In the preparation of the benzoins it is not necessary to isolate the α-bromo intermediates. The following procedure gives excellent results. After bromination (as described above), the solvent is evaporated under reduced pressure and enough warm absolute alcohol is added to dissolve the substance. Three equivalents of sodium ethylate in absolute alcohol are then added and the solution is allowed to stand until the sodium bromide ceases to be precipitated, which is indicated by the disappearance of the cloudiness. The mixture is now poured into 100 cc. of cold 15% hydrochloric acid. On further cooling and stirring the product soon crystallizes, after which it is separated, washed and dried *in vacuo*. The yields are based on this dried product which, in every case, was found to melt within two or three degrees of the melting point of the pure substance.

As a check on the above method α-hydroxybenzyl p-chlorophenyl ketone was also prepared by condensing the Grignard reagent made from 38.30 g. (0.20 mole) of p-chlorobromobenzene and 5.00 g. of magnesium turnings with 5.04 g. (0.033 mole) of mandelamide. The mixture was refluxed in an atmosphere of hydrogen for fifty-five hours and decomposed by pouring into 200 cc. of 10% sulfuric acid that had been cooled in a freezing mixture.

The following method of separation gave the best results. The ether solution was added to the cold dilute acid, stirred up and quickly separated. The acid solution thus freed from the ether layer was warmed on the hot-plate at 40 to 50° for thirty minutes and cooled. The product crystallized and was filtered and washed with water. After drying *in vacuo* it weighed 3.50 g., which was 42% of the theoretical (based on the amide) and melted at 85–88° (uncorr.). Recrystallized from dilute alcohol it melted at 90–91° (corr.).

Although the maximum yields are not obtained by this method, the crude product is of better grade, since the impurities are largely retained in the ether layer. The procedure takes advantage of the fact that the intermediate substance from which the ketone is derived by loss of ammonia is an amine and is therefore soluble in the dilute acid.
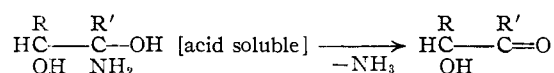
$$\begin{array}{ccc} \text{R} & \text{R}' & \text{R} \quad \text{R}' \\ \text{HC} \!\!\!-\!\!\!-\!\!\!\text{C}\!\!-\!\!\text{OH} \text{ [acid soluble]} \longrightarrow \text{HC}\!\!\!-\!\!\!-\!\!\!\text{C}\!\!=\!\!\text{O} \\ \text{OH} \quad \text{NH}_2 \qquad\qquad -\text{NH}_3 \quad \text{OH} \end{array}$$

TABLE I

YIELDS AND CONSTANTS OF KETONES, α-BROMO
DERIVATIVES AND BENZOINS

Letter	Ketone [Grignard method]	Appearance	Yield, %	M. p., °C. (corr.)	Mol. wt. (Rast) Calcd.	Found
A[4]	*p*-Methoxybenzyl phenyl	Plates	30	96.5	226	230
B[2α]	Benzyl *p*-methoxyphenyl	Plates	75	77	226	228
C[2d]	Benzyl *p*-chlorophenyl	Scales	77	107.5	230.5	231
D[2d]	*p*-Chlorobenzyl phenyl	Plates	70	138	230.5	233

	α-Bromobenzyl derivatives Appearance	Yield, %	M. p., °C. (corr.)	Mol. wt. (Rast) Calcd.	Found
A₁	Matted needles	84	93–94	305.02	300
B₁	Hair-like needles	80	72.5–73.5	305.02	298
C₁	Thick needles	78	67.5–68.5	309.45	305
D₁	Clusters of needles	79	62–62.5	309.45	302

	α-Hydroxybenzyl ketone Appearance	Yield, %	M. p., °C. (corr.)	Mol. wt. (Rast) Calcd.	Found
A₂	Long thin needles	74	90	242.11	240
B₂	Clusters of long, hair-like needles	94	106.5	242.11	240
C₂	Fine, cotton-like needles	94	90–91	246.54	248
D₂	Granules	93	116–117	246.54	243

(4) Tiffeneau and Orékhoff, *Bull. soc. chim.*, [1] **37**, 430 (1925).

p-Chloro-α-hydroxybenzyl phenyl ketone was obtained in a similar manner from phenylmagnesium bromide and *p*-chloromandelamide[5] in a yield of 25%.

The compounds are either white or cream colored.

TABLE II

ANALYTICAL DATA

α-Bromobenzylphenyl Ketones

	Formula	Bromine, % Calcd.	Found
A₁	$C_{15}H_{13}BrO_2$	26.20	26.24
B₁	$C_{15}H_{13}BrO_2$	26.20	26.46
C₁	$C_{14}H_{10}BrClO$	27.23	27.20
D₁	$C_{14}H_{10}BrClO$	27.23	27.41

Benzoins

	Formula	Chlorine (Parr bomb), % Calcd.	Found
A₂	$C_{15}H_{14}O_3$[6]		
B₂	$C_{15}H_{14}O_3$[7]		
C₂	$C_{14}H_{11}ClO_2$	14.38	14.26
D₂	$C_{14}H_{11}ClO_2$	14.38	14.30

Summary

A new method of synthesizing isomeric unsymmetrical benzoins, which is convenient and gives excellent yields, has been developed. The method is of general application since benzyl phenyl ketones, which can be obtained in several independent ways, are employed as the starting materials.

Two pairs of isomeric α-bromobenzyl phenyl ketones and the corresponding α-hydroxycarbonyl derivatives have been prepared and described. A convenient method of analyzing the desyl halides has been mentioned. It appears that five of the compounds have not been listed in the literature heretofore.

(5) Jenkins, THIS JOURNAL, **53**, 2341 (1931).

(6) McKenzie, Luis, Tiffeneau and Weill, *Bull. soc. chim.*, [1] **45**, 414 (1929).

(7) Ekecrantz and Ahlquist, *Ark. Kem. Min. Geol.*, **3**, No. 13, 1–26 (1908).