

808. *The Reaction of Phenacyl Halides with Grignard Reagents.
A Synthesis of Dibenzyl Ketones and Deoxybenzoins.*

By R. L. HUANG.

Conditions are reported for the preparation of dibenzyl ketones and deoxybenzoins by addition of a Grignard reagent to a phenacyl halide, and rearrangement of the resulting complex.

DIBENZYL KETONES may be prepared (a) from phenylacetic acids by pyrolysis or catalysis,¹ and (b) by the action of alkylzincs on the appropriate acid chloride.² The first method is of limited application, and the latter often involves difficultly accessible materials. For the synthesis of deoxybenzoins the following methods are available: (a) reduction of benzoins,³ (b) Friedel-Crafts reactions with substituted phenylacetyl chlorides,⁴ (c) reaction between benzylmagnesium halides and amides of aromatic acids,⁵ and (d) condensation

¹ Apitsch, *Ber.*, 1904, **37**, 1428; Senderens, *Ann. Chim. Phys.*, 1913, **23**, 243; Kistler, Swann, and Appel, *Ind. Eng. Chem.*, 1934, **26**, 388; Hurd and Thomas, *J. Amer. Chem. Soc.*, 1936, **58**, 1240.

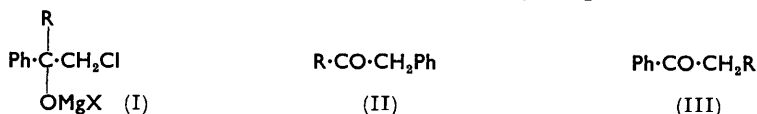
² Francias, *Ann. Chim.*, 1939, **11**, 212.

³ E.g., Ballard and Dehn, *J. Amer. Chem. Soc.*, 1932, **54**, 3970; Allen and Buck, *ibid.*, 1930, **52**, 312.

⁴ Petrenko-Kritschenko, *Ber.*, 1892, **25**, 2240; Szegő and Ostinelli, *Gazzetta*, 1930, **60**, 677; Newman and Gaertner, *J. Amer. Chem. Soc.*, 1950, **72**, 264; Brown and Mann, *J.*, 1948, 858.

⁵ (a) Jenkins, *J. Amer. Chem. Soc.*, 1933, **55**, 703, 2896; (b) Jenkins and Richardson, *ibid.*, p. 1618.

of benzylpyridinium salts with aromatic aldehydes.⁶ We now report an alternative synthesis for these two types of ketone involving the addition of a Grignard reagent to a phenacyl halide followed by rearrangement of the resulting complex.



From ethylmagnesium bromide and phenacyl chloride Tiffeneau⁷ obtained the complex (I; R = Et) which was converted by heat into benzyl ethyl ketone (II; R = Et). The migration of the phenyl in preference to the ethyl group is understandable considering the relative migratory aptitudes of such groups in the rearrangement of analogous systems, such as the chlorohydrins (or their magnesium complexes) derived from chlorocyclohexanone,⁸ pinacols,⁹ and related substances. Similarly benzylmagnesium chloride and the same halogeno-ketone should give dibenzyl ketone. This was the case. Hence the product from the same Grignard reagent and *p*-methoxyphenacyl bromide is most likely to be *p*-methoxydibenzyl ketone. The yields being 40 and 49%, respectively, this reaction between a benzylmagnesium halide and a phenacyl halide constitutes a practicable synthesis for certain dibenzyl ketones.

From an arylmagnesium halide and phenacyl chloride the product of rearrangement might similarly be pre-determined by application of the relative migratory aptitudes of the aryl and phenyl groups. Such aptitudes have been studied in several related rearrangements^{8,10} for which the following general qualitative relation for the effect of substituent groups has been found: *p*-OMe > *p*-Me > H > *p*-Cl, *o*-Me. Application of this known relation, however, was only partially successful. When R was *p*-tolyl or *p*-methoxyphenyl, fair yields (64 or 45%, respectively) were obtained of the expected deoxybenzoin (III), in which R had migrated in preference to phenyl. On the other hand, when R was *p*-chlorophenyl or *o*-tolyl, groups of low migratory capacities, the product in each case was an inseparable mixture of isomeric deoxybenzoin (II) and (III), both R and Ph having migrated.

The relative migratory capacities also provide a guide to the experimental conditions necessary for rearrangement. The complex from phenylmagnesium bromide and phenacyl chloride gave little or no deoxybenzoin in boiling ether but a 60% yield of the ketone after prolonged refluxing in benzene. Migration of the phenyl group therefore appears to require a temperature of 80° or higher, and consequently the metal complex was refluxed in benzene or higher-boiling solvent (*e.g.* xylene) in all the above syntheses involving migration of a phenyl group. On the other hand, the *p*-methoxyphenyl and the *p*-tolyl group migrated readily at the boiling point of ether, as shown in the synthesis of *p*-methoxydibenzyl ketone, 4-methyldeoxybenzoin, and 4-methoxydeoxybenzoin. Indeed, in the synthesis of the last-named compound, a purer product was obtained by a reverse Grignard reaction, *i.e.*, by adding the Grignard reagent to the phenacyl halide, presumably because rearrangement took place so readily that this procedure prevented the rearranged ketone from reacting further. This spontaneous rearrangement of the metal complexes is reminiscent of those obtained from chlorocyclohexanone⁸ and chloroacetone.^{10c}

EXPERIMENTAL

Microanalyses are by Dr. W. Zimmermann, Melbourne.

General Procedure.—The phenacyl halide (0.10 mole) in ether (50 c.c.) was added to a stirred solution of the Grignard reagent (0.12 mole) in ether (75 c.c.) at such a rate as to maintain

⁶ Kröhnke and Vogt, *Annalen*, 1954, **589**, 26.

⁷ Tiffeneau, *Ann. Chim. Phys.*, 1907, **10**, 368.

⁸ Huang, *J. Org. Chem.*, 1954, **19**, 1363.

⁹ Cf. *Annual Reports*, 1930, **27**, 114.

¹⁰ (a) Burr and Ciereszko, *J. Amer. Chem. Soc.*, 1952, **74**, 5426; (b) Bachmann and Ferguson, *ibid.*, 1934, **56**, 2081; (c) Huang, *J.*, 1954, 2539.

gentle refluxing (*ca.* 20 min.). Stirring and refluxing were continued for 2 hr. more (procedure *A*). In some cases, the ether was distilled off and progressively replaced by dry benzene until the vapour temperature reached 78–80°, refluxing and stirring being then continued for 4 hr. (procedure *B*). In other cases, *p*-xylene was used instead of benzene (procedure *C*). In each case, the reaction mixture was decomposed by ice, followed by 5*N*-sulphuric acid, the product extracted into ether, the extract washed with dilute sulphuric acid and water and dried (MgSO₄), and the ketone isolated by standard methods. All distillations were carried out under nitrogen.

Reactions of Phenacyl Chloride.—Phenylmagnesium bromide. By procedure *B* deoxybenzoin was obtained in a 62% yield, b. p. 124–126°/0.5 mm., m. p. 57° alone or mixed; semicarbazone, m. p. 148° (lit.: m. p.s 60° and 148°, respectively). Procedure *A* gave a mixture, b. p. 128–141°/0.5 mm., which contained little ketonic material.

Benzylmagnesium chloride. Method *C* gave dibenzyl ketone, b. p. 146–150°/*ca.* 2 mm. (39% yield), which when redistilled had b. p. 137–138°/1 mm., n_D^{25} 1.5737, m. p. *ca.* 29° (room temp.) (Found: C, 85.3; H, 6.9. Calc. for C₁₅H₁₄O: C, 85.7; H, 6.7%). The oxime melted at 123–125° (Francis¹¹ records m. p. 125°), and the semicarbazone at 122–123° (Senderens¹² gives m. p. 125°; however, Staudinger¹³ reports m. p. 140°). The 2:4-dinitrophenylhydrazone, yellow needles from ethanol-ethyl acetate, had m. p. 98–99° (Found: N, 14.1. C₂₁H₁₈O₄N₄ requires N, 14.35%). Procedure *B* gave a lower yield of a less pure product. A sample prepared from phenylacetic acid by Hurd and Thomas's method¹ had n_D^{25} 1.5712, m. p. *ca.* 29°; semicarbazone, m. p. 124–125°, alone or mixed with the semicarbazone obtained as above.

p-Tolylmagnesium bromide. The product, obtained by procedure *A*, was 4-methyldeoxybenzoin, b. p. 140°/0.4 mm. (64%), prisms, m. p. 94–97°, from cyclohexane (Newman and Gaertner⁴ report m. p. 92–95°; Brown and Mann⁴ report 90–92°) (Found: C, 85.7; H, 6.7. Calc. for C₁₅H₁₄O: C, 85.7; H, 6.7%). The oxime, prepared by Bachmann's¹⁴ method (pyridine), crystallised from ethanol in needles, m. p. 102–103.5° (Found: C, 79.8; H, 6.7. Calc. for C₁₅H₁₅ON: C, 80.0; H, 6.7%). Strassmann,¹⁵ however, reports m. p. 109°; a sample prepared by his method (potassium acetate in ethanol) melted at 101–103°. The isomeric 4'-methyldeoxybenzoin has m. p. 108–110° (Newman and Gaertner⁴), and forms an oxime, m. p. 131° (Strassmann¹⁵).

p-Methoxyphenylmagnesium bromide. The Grignard solution was stirred into a solution of phenacyl chloride (5.0 g.) in ether, the mixture being then refluxed for 2 hr., and the product isolated by ether extraction. After removal of the ether and addition of chilled methanol, 4-methoxydeoxybenzoin (2.1 g., crude) separated; it had m. p. 96–98° (from methanol) (Found: C, 79.1; H, 6.0. Calc. for C₁₅H₁₄O₂: C, 79.6; H, 6.2%). Barnes *et al.*¹⁶ report m. p. 98°, and for the 4'-isomer, m. p. 77–78°. The 2:4-dinitrophenylhydrazone, orange needles from ethyl acetate, melted at 198° (Found: N, 13.6. C₂₁H₁₈O₆N₄ requires N, 13.8%). The mother liquors were combined and distilled (slight decomposition) giving more of the deoxybenzoin, m. p. *ca.* 95° (1.2 g.).

By procedure *A* a 40% yield was obtained of a less pure product, which was chromatographed (benzene on alumina). A sparingly soluble by-product, m. p. 247° (benzene), was isolated in small quantities.

p-Chlorophenylmagnesium bromide. The product was distilled, b. p. 139–140°/0.4 mm. (50%), and after repeated crystallisation from ethanol had m. p. 92–95° (Found: C, 72.7; H, 4.9; Cl, 15.75. Calc. for C₁₄H₁₁OCl: C, 72.9; H, 4.8; Cl, 15.4%). Jenkins and Richardson⁵ report m. p. 107.5° for 4'-chlorodeoxybenzoin and m. p. 138° for 4-chlorodeoxybenzoin. The 2:4-dinitrophenylhydrazone (probably a mixture of isomers), prisms from ethanol-ethyl acetate, melted at 205–212° (Found: N, 13.3. C₂₀H₁₅O₄N₄Cl requires N, 13.6%).

o-Tolylmagnesium bromide. Procedure *B* gave a mixture of isomers, b. p. *ca.* 140°/1 mm. (25%), n_D^{24} 1.5921 (Found: C, 85.65; H, 6.7. Calc. for C₁₅H₁₄O: C, 85.7; H, 6.7%). The 2:4-dinitrophenylhydrazone after repeated recrystallisation (ethyl acetate-ethanol) had m. p. 167–181° (Found: N, 14.2. Calc. for C₂₁H₁₈O₄N₄: N, 14.35%) the semicarbazone, m. p. 138–151° after recrystallisations from ethanol (Found: N, 15.4. Calc. for C₁₆H₁₇ON₃: N, 15.7%).

¹¹ Francis, *J.*, 1899, **75**, 865.

¹² Senderens, *Bull. Soc. chim.*, 1910, **7**, 654.

¹³ Staudinger, *Ber.*, 1911, **44**, 533.

¹⁴ Bachmann, Fujimoto, and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 1995.

¹⁵ Strassmann, *Ber.*, 1889, **22**, 1229.

¹⁶ Barnes, Cooper, Tulane, and Delaney, *J. Org. Chem.*, 1943, **8**, 153.

Reaction of *p*-methoxyphenacyl bromide ¹⁷ with benzylmagnesium chloride. The product from procedure *A* was *p*-methoxydibenzyl ketone, b. p. 140—142°/0.4 mm. (49% yield), n_D^{23} 1.5751 (Found: C, 80.3; H, 6.7. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%). The *oxime*, needles from aqueous ethanol, had m. p. 102—105° (Found: C, 75.3; H, 6.6. $C_{16}H_{17}O_2N$ requires C, 75.3; H, 6.7%). It failed to give a crystalline semicarbazone.

UNIVERSITY OF MALAYA, SINGAPORE.

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¹⁷ Prepared as described by Kindler and Blaas, *Ber.*, 1944, **77**, B, 585, with addition of a trace of aluminium chloride (cf. *Organic Synth.*, Coll. Vol. II, 480).
