# 74. *Titanium Tetrachloride as a Catalyst in the Friedel–Crafts Reaction. Part I. Acylation.*

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The acylation of benzene, toluene, and anisole in contact with titanium tetrachloride as a catalyst has been studied, the ease of reaction being in the above order. Acids and acid chlorides and anhydrides were the acylating agents, acids being the least and acid anhydrides the most effective. From acid chlorides the yields of ketones increased in the order acetyl, *n*-propionyl, *n*-butyryl, benzoyl. In general, other conditions being constant, there was an optimum temperature and reaction time.

The most satisfactory yields were obtained when 2—3 equivalents of titanium tetrachloride were used. Moreover, in the acylation of toluene and anisole almost exclusive *para*-substitution occurred.

*o*-Benzoylbenzoic acid was not formed from phthalic anhydride and benzene, and with toluene the chief product was 3 : 3-di-*p*-tolylphthalide.

Titanium tetrachloride has been used only to a minor extent in reactions of the Friedel–Crafts type. Stadnikov and Kashtanov (*Ber.*, 1928, **61**, 1389) state that no benzophenone is formed from benzene and benzoyl chloride in the presence of this catalyst, and Galle (*J. Gen. Chem. Russia*, 1938, **8**, 402) claims that, though naphthalene is likewise unaffected, methoxynaphthalenes do react. Dermer *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 2881; 1942, **64**, 464) have compared the effect of several catalysts, including titanium tetrachloride, on the reaction between toluene and acetyl chloride.

In the present work, the acylation in contact with titanium tetrachloride of benzene, toluene, and anisole was studied; the yields of ketone increased in that order. In general the Perrier sequence (*Ber.*, 1900, **33**, 815) was followed, *i.e.*, the catalyst was first added to the acylating agent, forming a complex, the compound to be acylated being subsequently introduced. Although titanium tetrachloride was found to be less efficient than aluminium chloride, comparable yields of ketones were obtained in most cases. Both acetylation and benzoylation were investigated, and acid chlorides, anhydrides, and acids were used as acylating agents. Anhydrides, which gave the highest, and acids, which gave the lowest, yields, do not appear to have been previously used for acylations in conjunction with this catalyst. Also, the yields obtained in benzoylation were higher than in acetylation.

As well as acetyl chloride, *n*-propionyl and *n*-butyryl chlorides were used, increased yields of ketones being obtained as the series was ascended. The most satisfactory results were obtained when at least one equivalent of catalyst was employed; this was presumably due, as in the case of aluminium chloride, to the formation of an inactive complex with the ketone of the type CORR′,$TiCl_4$. In practice about 3 equivalents of catalyst were the most successful.

FIG. 1. *Variation of yield with time at constant temp. in reactions with toluene (molecular proportions of* $TiCl_4$ *to acylating agent in parentheses).*
1, Acetyl chloride at 0° (3). 2, *n*-Propionyl chloride at 0° (3). 3, *n*-Butyryl chloride at 0° (3). 4, Benzoyl chloride at 35° (1). 5, Acetic anhydride at 0° (2·2).

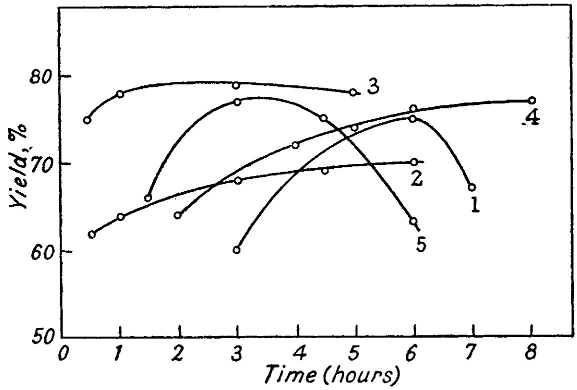
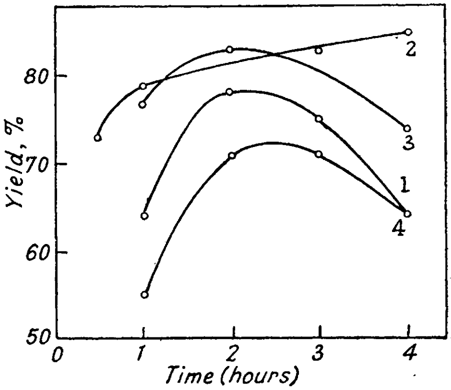


FIG. 2. *Variation of yield with time at constant temp. in reactions with anisole (molecular proportions of* $TiCl_4$ *to acylating agent in parentheses).*
1, Acetyl chloride at 40° (2). 2, *n*-Butyryl chloride at 25° (2). 3, Benzoic anhydride at 40° (2·2). 4, Acetic acid at 80° (3).



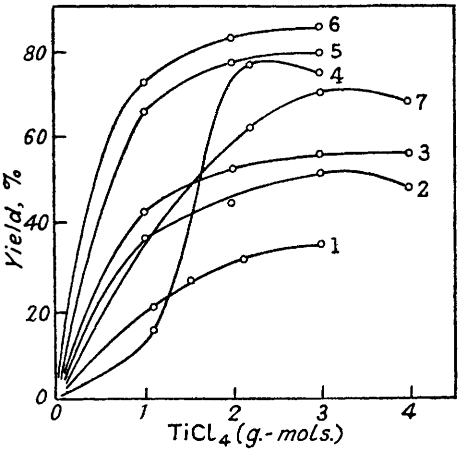


FIG. 3. *Effect on yield of variation in the proportion of catalyst at constant time and temperature.*
1, Acetyl chloride and toluene, 20 min. at 20—25° (Dermer *et al., loc. cit.*). 2, *n*-Propionyl chloride and toluene, 3 hours at 25°. 3, *n*-Butyryl chloride and toluene, 3 hours at 25°. 4, Acetic anhydride and toluene, 3 hours at 0°. 5, *n*-Propionyl chloride and anisole, 3 hours at 40°. 6, *n*-Butyryl chloride and anisole, 3 hours at 25°. 7, Acetic acid and anisole, 3 hours at 80°.

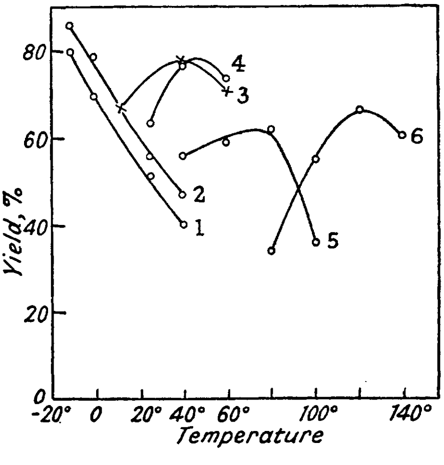


FIG. 4. *Effect on yield of variation in temperature with constant proportion of catalyst (molecular proportions of* $TiCl_4$ *to acylating agent in parentheses).*
1, *n*-Propionyl chloride and toluene, 3 hours (3). 2, *n*-Butyryl chloride and toluene, 3 hours (3). 3, Acetyl chloride and anisole, 2 hours (2). 4, *n*-Propionyl chloride and anisole, 3 hours (2). 5, Acetic acid and anisole, 3 hours (2·2). 6, Benzoic acid and anisole, 3 hours (3).

The anhydrides not only gave good yields, but also cleaner products with less formation of tars. Here at least 2 g.-mols. of catalyst per g.-mol. of anhydride were needed to give the best results; poor yields previously obtained with aluminium chloride have been ascribed by Noller and Adams (*J. Amer. chem. Soc.*, 1924, **46**, 1889) to the use of insufficient catalyst.

When acids were used for acylation about 3 equivalents were found to be the most satisfactory and although the yields obtained with benzene were small, a considerable improvement was noted with toluene and especially with anisole.

Fig. 3 gives a selection of reactions showing the effect on the yield of increasing the proportion of titanium tetrachloride, other conditions being constant. In general, the best results were obtained with 2—3 equivalents of titanium tetrachloride, and in many cases reduced yields were observed when more catalyst was used.

In reactions with anhydrides intermediate formation of acid chlorides took place. It was also found with toluene (Fig. 1) and anisole (Fig. 2) that, other conditions being constant, there was an optimum reaction period below or above which yields tended to diminish or at least not to increase. Furthermore, Fig. 4 indicates that in certain experiments increase of temperature resulted in diminution in yield.

*Acylations with* 0·1 *g.-mol. of acylating agent.*

(Quantities are given in terms of g.-mols., except those marked †, which are in terms of c.c.)

| TiCl$_4$ | C * | Temp. | Time (hours) | Yield, % | Note |
|---|---|---|---|---|---|
| *Benzene and acetyl chloride.* | | | | | |
| 0·15 | 0·2 | 0° | 24 | 7·5 | 1 |
| 0·3 | 0·2 | 0 | 24 | 4 | 2 |
| *Benzene and acetic anhydride.* | | | | | |
| 0·22 | 40 † | 0 | 24 | 35 | 3 |
| *Toluene and acetyl chloride.* | | | | | |
| 0·3 | 25 † | 25 | 3 | 66 | 6 |
| *Toluene and acetic acid.* | | | | | 7 |
| 0·3 | 25 † | 100 | 1 | 15 | 8 |
| 0·22 | 50 † | 100 | 3 | 10 | |
| *Anisole and acetyl chloride.* | | | | | 13 |
| 0·1 | 0·15 | 40 | 2 | 65 | — |
| *Anisole and* n-*propionyl chloride.* | | | | | |
| 0·2 | 0·2 | 40 | 1 | 79 | 14 |
| *Anisole and* n-*butyryl chloride.* | | | | | |
| 0·2 | 0·2 | 60 | 3 | 89 | 15 |
| *Anisole and acetic anhydride.* | | | | | 13 |
| 0·22 | 0·15 | 40 | 2 | 71 | 16 |
| 0·22 | 0·15 | 40 | 4 | 76 | 17 |
| 0·3 | 0·15 | 40 | 2 | 69 | |

| TiCl$_4$ | C * | Temp. | Time (hours) | Yield, % | Note |
|---|---|---|---|---|---|
| *Benzene and benzoyl chloride.* | | | | | |
| 0·2 | 25 † | ‡ | 11 | 32 | 4 |
| 0·2 | 25 † | 50° | 7 | 6 | — |
| 0·2 | 25 † | 15 | 65 | 3 | — |
| *Benzene and benzoic anhydride.* | | | | | |
| 0·22 | 40 † | ‡ | 10 | 65 | 5 |
| 0·22 | 40 † | 10 | 90 | 3 | — |
| *Toluene and benzoyl chloride.* | | | | | |
| 0·12—0·2 | 25 † | 17 | 24 | 81 | — |
| *Toluene and benzoic anhydride.* | | | | | |
| 0·22 | 40 † | 115 | 4 | 95 | 9 |
| 0·22 | 50 † | 100 | 6 | 85 | — |
| 0·22 | 50 † | 80 | 8 | 74 | 10 |
| 0·22 | 50 † | 13 | 63 | 60 | — |
| 0·22 | 50 † | 17 | 24 | 22 | — |
| *Toluene and benzoic acid.* | | | | | |
| 0·3 | 50 † | ‡ | 2 | 49 | 11 |
| 0·3 | 50 † | 110 | 5 | 30 | 12 |
| *Anisole and benzoyl chloride.* | | | | | 13 |
| 0·15 | 0·15 | 40 | 1 | 91 | 18 |
| *Anisole and benzoic anhydride.* | | | | | 19 |
| 0·22 | 0·15 | ‡ | 1 | 97 | — |
| *Anisole and benzoic acid.* | | | | | 20 |
| 0·4 | 0·2 | 120 | 1·5 | 63 | |
| 0·3 | 0·2 | 120 | 1·5 | 66 | 21 |

* C = compound acylated.

‡ = Reaction mixture heated under reflux.

*Notes.* With other conditions throughout as stated, further yields obtained were as follows : (1) After 13 hours 7%, 6 hours 6%. (2) At 25° 3%. (3) The same yield was obtained when the acetic anhydride was added to a mixture of titanium tetrachloride and benzene or by the Perrier sequence. (4) After 5 hours 16%, 8·5 or 15 hours 30%. (5) After 6·5 hours 54%. (6) Cf. Dermer *et al.* (*loc. cit.*). (7) Titanium tetrachloride was added to a mixture of toluene and acid. (8) After 3 hours 8%. (9) With 0·3 g.-mol. of titanium tetrachloride 90%. (10) At 60° 66%. (11) After 5 hours 31%. (12) At 100° 2%. (13) CS$_2$ (40 c.c.) also present. (14) After 0·5 hour 70%, 2 or 3 hours 77%. (15) At 25° 83%, 40° 85%. (16) Perrier sequence; when titanium tetrachloride was added to anisole and acetic anhydride, yield 80%. (17) After 0·5 hour 58%, 1 hour 64%, 3 hours 73%. (18) After 2 or 4 hours 85%. (19) CS$_2$ (60 c.c.) also present. (20) Titanium tetrachloride was added to a mixture of anisole and benzoic acid. (21) At 140° 60%.

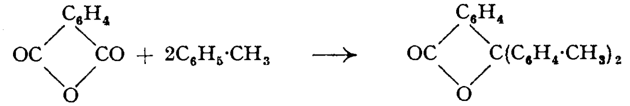
In all reactions with toluene and anisole almost exclusive *para*-substitution occurred.

Following Illari's views (*Gazzetta*, 1948, **78**, 687; cf. Groggins and Detwiler, *Ind. Eng. Chem.*, 1950, **42**, 1690) on the mechanism of the Friedel–Crafts synthesis with anhydrides and acids in the presence of aluminium chloride, the equations for the reactions with titanium tetrachloride may be indicated as follows :

$$(R{\cdot}CO)_2O + 3TiCl_4 = TiOCl_2 + 2R{\cdot}OCl,TiCl_4$$
$$R{\cdot}CO_2H + TiCl_4 = R{\cdot}CO{\cdot}O{\cdot}TiCl_3 + HCl$$
$$R{\cdot}CO{\cdot}O{\cdot}TiCl_3 + TiCl_4 = TiOCl_2 + R{\cdot}COCl,TiCl_4$$

In accordance with this view, 3 g.-mols. of catalyst are needed for the best yields with anhydrides, and 2 with acids. It should also be noted that, although intermediate formation of acid chlorides occurs when the anhydrides are used, yet with acids only negligible amounts of such products are obtained.

An unusual result was obtained when phthalic anhydride reacted with toluene in contact with titanium tetrachloride. No 2-*p*-toluoylbenzoic acid was formed, but 3 : 3-di-*p*-tolylphthalide was produced in good yield :



This compound was previously obtained from phthaloyl chloride (Limpricht, *Annalen*, 1898, **299**, 286; de Berchem, *Bull. Soc. chim.*, 1884, **42**, 168) or phthalic anhydride (Limpricht, *Annalen*, 1898, **299**, 300; von Pechmann, *Ber.*, 1881, **14**, 1865; Friedel and Crafts, *Ann. Chim. Phys.*, 1888, **14**, 447) and toluene in the presence of aluminium chloride, notably when the quantity of catalyst used was less than 1 equivalent.

## EXPERIMENTAL

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Numerous experiments were carried out under different conditions, the proportions and order of addition of the reactants and catalyst being varied as well as duration and temperature. All materials were dried and redistilled before use, and all essential precautions taken to exclude moisture. The yields stated, which are based in all cases on the acylating agent, are only approximate, though repetition of the experiments in many cases gave comparable results; these are summarised in the table and figures.

Though the yields given are based on the formation of 1 mole of ketone from 1 of anhydride, it should be pointed out that Groggins and Nagel (*Ind. Eng. Chem.*, 1934, **26**, 1313) claim that at least part of the second acyl group in an acid anhydride is available for reaction when a large excess of catalyst is employed.

Perrier's sequence was usually followed ; stirring and cooling were applied during the mixing process, and agitation was continued throughout each experiment. Water or dilute hydrochloric acid was then added, and the organic layer separated, washed successively with dilute hydrochloric acid and water, and dried ($CaCl_2$). In general, the ketones were obtained by fractional distillation at the ordinary or reduced pressure and, when solid, were purified by recrystallization and the weight of product was ascertained. Liquid ketones were estimated (as well as identified) by conversion into the 2 : 4-dinitrophenylhydrazone, this process having been found by test to give accurate results : 2 : 4-Dinitrophenylhydrazine (2 g.) was dissolved by warming in concentrated sulphuric acid (4 c.c.), followed by ethyl alcohol (20 c.c.). The product was kept for some time and then filtered. Sufficient of the reagent was added to the ketone (*ca.* 0·5 g.) dissolved in alcohol (20 c.c.), and heat was applied, whereupon precipitation occurred. The product was filtered off when cold and recrystallized from ethyl acetate or ethyl acetate–alcohol.

*Acylation of Benzene.*—With acetyl chloride, the best yields of acetophenone were obtained at 0°. The product was determined by conversion into the 2 : 4-dinitrophenylhydrazone, orange prisms, m. p. 237° (cf. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955). Acetic anhydride gave better yields, and here also low temperatures were most successful. Acetic acid gave only a negligible yield.

The best yields of benzophenone from benzoyl chloride or benzoic anhydride and benzene were achieved by refluxing the reactants. The anhydride was here also the superior acylating agent, and the acid failed to afford any ketone.

*Acylation of Toluene.*—Satisfactory yields were obtained with acetyl chloride and acetic anhydride, especially at low temperatures, but the acid gave only a small yield. The product in all cases consisted almost entirely of methyl *p*-tolyl ketone, b. p. 224°, m. p. 28°; 2 : 4-dinitrophenylhydrazone, red prisms, m. p. 257°. Roberts and Green (*J. Amer. Chem. Soc.*, 1946, **68**, 214) give m. p. 257—258°; Allen and Richmond (*J. Org. Chem.*, 1937, **2**, 222) give 248°.

Slightly improved yields were given with *n*-propionyl and still higher with *n*-butyryl chloride, low temperatures being again most effective. The products consisted almost entirely of the *para*-substituted derivatives. Ethyl *p*-tolyl ketone had b. p. 233° and gave a 2 : 4-*dinitrophenylhydrazone*, bright red needles, m. p. 201° (Found : N, 17·0. $C_{16}H_{16}O_4N_4$ requires N, 17·1%), and semicarbazone, m. p. 187° (cf. Baddeley, *J.*, 1944, 232). Propyl *p*-tolyl ketone had b. p. 250° and gave a 2 : 4-*dinitrophenylhydrazone*, orange-red plates, m. p. 191° (Found : N, 16·5. $C_{17}H_{18}O_4N_4$ requires N, 16·4%) and semicarbazone, m. p. 210° (cf. Tsukervanik and Terentieva, *J. Gen. Chem. Russia*, 1940, **10**, 1405).

Benzoic anhydride gave better yields than benzoyl chloride, and even the acid gave a moderately good yield. The product was almost entirely phenyl *p*-tolyl ketone, b. p. 328°, m. p. 58° [2 : 4-dinitrophenylhydrazone, orange crystals, m. p. 200° (cf. Grieve and Hey, *J.*, 1934, 1797)].

*Acylation of Anisole.*—Yields were consistently good, *para*-substituted ketones being almost exclusively formed. Use of carbon disulphide as solvent rendered the reaction mass easier to handle. The effectiveness of the acylating agents increased in the order acetyl < *n*-propionyl < *n*-butyryl < benzoyl chloride and moderate temperatures were most satisfactory except with acids, where higher temperatures gave the best yields.

*p*-Methoxyacetophenone had b. p. 258°, m. p. 38° [2 : 4-dinitrophenylhydrazone, scarlet prisms, m. p. 232° (cf. Borsche and Barthenheier, *Annalen*, 1942, **553**, 250)]. *p*-Methoxypropiophenone had b. p. 148°/15 mm., m. p. 27° [2 : 4-*dinitrophenylhydrazone*, red plates, m. p. 195° (Found : N, 16·2. $C_{16}H_{16}O_5N_4$ requires N, 16·3%). *p*-Methoxybutyrophenone had b. p. 160°/20 mm., m. p. 21° [2 : 4-*dinitrophenylhydrazone*, red prisms, m. p. 169° (Found : N, 15·5. $C_{17}H_{18}O_5N_4$ requires N, 15·6%)]. Phenyl *p*-tolyl ketone had m. p. 58°. *p*-Methoxybenzophenone had m. p. 62° [2 : 4-dinitrophenylhydrazone, orange prisms, m. p. 180° (cf. Chrodroff and Klein, *J. Amer. Chem. Soc.*, 1948, **70**, 1647)].

*Action of Phthalic Anhydride on Toluene in the Presence of Titanium Tetrachloride.*—A 60% yield of 3 : 3-di-*p*-tolylphthalide was obtained when toluene (40 c.c.) followed by titanium tetrachloride (57 g., 0·3 g.-mol.) was added to the anhydride (15 g., 0·1 g.-mol.). Hydrogen chloride was rapidly evolved as the mixture was heated to 100°. After 8 hours the contents were decomposed with dilute hydrochloric acid, excess of toluene was removed by distillation in steam, and the product cooled in ice and filtered off. The brown sticky solid was treated with excess of sodium carbonate solution, from which on acidification a little phthalic acid was obtained. The residue was washed with water and dried, the tarry portion being removed by grinding it with small amounts of ether, whereupon a white crystalline solid resulted. Recrystallisation from alcohol afforded white prisms, m. p. 117° (cf. Limpricht, *loc. cit.*).

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