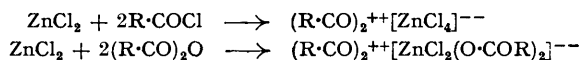


**157. Acylation Reactions catalysed by Strong Acids. Part V. Mixtures of Zinc Chloride and Acetyl Chloride or Acetic Anhydride as Sources of Acetylium Ions.**

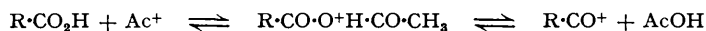
By H. BURTON and P. F. G. PRAILL.

Mixtures of zinc chloride and an excess of acetyl chloride or acetic anhydride are good sources of acetylium ions and will convert anisole into *p*-methoxyacetophenone in high yields. The catalytic activity of the salt for the reaction between anisole and acetyl chloride is considerable.

THE electronic configuration of zinc chloride is such that, when it is used as a catalyst for the Friedel-Crafts reaction, there could be produced from an acid chloride or acid anhydride twice as many acylium ions (acyl cations) per molecule of salt as when aluminium chloride is employed. Completion of the outer octet of electrons would necessitate the following reactions :



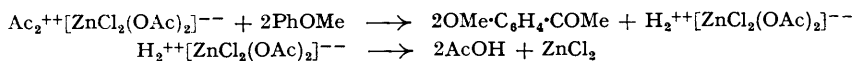
If the production of acylium ions was the sole factor in determining the success of the Friedel-Crafts reaction, then clearly zinc chloride should be a far more efficient catalyst than aluminium chloride, which can give rise to only one acyl cation per molecule. It is well known however that zinc chloride is generally considered to be a not very efficient catalyst. We would point out however that mixtures of zinc chloride and acetic anhydride-acetic acid have often proved useful (see Johnson, "Organic Reactions," Vol. II, 1944, p. 114) for the intramolecular Friedel-Crafts reaction leading to cyclic ketones. It seems probable in these cases that the carboxylic acid and the acetylium ion (or its equivalent) react as follows :



and that cyclisation depends on the loss of a proton from the  $\text{R}\cdot\text{CO}^+$  ion which must, of necessity, be suitably constituted if the overall reaction is to take place.

We now show that zinc chloride (1 mol.) with an excess of acetic anhydride will rapidly convert, under relatively mild conditions, more than 1 mol. of anisole into *p*-methoxyacetophenone. Thus with a molecular ratio of zinc chloride, anisole, and acetic anhydride of 1 : 2 : 4

there is an extremely rapid production of 1.2 mols. of isolable ketone.\* With a ratio of 1 : 3 : 4 in the presence of nitromethane we isolated as much as 1.4 mols. of *p*-methoxyacetophenone after the same time interval, presumably because of the increased rate of reaction. We conclude that these results prove that the above reaction between acetic anhydride and zinc chloride does in fact occur. During these experiments there is no evolution of hydrogen chloride or acetyl chloride and it is thus clear that the reaction with anisole proceeds as follows :



We have also shown that mixtures of zinc chloride and acetic acid have no action on anisole : furthermore, acetic anhydride and anisole alone do not give any ketone when an equimolecular mixture is boiled for several hours.

It will be apparent from the above scheme that, provided no side reactions involving the zinc chloride occurred, the process should be a strictly catalytic one. Actually, the *p*-methoxyacetophenone formed reacts with acetic anhydride and zinc chloride to give a yellow crystalline compound (containing zinc), which is highly fluorescent in alcoholic solution and is undoubtedly a pyrylium salt of the type described by Dilthey (*J. pr. Chem.*, 1916, [ii], 94, 75). We have mentioned previously (*J.*, 1950, 1203) the formation of an analogous compound in experiments with anisole, acetic anhydride, and perchloric acid.

The formation of the fluorescent salt clearly occurs at a much slower rate than the acetylation of anisole, and accordingly we have carried out a series of experiments using an equimolecular mixture of anisole and acetyl chloride to which was added very small amounts of some typical Friedel-Crafts catalysts, in an attempt to decide whether a strictly catalytic effect could, in fact, be observed. We first showed that *p*-methoxyacetophenone, acetyl chloride, and zinc chloride gave, under similar conditions, the same type of yellow fluorescent solid. Incidentally we found that such mixtures gave an intense deep blue colour as soon as the mixture was warmed.

It has however been reported by Dermer, Wilson, Johnson, and Dermer (*J. Amer. Chem. Soc.*, 1941, 63, 2881, footnote) that anisole and acetyl chloride react in the absence of any catalyst to give an approximately 30% yield of *p*-methoxyacetophenone : no experimental details were given. We have therefore carried out all our experiments with AnalaR acetyl chloride and purified anisole which when refluxed for 4—8 hours in equimolecular proportions gave only traces (maximum yield, 0.15% of anisole used) of the ketone. Our experiments clearly indicate that these authors must have been using acetyl chloride which was probably contaminated with a metallic chloride : we shall refer to this point at a later stage.

Our experiments with traces of three typical metal chlorides, namely, aluminium, ferric, and zinc, indicate clearly that for added small amounts (0.075% of the weight of acetyl chloride) and a reaction period of 4 hours the yield of *p*-methoxyacetophenone is increased out of all proportion to the amount of catalyst used. The amounts of ketone actually isolated, as such or as the 2 : 4-dinitrophenylhydrazone, were of the order of 2.2% for aluminium and ferric chlorides and 7.2% for zinc chloride. The result with zinc chloride was not altogether unexpected since it seemed that the zinc chloride was inactivated at a much slower rate than either aluminium or ferric chloride. We decided therefore to investigate the activity of zinc chloride in more detail. An increase in the reaction time from 4 to 7 hours for the same amount of catalyst resulted in an improved yield (at least 8.4%), and an increase in the amount of the salt (to 0.19%) resulted in a further increase in the yield of ketone to at least 11.7% after 7 hours. The last result is more illuminating if expressed in the following way : addition of approximately 0.00025 g.-mol. of zinc chloride (technical or its equivalent of pure or AnalaR anhydrous zinc acetate, which must be converted into the chloride under the experimental conditions) to a mixture of 0.2 g.-mol. each of anisole and acetyl chloride results in the production after 7 hours' refluxing of no less than 0.0233 g.-mol. of *p*-methoxyacetophenone. The molecular ratio of ketone isolated to catalyst used is thus at least 93 : 1.

In this series of experiments with anisole we observed some striking colour changes : a purple colour of varying intensity develops with the use of the metal chlorides and in the case of zinc chloride becomes progressively more brown. At the same time orange crystalline material separates slowly during the reaction and this is undoubtedly a pyrylium zincichloride since it resembles, and is probably identical with, that produced in the zinc chloride-acetic anhydride experiments. It is clear that the zinc chloride is slowly inactivated in this way.

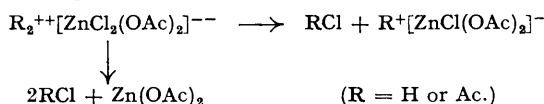
\* This method is recommended as a rapid, simple, and cheap method of preparation of *p*-methoxyacetophenone.

We have referred above to the reported production (Dermer *et al.*, *loc. cit.*) of a large amount of *p*-methoxyacetophenone from anisole and acetyl chloride alone. We cannot substantiate this claim and our suggestion that their acetyl chloride was probably contaminated with a metallic chloride was prompted by our own results : it appears to us that zinc chloride was the most probable impurity. We have shown incidentally that the impurity could not have been pyridine, thionyl chloride, sulphur monochloride, or phosphoryl chloride since no ketone could be isolated in the first three cases and only about 0.5% in the last case. We attach some importance to the probable, doubtful quality of the acetyl chloride used by Dermer *et al.* (*loc. cit.*) in their work, since their results on the efficiency of a series of metallic chlorides, admittedly towards toluene and the acetyl chloride, is now quoted in the literature (see, for example, Sidgwick, "Chemical Elements and their Compounds," Oxford, 1950, p. 437). We feel that this series should be accepted with some reserve since it is probable that all the metallic chlorides used had an impurity added to them in the acetyl chloride.

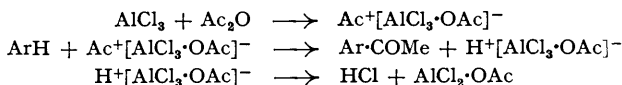
It is noteworthy that, in all the experiments using zinc chloride as the catalyst, the salt goes into solution in the reaction mixture. Salts of similar electronic configuration, for example, mercuric chloride, cadmium chloride, calcium chloride, have not been studied very extensively. Dermer *et al.* (*loc. cit.*) state that these salts are inactive for toluene and we have shown that cadmium and calcium chlorides were both insoluble in acetic anhydride-anisole mixtures and hence inactive. Mercuric chloride however did dissolve in a boiling mixture of the reagents and an appreciable amount of *p*-methoxyacetophenone was produced : in addition, much crystalline material which was probably mercurated substance, but which was not investigated, was also formed.

We conclude that our experiments involving the use of zinc chloride, with either acetyl chloride or acetic anhydride, prove conclusively that acetylum ions are formed; these are sufficiently reactive, as we have shown previously (*J.*, 1950, 1203, 2034), to acetylate the highly activated anisole molecule. It would appear from our results that zinc chloride is a more efficient catalyst than aluminium chloride for the *C*-acetylation of anisole. We attribute this higher efficiency entirely to the slower rate of inactivation of the salt. We wish to make it quite clear that we do not suggest that zinc chloride is, in general, a more efficient catalyst than is aluminium chloride. On the contrary, we now show that for benzene and acetic anhydride the use of zinc chloride gives, even in the presence of nitromethane, only a trace of acetophenone, whereas aluminium chloride, benzene, and acetic anhydride are known (Adams, *J. Amer. Chem. Soc.*, 1924, 46, 1889) to afford the ketone rapidly and in high yield.

We have pointed out (p. 727) that in our experiments with anisole, acetic anhydride, and zinc chloride there was no evolution of either hydrogen chloride or acetyl chloride. We conclude from this that there is no tendency, in this particular system,\* for either of the following modes of decomposition of the complex salts to occur :



The result for  $R = Ac$  is in marked contrast to the use of aluminium chloride (Adams, *loc. cit.*), which clearly reacts with acetic anhydride and an aromatic compound ( $ArH$ ) as follows :



We have shown that acetoxyaluminium dichloride,  $AlCl_2 \cdot OAc$ , which we believe to be formed (in solution) from aluminium chloride (1 mol.) and acetic anhydride (1 mol.) in nitrobenzene with subsequent removal of acetyl chloride is, for all practical purposes, inactive as a catalyst for the reaction between anisole and acetic anhydride.

#### EXPERIMENTAL.

*Materials.*—Zinc chloride was a commercial preparation of 95% purity. Zinc acetate (pure and AnalaR) was dried to constant weight at 110° before use. Acetyl chloride and acetic anhydride were AnalaR reagents.

*p*-Methoxyacetophenone from Anisole, Acetic Anhydride, and Zinc Chloride.—(a) A mixture of zinc chloride (0.2 g.-mol.), acetic anhydride (0.8 g.-mol.), and anisole (0.4 g.-mol.) was well shaken for

\* With benzene, acetic anhydride, and zinc chloride in nitromethane there is some evolution of hydrogen chloride; in the absence of nitromethane no evolution occurred.

5—7 minutes during which the internal temperature rose to 50—60° and dissolution of the zinc chloride occurred. The solution was then heated on the steam-bath to 80°, the total reaction time being 12 minutes. The mixture was then cooled rapidly to 25—30° and poured on crushed ice (*ca.* 300 g.). Addition of ether caused the separation of a variable amount of an orange solid (*A*); this was filtered off from the ethereal solution and washed with ether. The filtered ethereal extract of the oily reaction product was washed successively with water, dilute sodium carbonate solution, an excess of dilute sodium hydroxide solution (which appeared to remove a little phenolic product), and finally with water. The dried ( $\text{Na}_2\text{SO}_4$ ) extract was then evaporated and the residue fractionated at about 4 mm., whereby a good separation of *p*-methoxyacetophenone (0.24 g.-mol.), *b. p.* 110—115°/3.8—4 mm., from a little unchanged anisole was obtained. The ketone solidified, on cooling, to a pale yellow mass of crystals, *m. p.* 34—37°, identified as its 2 : 4-dinitrophenylhydrazone, *m. p.* and mixed *m. p.* 223°.

Solutions of the solid (*A*) in alcohol or acetone showed an intense green fluorescence.

(*b*) A mixture of zinc chloride (0.1 g.-mol.), acetic anhydride (0.4 g.-mol.), anisole (0.3 g.-mol.), and nitromethane (147 g.), under conditions identical with those described in (*a*), gave 0.14 g.-mol. of *p*-methoxyacetophenone.

With zinc chloride (0.05 g.-mol.), acetic anhydride (0.1 g.-mol.), anisole (0.1 g.-mol.), and nitromethane (42 g.) under the same conditions, 0.056 g.-mol. of *p*-methoxyacetophenone was isolated.

In all the experiments a dark residue (1.1—1.9 g.) remained in the distillation flask; this contained an appreciable amount of the ketone which was identified as its 2 : 4-dinitrophenylhydrazone. There was no evolution of hydrogen chloride or other volatile product in any of the experiments. A longer reaction time or the use of a higher temperature gave increasing amounts of the solid (*A*) and a diminished yield of ketone.

*p*-Methoxyacetophenone from Anisole, Acetic Anhydride, and Mercuric Chloride.—In this case it was found necessary to use a much larger amount of acetic anhydride to obtain complete dissolution. A mixture of mercuric chloride (0.2 g.-mol.), anisole (0.4 g.-mol.), and acetic anhydride (1.6 g.-mols.) was boiled under reflux until complete dissolution occurred. The orange-yellow crystalline material which separated on cooling was filtered off and the filtrate added to crushed ice. Extraction of the oily reaction product with ether followed by repeated washing with water and finally with dilute sodium hydroxide solution gave (as above) 0.11 g.-mol. of *p*-methoxyacetophenone. The crystalline material was not further investigated.

*Reaction of Anisole and Acetyl Chloride in Absence and Presence of Small Amounts of Zinc Chloride and Other Substances.*—In the preliminary experiments, a mixture of acetyl chloride (0.1 g.-mol.), anisole (0.1 g.-mol.), and a small crystal of the solid or a drop of the liquid under investigation was boiled under reflux with a calcium chloride guard-tube for 4—8 hours. Unchanged reagents were removed by distillation at atmospheric pressure using a small column, and the residue treated with an alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate. The yield of ketone was then calculated from the weight of *p*-methoxyacetophenone 2 : 4-dinitrophenylhydrazone, *m. p.* and mixed *m. p.* 223°. Acetyl chloride and anisole alone gave a trace of ketone after 4 hours and 0.15% after 8 hours. No ketone could be detected when using sulphur and thionyl chlorides for 4 hours or pyridine for 6 hours. With phosphoryl chloride, ferric chloride, and aluminium chloride for 4 hours the yields of ketone were 0.54, 2.2, and 2.3%, respectively; under the same conditions zinc chloride gave 7.2% of the ketone which was isolated as such by distillation in a vacuum; it had *b. p.* 125°/5.5 mm., *m. p.* 39°.

In subsequent experiments with zinc chloride and zinc acetate, 0.2 g.-mol. each of acetyl chloride and anisole were used and the mixture was boiled for 7 hours. It was noticed that the zinc salt did not dissolve in the acetyl chloride but rapid dissolution occurred when the anisole was added and a purple colour developed. A fairly rapid evolution of hydrogen chloride occurred during the initial stage of the reaction and, after about 1½ hours, bright orange crystals began to separate and the colour of the reaction mixture became browner. When the reaction mixture had cooled the crystals (*B*) were filtered off and washed with ether. The *p*-methoxyacetophenone was isolated by distillation. The yields of ketone and (*B*), when 32 mg. of zinc chloride were used, were 3.5 g. (11.7%) and 83 mg., respectively. With 39 mg. of zinc acetate the yields were 11.3% and 88 mg., respectively, and with 29 mg. of zinc acetate the yield of ketone was 9.7%.

The solid (*B*) had *m. p.* 258—260° (decomp.) and on ignition gave a residue of zinc oxide. It was sparingly soluble in alcohol; solutions showed an intense green fluorescence.

*Reaction between Benzene and Acetic Anhydride—Zinc Chloride.*—(*a*) A mixture of benzene (0.4 g.-mol.), acetic anhydride (0.8 g.-mol.), and zinc chloride (0.2 g.-mol.) was heated on a boiling water-bath with occasional shaking until all the zinc chloride had dissolved (*ca.* 5 minutes). After a further 30 minutes, during which no evolution of hydrogen chloride occurred, the dark solution (initially deep red) was cooled rapidly and poured on crushed ice. The aqueous phase was extracted with ether and the combined benzene-ether extracts were washed successively with water, dilute sodium carbonate solution, 2*N*-sodium hydroxide (whereby most of the colour was removed), and water. The small amount of residue from the dried ( $\text{Na}_2\text{SO}_4$ ) extract gave 60 mg. of impure acetophenone 2 : 4-dinitrophenylhydrazone.

(*b*) A mixture of benzene (0.1 g.-mol.), acetic anhydride (0.2 g.-mol.), zinc chloride (0.05 g.-mol.), and nitromethane (56.4 g.) was similarly heated until all the zinc chloride had dissolved (*ca.* 30 minutes); a very slow evolution of hydrogen chloride occurred. After a further 30 minutes the mixture was treated as described in (*a*). The small residue from the dried extract gave a trace of impure acetophenone 2 : 4-dinitrophenylhydrazone.

*Acetoxyaluminium Dichloride.*—Acetic anhydride (0.1 g.-mol.) was added dropwise to a solution of aluminium chloride (0.1 g.-mol.) in nitrobenzene (53.6 g.), whereby a white translucent paste separated

and the mixture became warm. The mixture was then heated (oil-bath) gradually during 1—1½ hours to 170°, the volatile product being allowed to distil. The mixture was then cooled and reheated to 110° in a vacuum (water-pump) during 30 minutes. The resulting dark brown solution was mixed with anisole (0.1 g.-mol.) and acetic anhydride (0.2 g.-mol.) and heated (bath) at 110—120° for 2 hours. After cooling, the mixture was poured into 2N-hydrochloric acid (150—200 c.c.), then filtered, and the filtrate extracted with ether. The ethereal extract was washed twice with 2N-sodium hydroxide and then with water. Fractionation of the residue from the dried ( $\text{Na}_2\text{SO}_4$ ) extract gave anisole (0.065 g.-mol.) and a small amount of *p*-methoxyacetophenone identified as the 2 : 4-dinitrophenyl-hydrazone (yield, 0.4 g.).

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