[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Reaction of Grignard Reagents with the Anils of Benzophenone and *o*-Methoxybenzophenone[1]

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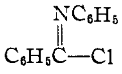
N-Phenylbenzimidyl chloride (I) has been found to react with *o*-methoxyphenylmagnesium bromide to give the anils (III and II) of *o*-methoxybenzophenone and *o*-(*o*-methoxyphenyl)-benzophenone. The same reagent was found to convert anil III to anil II by methoxyl group displacement. This displacement was realized also with *p*-methoxyphenylmagnesium bromide. With the phenyl reagent anil III suffered replacement of the methoxyl group by the phenyl radical. Benzylmagnesium chloride was found to react with anil VIII in the 1,2-manner. Evidence was obtained which indicated that the *t*-butyl reagent combined with anil VIII in the 1,6-manner.

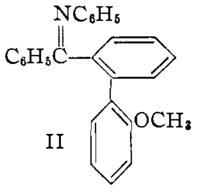
The classic discovery of Gilman, Kirby and Kinney,[3] that phenylmagnesium bromide combines in the conjugate manner with benzophenone anil suggested that methoxyl group replacement[4] might be possible in suitable methoxyl derivatives of this anil.

As a test of this possibility, *o*-methoxybenzophenone anil (III) was studied. In an attempt to prepare this anil, N-phenylbenzimidyl chloride (I), prepared by the method of Hölljes and Wagner,[5] was treated with *o*-methoxyphenylmagnesium bromide. The product, however, was not the desired anil III but *o*-(*o*-methoxyphenyl)-benzophenone anil (II). It seemed certain that the expected anil III had actually been formed and then had undergone methoxyl group displacement by reaction with the Grignard reagent. This supposition was supported by a later series of experiments in which *o*-methoxybenzophenone anil (III) was prepared and treated with the *o*-methoxyphenyl reagent. The product, *o*-(*o*-methoxyphenyl)-benzophenone anil (II), was identical with that obtained directly from N-phenylbenzimidyl chloride. The yield was 86%. This compound was found to exist in two forms (m.p. 120 and 135°), presumably *syn* and *anti*, both of which yielded the corresponding ketone IV when hydrolyzed. A high-melting (197°) by-product, isolated in a 1% yield, is still under investigation.

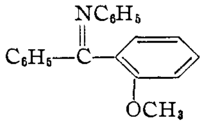


$C_6H_5C(=NC_6H_5)—Cl$

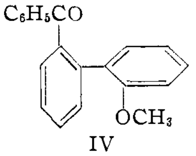
I



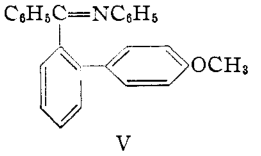
II



III



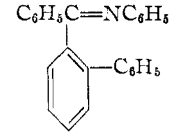
IV



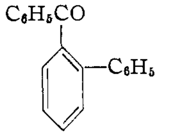
V

The result with *p*-methoxyphenylmagnesium bromide was similar; the product, *o*-(*p*-methoxyphenyl)-benzophenone anil (V), was isolated in a yield of 77%.

With phenylmagnesium bromide, methoxy anil III suffered methoxyl group displacement to give *o*-phenylbenzophenone anil (VI) in a yield of 64%. Hydrolysis of VI with hydrochloric acid afforded the corresponding ketone VII. The melting points of the ketone and its anil are the same as those given in the literature.[6]

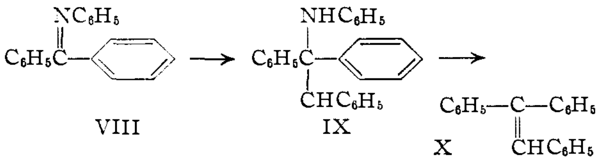


VI



VII

Benzylmagnesium chloride reacted with benzophenone anil (VIII) to give a surprising result: the product, obtained in a 67% yield, was 1-anilino-1,1,2-triphenylethane (IX), *i.e.*, the 1,2-addition product. When this compound was heated with hydrochloric acid, it was converted to triphenylethylene (X). The melting point of our amine is 143.5–144.5°, whereas that reported in the literature is 152–153°.[7]



VIII IX X

The benzyl reagent failed to displace the methoxyl group in anil III; the product appears to be that formed by 1,2-addition.

The reaction of *t*-butylmagnesium chloride on anil VIII appears to have brought about the change expected, giving a dihydro derivative of *p*-*t*-butylbenzophenone anil. The yield, however, was only 6%.

Experimental[8]

Reaction of N-Phenylbenzimidyl Chloride (I) with *o*-Methoxyphenylmagnesium Bromide.—A Grignard reagent, prepared from 39.2 g. of *o*-bromoanisole, 4.86 g. of magnesium and 85 ml. of anhydrous ether, was filtered through glass wool. To the filtrate, cooled in an ice-bath, a solution of 21.6 g. of N-phenylbenzimidyl chloride[6] in 100 ml. of ether was added dropwise, with stirring. The mixture was heated under reflux for one hour after completion of the addition and, after being allowed to stand overnight, was poured into a solution of 10.7 g. of ammonium chloride, 10 ml. of concentrated ammonium hydroxide and 50 ml. of

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[1] This investigation was supported in part by a grant from the Office of Ordnance Research, U. S. Army (Contract No. DA-11-022-ORD-874).

[2] United States Rubber Company Fellow, 1955–1956.

[3] H. Gilman, J. E. Kirby and C. R. Kinney, THIS JOURNAL, **51**, 2252 (1929).

[4] See R. C. Fuson and W. S. Friedlander, *ibid.*, **75**, 5410 (1953).

[5] E. L. Hölljes, Jr., and E. C. Wagner, *J. Org. Chem.*, **9**, 31 (1944).

[6] H. H. Hatt, A. Pilgrim and E. F. M. Stephenson, *J. Chem. Soc.*, 478 (1941).

[7] T. W. J. Taylor, J. S. Owen and D. Whittaker, *ibid.*, 206 (1938).

[8] All melting points are corrected.

water. The resulting mixture was filtered to remove inorganic salts, and the *o*-(*o*-methoxyphenyl)-benzophenone anil (II), isolated in the usual way, was recrystallized from absolute ethanol, m.p. 121.5–122.5°, yield 19.3%. This melting point was observed with a sample of material which had been air-dried. The sample which was analyzed had been dried at 76° and melted at 135–136°.

Anal.[9] Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; OCH_3, 8.54. Found: C, 85.71; H, 5.90; OCH_3, 8.58.

It is possible that the two samples are geometric isomers and that the low-melting form rearranges to the high-melting form when heated.

***o*-(*o*-Methoxyphenyl)-benzophenone.**—Six milliliters of concentrated hydrochloric acid was added to a mixture of 0.8 g. of the anil of *o*-(*o*-methoxyphenyl)-benzophenone and 50 ml. of 95% ethanol and the resulting bright yellow mixture was heated under reflux for one hour. The mixture, which had become nearly colorless, was allowed to cool and stand 12 hours and was then poured over 25 g. of ice. The ketone crystallized from aqueous ethanol in colorless prisms, m.p. 96.5–97.5°; yield 87%.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.12; H, 5.57.

***o*-Methoxybenzophenone Anil (III).**—This anil was prepared in 48.5% yield by the method of Graebe and Keller.[10] In one experiment in which three drops of 25% hydrobromic acid was added to the reaction mixture the product was *o*-hydroxybenzophenone anil.

The methoxy anil was prepared also from N-phenylbenzimidyl chloride and *o*-methoxyphenylmagnesium bromide by employing conditions different from those described above. The experiment which gave the highest yield of anil is recorded. To a Grignard reagent prepared from 10.25 g. of magnesium and 80.5 g. of *o*-bromoanisole in 250 ml. of ether was added, over a period of 25 minutes, a solution of 87.0 g. of benzimidyl chloride in 500 ml. of ether and 200 ml. of benzene. The mixture was stirred for 45 minutes and poured into a cold solution of 23 g. of ammonium chloride, 45 ml. of ammonium hydroxide and 300 ml. of water. The residual dark green oil crystallized when stirred with ethanol; the crude yellow-green crystals weighed 46 g. After two recrystallizations from ethanol (charcoal), the anil was obtained pure, m.p. 77–78°, yield 33%.

Reaction of *o*-Methoxybenzophenone Anil (III) with *o*-Methoxyphenylmagnesium Bromide.—A solution of 14.0 g. of *o*-methoxybenzophenone anil in 200 ml. of benzene was added dropwise to a Grignard reagent prepared from 4.38 g. of magnesium and 36.5 g. of *o*-bromoanisole in 180 ml. of ether. The reaction mixture, which was kept under nitrogen with a Gilman trap,[11] was heated under reflux for 20 hours, cooled and poured into a solution of 10.5 g. of ammonium chloride in 200 ml. of water. The product, isolated by usual procedures, was triturated with cold ethanol, m.p. 119–120°; yield 14.6 g. (82%). Conversion to the high-melting isomer was achieved easily by dissolving the product in boiling ethanol and allowing the solution to cool, m.p. 135–136°. The two forms have identical infrared spectra, which are identical to that of *o*-(*o*-methoxyphenyl)-benzophenone anil described earlier. Absorption bands assignable to a conjugated imine group (1620 cm.$^{-1}$) and to an ether linkage (1260 cm.$^{-1}$) are present.

Chromatographic separation of the oily residue, obtained by concentration of the alcoholic mother liquor, yielded, in addition to more of the major product, *o*-(*o*-methoxyphenyl)-benzophenone anil (0.6 g.) (total yield 86%), a yellow crystalline by-product, weight 0.2 g. It was purified by recrystallization from ethanol; m.p. 197–197.5°.

Anal. Calcd. for $C_{32}H_{25}NO$: C, 87.44; H, 5.73. Found: C, 87.75; H, 5.59.

The infrared spectrum contains absorption bands assignable to a conjugated imine group (1620 cm.$^{-1}$), an ether linkage (1050, 1250 cm.$^{-1}$), mono-substituted benzene (690 cm.$^{-1}$) and *ortho*-disubstituted benzene (760 cm.$^{-1}$).

Reaction of *o*-Methoxybenzophenone Anil with *p*-Methoxyphenylmagnesium Bromide.—This reaction was carried out in the same manner as that described for the preceding experiment. To a Grignard reagent, prepared from 2.70 g. of magnesium, 23.4 g. of *p*-bromoanisole and 100 ml. of ether, was added a solution of 8.0 g. of the anil of *o*-methoxybenzophenone in 120 ml. of benzene. The red-brown mixture was heated under reflux for 20 hours and hydrolyzed with a solution of dilute ammonium chloride. The crude yellow crystals, m.p. 115–116°, yield 77%, were purified by two recrystallizations from ethanol; m.p. 118.8–119.2°.

Anal. Calcd. for $C_{26}H_{21}ON$: C, 85.92; H, 5.82; N, 3.86. Found: C, 85.70; H, 5.88; N, 4.03.

The infrared spectrum contains absorption bands indicative of a conjugated imine group (1620 cm.$^{-1}$) and an ether linkage (1055, 1265 cm.$^{-1}$).

Two colorless crystalline by-products (m.p. 163–165° and 167–168.5°), obtained from the reaction mixture of chromatographic separation, have not been identified.

Reaction of *o*-Methoxybenzophenone Anil with Phenylmagnesium Bromide.—In the same manner as described above a solution of phenylmagnesium bromide was prepared from 2.84 g. of magnesium and 18.5 g. of bromobenzene in 100 ml. of ether and to it was added a solution of 8.0 g., of the anil in 100 ml. of benzene. The mixture was heated under reflux for 20 hours and decomposed with a solution of dilute ammonium chloride. The desired product, *o*-phenylbenzophenone anil (VI), was obtained from the reaction mixture by chromatography, m.p. 89–91°; yield 64%. Two recrystallizations of the anil raised the melting point to 91.2–92.0°; the literature melting point is 91–92°.[7]

Anal. Calcd. for $C_{25}H_{19}N$: C, 90.05; H, 5.74. Found: C, 90.12; H, 5.85.

The infrared spectrum exhibits an absorption band assignable to a conjugated imine group (1615 cm.$^{-1}$).

***o*-Phenylbenzophenone (VII).**—A mixture of 0.5 g. of the yellow *o*-phenylbenzophenone anil, 6 ml. of acetone, 2 ml. of water and 2 ml. of concentrated hydrochloric acid was heated under reflux for 20 minutes and then poured over ice. The crude ketone separated from ethanol, in colorless crystals, m.p. 91–92°; yield 52%; the melting point reported for *o*-phenylbenzophenone is 92°.[7] The infrared spectrum has an absorption band assignable to an aromatic ketone (1668 cm.$^{-1}$).

Reaction of Benzophenone Anil with Benzylmagnesium Chloride.—A Grignard reagent, prepared from 9.5 g. of magnesium, 39 g. of benzyl chloride and 180 ml. of ether, was filtered through glass wool to remove unchanged magnesium. To the filtered solution was added, dropwise, a solution of 8.0 g. of benzophenone anil in 150 ml. of dry benzene. The color of the reaction mixture changed from green to yellow as the addition proceeded. The mixture was heated under reflux, with stirring, for 15 hours. The boiling point of the mixture was raised to 60° by the addition of 50 ml. of dry *n*-butyl ether, and the heating and stirring were continued for 10 more hours. A precipitate began to form in the yellow solution.

At this point a stream of nitrogen was passed through the flask to drive out ether vapors. Another 50-ml. portion of *n*-butyl ether was added and, at the end of 49 hours of stirring and heating, the temperature of the solution was 93°. Additional amounts of precipitate had formed by this time and the mixture had become bright yellow and opaque. It was poured into a mixture of 210 g. of ice and 40 ml. of concentrated hydrochloric acid, and the 1-anilino-1,1,2-triphenylethane (IX) was isolated by conventional procedures. It was purified by recrystallization from a mixture of 95% ethanol and ethyl acetate, m.p. 143.5–144.5°, yield 67%.

Anal. Calcd. for $C_{26}H_{23}N$: C, 89.36; H, 6.63. Found: C, 89.32; H, 6.59.

Reaction of 1-Anilino-1,1,2-triphenylethane (IX) with Hydrochloric Acid.—A mixture of 1 g. of the amine, 20 ml. of ethanol and 2.5 ml. of concentrated hydrochloric acid was heated under reflux for 5 minutes and cooled. The product separated as a colorless, sticky oil, which crystallized when allowed to stand overnight. After recrystallization from aqueous ethanol it melted at 68.3–68.5°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.71; H, 6.29; Found: C, 93.54; H, 6.19.

The infrared and ultraviolet spectra of this compound are identical with those of triphenylethylene (X).

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[9] Microanalyses by Mrs. Esther Fett, Mrs. Lucy Chang, Mrs. Katherine Pih, Miss Alice Terra, Mrs. R. Maria Benassi, Mr. Joseph Nemeth and Mr. R. J. Nesset.

[10] C. Graebe and F. Keller, *Ber.*, **32**, 1683 (1899).

[11] H. Gilman and A. P. Hewlett, *Rec. trav. chim.* **48**, 1124 (1929).

Reaction of *o*-Methoxybenzophenone Anil with Benzylmagnesium Chloride.—To a Grignard reagent prepared from 7.0 g. of magnesium and 37.2 g. of benzyl chloride in 140 ml. of ether was added a solution of 8.0 g. of *o*-methoxybenzophenone anil in 150 ml. of benzene. The mixture was heated under reflux for 20 hours and then poured into a dilute solution of ammonium chloride. The product, isolated by usual procedures, was recrystallized from carbon tetrachloride; m.p. 151–152°; yield 88%.

Anal. Calcd. for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.63; H, 6.52; N, 3.93.

Absorption bands assignable to a secondary nitrogen group (3420 cm.$^{-1}$), an ether linkage (1040, 1250 cm.$^{-1}$), mono-substituted benzene (690, 698 cm.$^{-1}$) and *ortho*-disubstituted benzene (750 cm.$^{-1}$) were present in its infrared spectrum. The absence of *para*-disubstituted benzene absorption indicates that the benzyl group did not enter the *para*-position.

Reaction of Benzophenone Anil with *t*-Butylmagnesium Chloride.—The *t*-butylmagnesium chloride was prepared from 3.98 g. of magnesium and 18.4 g. of *t*-butyl chloride in 50 ml. of ether. A solution of 8.0 g. of benzophenone anil in 60 ml. of benzene was added and the mixture was heated under reflux for 7 hours before it was decomposed with a solution of dilute ammonium chloride. The yellow solid, obtained from the reaction mixture by chromatographic separation, weighed 0.5 g., m.p. 142–146°. Two recrystallizations of the compound from ethanol raised the melting point to 152–152.5°.

Anal. Calcd. for $C_{23}H_{25}N$: C, 87.57; H, 7.99. Found: C, 87.65; H, 8.24.

The infrared spectrum has bands assignable to a conjugated imino group (1595 cm.$^{-1}$), to C–CH_3 (1370, 1410 cm.$^{-1}$), to a conjugated olefin (1565 cm.$^{-1}$) and to monosubstituted benzene (693 cm.$^{-1}$).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Synthesis of Certain β-Diketones from Acid Chlorides and Ketones by Sodium Amide. Mono *versus* Diacylation of Sodio Ketones with Acid Chlorides[1]

BY BRUCE O. LINN[2] AND CHARLES R. HAUSER

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A number of acylations of sodio ketones that have not been satisfactory with ethyl or methyl esters were effected successfully with acid chlorides to form β-diketones. The sodio ketone was prepared by means of sodium amide, and three equivalents of it treated with one equivalent of the acid chloride. This ratio of reactants avoided the possible further acylation of the β-diketone. The present method is particularly useful for acylations of sodio ketones with α,β-unsaturated acid chlorides or nitrobenzoyl chlorides, and for acylations of cyclopentanone. It is comparable to an earlier phenyl ester method for certain acylations.

The acylation of methyl or methylene ketones with esters by means of bases furnishes probably the best general method for the synthesis of many β-diketones.[3] However, a number of such acylations with the common ethyl or methyl esters have been unsuccessful even when the ester was added to the reactive, intermediate sodio ketone which was prepared by means of sodium amide (equation 1).

$$CH_3COR + NaNH_2 \longrightarrow NaCH_2COR + NH_3 \quad (1)$$

Recently[4–6] some of these acylations of sodio ketones were effected satisfactorily with phenyl esters which are more reactive than the corresponding ethyl or methyl esters.

In the present investigation certain of these and some other acylations of sodio ketones were carried out with the still more reactive acid chlorides. As with an ester,[3] the acylation of a sodio ketone with an acid chloride is accompanied by a relatively rapid acid–base reaction between the resulting β-diketone and the sodio ketone (equations 2 and 3).

$$R'COCl + NaCH_2COR \longrightarrow R'COCH_2COR + NaCl \quad (2)$$

$$R'COCH_2COR + NaCH_2COR \longrightarrow Na(R'COCHCOR) + CH_3COR \quad (3)$$

However, in contrast to an ester,[7] an acid chloride may effect the further acylation of the sodio β-diketone[8] to form the sodio triketone[9] (equations 4 and 5) or the O-acyl derivative of the β-diketone. The over-all reaction may be regarded as the diacylation of the sodio ketone.

$$R'COCl + Na(R'COCHCOR) \longrightarrow (R'CO)_2CHCOR + NaCl \quad (4)$$

$$(R'CO)_2CHCOR + NaCH_2COR \longrightarrow Na[(R'CO)_2CCOR] + CH_3COR \quad (5)$$

Such a diacylation to form the triketone (66%) has been observed, for example, in connection with a general study of 1,2- *versus* 1,4-addition[5] in which sodio acetophenone was treated with an equivalent of cinnamoyl chloride. Similarly diacylation to give the O-acyl derivative of the β-diketone has been reported with sodio cyclohexanone and benzoyl chloride.[10] Of course diacylation is to be expected with equivalents of the reactants since half of the sodio ketone is then neutralized according to

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[1] Supported in part by the Office of Naval Research.

[2] American Cyanamid Company Fellow, 1954–1955.

[3] See C. R. Hauser, F. R. Swamer and J. T. Adams, "Organic Reactions," Vol. VIII, Chapter 3, John Wiley and Sons, Inc., New York, N. Y., 1954.

[4] C. R. Hauser, B. I. Ringler, F. W. Swamer and D. R. Thompson, THIS JOURNAL, **69**, 2649 (1947).

[5] C. R. Hauser, R. S. Yost and B. I. Ringler, *J. Org. Chem.*, **14**, 261 (1949).

[6] E. H. Man, F. W. Swamer and C. R. Hauser, THIS JOURNAL, **73**, 901 (1951).

[7] Although ethyl esters do not effect appreciable acylation of sodio β-diketones or sodio β-ketoesters, such an acylation evidently occurs, accompanied by cleavage, on heating ethyl benzoate with sodio acetoacetic ester in which the relatively volatile ethyl acetate is removed by distillation to form sodio ethyl benzoylacetate; see S. M. McElvain and K. H. Weber, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 379.

[8] Analogous acylations of sodio β-keto esters with acid chlorides are well known. In fact the acylation of sodio acetoacetic ester with acid chlorides, followed by cleavage of the resulting triketone, furnishes a useful method of synthesis of certain β-keto esters; see C. R. Hauser and B. E. Hudson, Jr., "Organic Reactions," Vol. I, Chapter 9, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 298.

[9] Even the further acylation of the sodio triketone to form a tetraketone or the O-acyl derivative of the triketone is possible; see L. Claisen, *Ann.*, **277**, 196 (1893).

[10] E. Bauer, *Ann. chim. et phys.*, [9] **1**, 408 (1914).