THE FRIEDEL-CRAFTS SYNTHESES

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I. INTRODUCTION

In all of organic chemistry there are, perhaps, no reactions which have been so widely studied and still are so poorly understood as the Friedel-Crafts reactions. It is difficult to find other reactions which have been as generally applied in industry and in the laboratory as the Friedel-Crafts reactions, since they constitute one of the most generally applicable classes of reactions for the synthesis of all types of compounds.

The original Friedel-Crafts reaction has been extended, revised, and modified. A variety of condensing agents will introduce groups ranging from methyl, alkenyl, and phenyl to acyl groups of such varied nature as acetyl or nitro. Single atoms, such as sulfur, oxygen, arsenic, and phosphorus, may also be introduced into the benzene nucleus.

The mechanism of this reaction is not always clear. In many cases it appears to vary with the nature of the reactants, the condensing agent, and the solvent. Since the reaction has been applied with success to the alkylation and acylation of aliphatic substances, it seems reasonable to believe that there is no single class of compounds that will resist all types of Friedel-Crafts reactions if the proper conditions are selected. *Thus we prefer to think of a group of Friedel-Crafts reactions of which there are several types.*

A. Historical

The new interest injected into organic chemistry by Frankland's discovery of the organozinc compounds stimulated a series of studies on the action of various metals on alkyl halides, one of which resulted in the discovery of the Friedel-Crafts reaction. Historically, it is of interest to note that prior to the observations of Charles Friedel and James Crafts, which led to the discovery of the Friedel-Crafts reaction, several cases of alkylation and acylation of aromatic compounds by means of metals and metallic compounds had been reported.

In 1869, Zincke (467) reported the synthesis of diphenylmethane from benzyl chloride and zinc in benzene solution. In subsequent reports (468, 469, 470), up to the year 1872, Zincke reported similar syntheses. In 1873, Grucarevic and Merz (162) reported the acylation of aromatic types using acid halides in the presence of zinc dust (330). Doebner and Stackman (84a), in 1876, found that zinc oxide would introduce chloroform or phenyltrichloromethane into phenol to yield salicylaldehyde or *o*-benzoylphenol. It was pointed out in this latter report that zinc chloride was formed during the reaction. As Friedel and Crafts later showed (122), zinc chloride was the active condensing agent in all of these syntheses.

In 1877, Charles Friedel and James Crafts (119, 121) treated amyl chloride with thin aluminum strips. A reaction occurred with the formation of long chain alkyl halides and hydrocarbons. In seeking an explanation for this peculiar behavior, Friedel and Crafts suggested that the hydrogen of one amyl radical united with the halogen of another with the elimination of hydrogen chloride.

$$C_5H_{11}Cl + C_5H_{11}Cl \xrightarrow{Al} C_{10}H_{21}Cl + HCl$$

Thus, the first reported case of a Friedel-Crafts reaction was with an aliphatic compound. Yet this valuable class of aliphatic reactions was to remain undeveloped for over fifty years, while the mistaken concept prevailed that the Friedel-Crafts reaction was confined to aromatically bound hydrogen!

In these same studies, Friedel and Crafts found that the active substance for catalyzing the reaction was aluminum chloride, formed by the union of the chlorine from the alkyl halides and the aluminum.

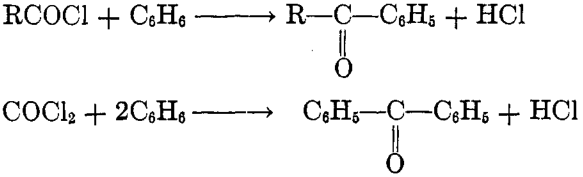
In benzene the reaction was observed to yield well-defined substances with alkyl halides. Short- or long-chained alkylbenzenes were obtained using benzene, aluminum chloride,[1] and alkyl halides. In every case hydrogen halide was eliminated.

$$C_6H_6 + CH_3Cl \xrightarrow{AlCl_3} C_6H_5CH_3 + HCl$$
$$C_6H_6 + C_5H_{11}Cl \longrightarrow C_6H_5C_5H_{11} + HCl$$

Alkyl polyhalides were found to react (69) with the same ease to yield polyphenyl compounds.

$$3C_6H_6 + CHCl_3 \rightarrow (C_6H_5)_3CH$$

In an analogous manner, it was found that ketones could be synthesized by this aluminum chloride condensation.



$$RCOCl + C_6H_6 \longrightarrow R\text{—}\underset{\underset{O}{\|}}{C}\text{—}C_6H_5 + HCl$$
$$COCl_2 + 2C_6H_6 \longrightarrow C_6H_5\text{—}\underset{\underset{O}{\|}}{C}\text{—}C_6H_5 + HCl$$

This latter reaction was shown not to yield anthraquinone (124a).

In these early papers, it was pointed out that halogenobenzenes would not react in the manner of alkyl halides (121), and that alkyl iodides were too unstable to be generally useful in this reaction (119). It was found that ethyl chlorocarbonate did not behave normally (121) as an acid halide; on the contrary, it decomposed in the reaction with benzene to yield as final products ethylbenzene, carbon dioxide, and hydrogen chloride.

$$C_6H_6 + ClCO_2C_2H_5 \rightarrow C_6H_5C_2H_5 + CO_2 + HCl$$

Aluminum chloride was not the only efficient condensing agent (122). Ferrous chloride, ferric chloride, zinc chloride, and sodium aluminum chloride were found to be of value. It was further pointed out that only the anhydrous salts were suitable as condensing agents.

Thus, in a brief period of about six weeks Friedel and Crafts published three papers which laid the foundation and set the outline of the reaction named for these investigators (6).

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[1] In order to simplify reactions, $AlCl_3$ will be used throughout instead of Al_2Cl_6 as the formula for aluminum chloride.

B. *Definition and scope*

At the present time it appears to be virtually impossible to define the Friedel-Crafts "reaction" so that the definition embraces a workable picture of the facts. The simple explanation that the Friedel-Crafts reactions introduce alkyl, aryl, and acyl groups into various classes of compounds in the presence of certain metal halides does not by any means truly represent the case. Yet the Friedel-Crafts reactions are generally used at the present time to introduce either alkyl or keto groups, although many of these reactions introduce highly specialized groups such as nitro, carboxyl, sulfo, hydroxyl, sulfonic, nitrilo, phenyl, and others. Apart from the aluminum chloride, the condensing agent may be, among others, ferric, stannic, boron, mercury, zinc, titanium, or antimony chlorides.

Essentially, the Friedel-Crafts "reaction" is an *activation reaction* (304). Either the hydrogen of the nucleus or a radical of the other reactant, or both, undergoes activation by the aluminum chloride. This means that the cases where activation is obtained essentially by metal halides should fall into the classes of *reactions* that are generally incorporated in and collectively known as the *Friedel-Crafts Reaction.* Thus the Gattermann, Gattermann-Koch, Hoesch-Houben, Fries, Scholl, polymerization, and cracking reactions would become subdivisions of the Friedel-Crafts reactions. While this is a fine picture of the facts, for the benefit of a reasonable clarity it is necessary to limit the sweeping embrace of the reactions.

To facilitate discussion, the reactions will be divided into alkylation and acylation. Under alkylation will be discussed all reactions that join carbon to carbon in such manner that the introduced carbon joined directly to the nucleus in the final product does not hold a doubly bound oxygen, a nitrogen-containing derivative of it, or a similar group. All other reactions are classed as acylations. There are indefinite borderline cases. However, this classification seems to be a reasonable division, although it fails to account for the catalysts, solvents, or other experimental conditions. It is understood that metal halides serve as the condensing agents.

Unfortunately, the exigencies of space demand limitation of the discussion to a superficial consideration of highly specialized cases of the use of metal halides in cracking, reduction, polymerization, or the Scholl reaction, although these fields are intimately concerned with the Friedel-Crafts syntheses.

It has not been possible to include *all* references or to include a complete discussion of the industrial applications of the reaction as revealed in part by the patent literature.

II. ALKYLATION

As one of the most general of the Friedel-Crafts reactions, alkylation has become valuable for the synthesis of alkylated substances, principally hydrocarbons of the aromatic series. The methods of introducing alkyl groups vary. The reactants may be of the most varied nature, as may also the nuclei undergoing substitution and the condensing agent, the solvent, and the conditions of reaction.

It is noteworthy that practically all of the unreliable Friedel-Crafts reaction types are reported in cases of alkylation. Generally, neither the configuration of the entering group nor the orientation in the nucleus can be accurately predicted in alkylation. In fact, alkylation appears to be of an entirely different nature as compared with acylation in respect to reliability, yields, or mechanism.

Unfortunately, in many cases the experimental facts have not warranted the generalizations made, and the *residual products* have been separated from the principal products and discarded. Thus the true nature of many reactions has remained obscure until comparatively recent years.

A. Aromatic compounds

1. The reaction of alkyl halides. The general reaction for the alkylation of aromatic compounds may be represented by the union of an alkyl radical of a halide with an aromatic nucleus with the elimination of hydrogen halide. Aluminum chloride may be used as a typical condensing agent.

$$R'H + RX \rightarrow R\text{—}R' + HX$$

where R and R′ are alkyl and aryl groups, respectively.

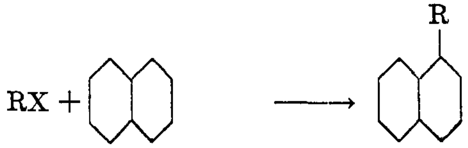
Friedel and Crafts (119) showed that one of the simplest alkyl halides, methyl chloride, would react with benzene to yield toluene.

$$CH_3Cl + C_6H_6 \rightarrow C_6H_5CH_3$$

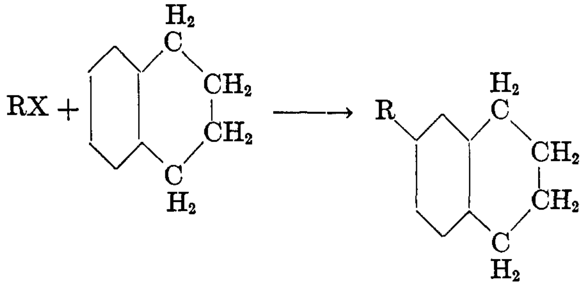
However, the reaction was found to be difficult to control and polymethylated benzenes, including xylene and hexamethylbenzene, also resulted. Jacobson (209) found that the yields of methylaryl compounds could be improved by introducing the methyl chloride under a slight pressure. Others (5) have observed that the methylation may be of a varied nature. That is, mono-, di-, tri-, tetra-, penta-, and hexa-methylbenzenes are all produced in the same reaction in varying proportions, depending on the conditions.

Ethyl halides have been observed to behave in a similar manner to yield mono- or poly-ethyl compounds (119, 446, 191, 192, 11).

The simple benzene nuclei are, of course, not the only types to undergo alkylation. Substituted nuclei, such as are present in phenols (163), aldehydes (144, 147), esters (144), and alkylbenzenes (15, 20, 119, 209), and the condensed aromatic rings, such as naphthalene (191, 192) or tetralin (11), undergo similar substitutions.



(1)



(2)

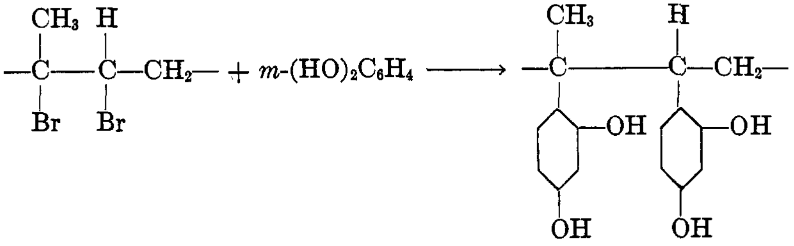
Reaction 1 gives α-substitution, while reaction 2 appears to result in β-substitution exclusively.

Higher alkyl halides react similarly to the simple halides. Propyl (144, 446), butyl (167, 163, 20, 291a), and amyl (119, 144) halides react to yield, largely, branched alkyl substances. Generally, regardless of the configuration of the alkyl halide, the final product contains an alkyl group of the highest possible branching (144). (See the discussion of orientation and reliability, on p. 367.)

$$C_6H_6 + n\text{- or iso-}C_4H_9Cl \rightarrow tert\text{-}C_4H_9C_6H_5$$

The alkyl polyhalides also react as predicted to yield progressively phenylated compounds (42). Carbon tetrachloride yields aryltrichloromethane, diaryldichloromethane, and triarylchloromethane. The fourth chlorine atom is not replaced by a phenyl radical (42, 121, 191, 192). The reaction is easily controllable.

The very high molecular weight alkyl halides behave as the simpler one (93). Rubber dibromide (141), for example, will alkylate certain substituted benzenes, such as the mono- and poly-phenols, the cresols, anisole, or phenetole. The condensing agent may be either ferric or aluminum chloride.

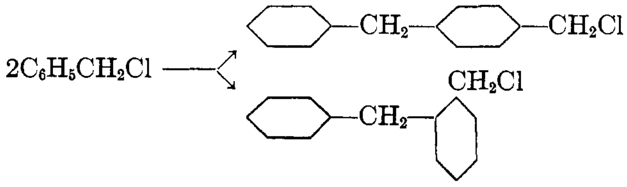


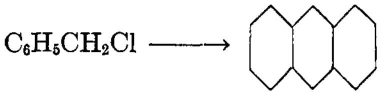
Guttapercha dibromide behaves in a similar manner (141).

Chloropicrin yields with benzene (28) triphenylcarbinol and triphenylmethane. The hydroxyl and hydrogen attached to the methane carbon atoms, respectively, apparently arise from the hydrolysis of the reaction complex in the course of working up the products.

Alkyl halides containing aromatic nuclei react easily with various nuclei to yield substituted products. Benzyl chloride will react with benzene (467, 470, 237, 404) to form diphenylmethane. Benzyl chloride was observed to react with itself to form anthracene (237) and substituted benzyl chlorides (445).

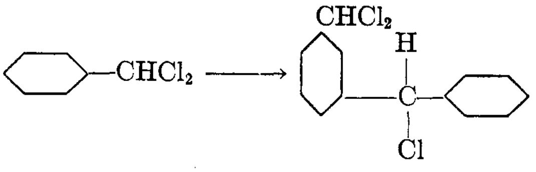
$$C_6H_5CH_2Cl \xrightarrow{C_6H_6} C_6H_5CH_2C_6H_5$$



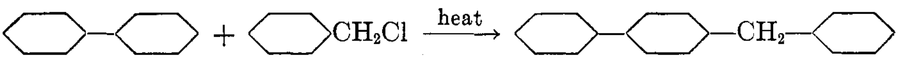


This last reaction probably takes place in two stages. The dihydroanthracene first formed is dehydrogenated to yield anthracene (383).

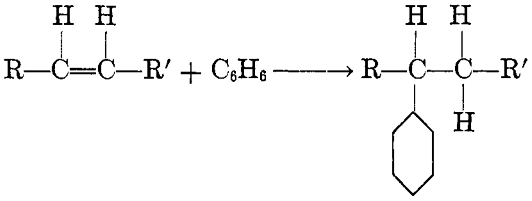
The phenylalkyl dihalides behave in a similar manner (445) to yield a small quantity of meta-substituted products.



It is of significance that diphenylmethyl bromide and phenol (51) or benzyl chloride with diphenyl, benzene, toluene, *o*-xylene, or mesitylene will yield, at elevated temperatures *without a catalyst*, normal condensation products (292). This emphasizes the fact that the alkylation by metal halides is essentially an activation reaction occurring when suitable activity of the nuclear hydrogen and the aliphatic halogen are realized. This throws new light on the mechanics of the reaction (292) (see the discussion of mechanism, p. 378).



2. Alkylation by unsaturated substances. By using one of the active metal halides, it has been found possible to introduce alkyl groups into various nuclei by means of unsaturated compounds. The reaction may be represented by a simple equation using benzene as a type-reactant.



where R and R′ are either hydrogen or a radical. Actually, the reaction has been observed not to take place unless hydrogen chloride is present (275). This indicates the prior formation of an alkyl halide followed by the normal course of alkylation as discussed above (437).

As early as 1879 Balsohn (10) showed that olefins reacted with benzene in the presence of aluminum chloride to yield alkylbenzenes.

$$C_6H_6 + C_2H_4 \xrightarrow{AlCl_3} C_6H_5C_2H_5$$

Because of the availability of ethylene, the reaction was studied more closely later. Fair yields of ethylbenzene may be obtained by passing a stream of ethylene into a rapidly stirred suspension of finely pulverized aluminum chloride in benzene (275). It was found that the higher ethylated benzenes could be prepared by varying the reaction conditions. Prolonged reaction favored a higher yield of polyethylbenzenes, including pentaethylbenzene.

The higher members of the olefin series behave in a similar manner (10, 144, 54). The benzene ring adds to the carbon atom holding the least number of hydrogen atoms.

With cyclic olefins alkylation occurs to yield cyclic alkyl groups in the nucleus (26). For example, cyclohexene yields with *p*-cymene, 2-cyclohexenyl-4-isopropyltoluene.

Niederl and coworkers (299)[2] have demonstrated that it is unnecessary to use vigorous reagents like aluminum chloride when phenolic compounds are being substituted. A condensing agent such as sulfuric acid dissolved in acetic acid is satisfactory to realize an efficient alkylation of phenols and cresols.

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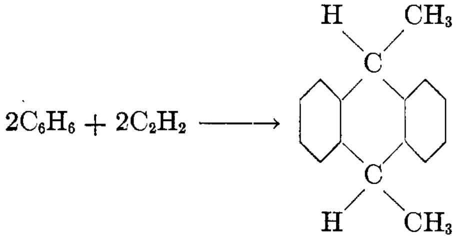
[2] Leading references may be found here.

Certain negatively substituted benzenes are also alkylated by olefins. Nieuwland and coworkers have demonstrated that boron trifluoride will introduce propyl groups into salicylic acid (72), as well as into activated benzene nuclei like the phenols (405), to yield mono- and di-alkylated substances. The entering alkyl groups are oriented normally, i.e., ortho and para to the hydroxyl group and meta to the carboxyl group.

Not only do olefins behave in this manner, but acetylenes yield the predicted compounds, by the addition of two aromatic nuclei to give a diaryl or related compound. Acetylene reacts in the presence of aluminum chloride to yield *as*-diphenylethane and 9,10-dimethyl-9,10-dihydroanthracene (62, 34, 12).

$$2C_6H_6 + C_2H_2 \longrightarrow (C_6H_5)_2CHCH_3$$



Toluene and chlorobenzene yield the corresponding compounds, and dimethylaniline gives a small quantity of *as*-(*p*-tetramethyldiaminodiphenyl)ethane. Nitrobenzene and ethyl benzoate give no products. These latter facts are not disturbing, since highly negative groups markedly retard or prohibit the Friedel-Crafts reaction in general (see the discussion of activating and inhibiting groups, on p. 370).

That acetylene reacts with benzene progressively as expected, that is, first to give styrene, then to yield the final products, finds support in the fact that styrene (433a) and polymers of styrene have been found in the reaction (34). Further evidence is found in the isolation of vinylresorcinol from the reaction of acetylene and resorcinol in the presence of a mercury sulfate–sulfuric acid catalyst (113a).

The halogenoölefins behave as might be expected, when it is considered that they contain both aliphatically bound halogen and a double bond. Vinyl chloride yields with benzene and aluminum chloride *as*-diphenylethane and a small quantity of 9,10-dimethyl-9,10-dihydroanthracene; *as*-dichloroethylene yields the normal product, triphenylethane, and two other products, *s*-diphenylethane and *s*-tetraphenylethane (12, 33, 75). The reaction appears to proceed through a monoarylhalogenoethane (33).

With allyl chloride and benzene, ferric chloride or zinc chloride gives

1,2-diphenylpropane and 2-chloro-*n*-propylbenzene. Freshly sublimed aluminum chloride yields as the sole product 1,2-diphenylpropane. This is in contrast to aluminum chloride which contains a little moisture. The latter substance produces, with benzene and allyl chloride, propylbenzene and 9,10-diethylanthracene (see the discussion of condensing agents, on p. 374).

The general course of the reaction is not affected by the presence of such radicals as may contain the carbonyl group (437, 459, 94, 441, 128).

$$C_6H_6 + C_6H_5CH{=}CHCOC_6H_5 \rightarrow (C_6H_5)_2CH{-}CH_2COC_6H_5$$

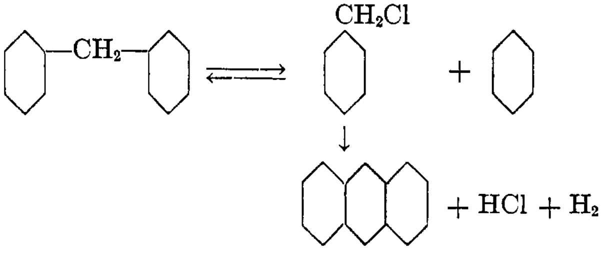
3. Alkylation by hydrocarbons. As early as 1885, it was shown that the Friedel-Crafts alkylations were reversible (5). Methyl groups were found to rearrange from one nucleus to another. Polymethylated benzenes were obtained from toluene or *m*- or *p*-xylene. *o*-Xylene did not rearrange with aluminum chloride.

In an extended study, Boedtker and Halse (29) found that the mass law affected the movement of alkyl groups. Large quantities of alkylating agent and condensing agent tended to give polysubstituted benzenes, while the reverse conditions gave monoalkylated substances. This reversibility may be represented as follows, where R is an alkyl group:

$$C_6H_{(6-n)}R_n + (n - 1)C_6H_6 \rightleftharpoons nC_6H_5R$$

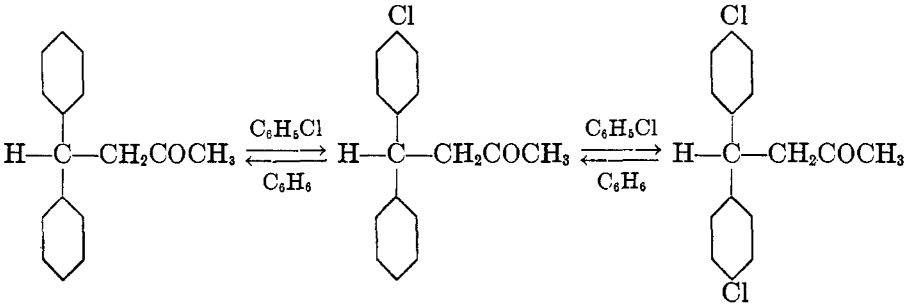
As the weight of the alkyl group increases, the ease of rearrangement increases. Thus the polyamylbenzenes alkylate benzene with great ease (29). With *p*-cymene, aluminum chloride transplants the methyl as well as the isopropyl group to yield benzene, toluene, *m*-xylene, *s*-tetramethylethane, and 3,5-diisopropyltoluene (385).

The heavier hydrocarbons tend to give this same type of reaction. Diphenylmethane, for example, gives anthracene when treated with aluminum chloride. This is offered in support of the theory of splitting, followed by recombination of part of the reactants (344).



Naphthalene also may be alkylated by means of hydrocarbons. Diethyl-benzene, naphthalene, and aluminum chloride give as the principal products ethylnaphthalene and ethylbenzene.

In an extended and detailed study of the reversibility of the Friedel-Crafts alkylations, Fuson and coworkers (459, 94, 441, 128, 188) have shown that the heavy hydrocarbons are applicable to the equilibrium reactions, the aryl nuclei may contain certain so-called negative substituents, and the aryl radicals are apparently replaced mole for mole by the new aryl group. An example is the stepwise interconversion of benzohydrylacetone and di-*p*-chlorobenzohydrylacetone.



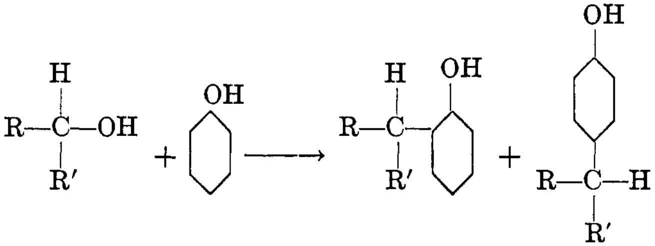
Di-*p*-methylbenzohydrylacetone behaves in a similar manner (459).

Benzene itself may introduce various alkyl groups into aromatic nuclei. On refluxing benzene with aluminum chloride, ethylbenzene (206) and cyclohexylbenzene (443) may be isolated, among other products. This is further discussed under the subject of mechanism (p. 378).

In attempts to alkylate naphthalene using saturated paraffins, no alkylnaphthalenes were isolated (300), indicating an absence of reactivity on the part of the paraffins.

4. Alkylation by alcohols. Alcohols will alkylate certain aromatic compounds in the presence of active metal halides. It is not clear whether an alkyl halide is formed as an intermediate or whether the reaction is essentially a dehydration, since it is well known that sulfuric acid will bring about a similar alkylation.

Zinc chloride (109, 149) or aluminum chloride seem to give identical reactions (202, 203). However, aluminum chloride alkylates by means of an alcohol only where there is a "strained" carbon atom attached to the hydroxyl (203). Phenyl groups, high degrees of branching, or strained rings so activate alcohols that they readily undergo a reaction with an aromatic nucleus. Thus saturated primary alcohols or cyclohexylcarbinol do not react, while phenyl- or cyclopentyl-carbinols do alkylate benzene in the presence of aluminum chloride.



where R is aryl and R′ is hydrogen or alkyl.

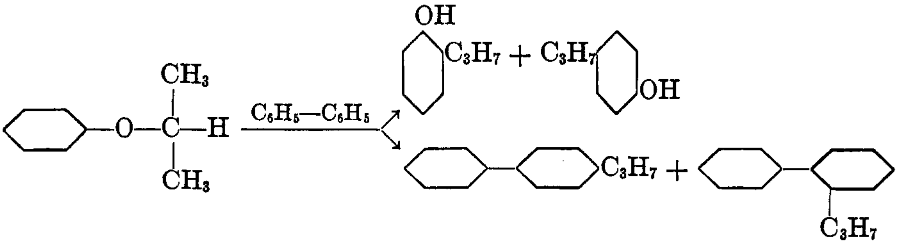
$$(\text{cyclo})\ C_5H_9OH + C_6H_6 \longrightarrow (\text{cyclo})\ C_5H_9—C_6H_5.$$

5. Alkylation by ethers and esters. It is well established that aromatic ethers will rearrange to yield alkylated phenols under a variety of conditions (401, 299, 72, 405). In some instances heat alone is sufficient to bring about the rearrangement (401, 288). In view of this ease of cleavage of the oxygen linkage in ethers, it is not surprising to find that aliphatic or mixed ethers will alkylate certain types of compounds by means of the Friedel-Crafts reaction. Aliphatic ethers give well-defined products with aromatic nuclei (214, 407).

$$ROR + C_6H_6 \rightarrow RC_6H_5$$

where R is an alkyl group.

In showing that the rearrangement of mixed ethers, such as isopropyl phenyl ether, is not necessarily bimolecular (288), it was demonstrated that with acidic reagents such as zinc or aluminum chlorides the reaction becomes complex and that the alkyl group of the ether apparently splits off to yield an alkyl halide which will alkylate the newly formed phenol or a foreign molecule (288, 402). Isopropyl phenyl ether yields, with aluminum chloride and diphenyl, *o*- and *p*-isopropylphenol, diisopropylphenol, and *o*- and *p*-isopropyldiphenyl.



Fifty per cent of the products is represented by the substituted phenols. *s*-Dibromodimethyl ether behaves as methylene bromide (343). In the reaction with benzene the final products are identical with those that would result with benzene, aluminum chloride, and methylene bromide.

Since esters contain a modified ether linkage, it is not surprising that they, too, alkylate in the Friedel-Crafts reaction. It was observed in 1877 that ethyl chlorocarbonate would introduce an ethyl group instead of an acyl group (112). This early observation has been followed by the use of esters as alkylating agents. A variety of esters will introduce alkyl groups. Alkyl esters of aliphatic acids (235, 214), boric acid (216), chlorocarbonic acid, and sulfonic acids (58) all introduce alkyl groups in a manner similar to alkylation by alkyl halide.

This type of alkylation offers great possibilities for the alkylation of highly sensitive types, since the complex formed between the ether or ester and the condensing agent materially lessens the drastic resinifying and polymerizing action of the anhydrous condensing agents such as aluminum, stannic, or zinc chlorides. In fact, it has been possible to realize syntheses in the thiophene series by means of ethers where all efforts with alkyl halides have failed (407).

In connection with alkylation by esters, it is interesting to note that ethyl nitrate introduces the nitro group instead of the alkyl group (28). The behavior of this ester, for some reason, appears to illustrate a case of an anomalous reaction. Indeed, it is possible that the ethylbenzene did form but in exceedingly small quantity, since nitration may be a more rapid reaction under the experimental conditions.

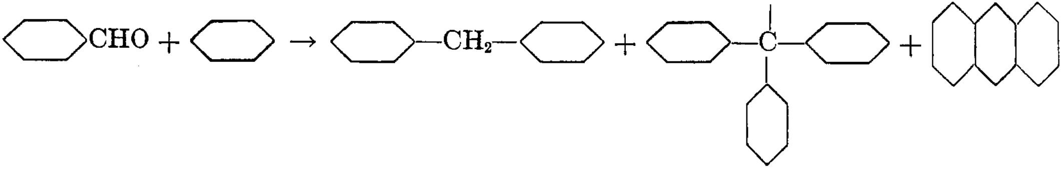
6. Alkylation by oxides, aldehydes, and ketones. As another group of unusual alkylating agents, we find that alkyl oxides, aldehydes, and ketones will introduce the corresponding substituted or unsubstituted alkyl groups.

Ethylene oxide yields with benzene and aluminum chloride a small quantity of β-phenylethyl alcohol and a large quantity of s-diphenylethane (365).

$$C_6H_6 + C_2H_4O \rightarrow C_6H_5CH_2CH_2OH + C_6H_5CH_2CH_2C_6H_5$$

Homologs of ethylene oxide behave in a similar manner (432).

Both alkyl- and aryl-aldehydes will alkylate benzene. Generally the product is an alkylated hydrocarbon containing two or three aryl groups. For example, benzaldehyde yields diphenylmethane, triphenylmethane, and anthracene, which is a product from the benzaldehyde alone (365).



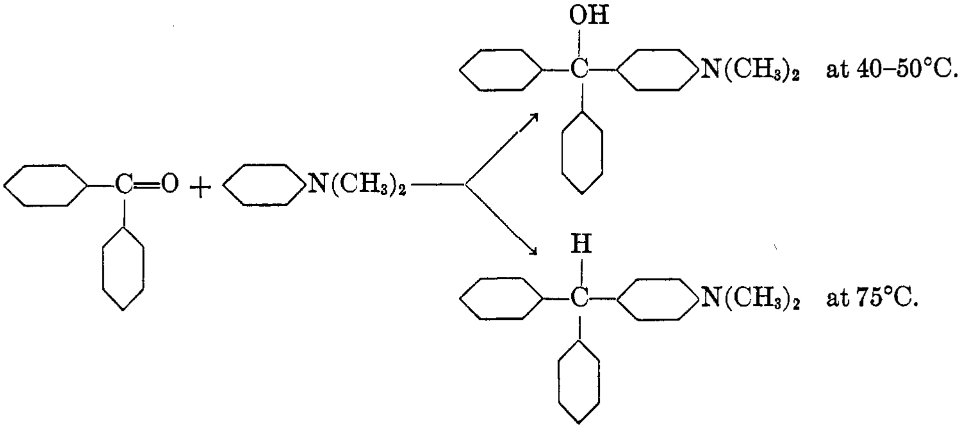
In a similar manner, the straight chain aliphatic aldehydes yield alkylated hydrocarbons with *unbranched* chains. Aldehydes with one (115, 197, 287), two, three, four (22), and five (365) carbon atoms have yielded this type of reaction.

If formaldehyde is used with hydrogen chloride and zinc chloride in benzene solution, benzyl chloride results (362).

$$C_6H_6 + CH_2O + HCl \xrightarrow{ZnCl_2} C_6H_5CH_2Cl$$

Chloral, bromal, and their hydrates behave in the predicted manner to yield condensation products with the formyl group, the halogens, or both (115, 116, 117).

Since it is undoubtedly the activity of the carbonyl group that accounts for alkylation by aldehydes, it is naturally anticipated that ketones would behave in a similar manner. This is the case, for ketones yield carbinols at lower temperatures and hydrocarbons at higher temperatures (67, 436).

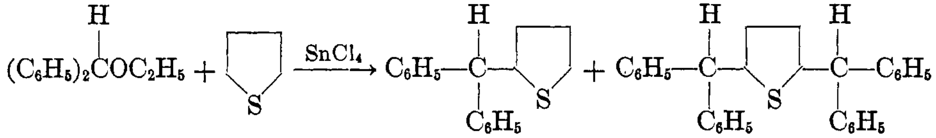


7. *Relative reactivities of the various alkylating agents.* Unfortunately no rigorous experimental comparison of the activity of the various alkylating agents has been made. However, conclusions from the meagre information available tend to show that alkyl attached to halogen is perhaps the most reactive alkylating group. The danger in attempting to correlate relative activities from a survey of the literature lies in the fact that the catalyst may vary in regard to purity. The solvent may vary in the same way, and conditions of reaction, such as stirring, particle size, solubility of reactants, temperature, and oxygen exclusion, may vary to a marked degree. All of these factors affect the reaction.

The conclusion is not to be drawn that all aromatic nuclei undergo alkylation. So far nitrobenzene, unsubstituted benzoates, and simple phenyl nuclei in ketones and nitriles have not been alkylated. The presence of so-called negative groups appears to inhibit reaction, if indeed they do not completely prohibit substitution in the Friedel-Crafts reactions. (See the discussion of activating groups, p. 370.)

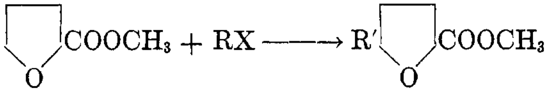
B. Alkylation of the heterocyclic rings

Very little work has been published on the alkylation of heterocyclic compounds. This is explainable, partly, by the sensitivity of the substances. Generally, the heterocyclic compounds contain oxygen, sulfur, or nitrogen linkages. For this reason these compounds are either highly sensitive to drastic condensing agents, or they form complexes with the metal halide so that substitution in the Friedel-Crafts reaction is inhibited. Attempts to acylate unsubstituted heterocyclic rings, such as pyrrole, thiophene, or furan, have been fairly successful. On the other hand, attempts to *alkylate* these unsubstituted rings have been generally unsuccessful. The apparent exception is the case of thiophene, which, when treated with stannic chloride and benzohydryl ethyl ether, yields 2-benzohydrylthiophene and 2,5-dibenzohydrylthiophene (407) (compare also references 416 and 417).



When benzohydryl chloride was substituted for the ether, no alkylated product was obtained.

It has been found (144) that no direct alkylation of furan itself occurs. An easy approach to the 2-alkylfurans through the Friedel-Crafts reaction was found in the discovery that methyl 2-furoate would alkylate smoothly to yield methyl 5-alkyl-2-furoates. This product could be hydrolyzed to the acid, which could in turn be decarboxylated to yield the 2-alkylfuran (144).

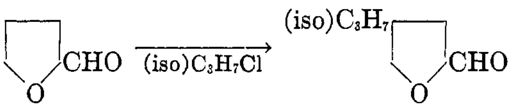


where R and R′ are isomeric alkyl groups. An interesting fact in this connection was established by the observation that methyl and ethyl halides would not alkylate the esters of furoic acid. Perceptible alkylation began with the propyl halides and extended at least through the hexyl halides. The yields in these reactions were excellent (144), and it is now possible to obtain almost quantitative yields with propyl and butyl halides (53).

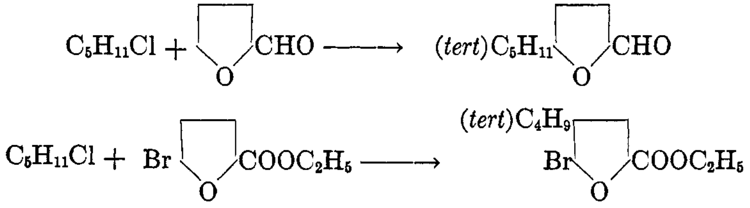
In every case, the product isolated contained the most highly branched alkyl groups possible. For example, normal-, iso-, secondary-, and tertiary-butyl halides give the same product in this reaction,—5-*tert*-butyl-2-furoic acid esters. This rearrangement of the alkyl group is in line with observations on the alkylation of benzene.

Ketones of furan were observed to undergo alkylation in a similar manner. When phenyl 2-furyl ketone was used, the alkyl group entered the furan ring. These alkylations, coupled with the fact that corresponding benzene compounds, methyl benzoate for example, do not undergo alkylation under corresponding conditions, and that benzene may be used as a solvent for Friedel-Crafts reactions in the furan series (346 to 378) have been discussed at length elsewhere (144).

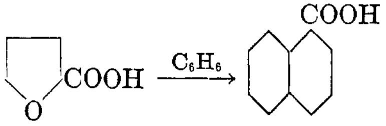
Furfural also was found to undergo the Friedel-Crafts alkylation (146). This was surprising when it is considered that furfural is highly sensitive to acid substances (143a, 54). The alkylation took a course that was unprecedented in furan chemistry. Hitherto in every case when a monosubstituted furan was further substituted, the entering group went to either the 2- or the 5-position (143a). In this alkylation, using isopropyl chloride, the group enters the 4-position (146, 147).



As indicative as the above studies were of the unreliability of Friedel-Crafts alkylations, the interesting observation has been made that when the higher homologous halides, like the variously branched butyl or amyl chlorides, are used to alkylate furfural, the group enters not the 4- but only the *5-position.* Furthermore with certain furanic compounds, in addition to the isopropyl residue (146, 147) no group except the tertiary-butyl group has been introduced (145c), regardless of whether the starting reagents were butyl, amyl, or hexyl halides. This indicates that with amyl and hexyl halides methylene groups are eliminated somewhere in the reaction.



With benzene and aluminum chloride, 2-furoic acid (146) and methyl 2-furoate (146a) yield α-naphthoic acid and methyl α-naphthoate, respectively. The latter reaction produced also a quantity of an indefinite high molecular weight ester of undetermined constitution (144a, 218).

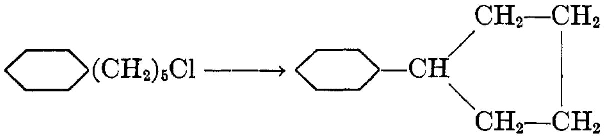


C. The alkylation of aliphatic compounds

When considered from the standpoint of smoothness of reaction, yield, ease of control, and general practicability, the Friedel-Crafts syntheses are essentially transformations that apply to the so-called aromatic nuclei. But as has been pointed out (144), the divisions generally made in substitution reactions such as aliphatic, aromatic, and heterocyclic, are divisions based essentially on rates rather than on the kind of reactions, and those that are commonly considered as typically aromatic find their counterparts in the chemistry of aliphatic substances. So it is with alkylation by the Friedel-Crafts syntheses.

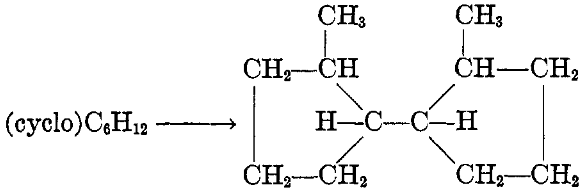
Relatively few cases have been reported of the alkylation of aliphatic types. Yet the significant fact remains that well-authenticated examples have been reported in which aliphatically bound hydrogen is replaced by alkyl groups under the influence of such condensing agents as aluminum chloride. As has been mentioned above, the very first report of the Friedel-Crafts reaction concerned the replacement of hydrogen in an aliphatic substance. This observation was made by Friedel and Crafts in 1877 (119).

One of the first clean-cut aliphatic alkylations was reported in 1912 by von Braun (49). It was observed that attempts to bring about ortho intra-ring closures of 5-phenyl-*n*-amyl chloride did not yield the expected substance, but gave instead cyclopentylbenzene in 85 per cent yields.



In later communications (47, 48), it was shown that reaction undoubtedly did not take place by eliminating hydrogen chloride from the adjacent terminal carbon atoms followed by an isomerization of the 5-phenylamylene-1. All attempts to isomerize 5-phenylamylene-1 to cyclopentylbenzene led to polymeric substances.

An attempt to alkylate cyclohexane by using ethyl, *n*-propyl, isopropyl, isobutyl, and cyclohexyl halides as well as chloroform and carbon tetrachloride with aluminum chloride as the condensing agent, led to indefinite, saturated and unsaturated hydrocarbons (296). Interestingly enough, however, cyclohexane was isomerized and coupled to yield 2-methylcyclopentyl-2-methylcyclopentane.



This interesting case of rearrangement is a commonly observed one, which is discussed at greater length elsewhere in this paper.

In attempting to establish the mechanism of polymerization of simple, low molecular weight olefins by aluminum chloride to yield lubricating oils, it has been suggested that actually a series of alkylations occurs, which results in the formation of long-chain saturated or near-saturated compounds (409, 285, 286).

$$CH_2{=}CH_2 \xrightarrow{HCl} CH_3CH_2Cl \xrightarrow{C_2H_4} CH_3CH_2CH{=}CH_2 \xrightarrow{HCl} \text{etc.}$$

The process represented by the above reaction is only an early step in a series of reactions which involves addition of hydrogen chloride to butylene-1, followed by reaction with another molecule of ethylene and so on until high molecular weight oils are formed.

III. ACYLATION

A. Aromatic types

1. The introduction of the keto group by various reagents. By far the greatest amount of work on the Friedel-Crafts syntheses has been done on the reactions that introduce acyl groups. This is particularly true of the introduction of the keto group. This extensive study has produced a literature that is especially rich in details which give a rather complete picture of the reaction.

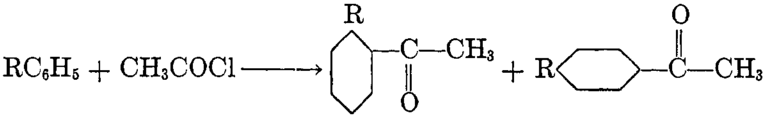
The stimulus to close study of acylations has resulted from several factors. One of the foremost actuating influences has been the demand for ketones of varied nature for industry, particularly as dye intermediates. Furthermore, the acylations lend themselves to a relatively simple and facile study, since they are easy to control and give, generally, monoacylated products. These facts render the reactions highly practical and obviously of value for routine laboratory or industrial syntheses, since many of the acylations give yields of 80 to 97 per cent of the theoretical quantity of products.

(a) Acyl halides. The general reaction for the introduction of keto groups may be simply formulated using benzene, aluminum chloride, and an acyl halide.

$$RH + R'COX \xrightarrow{AlCl_3} RCOR' + HX$$

where R′ is alkyl or aryl and R is aryl.

It was early realized (119, 121, 122) that alkylations had their counterparts in acylation by means of the Friedel-Crafts syntheses. It was observed that acetyl chloride would undergo a condensation with benzene, or alkylbenzenes, and aluminum chloride to give ketones in good yield (122, 270, 293, 257, 136).



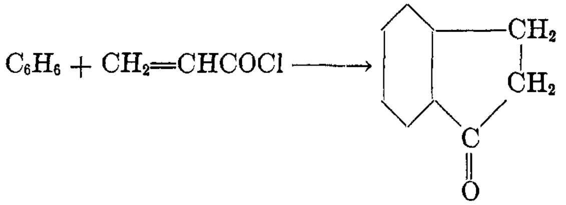
where R = hydrogen or alkyl. The higher acyl halides behave in a similar manner (291a, 144, 136, 220). Propionyl, butyryl, and caproyl halides yield ketones with alkyl groups of configurations which correspond to the branching of the alkyl group in the acid halide. For example normal- or iso-butyryl chlorides will yield with benzene and aluminum chloride the corresponding normal- and iso-propyl phenyl ketones, respectively. This absence of side chain rearrangement has made acylations by active metal halides doubly valuable, since on subsequent reduction the ketones give good yields of hydrocarbons of predicted configuration. Johnson's work (211a) on the synthesis of the alkylresorcinols has emphasized this point. Thus direct access is had to the normal or variously branched homologs of benzene and its derivatives.

Not only do the branched acyl halides undergo this condensation, but the cyclic acid halides behave in a similar manner. With benzene and aluminum chloride, cyclopropanecarboxylic acid chloride gives an excellent yield of phenyl cyclopropyl ketone (220).

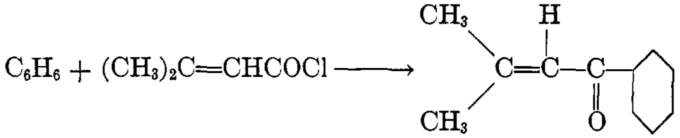
Besides the fatty acid halides, other types may be utilized. It was early shown that carbonyl chloride would give the expected ketones (2, 121, 453).

$$C_6H_6 + COCl_2 \rightarrow C_6H_5COC_6H_5$$

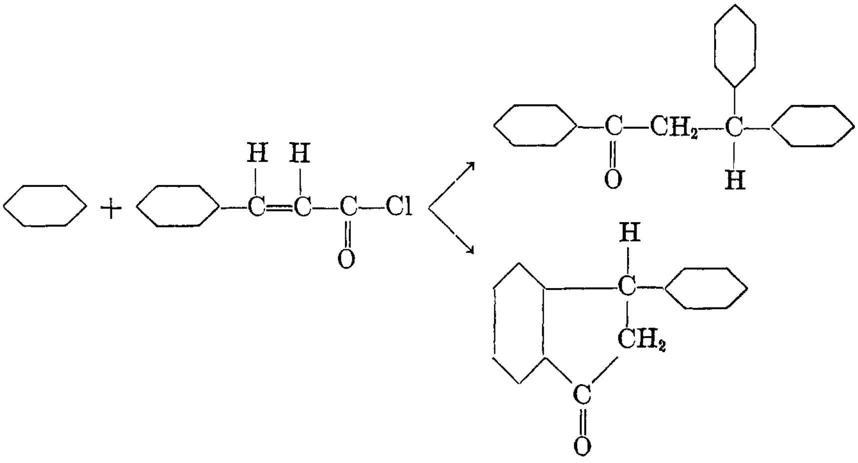
This ketone synthesis seems to be generally applicable to unsaturated acid halides, although some halides unavoidably give complicating reactions on account of the unsaturation. For example, acryloyl chloride yields hydrindone and not vinyl phenyl ketone (225a).



The higher unsaturated acid halides yield the expected unsaturated ketone. 2,2-Dimethylacryloyl chloride gives a 40 per cent yield of 2,2-dimethylvinyl phenyl ketone (77).



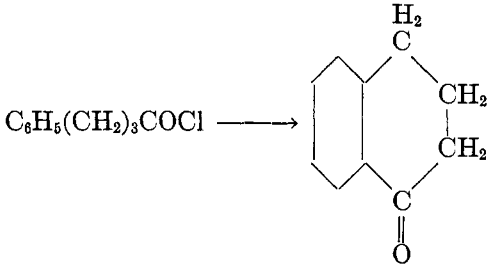
Cinnamoyl chloride behaves as might be predicted on the basis of the presence of an ethylenic linkage and an acyl halide grouping. With benzene the tendency is to yield 2,2-diphenylethyl phenyl ketone and 3-phenylhydrindone-1 (225).



However, bromobenzene, diphenyl ether (225), diphenyl (7), or methoxy compounds (397, 398) give principally the expected para-substituted unsaturated ketones.

Phenylpropiolic acid chloride yields an acetylenic ketone (397). The halogeno fatty acid halides react to yield the corresponding halogenoalkyl aryl ketones. For example, 1,2-dibromopropionyl chloride and benzene give 1,2-dibromoethyl phenyl ketone (225a).

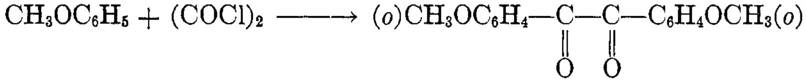
When phenyl nuclei are substituted into the alkyl groups of the longer fatty acids, their halides may undergo a ring closure (259).



When oxalyl chloride is used in the synthesis of ketones, the nature of the product depends in a large measure on the substance undergoing substitution. Compounds that acylate with relative ease yield diketones, while substances that acylate with difficulty yield simple ketones as a result of the rapid decomposition of the oxalyl chloride by the condensing agent. This decomposition follows a course that yields carbon monoxide and carbonyl chloride. The latter decomposition product reacts normally to yield a monoketone (414).

$$C_6H_6 + (COCl)_2 \rightarrow C_6H_5COC_6H_5 + CO + HCl$$

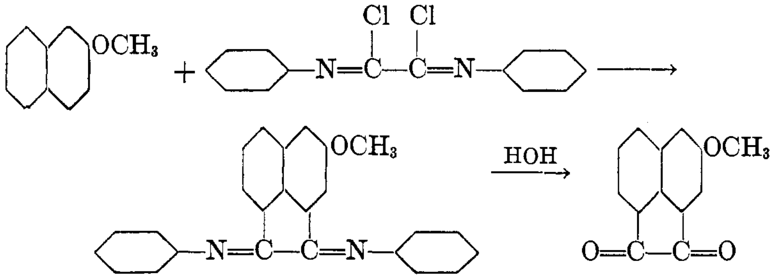
With a more active nucleus, such as anisole or dimethylaniline, a diketone results, since the substitution proceeds more rapidly than the decomposition of oxalyl chloride (410, 411, 244).



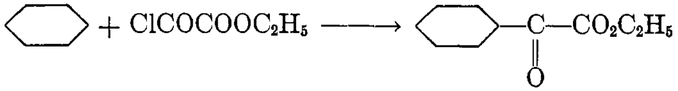
$$CH_3OC_6H_5 + (COCl)_2 \longrightarrow (o)CH_3OC_6H_4-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-C_6H_4OCH_3(o)$$

In this connection, it is interesting to note that oxalyl bromide will give a very small yield of benzil when condensed with benzene and aluminum halide, although the oxalyl chloride does not (410).

The synthesis of diketones may be effected in poor yields by using diphenylimidochlorides of oxalic acid. Here again, only the more active nuclei such as anisole or the alkoxynaphthalenes, allow substitution (412). Methoxynaphthalene, upon reaction with the diphenylimidochloride of oxalic acid and aluminum chloride, gave, after hydrolysis, methoxyacenaphthenequinone.

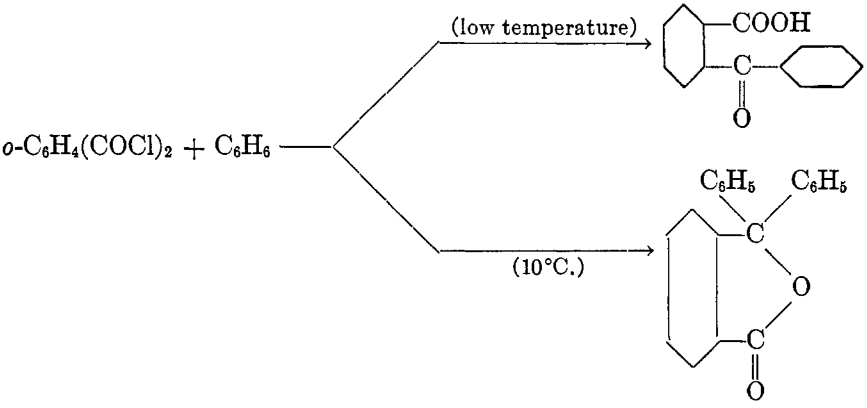


An approach to the substituted keto acids may be realized by using the half-ester of oxalyl chloride. For example, ethyl chloroglyoxylate with benzene and an active metal halide will yield ethyl phenylglyoxalate (335).



The aromatic acyl halides behave in the expected manner to yield diaryl ketones. Benzoyl chloride will give excellent yields of ketones with the substituted or unsubstituted nuclei (132, 177). Substituted benzoyl halides behave in a similar manner (278, 391).

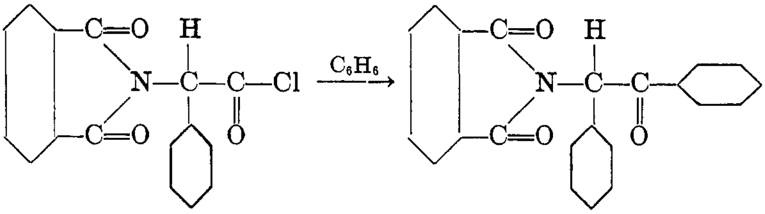
Phthalyl chloride reacts in its two isomeric forms (63). At very low temperatures, the product with benzene and aluminum chloride is *o*-benzoylbenzoic acid. At 10°C. or above the product is diphenylphthalide.



With a large excess of benzene at higher temperatures, the products are *o*-triphenylmethylbenzoic acid and 9-diphenylanthrone (63).

With *o*-carboethoxybenzoyl chloride, the product from benzene and aluminum halide is the expected ethyl *o*-benzoylbenzoate (403).

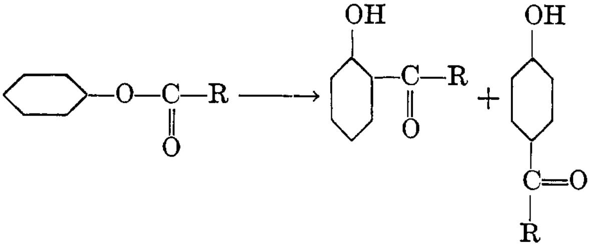
Aminoketones may be synthesized by this reaction if the amino group is protected by acylation. A modified Gabriel phthalimide synthesis of amines may be used as follows (106).



In general, the aromatic substances which will undergo acylation to introduce a keto group are those that undergo alkylation. The typical classes are, besides the unsubstituted nuclei, the halogenobenzenes (132), aromatic ethers (136), biphenyl (59, 393), amines (274a, 410), alkylbenzenes (2, 270), and hydroxybenzenes (20, 126, 458, 143).

Usually the so-called negative groups that contain double bonded oxygen inhibit acylations of the benzene nucleus. This inhibiting action may be overcome in part by the presence of activating groups, such as hydroxyl, alkoxyl, or methyl. Thus benzaldehyde, benzoic acid and its esters, unsubstituted phenyl ketones, and nitrobenzene do not, generally, undergo acylations. This behavior is discussed at greater length in the section on activating groups.

In any discussion of the introduction of keto groups by metal halides, the Fries reaction must be considered. Although it is customary to consider the Fries reaction as separate and distinct from the Friedel-Crafts syntheses, it is difficult to differentiate accurately, since the Friedel-Crafts synthesis of ketones from phenols may, and in many cases does, pass through the intermediate formation of phenyl esters (356). The Fries transformation is essentially the rearrangement of esters of phenols and related compounds to hydroxyketones. This reaction is generally carried out in an inert solvent like carbon disulfide or nitrobenzene, and is actuated by active metal halides, such as aluminum or ferric chloride.



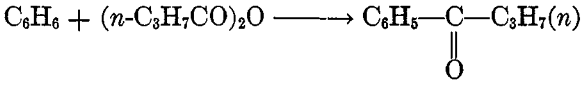
Fries and Finck reported in 1908 that aluminum chloride would rearrange the esters of phenol to yield aryl alkyl or diaryl ketones (126). The esters of polyphenols like resorcinol undergo rearrangement to yield polyketo substances (9). The substituted phenyl esters behave in a similar manner, to yield the corresponding substituted ketone (355).

(b) Anhydrides. Generally anhydrides react with an aromatic nucleus to yield one equivalent of ketone for each mole of anhydride when two equivalents of aluminum halide are used (302, 181, 359).

$$C_6H_6 + (RCO)_2O \rightarrow C_6H_5COR$$

This is a rough picture, although the fate of the remaining fragments of the anhydride is important, since it has recently been demonstrated that these fragments may in part also acylate the ring to increase the yield (159). This angle of the problem is further discussed under the subject of the mechanism of the reaction (p. 378).

The simple aliphatic anhydrides behave as expected, to yield the alkyl aryl ketones (302). Using *n*-butyric anhydride the reaction may be represented by the following equation.



$$C_6H_6 + (n\text{-}C_3H_7CO)_2O \longrightarrow C_6H_5-\underset{\underset{O}{\|}}{C}-C_3H_7(n)$$

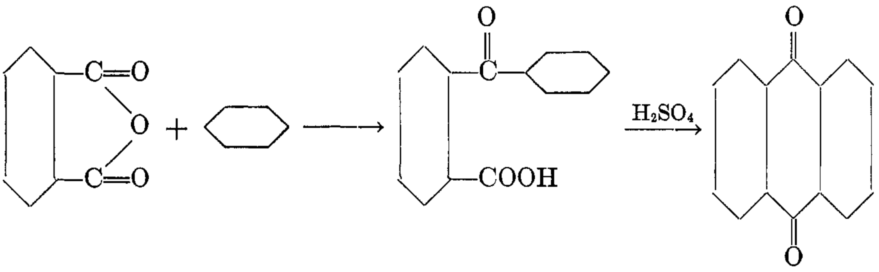
The absence of rearrangement in the alkyl group is to be noted.

When polyanhydrides are used, for example, those of adipic or sebacic acids, the products with benzene and aluminum chloride are ω-benzoyl acids and α, ω′-dibenzoylated hydrocarbons (181).

$$[C_4H_8O_3]_n \xrightarrow{C_6H_6} C_6H_5CO(CH_2)_4COOH \text{ and } C_6H_5CO(CH_2)_4COC_6H_5$$

Benzoic anhydride may be used in a similar manner to yield diaryl ketones (70, 359). Of the aromatic anhydrides, the most valuable is phthalic anhydride. In fact there are few reactions of organic chemistry that have meant more to industry than the formation of *o*-aroylbenzoic acids from phthalic anhydride and an aromatic nucleus in the presence of an active metallic halide, generally aluminum chloride. By means of sulfuric acid, the *o*-aroylbenzoic acids may undergo ring closure to yield various quinones which are prepared in large quantities as dye intermediates.

Although early observations showed the feasibility of using aluminum chloride and phthalic anhydride for the synthesis of anthraquinone and naphthanthraquinone (1), it is only comparatively recently that large quantities of these dye intermediates have been prepared by this reaction (6). This synthesis may be represented by a simple equation:



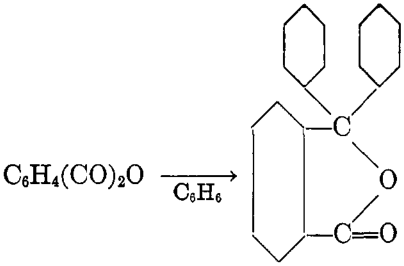
As a result of the absence of impurities, the commercial anthraquinone prepared by this reaction is superior as a dye intermediate to the anthraquinone obtained by the oxidation of anthracene (329) by chromic acid; it is also less expensive than that derived from crude anthracene by catalytic oxidation.

The phthalic anhydride approach to anthraquinone or its simple derivatives is essentially a quantitative transformation from phthalic anhydride and benzene to *o*-benzoylbenzoic acid. It has been demonstrated that actually 97 per cent of the theoretical quantity of *o*-benzoylbenzoic acid may be isolated (176, 359, 2, 54).

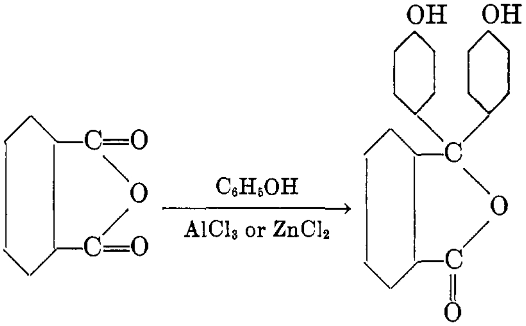
A variety of nuclei will condense with phthalic anhydride to give the corresponding *o*-aroylbenzoic acids. Benzene (159, 254), toluene (239, 176), halogenobenzenes (156, 284), halogenotoluenes (176, 175), diphenyl (161, 86, 378), aromatic ethers (350), naphthalene (176), substituted naphthalenes (178), anthracene (1, 129, 151, 176, 178), phenanthrene (178), and fluorene (74) all undergo acylation by phthalic anhydride and aluminum chloride. Here again we find that highly negatively substituted nuclei, such as benzaldehyde, benzoic acid and its esters, phenyl ketones, and nitrobenzene, do not undergo acylation.

The phthalic anhydride may contain a variety of substituents, the nature of which does not affect the course of the reaction. In every case, regardless of the substituents present in the phthalic anhydride, the product is a substituted *o*-benzoylbenzoic acid. Some of the substituted phthalic anhydrides that have been used contained the following substituents: 4-bromo- (420), 4-nitro- (240), 4-acetamino- (240), tetrachloro-, tetrabromo-, tetraiodo- (239), 3-sulfo-, and 4-sulfo- (390).

The phthalic anhydrides may condense in another manner, since simultaneously with *o*-aroylbenzoic acid formation, there may be phthalide formation (331). It has been noticed that under adverse conditions of reaction, the yield of *o*-benzoylbenzoic acid is reduced and phthalides tend to form instead (359). Some foreign substances, such as acetic anhydride (241), or non-equivalent quantities of the reactants (359) favor the formation of phthalides. In fact the addition of acetic anhydride may increase the yield of phthalides to 93 per cent of the theoretical, with no keto acid formation (241).



On the basis of the phthalide formation, it is not surprising to find that phenolphthalein may be synthesized by the reaction of excess phenol and phthalic anhydride in the presence of aluminum halide (439). Zinc chloride with better results and ferric chloride with poorer results may be substituted for the aluminum chloride.

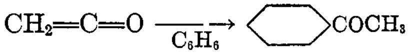


(c) Ketenes. The highly unsaturated ketene reacts with an aromatic nucleus in the presence of aluminum halide to yield ketones. This is not unusual, since ketene in acylation may be compared with ethylene in alkylation. Both add hydrogen halide and both yield reaction products in the Friedel-Crafts reactions as if prior addition of hydrogen halide occurred.

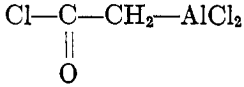
$$CH_2{=}C{=}O + HX \rightarrow CH_3COX \tag{1}$$

$$CH_2{=}CH_2 + HX \rightarrow CH_3CH_2X \tag{2}$$

The general case for the reaction of ketene with benzene and aluminum halide may be represented by a simple transformation.



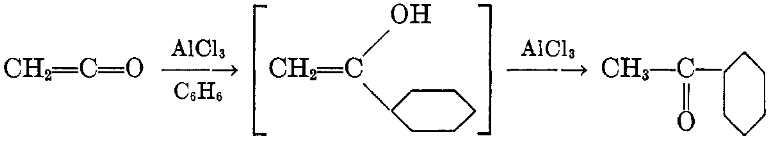
It is not clear whether there occurs direct addition to the ethylenic linkage, the prior formation of acetyl chloride, or the intermediate formation of an organoaluminum compound (319). That is,



$$Cl{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}AlCl_2$$

may be formed. Although there is little direct experimental evidence, a consideration of the known facts seems to indicate the intermediate formation of acetyl chloride. First, the general information on ketene fails to indicate that direct addition to the ethylenic linkage occurs. Secondly, the direct addition of nuclei to an ethylenic linkage in the Friedel-Crafts reactions has not been verified. Thirdly, no case of the definite intermediate formation of an organoaluminum compound has been demonstrated in the Friedel-Crafts reactions. Fourth, the presence of hydrogen halide appears to increase the yield of ketone when ketene is used as the acylating agent (333).

There is, of course, the possibility that a preliminary addition to the carbonyl group is followed by rearrangement. However, there is no evidence to support this view in regard to the Friedel-Crafts reaction.



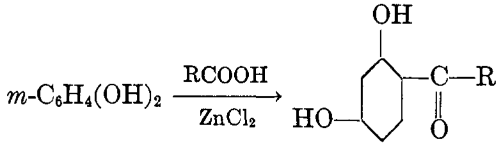
Benzene, anisole, naphthalene (201), or veratrole (333) may be acylated by ketene, while the negatively substituted benzenes like acetophenone again fail to undergo acylation (201).

(d) Acids and esters. Access to the ketones may be had through carboxylic acids. It is possible to introduce the keto group by condensing aliphatic and aromatic acids with nuclei in the presence of active metal halides.

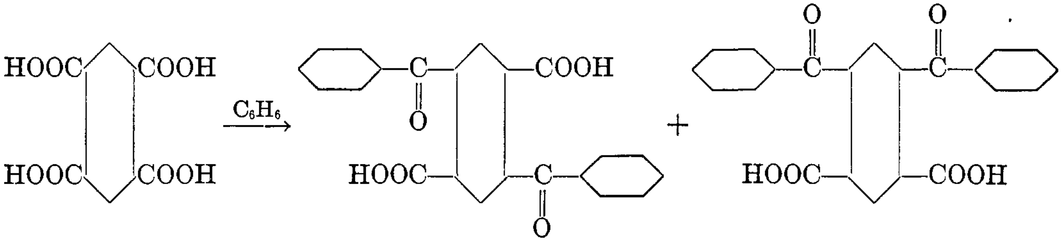
The aliphatic acids, such as acetic or propionic, when heated with excess of aluminum chloride in benzene give ketones in good yields, 60 to 80 per cent (157). The evidence strongly indicates that the reaction is not a direct acylation by the acid, but instead there is intermediate formation of acid halide followed by the orthodox Friedel-Crafts acylation. Thus three moles of aluminum halide are required for each mole of ketone formed.

$$RCOOH \xrightarrow{2AlCl_3} RCOCl \xrightarrow[C_6H_6]{AlCl_3} C_6H_5COR$$

Although this method of ketone synthesis appears to require three times the quantity of aluminum chloride used in acylations by acid halides, the reaction should prove valuable for commercial work and for industrial syntheses when the inexpensiveness of aluminum chloride is considered (251, 252, 6, 157). Already acids have been applied commercially to the preparation of ketones. A case in point is the preparation of *n*-hexylresorcinol, which is acylated and then reduced to the alkylated compound (291b). Zinc chloride gives particularly good results when it is the condensing agent.



Aromatic acids also acylate under these conditions. Even polycarboxylic acids, such as pyromellitic acid, condense to yield keto acids (328).

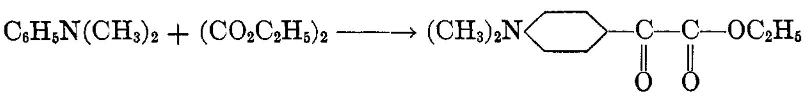


Instead of metallic halides, surface catalysts may be used to bring about a condensation of aromatic hydrocarbons, aromatic amines, phenols, or naphthols with carboxylic acids or their anhydrides to yield ketones. This interesting condensation may be catalyzed by activated carbon, silica gel, and bleaching earths (369) instead of aluminum halide.

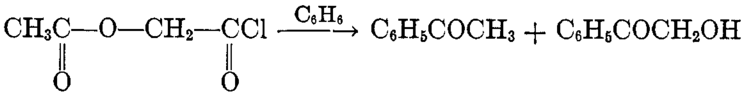
Esters also will acylate aromatic compounds. This reaction has not been extensively studied, but it appears to be of fairly general application. It may occur simultaneously with alkylation by esters.

$$RCOOR' \xrightarrow{C_6H_6} C_6H_5COR$$

Such substances as phenyl acetate, *O*-acetylsalicylic acid, or ethyl acetate will yield, with benzene and aluminum chloride, acetophenone (70). *O*-acetylsalicylic acid gives a 70 per cent yield. The dialkylanilines are acylated by diethyl oxalate to give ethyl *p*-dialkylaminophenylglyoxylate in 60 per cent yields (170, 171).



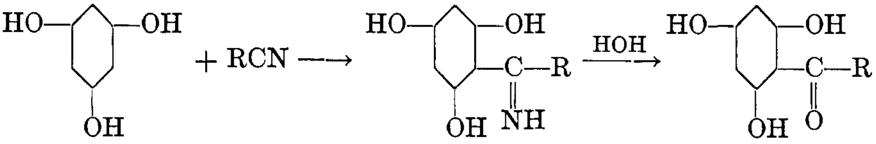
When acetylglycollyl chloride reacts with benzene, an interesting reaction occurs (4).



$$CH_3\underset{\underset{O}{\|}}{C}-O-CH_2-\underset{\underset{O}{\|}}{C}Cl \xrightarrow{C_6H_6} C_6H_5COCH_3 + C_6H_5COCH_2OH$$

(e) Nitriles (the Hoesch-Houben reaction). If a nitrile is used as the acylating agent there is formed as an intermediate product a ketimine, which upon hydrolysis yields a ketone; this is termed the Hoesch-Houben reaction. As a distinct reaction from the Friedel-Crafts type it deserves a fuller discussion than can be given here.

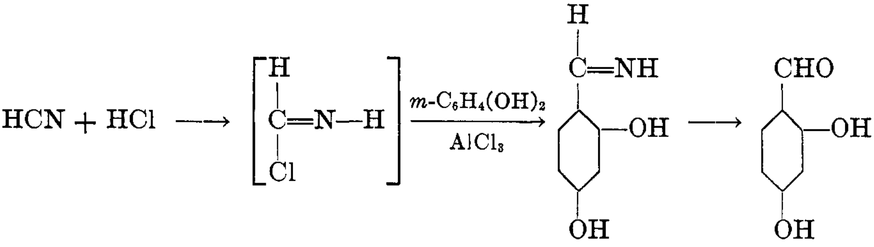
Generally the nitrile is condensed with an aromatic nucleus in the presence of a metal halide such as anhydrous zinc chloride (186).



Aluminum chloride may be used as the condensing agent (234) as well as other active anhydrous metal halides.

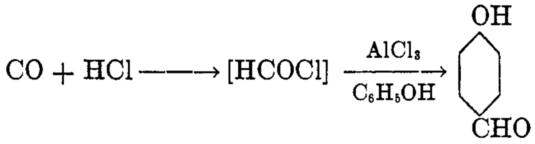
2. Introduction of formyl groups by various reactants. Actually a formyl group may be regarded as a keto group in which one of the radicals is hydrogen. Therefore, just as acids or acid derivatives condense with various substances by certain anhydrous metal halides to yield ketones, the formyl group is introduced by an acid or its derivatives. In the latter case the acid must contain one carbon atom and be of the fatty acid series. The one substance that fulfills these requirements is formic acid. Thus we find that in every case the formyl group is introduced by formic acid or a derivative of it.

(a) Hydrogen cyanide and hydrogen chloride (the Gattermann reaction). One of the best known reactions for introducing the aldehyde group is by means of the hypothetical formimine chloride formed from the simultaneous introduction of dry hydrogen chloride and anhydrous hydrogen cyanide. In the presence of aluminum chloride, reaction proceeds smoothly to give good yields of the intermediate aldimine, which on hydrolysis yields the aldehyde. The phenols react with great ease (134, 138).



The reaction proceeds at low temperature with the phenols and aromatic ethers (133). More difficulty is experienced in substitutions with the alkylbenzenes or benzene itself. However, it may be accomplished by using higher temperatures and pressures (182).

(b) Carbon monoxide and hydrogen chloride (the Gattermann-Koch reaction). If carbon monoxide is substituted for the hydrogen cyanide in the above reactions, a formyl group may be introduced directly. Formyl chloride is probably formed as an intermediate (139).



An interesting fact established in connection with this reaction is the extreme catalytic effect of a small quantity of cuprous halide when used in conjunction with aluminum chloride.

Nickel carbonyl, possibly as a carbon monoxide carrier, in the presence of aluminum bromide introduces the formyl group into benzene (190).

In quite recent work (157) it has been shown that formic acid will introduce the formyl group directly. This reaction appears to proceed through the formation of formyl chloride by the aluminum chloride. This interesting reaction deserves further study, which it is receiving (161a).

$$HCOOH \xrightarrow{AlCl_3} [HCOCl] \xrightarrow[C_6H_6]{AlCl_3} C_6H_5CHO$$

3. The introduction of carboxyl groups by various reagents. In general the methods of introducing carboxyl groups depend on a derivative of carbonic acid.

(a) Urea chloride. It is not surprising to find that urea chloride will acylate some aromatic types to yield amides of carboxylic acids. These amides hydrolyze easily, yielding the corresponding acid (137, 140). By this means naphthalene, phenol ethers, and alkylbenzenes have been carboxylated with greater ease than has benzene (140).

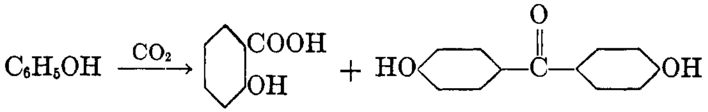
$$ClCONH_2 \xrightarrow[C_6H_6]{} C_6H_5CONH_2 \xrightarrow{HOH} C_6H_5COOH$$

(b) Carbonyl chloride. When carbonyl chloride reacts with the various aromatic types, one of the products is an acid chloride which yields an acid on hydrolysis (2, 121, 453, 274). Any of the various aromatic nuclei that undergo acylations may thus be carboxylated. The yield of acid depends on the conditions which are adverse to ketone formation, such as low temperature. Small concentration of hydrocarbon or short reaction periods tend to favor acid production.

$$C_6H_6 \xrightarrow{COCl_2} C_6H_5COCl \xrightarrow{HOH} C_6H_5COOH$$

Since, as has been shown above, oxalyl chloride decomposes under the influence of aluminum chloride to yield phosgene, it is to be expected that acids may form a part of the products in acylation by oxalyl chloride. This is often true. In fact, with diphenyl, *s*-diphenylmethane, retene, or xanthene the product may consist largely of the corresponding acid (245) instead of a ketone or diketone.

(c) Carbon dioxide. It is interesting that carbon dioxide itself will introduce the carboxyl group in a Friedel-Crafts acylation. The more active nuclei, under high pressures, are required to show any appreciable acylation. Thus the hydroxy- and amino-benzenes react at 70 to 120 atmospheres at 100-150°C. to yield ketones and acids. The catalysts may be anhydrous aluminum, zinc, or ferric chlorides (280).



This reaction has great possibilities. If it were possible to attain acid and ketone syntheses in good yields under conditions easily and cheaply available, the above reaction should prove of inestimable value as an inexpensive avenue to certain acids and ketones.

4. The introduction of specialized groups. The definitions of alkyl and acyl groups that have been made for purposes of discussion in this paper place such groups as sulfonyl, hydroxy, thio, thioketo, and others in the class of acyl groups. As has been pointed out earlier, this need not be considered as a hard and fast classification.

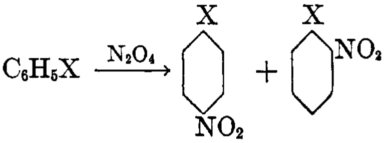
(a) The introduction of the nitrile group. The nitrile group may be introduced into benzene in a direct substitution using aluminum halide. The acylating reactant may be mercury fulminate. This substance may produce fulminyl chloride (or chlorocyanogen) *in situ*, which then reacts to yield benzonitrile (376).

$$Hg(ONC)_2 \xrightarrow{HCl} HONC \xrightarrow{AlCl_3} [ClNC \text{ or } ClCN] \xrightarrow[AlCl_6]{C_6H_6} C_6H_5CN$$

In a similar manner toluene yields *o*- and *p*-toluonitriles.

By an analogous reaction, bromocyanogen will yield benzonitrile (123).

(b) Introduction of the nitro group. Nitration may be effected by an aluminum chloride catalyzed reaction. If nitrogen tetroxide is used as the nitrating agent, the yields are markedly improved by the presence of aluminum or ferric halides (367). Even a substance such as fluorobenzene or iodobenzene gives 80 to 90 per cent of the theoretical yields (364).

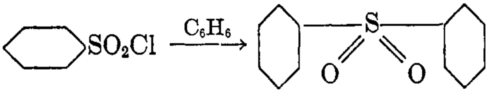


The products contain a preponderance of the para-isomer.

Ethyl nitrate will also introduce the nitro group (28). With benzene and aluminum chloride, nitrobenzene results; with toluene, *o*- and *p*-nitrotoluene are the products. The *p*-isomer forms 80 per cent of the product.

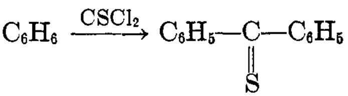
$$C_2H_5NO_3 \xrightarrow{C_6H_6} C_6H_5NO_2$$

(c) The synthesis of sulfones. It is to be expected that the sulfonyl chlorides will generally introduce a sulfone group in the Friedel-Crafts acylations. In fact, the reaction is generally applicable to sulfonyl chlorides and to aromatic nuclei which undergo acylation (35, 308, 312, 452, 313).



The alkyl- or halogeno-benzenes yield generally the para-substituted sulfones. Here again the so-called "highly negative" groups, such as carboxyl, formyl, keto, and nitro, inhibit reaction when they occur alone in the benzene nucleus (see the section on activating groups, p. 370).

(d) Formation of thioketones, thioanilides, and dithiocarboxylic acids. Certain sulfur-containing substances, such as thiophosgene, behave as do their oxygen-containing counterparts in the Friedel-Crafts reaction. Thiophosgene yields with benzene derivatives and aluminum chloride the corresponding thioketones (135).



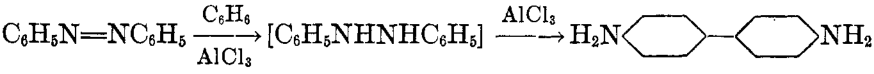
$$C_6H_6 \xrightarrow{CSCl_2} C_6H_5-\underset{\underset{S}{\|}}{C}-C_6H_5$$

Thioanilides may be formed by reaction of benzene with phenyl isothiocyanate and aluminum chloride (125, 354), in a manner analogous to that used for the oxygen-containing phenyl isocyanate.

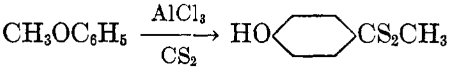
$$C_6H_6 \xrightarrow{C_6H_5NCO} C_6H_5NHCOC_6H_5$$

$$C_6H_6 \xrightarrow{C_6H_5NCS} C_6H_5NHCSC_6H_5$$

In connection with doubly bound nitrogen, it is of note that azobenzene does not give triphenylhydrazine, as might be expected. Instead it undergoes a reduction and rearrangement to yield benzidine.



Even carbon disulfide, widely used as a solvent for the Friedel-Crafts reaction, will actually enter the condensations. The easily substituted types, such as the phenol ethers, yield an interesting product with carbon disulfide and aluminum chloride (212). Anisole, for example, yields *p*-dithiocarbomethoxyphenol. It has been suggested that the alkyl group is apparently cleaved from the ether linkage and combined with halogen of the aluminum halide to form an alkyl halide, which reacts with the carbon disulfide to form methyldithiocarbonic acid chloride, $ClCS_2CH_3$. This latter compound then acylates the phenol in a normal manner. The net reaction is

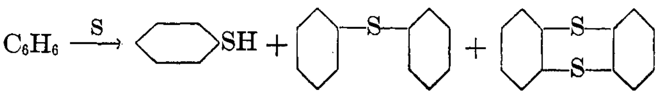


Since gaseous methyl chloride will actually enter into this reaction without alkylating the nucleus, the above mechanism seems logical (144). Many of the sometimes troublesome red residues in the Friedel-Crafts alkylations are these dithiocarboxy compounds. The dithiocarbomethoxy esters have also been observed in the alkylation of the furan nucleus (144).

(e) The introduction of oxygen, sulfur, selenium, arsenic, and phosphorus. It is interesting to note that oxygen may be introduced into a nucleus as inert as benzene by means of the Friedel-Crafts reaction. It is an established fact that when oxygen is not excluded from Friedel-Crafts syntheses, one of the complicating reactions is the introduction of oxygen into the nucleus to form phenolic substances (443, 206).

$$C_6H_6 \xrightarrow{O_2} C_6H_5OH$$

Sulfur behaves in a manner similar to oxygen to form thiophenol (43), diphenyl sulfide, and thianthrene (345).

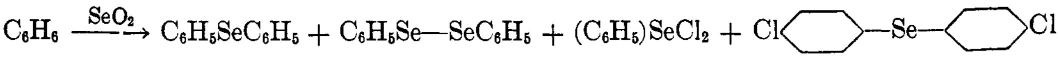


Sulfur monochloride yields diphenyl sulfide, diphenyl persulfide, and sulfur (43) when condensed with benzene by means of aluminum chloride.

$$C_6H_6 \xrightarrow{S_2Cl_2} C_6H_5SC_6H_5 + C_6H_5S\text{—}SC_6H_5 + S$$

Toluene undergoes these reactions with greater ease than benzene, while chlorobenzene does not yield a sulfur-containing product. If the starting substances are thiophenols, or diphenyl sulfide with aluminum chloride, the products of the reaction are essentially the same as if benzene and sulfur were used (81, 82).

As might be expected, selenium behaves very much as does sulfur in the Friedel-Crafts syntheses. Benzene, selenium dioxide, and aluminum chloride yield, upon reaction, diphenyl selenide and diphenyl perselenide as the essential products (250). Smaller quantities of diphenylselenium dichloride, and di-p-chlorophenyl selenide were isolated. It is interesting to note the chlorination of the benzene ring.



Toluene behaves in a manner analogous to benzene (71), to yield as the main product tri-p-tolylselenium chloride.

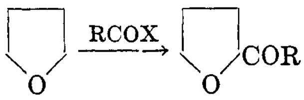
Certain arsines have also been synthesized by this method. Aluminum chloride, benzene, and methylphenylarsine chloride react to give methyldiphenylarsine (50). The corresponding p-tolyl compound may be obtained from toluene (199).

Similarly, phosphorus may be introduced into the benzene nucleus from phosphorus trichloride (231, 122) by aluminum chloride.

B. The acylation of heterocyclic compounds

(a) The oxygen-containing rings. Partly as a result of the sensitivity of the oxygen-containing rings, coupled with the lack of demand for the products, there is no extensive literature on the oxygen-containing heterocyclic rings in regard to acylation by the Friedel-Crafts reaction. The principal nucleus of this nature that has been studied is that of furan.

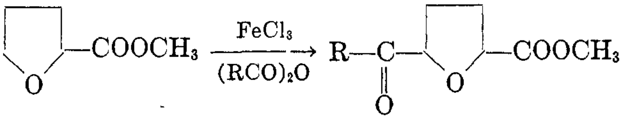
As was pointed out above, unsubstituted furan has not been alkylated. To be contrasted with this is its ready acylation in good yields. Furan will undergo the Friedel-Crafts reaction to yield ketones or an aldehyde. If furan is treated with aluminum chloride and an acid chloride in a suitable solvent, ketones may be obtained in good yields (144, 347).



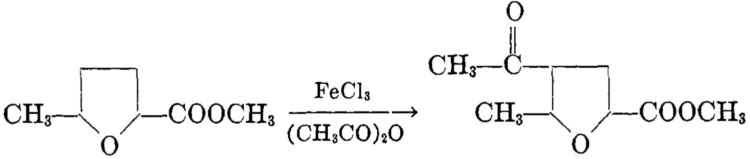
The general observation that the entering group goes to the usual position, that is, either 2 or 5 (143a), is valid in every case of furan acylation, regardless of the nature of the entering group (144).

Furan also acylates easily with anhydrides to yield ketones (145b, 144).

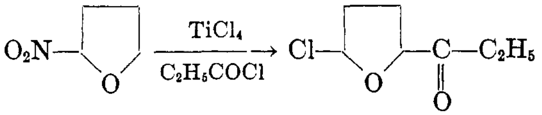
The substituted furans may be acylated to give substituted furyl ketones. 2-Methylfuran is acylated in the 5-position by means of an acid chloride (347) or an anhydride to yield a ketone (145b). Methyl furoate will acylate in the 5-position to yield the corresponding ketone. Strangely enough neither an acid chloride nor an acid anhydride would acylate methyl-2-furoate with aluminum chloride as the condensing agent. In contrast to this latter fact, ferric or stannic chloride acylates methyl 2-furoate with relative ease (144).



When a methyl group occupies the 5-position, as in methyl 2-methyl-5-furoate, the entering acyl group goes to the 4-position (145). In the event the 5-position is occupied by a nitro group or bromine atom, no reaction occurs (144a, 145b).

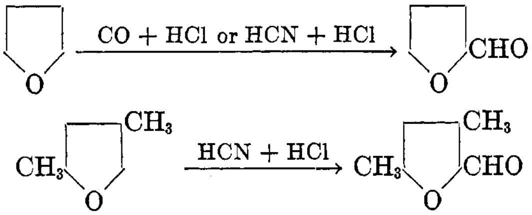


Although certain negatively substituted furans will undergo the Friedel-Crafts acylations, as is shown above and as is true with 2-bromofuran, so far all attempts to acylate a nitrofuran have been futile (54). 2-Nitrofuran generally decomposes badly in attempts to acylate it. However, titanium tetrachloride produces an interesting reaction in which the nitro group is replaced by a chlorine atom and a keto group is introduced into the ring (145b).



Stannic, ferric, aluminum, and titanium chlorides may be used to acylate furan. This is the suggested order of their decreasing activity for the acylation of the furan nucleus (54). For a further discussion see the section on condensing agents (p. 374).

The introduction of formyl groups by the use of either the hypothetical formyl chloride or formimine chloride into either unsubstituted or alkylated furan yields the corresponding 2-furfural (346, 349, 348).

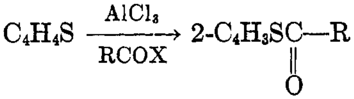


So far it has not been possible to introduce the formyl group into the β-position or into negatively substituted furans (348, 54).

The relative ease with which furan undergoes the Friedel-Crafts reaction is emphasized by the fact that benzene may be used as the solvent for acylations (144, 347). Benzene is a particularly good solvent if stannic chloride is the condensing agent.

Unfortunately, very few stable hydroxyfurans are known. This has prevented an application of the Fries rearrangement to the furan nucleus. However, when phenols and furoyl chloride or phenolic esters of furoic acid are treated with aluminum chloride a Fries transformation occurs (143).

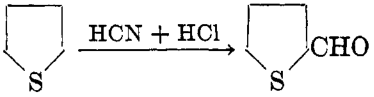
(b) The sulfur-containing rings. Thiophene, like other aromatic types, will undergo acylation. Acid halides with aluminum chloride may be used to obtain excellent yields of the 2-substituted thiophene (276, 368).



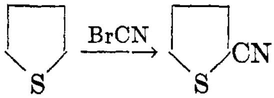
$$C_4H_4S \xrightarrow[RCOX]{AlCl_3} 2\text{-}C_4H_3S\underset{\underset{O}{\|}}{C}\text{—}R$$

Besides aluminum, stannic (408, 148), or titanium chlorides, the condensing agent may be phosphorus pentoxide. The reaction occurs with the phosphorus pentoxide at elevated temperature to give good yields of ketones (416, 419).

By using hydrogen cyanide and hydrogen chloride with aluminum chloride, a formyl group may be introduced into thiophene (348).

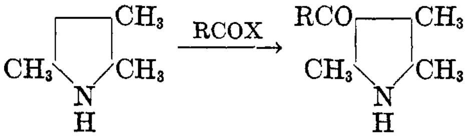


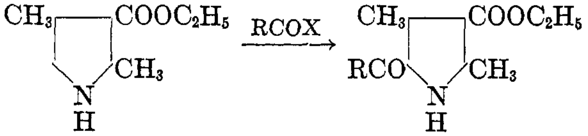
The nitrile group has been introduced into thiophene by means of the Friedel-Crafts reaction. This is analogous to the corresponding reaction with benzene (417, 123).



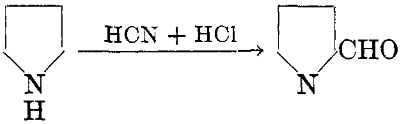
(c) Nitrogen-containing rings. Generally the nitrogen-containing rings are peculiarly resistant to the Friedel-Crafts substitutions. Apparently the only unsubstituted nitrogen ring which has been acylated by the Friedel-Crafts method is pyrrole. In fact, pyrrole will acylate without a catalyst when it is refluxed with acetic anhydride (370). It was at first suspected that this product was the *N*-acetylpyrrole, but it was later shown to be 2-acetylpyrrole (56a).

Substituted pyrroles may be acylated in the normal Friedel-Crafts manner. The entering keto group goes to an open 2- or 5-position. If both of these positions are blocked, then the keto group enters the available position (111).

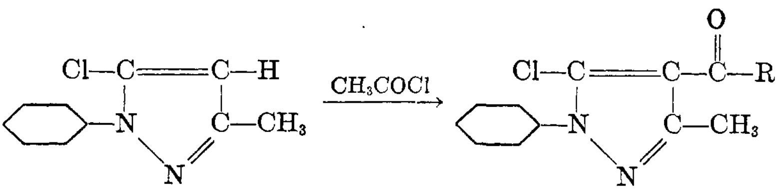




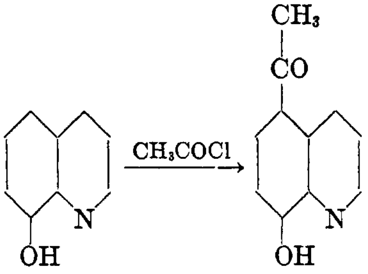
The aldehyde group is introduced with great ease, using hydrogen cyanide and hydrogen chloride (346, 112).



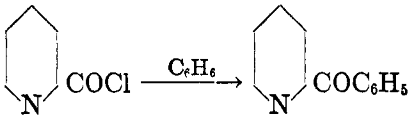
The information on the acylation of the pyrazoles is exceedingly meagre. 1-Phenyl-3-methyl-5-chloropyrazole will acylate to yield the 4-acyl derivatives (272).



With quinoline only an isolated case of acylation has been reported. In this instance it was found possible to introduce the acetyl group into the 5-position if an hydroxyl group occupied the 8-position (256, 256a).

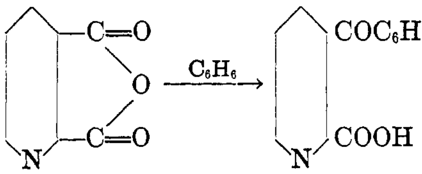


Although the following cases are not examples of the acylation of nitrogen-containing rings, these rings enter into the reaction, yielding acylated substances of such a nature that the product is identical with the product that would be obtained if the rings underwent acylation. For example, it has not been found possible to acylate pyridine. However, acid derivatives of pyridine will acylate benzene (157). Picolinic acid chloride yields with benzene and aluminum chloride the corresponding α-benzoylpyridine.

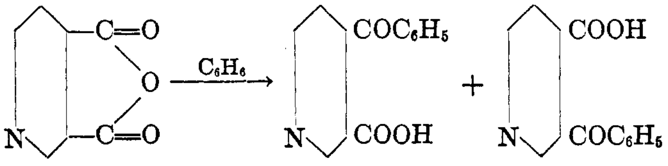


Nicotinic acid halides behave in a similar manner (219b).

Quinolinic anhydride reacts with benzene as does phthalic anhydride to yield β-benzoylpicolinic acid (219, 208, 19). The benzene rings reacts with the carbonyl furthest removed from the nitrogen atom.



Cinchomeronic acid anhydride behaves in a similar manner to give the isomeric substances, β-benzoylisonicotinic acid and γ-benzoylnicotinic acid (219a).



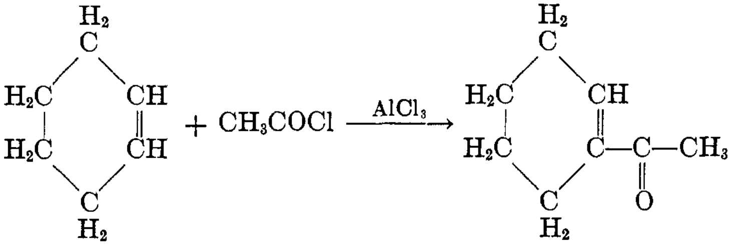
C. The acylation of aliphatic types

(a) Unsaturated compounds. If benzene is considered an unsaturated hydrocarbon, it is not surprising that some unsaturated hydrocarbons acylate by the Friedel-Crafts method. The simplest unsaturated hydrocarbon, ethylene, acylates by means of benzoyl chloride to produce vinyl phenyl ketone in 25 per cent yields (305).

$$CH_2{=}CH_2 \xrightarrow{C_6H_5COCl} CH_2{=}CHCOC_6H_5$$

Other open chain unsaturated hydrocarbons behave in a similar fashion. Propylene, the butylenes, trimethylethylene, hexylene, and heptylene yield ketones with acyl halides (232).

The cyclic olefins behave in the expected manner, to yield ketones. For example, cyclohexene yields methyl cyclohexenyl ketone when condensed with acetyl chloride and aluminum chloride (449).

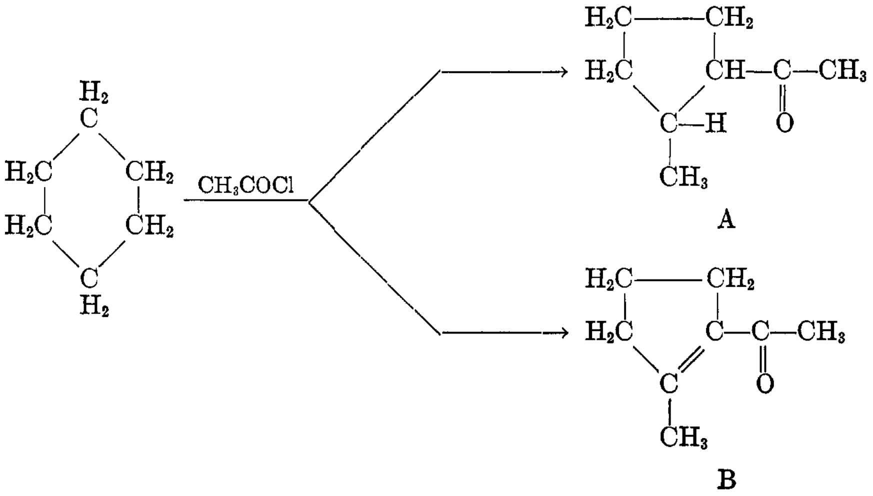


Of the more complex unsaturated substances, cholesterol, ergosterol, and dicyclopentadiene give no acylated products (448), while camphene does give a ketone (247, 450).

(b) Saturated substances. The saturated hydrocarbons undergo the Friedel-Crafts acylation to yield saturated and unsaturated ketones. The higher members of the paraffins undergo this replacement, while methane, ethane, and propane do not (194, 295). Thus, pentane yields 2-acetylpentane when condensed with acetyl chloride in the presence of

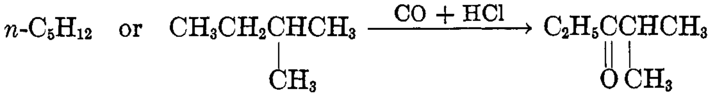
$$n\text{-}C_5H_{12} \xrightarrow{CH_3COCl} 2\text{-}(CH_3CO)C_5H_{11}$$

aluminum halide. Cyclohexane, on the other hand, rearranges as it acylates to yield with acetyl chloride, for example, 1-methyl-2-acetylcyclopentane (A) and 1-methyl-2-acetylcylopentene-1 (B) (431, 193, 462, 297).



The relative quantities of A and B produced depend on the purity of the aluminum chloride. Very pure, absolutely anhydrous aluminum chloride yields A in a quite pure form, while moisture- or oxygen-containing substances (295), as well as the presence of ferric chloride (262), may produce pure B.

Attempts to carry out the so-called Gattermann-Koch synthesis of aldehydes led to interesting but anomalous results. *n*-Pentane and 2-methylbutane with carbon monoxide, hydrogen chloride, and aluminum chloride under 150 atmospheres pressure gave ethyl isopropyl ketone (194). Here we have a novel reaction which, in essence, cleaves an aliphatic chain, introduces a carbonyl group, and then recombines the fragments. There was also isolated a small quantity of α-methylvaleric acid,



$$n\text{-}C_5H_{12} \quad \text{or} \quad \underset{\displaystyle CH_3}{CH_3CH_2\overset{|}{C}HCH_3} \xrightarrow{CO + HCl} C_2H_5\underset{\displaystyle O}{\overset{\|}{C}}\underset{\displaystyle CH_3}{CHCH_3}$$

which indicates that the so-called normal course of the reaction was followed in part with subsequent oxidation.

Another observation, as interesting as the above reaction, was made on the treatment of alkyl halides with carbon monoxide and aluminum chloride. Acid chlorides were produced: *n*-propyl chloride, for example, gave *n*-butyryl chloride (194).

$$n\text{-}C_3H_7Cl \xrightarrow[AlCl_3]{CO + HCl} n\text{-}C_3H_7COCl$$

A patent covers a similar reaction (90).

IV. ORIENTATION AND RELIABILITY

In some cases the Friedel-Crafts reactions are reliable, but in all cases of the synthesis of a new product by this reaction it is advisable to determine the structure and orientation by other means. Thus for proof of structure, the transformations effected by active metal halides are generally invalid.

As gloomy a picture as this may be, the Friedel-Crafts syntheses remain, as is well known, most valuable reactions for laboratory and industry. A note of warning is in order, however, since unpredictable and unparalleled results are constantly occurring.

It may be generally said that alkylations are more variable and unreliable than acylations, but it must be remembered that the reliability of the reaction depends on several factors. Foremost among these contributing effects are the nature and purity of the catalyst, the solvent, the alkylating or acylating reagent, the substance undergoing reaction, the foreign bodies present, and the temperature.

In spite of the lack of uniform behavior in these reactions, there are certain general rules of behavior that may be observed. First, substituents already present in a nucleus generally direct normally as they would for other substitution reactions, such as nitration and halogenation, although this is not always true. Secondly, alkyl halides undergo rearrangement during reaction to give, usually, the most highly branched alkyl groups. This makes it virtually impossible to introduce an alkyl group with a normal chain of more than two carbon atoms.

The question of the orientation is a vital one. However, a highly detailed discussion of the orienting influences in Friedel-Crafts syntheses would take us far afield. Table 1 lists the various groups, their directing influences, and the pertinent references.

No discussion of the general reliability of the Friedel-Crafts syntheses is complete without mentioning some of the unusual conditions that affect the yield and the nature of the product. The ease with which alkyl halides undergo rearrangement to yield more highly branched alkyl groups is of paramount importance. Alkyl halides rearrange under a variety of conditions. Heat (271, 108) or catalysts (392a, 144, 168) will effect this rearrangement. Thus it is to be expected that in the Friedel-Crafts alkylations the normal and slightly branched chains tend to yield the highly branched alkyl groups. For example, *n*-butyl chloride rearranges to yield secondary and tertiary (144) groups.

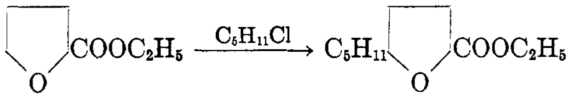
A discrepancy in the rules of orientation is noted with the methyl group, which will at times direct in part to the meta position and not to the ortho position. This seems to be particularly true when the entering group is highly branched, such as *tert*-butyl (392a) or isopropyl (236). It is to be remembered that with lower alkyl groups the benzene ring may be completely alkylated to produce hexaalkylbenzenes (5, 11).

Besides the rearrangement, the alkyl group may be cleaved to yield short alkyl groups, that is, a long chain alkyl halide, for instance, amyl or hexyl, may yield on reaction a butyl group. This appears to depend on the substance undergoing reaction. For example, ethyl 2-furoate gave with the amyl or hexyl halides the expected alkylated substances (144, 147).

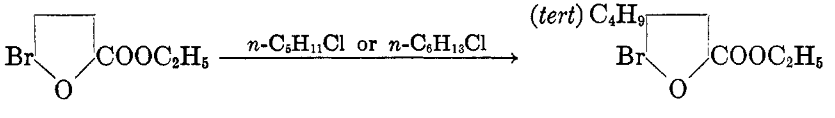
TABLE 1

Directing influence of various groups in benzene

GROUPS	ORIENTATION	REFERENCE
Hydroxyl	*o, p*	(277, 117)
Alkoxyl	*o, p*	(257)
Phenoxyl	*o, p*	(350)
Methyl	*o, p*	(236, 197, 176, 453)
Chloro	*o, p*	(156)
Bromo	*o, p*	(156)
Amino	*o, p*	(67, 410, 274a)
Chloromethyl	*o, p*	(362)
Diphenyl	*o, p*	(161, 378)
Benzyl	*o, p*	(343, 445)
Formyl	*m*	(144a, 147, 145c)
Carboxyl	*m*	(144, 20)
Nitro	*m*	(422)
Dichloromethyl	*m*	(445)
Keto	*m*	(257)



But when ethyl 5-bromo-2-furoate was substituted for ethyl 2-furoate, thus forcing the entering substituent into the 4-position, *all alkyl halides with more than four carbon atoms gave only ethyl 5-bromo-4-tert-butyl-2-furoate* (145c).



Even *n*-octadecyl bromide cleaved to yield the above *tert*-butyl ester (147a).

A similar observation has been made in alkylation by olefins. Diamylene and benzene yield butyl-, amyl- and hexyl-benzenes (428a), and not a decylbenzene.

These reactions are not particularly surprising when it is reflected that aluminum chloride is an excellent agent for "cracking" paraffins (251, 252, 253). The action of the aluminum chloride generally takes a course that yields a smaller molecule than the one contained in the initial reactant. The lighter and gaseous members of the hydrocarbons may be formed (95, 98), as well as certain higher hydrocarbons.

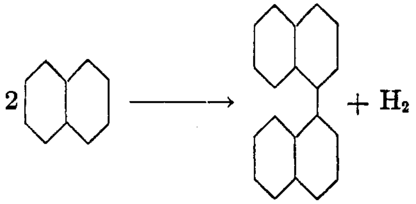
Attention must also be given to the side reactions which the compound undergoing substitution may suffer. In general these reactions are of two forms, disproportionation and cleavage of chains and rings.

Under disproportionation come the reactions that couple the nuclei undergoing substitution and that result in such changes as the removal and wandering of halogens, the movement of alkyl groups in alkylated substances, and the production of tars and gums of an undefinable nature. These reactions take place under anhydrous conditions in an inert atmosphere. If oxygen, moisture, or carbon dioxide be admitted, then the reactions characteristic of these substances will occur.

Benzene, for example, with aluminum chloride yields a minute quantity of diphenyl (206). However, with other hydrocarbon types, this reaction is prevalent. This is the so-called Scholl reaction and is fundamentally an elimination of a molecule of hydrogen to give a coupled product (379, 380, 381). Although the heavier aromatic types such as naphthalene and anthracene give better yields of coupled products, the simple aromatic nuclei undergo a similar coupling (64).

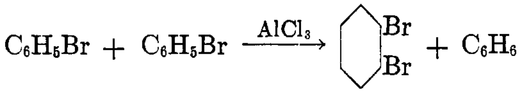
Even the cycloparaffins tend to couple with evolution of hydrogen as the aromatic nuclei do (296, 293, 206).

The liberated hydrogen may cause reductions of the other reactants. For example, the acid halides may be reduced to aldehydes (296).

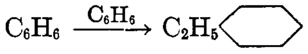


$$H_2 + C_6H_5COCl \longrightarrow C_6H_5CHO$$

Under the influence of aluminum chloride, even the halogens attached to the aromatic nuclei may migrate in the ring or to another ring (64, 89, 226).



As might be expected the cleavage reactions take a variety of courses. Besides those cleavage reactions already mentioned, the aromatic rings may undergo complete decomposition to form fragments that undergo simultaneous reduction to yield alkyl groups that will enter the remaining nuclei. This process has been pictorially described as "destructive alkylation" (206). The over-all reaction is represented simply:—



Even methyl radicals of methoxyl groups may be eliminated by an active metal halide (327). However, the methyl radical does not tend to rearrange to the nucleus under these conditions (337). Although these reactions take place in the average Friedel-Crafts reaction, they are usually found to produce a more or less small fraction of the total products, depending largely on the conditions. Generally, high temperatures, high concentration of condensing agent, and a long reaction time favor the side reactions, although these same conditions may be required to effect the condensation. It is worthy of note here that in carbon disulfide these side reactions appear to be materially diminished. It has been shown that methyl groups do not migrate or rearrange when the solvent is carbon disulfide (358).

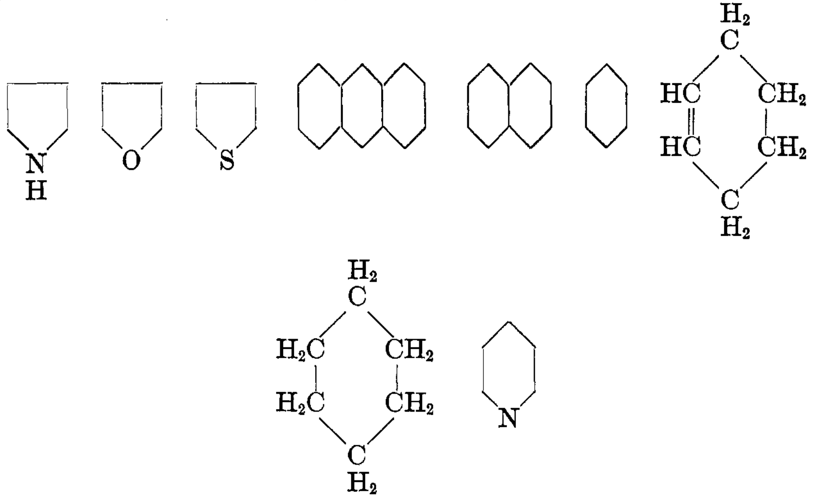
Although these reactions do not represent the entire picture of the side reactions, they are typically representative and give an idea of the complexity that may be attained in the Friedel-Crafts syntheses.

V. ACTIVATING AND INHIBITING GROUPS

It is in line with observations on orientation in the Friedel-Crafts syntheses to note that just as in other substitution reactions the presence of substituents may increase or decrease the ease of further substitution into the nucleus.

The Friedel-Crafts reactions are definitely substitution reactions. As such they are not violent reactions nor are they necessarily, as a class, vigorous. In fact the introduction of alkyl and acyl groups may be made a mild reaction by controlling the conditions. The reactions *are* unreliable sometimes and even decompose the reactants. But these are eccentricities and are not properly viewed as an aspect of being violent or unduly vigorous. Many compounds that undergo nitration, halogenation, or sulfonation with comparative ease, either react with difficulty or entirely fail to substitute in a Friedel-Crafts reaction. Even benzene itself is resistant to *some* types of Friedel-Crafts substitutions, such as the Gattermann or Gattermann-Koch modifications.

Generally, unsubstituted rings will undergo the Friedel-Crafts substitutions. These appear to fall in an order that may be discerned from the various researches. Some have been compared directly. Others must be placed by a comparison of the work of different investigators (144, 346, 347, 348, 53, 54). On the basis of a general review, the unsubstituted rings arrange themselves from left to right, in the order of their decreasing ease of substitution in a series that is not exact for all alkylations and acylations but is undoubtedly general.



Pyrrole is given the most active position here with the understanding that the reactions probably proceed through the intermediate formation of *N*-alkyl or *N*-acyl compounds which rearrange. Because of this activity of the =NH group, perhaps pyrrole should not be included in the series.

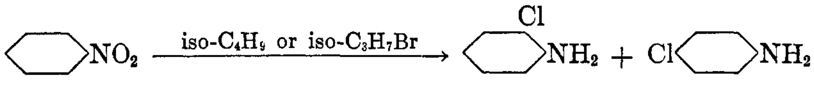
For the substituted types, it is easy to point out the compounds which will and will not undergo the Friedel-Crafts syntheses, but it is more difficult to arrange the groups in an *order* of activity, since few direct comparisons have been made. Nevertheless, judging from the available material and from comparisons from scattered sources, the following order is approximately correct. It is certain that the general scheme and classification is correct for a decreasing activity from left to right. Some of the groups may, under varying conditions, assume a slightly altered order (144, 53, 308, 43).

$$\text{—OH and —OCH}_3,\ (\text{CH}_3)_2\text{N—},\ \text{CH}_3\text{—},\ \text{H—},\ \left\{\begin{matrix}\text{Cl—}\\ \text{Br—},\\ \text{I—}\end{matrix}\right.\ \left\{\begin{matrix}\text{—CHO}\\ \\ \text{—COCH}_3\end{matrix}\right.,$$

$$\text{—COOR},\ \text{—NO}_2,\ \text{—C}\equiv\text{N}$$

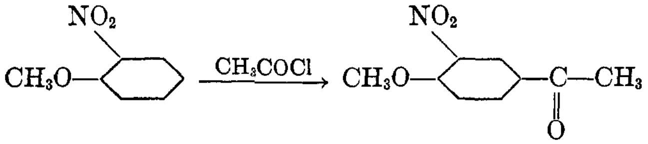
In general an increasing so-called electronegativity (217a) of the group increases the difficulty of substitution. So far no successful attempts to alkylate or acylate nitriles have been reported.

The fact that nitrobenzene is used as a solvent for many Friedel-Crafts transformations indicates its inert nature in regard to substitutions in alkylation or acylation. All attempts to introduce an alkyl or acyl group into nitrobenzene have been futile. On prolonged reaction in attempting to alkylate nitrobenzene, reduction ensues and amines result. After thirty days reaction at room temperature, or in a shorter time at elevated temperature, isopropyl or isobutyl bromides with aluminum chloride and nitrobenzene give small quantities of *o*- and *p*-chloroaniline (145b) with a large fraction of unchanged nitrobenzene.



These products may be considered anomalous, although both reduction of the nitro group (87, 222) and halogenation of the benzene nucleus (250, 159) have been observed separately. This work emphasizes the desirability of careful isolations in the Friedel-Crafts transformations.

If one of the highly activating groups such as methoxyl is present, the nitro group no longer prohibits reaction (422).



The carboxyl group which normally prohibits reaction (144, 406, 20) will not interfere if a group such as methoxyl is present in the ring. Thus methyl anisate alkylates with ease, while methyl benzoate does not.

For ketones, the presence of alkyl groups (270, 137) is sufficient to cause activation of such a nature that substitution will occur, notwithstanding the fact that the keto group markedly inhibits reaction (124a) in such a way that only mono keto substances may be obtained when unsubstituted benzene is acylated. That is, only one acetyl or benzoyl group enters benzene, while two or more will enter durene (270) and hydroxy- or alkoxybenzenes (257, 357a, 291).

Similarly the formyl group inhibits reaction. However, it has been found possible to alkylate benzaldehyde in exceedingly low yields (147). Here again the alkoxyl group is of sufficient activating influence to cause anisaldehyde to alkylate smoothly (144a).

Numerous observations have been made that the halogens deter substitution in alkylation or acylation. Thus the difficulty in acylating or alkylating is increased in a halogenobenzene (42, 43), although the exact order of interference for the halogens is not established definitely. In this connection, it has been shown that for sulfone formation chlorobenzene is more resistant than bromobenzene (308).

Besides the examples mentioned above there are many cases in which methyl (259, 391, 98, 172), amino (274, 410), and methoxyl (410, 256, 256a, 134) activate the nucleus so that substitution occurs with increased ease.

VI. SOLVENTS

Although the actual technique of the Friedel-Crafts syntheses cannot be dealt with in detail here, a word must be said concerning the solvents used, since they vitally affect the reactions. Perhaps the most general practice is to use as the solvent an excess of the hydrocarbon or substituted hydrocarbon that is undergoing substitution. Obviously unless this reactant is liquid under the conditions of the reaction, it cannot be used. Thus, for the substitution of alkyl and acyl groups into benzene, the latter compound is almost invariably the solvent. Although this practice yields ketones effectively, it is not generally a desirable method for alkylation, where a definite product and high yield are the major interests. Not only is benzene used in this way, but other liquid reactants such as toluene and chloro- or bromo-benzene may be used (308, 160). In some cases a substance like carbon tetrachloride may be used if it is one of the reactants (353).

Obviously there are often reasons why one of the reactants cannot be used as the solvent. Sometimes no solvent is necessary; the reactants, even though solid, are made to react directly by grinding together molecular quantities and fusing the mass. In many cases this affords excellent results (284, 161, 176, 354).

When it is desired to eliminate one of the reactants as the solvent, an inert solvent may be used. Generally, this is either carbon disulfide or a petroleum ether. Carbon disulfide appears to have a specific action on the Friedel-Crafts syntheses, tending to prevent migration of groups (358). It is generally an excellent solvent for a variety of alkylations (144, 343) or acylations (302, 257, 308). In some cases, carbon disulfide may influence the reaction markedly and in a few cases actually reduce the yield (278) or control the velocity of reaction (353). But it remains as one of the best general solvents for the Friedel-Crafts syntheses.

The exact nature of the rôle that the solvent plays here is uncertain. As has been so well pointed out (277a, 184), the action of the solvent is at times subtle and deep-seated and far more significant than one would expect of a simple medium for reaction.

Petroleum ethers exhibit properties similar to those of carbon disulfide when used as solvents (358, 202, 103, 81).

When highly reactive compounds are used, or when mild condensing agents are employed, solvents such as *o*-dichlorobenzene (160), acetylene tetrachloride (350), benzene (144, 347, 178), and diethyl ether (347, 170, 171) may be used. Under these conditions the alkylation or acylation of the substance in question must be so rapid that the solvent, though reactive under some conditions, does not have an opportunity to react. For example, when benzene is used as a solvent for the acylation of furan by acetic anhydride and stannic chloride, the major product is the acylated furan (347, 144), although benzene will undergo slow acylation under these conditions. Also, anthracene may be acylated in benzene solution by phthalic anhydride and aluminum chloride (178). This is to be compared with the quantitative yield of ketone that may be obtained from benzene, aluminum chloride, and phthalic anhydride (359) when the anthracene is absent.

Nitrobenzene finds its use as a solvent not only as a result of its high boiling point and excellent solvent nature, but largely because of the fact that it forms complexes with the metal halide, thereby materially reducing its activity. This complex formation lessens the charring and disproportionating action of the aluminum chloride, thereby making the introduction of alkyl and acyl groups essentially a mild reaction (308, 355, 385, 256) applicable to sensitive types like phenols, amines, benzyl halides, or quinolines (308, 355, 383, 256).

VII. THE CONDENSING AGENTS

Generally, the mention of the Friedel-Crafts reactions immediately calls to mind aluminum chloride. This is perfectly reasonable, since aluminum chloride was the first well-described condensing agent and the one that is in by far the most general use, although no less than fifteen different substances have been used in the various Friedel-Crafts reactions as condensing agents. The resublimed aluminum chloride is obtainable commercially in a state of high purity and at a low cost per pound (158). When all factors are considered, there is little doubt that aluminum chloride is the best general catalyst for the Friedel-Crafts syntheses. For the alkylation or acylation of substances that undergo replacement with ease, other condensing agents may be found superior to aluminum chloride. Regardless of the pseudospecific action of certain condensing agents, they all have essential characteristics in common. Usually they are metal halides. Under all circumstances they are essentially anhydrous. Although we have limited ourselves here to discussions of alkylations and acylations by active metal halides, there are a few special cases where closely related catalysts are used, and these are not metallic halides. It is found that the anhydrous substances listed in table 2 catalyze some of the Friedel-Crafts reactions. While under certain conditions the substances listed in table 3 may be used as condensing agents, they have not been shown to be generally applicable. The substances listed in table 4

TABLE 2

Condensing agents

SUBSTANCE	TYPE OF REACTION	REFERENCES
$AlCl_3$	Acylations and alkylations	(144, 294, 64, 154, 298)
$AlBr_3$	Acylations and alkylations	(64)
$SbCl_5$	Acylations	(60a)
$SbCl_3$	Acylations	(264)
BF_3	Alkylations	(405, 187, 72)
$FeCl_3$	Acylations and alkylations	(444, 144, 298, 353, 260)
$SnCl_4$	Acylations and alkylations	(406, 148, 76)
$NaCl \cdot AlCl_3$	Alkylations	(122)
$TiCl_3$	Acylations and alkylations	(214)
$TiCl_4$	Acylations and alkylations	(213, 408)
$ZrCl_4$	Acylations and alkylations	(233)
$ZnCl_2$	Acylations and alkylations	(444, 134, 412, 138)
Hg·Al	Acylations and alkylations	(130, 345, 34)

TABLE 3

Condensing agents not generally applicable

SUBSTANCE	TYPE OF REACTION	REFERENCES
$ClCH_2COOH$	Acylations	(730)
$HgCl_2$	Acylations	(53)
P_2O_5	Acylations	(419)

TABLE 4

Substances which have given no indication of catalytic activity

SUBSTANCE	TYPE OF REACTION	REFERENCES
$PbCl_2$	Acylations	(53)
$CuCl_2$	Alkylations	(122)
$CoCl_2$	Alkylations	(122)
$MgCl_2$	Acylations	(122)
$SiCl_4$	Acylations	(53)
$CaCl_2$	Acylations	(53)
$CrCl_3$	Acylations	(131)

have given no indication of catalytic activity. It is to be noted that beryllium chloride is essentially inactive (444).

There are a few general characteristics which the efficient condensing agents (table 2) have in common. With the excepton of iron, they arise from the elements that are centrally located in the periodic table. All the elements are more or less amphoteric and form highly hygroscopic anhydrous halides. These anhydrous halides are essentially non-polar in the anhydrous form and possess typically quite low boiling points (395, 207, 21), with the exception of zinc chloride (m.p. 365°C. b.p. 730°C.). However, all substances that show these properties are not active catalysts in the Friedel-Crafts condensations. For example, the carbon and silicon tetrahalides do not catalyze the elimination of hydrogen halide.

Thus the nature of the catalyst appears to depend not only on the polarity of the halogen bonds, but fundamentally on the complex electronic structure of the central atom. The problem forms a phase of the Friedel-Crafts reactions that is greatly in need of elucidation. It appears from present knowledge that one essential feature that all of the condensing agents must have is a great facility for forming a highly active complex with one or both reactants.

It is not to be inferred that the condensing agents must necessarily be usable interchangeably. It is sometimes true that these catalysts may be substituted for each other, but many of them show a definite activity which limits their use to certain nuclei or substituted rings. For example, while aluminum chloride will introduce groups into benzene, thiophene, furan, or the substituted benzenes, stannic chloride fails to produce a reaction with certain substances such as chlorobenzene. Stannic chloride, however, does activate a reaction slowly with benzene (53), and it produces a reaction easily with furan (144) or thiophene (148). Similar observations have been made with titanium tetrachloride (408), zirconium tetrachloride (233), ferric chloride (131, 353), zinc chloride (131), and others, so that it is possible to formulate a series of general activity. It must be realized, however, that conditions of comparison were not always exactly the same. But there is sufficient cumulative evidence as to the commonly used reagents to show that the following decreasing order of activity is generally valid.

$$\mathrm{AlCl_3},\ \mathrm{FeCl_3},\ \mathrm{ZnCl_2},\ \mathrm{SnCl_4},\ \left\{\begin{matrix}\mathrm{TiCl_4}\\ \mathrm{ZrCl_4}\end{matrix}\right.$$

The other condensing agents have not been sufficiently studied to warrant placing them in the series, but all appear to be less active than stannic chloride. Thus from this series it is seen that it is possible to select a condensing agent so that preferential substitution will occur. For example, by using stannic, titanium, or zirconium halides it is possible for some active substances such as anisole, thiophene (407, 408), or furan (144, 347), to be alkylated or acylated in benzene solution.

One factor that vitally affects the behavior of the condensing agent is the presence of impurities. In fact, traces of various foreign substances markedly alter both the yield and the direction of the reaction. A trace of moisture, for example, will tend to promote the removal of hydrogen from aliphatic substances (295), or it may increase the disproportionating and rearranging tendency of the catalyst (294). Water, however, is not the only substance that will produce this behavior. Other oxygen-containing substances besides water, such as phosphorus oxychloride, nitrobenzene, benzophenone, or acetone, behave in a similar manner (295).

Occasionally substances may be found that increase reaction yields when used in conjunction with the regular condensing agent. In the introduction of the formyl group by carbon monoxide and hydrogen chloride, using aluminum chloride as the condensing agent, it has been found that cuprous chloride markedly increases the yield (139). More recently it has been observed that mercury will influence the alkylation of benzene by vinyl chloride, changing the course of the reaction to inhibit the entrance of more than one benzene nucleus (75). In acylating benzene by organic acids in the presence of aluminum chloride, phosphorus trichloride and thionyl chloride increase the yields, while potassium perchlorate decreases the quantity of ketone obtained (157). Ferric chloride, under some conditions, may increase the yield of product in certain Friedel-Crafts reactions (352), when used with aluminum chloride.

The highly specific condensing agents (table 3) are interesting. As has been pointed out, many types of alkylations and acylations may be effected by means of catalysts other than the anhydrous metal halides. These reactions do not belong in the classes of transformations known as the Friedel-Crafts syntheses, but a few warrant mention here.

One of the most interesting is the use of aliphatic chloro acids or chloro anhydrides to act as the condensing agent. Chloroacetic acid, for example, with anisole and an anhydride yields a ketone in 80 to 90 per cent yields on prolonged refluxing, whereas without the chloroacetic acid a yield of only 1.5 per cent is obtained (430).

$$CH_3OC_6H_5 + (CH_3CO)_2O \xrightarrow{ClCH_2COOH} p\text{-}CH_3OC_6H_4COCH_3$$

Chloroacetic acid anhydride behaves in an analogous manner.

Phosphorus pentoxide is useful in the acylation of thiophene by means of anhydrides (419), while mercuric chloride will condense furan with acid chlorides (53). The latter reaction may possibly proceed through the intermediate formation of a chloromercuri compound (143a).

VIII. MECHANISM OF THE REACTIONS

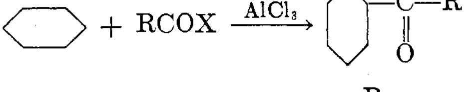
With such a variety of reactions to include in the classes of the Friedel-Crafts syntheses, it is exceedingly difficult to give a concise and yet clear picture of these transformations. To say that the Friedel-Crafts reactions are fundamentally substitution reactions is to present only part of the picture, for the cleavage reactions are as important as the substitution reactions. Indeed, the former frequently accompanies the latter.

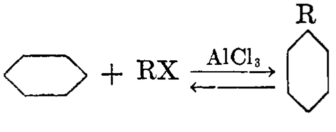
It may be that there is not sufficient information available to warrant any attempt to explain fully the mechanism of the Friedel-Crafts syntheses on a single basis. Certainly no one mechanistic view will adequately provide for alkylations and acylations in all of their ramifications. Neither is there evidence that will rationalize the rearranging, disproportionating, reducing, and disrupting or cracking action of metal halides with the smooth introduction of groups into a nucleus. Yet they all appear to be associated with some one property of the condensing agents.

Of course we may adequately explain the entire field of phenomena concerning these reactions if we use such terms as "activating influence," "catalysis," "complexes," "equilibria," etc. Obviously an explanation couched in such broad terms is not fruitful. An explicit interpretation of the mechanism of the Friedel-Crafts syntheses must await further experimental work.

It is necessary to limit the discussion to the action of aluminum halides, and it is unreasonable to expect *all* the condensing agents to behave in the same manner. A glance at the tables of condensing agents raises the question whether or not all of these condensing agents *can* act in the same manner. This is yet to be demonstrated.

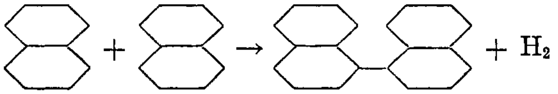
Furthermore, it is necessary to limit the discussion to the alkylating and acylating reactants that are halides, that is, alkyl and acyl halides. Here again, there is no evidence to prove that all of the alkylations or the heterogeneous acylations pass through the intermediate formation of halides, although this is a possibly valid view. It is known, however, that many of the alkylating and acylating agents do yield alkyl (262, 18, 447, 243) and acyl (159, 44, 157, 3, 424) halides under influence of aluminum chloride. Thus the two reactions which are to be considered are represented as follows:





where R is alkyl.

There is a definite activating action by the condensing agent. The action appears to affect the nuclear hydrogen and the organic halide. This is brought out by the fact that many types of alkylation (112a, 292) and acylation (68, 430) may be effected in poor yield and at high temperatures without a condensing agent. In these cases, then, the condensing agent only serves to increase the rate of reaction, thereby making it possible to carry out the synthesis at a lower temperature (304). The fact that in the Scholl modification of syntheses by aluminum chloride, hydrogen is actually evolved, gives strong support to the view that in some cases at least the hydrogen undergoes a marked activation by the condensing agent (383, 381, 380).

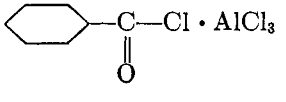


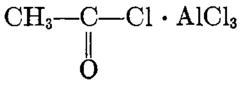
In the "cracking" reactions (16, 428, 443, 292) and in the acylation or alkylation of various nuclei this increased activity of hydrogen is noticed (304, 60, 455, 341).

There appears to be an equal, if not more pronounced, activating influence on the halogen of the alkyl or acyl halide (159, 37, 455).

This activating influence of the condensing agent is catalytic. There is no evidence to support the earlier view that an intermediate organoaluminum compound, such as $C_6H_5AlCl_2$, forms, followed by reaction with alkyl or acyl halides (373, 387). There are two pieces of information against the theory of intermediate formation of organoaluminum compounds. In the first place, no evidence has ever been established to support the view that such compounds form under the experimental conditions. In the second place, while organoaluminum compounds, such as $C_6H_5AlCl_2$, will react with alkyl halides to form alkylbenzenes in poor yields, acyl halides do not yield ketones but condense with themselves (375). This latter fact is to be contrasted with the observation that the Friedel-Crafts ketone synthesis may become quantitative (359, 254).

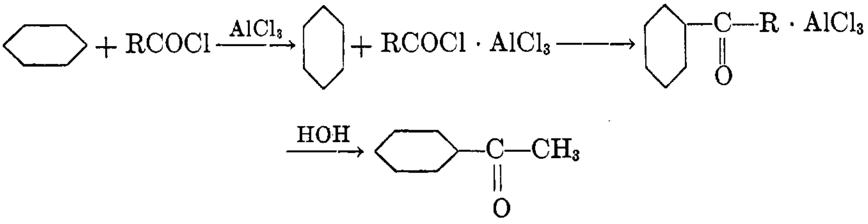
The catalytic activity of the Friedel-Crafts reaction is promoted through its strong tendency to form complexes with the most diverse types of substances. Alcohols (127), nitriles (283), nitro compounds (334), ethers (326), ketones, and even hydrogen sulfide (429) are some of the substances that form complexes with aluminum halides. In a similar manner aluminum halides form complexes with acyl halides (312, 265, 321, 322).





$$CH_3-\underset{\underset{O}{\|}}{C}-Cl \cdot AlCl_3$$

Thus the reaction for the formation of ketones may be represented by two steps.



This course of the reaction has been adequately demonstrated (38, 35, 310).

The reaction appears to be essentially non-reversible in ketone formation (306). However, there are instances in which the removal (14) and migration (61) of keto groups have been reported.

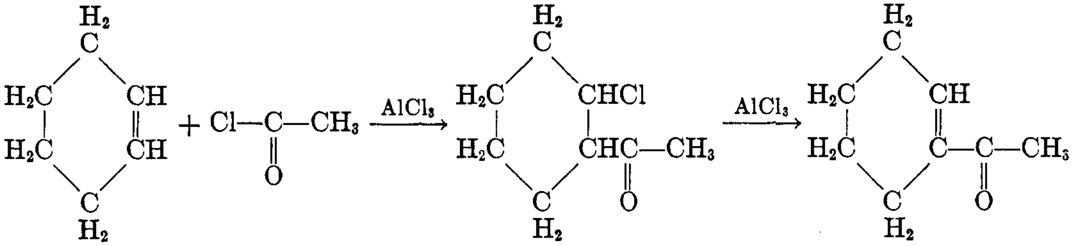
In the cases of acylations, a mole of condensing agent is required for each mole of ketone formed when the acylating agent is an acyl halide (309, 310, 158). When the acylation is carried out using anhydrides, two moles of condensing agent are required for each mole of ketone formed (352, 158).

In spite of the demand for one mole of condensing agent for each mole of ketone formed, the reaction is catalytic. However, the ketone formed in the reaction converts the aluminum chloride to a molecular complex, $C_6H_5COR \cdot AlCl_3$ for example, which is not catalytically active (309). A slight excess of the condensing agent increases the velocity of reaction enormously (311). This latter fact emphasizes the catalytic action of the condensing agent.

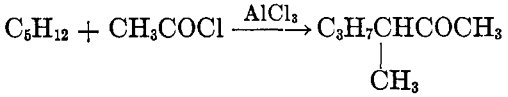
Alkylation is a reversible reaction as shown above (174, 344, 459), and its mechanism differs strikingly from that of acylation. There is no demonstrable complex formation between the aluminum halide and the alkyl halide or benzene, if benzene is being alkylated (268, 212a, 269). However, there is strong evidence that a ternary complex may be formed in which the benzene, aluminum halide, and alkyl halide take part (373, 455, 446). The aluminum halide retains its activity, so that a small quantity of metallic halide may be used to alkylate large quantities of many benzene derivatives. Here a more apparent catalytic relationship exists between the condensing agent and the other reactants (291a, 167, 20).

As to the actual mechanism of the entrance of the group, there is little information. From the fact that aluminum halides will catalyze the addition of alkyl and acyl halides to unsaturated linkages (18, 318, 215, 41), it has been suggested that there is a preliminary addition of alkyl or acyl halide to an unsaturated unit followed by elimination of hydrogen halides

(449). Actually, these addition compounds may be isolated when the substance being acylated is an olefin. The addition compounds eliminate hydrogen halide on further treatment with the condensing agent (449, 232, 421). The following mechanism has been suggested to account for this behavior, although hydrogen chloride may have added to the unsaturated ketone instead.



In what may be opposition to this view, there is the case for saturated hydrocarbons in which paraffins or cycloparaffins undergo acylation (194) to yield saturated ketones.



$$C_5H_{12} + CH_3COCl \xrightarrow{AlCl_3} C_3H_7\underset{\displaystyle CH_3}{\underset{|}{C}}HCOCH_3$$

As is readily apparent, the question of mechanism and catalysis in the Friedel-Crafts syntheses merits a searching experimental study. Elegant work has already been done on the question. Furthermore, the intensely reactive, hygroscopic, and generally insoluble complexes do not lend themselves to an easy study. And, as is true generally with catalytic reactions, there are many uncontrolled contributing factors (184, 185, 277b) that make it rather difficult to inquire into the intricate behavior of the catalysis by active metal halides.

IX. SUMMARY

1. As a result of the number of different groups that may be introduced by active metal halides, coupled with the diversity of reactants, solvents, and condensing agents, the expression "Friedel-Crafts *Syntheses*" is preferred to "Friedel-Crafts Reaction."
2. Alkylation is a reversible reaction applicable to practically all types of organic compounds.
3. Acylations are essentially non-reversible and are also applicable to a variety of types of reactants.
4. Rearrangements are prevalent in alkylation, but acylations are more reliable.

5. The orientation of entering groups is essentially that found in other substitution reactions.

6. A variety of condensing agents may be used. Aluminum chloride is apparently the most active.

7. The Friedel-Crafts reaction is catalytic. There is apparently no formation of intermediate organoaluminum substances.

To Mr. Walter Williams, Librarian of Tuskegee Institute, go most sincere thanks for his efforts to obtain obscure references. The chemical libraries at Iowa State College and the Alabama Polytechnical Institute have allowed us to have access to the references not available in the local library.

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