[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

RELATIVE REACTIVITIES OF CERTAIN ACYLATING AGENTS IN FRIEDEL-CRAFTS REACTIONS

EUGENE H. MAN[1] AND CHARLES R. HAUSER

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On the basis of the generally accepted mechanism, the Friedel-Crafts type of acylation (equation 1) might be expected to depend not only on the reactivity of the aryl compound as an electron-donor, but also on that of the acylating agent or its aluminum chloride coordination complex as an electron-acceptor. The reactivity of the acylating agent, in turn, might depend on the nature of both R and X.

$$1. \qquad \text{RCOX} + \text{H-Aryl} \xrightarrow{\text{AlCl}_3} \text{RCO-Aryl} + \text{HX}$$

With regard to the influence of X in the acylating agent, the acetylation of bromobenzene to form *p*-bromoacetophenone has been reported in *Organic Syntheses* (1) to produce a better yield with acetic anhydride (in which X is acetate) than with acetyl chloride (in which X is chlorine). This better yield with the anhydride was accounted for on the basis that the acetic acid, formed as by-product, also produced some of the ketone.[2] However, we have found that even toluene, which is a better electron-donor than bromobenzene (2), fails to be acetylated with acetic acid under similar conditions. Thus, the aluminum chloride coordination complex of the anhydride is evidently either formed more readily or, once formed, is more reactive than that of the acid chloride. We have further found that, in the analogous acetylation of the more reactive toluene under similar conditions, the apparently greater reactivity of the anhydride is not detected, and even acetyl chloride is sufficiently reactive to produce the maximum yield with this hydrocarbon (Table I). Also, *p*-nitrophenyl acetate probably produced a yield equally as good as the anhydride or acid chloride but, because of the difficulty of isolation, the actual yield obtained was somewhat lower. In corresponding benzoylations, benzoyl chloride and *p*-nitrophenyl benzoate produced equally good yields but benzoic anhydride gave a considerably lower yield (Table I). The lower yield in the latter case may have been due to the lower solubility of the anhydride in the medium.

With regard to the influence of variations in R of the acylating agent, we have obtained more precise comparisons by determining the relative yields of the two possible ketones produced when one molecular equivalent of each of two acylating agents is allowed to compete for one equivalent of toluene or anisole. These competitive reactions were effected with aluminum chloride in carbon disulfide, nitrobenzene, or ethylene chloride by one or more of the following procedures. In Procedure I, the two acylating agents were first mixed with excess aluminum chloride in the solvent and the aromatic compound then added slowly; in Pro-

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[1] Du Pont Fellow, 1950–1951.

[2] See note 7, ref. 1.

cedure II, the two acylating agents were mixed with the aromatic compound in the solvent and the aluminum chloride then added slowly until it was in excess; and in Procedure III, the aromatic compound and excess aluminum chloride were first mixed and a mixture of the two acylating agents then added slowly. The results are summarized in Table II. Although the yields of ketones isolated from most of the experiments were only around 50%, we believe that the ratio

TABLE I

ACYLATIONS OF TOLUENE WITH CERTAIN ANHYDRIDES, ACID CHLORIDES, AND ESTERS

ACYLATING AGENT	PRODUCT	YIELD, %
Acetic anhydride	*p*-Methylacetophenone	84
Acetyl chloride	*p*-Methylacetophenone	85
p-Nitrophenyl acetate	*p*-Methylacetophenone	78
Acetic acid	*p*-Methylacetophenone	0
Benzoic anhydride	*p*-Methylbenzophenone	48
Benzoyl chloride	*p*-Methylbenzophenone	72
p-Nitrophenyl benzoate	*p*-Methylbenzophenone	70

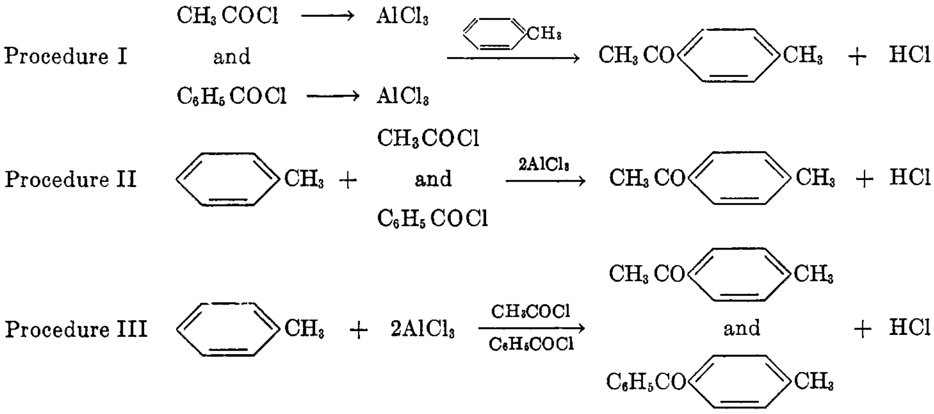
TABLE II

COMPETITIVE FRIEDEL-CRAFTS ACYLATIONS WITH MIXTURES OF TWO ACYLATING AGENTS

MIXTURE OF ACYLATING AGENTS	AROMATIC COMPOUND	SOLVENT	ACYL DERIVATIVE	YIELDS IN PROCEDURES, %		
				I	II	III
Acetyl chloride	Toluene	Carbon disulfide	Acetyl	56	60	39
Benzoyl chloride			Benzoyl	<1	<1	42
Acetyl chloride	Toluene	Ethylene chloride	Acetyl	53		
Benzoyl chloride			Benzoyl	<1		
Acetyl chloride	Anisole	Nitrobenzene	Acetyl	56	45	
Benzoyl chloride			Benzoyl	15	<1	
p-Nitrophenyl acetate	Anisole	Nitrobenzene	Acetyl	45		
p-Nitrophenyl benzoate			Benzoyl	<1		
Acetyl chloride	Toluene	Carbon disulfide	Acetyl		43	44
2-Ethylbutyryl chloride			2-Ethylbutyryl		<1	45
2-Ethylbutyryl chloride	Toluene	Carbon disulfide	2-Ethylbutyryl	5		
Benzoyl chloride			Benzoyl	33		
Acetyl chloride	Toluene	Ethylene chloride	Acetyl	76		
p-Nitrophenyl benzoate			Benzoyl	<1		
Benzoyl chloride	Toluene	Ethylene chloride	Acetyl	63		
p-Nitrophenyl acetate			Benzoyl	<1		

of the two possible ketones is significant. In experiments with acetyl and benzoyl chloride in which only the acetyl derivative was formed, this derivative was somewhat difficult to separate from unreacted benzoyl chloride.

The three procedures were employed with acetyl and benzoyl chlorides against toluene. The reactions are represented schematically below in which the component (or components) added slowly to the remainder of the reactants is given over the arrow.



In procedure I, the aluminum chloride presumably first forms coordination complexes with both of the acid chlorides but, since the acetyl derivative of toluene is produced almost exclusively, only the complex with the acetyl chloride evidently reacts. In procedure II, the acetyl chloride and benzoyl chloride compete for the aluminum chloride as it is added slowly and, since the acetyl derivative is again formed almost exclusively, apparently only the acetyl chloride forms the complex with the reagent. Of course, some of the benzoyl chloride might coordinate with the aluminum chloride and then, before this complex can react, give up the aluminum chloride to the acetyl chloride. In procedure III, the effect of the competition is lost since not only is sufficient aluminum chloride present at all times to coordinate with both the acetyl and benzoyl chlorides as they are added, but the toluene is present in local excess to the two acid chlorides until all of the hydrocarbon is used up. Although the complex with acetyl chloride presumably reacts faster with the toluene, the complex with benzoyl chloride also reacts, and roughly equal yields of the two possible ketones are obtained. This procedure demonstrates that the benzoyl chloride complex also is capable of reacting with the toluene under the conditions employed, and that its failure to react to an appreciable extent in Procedures I and II must be due to a relatively lower reactivity than that of the acetyl chloride complex.

These results may be considered to show that the coordination complex with acetyl chloride is not only more reactive than that with benzoyl chloride but that the complex is apparently formed more readily with acetyl chloride. Also, the complex of aluminum chloride with *p*-nitrophenyl acetate is more reactive than that with *p*-nitrophenyl benzoate towards anisole (Table II). The greater reactivity of the acetyl chloride (or the acetate) must not be due to a solubility factor since, although the coordination complexes were not completely soluble in carbon disulfide, they were soluble in ethylene chloride (3) and nitrobenzene (3) in which similar results were obtained (Table II).

In a similar manner, the aluminum chloride complexes of both acetyl and benzoyl chloride were found more reactive towards toluene than that of 2-ethylbutyryl chloride. Thus, the order of the reactivities of these acid chlorides in the form of their complexes decreases in the following order:

acetyl chloride > benzoyl chloride > 2-ethylbutyryl chloride.

In the last two experiments listed in Table II, the acetyl derivative was again formed preferentially to the benzoyl derivative. However, these experiments do not necessarily show that the particular acetylating agents listed are more reactive than the benzoylating agents, since an exchange reaction between the two acylating agents may have first occurred followed by reaction of the new acetylating agent with the toluene. For example, benzoyl chloride and *p*-nitrophenyl acetate have been shown to undergo partial exchange to form *p*-nitrophenyl benzoate (41%) and acetyl chloride (equation 2). Thus, in the last experiment listed in Table II, this exchange may have occurred partly (equation 2) followed by the acetylation of toluene by the acetyl chloride produced (equation 3). Actually, *p*-nitrophenyl benzoate (55%) was also isolated in this experiment.

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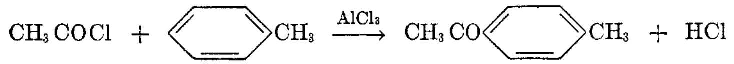
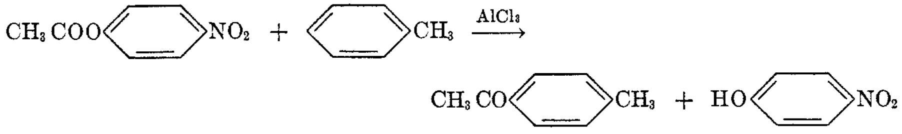
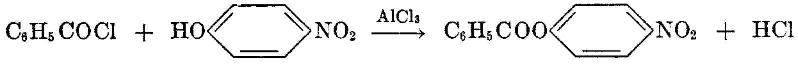
3. 

On the other hand, acetylation by the original acetylating agent, *p*-nitrophenyl acetate (equation 4), may also have occurred since this acetylating agent is probably at least as reactive as acetyl chloride. The *p*-nitrophenyl benzoate may then be formed by subsequent benzoylation of the by-product, *p*-nitrophenol (equation 5).

4. 

5. 

EXPERIMENTAL[3]

Essentially constant boiling *acetyl chloride* (distilled from dimethylaniline), *benzoyl chloride*, and *2-ethylbutyryl chloride* (prepared from 2-ethylbutyric acid[4] and thionyl chloride) were used.

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[3] Boiling points and melting points are uncorrected. Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

[4] We are indebted to the Carbide and Carbon Chemicals Corporation for a generous supply of 2-ethylbutyric acid.

p-Nitrophenyl acetate was prepared from *p*-nitrophenol (1 mole) and acetyl chloride (2 moles). After refluxing 40 hours, the mixture was poured onto ice (1 kg.). The solid was recrystallized from ethanol-water to give 126.1 g. (70%) of the ester, m.p. 75.5–77° (reported m.p. 81–82°) (4).

p-Nitrophenyl benzoate was prepared similarly from *p*-nitrophenol and benzoyl chloride. After nine-hours heating at 160°, the mixture was poured onto ice and the solid recrystallized from acetone to give, after washing with boiling 95% ethanol, 150.6 g. (62%) of the ester, m.p. 140–141.5° (reported m.p. 142.5°) (4).

Acylations of toluene to give results shown in Table I. Toluene (0.25 mole) was acylated with anhydrides (0.2 mole) or acid chlorides (0.2 mole) by means of aluminum chloride (0.56 mole) in 100 ml. of dry carbon disulfide essentially as described in *Organic Syntheses* for the acetylation of bromobenzene (1).

The acylations of toluene with *p*-nitrophenyl esters were carried out in a similar manner with the following modifications. The solid esters (0.2 mole) were added to the toluene-aluminum chloride solution from an Erlenmeyer flask attached to the reaction flask by means of a short section of rubber Gooch tubing. Before drying and distilling to isolate the ketone, the ether extracts of the decomposed reaction mixtures were combined and extracted with successive portions of dilute (1–3%) sodium hydroxide solution until no precipitate (*p*-nitrophenol) was obtained on acidifying the alkaline extract. The intense color of the sodium *p*-nitrophenoxide and the tendency for emulsification made this extraction process somewhat tedious.

The physical properties of the ketones shown in Table I are given below. The yields indicated in the table are based on the moles of acylating agent. In the *Organic Syntheses* preparation of *p*-bromoacetophenone the yield was based on the moles of aromatic compound even though it was used in excess.[5]

Competitive experiments (*Table II*). *Procedure I.* In a 500-ml. round-bottom three-necked flask fitted with a condenser, dropping funnel, thermometer, and sealed stirrer was placed 0.2 mole each of two acylating agents in 100 ml. of dry carbon disulfide. To the stirred solution was added 0.56 mole of aluminum chloride over a period of 15 minutes, while occasionally cooling the mixture with a water-bath. The solution was stirred with refluxing for one-half hour to complete the formation and solution of the aluminum chloride complexes. A solution of toluene (0.2 mole) in 25 ml. of carbon disulfide was added to the stirred and refluxing mixture over a period of 45 minutes. After refluxing an additional hour the carbon disulfide was distilled rapidly, and the residue poured onto 500 g. of ice containing 35 ml. of hydrochloric acid. The decomposed mixture was extracted with ether, and the combined ether extracts washed with water, 10% sodium hydroxide solution, and once more with water. After drying over Drierite, the ether was distilled, and the residue fractionated *in vacuo* to obtain the ketones.

With nitrobenzene as solvent, the procedure was modified as follows. After adding the aluminum chloride, the mixture was stirred one-half hour at room temperature. Anisole (0.2 mole) was then added over a period of 40 minutes, cooling the mixture occasionally. The resulting reaction mixture was stirred at room temperature for two hours, poured onto ice containing hydrochloric acid, and worked up as described above.

With ethylene chloride as solvent, the procedure was modified in a third manner. After adding the aluminum chloride, the mixture was stirred at 35° for one-half hour. A solution of 0.2 mole of toluene in 25 ml. of ethylene chloride was added over a period of 45 minutes, with the heat of reaction maintaining the temperature at 35–45°. The resulting mixture was stirred an additional hour at 50–60°, poured onto ice and hydrochloric acid, and worked up as described above.

Procedure II. To a stirred solution of 0.2 mole each of the two acylating agents and toluene in 100 ml. of dry carbon disulfide was added 0.56 mole of aluminum chloride over a period of one hour, cooling the mixture occasionally. After refluxing for one hour with

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[5] See note 7, ref. 1.

stirring, the carbon disulfide was distilled rapidly, and the residue poured onto the ice-hydrochloric acid mixture and worked up as described above in Procedure I.

With nitrobenzene as solvent (and anisole as the aromatic compound), the reaction mixture was cooled in an ice-bath during the addition of the aluminum chloride, and then stirred for 30 minutes at room temperature before being decomposed and worked up as described above in Procedure I.

Procedure III. A mixture of 0.2 mole each of two acylating agents was added over a period of 1¼ hours to a stirred solution of 0.2 mole of toluene and 0.56 mole of aluminum chloride in 100 ml. of carbon disulfide. After refluxing one hour, the carbon disulfide was rapidly distilled, and the residue poured onto an ice-hydrochloric acid mixture and worked up as described above in Procedure I.

Data for products. The boiling points and melting points of the ketones, on which the yields given in Table I and Table II are based, are listed below. In Procedures I and II (Table II) where essentially only one ketone was obtained, a small residue generally remained after distilling the main product. This residue might have contained a small amount of the second ketone, but the yield is estimated to represent less than 1%.

p-Methylacetophenone, b.p. 94–96° at 10 mm. (reported b.p. 93.5° at 7 mm.) (4).

p-Methylbenzophenone, b.p. 150–152° at 3 mm. M.p. 54–56°. (reported b.p. 311–312° at 720 mm.; m.p. 55° or 59–60°) (4).

p-Methoxyacetophenone, b.p. 138–139° at 15 mm. (reported b.p. 138–139° at 15 mm) (4).

p-Methoxybenzophenone, m.p. 60–61° (not distilled). (reported m.p. 61–62°) (4).

p-Methyl-2-ethylbutyrophenone, b.p. 127–130° at 10 mm. The pure ketone boiled at 129–130° at 10 mm.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.06; H, 9.53.
Found: C, 82.38; H, 9.32.

In the reaction of benzoyl chloride and *p*-nitrophenyl acetate against toluene, (Table II), there was obtained in addition to the 63% yield of *p*-methylacetophenone, 26.7 g. (55%) of *p*-nitrophenyl benzoate, m.p. 142–144° (reported m.p. 142.5°) (4) resulting from an exchange reaction between the benzoyl chloride and the *p*-nitrophenyl acetate (see discussion).

Exchange reaction between benzoyl chloride and p-nitrophenyl acetate. A solution of 0.175 mole each of benzoyl chloride and *p*-nitrophenyl acetate in 100 ml. of ethylene chloride was treated with 0.49 mole of aluminum chloride. The solution was heated at 30–60° for one hour with stirring, poured onto ice containing hydrochloric acid, and worked up as described above. The solid residue remaining after the solvents were removed contained some recovered benzoyl chloride and was purified by extraction with ethanol in a Soxhlet extractor. In this manner there was obtained 17.5 g. (41%) of *p*-nitrophenyl benzoate, m.p. 142–144°. By carefully fractionating the distilled solvents, it was possible to collect a fraction boiling in the range of acetyl chloride which gave a positive test with aniline.

SUMMARY

1. The influence of variations in R and X in acylating agents, RCOX, in certain Friedel-Crafts acylations have been considered.

2. Acetic anhydride appears to be more reactive than acetyl chloride in the acetylation of bromobenzene but not in the acetylation of toluene. Other acylations of toluene are discussed.

3. By means of competitive reactions between two acid chlorides for toluene or anisole, the relative reactivities of the acid chlorides were found to decrease in the order: acetyl chloride > benzoyl chloride > 2-ethylbutyryl chloride. Similarly, *p*-nitrophenyl acetate was found more reactive than *p*-nitrophenyl benzoate.

4. Benzoyl chloride and *p*-nitrophenyl acetate were found to undergo exchange to form *p*-nitrophenyl benzoate and acetyl chloride.

DURHAM, NORTH CAROLINA

REFERENCES

(1) ADAMS AND NOLLER in *Org. Syntheses*, Coll. Vol. I. 2d Ed., 109 (1941).
(2) HAMMETT, *Physical Organic Chemistry*, McGraw-Hill Book Company, New York, 1940, p. 198.
(3) See BADDELEY, *J. Chem. Soc.*, S99 (1949).
(4) HEILBRON, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1938.