Efficient and selective bromination of acetophenones

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Abstract: Acetophenone is recovered as a by-product of the oxidation of ethylbenzene to ethylbenzene hydroperoxide. Ethylbenzene hydroperoxide is an intermediate in the commercial production of propylene oxide via the propylene oxide - styrene co-product process.[1] Ethylbenzene hydroperoxide is primarily converted to 1-phenylethanol (α-methylbenzyl alcohol) in the process with a small amount of by-product acetophenone. Acetophenone is recovered or hydrogenated to 1-phenylethanol which is then dehydrated to produce styrene.

Introduction:

Halogenation by reaction type: Several pathways exist for the halogenation of organic compounds, including free radical halogenation, ketone halogenation, electrophilic halogenation, and halogen addition reaction. The structure of the substrate is one factor that determines the pathway.

Free radical halogenations: Saturated hydrocarbons typically do not add halogens but undergo free radical halogenation, involving substitution of hydrogen atoms by halogen. The regiochemistry of the halogenation of alkanes is usually determined by the relative weakness of the available C–H bonds. The preference for reaction at tertiary and secondary positions results from greater stability of the corresponding free radicals and the transition state leading to them. Free radical halogenation is used for the industrial production of chlorinated methanes:[1]
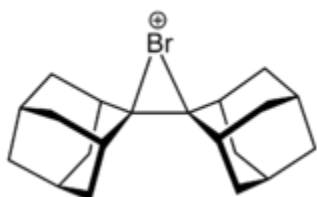
$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$
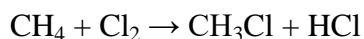
Rearrangement often accompany such free radical reactions.

Addition of halogens to alkenes and alkynes

Unsaturated compounds, especially alkenes and alkynes, add halogens:
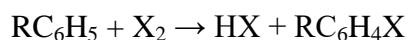
$$RCH{=}CHR' + X_2 \rightarrow RCHX{-}CHXR'$$
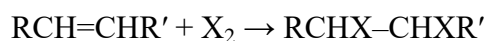
The addition of halogens to alkenes proceeds via intermediate halonium ions. In special cases, such intermediates have been isolated.

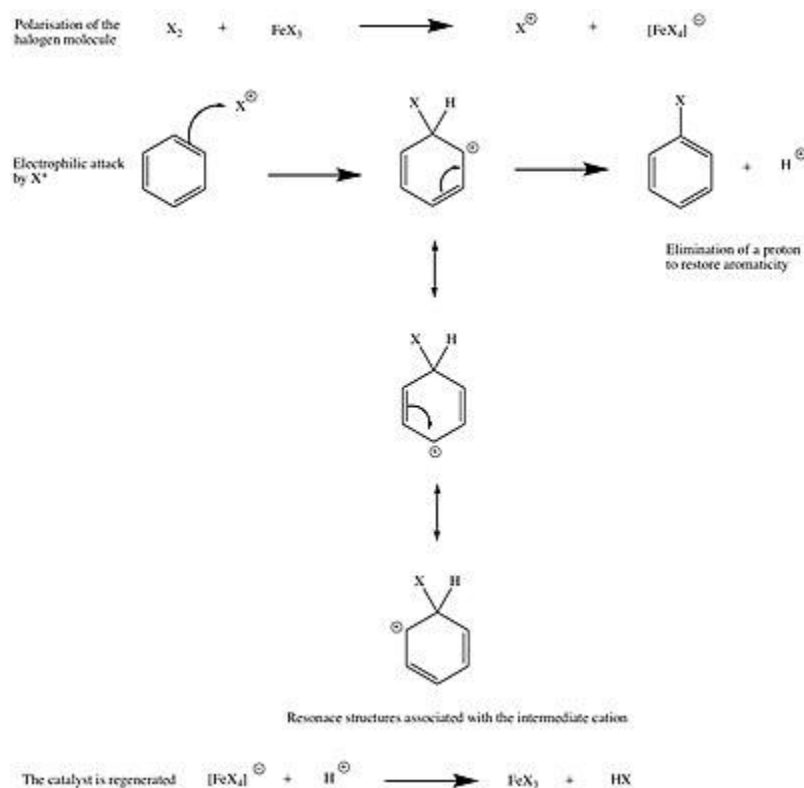Structure of a bromonium ion

Halogenation of aromatic compounds:

Aromatic compounds are subject to electrophilic halogenation:

$$RC_6H_5 + X_2 \rightarrow HX + RC_6H_4X$$

This reaction works only for chlorine and bromine and is carried in the presence of a Lewis acid such as FeX_3 (laboratory method). The role of the Lewis acid is to polarize the halogen-halogen bond, making the halogen molecule more electrophilic. Industrially, this is done by treating the aromatic compound with X_2 in the presence of iron metal. When the halogen is pumped into the reaction vessel, it reacts with iron, generating FeX_3 in catalytic amounts. The reaction mechanism can be represented as follows:

Polarisation of the halogen molecule

Electrophilic attack by X⁺

Elimination of a proton to restore aromaticity

Resonace structures associated with the intermediate cation

The catalyst is regenerated

Halogenation of benzene:

Because fluorine is very reactive, the protocol described above would not be efficient as the aromatic molecule would react destructively with F_2. Therefore, other methods, such as the Balz–Schiemann reaction, must be used to prepare fluorinated aromatic compounds.

For iodine, however, oxidising conditions must be used in order to perform iodination. Because iodination is a reversible process, the products have to be removed from the reaction medium in order to drive the reaction forward, see Le Chatelier's principle. This can be done by conducting the reaction in the presence of an oxidising agent that oxidises HI to I_2, thus removing HI from the reaction and generating more iodine that can further react. The reaction steps involved in iodination are the following:
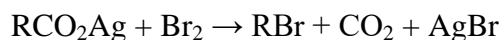
$$5\ HI\ +\ HIO_3 \longrightarrow 3\ I_2\ +\ 3\ H_2O$$
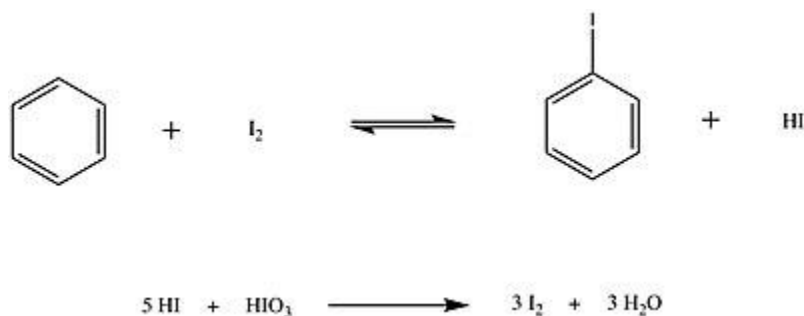
Iodination of benzene

Another method to obtain aromatic iodides is the Sandmeyer reaction.

Other halogenation methods

In the Hunsdiecker reaction, from carboxylic acids are converted to the chain-shortened halide. The carboxylic acid is first converted to its silver salt, which is then oxidized with halogen:

$$RCO_2Ag + Br_2 \rightarrow RBr + CO_2 + AgBr$$

The Sandmeyer reaction is used to give aryl halides from diazonium salts, which are obtained from anilines. In the Hell–Volhard–Zelinsky halogenation, carboxylic acids are alpha-halogenated. In oxychlorination, the combination of hydrogen chloride and oxygen serves as the equivalent of chlorine, as illustrated by this route to dichloroethane:

$$2\ HCl + CH_2{=}CH_2 + {}^{1}\!\!/_{2}\ O_2 \rightarrow ClCH_2CH_2Cl + H_2O$$
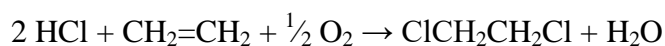
Halogenation by halogen type

The facility of halogenation is influenced by the halogen. Fluorine and chlorine are more electrophilic and are more aggressive halogenating agents. Bromine is a weaker halogenating agent than both fluorine and chlorine, while iodine is the least reactive of them all. The facility of dehydrohalogenation follows the reverse trend: iodine is most easily removed from organic compounds, and organofluorine compounds are highly stable.

Fluorination

Organic compounds, saturated and unsaturated alike, react readily, usually explosively, with fluorine. Fluorination with elemental fluorine (F_2) requires highly specialised conditions and apparatus. Many commercially important organic compounds are fluorinated electrochemically using hydrogen fluoride as the source of fluorine. The method is called electrochemical fluorination. Aside from F_2 and its electrochemically generated equivalent, a variety of fluorinating reagents are known such as xenon difluoride and cobalt(III) fluoride.

References

(i) Illustrative procedure for chlorination of an aromatic compound: *Edward R. Atkinson, Donald M. Murphy, and James E. Lufkin (1951). "dl-4,4',6,6'-Tetrachlorodiphenic Acid". Organic Syntheses.*; *Collective Volume, 4, p. 872*

(ii) Organic chemistry by Jonathan Clayden, Nick Grieves, Stuart Warren, Oxford University Press.

(iii) *Synthesis of essential drugs*, Ruben Vardanyan, Victor Hruby; Elsevier 2005 ISBN 0-444-52166-6.

(iv) Gordon W. Gribble "The diversity of naturally occurring organobromine compounds" *Chemical Society Reviews*, 1999, volume 28, pages 335–346.