[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE UNIVERSITY]

Halogen Migration in the Friedel–Crafts Acylation of Olefins[1]

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RECEIVED NOVEMBER 15, 1952

4-Chlorocyclohexyl phenyl ketone was isolated from the reaction of cyclohexene with benzoyl chloride in the presence of aluminum chloride and the structure of the chloro ketone proven by independent synthesis. The initial reaction in the presence of benzene gave 4-phenylcyclohexyl phenyl ketone. 2-Chlorocyclohexyl phenyl ketone rearranged to 4-chlorocyclohexyl phenyl ketone in the presence of aluminum chloride.

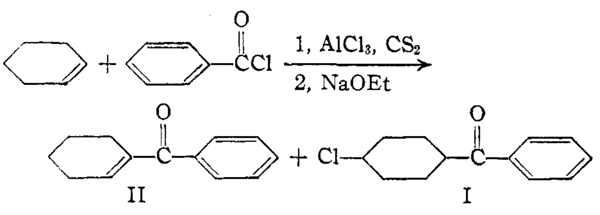
The reaction of an olefinic bond with an acyl halide in the presence of a Friedel–Crafts type catalyst often gives products different from those expected from simple addition to the double bond.[3,4] The present work deals with the isolation and proof of structure of 4-chlorocyclohexyl phenyl ketone (I), which was isolated in 3.5–5% yield from the reaction of cyclohexene and benzoyl chloride in the presence of aluminum chloride. Also, the aluminum chloride catalyst was shown to cause the rearrangement of 2-chlorocyclohexyl phenyl ketone (III) to the 4-chloro ketone (I).

Nenitzescu[3] found that the reaction of acetyl chloride with 1-butene gave 2-butenyl methyl ketone. In the presence of benzene, this reaction gave 3-phenylbutyl methyl ketone. The tendency for the entering group to take the ω-position in this type reaction was illustrated by the work of Johnson[5] who prepared 4-phenylcyclohexyl methyl ketone from the reaction of cyclohexene, acetyl chloride and benzene in the presence of aluminum chloride. Recently, Friess[6] has shown that carbon skeleton rearrangement of the olefin fragment can accompany the reaction of acetyl chloride, cycloheptene and aluminum chloride.

Except for the isolation of a 2-chloro ketone from the simple addition of an acyl chloride to an olefin,[7] no isomeric chloro ketones had previously been isolated in this reaction. Royals[8] reported a chlorine containing impurity in the reaction of acetyl chloride, cyclohexene and stannic chloride, but did not isolate or identify the compound.

From the reaction of benzoyl chloride and cyclohexene in the presence of aluminum chloride, after dehydrohalogenation of the crude chloro ketone mixture with sodium ethoxide, a 40% yield of cyclohexenyl phenyl ketone (II) and a 4% yield of a white crystalline solid[9] were obtained.

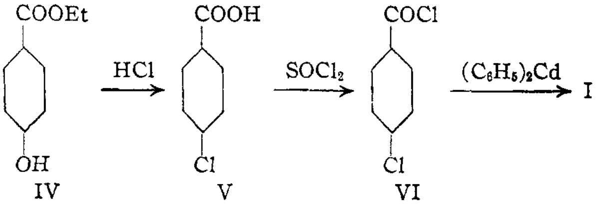
The solid contained chlorine and gave a positive test for a ketone group. The elemental analysis together with the boiling point indicated a molecular formula of $C_{13}H_{15}OCl$, which corresponded to the addition of the elements of benzoyl chloride to cyclohexene. Although Friess[6] reported a case of rearrangement of the olefin fragment in this type reaction, reduction of the chloro ketone with sodium in liquid ammonia gave cyclohexyl phenyl ketone which indicated no carbon skeleton rearrangement in this series.



Oxidation of I gave a 34% yield of benzoic acid which showed that the chlorine was not attached to the benzene ring. Further hydrolysis of the amide resulting from the Beckmann rearrangement of the oxime of the chloro ketone (I) gave benzoic acid.

The 1-chloro ketone was prepared by chlorination of cyclohexyl phenyl ketone,[10] and the 2-chloro ketone (III) was prepared by the addition of hydrogen chloride to the α,β-unsaturated ketone (II) in 58% yield. Each of these chloro ketones was found to be different from I in their physical and chemical properties.

The chloro ketone (I) was shown to be identical in physical and chemical properties with 4-chlorocyclohexyl phenyl ketone prepared by the independent synthesis



The saturated ester (IV) was obtained in 55% yield from ethyl *p*-hydroxybenzoate by reduction[11] using Raney nickel catalyst. The 4-chloro acid (V) was obtained by refluxing the ester (IV) with concentrated hydrochloric acid, after which the 4-chloro acid (V) was converted to the acid chloride (VI) in 42% over-all yield. The acid chloride was then added to a benzene solution of cadmium diphenyl from which 23% of 4-chlorocyclohexyl phenyl ketone (I) was obtained.

The 4-chloroketone also could be obtained by rearrangement of the 2-chloro ketone in the presence of aluminum chloride. The crude chloro ketone mixture was separated by treatment with alcoholic sodium ethoxide, to which reagent the 4-chloro ketone was stable. From this procedure an 8% yield of 4-chloro ketone (I) was obtained and the remaining material consisted largely of α,β-un-

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[1] Presented before the Organic Division at the 119th Meeting of the American Chemical Society in Boston, Mass., March, 1951.

[2] Ethyl Corporation Fellow, 1950–1951.

[3] C. D. Nenitzescu and I. G. Gavat, *Ann.*, **519**, 260 (1935).

[4] C. D. Nenitzescu and I. G. Gavat, *Ber.*, **70**, 1883 (1937).

[5] W. S. Johnson and R. D. Offenhauer, THIS JOURNAL, **67**, 1045 (1945).

[6] S. L. Friess and R. Pinson, Jr, *ibid.*, **73**, 3512 (1951).

[7] J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.*, 278 (1948).

[8] E. E. Royals and C. M. Hendry, *J. Org. Chem.*, **15**, 1149 (1950).

[9] R. C. Fuson and R. E. Christ (THIS JOURNAL, **59**, 895 (1937)), obtained but did not identify the solid from this reaction.

[10] C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952).

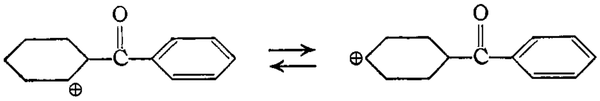
[11] L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 326 (1949).

saturated ketone. No evidence could be obtained that the 4-chloro ketone would rearrange to the 2-chloro ketone under the same conditions.

The reaction of cyclohexene with benzoyl chloride followed by the addition of benzene can be used for the preparation of 4-phenylcyclohexyl phenyl ketone (VII). The reaction is similar to the one used by Johnson[5] for the preparation of open models of estrone. The yield was low (23%) but comparable to the previous work.

The structure of the phenyl ketone (VII) was proven by an independent synthesis from 4-phenylcyclohexanecarbonyl chloride and cadmium diphenyl. Also, when the 4-chloro ketone (I) was allowed to react with benzene and aluminum chloride, a 67% yield of 4-phenyl ketone (VII) was obtained.

The formation of the 4-chloro ketone in the Friedel–Crafts reaction of cyclohexene and benzoyl chloride can be explained by a mechanism similar to that proposed by Johnson.[12] In the present example, the initially formed carbonium ion (VIII) is considered to rearrange in a stepwise fashion to the carbonium ion (IX) in which the charge is furthest removed from the carbonyl group. This carbonium ion (IX) can then combine with chloride ion to form I or alkylate benzene if present to give VII.



VIII IX

The 4-chloro ketone proved very resistant toward dehydrohalogenation and could be separated easily from the 2-chloro isomer, which dehydrohalogenated very readily, even on heating at 80°, to give the α,β-unsaturated ketone. These properties indicate that the chlorine containing impurity cited by Royals[8] to be present after the acylation of cyclohexene with acetyl chloride is 4-chlorocyclohexyl methyl ketone which should be stable to the isolation procedure used.

In the present work, a pure sample of cyclohexenyl phenyl ketone (II), m.p. 32–34°, was prepared in 78% yield from pure 2-chlorocyclohexyl phenyl ketone (III) by heating III at 125° until the hydrogen chloride ceased to be evolved. The cyclohexenyl phenyl ketone (II) from the Friedel–Crafts reaction was slightly impure as shown by the fact that the material failed to crystallize.

Experimental

Cyclohexenyl Phenyl Ketone and 4-Chlorocyclohexyl Phenyl Ketone.—The ketones were prepared from cyclohexene and benzoyl chloride in the presence of aluminum chloride following the method of Fuson and Christ.[9] After distillation of the cyclohexenyl phenyl ketone fraction, the 4-chloro ketone fraction, b.p. 110–115° (0.5 mm.), crystallized and was recrystallized from ethanol, m.p. 113–114°. From 86 g. (1.05 moles) of cyclohexene, 75 g. (40%) of cyclohexenyl phenyl ketone was obtained along with 7.8 g. (3.5%) of the 4-chlorocyclohexyl phenyl ketone. Other similar experiments gave up to 5% yield of the 4-chloroketone. A higher boiling fraction always was obtained which failed to crystallize.

Anal. Calcd. for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79; Cl, 15.92. Found: C, 69.87; H, 6.36; Cl, 15.78.

The oxime of this chloro ketone could be prepared in 82% yield, m.p. 155–157°.

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.79; Cl, 14.91. Found: C, 65.28; H, 7.07; Cl, 14.54.

Reduction of 4-Chlorocyclohexyl Phenyl Ketone.—To a solution of 1 g. of sodium in 80 ml. of liquid ammonia was added with swirling a previously cooled solution of 0.199 g. of the 4-chloro ketone in 6 ml. of anhydrous ether. The resulting mixture was shaken for three minutes and then an excess of ammonium nitrate was added to stop the reaction. Upon evaporation of the solvents the cyclohexyl phenyl ketone was isolated as the 2,4-dinitrophenylhydrazone derivative, 0.15 g. (45%), m.p. 189–190°. A mixed melting point determination with an authentic sample was not depressed, 189–190°.

Oxidation of 4-Chlorocyclohexyl Phenyl Ketone.—The 4-chloro ketone (0.530 g., 2.30 millimoles) was dissolved in 5 ml. of acetic acid. To this solution was added a solution of 1.1 g. of potassium dichromate, 3 ml. of sulfuric acid, 3 ml. of water and 30 ml. of acetic acid. The resulting mixture was stirred at the reflux temperature for three hours. The volatile solvents were removed with the aid of a vacuum pump and the residue was washed with 15 ml. of boiling water. Cooling the solution in an ice-bath gave 0.098 g. (34%) of benzoic acid, m.p. 119–121°.

Rearrangement of the Oxime of I and Hydrolysis of the Resulting Amide.—The oxime of I (0.278 g., 0.001 mole) was dissolved in 30 ml. of anhydrous benzene and 6 g. (0.0028 mole) of phosphorus pentachloride added. The resulting mixture was heated at reflux for a half hour and then poured into cracked ice. The organic layer was extracted several times with water and the excess solvent was removed. Recrystallization from carbon tetrachloride gave 0.195 g. (70%) of N-4-chlorocyclohexyl benzamide, m.p. 189–190°.

Anal. Calcd. for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.79. Found: C, 65.54; H, 7.14.

From the hydrolysis of 0.32 g. of the amide using concentrated hydrochloric acid was obtained 0.03 g. (15%) of benzoic acid, identified by melting point and mixed melting point determinations, m.p. 119–121°.

1- and 2-Chlorocyclohexyl Phenyl Ketones.—The 1-chloro ketone, m.p. 53–54°, was obtained in 81% yield by the previously described procedure.[10]

2-Chlorocyclohexyl phenyl ketone was prepared by slowly bubbling dry hydrogen chloride into a cold solution of 10 g. (0.054 mole) of cyclohexenyl phenyl ketone in 12 ml. of glacial acetic acid. After an hour, the precipitate which had formed was filtered. Recrystallization from cyclohexane gave 6.8 g. (58%) of the 2-chloro ketone, m.p. 100–101°. During the recrystallization, partial dehydrochlorination will occur if the temperature rises above 85°.

Anal. Calcd. for $C_{13}H_{13}ClO$: C, 70.11; H, 6.79; Cl, 15.92. Found: C, 70.52; H, 7.20; Cl, 15.31.

Independent Synthesis of 4-Chlorocyclohexyl Phenyl Ketone.—Ethyl *p*-hydroxybenzoate, m.p. 115–116°, was prepared in 85% yield from *o*-hydroxybenzoic acid by the method of Cavill.[13]

Ethyl 4-hydroxycyclohexane carboxylate was prepared in 55% yield by the reduction of ethyl *p*-hydroxybenzoate according to the procedure of Owen and Robins[11] except that 6 drops of 10% potassium hydroxide was added to the reaction mixture before hydrogenation. The ester was purified by distillation, b.p. 88–90° (0.3 mm.), $n^{25}\mathrm{D}$ 1.4660.

4-Chlorocyclohexanecarboxylic acid chloride was obtained by treatment of 4.3 g. (0.026 mole) of the ester with 10 ml. of concentrated hydrochloric acid. After the mixture was heated to reflux for four hours, the chloro acid was separated from the solution and was removed by extraction with 25 ml. of benzene. The benzene was removed by evaporation and to the resulting oil was added 6 ml. of thionyl chloride. The solution was then heated at reflux for two hours, after which the excess thionyl chloride was removed and the chloro acid chloride was distilled to give 2 g. (42%) of 4-chlorocyclohexanecarboxylic acid chloride b.p. 75–77° (1.2 mm.).

Anal. Calcd. for $C_7H_{10}Cl_2O$: Cl, 39.18. Found: Cl, 38.62.

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[12] W. S. Johnson, *Record Chem. Progress*, **10**, 53 (1949).

[13] G. W. K. Cavill and J. M. Vincent, *J. Soc. Chem. Ind.*, **66**, 175 (1947).

4-Chlorocyclohexyl phenyl ketone was prepared from the acid chloride by treatment with diphenyl cadmium. The Grignard reagent was prepared in the usual manner from 0.98 g. (0.196 atom) of magnesium ribbon and 2 g. (0.196 mole) of bromobenzene. The mixture was cooled in an ice-bath and 5.5 g. of anhydrous cadmium chloride was slowly added over a period of three minutes. After stirring at room temperature for an additional 45 minutes, a negative test for the presence of Grignard reagent was obtained by the use of Michler ketone.

The ether was removed under vacuum and 30 ml. of anhydrous thiophene-free benzene was added. A solution of 5.0 g. (0.0304 mole) of the acid chloride in 20 ml. of benzene was added slowly with vigorous stirring and the resulting mixture was stirred at the reflux temperature for three hours. After hydrolysis, the benzene layer was separated and the excess solvent was removed. The remaining material was dissolved in 40 ml. of ethanol in which sodium ethoxide had been prepared from 0.8 g. of sodium.

After refluxing for three hours the solvent was removed and the organic material dissolved in ether was washed with water. On removal of the ether the ketone crystallized and was recrystallized from ethanol to give 1.5 g. (23%) of the 4-chlorocyclohexyl phenyl ketone, m.p. 112–114°, with no depression of mixed melting point with the ketone from the Friedel–Crafts reaction.

Rearrangement of 2-Chlorocyclohexyl Phenyl Ketone.—The 2-chloro ketone (4 g., 0.018 mole) was dissolved in 60 ml. of dry carbon disulfide and the resulting solution was cooled in an ice-bath. Anhydrous aluminum chloride (4 g., 0.030 mole) was then slowly added and the resulting mixture was stirred in the ice-bath for one-half hour and at room temperature for 2 hours.

After hydrolysis, the excess solvent was removed from the organic layer. To the residue was added a sodium ethoxide solution prepared from 0.4 g. (0.018 atom) of sodium. The resulting solution was heated at reflux for three hours, after which the ethanol was removed. The residue was dissolved in ether and washed with water. The ether solution was dried with sodium sulfate and distilled to give 0.32 g. (8%) of 4-chlorocyclohexyl phenyl ketone, b.p. 107–115° (0.15 mm.), m.p. 110–112°, mixed melting point, 110–112°. A forerun, b.p. 94–107° (0.15 mm.), consisted mostly of cyclohexenyl phenyl ketone. A higher boiling fraction, b.p. 115–120° (0.15 mm.), failed to crystallize.

Attempted Rearrangement in 4-Chlorocyclohexyl Phenyl Ketone.—The 4-chloro ketone (3 g., 0.015 mole) was subjected to the same reaction conditions used for the 2-chloro ketone. After treatment with ethanolic sodium ethoxide, 1.13 g. (38%) of starting 4-chloro ketone could be recovered. No cyclohexenyl phenyl ketone was formed indicating no 2-chloro ketone was present in the original reaction mixture. The remainder of the material had b.p. 120–140° (0.7 mm.) and failed to crystallize.

4-Phenylcyclohexyl Phenyl Ketone.—In a reaction flask was placed 50 g. (0.356 mole) of benzoyl chloride, 180 ml. of carbon disulfide and 60 g. (0.45 mole) of anhydrous aluminum chloride. After cooling to −5°, 30 g. (0.366 mole) of cyclohexene was added slowly. After addition of the cyclohexane the reaction temperature was kept at −20° for an additional 15 minutes. The solvent was poured from the thick mass and 300 ml. of dry benzene was added. The mixture was heated at 40–45° with stirring for 3 hours. After hydrolysis with dilute hydrochloric acid, the material was distilled through a Claisen-type flask to give two fractions, b.p. 125–135° (0.7 mm.) and b.p. 178–205° (0.8 mm.). The latter fraction crystallized and gave 21.6 g. (23%) of white crystalline 4-phenylcyclohexyl phenyl ketone, m.p. 102–103°, after recrystallization from ligroin.

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.62. Found: C, 86.39; H, 7.94.

Independent Synthesis of 4-Phenylcyclohexyl Phenyl Ketone.—4-Phenylbenzoic acid was prepared in 50% yield by carbonation of the Grignard reagent made from 8.3 g. (0.344 atom) of magnesium ribbon, 40 g. (0.172 mole) of 4-phenylbromobenzene and 24.4 g. (0.172 mole) of methyl iodide. The acid, 17.1 g., was recrystallized from ethanol, m.p. 221–222°.

Following the procedure of Johnson,[6] 4-phenylcyclohexanecarboxylic acid, m.p. 201–202°, was obtained in 68% yield from 5 g. of the 4-phenylbenzoic acid.

The 4-phenylcyclohexanecarboxylic acid (1.5 g., 7.4 millimoles) was converted to the acid chloride using thionyl chloride and then to 1.01 g. (52%) of 4-phenylcyclohexyl phenyl ketone utilizing the reaction of an acid chloride with diphenyl cadmium as described above. The ketone had m.p. 101–102° and the mixed melting point with material from the Friedel–Crafts reaction was not depressed.

4-Phenylcyclohexyl Phenyl Ketone from 4-Chlorocyclohexyl Phenyl Ketone.—The 4-chloro ketone (2.8 g., 0.014 mole) was dissolved in 50 ml. of anhydrous benzene. After cooling the mixture in an ice-bath, 2.2 g. of aluminum chloride was added slowly and the resulting mixture was stirred in the ice-bath for one-half hour and at 40–45° for one hour. After hydrolysis, 2.5 g. (67%) of the 4-phenyl ketone, m.p. 101–102°, could be isolated from the organic layer. A mixed melting point with the previously prepared ketone was not depressed.

Cyclohexenyl Phenyl Ketone from 2-Chlorocyclohexyl Phenyl Ketone.—In a small flask was placed 1 g. (4.5 millimoles) of the 2-chloro ketone. The flask was heated in an oil-bath at 125° until all evolution of hydrogen chloride ceased. The resulting material was dissolved in refluxing petroleum ether. After the solution cooled, 0.65 g. (78%) of white, crystalline cyclohexenyl phenyl ketone,[14] m.p. 32–34°, was obtained. In a carbon tetrachloride solution, the ketone readily absorbed an equivalent of bromine.

DETROIT 1, MICHIGAN

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[14] C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 5352 (1952).