[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Grignard Reagents with Cyclic α-Chloroketones

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Attractive intermediates for polynuclear syntheses are obtainable from the reaction of aryl Grignard reagents and cyclic α-chloroketones. The addition reaction leads predominately to the formation of the *cis*-chlorohydrin which rearranges in good yield to the α-aryl ketone. Factors affecting the yield of the latter have been investigated.

The reaction of Grignard reagents with cyclic α-haloketones may lead to a number of products[1] among which are the *cis*- and *trans*- halohydrin isomers resulting from addition to the carbonyl function. One of these isomers can be converted in good yield to the corresponding ketone simply by heating the halomagnesium addition product.[2] All of the evidence, including stereochemical[1c,3] and mechanistic considerations,[4] seems clearly to establish that this is the *cis* isomer. The *trans* isomer, when similarly treated, on the other hand, appears to rearrange by way of the epoxide and gives rise to a mixture of products.[3a,3b,4]

This reaction has considerable appeal as a synthetic procedure to obtain intermediates for polycyclic compounds and has been used in such syntheses with 2-chlorocyclohexanone[2b,3d,5] and with 4-methyl-2-chlorocyclohexanone.[3d] Because of dipolar repulsion the halogen atom in simple α-halocyclohexanones exists in an axial conformation.[6] Consequently, the least hindered side for the approach of the entering group to the carbon of the coordinated carbonyl group would be predicted to be the side opposite to the axial halogen atom.[7] The *cis*-halohydrin should therefore predominate in the addition of a Grignard reagent to simple α-halocyclohexanones or polycyclic haloketones such as 2-chloro-1-tetralone and 2-chloroindanone. This is the isomer which can be rearranged to give good yields of substituted cyclic ketone.

We report here a study of the reaction of 2-chlorocyclohexanone, 2-chloro-1-tetralone, 2-bromo-1-tetralone, 2-chloroindanone, and 2-chloro-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene with aryl Grignard reagents. It is possible to isolate the corresponding ketones, in which chlorine has been replaced by the organic portion of the Grignard reagent, in yields of 50–70% by adding the Grignard reagent to a cooled solution of the chloroketone in ether-benzene followed by a period at reflux. If the reflux period is omitted, it is also possible to isolate the halohydrin addition products (except where rearrangement occurs even at low temperature or when the molecular weight of the chlorohydrin makes distillation difficult) in yields of 60–80%. These may subsequently be rearranged in 80–90% yield. The two-step procedure often results in a better over-all yield but the improvement in yield does not generally offset the extra work involved. These results are summarized in Table I.

TABLE I

REACTION OF PHENYLMAGNESIUM BROMIDE WITH α-CHLOROKETONES

α-Chloroketone	Product Yield, % Ketone	Halohydrin	Ketone from halohydrin
2-Chlorocyclohexanone	68[a]	83[b]	86[b]
2-Chloro-1-tetralone	43[c]	60	81
2-Chloro-1-indanone	60	70	92
2-Chloro-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene	52	—	—

[a] With *p*-tolyl, *m*-anisyl, and α-naphthyl Grignard reagents the yields of ketone were 68%, 52%, and 50%, respectively. [b] With *m*-anisyl Grignard reagent the yields of halohydrin and its rearrangement product were 67% and 90%, respectively. [c] 2-Bromo-1-tetralone furnished 24% of ketone product.

The results of this study may be generalized in the following statements:

(1) For optimum yield, the addition of Grignard reagent in ether to a solution of the chloroketone (in benzene to prevent precipitation) is to be preferred, particularly where the chlorohydrin inter-

(1) (a) G. Vavon and B. Tchoubar, *Bull. soc. chim.*, **45**, 965 (1929). (b) E. P. Kohler and M. Tishler, *J. Am. Chem. Soc.*, **54**, 1594 (1932); **57**, 217 (1935). (c) M. Tiffeneau and B. Tchoubar, *Compt. rend.*, **198**, 941 (1934); **199**, 360 (1934). (d) B. Tchoubar and O. Sackur, *Compt. rend.*, **207**, 1105 (1938).

(2) (a) M. Tiffeneau, B. Tchoubar, and S. Letellier, *Compt. rend.*, **216**, 856 (1943). (b) M. S. Newman and M. D. Farbman, *J. Am. Chem. Soc.*, **66**, 1550 (1944).

(3) (a) P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934). (b) P. D. Bartlett and R. V. White, *J. Am. Chem. Soc.*, **56**, 2785 (1934). (c) M. Tiffeneau, B. Tchoubar, and S. Letellier, *Compt. rend.*, **217**, 588 (1943). (d) M. S. Newman and W. T. Booth, *J. Org. Chem.*, **12**, 737 (1947).

(4) T. A. Geissman and R. I. Akawie, *J. Am. Chem. Soc.*, **73**, 1993 (1951).

(5) W. E. Bachmann, G. I. Fujimoto, and L. B. Wick, *J. Am. Chem. Soc.*, **72**, 1995 (1950).

(6) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); **77**, 5418 (1955).

(7) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

mediate rearranges easily. This order of addition minimizes secondary reaction of the Grignard reagent with the ketone rearrangement product.

(2) When the addition is carried out at 0 to 5°, it is often possible to isolate the intermediate chlorohydrin in good yield; when the addition is followed by several hours at reflux, the ketone rearrangement product is obtained.

(3) Improved yield of ketone product may be realized in some cases by the isolation of the chlorohydrin followed by subsequent rearrangement by treatment with an equivalent of Grignard reagent and refluxing.

(4) The principal side reactions appear to be reaction of the chloroketone forming enolate and consuming Grignard reagent and formation of tertiary alcohols by the reaction of the ketone product with Grignard reagent.

(5) Chlorohydrin products formed in this reaction appear to be predominately the *cis* stereoisomers. These are not rearranged by refluxing in ether with powdered potassium hydroxide,[8] nor in benzene ether with sodium hydride, but are readily rearranged with one equivalent of Grignard reagent followed by refluxing.

(6) Ketone products in yields of 50% to 70% may reasonably be expected from the reaction of aryl Grignard reagents with cyclic α-chloroketones.

EXPERIMENTAL[9,10]

2-Chlorocyclohexanone. 2-Chlorocyclohexanone was prepared by the chlorination of cyclohexanone as described earlier.[11]

2-Chloro-1-phenylcyclohexanol (Procedure A). To an ice-cold solution of 19.5 g. (0.15 mole) of 2-chlorocyclohexanone in 150 cc. of dry benzene was added 100 cc. of 2.3*M* phenylmagnesium bromide solution in ether (0.23 mole) over a 15-min. period. After the addition, the mixture was allowed to stir in the ice bath for 0.5 hr. and was then hydrolyzed by pouring into ice and hydrochloric acid. The residue, after removal of the solvent, was distilled at 0.2–0.3 mm. to give 3 g. forerun (mostly biphenyl), 26 g. (83%) of 2-chloro-1-phenylcyclohexanol, m.p. 32–36°, and 2 g. residue. After several recrystallizations from petroleum pentane, a sample for analysis melted at 37–38°.[3c]

Anal. Calcd. for $C_{12}H_{15}OCl$: C, 68.4; H, 7.2. Found: C, 68.6; H, 7.5.

Rearrangement of 2-chloro-1-phenylcyclohexanol with phenylmagnesium bromide (Procedure B). A solution of 7.0 g. (0.033 mole) of 2-chloro-1-phenylcyclohexanol in 60 cc. of dry benzene was cooled in an ice bath and 15.9 cc. of 2.1*M* phenylmagnesium bromide solution in ether (0.033 mole) was added rapidly. The mixture was refluxed for 6 hr. in an atmosphere of dry nitrogen then hydrolyzed by pouring into iced hydrochloric acid. After extracting with ether, washing, and removing the solvent, the residue crystallized to give 6.0 g. of crude product. One recrystallization from petroleum hexane furnished 5.0 g. (86%) of 2-phenylcyclohexanone m.p. 45–50° (pure m.p. 59–60°).[5] One g. of the ketone gave 1.96 g. of the *2,4-dinitrophenylhydrazone* derivative, m.p. 121–125°. After two recrystallizations from methanol pyridine, the derivative melted at 137–138°.[5] *With potassium hydroxide in ether*[3a]: A solution of 6 g. (0.029 mole) of 2-chloro-1-phenylcyclohexanol in 100 cc. of dry ether was refluxed with 3.2 g. (0.053 mole) of crushed potassium hydroxide for 4 hr. The product proved to be 5.5 g. (92%) unchanged chlorohydrin. A mixed melting point with the starting material showed no depression.

2-(p-Tolyl)cyclohexanone (Procedure C). To a solution of 164 g. (1.24 moles) of 2-chlorocyclohexanone in 600 cc. dry benzene was added 830 cc. (1.24 moles) of 1.5*M* *p*-tolylmagnesium bromide solution with good cooling in an ice bath. The mixture was allowed to come to room temperature, then refluxed for 2 hr. Hydrolysis was accomplished by pouring into dilute ammonium chloride solution. Distillation of the washed ether solution gave 169 g. of crude product distilling below 135° at 1.0 mm. Redistillation gave 160 g. (68%) of 2-(*p*-tolyl)cyclohexanone, b.p. 121–125° at 0.7 mm., m.p. 40–45°. A sample recrystallized from ether and from alcohol melted at 49–50°.

Anal. Calcd. for $C_{13}H_{16}O$: C, 83.0; H, 8.5. Found: C, 82.8; H, 8.6.

The *2,4-dinitrophenylhydrazone* derivative melted at 156–157°.

Anal. Calcd. for $C_{19}H_{20}O_4N_4$: N, 15.2. Found: N, 15.0.

1-(m-Anisyl)-2-chlorocyclohexanol. A Grignard solution prepared from 47 g. (0.25 mole) of *m*-anisyl bromide was added to 19.5 g. (0.15 mole) of 2-chlorocyclohexanone under the conditions of Procedure A. The product was 24 g. (67%) of 1-(*m*-anisyl)-2-chlorocyclohexanol, b.p. 147–148° at 0.3 mm.

Anal. Calcd. for $C_{13}H_{17}O_2Cl$: C, 64.9; H, 7.1. Found: C, 65.7; H, 7.1.

Rearrangement of 1-(m-anisyl)-2-chlorocyclohexanol. Under conditions as described in Procedure B, but with 22 hr. refluxing, 21.5 g. (0.09 mole) of 1-(*m*-anisyl)-2-chlorocyclohexanol was treated with 43 cc. of 2.1*M* phenylmagnesium bromide in ether solution (0.09 mole) to give 17 g. (90%) of 2-(*m*-anisyl)cyclohexanone, b.p. 124–127° at 0.2 mm.[5]

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 75.6; H, 7.9.

The *2,4-dinitrophenylhydrazone* derivative melted at 124–125°.[5]

2-(1-Naphthyl)cyclohexanone. A Grignard solution prepared from 31 g. (0.15 mole) of 1-bromonaphthalene was added to 20 g. (0.15 mole) of 2-chlorocyclohexanone under conditions of Procedure C to give 15.5 g. (48% based on the bromide) of 2-(1-naphthyl)cyclohexanone, m.p. 71–76°. A sample for analysis melted at 86–87°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.1. Found: C, 85.3; H, 7.3.

The *2,4-dinitrophenylhydrazone* derivative melted at 144–145°.

2-Bromo-1-tetralone. 2-Bromo-1-tetralone was prepared by the bromination of 1-tetralone as described by Wilds.[12]

2-Chloro-1-tetralone. 1-Tetralone was chlorinated in glacial acetic acid as previously described.[13] A 50% yield of 2-chloro-1-tetralone was obtained, m.p. 40–42°, b.p. 123–126° at 1.0 mm., n_D^{25} 1.590.

2-Phenyl-1-tetralone. A. From 2-bromo-1-tetralone. The reaction of 15.0 g. (0.066 mole) of 2-bromo-1-tetralone with 45 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.068 mole) under conditions of Procedure C (with 1 hr. at reflux) gave 3.5 g. (24%) of crude 2-phenyl-1-tetralone. Several recrystallizations from alcohol gave a product melting at 76–77°.[14]

(8) P. D. Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).

(9) All m.p.'s corrected unless otherwise indicated.

(10) Microanalyses by J. Sorensen, V. Hobbs, and M. Hines, Microanalytical Laboratory, Department of Chemistry, Northwestern University.

(11) M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syntheses*, **25**, 22 (1945).

(12) A. L. Wilds and J. A. Johnson, Jr., *J. Am. Chem. Soc.*, **68**, 86 (1946).

(13) German Patent **377,587**, *Chem. Centr.*, **95**, I, 956 (1924).

(14) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.5; H, 6.3. Found: C, 87.2; H, 6.0.

The *2,4-dinitrophenylhydrazone* derivative melted at 197–198°.[15]

B. From 2-chloro-1-tetralone. The reaction of 27 g. (0.15 mole) of 2-chloro-1-tetralone with 100 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.15 mole) under conditions of Procedure C gave 14 g. (43%) of 2-phenyl-1-tetralone with 10.0 g. chlorotetralone recovered. Recrystallization of the ketone from alcohol yielded 12.0 g. crystals, m.p. 71–74°.

Reaction of 2-chloro-1-tetralone with excess Grignard reagent. Under the conditions of Procedure C, 27 g. (0.15 mole) of 2-chloro-1-tetralone was treated with 200 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.30 mole) to give a product consisting of 10 g. of recovered 2-chloro-1-tetralone and 24 g. of residue which would not distill at 1 mm. No fraction corresponding to 2-phenyl-1-tetralone was obtained.

2-Chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol. Eighteen g. (0.1 mole) of 2-chloro-1-tetralone was treated with 100 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.15 mole) according to Procedure A to give 15.5 g. (60%) of 2-chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol (140–160° at 0.5 mm.) m.p. 90–95°, with 6.0 g. chlorotetralone recovered. A sample of the chlorohydrin recrystallized several times from ligroin melted at 98–99°.

Anal. Calcd. for $C_{16}H_{15}OCl$: C, 74.3; H, 5.8. Found: C, 74.2; H, 5.8.

This experiment was repeated and the reaction mixture was carbonated by adding powdered Dry Ice before hydrolysis. No benzoic acid was obtained. The product consisted of 42% 2-chloro-1-tetralone and 58% chlorohydrin.

Rearrangement of 2-chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol. A. With Phenylmagnesium bromide. Under conditions of Procedure B, 10 g. (0.039 mole) of 2-chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol was added to 26 cc. (0.039 mole) of 1.5*M* phenylmagnesium bromide solution to give 7.0 g. (81%) of 2-phenyl-1-tetralone, m.p. 71–74°.

B. With sodium hydride. Thirteen g. (0.05 mole) of the chlorohydrin, when refluxed for 3 hr. with 1.3 g. (0.055 mole) of sodium hydride In dry benzene ether, gave 12.0 g. of starting material unchanged, m.p. 85–90°.

(15) A. A. Plentl and M. T. Bogert, *J. Am. Chem. Soc.*, **63**, 989 (1941).

2-Chloroindanone. The procedure used was that described for 2-chloro-1-tetralone. Fractionation of the product obtained from 132 g. (1.0 mole) of 1-indanone gave 92 g. (55%) of 2-chloroindanone [with 28 g. (21%) of 1-indanone recovered]; m.p. 34–38°, from petroleum heptane.[16]

2-Chloro 1-phe l-1-indanol. Under the conditions of Procedure A 25 g. (0 15 mole) of 2-chloroindanone was treated with 100 cc. of 2.1*M* phenylmagnesium bromide solution in ether (0.21 mole) to give 25 g. (69%) of 2-chloro-1-phenyl-1-indanol, m.p. 81–84°. A sample for analysis melted at 87–88°.

Anal. Calcd. for $C_{15}H_{13}OCl$: C, 73.6; H, 5.3. Found: C, 73.3; H, 5.2.

2-Phenylindanone. Ten g. (0.06 mole) of 2-chloroindanone was treated with 51 cc. (0.077 mole) of 1.5*M* phenylmagnesium bromide solution according to Procedure C to give 7.6 g. (60%) of 2-phenylindanone, m.p. 73–75°.[17] The *2,4-dinitrophenylhydrazone* derivative melted at 226–227°

Anal. Calcd. for $C_{21}H_{16}O_4N_4$: N, 14.4. Found: N, 14.1.

1-Keto-1,2,3,4,5,6,7,8-octahydroanthracene. This ketone was prepared as described by Krollpfeiffer and Schäfer.[18] A 75% yield of the ketone, m.p. 41–44°, was obtained.

2-Chloro-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene. The procedure used was that described for the chlorination of 1-tetralone. Twenty-six g. of the ketone gave 20 g. (66%) of the chloroketone, m.p. 61–65°, after crystallization from alcohol. A sample for analysis melted at 66–67°.

Anal. Calcd. for $C_{14}H_{15}OCl$: C, 71.6; H, 6.4. Found: C, 71.1; H, 6.4.

2-Phenyl-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene. Under the conditions of Procedure C, 16.5 g. (0.07 mole) of the chloroketone was treated with 33 cc. of 2.1*M* phenylmagnesium bromide solution in ether (0.07 mole) to give 10.0 g. (52%) of the phenyl ketone, m.p. 132–140°. A sample for analysis melted at 144–145°.

Anal. Calcd. for $C_{20}H_{20}O$: C, 87.0; H, 7.2. Found: C, 87.1; H, 7.3.

The *2,4-dinitrophenylhydrazone* derivative melted at 209–210°.

Anal. Calcd. for $C_{26}H_{24}O_4N_4$: N, 12.2. Found: N, 11.7.

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(16) C. Courtot, A. Fayet, and P. Parant, *Compt. rend.*, **186**, 372 (1928).

(17) P. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, **29**, 1604 (1946).

(18) F. Krollpfeiffer and W. Schäfer, *Ber.*, **56**, 620 (1923).

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Triacylhalomethanes: 2-Halo-2-acyl-1,3-indandiones

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Various 2-halo-2-acyl-1,3-indandiones were prepared for evaluation as blood anticoagulants. Stability and activity paralleled the degree of branching in the acyl group. A halogenation procedure was developed which was particularly useful for the synthesis of the more labile products. The structures of some anomalous bromination products are discussed.

Certain 3-alkyl-4-hydroxycoumarins and 2-acyl-1,3-indandiones have been found to be potent blood anticoagulants[2] and are in general use for the treatment of thrombo-embolism. Somewhat erratic dose-response relationships present the alternative hazards of embolism or hemorrhage and have required that such therapy be very carefully controlled. In a search for improved anticoagulants there have been prepared a number of 2-halo-2-acyl-1,3-indandiones (I), novel triacylhalomethanes.

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(2) W. H. Seegers, *Pharm. Rev.*, **3**, 278 (1951).