Chapter 1

General Introduction
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1.1. Introduction

Bromine and organic bromine compounds have traditionally played an important role in various fields. The bromo organics are very important group of organic halogen compounds. Even the marine and terrestrial plants, bacteria, fungi, insects, marine animals, and some higher animals produce naturally occurring bromine containing organic compounds. However, far more important are synthetic organic bromine compounds. Elemental bromine is used to manufacture a wide variety of bromine compounds used in industry and agriculture.¹

Bromine - a heavy, volatile, corrosive, reddish-brown, nonmetallic liquid element, having a highly irritating vapor, is one of the most important and essential member in the periodic table. It was discovered independently by two chemists Antoine Balard² and Carl Jacob Löwig³ in 1825 and 1826.⁴ Bromine, from Greek brómos, meaning ‘stench’ (of he-goats)⁵ is classified as an element in the 'Halogens' section which can be located in group 7 of the Periodic Table. It is the only non metallic element that is a liquid at room temperature. The pure chemical element has the physical form of a diatomic molecule Br₂. It evaporates easily at standard temperature and pressure to give a red vapor that has a strong disagreeable odor resembling that of chlorine. Bromine is highly reactive and is a powerful oxidizing agent in the presence of water. It reacts vigorously with amines, alkenes and phenols as well as aliphatic and aromatic hydrocarbons, ketones and acids (these are brominated by either addition or substitution reactions). With many of the metals and elements, anhydrous bromine is less reactive than hydrated bromine; however, dry bromine reacts vigorously with aluminium, titanium, mercury, as well as alkaline earth metals and alkaline metals.⁶

The industrially produced organic bromine compounds can be divided into two main groups.¹

1) Organic bromine compounds in which the bromine atom is retained in the final molecular structure, and where its presence contributes to the properties of the desired products. It
includes mainly flame retardants, biocides, gasoline additives, halons, bromobutyl rubber, pharmaceuticals, agrochemicals, and dyes.

(2) Organic bromine compounds have traditionally played an important role as intermediates in the production of agrochemicals, pharmaceuticals and dyes. New process developments also result in new applications in ultraviolet (UV) sunscreens, high performance polymers, and others.

1.2. Applications of bromine and bromo compounds

1.2.1. As Flame retardant

One of the most important uses of bromine is to make brominated flame retardants as they help in the inhibition of combustible materials. These are used as chemical flame retardants in the plastic industry and in products, such as cables, connectors, plastic covers. It is also used in the clothing and furniture industries to prevent the products from catching fire. In the electronics industries, especially in computers, it is used to make printed circuit boards safe from fire.\(^7\) If the material burns the flame retardants produce hydrobromic acid which interferes in the radical chain reaction of the oxidation reaction of the fire.\(^8\)\(^9\) Brominated flame retardants are produced via direct bromination of organic molecules or via addition of bromine to alkenes. Tetrabromobisphenol A, polybrominated biphenyls, penta-, octa-, deca-brominated diphenyl ether (oxide) formulation and hexabromocyclododecane are few of the examples of flame retardants that are made using bromine.\(^7\)

1.2.2. Gasoline additive

Ethylene bromide was an additive in gasolines containing lead anti-engine knocking agents to raise the octane number. It allows engines to run more smoothly. It scavenges lead by forming volatile lead bromide, which is exhausted from the engine.\(^7\)
1.2.3. Pesticide

Bromine is also used to make chemicals that work as pesticides and destroy pests. Methyl bromide was widely used as pesticide to fumigate soil. Some important biocides are - bromopropylate (acaricide), bromacil, bromobutide (herbicides), bromofos (insecticides), benzyl bromoacetate, bis-1,2-(bromoacetoxy)ethane (microbicides (water treatment biocides)), 1,2-dibromo-3-chloropropane, 1,2,3-tribromopropane (nematocides) etc.\(^1\)

1.2.4. Medical and veterinary

Bromine has been used as a drug, for a long time. Primarily, chemical compounds derived from bromine are used as oral sedatives, to treat epilepsy and as diuretics. Bromine is also well known for its central nervous system depression role in bromide poisoning. Bromide compounds, especially potassium bromide, were frequently used as sedatives in the 19\(^{th}\) and early 20\(^{th}\) century. Bromides in the form of simple salts are still used as anticonvulsants in both veterinary and human medicine\(^1,10\). Some bromine containing pharmaceuticals are- bromindione (anticoagulant), bromadoline (analgesic), bromodiphenhydramine (antihistaminic), zimeldine (antidepressant), halothane, roflurane (anesthetic (inhalation)), broperamole (antiinflammatory).\(^1\)

1.2.5. Disinfectant

Bromine substances are disinfectants and can be used as an alternative for chlorine. In swimming pools, bromine is used against the formation and growth of algae, bacteria and odors in swimming water. Bromine can be used for the disinfection of cooling tower water.\(^1\) The most common bromine compounds used in cooling water are 1-bromo-3-chloro-5,5-dimethylhydantoin and mixtures of sodium bromide with sodium hypochlorous acid.\(^11\) It is also used as a sanitizer, in areas, where there is less or no chances of it coming in contact with food. Such compounds are used as a sanitizer and a germicide in hospitals, commercial industries and households to control bacteria, algae and fungi. Bromine is, also, preferred for disinfection of industrial water.\(^1\) The use of bromine compounds is growing in sanitizing applications in the pulp and paper industry and food-washing applications. The sanitary preparation field is an area where bromine was found to be safer than its substitutes because bromine has a higher biocidal activity level for the same volume of product.\(^11\)
1.2.6. Biological role

Bromine has no known essential role in human or mammalian health, but inorganic bromine and organobromine compounds do occur naturally, and some may be of use to higher organisms in dealing with parasites. For example, in the presence of H₂O₂ formed by the eosinophil, and either chloride or bromide ions, eosinophil peroxidase provides a potent mechanism by which it kill multicellular parasites (such as, for example, the nematode worms involved in filariasis). Eosinophil peroxidase is a haloperoxidase that preferentially uses bromide over chloride for this purpose, generating hypobromite (hypobromous acid).¹² Marine organisms are the main source of organobromine compounds. Methyl bromide produced by marine algae is the most abundant one.¹³ The essential oil of the Hawaiian algae Asparagopsis taxiformis consists of 80% methyl bromide.¹⁴ Tyrian purple, a bromine containing organic compound, has been used by humans for a long time.¹⁵ Most organobromine compounds in nature arise via the action of vanadium bromoperoxidase.¹⁶ Of the nearly 3200 known naturally occurring organohalogen compounds, more than 1600 contain bromine. Numerous simple bromoalkanes like CH₃Br, CH₂Br₂, CHBr₃, CBr₄, CH₂ClBr etc. have been isolated from marine algae. A large number of bromine-containing C₁₅ acetogenins are also found in marine plants and in sea hares of genus Aplysia that feed on these seaweeds.¹⁷ The wood-rotting fungus Lepista nuda (common wood blewitt) produces the bromocompounds 3-5 (Fig 1.1).¹⁸

![Fig 1.1](image_url)

1.2.7. Photography Film

Another important use of bromine compound is in making photographic films. Silver bromide is light sensitive and is used in photography. Potassium bromide is used in
photography, to prevent undesired reduction of silver, which causes fogging in a photograph.\textsuperscript{19}

\subsection*{1.2.8. Dyestuffs}

German chemist Paul Friedländer found that the Tyrian purple dye contains bromine in 1909. Tyrian purple dye is nothing but a chemical 6,6'-dibromoindigo. There are many applications of bromine in the textile industry. One such dye used is tetrabutylammonium bromide.\textsuperscript{1}

\subsection*{1.2.9. Drilling fluids}

The bromides of calcium, sodium, and zinc form dense solutions in water that are used as drilling fluids (clear brine fluids).\textsuperscript{20} About 95\% of calcium bromide produced was used as an oil and gas completion fluid. Use of calcium, sodium, and zinc bromides in oil well completion fluids has benefitted in recent years from the rebound in world oil prices.\textsuperscript{11}

\subsection*{1.2.10. Brominated vegetable oil}

Bromine is used to make brominated vegetable oil, which is used as an emulsifier in many citrus-flavored soft drinks.\textsuperscript{21} The compound was extensively used until alternative emulsifiers were developed.\textsuperscript{22}

\subsection*{1.2.11. Reduce mercury pollution}

Bromine is also used to reduce mercury pollution from coal-fired power plants. This can be achieved either by treating activated carbon with bromine or by injecting bromine compounds onto the coal prior to combustion.\textsuperscript{10}
1.2.12. As intermediates in organic synthesis

It is also used to form intermediates in organic synthesis where it is preferred to iodine due to its much lower cost. As a rule, the reactivity of bromine compounds in the nucleophilic substitution is greater than the corresponding chlorine derivatives, owing to the difference in the bond energies (C-Br 276 kJ/mol vs. C-Cl 328 kJ/mol). This reactivity is the main advantage of using bromine compounds as intermediates. The reaction of aliphatic bromides with aqueous solutions of bases or with carbonyl compounds gives varieties of alcohols, the reaction with alcoholates gives ethers, the reaction with salts of carbonic acids gives esters, and the reaction with sodium cyanide gives nitriles. Interaction with ammonia, both in solution and in the gaseous phase, gives primary, secondary, or tertiary amines and quaternary ammonium salts, depending on the reaction conditions. Aldehydes and ketones are formed by the hydrolysis of dibromides, RCHBr₂ or RCBr₂R, respectively, and the hydrolysis of tribromides, RCBr₃, gives carbonic acids.

1.3. Methods of bromination

1.3.1. Direct use of elemental bromine

The elemental bromine can be directly used for bromination of various substrates. In literature, legion of examples are found. Bromine is most widely used for determination of organic unsaturation. This involves the reaction of bromine with the unsaturated compound (Scheme 1.1). Again α hydrogens of carboxylic acids can be replaced by bromine in presence of phosphorus halide as catalyst. The reaction is known as Hell-Volhard-Zelinskii reaction. Aromatic compounds react with bromine vapor to yield products in which the p-positions of unsubstituted phenyl groups are brominated and in which olefinic double bonds, not highly substituted, had added bromine. Various types of alkyl bromides can be prepared by the reaction of equal molar amounts of bromine with the silver salts of carboxylic acids. The

\[
\begin{align*}
\text{Br}_2 & \quad \rightarrow \quad \text{Br} \quad \text{Br} \\
\text{Scheme 1.1}
\end{align*}
\]
bromination of pyrazole by aqueous Br$_2$ is a facile reaction. Treatment of [Co(NH$_3$)$_5$pyzH]$^{3+}$ with 1 mol equiv. of aqueous bromine for 3.5 hour gave the monobrominated complex [Co(NH$_3$)$_5$4-Br pyzH]$^{3+}$.

Cohen investigated the natural autocatalytic reaction between acetone and bromine (Scheme 1.2).

![Scheme 1.2](image)

Again, aromatic compounds can be brominated by treatment with bromine in presence of a catalyst, most often iron. For active substances, including amines, phenols, naphthalene and polyalkylbenzenes no catalyst is needed. The ortho bromination of phenol can be achieved using elemental bromine at low temperature. Schimid reported a method for Lewis acid promoted bromination of aromatic compounds. A combination of Br$_2$, SbF$_3$ and HF was used by Jacquesy et al. as a brominating mixture for bromination of activated aromatics. Recently, bromination of aromatic compounds has been reported using hexamethylenetetraamine-Br$_2$ in dichloromethane. The reactivity of this reagent was increased by supporting it to silica gel for bromination of less activated compounds (Scheme 1.3).

![Scheme 1.3](image)

A new selective brominating system Br$_2$/SO$_3$Cl$_2$/zeolite, was brought out by Gnaim et al. for regioselective bromination of aromatic compounds. Bromination of 5,6-disubstituted indane-1-one can be carried out using Br$_2$ under acidic and basic conditions. Substituted bromobenzenes have been synthesized in acceptable yields using a novel Sandmeyer type reaction with molecular bromine (Scheme 1.4).

![Scheme 1.4](image)
Again when aniline was successively treated with \( n \)-BuLi, B(OMe)\(_3\) and Br\(_2\) at -78°C, 4-bromoaniline was formed.\(^{44}\) Selective bromination of alkylbenzenes with bromine in carbon tetrachloride in the presence of K10- montmorillonite is reported by Pitchumani et al. (Scheme 1.5).\(^{45}\)

![Scheme 1.5](image)

The bromination reaction of tricyclo [7.2.1.0\(^2.7\)] dodeca-2,4,6,10-tetraene derivatives was done by using elemental bromine.\(^{46}\) Naae studied the electrophilic bromination of fluoro olefins. The ionic addition of bromine in glacial acetic acid to 4-RC\(_6\)H\(_4\)CF=CFX (R = CO\(_2\)H, Br, H, CH\(_3\), OCH\(_3\); X = Cl, CF\(_3\)) and 4-RC\(_6\)H\(_4\)CH=CFCl (R = Br, CH\(_3\)) has been studied. For all olefins, the 1,2-dibromo adduct is the predominant product (Scheme 1.6).\(^{47}\)

![Scheme 1.6](image)

Bromination of petroleum hydrocarbons and their utilization are becoming increasingly important and have received considerable impetus in recent times. Ijam et al. reported such a study for a kerosene fraction boiling between 180 and 220°C obtained from a Kuwait oil field and having a low aromatic content (high furfural miscibility temperature). This kerosene was brominated from 6.5 to 36% bromine content in steps of approximately 0.2 mol of bromine.\(^{48}\)

Choudary et al. reported a novel integrated approach of bromination coupled with oxybromination of aromatic compounds using LDH-WO\(_4\) as a catalyst, aqueous H\(_2\)O\(_2\) as an oxidant in a biphase comprising dichloroethane and water for the first time (Scheme 1.7).\(^{49}\)

![Scheme 1.7](image)

Zeolites were also used as catalyst in such bromination reactions. Bromination of aromatic substrates, namely, toluene, phenol, phenyl acetate and chlorobenzene had resulted predominantly in the formation of para bromo derivatives.\(^{50}\) Al- Hassan did the bromination
of alkynes and alkynylsilanes with liquid bromine to give 1,2 dibromoalkenes and 1,2 dibromovinylsilanes (Scheme 1.8).\textsuperscript{51}

\[
\text{RC≡CSiMe}_3 \xrightarrow{\text{1.2 equiv. Br}_2/\text{CCl}_4 \text{-12°C/0.5h}} \text{Br}_2
\]

\textbf{Scheme 1.8}

Firouzabadi et al. reported that heteropoly acid cesium salt/cetyltrimethylammonium bromide (a catalytic heterogeneous system) could highly control regioselective bromination of aromatic compounds with bromine.\textsuperscript{52} Smith et al. reported regioselective one pot bromination of aromatic amines treating with n-butyllithium and trimethyltin chloride to give p-bromoaniline.\textsuperscript{53} Tanko et al. introduced a new bromination method with liquid bromine in supercritical CO\textsubscript{2}. Direct bromination of toluene and ethylbenzene gave the corresponding benzyl bromides in high yield.\textsuperscript{54} Amino-substituted arylmethylketones were selectively brominated in sulfuric acid to afford the corresponding dibromomethylarylketones (Scheme 1.9).\textsuperscript{55}

\[
\text{R-O} \xrightarrow{\text{Br}_2} \text{R-CHBr}_2
\]

\textbf{Scheme 1.9}

Park et al. used tetrabutylammonium peroxydisulfate in the bromination of the aromatic compounds substituted with electron donating groups such as methoxy, hydroxy, or amino groups with Br\textsubscript{2}.\textsuperscript{56}

There are numbers of such examples where molecular bromine is used for bromination. However, there is risk in handling bromine because elemental bromine is a hazardous material and strong irritant. It produces painful blisters on exposed skin and especially mucous membrane. Even low concentration of bromine vapour can affect breathing and significant amounts of bromine can damage respiratory system. Bromine on the skin causes painful burns that heal very slowly. The most important health effects that can be caused by bromine-containing organic contaminants are malfunctioning of the nervous system and disturbances in genetic materials.\textsuperscript{57}

So, the use and handling of bromine needs special precautions. Sometimes, this reagent is not selective. In some cases an extra catalyst has to be added to promote
bromination using bromine. Therefore different brominating reagents are developed to make bromination procedure more effective and selective.

1.3.2. Use of bromo compounds for bromination

Numerous examples of brominating agents are found in literature developed by the chemists in the passing years. We are discussing here some of the important brominating agents.

(1) *N*-Bromo Succinimide (NBS)

NBS is most popular brominating agent. So many reactions have already been done using this reagent. Different aromatic substitution resulting in excellent yields of product takes place under easily attainable experimental conditions with different reagent systems and with various kinds of catalysts (Scheme 1.10).

![Scheme 1.10](image)

Kharasch et al. observed the bromination of 1-octene with NBS. Monobromination of pyrrole and 1-methyl-, 1-benzyl-, and 1-phenylpyrrole with 1 mol of *N*-bromosuccinimide in tetrahydrofuran results in the regiospecific formation of the 2-bromopyrroles was observed by Gilow et al. Shusherina et al. brominate 1-alkyl-2-pyridones to the corresponding monobromides with the help of NBS. Bromination of 4-(2-thienyl)thiazoles and 2-(2-thienyl)quinoline was done by Smirnov et al. using NBS in glacial acetic acid or acetic anhydride. Bromination of 8R-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepinones-2 containing substituents of different types in the benzene ring of the heterocycle was studied by Sobol et al. Zhu et al. treated apogossypol hexamethyl ether with NBS in DMF at room temperature. Shaw et al. selectively brominated α-chloro and α-bromo carboxylic acid derivatives. Liquid phase bromination of chlorobenzene, toluene and xylenes using zeolite as catalyst and *N*-bromosuccinimide as the brominating agent was also done. Kruglenko studied the bromination of substituted 5 H- imidazo[1,2-b]-1,2,4-triazepin-4-ones and thiones with the help of NBS. Heropoulos and coworkers did bromination with NBS assisted by ultrasound and microwave. Various alkylaryls with *N*-bromosuccinimide, either neat or in water, showed diverse chemoselectivity.
Benzyl bromination takes place with NBS when radical initiator is present. Numerous examples are found in literature. Horman and coworkers did benzylic bromination in the reactions of benzyl methyl ether and related compounds with N-bromosuccinimide. The bromination of carbonyl compounds was done using N-bromosuccinimide in the presence of different kind catalyst and reagent system. The reaction of olefins with N-bromosuccinimide to form bromohydrins was also done by different workers.

(2) Pyridine hydrobromide perbromide, C₅H₅N.HBr.Br₂

Pyridine hydrobromide perbromide can be considered as a general brominating agent, which may be used in brominations ordinarily performed with molecular bromine, such as substitution on aromatic rings and additions to double bonds. It is a useful reagent for brominations of ketones. Monobromination and dibromination of steroid ketones were done successfully. Vona and Merker brominated various organic substrates like β naphthol, styrenes, phenols and anilines using this reagent. Lorette et al. used this reagent in the flavone chemistry to convert acetylated hesperidin and naringin into diosmin and apigenin-7-rhamnoglucoside, respectively. The bromination of tetraphenylcyclobutadiene-nickel bromide complex was achieved by the action of pyridinium hydrobromide perbromide. The product was 3,4-dibromotetraphenylcyclobutene and 2,5-di-p-bromotetraphenylfuran. 5-vinyldole was brominated regioselectively with this reagent (Scheme 1.11).

![Scheme 1.11](image)

Samath et al. tried this reagent as brominating agent for the bromination of many metal acetylacetones. Reeves and his coworkers selectively mono- and dibrominated anisole, p-methylanisole and p-dimethoxybenzene. Tanaka et al. introduced a new method of stereoselective bromination with this reagent for stilbene and chalcone in water suspension medium (Scheme 1.12).

![Scheme 1.12](image)
Regiospecific bromination-rearrangement of the 5-substituted 2-alkylidene-4-oxothiazolidine derivatives induced by pyridinium hydrobromide perbromide (PHBP) provides a new synthetic approach to the corresponding push-pull thiazolidines with two exocyclic double bonds (Scheme 1.13).

Pyridinium hydrobromide perbromide (PyHBr₃) was used by Raman et al. for the bromination of the Schiff base chelates of copper(II), nickel(II), cobalt(II) and zinc(II) derived from acetylacetonate and p-anisidine under acidic and ammoniacal conditions at room temperature. A convenient and practical method for the one-pot synthesis of ω-bromoesters from aromatic aldehydes and diols in the presence of PHPB as brominating reagent and triethoxymethane as dehydrating agent was developed by Aoyama et al. (Scheme 1.14).

(3) Cyanogen bromide

In very earlier days, von Braun studied the action of cyanogen bromide on benzyl cyanide in presence of sodium ethoxide. The brominated benzyl cyanide, C₆H₅CHBr.CN was isolated. Steinkopf and his coworkers did some experiments regarding BrCN as brominating agent. Bunce et al. found that the photolysis reaction took place between cyanogen bromide and cyclohexane to give cyclohexyl bromide with small amount of gaseous product. Again, in the synthesis of α-Bromo-β- aminoenones, this reagent was used as a brominating agent (Scheme 1.15).
Ramalingam et al. used the reagent for the selective bromination of coordinated β-diketones. Actually cyanogen bromide was used as a new twin purpose reagent for bromination as well as cyanation of β-diketonates.\textsuperscript{106}

(4) Selenium oxybromide

The oxybromide of selenium, SeOBr\textsubscript{2}, was originally prepared by Schneider and later it was described as a powerful solvent, as an oxidizing and brominating agent.\textsuperscript{107} In 1995, Lee et al. brominated aldehydes and ketones by selenium oxybromide which was generated \textit{in situ} from selenium dioxide and bromotrimethylsilanes (Scheme 1.16).\textsuperscript{108}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{SeO}_2-\text{TMSBr}}; \node (b) at (2,0) {\text{CCl}_4}; \node (c) at (4,0) {\text{Br}}; \node (d) at (6,0) {\text{H}}; \node (e) at (0,-1) {\text{H}}; \node (f) at (1,-1) {\text{O}}; \node (g) at (2,-1) {\text{Br}}; \node (h) at (3,-1) {\text{C}}; \node (i) at (4,-1) {\text{C}}; \node (j) at (5,-1) {\text{O}}; \node (k) at (6,-1) {\text{H}}; \draw (a) -- (b); \draw (b) -- (c); \draw (c) -- (d); \draw (d) -- (e); \draw (e) -- (f); \draw (f) -- (g); \draw (g) -- (h); \draw (h) -- (i); \draw (i) -- (j); \draw (j) -- (k); \end{tikzpicture}
\end{center}

\textit{Scheme 1.16}

(5) Bromide – bromate couple

(a) Aqueous solution of potassium bromide and bromate, KBr + KBrO\textsubscript{3}

In 1903, Bogert and Hand used aqueous solution of potassium bromide and bromate to brominate anthranilic nitrile.\textsuperscript{109}

(b) Mixture of Sodium bromide and bromate

Adimurthy et al. use an alternative method for the regio and stereoselective bromination of alkenes, alkynes, toluene derivatives and ketones using sodium bromide/ bromate couple.\textsuperscript{110} Again the same bromide/ bromate couple was used by Patil et al. for the synthesis of α-bromoketones, where bromide/ bromate couple act as a non hazardous brominating agent.\textsuperscript{111}

(6) (a) 3-Bromo-5,5-dimethylhydantoin

It can brominate cyclohexene to 3-bromocyclohexene and cyclohexanone to its 2-Br derivative. Like NBS, it can brominate in benzylic position. For example, the reagent gives benzyl bromide with toluene.\textsuperscript{112}
(b) 1,3-Dibromo-5,5-dimethylhydantoin

Orazi et al reported that higher yields with shorter reaction time were obtained with this reagent than 3-bromo-5,5-dimethylhydantoin in aromatic bromination.\textsuperscript{113} This reagent is capable of doing at least three types of bromination reaction.

(1) Allylic Bromination
(2) Hydrobromination
(3) Substitution of active H.\textsuperscript{114}

Again, this reagent was used as a regioselective brominating agent for the preparation of 3-phenoxybenzyl alcohol.\textsuperscript{115}

(7) HOBr

When HOBr was added to a H\textsubscript{2}SO\textsubscript{4} solution of C\textsubscript{6}H\textsubscript{6} in water, immediately PhBr was separated. Similarly benzoic acid was converted to \textit{m}-bromobenzoic acid in fairly strong HNO\textsubscript{3} or H\textsubscript{2}SO\textsubscript{4}. This reactivity accords with the view that Br\textsuperscript{+} or (H\textsubscript{2}O)Br\textsuperscript{+} is present as a result of equilibrium.\textsuperscript{116}

(8) Tribromo-\textit{m}-cresol bromide

Goldhahn reported that tribromo-\textit{m}-cresol bromide could be used as a brominating agent. He showed that tribromo-\textit{m}-cresol bromide on boiling with \textit{m} cresol gave 2,4,6-tribromo-\textit{m}-cresol. On the other hand, MePh, xylene or EtPh were brominated in the side chain.\textsuperscript{117}

(9) Iodine monobromide

In 1938, Militzer reported that IBr is mild brominating agent for substitution on the aromatic ring.\textsuperscript{118} Bennett and Sharpe repeated Militzer's experiments with iodine monobromide with nitrobenzene as solvent and phenol and salicylic acid as substances to be brominated.\textsuperscript{119} IBr is an effective reagent in the asymmetric monobromination of steroid aldehydes. Yanuka and coworker reported that iodine bromide affected the monobromination cholanal, norcholanal and 3\textalpha-acetoxycholanal in high yields.\textsuperscript{120}

(10) Carbon tetrabromide:

Hunter and Edgar, in 1932 investigated the possibility of the use of carbon tetrabromide as a brominating agent. Bromination took place with majority of the compounds they studied with a side product bromoform. The reagent brominates selectively the side chain of the benzene hydrocarbons instead of attacking the ring.\textsuperscript{121} In 1985, Camino and Guaita carried out bromination with carbon tetrabromide to low molecular weight
polybutadienes and studied the fire retardant action of the brominated product. Lukevics et al. developed a new, simple and selective phase transfer catalysed bromination method for a variety of terminal acetylenes. They used carbon tetrabromide as the brominating agent (Scheme 1.17).

\[
\begin{align*}
\text{PhC}≡\text{CH} & \xrightarrow{\text{CBr}_4/\text{base/catalyst (5 mol%)} \text{Benzene/20° C}} \text{PhC}≡\text{CBr}
\end{align*}
\]

**Scheme 1.17**

The catalytic bromination of alkanes, cycloalkanes and arylalkanes with near 100% yields was performed using CBr\(_4\) as a brominating agent in the presence of copper- and nickel-containing catalysts. Smirnov et al. described catalytic bromination of alkanes (decane and dodecane), cycloalkanes (cyclohexane and adamantane), haloalkanes (butyl chloride) and arylalkanes (toluene, p- and m-xylene, and mesitylene) by the action of CBr\(_4\) in the presence of metal-complex catalyst.

(11) 2,2-Dibromo-2-cyano-N,N-dimethylacetamide

Vyas et al. described a new brominating agent named 2,2-dibromo-2-cyano- N,N-dimethylacetamide. It is an effective and preferential brominating agent for monobromination at \(\alpha\) carbon atoms of ketones.

(12) 2-Bromo-2-cyano-N,N-dimethylacetamide

It was found that 2-bromo-2-cyano-N,N-dimethylacetamide (BCDA) was an effective for monobromination at \(\alpha\) carbon of ketones with high selectivity (Scheme 1.18).

![Scheme 1.18](image)

(13) Potassium bromate

Kraft first reported potassium bromate in sulfuric acid to brominate benzene to bromobenzene. Again it was reported that potassium bromate brominated benzene in acetic acid in the presence of a catalytic amount of sulfuric acid. Harrison et al. reported that potassium bromate in sulfuric acid was a convenient and powerful brominating agent capable of brominating aromatic rings containing deactivating groups.
(14) 5,5-Dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane

It is a brominating agent for bromination of saturated and α, β unsaturated carbonyl compounds. The brominations were carried out at room temperature without using any catalyst.

(15) Phosphorus tribromide – DMF

Yazima and Munakata used the brominating agent PBr₃- DMF for the synthesis of 2- and 4- bromoquinolines from the corresponding methoxyquinolines.

(16) 3- Bromo-4,4-dimethyl-2-oxazolidinone

Bodor et al. prepared a new brominating agent, 3-bromo-4,4-dimethyl-2-oxazolidinone (NBDMO). They investigated the reagent and compared to that of NBS and found that it had a better or equivalent brominating and oxidising property than NBS.

(17) Bromine chloride

Schulek and Burger reported bromine chloride exclusively as a brominating agent. It can brominate most of the aromatic compounds like benzene, phenols, anisole, toluene, cresols, salicylic acids etc. Boudakian et al. did the vapour phase bromination of pyridine with bromine chloride to give 2-bromopyridine (75%) as the major product.

(18) 2,4,4,6-Tetrabromocyclohexa-2,5-dienone

Schmidt et al. studied the reaction of 2,4,4,6-tetrabromocyclohexa-2,5-dienone with cyclohexene and methanol and reported the formation of 1-bromo-2-methoxycyclohexane. Tsubota and coworkers reported various reactions with alkenes in presence of different bases. The reagent was also investigated for aromatic bromination and selective α bromination of α, β unsaturated ketones. In 1974 Calo et al. studied the solvent effect on the ortho: para ratio in the bromination of phenol with 2,4,4,6-tetrabromocyclohexa-2,5-dienone. Hallas et al. used this reagent for p- bromination of aromatic and heteroaromatic amines with a very good yield. Then this reagent was used as a useful reagent for brominative cyclization of polyene and the cation radical bromination of a broad range of organic compounds and for the electrophilic bromination of phenols and dialkylanilines. Again, this tetrabromide was also successfully used in the nucleophilic substitution of bromine for hydroxyl, i.e., served as a source of nucleophilic halogen in presence of
triphenylphosphine. \(^{145}\) Again, the reaction of flavones with this reagent gave the corresponding 3-bromoflavones under the mild reaction condition. \(^{146}\)

(19) **Bromo derivative of isocyanuric acid**

(a) **Sodium monobromoisocyanurate (SMBI)**

Sodium monobromoisocyanurate (SMBI) was developed as a new brominating reagent by Kaminski. \(^{147}\) SMBI brings about ionic and regioselective bromination in acidic conditions. \(^{148}\) Imafuku et al. reported bromination of azulenic compounds in neutral conditions. \(^{149}\)

(b) **Dibromoisocyanuric acid**

Gottardi did bromination reactions with dibromoisocyanuric acid under ionic conditions. \(^{150}\) Gottardi studied dibromo isocyanuric acid for bromination of perbrominations of aromatic compounds. \(^{151}\) Brown et al. monobrominated isoquinoline regioselectively in CF\(_3\)SO\(_3\)H using \(N,N\)′-dibromoisocyanuric acid (DBI) to give 5-bromoisoquinoline. \(^{152}\)

(c) **Tribromoisocyanuric acid**

An efficient and highly regioselective bromination of activated aromatic rings promoted by tribromoisocyanuric acid by in situ generation of Br\(^{+}\) was developed by Almeida et al. \(^{153}\) Tozetti et al. utilized this reagent to perform the vicinal vicinal dihalogenation of alkenes. \(^{154}\)

(20) **Pyrrolidinone hydrotribromide**

Awang et al. used this reagent for selective bromination of ketones. It shows keto selectivity (Scheme 1.19). \(^{155}\)

![Scheme 1.19](image)

(21) **Organic ammonium bromides**

(a) **Tetramethylammonium tribromide (TMATB)**

In 1923, Cattaway and coworkers synthesised and studied the properties of tetramethylammonium tribromide. \(^{156}\) Avramoff investigated the effect of this reagent on
several aromatic hydrocarbons, which could undergo either nuclear or benzylic bromination.\textsuperscript{157}

(b) Tetraethylammonium tribromide

Borah and Thakur did various reactions using this reagent. At first they have synthesised alkyl ammonium tribromides with a green procedure using ceric ammonium nitrate (CAN) as oxidant.\textsuperscript{158}

(c) Phenyltrimethylammonium tribromide (PTATB)

It is used for brominating the α-position of carbonyl compounds\textsuperscript{159-164} α′ bromination of α,β-unsaturated ketones\textsuperscript{165} and for the addition of bromine to alkenes.\textsuperscript{166}

(d) Cetyltrimethylammonium tribromide (CetTMATB)

Borah et al. use this reagent to brominate variety of aromatics and some other substances like aniline, phenol, anthracene, imidazole, cresols, phluoroglucinol, methyl-3-phenyl-2-propenoate, 1,3-diphenyl-2-propen-1-one, 1,4-(4′-methoxy-phenyl)- diphenyl-3-propen-1-one, 16-dehydro pregnonalone acetate etc.\textsuperscript{167}

(e) Tetrabutylammonium tribromide (TBATB)

Bromination of substituted alkenes with tetrabutylammonium tribromide is one of the easiest method for the preparation of vicinal dibromoalkanes.\textsuperscript{168} This reagent is used to brominate various alkenes.\textsuperscript{169-170} Various acyclic α-bromo enones as well as cyclic α-bromo enones were prepared from the corresponding acyclic cyclic enones respectively by Bose et al.\textsuperscript{171} Bose et al. prepared a wide range of aurones exclusively from 2′-acetoxychalones.\textsuperscript{172} Wu et al. used this reagent to synthesised 6-bromocoumarins.\textsuperscript{173}

(f) Benzytrimethylammonium tribromide

Those involve electrophilic bromination of aromatic compounds such as phenols, aromatic amines, aromatic ethers, acetanilides, arenes, and thiophene, α-bromination of arenes and acetophenones, and also bromo-addition to alkenes were done by the use of this reagent.\textsuperscript{174-177}
(g) **Tetraethylammonium bromide**

Recently, Kirschning reported that a combination of Et$_4$NBr and PhI(OAc)$_2$ was used in a bromoacetoxylation of olefin.$^{178-179}$ R$_4$NBr/PhI(OAc)$_2$ system is also a very good bromination source for flavone.$^{180}$

(h) **Tetrabutylammonium bromide (TBAB)**

The regioselective bromination of activated aromatics was done using this reagent.$^{181-182}$

(i) **Tetramethylammonium bromide**

Farkas et al. did bromination with tetramethylammonium bromide-bromine mixtures. This mixture was used for the convenient preparation of dibromopropanol from allyl alcohol.$^{183}$

(22) **Cupric bromide**

Unsaturated aldehydes$^{184}$ have been successfully brominated with cupric bromide in methanol, aqueous methanol, or toluene at the α-carbon atom. Fort reported that bromination of isophorone, 3,4,5-trimethylanisole, β-naphthol, and 5,5-dimethylcyclohexane-1,3 dione by using cupric bromide in methanol or methanol-water at room temperature.$^{185}$ Doifode studied the reaction between cupric bromide and either chalcones or 7-hydroxycoumarins.$^{186}$ Again cupric bromide can be used for selective bromination like brominate steroidal ketones in the presence of an isolated double bond.$^{187}$ Doifode and Marathey studied the action of cupric bromide in dioxane on o-hydroxyacetophenone and on some of its derivatives.$^{188}$ Cupric bromide when refluxed in methanol and higher alcohols, α-bromination of carbonyl-conjugated vinyl groups, bromination of isolated double bonds, *trans* bromination of internal acetylenes, and tribromination of terminal acetylenes were observed.$^{189}$ Mosnaim et al. found that 9-alkyl and 9-arylanthracenes underwent halogenation with cupric halides to give good yields of their 10-halogenated derivatives.$^{190}$ Bair et al. investigated a synthetic technique, which was based on the reaction of olefins with copper (II) halides in presence of strong coordinating agents. Olefins reacted readily with copper (II) bromide in the presence of a variety of ligands to produce exclusively vicinal dibromoalkanes.$^{191}$ Chaintreau et al. studied cupric bromide as benzylic bromination reagent in polar media. The reaction in acetonitrile with diisopropyl-peroxydicarbonate as oxidising agent yielded 18% of the product, however without solvent and oxidising agent the yield was 2.5%.$^{192}$ Rodebaugh et al. reported a new
method for dibromination of n-pentenyl glycosides. They used the reagent combination CuBr₂/LiBr. El-Qisairi reported a direct, regioselective and enantioselective approaches for the synthesis of chiral α-bromo carbonyl compounds in moderate to high ee’s and good yields in presence of cupric bromide (Scheme 1.20).

\[ \text{Scheme 1.20} \]

Bhatt and Nayak investigate the use of CuBr₂ as a brominating agent for electron-rich aromatics.

(23) Dioxane dibromide

Pasaribu and Williams did some selective bromination of the side chain of substituted acetophenones with this mild brominating agent. Kotlyar et al. studied the kinetics and mechanism of the bromination of cyclic acetics with 1,4-dioxane dibromide. Shusherina et al. reported that the corresponding monobromides were obtained in the bromination of 1-alkyl-2-pyridones with dioxane dibromide (Scheme 1.21).

\[ \text{Scheme 1.21} \]

Again, selective synthesis of α-bromo and α,α-dibromoalkanones using dioxane–dibromide and silica gel was reported by Paul and coworkers. Chaudhuri et al. reported a mild, solvent-free protocol using dioxane dibromide for highly regioselective aromatic electrophilic bromination.

(24) Pyridinium bromochromate (PBC)

Muathen studied this reagent as a new stable brominating agent for aromatic compounds. Again pyridinium bromochromate was used to brominate various substituted hydroxy-acetophenones, aldehydes and phenols for efficient and selective nuclear bromination.
(25) Trimethylsilylbromide

The possible value of trimethylsilyl halide for the preparation of anomeric halides was suggested by Jung and Lyster. Gillard et al. used this brominating agent under mild condition in presence of various protecting groups. They utilised this reagent to Stereoselective bromination of anomeric glycosyl acetates. Again, for stereo and chemoselective dibromination of alkenes this reagent can be used. Hazra et al. prepared tetradecyltrimethylammonium permanganate (TDTAP), a reagent which in combination with trimethylbromosilane (TMBS) provided a simple and mild method for stereo- and chemoselective transdibromination of alkenes.

(26) 2,4-Diamino-1,3-thiazole hydrotribromide

This solid reagent was prepared by Forlani and efficiently applied for bromination of aryl and styryl methylene ketones to give the corresponding 1-bromoalkyl ketones in high yield.

(27) 1,8-diazabicyclo [5. 4. 0] undec-7-ene hydrobromide per bromide

Muathen reported the brominating properties of DBUHBr₃, with a number of aromatics and heteroaromatics. Four different general procedures were employed for aromatic bromination with this reagent depending on the nature of the aromatic ring.

(28) Benzimidazolium bromochromate

Özgün and Degirmenbaşı introduced this reagent for bromination of various aromatic compounds in acetic acid solution of the reagent.

(29) Tetraalkyl ammonium dichlorobromate

Negero et al. utilised this reagent to brominate phenols. Then they tried bromination of some aromatic hydrocarbons also.

(30) Quinolinium bromochromate (QBC)

The new reagent, quinolinium bromochromate (QBC) functions as a good brominating agent for aromatic compounds.
(31) \(N,N\) - Dibromo benzene sulfonamide (Dibromoamine - T)

In 1971, Robinson tried to brominate norbornene and in this regard, he used this reagent as a brominating agent.\(^{213}\) Tajbakhsh et al. used this reagent as a regenerable brominating agent for bromination of carbanionic substrates under mild conditions. \(\beta\)-diketones and \(\beta\)-ketoesters were brominated by this reagent without using any bases.\(^ {214}\) Revesz et al prepared the scaffold of 3,7,9-triazabicyclo[3.3.1]nonane from \(N,N\)-dibromobenzenesulfonamide as brominating agent and ethyl acrylate.\(^ {215}\)

(32) Sodium bromate

Masuda et al. used sodium bromate as a brominating agent to synthesised bromohydrins from alkenes.\(^ {216}\) Kikuchi et al. again used this reagent for selective selective side chain and ring brominations of alkylbenzenes.\(^ {217}\) Groweiss used sodium bromate as a powerful brominating agent for aromatic compounds that contain deactivating substituents.\(^ {218}\)

(33) HBr

In 1942, Couper et al. studied the action of HBr in acetic acid on unsaturated 1,4-diketones. They found that HBr in acetic acid not only acted as brominating agent.\(^ {219}\) Davis et al. used HBr to prepare brominated pentaerythritols.\(^ {220}\) Later it was found that combination of aqueous \textit{tert}-butylhydroperoxide or hydrogen peroxide and hydrobromic acid as an effective reagent for bromination of aromatic compounds with or without a catalyst in various solvent systems.\(^ {221-226}\) A new method of bromination was reported by Gavara et al. with \textit{iso}-amyl nitrite/HBr system. The reaction succeeded with slightly activated arenes and heterocyclic compounds.\(^ {227}\)

1.4. \(N,N\)-Dibromo-\(p\)-toluenesulfonamide: The titled brominating agent

1.4.1. Review of literature

\(N,N\)-Dibromo-\(p\)-toluene sulfonamide is a brominating agent which was first used by Kharasch for the synthesis of 1-phenyl-2-(\(p\)-toluenesulfonylido)-1 bromoethane.\(^ {228}\) The same reagent was also used by Paul et al. for the synthesis of 3,5-dihydroxy-1-substituted piperidines from 1,4-pentadiene.\(^ {229}\) In both the cases, the reagent was not studied
expeditiously. Recently, this reagent attracts much attention from the chemists. Phukan et al. synthesized bromohydrins using this reagent. A very rapid and efficient method has been developed for the synthesis of vicinal bromohydrins and alkoxybromides directly from an olefin without any catalyst. The reaction was performed in CH$_3$CN water (4:1) or alcohol. Bromohydrins are formed instantaneously, whereas formation of alkoxybromides takes 30-60 min (Scheme 1.22).\(^{230}\)

\[
\begin{align*}
R' &\rightarrow R'' \\
\text{TsNBr}_2 &\rightarrow R \quad \text{Br} \\
\text{MeCN} &\text{H}_2\text{O} (4:1), rt \\
or \text{ROH}, rt
\end{align*}
\]

\(R' = \text{H, Ar}; R'' = \text{H, CO}_2\text{Et, CO}_3\text{Me}
\]

\(X = \text{OH or OR}
\]

Scheme 1.22

Huang et al. proposed a novel reaction pathway of 2,3-allenoates with TsNBr$_2$ as an electrophile in the presence of K$_2$CO$_3$ to produce (1\(E,2E\))-3-bromo-4-oxo-N-tosyl-2-alkenoxylimidic acid ethyl esters (Scheme 1.23).\(^{231}\)

\[
\begin{align*}
\text{R'} &\rightarrow \text{H or naphthyl} \\
\text{TsNBr}_2 &\rightarrow \quad \text{via} \\
\text{2.0 eq. K}_2\text{CO}_3 &\rightarrow \text{30 min}
\end{align*}
\]

\(\text{R'} \quad (+)\)

Scheme 1.23

Again an efficient dianimation reaction of alkenes has been developed for the synthesis of bromoalkylbranched imidazolines by using CuI–PPh$_3$ as the catalyst and \(N,N\)-dibromo-p-toluenesulfonamide as the nitrogen/halogen sources by Han et al. (Scheme 1.24).\(^{232}\)

\[
\begin{align*}
\text{Ph} &\rightarrow \text{COPh} \\
\text{TsNBr}_2 &\rightarrow \quad \text{+ CuI–PPh}_3 (20 \text{ mol %})
\end{align*}
\]

\(\text{CH}_2\text{CN, 4A MS}
\]

Scheme 1.24

Huang et al. also reported a novel electrophilic addition reaction of \((Z)\)-alk-2-en-4-ynoates and TsNBr$_2$ providing a facile and highly stereoselective synthesis of densely functionalized aziridine derivatives (Scheme 1.25).\(^{233}\)
Recently, it is proved that this reagent has oxidizing power. It can oxidize varieties of alcohols to the corresponding aldehydes without using any catalyst (Scheme 1.26).

It can be stated that there is much more scope in this reagent as a brominating agent. That’s why; we have thought to explore some new organic transformation using the same.

### 1.4.2 Preparation of the reagent

The reagent can be prepared by following literature procedure. It can be prepared from chloramine-T as well as p-toluene sulfonamide.

(a) From Chloramine-T

Recrystallised chloramine-T (10 g) was dissolved in water (200 ml) and liquid bromine (2 ml) was added dropwise from burette with constant stirring at the solution. The golden yellow precipitate of \(N,N\)-dibromo-p-toluene sulfonamide was thoroughly washed with water, filtered under suction and dried in a desiccator for 24 hours (Scheme 1.27).

\[
\text{Chloramine-T} + \text{Liq Br}_2 \xrightarrow{\text{H}_2\text{O, Stirr}} \text{Golden yellow ppt of TsNBr}_2
\]
(b) From p-Toluene sulfonamide

In a 250 ml three necked flask were placed with 5 g of p-toluene sulfonamide in aq KOH solution (3.6 g of KOH in 25 ml water). Then 10g of bromine were added with vigorous stirring. The resulting precipitate of N,N-dibromo-p-toluene sulfonamide was filtered, washed with water and dried (yield 9.8 g, 98%) (Scheme 1.28).

\[
\text{p- Toluene sulfonamide} + \text{Liq Br}_2 \xrightarrow{\text{Aq KOH, Stirr}} \text{Golden yellow ppt of TsNBr}_2
\]

Scheme 1.28

However, TsNBr\textsubscript{2} prepared from chloramine-T shows better activity than that produced from p-toluene sulfonamide.
1.5. References


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