Friedel–Crafts reaction

The **Friedel–Crafts reactions** are a set of reactions developed by Charles Friedel and James Crafts in 1877 to attach substituents to an aromatic ring.[1] Friedel–Crafts reactions are of two main types: alkylation reactions and acylation reactions. Both proceed by electrophilic aromatic substitution.[2][3][4][5]

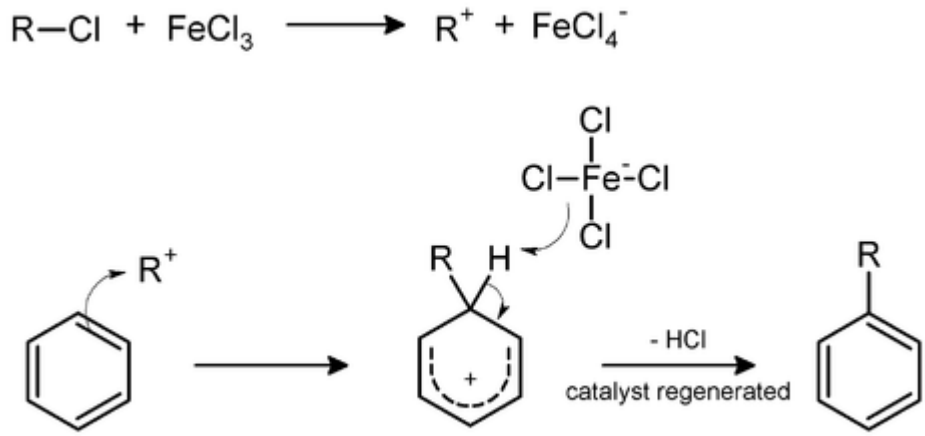
Friedel-Crafts reaction	
Named after	Charles Friedel James Crafts
Reaction type	Coupling reaction
Identifiers	
RSC ontology ID	RXNO:0000369

Contents

Friedel–Crafts alkylation

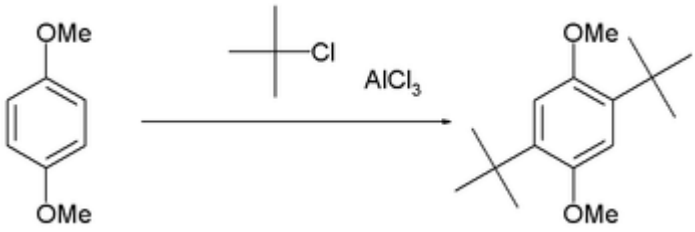
Friedel–Crafts alkylation involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid, such as aluminium chloride, ferric chloride, or other MX_n reagent, as catalyst.[6] The general mechanism for tertiary alkyl halides is shown below.[7]

Friedel-Crafts alkylation	
Named after	Charles Friedel James Crafts
Reaction type	Coupling reaction
Identifiers	
Organic Chemistry Portal	friedel-crafts-alkylation
RSC ontology ID	RXNO:0000046



For primary (and possibly secondary) alkyl halides, a carbocation-like complex with the Lewis acid, $[R^{(+)}\text{---}(X\text{---}MX_n)^{(-)}]$ is more likely to be involved, rather than a free carbocation.

This reaction suffers from the disadvantage that the product is more nucleophilic than the reactant because alkyl groups are activators for the Friedel–Crafts reaction. Consequently, overalkylation can occur. Steric hindrance can be exploited to limit the number of alkylations, as in the *t*-butylation of 1,4-dimethoxybenzene.[8]

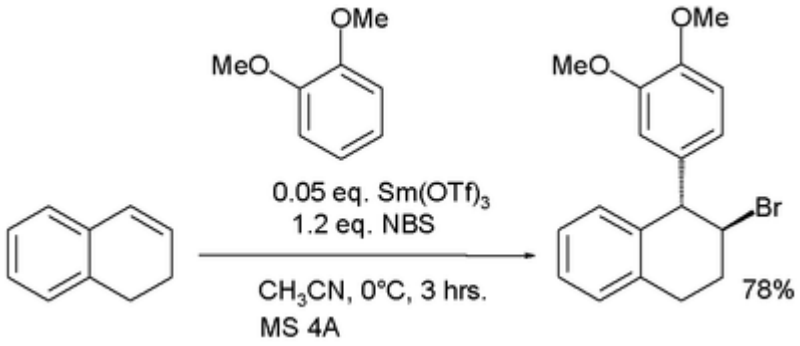


Furthermore, the reaction is only useful for primary alkyl halides in an intramolecular sense when a 5- or 6-membered ring is formed. For the intermolecular case, the reaction is limited to tertiary alkylating agents, some secondary alkylating agents (ones for which carbocation rearrangement is degenerate), or alkylating agents that yield stabilized carbocations (e.g., benzylic or allylic ones). In the case of primary alkyl halides, the carbocation-like complex ($R^{(+)}\text{---}X\text{---}Al^{(-)}Cl_3$) will undergo a carbocation rearrangement reaction to give almost exclusively the rearranged product derived from a secondary or tertiary carbocation.[7]

Alkylations are not limited to alkyl halides: Friedel–Crafts reactions are possible with any carbocationic intermediate such as those derived from alkenes and a protic acid, Lewis acid, enones, and epoxides. An example is the synthesis of neophyl chloride from benzene and methallyl chloride:[9]

$$H_2C{=}C(CH_3)CH_2Cl + C_6H_6 \rightarrow C_6H_5C(CH_3)_2CH_2Cl$$

In one study the electrophile is a bromonium ion derived from an alkene and NBS:[10]

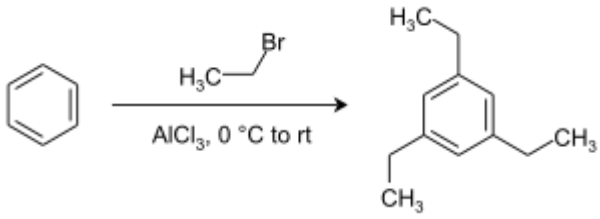


In this reaction samarium(III) triflate is believed to activate the NBS halogen donor in halonium ion formation.

Friedel–Crafts dealkylation

Friedel–Crafts alkylation has been hypothesized to be reversible. In a **retro-Friedel–Crafts reaction** or **Friedel–Crafts dealkylation**, alkyl groups are removed in the presence of protons or other Lewis acid.

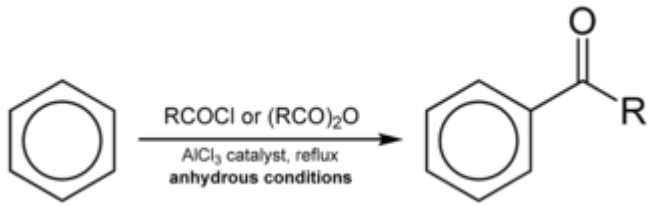
For example, in a multiple addition of ethyl bromide to benzene, *ortho* and *para* substitution is expected after the first monosubstitution step because an alkyl group is an activating group. However, the actual reaction product is 1,3,5-triethylbenzene with all alkyl groups as a *meta* substituent.[11] Thermodynamic reaction control makes sure that thermodynamically favored *meta* substitution with steric hindrance minimized takes prevalence over less favorable *ortho* and *para* substitution by chemical equilibration. The ultimate reaction product is thus the result of a series of alkylations and dealkylations.[12]



Friedel–Crafts acylation

Friedel–Crafts acylation involves the acylation of aromatic rings. Typical acylating agents are acyl chlorides. Typical Lewis acid catalysts are acids and aluminium trichloride. However, because the product ketone forms a rather stable complex with Lewis acids such as $AlCl_3$, a stoichiometric amount or more of the "catalyst" must generally be employed, unlike the case of the Friedel–Crafts alkylation, in which the catalyst is constantly regenerated. Friedel–Crafts acylation is also possible with acid anhydrides.[13] Reaction conditions are similar to the Friedel–Crafts alkylation. This reaction has several advantages over the alkylation reaction. Due to the electron-withdrawing effect of the carbonyl group, the ketone product is always less reactive than the original molecule, so multiple acylations do not occur. Also, there are no carbocation rearrangements, as the acylium ion is stabilized by a resonance structure in which the positive charge is on the oxygen.

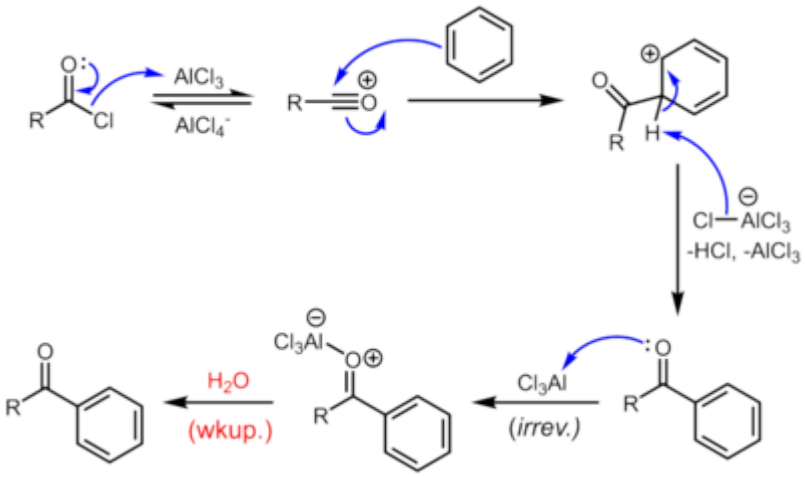
Friedel-Crafts acylation	
Named after	Charles Friedel James Crafts
Reaction type	Coupling reaction
Identifiers	
Organic Chemistry Portal	friedel-crafts-acylation
RSC ontology ID	RXNO:0000045



The viability of the Friedel–Crafts acylation depends on the stability of the acyl chloride reagent. Formyl chloride, for example, is too unstable to be isolated. Thus, synthesis of benzaldehyde through the Friedel–Crafts pathway requires that formyl chloride be synthesized *in situ*. This is accomplished by the Gattermann-Koch reaction, accomplished by treating benzene with carbon monoxide and hydrogen chloride under high pressure, catalyzed by a mixture of aluminium chloride and cuprous chloride.

Reaction mechanism

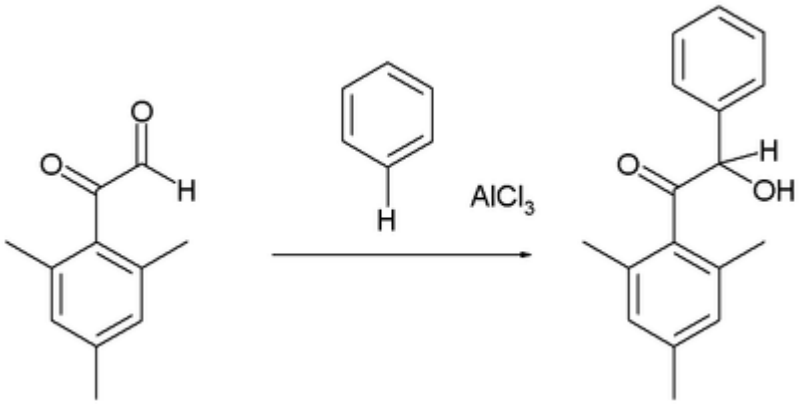
The reaction proceeds through generation of an acylium center. The reaction is completed by deprotonation of the arenium ion by $AlCl_4^-$, regenerating the $AlCl_3$ catalyst. However, in contrast to the truly catalytic alkylation reaction, the formed ketone is a moderate Lewis base, which forms a complex with the strong Lewis acid aluminum trichloride. The formation of this complex is typically irreversible under reaction conditions. Thus, a stochiometric quantity of $AlCl_3$ is needed. The complex is destroyed upon aqueous workup to give the desired ketone. For example, the classical synthesis of deoxybenzoin calls for 1.1 equivalents of $AlCl_3$ with respect to the limiting reagent, phenylacetyl chloride.[14] In certain cases, generally when the benzene ring is activated, Friedel-Crafts acylation can also be carried out with *catalytic* amounts of a milder Lewis acid (e.g. Zn(II) salts) or a Brønsted acid catalyst using the anhydride or even the carboxylic acid itself as the acylation agent.



If desired, the resulting ketone can be subsequently reduced to the corresponding alkane substituent by either Wolff–Kishner reduction or Clemmensen reduction. The net result is the same as the Friedel–Crafts alkylation except that rearrangement is not possible.[15]

Friedel–Crafts hydroxyalkylation

Arenes react with certain aldehydes and ketones to form the hydroxyalkylated products, for example in the reaction of the mesityl derivative of glyoxal with benzene:[16]

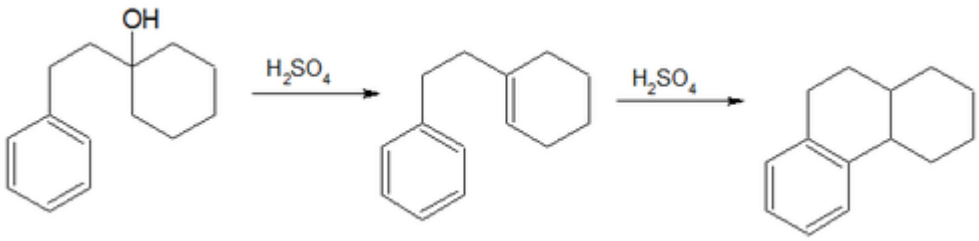


As usual, the aldehyde group is more reactive electrophile than the phenone.

Scope and variations

This reaction is related to several classic named reactions:

- The acylated reaction product can be converted into the alkylated product via a Clemmensen reduction.[17][18][19]
- The Gattermann–Koch reaction can be used to synthesize benzaldehyde from benzene.[20]
- The Gatterman reaction describes arene reactions with hydrocyanic acid.[21]
- The Houben–Hoesch reaction describes arene reactions with nitriles.[22][23]
- A reaction modification with an aromatic phenyl ester as a reactant is called the Fries rearrangement.
- In the Scholl reaction two arenes couple directly (sometimes called **Friedel–Crafts arylation**).[24][25]
- In the Zincke–Suhl reaction *p*-cresol is alkylated to a cyclohexadienone with tetrachloromethane.[26]
- In the Blanc chloromethylation a chloromethyl group is added to an arene with formaldehyde, hydrochloric acid and zinc chloride.[27][28]
- The **Bogert–Cook synthesis** (1933) involves the dehydration and isomerization of *1-β-phenylethylcyclohexanol* to the octahydro derivative of phenanthrene[29]

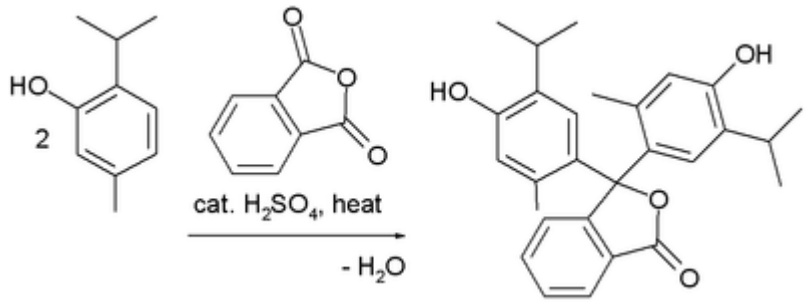


- The **Darzens–Nenitzescu synthesis of ketones** (1910, 1936) involves the acylation of cyclohexene with acetyl chloride to methylcyclohexenylketone.
- In the related **Nenitzescu reductive acylation** (1936) a saturated hydrocarbon is added making it a reductive acylation to methylcyclohexylketone
- The **Nencki reaction** (1881) is the ring acetylation of phenols with acids in the presence of zinc chloride.[30]
- In a green chemistry variation aluminium chloride is replaced by graphite in an alkylation of *p*-xylene with 2-bromobutane. This variation will not work with primary halides from which less

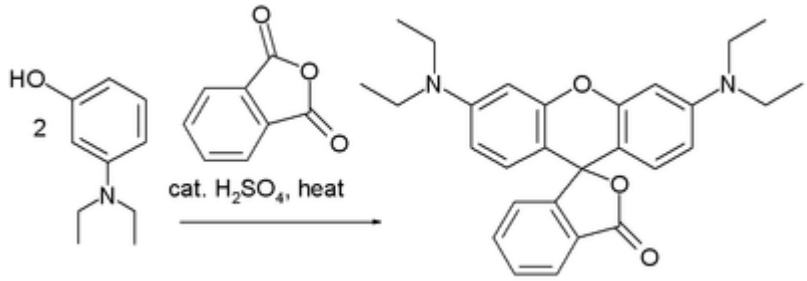
carbocation involvement is inferred.[31]

Dyes

Friedel–Crafts reactions have been used in the synthesis of several triarylmethane and xanthene dyes.[32] Examples are the synthesis of thymolphthalein (a pH indicator) from two equivalents of thymol and phthalic anhydride:

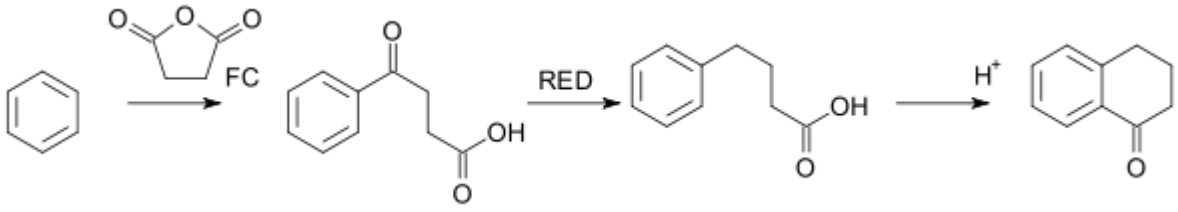


A reaction of phthalic anhydride with resorcinol in the presence of zinc chloride gives the fluorophore fluorescein. Replacing resorcinol by N,N-diethylaminophenol in this reaction gives rhodamine B:

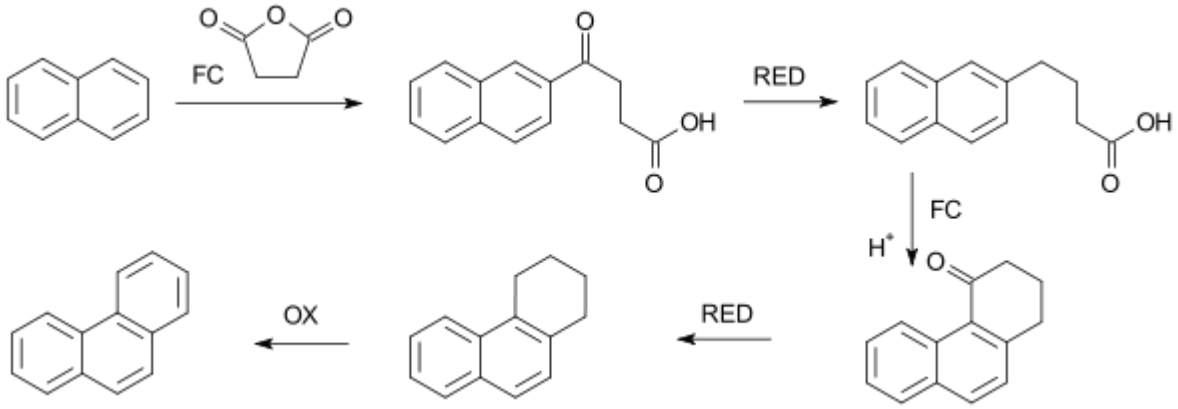


Haworth reactions

The **Haworth reaction** is a classic method for the synthesis of 1-tetralone.[33] In this reaction, benzene is reacted with succinic anhydride, the intermediate product is reduced and a second FC acylation takes place with addition of acid.[34]



In a related reaction, phenanthrene is synthesized from naphthalene and succinic anhydride in a series of steps which begin with FC acylation.



Friedel–Crafts test for aromatic hydrocarbons

Reaction of chloroform with aromatic compounds using an aluminium chloride catalyst gives triarylmethanes, which are often brightly colored, as is the case in triarylmethane dyes. This is a bench test for aromatic compounds.[35]

See also

- Ethylene oxide
- Friedel family, a rich lineage of French scientists
- Hydrodealkylation
- Transalkylation

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