Summary

t-Butyl chloride in 10–17% yields has been obtained by treating *t*-amyl chloride with anhydrous hydrogen fluoride at 0°.

In addition to the *t*-butyl chloride, there was obtained a mixture probably containing hexyl, heptyl, decyl or undecyl, and pentadecyl chlorides.

STATE COLLEGE, PENNSYLVANIA RECEIVED JULY 1, 1938

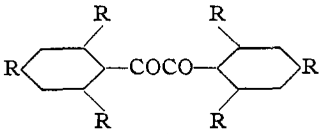
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Action of Methylmagnesium Halides on 2,4,6-Trisubstituted Benzoyl Chlorides

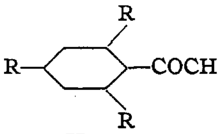
BY REYNOLD C. FUSON, J. H. VAN CAMPEN AND D. E. WOLF

The reaction of 2,4,6-trisubstituted benzoyl chlorides with methylmagnesium halides has been shown to give rise to three different types of products, depending on the nature of the substituents. In order to determine the influence of the substituents on the course of the reaction we have studied the action of methylmagnesium halides on certain benzoyl chlorides carrying alkyl groups or halogen atoms in the *ortho* positions.

In all cases the initial reaction is evidently either (1) coupling of the acid chloride to yield a benzil or (2) methylation to give the corresponding methyl ketone. For example, with 2,4,6-trimethylbenzoyl chloride and 2,4,6-triethylbenzoyl chloride both types of reactions are observed. The corresponding hexaalkylbenzils (I) and 2,4,6-trialkylacetophenones (II) are formed in nearly equal amounts.[1]

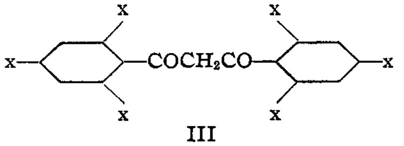


I



II

However, halogen atoms in the *ortho* positions suppress the coupling reaction entirely. 2,4,6-Trichlorobenzoyl chloride gives none of the benzil. The methyl ketone appears to be the primary product. It is of interest that this ketone is acylated readily, and under the conditions used is isolated chiefly as the corresponding 1,3-diketone (III, x = Cl).[2]

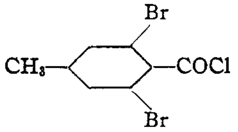


III

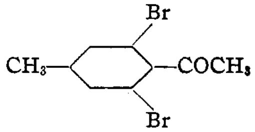
2,4,6-Tribromobenzoyl chloride reacted very sluggishly with methylmagnesium bromide or iodide, and the chief product was the 1,3-diketone, di-(2,4,6-tribromobenzoyl)-methane. The methyl ketone also was isolated in small amounts. Bromination of the diketone gave a heptabromo derivative, which could be reduced to the parent diketone by treatment with hydrogen iodide. The heptabromo compound, like the original diketone, gave a red color with an alcoholic ferric chloride solution. These facts serve to confirm the structures of the compounds in question.

Some evidence also is available to indicate that the 1,3-diketone is the result of a secondary reaction involving the methyl ketone. When the iodomagnesium enolate of the latter was treated with 2,4,6-tribromobenzoyl chloride the 1,3-diketone (III, x = Br) was formed.

One condensation was carried out with 2,6-dibromo-4-methylbenzoyl chloride (IV) and methylmagnesium iodide.



IV



V

The chloride was added slowly to a concentrated solution containing a great excess of the Grignard reagent. In this case also the reaction was exclusively of the second type; however, it stopped at the first stage giving only the methyl ketone (V). The identity of the latter was confirmed by converting it into the benzal derivative.

Experimental

A. Preparation of the Acid Chlorides

2,4,6-Trichlorobenzoyl Chloride.—This compound was prepared from 2,4,6-trichloroaniline by way of the nitrile and acid. For the synthesis of the nitrile a modification of Montagne's method[3] was employed. The nitrile was isolated by extraction and used without further purification.

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(1) Fuson and Corse, THIS JOURNAL, **60**, 2063 (1938).

(2) Ross and Fuson, *ibid.*, **59**, 1508 (1937).

(3) Montagne, *Rec. trav. chim.*, **21**, 376 (1902).

It was converted into the acid chloride by the method of Fuson, Bertetti and Ross.[4]

2,4,6-Tribromobenzoyl Chloride.—Attempts were made to prepare 2,4,6-tribromobenzonitrile using the diazotization methods of Montagne[3] and de Milt and Van Zandt.[5] However, a modification of the method of Schoutissen[6] proved to be more satisfactory. The following is an illustrative procedure for the diazotization and subsequent replacement.

One hundred grams of 2,4,6-tribromoaniline was dissolved in 300 cc. of concentrated sulfuric acid and the solution cooled to 0°. To this mixture was added an ice-cold solution of nitrosyl sulfuric acid, prepared by adding 28 g. of sodium nitrite to 300 cc. of ice-cold concentrated sulfuric acid, warming and stirring until clear. The temperature was kept below 10° while 600 cc. of 85% phosphoric acid was added dropwise, with vigorous stirring. The stirring was continued for an hour after the addition was complete. The solution was poured, with stirring, into a warm (60°) solution of 280 g. of potassium cyanide and 275 g. of copper sulfate in 600 cc. of water. After about ten hours the mixture was filtered and the nitrile was removed from the mixture of solids by extraction with ether. The nitrile was used without purification. The yield of crude product was 90–100 g.

The hydrolysis of the nitrile was carried out according to the method of Fuson, Bertetti and Ross.[4] The reaction mixture was stirred and refluxed for seven to eight hours instead of three.

Dry, crystalline 2,4,6-tribromobenzoic acid was mixed with slightly less than the molar equivalent of phosphorus pentachloride. The reaction commenced spontaneously and the mixture soon liquefied. The mixture was then heated on the steam cone for two hours. The phosphorus oxychloride was distilled under slightly reduced pressure and the acid chloride collected at 140–141° (2 mm.); 152–154° (4 mm.). The colorless distillate solidified in the receiver; m. p. 47–49°.[7] The yield was 88–92% of the theoretical.

2,6-Dibromo-4-methylbenzoyl Chloride.—2,6-Dibromo-4-methylbenzonitrile, prepared from the corresponding amine by the method of Montagne,[3] was dissolved in a mixture of sulfuric acid, acetic acid and water in the ratio 2:1:1 by volume. After being refluxed, with stirring, for eight or nine hours the reaction mixture was cooled to 0° and an excess of sodium nitrite was added in concentrated aqueous solution. The resulting acid was converted to the acid chloride by the action of phosphorus pentachloride. The melting point of the acid chloride corresponded to that reported by Buning.[8]

B. Reaction of the Acid Chlorides with Methylmagnesium Halides

2,4,6-Trichlorobenzoyl Chloride.—A number of runs according to the procedure of Ross and Fuson[2] gave yields of 32–40% of the theoretical amount of di-(2,4,6-trichlorobenzoyl)-methane. The use of a two-fold excess of 0.5 molar solution of methylmagnesium bromide solution seems to give the best results.

The structure of the diketone was confirmed by transforming it into the dibromide and reducing the latter to regain the original diketone. The reduction of the dibromide was carried out as follows.

One gram of powdered potassium iodide and 0.8 cc. of water were added to 100 cc. of a saturated solution of potassium iodide in acetone. A solution of 1 g. of di-(2,4,6-trichlorobenzoyl)-dibromomethane and 1 cc. of concentrated hydrochloric acid in 25 cc. of acetone was added dropwise, with stirring, to the iodide solution over a period of about thirty minutes. The solution was stirred for twelve hours, condensed with a stream of air to about 35 cc. and then poured into 150 cc. of water. The iodine was removed with sodium bisulfite, the solution extracted with ether, and the ethereal extract dried over anhydrous magnesium sulfate. Distillation of the ether left a solid residue which was recrystallized from methyl alcohol, giving 0.7 g. of di-(2,4,6-trichlorobenzoyl)-methane, m. p. 158–160°. The yield was 96% of the theoretical amount.

Di-(2,4,6-trichlorobenzoyl)-bromomethane.—One and five-tenths grams of di-(2,4,6-trichlorobenzoyl)-methane was dissolved in 150 cc. of glacial acetic acid, 5 cc. of bromine was added all at once, and the mixture was allowed to stand at room temperature for three to five days. The solution was poured, with stirring, into 1500 cc. of water and sodium bisulfite added to discharge the bromine color; an excess of bisulfite was carefully avoided. After standing for several hours the product was collected on a filter and dried. The crude di-(2,4,6-trichlorobenzoyl)-bromomethane weighed 1.7 g. After repeated recrystallization from low-boiling petroleum ether this material melted at 163–164°. It was very soluble in ether, chloroform, carbon tetrachloride, benzene and dioxane, and was slightly soluble in ethyl alcohol, methyl alcohol, ethyl acetate and petroleum ether. It was insoluble in dilute alkali, gave a red color immediately with alcoholic ferric chloride solution and imparted a yellow color to concentrated sulfuric acid.

One gram of this material was recovered unchanged after refluxing for three days in a solution of 5 cc. of bromine in 100 cc. of chloroform.

Anal. Calcd. for $C_{15}H_5O_2Cl_6Br$: C, 35.33; H, 0.99; mol. wt., 510. Found: C, 35.46; H, 1.09; mol. wt., 489.

2,4,6-Tribromobenzoyl Chloride.—2,4,6-Tribromobenzoyl chloride was refluxed for ninety hours at 50° with two equivalents of 0.5 molar methylmagnesium bromide or iodide and the resulting mixture decomposed with dilute hydrochloric acid. The ether was evaporated by a stream of air and the solid separated by decantation through a Büchner funnel. The solid was twice washed with ether by decantation and the aqueous solution extracted with three portions of ether. The combined ethereal extract was dried over anhydrous sodium sulfate.

The yield of this crude solid, di-(2,4,6-tribromobenzoyl)-methane, was 38% of the theoretical. After four recrystallizations from a mixture of benzene and alcohol, this compound melted at 244–245°, with decomposition.

Anal. Calcd. for $C_{15}H_6O_2Br_6$: C, 25.78; H, 0.86; Br, 68.77; mol. wt., 698. Found: C, 25.84; H, 0.89; Br, 68.79; mol. wt., 669.

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(4) Fuson, Bertetti and Ross, THIS JOURNAL, **54**, 4380 (1932).

(5) De Milt and Van Zandt, *ibid.*, **58**, 2044 (1936).

(6) Schoutissen, *ibid.*, **55**, 4531 (1933).

(7) Sudborough, *J. Chem. Soc.*, **67**, 587 (1895).

(8) Buning, *Rec. trav. chim.*, **40**, 327 (1921).

The di-(2,4,6-tribromobenzoyl)-methane was soluble in chloroform, carbon tetrachloride and benzene, slightly soluble in *n*-butyl alcohol and petroleum ether, but quite insoluble in ether, alcohol, acetic acid, ethyl acetate and methyl alcohol. It was not affected by boiling for three days with a 50% solution of sodium hydroxide in 20% alcohol. The compound gave a red color in alcoholic ferric chloride solution and a yellow color with concentrated sulfuric acid. A blue-gray copper derivative was formed when a benzene solution of the compound was shaken for thirty minutes with a saturated aqueous solution of copper acetate. The copper derivative could be purified by dissolving in chloroform and reprecipitating with a small amount of alcohol.

Distillation of the ether from the ethereal extract obtained above left a dark, oily residue. By steam distillation and subsequent recrystallization from high-boiling petroleum ether 2,4,6-tribromoacetophenone was obtained, m. p. 86–90°. After recrystallization this material melted at 93°. No depression in the melting point was noted when this material was mixed with an authentic sample of 2,4,6-tribromoacetophenone prepared by diazotization of 3 - amino - 2,4,6 - tribromoacetophenone. The yield of methyl ketone was about 16% of the theoretical.

No advantage was apparent in using chlorobenzene along with ether as a solvent and at the same time carrying out the reaction at 80–90°.[9]

2,4,6-Tribromoacetophenone.—Seventy-five cubic centimeters of 2.2 molar methylmagnesium iodide was heated on a water-bath until no more ether would distil. At this point 45 cc. of ether had been collected. The condenser was then set for refluxing and stirring begun. A solution of 5 g. of 2,4,6-tribromobenzoyl chloride in 15 cc. of anhydrous benzene was added dropwise, the rate of addition being adjusted so that forty-five minutes was required for the entire operation. Throughout the reaction the temperature was maintained at 95° by means of a water-bath. The stirring was continued for eighty minutes, the mixture cooled, and 50 cc. of anhydrous ether added. The resulting solution was poured into ice and hydrochloric acid, the ether layer separated and the aqueous layer extracted with ether. The combined ethereal extract was washed with dilute bicarbonate solution, with water and then dried over anhydrous magnesium sulfate. Distillation of the ether left a brown oil. After steam distillation of this oil and recrystallization of the distillate from high-boiling petroleum ether, 2.2 g. of a solid material was obtained; m. p. 80–86°. After recrystallization this material melted at 92°. It was shown by mixed melting point to be 2,4,6-tribromoacetophenone. The yield was 46% of the theoretical.

Di-(2,4,6-tribromobenzoyl)-methane from 2,4,6-Tribromoacetophenone and 2,4,6-Tribromobenzoyl Chloride.—Two grams of 2,4,6-tribromoacetophenone was dissolved in 25 cc. of anhydrous benzene and to this was added 3.1 cc. of 2.2 molar methylmagnesium iodide. The solution was refluxed for two hours. Two and one-tenth grams of 2,4,6-tribromobenzoyl chloride was added and the resulting mixture was refluxed for thirty hours. The mixture was poured into dilute hydrochloric acid, stirred well and the benzene layer separated and dried. Distillation of the benzene left a residue of liquid and solid. Alcohol was added and the solid collected on a filter. The di-(2,4,6-tribromobenzoyl)-methane thus obtained weighed 2.1 g. and melted at 239–241°, with decomposition. After recrystallization from benzene and alcohol the compound melted at 244–245°, with decomposition. The yield of diketone was 54% of the theoretical.

Di-(2,4,6-tribromobenzoyl)-bromomethane

1. With Bromine in Chloroform.—Eighty-five hundredths of a gram of di-(2,4,6-tribromobenzoyl)-methane was dissolved in 100 cc. of chloroform. Six cubic centimeters of bromine was added all at once and the mixture allowed to stand for three days at room temperature under the light of a 300-watt lamp. The resulting solution was washed with dilute sodium bisulfite solution, with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent and recrystallization from chloroform gave 0.7 g. of di-(2,4,6-tribromobenzoyl)-bromomethane which softened at 264° and melted, with decomposition, at 270–272°. The yield was 74% of the theoretical. After four recrystallizations from chloroform the compound softened at 264° and decomposed at 272–273°. If the tube containing the material was inserted in the bath at 260°, the compound softened at 266° and decomposed at 274–276°. The decomposition point as determined on the Maquenne block was 282°.

Anal. Calcd. for $C_{15}H_5O_2Br_7$: C, 23.20; H, 0.65. Found: C, 23.45; H, 1.01.

The solubility of this compound is very similar to that of di-(2,4,6-tribromobenzoyl)-methane. The substance gives a red color with alcoholic ferric chloride solution, the color deepening with warming, and imparts a yellow color to concentrated sulfuric acid.

2. With Sodium Hypobromite.—One gram of di-(2,4,6-tribromobenzoyl)-methane was dissolved in 20 cc. of pyridine and this solution added to 100 cc. of 10% sodium hypobromite solution. The mixture was shaken for seven days at room temperature and then extracted with two 75-cc. portions of benzene. This extract was dried over calcium chloride and the solvent distilled under reduced pressure. Recrystallization of the solid residue from chloroform gave 1 g. of di-(2,4,6-tribromobenzoyl)-bromomethane which softened at 264° and decomposed at 270–272°. The yield was 90% of the theoretical.

Reduction of Di-(2,4,6-tribromobenzoyl)-bromomethane.—One gram of this compound was reduced by the method described above for di-(2,4,6-trichlorobenzoyl)-bromomethane. Eight-tenths of a gram of di-(2,4,6-tribromobenzoyl)-methane was obtained, m. p. 233–238°.

Reaction of 2,6-Dibromo-4-methylbenzoyl Chloride with Methylmagnesium Iodide.—Thirty-two grams of the acid chloride in twice its volume of dry ether was added over a period of one hour to a boiling 5 molar solution of methylmagnesium iodide which contained a nine-fold excess of the reagent. The addition was accompanied by vigorous stirring. .The reaction mixture was diluted with 800 cc. of ether and poured slowly into ice and dilute hydrochloric acid. By extraction with ether the methyl ketone was obtained as a red oil which crystallized when cooled. After five recrystallizations from 95% ethanol,

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[9] Gilman and St. John, *Rec. trav. chim.*, 49, 222 (1930).

the solution being treated each time with Darco, the white crystalline product melted at 53–54°.

Anal. Calcd. for $C_9H_8OBr_2$: C, 37.03; H, 2.74; Br, 54.75; mol. wt., 292. Found: C, 37.41; H, 3.08; Br, 54.69; mol. wt., 286.

The Benzal Derivative of 2,6-Dibromo-4-methylacetophenone.—The identity of the methyl ketone was confirmed by condensing it with benzaldehyde. About 6 g. of the crude ketone was mixed with 20 cc. of 10% sodium hydroxide solution, 10 cc. of 95% ethyl alcohol and 10 cc. of benzaldehyde. The mixture was shaken for twenty hours at room temperature. At the end of this period there was a yellow mixture of crystals and oil at the bottom of the flask. The entire mixture was shaken with ether which was then washed with bisulfite solution. The ether solution was washed with water, dried and evaporated giving a crystalline residue. After the crystals were washed with petroleum ether and recrystallized three times from ethyl alcohol they melted at 96–97°.

Anal. Calcd. for $C_{16}H_{12}OBr_2$: C, 50.57; H, 3.16; Br, 42.06; mol. wt., 380 Found: C, 51.06; H, 3.21; Br, 42.43; mol. wt., 379.

Summary

2,4,6-Trihalobenzoyl chlorides react with methylmagnesium halides to give the corresponding di-(2,4,6-trichlorobenzoyl)-methanes. Under suitable conditions the methyl ketone, undoubtedly an intermediate in the reaction, can be isolated.

The structure of the 1,3-diketones was proved by converting them to the corresponding mono- or dibromides and then regaining the original diketone by debromination.

2,6-Dibromo-4-methylacetophenone was obtained by the interaction of 2,6-dibromo-4-methylbenzoyl chloride and an excess of methylmagnesium iodide.

URBANA, ILLINOIS RECEIVED JUNE 17, 1938

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

Reformatsky Condensations Involving Vinylogs of Haloacetic Esters

BY REYNOLD C. FUSON, R. T. ARNOLD AND H. G. COOKE, JR.

The extension of the Reformatsky method to vinylogs of haloacetic esters was attempted with the hope of obtaining a method of synthesizing carotenoid chains. The general reaction sought was the following

$$XCH_2(CH{=}CH)_nCOOR \xrightarrow[Zn]{RCHO} R(CH{=}CH)_{n+1}COOR$$

Results obtained with ethyl γ-bromo- and γ-iodocrotonate show that the desired reaction takes place. The value of the method in synthetic work would appear to be conditioned by the availability of the γ-halocrotonates.

Ethyl γ-bromo- and γ-iodocrotonate react with benzaldehyde in the presence of zinc to give an oil which can be hydrolyzed to cinnamylideneacetic acid

$$XCH_2CH{=}CHCOOC_2H_5 \xrightarrow{C_6H_5CHO} C_6H_5(CH{=}CH)_2COOH$$

Cyclohexanone reacts similarly, giving the expected unsaturated ester, $C_6H_{11}(CH{=}CH)_2COOC_2H_5$.

Ethyl iodocrotonate also was condensed with *p*-chlorobenzaldehyde to give *p*-chlorocinnamylideneacetic acid. This acid was synthesized for comparison from *p*-chlorocinnamaldehyde and malonic acid.

It was of particular interest to compare the behavior of ethyl γ-iodocrotonate with that of the corresponding saturated ester, ethyl γ-iodobutyrate, to see what influence the vinylene linkage really had. The condensation reaction depends chiefly on the reactivity of the halogen atom which in turn is due presumably to the activating influence of the carbethoxy group. The transfer of this effect should be much more efficient in the vinylogs of haloacetic esters than in the corresponding saturated esters. This was found to be the case. Ethyl γ-iodobutyrate condenses with benzaldehyde in the presence of zinc to give the normal Reformatsky condensation but the reaction proceeds very slowly and the yields are almost negligible.

Experimental

The Condensation of Ethyl γ-Bromo- and γ-Iodocrotonate with Benzaldehyde.—Nineteen grams of ethyl γ-iodocrotonate[1] in 20 cc. of dry, peroxide-free butyl ether was added dropwise to a mixture of 16 g. of benzaldehyde, 30 cc. of butyl ether and 5.5 g. of zinc dust. The zinc dust was cleaned by treatment for a few seconds with dilute hydrochloric acid and subsequent washing with water, acetone and dry benzene. It was not allowed to stand in contact with the air. The mixture was refluxed, with stirring, for thirty-six hours, then decomposed with very

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(1) Braun, THIS JOURNAL, **52**, 3174 (1930).