[Contribution from the Department of Chemistry, Massachusetts Institute of Technology]

Grignard Reagent Derived from the Ethylene Ketal of ω-Bromobutyrophenone

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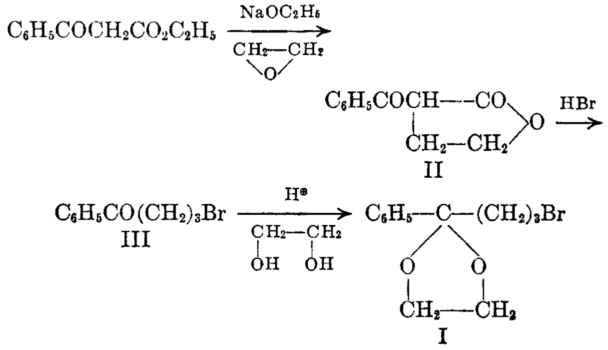
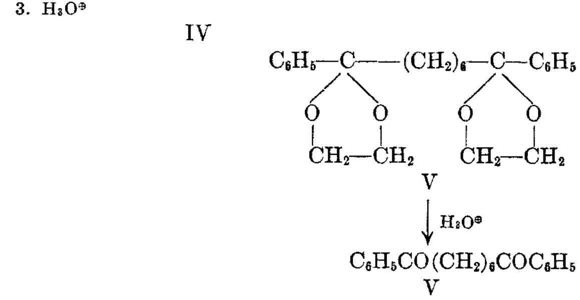
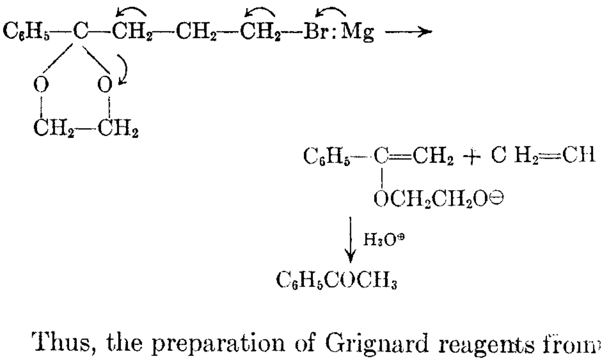
Reaction of the ethylene ketal of ω-bromobutyrophenone with magnesium followed by carbonation of the reaction mixture yielded a mixture of γ-benzoylbutyric acid and the diketal of 1,6-dibenzoylhexane.

As part of an investigation concerned with synthesis of certain polycyclic aromatic systems, we were led to study methods for the introduction of a γ-benzoylpropyl group. Consideration of one of these methods, use of an organometallic intermediate, resulted in the study of the formation of the Grignard reagent derived from the ethylene ketal of ω-bromobutyrophenone (I) which is reported here. Reaction of the sodium enolate of ethyl benzoylacetate with ethylene oxide produced the lactone II which was converted to the bromide III by treatment with hydrobromic acid. Condensation of the bromide III with ethylene glycol produced the bromo ketal I. The bromo ketal I reacted slowly with magnesium in tetrahydrofuran; carbonation of the resultant reaction mixture followed by hydrolysis produced the known γ-benzoylbutyric acid (IV, 54%) accompanied by the diketal V (23%), the coupling product of I. The structure of the diketal V was established by hydrolysis to form the known diketone VI.





Previous studies have indicated that α- and β-halo ketals and acetals do not react with magnesium to form stable Grignard reagents.[2-4] The α-halo ketals and acetals were found to undergo elimination and coupling reactions when treated with magnesium; the similar failure of the β-halo compound may be attributable to the formation of a cyclopropane derivative according to the scheme of Boord and co-workers.[5] One possible side reaction which was anticipated with the γ-bromo ketal I was the cleavage represented in the accompanying equation. This reaction would be analogous to the cleavage of 1,4-dihalides described by Grob and Baumann.[6] However, in no case did we isolate any acetophenone, one of the products expected from this side reaction. Also, no products were isolated which corresponded to either intramolecular or intermolecular attack on the dioxolane ring by the Grignard moiety, although an intermolecular reaction of this type has been observed when acetals and ketals have been allowed to react with Grignard reagents under forcing conditions.[7]



Thus, the preparation of Grignard reagents from γ-halo ketals appears to be a satisfactory synthetic procedure.

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EXPERIMENTAL[8]

α-Benzoyl-γ-butyrolactone (II). Ethyl benzoylacetate (194 g., 1.0 mole) was added with stirring to a cold (0°) solution of sodium ethoxide prepared from 23 g. (1.0 g.-atom) of sodium and 1.2 l. of ethanol. Ethylene oxide (44 g., 1.0 mole) was distilled into the cold reaction mixture. After the addition was complete the mixture was allowed to warm to room temperature and stirred under a Dry Ice condenser until all of the ethylene oxide was consumed. After the bulk of the alcohol had been distilled from the mixture under reduced pressure, the residue was neutralized with 5% aqueous sulfuric acid and extracted with ether. The extract was dried over magnesium sulfate, concentrated and distilled through a 30-cm. Vigreux column under reduced pressure. The desired lactone, yield 57.96 g. (33%), b.p. 164° (2 mm.), n_{D}^{25} 1.5599 [lit.[9] 193–195° (8 mm.)], was accompanied by 85.40 g. (44%) of unchanged ethyl benzoylacetate, b.p. 118° (25 mm.). The lactone, previously described as an oil, crystallized from a benzene–petroleum ether mixture as white needles, m.p. 57–58°. The ultraviolet spectrum of the product has a maximum at 242 mμ (ε 12,800); the infrared spectrum[10] has bands at 1765 cm.$^{-1}$ (C=O of a γ-lactone) and 1680 cm.$^{-1}$ (conj. C=O).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.29. Found: C, 69.36; H, 5.56.

ω-Bromobutyrophenone (III). A mixture of 9.5 g. (0.05 mole) of α-benzoyl-γ-butyrolactone and 100 g. of 40% hydrobromic acid was heated on a steam bath for 2 hr., cooled and extracted with ether. The extract was dried over magnesium sulfate and concentrated. A solution of the residual oil in petroleum ether deposited 8.8 g. (78%) of the bromo ketone as pale yellow plates, m.p. 34–35° (lit.[9] 36°). The ultraviolet spectrum of the product has a maximum at 242 mμ (ε 9680); the infrared spectrum[10] has a band at 1680 cm.$^{-1}$ (conj. C=O).

ω-Bromobutyrophenone ethylene ketal (I). A solution of 12.55 g. (0.055 mole) of the bromo ketone, 3.0 g. (0.055 mole) of ethylene glycol, 0.1 g. of *p*-toluenesulfonic acid, and 100 ml. of benzene was refluxed until the theoretical amount of water had been separated in a Dean-Starke trap. An additional equivalent of ethylene glycol was added and the solution was refluxed for an additional 4 hr., cooled, washed with 5% aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated. A solution of the residue in petroleum ether deposited 11.46 g. (76.4%) of the bromo ketal as colorless prisms, m.p. 63–65°. The ultraviolet spectrum of the ketal has a maximum at 245 mμ (ε 830) and the infrared spectrum[10] has doublet at 1030 and 1045 cm.$^{-1}$ (C—O of a ketal) with no absorption in the carbonyl region.

Anal. Calcd. for $C_{12}H_{15}BrO_2$: C, 53.15; H, 5.58; Br, 29.47. Found: C, 52.87; H, 5.72; Br, 29.48.

Reaction of ω-bromobutyrophenone ethylene ketal (I) *with magnesium.* To a suspension of 0.66 g. (0.025 mole) of magnesium turnings in 25 ml. of freshly distilled tetrahydrofuran was added, dropwise and with stirring under nitrogen, a solution of 6.8 g. (0.025 mole) of the bromo ketal in 200 ml. of tetrahydrofuran. The resulting mixture was stirred at room temperature for 4 hr. at which time the concentration of Grignard reagent, determined by titration of aliquots from the reaction mixture with standard acid, had become constant. The solution was poured into a slurry of Dry Ice in tetrahydrofuran and the resulting mixture was allowed to warm to room temperature, then treated with cold, dilute hydrochloric acid, and, finally, extracted with ether. Extraction of the ether solution with 10% aqueous sodium hydroxide followed by acidification of the aqueous solution and extraction with ether afforded the crude *γ-benzoylbutyric acid* which was recrystallized from water. The yield of pure acid, m.p. 126–127° (lit.[11] 125–126°), was 2.49 g. (54%). The ultraviolet spectrum of the acid has a maximum at 241 mμ (ε 14,000); the infrared spectrum[10] has a broad band at 3000 cm.$^{-1}$ (associated O—H) as well as bands at 1710 cm.$^{-1}$ (COOH) and 1680 cm.$^{-1}$ (conj. C=O).

The neutral ether solution from the carbonation was dried over magnesium sulfate and concentrated. The residual *diketal of 1,6-dibenzoylhexane* crystallized from a benzene-petroleum ether mixture as colorless plates, m.p. 97–98°, yield 1.1 g. (23%). The ultraviolet spectrum of the diketal has a maximum at 241 mμ (ε 3600); the infrared spectrum[10] exhibits no absorption in the carbonyl region but has a doublet at 1030 and 1040 cm.$^{-1}$ (C—O of a ketal).

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.57; H, 7.91.

A solution of 100 mg. of the diketal in aqueous ethanol which contained a few drops of hydrochloric acid was boiled for 30 min. and cooled. The cold solution deposited *1,6-dibenzoylhexane* as white crystals, m.p. 86–87° (lit.[12] 83–85°), yield 70 mg. (94%). The ultraviolet spectrum of the diketone has maxima at 243 mμ (ε 25,400) and 279 mμ (ε 2030); the infrared spectrum[10] has a band at 1680 cm.$^{-1}$ (conj. C=O).

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[8] All melting points are corrected and all boiling points are uncorrected. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model MS. The infrared spectra were determined either with a Perkin-Elmer, model 21, or a Baird, model B, double beam infrared recording spectrophotometer fitted with a sodium chloride prism. The microanalyses were performed by Dr. S. M. Nagy and his associates.

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[10] Determined in chloroform solution.

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