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Development of synthetic protocols for Quarternary Ammonium Tribromides - A Brief Account

Upasana Bora Sinha[1*] and Latonglila Jamir[2]

1. Department of Chemistry, Nagaland University, Lumami-798627, Nagaland, **INDIA**
2. School of Engineering and Technology, Nagalanad University, Dimapur, Nagalanad-797112, **INDIA**

Email: upasanaborasinha@gmail.com

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ABSTRACT

Quaternary ammonium tribromides have in recent years been looked at as greener alternatives of the toxic reagent bromine and literature reports a number of such tribromide reagents. These reagents are efficient and allow various types of organic transformations to be carried out with environmental benignity. Their applications have been reported for various organic transformations such as bromination of organic substrates, oxidative cyclization reactions, in the construction of heterocycles, acylation reactions, etc. The utility of these reagents has led to the establishment of various methods for their preparation over the years. However, in recent times, environmental protection requirements make it important that a reagent is not only benign in its reactivity, but its method of synthesis should also be environmentally favourable. Thus, a study of the methods in which quaternary ammonium tribromide reagents have been designed and developed of has an importance of its own.

Keywords: Tribromides, environmentally benign, peroxo-mediated, green chemistry.

INTRODUCTION

Contemporary life is greatly benefited by chemicals and chemical processes through the development, production, use, and disposal of the huge variety of goods that are produced for the syntheses of new materials, dyes, agrochemicals, pharmaceuticals, etc. Unfortunately however, chemistry and chemicals often also become associated with unexpected environmental problems. Therefore, in order that the quality of the environment is not compromised, there is a requirement to assess chemical processes and ensure their compliance with the requirements for environmental benignity [1-3]. Bromination chemistry is an important area of research in organic chemistry because of the significance of bromoorganic compounds [4,5]. Conventional methods of bromination of organic substrates mostly use liquid bromine as brominating reagent. However, bromine is a corrosive liquid reagent (boiling point 7°C) and maintenance of stoichiometry is difficult, and also special care is required for its storage and transportation. It is very harmful in both of its liquid and vapour form and is corrosive to all body tissues and may cause serious burns. Excessive inhalation of vapors may be very irritating and damaging to the respiratory tract and lungs. Symptoms include headache, cough, nosebleed, vertigo, pulmonary edema, and abdominal pain. Upon ingestion, it causes sore throat, vomiting and abdominal spasms. The estimated lethal dose is l4 mg/kg [6]. Even though bromine is a very toxic chemical, it is very important for a host of organic transformations. Therefore there has been a search for benign reagents which can act as bromine alternatives. A number of such reagents have been developed and among bromine-alternatives that have so far been developed, a group of reagents that have become vastly popular are the quaternary ammonium tribromides.

Quaternary ammonium tribromides (QATBs) have gained enormous attention in recent years as versatile bromine alternatives and reports of many such tribromides are available in literature. Some of the nitrogen-based tribromides which have been reported so far include tetramethylammonium tribromide (TMATB), tetraethylammonium tribromide (TEATB), tetrapropylammonium tribromide (TPATB), tetrabutylammonium tribromide (TBATB), cetyltrimethylammonium tribromide (CTMATB), cetylpyridnium tribromide (CetPyTB), phenyltrimethylammonium tribromide (PTATB), benzyl trimethylammonium tribromide (BTMATB), pyridine hydrobromide perbromide (PHPB), pentylpyridinium tribromide (PPTB), 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide(DABCO tribromide), 1,8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide (DBUHBr$_3$), and 1-butyl-3-methylimidazoliumtribromide (bmimTB) and 1,2-dipyridiniumditribromide-ethane (DPTBE), etc (Figure 1) [7-19].

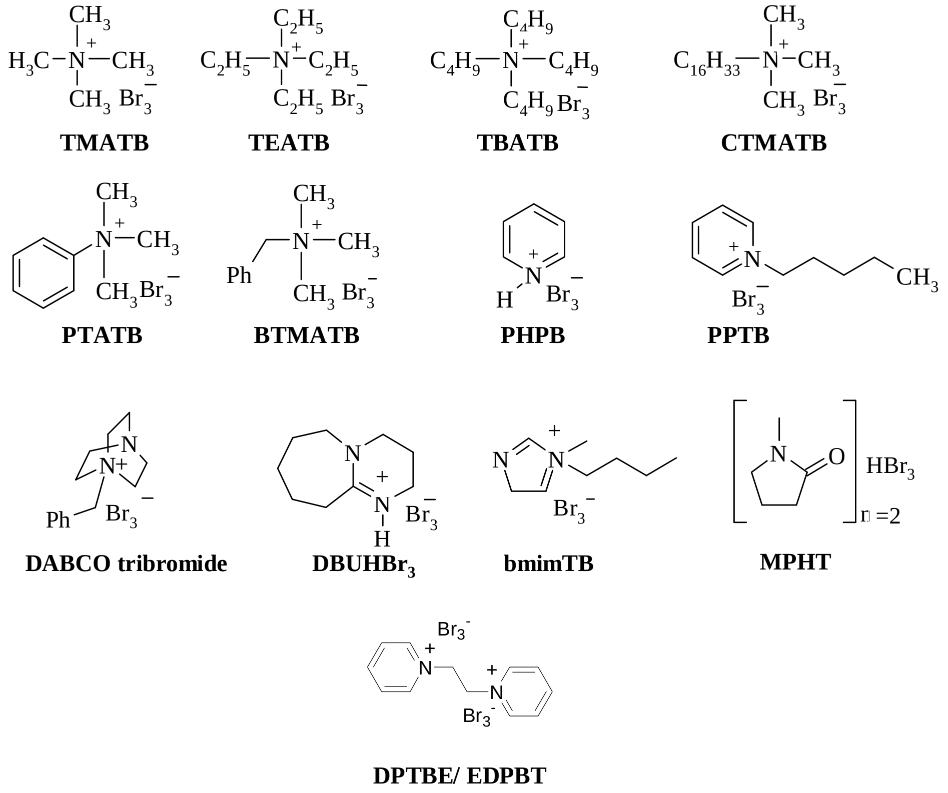


Figure 1 Some Quaternary Ammonium Tribromides

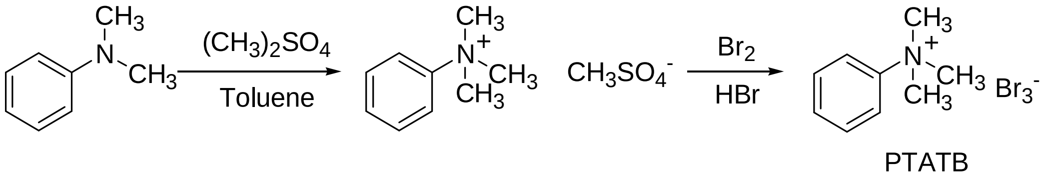
The versatility of quaternary ammonium tribromides have allowed them to have numerous applications in various organic transformations such as bromination reactions, esterifications, sulfide oxidations, heterocyclic synthesis, oxidative cyclizations, etc [7]. Moreover, due to solid nature of QATBs, their storage and handling is easy. Storage does not require any special arrangement and maintaining exact stoichiometry during reactions is also easy with these reagents. These reagents do not lose their identity as tribromide even after keeping for several years. Moreover, most of the tribromides are stable up to temperatures of about 200^{o}C [20,21], and thus can be used for reactions at elevated temperature, making them reagents of choice for solvent-free reactions under microwave conditions and at elevated temperatures [22-24].

The QATBs can be easily synthesized in the laboratory. Even though some of these reagents are now commercially available, efforts still continue to design and develop newer synthetic methodologies for these reagents, which, in keeping with one of the tenets of green chemistry, use and generate substances that possess little or no toxicity to human health and the environment. Acknowledging the role of quaternary ammonium tribromides as bromine alternatives, this review traces the historical developments in the synthesis of this important group of reagents.

MATERIALS AND METHODS

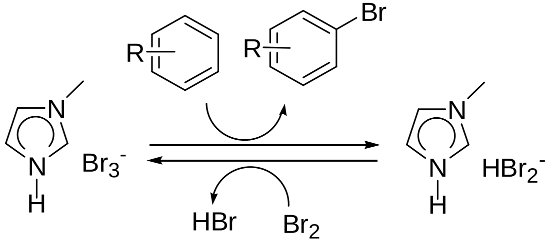
Account of methods of preparation of QATBs

Methods of Preparation involving Bromine: Earlier reports of organic quaternary ammonium tribromide synthesis reveal that their methods of preparation often used toxic chemicals like elemental bromine and hydrobromic acid. Chattway and Hofle were the first to report the preparation of tetramethylammonium tribromide (TMATB) [14]. It was synthesized by treating tetramethylammonium bromide with bromine in acetic acid. The product TMATB was reported to contain 50.9% of active bromine.
Tetrabutylammonium tribromide (TBATB) was first synthesized by Buckles *et al.* from tetrabutylammonium bromide and molecular bromine [15]. It had an active bromine content of 33%.
Phenyltrimethylammonium tribromide (PTATB) was reported with 42.5% active bromine content by treating one mole of phenyltrimethylammonium sulfomethylate with 1.2 mole of bromine (*Scheme 1*) to get an orange-yellow precipitate which was recrystallized to get the pure product (PTATB) [16].



Scheme 1. Synthesis of phenyltrimethylammonium tribromide [16]

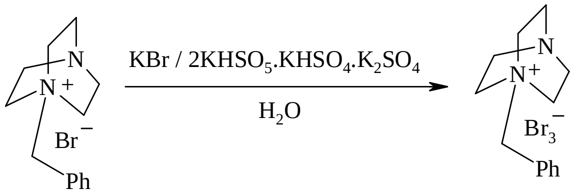
Djerassi and Scholz introduced another brominating agent, pyridine hydrobromide perbromide ($C_5H_5N.HBr.Br_2$ or PHPB) which was synthesized by using equimolar amounts of bromine, pyridine and HBr (48% aq. solution). The red prismatic crystals of PHPB with a melting point of 134°C were crystallized from acetic acid with 45% available bromine [8]. Salazar *et al.* reported the synthesis of an ionic liquid tribromide at room temperature, pentylpyridinium tribromide (PPTB) by the addition of an equimolar amount of bromine to solid crushed pentylpyridinium bromide [9]. 3-methylimidazolium tribromide [$(Hmim)Br_3$], a red solid stable compound (m.p. 70°C) was reported by Chiappe *et al.* It was prepared by addition of 3-methylimidazolium bromide with molecular bromine (*Scheme 2*) [10].



Scheme 2. Synthesis of 3-methylimidazolium tribromide [10]

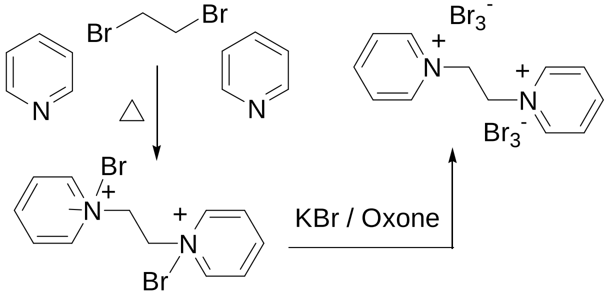
Muathen reported the synthesis of a stable tribromide, 1, 8-diazabicyclo [5.4.0] undec-7-ene hydrotribromide (DBUHBr$_3$), which can be readily obtained by reacting an equimolar amount of bromine with DBU in presence of HBr in acetic acid [17]. This crystalline compound is reported to exhibit higher stability than pyridine hydrobromide perbromide, but the compound formed is reported to have three different bromine compositions as well as three different melting points. Thus it can be understood that the importance of the quaternary ammonium tribromides as reagents led to the synthesis of a number of such compounds, even though bromine was needed to be used for synthesis.

Methods for preparation of QATBs using other reagents: In order to circumvent the use of bromine as reagent in tribromide synthesis, methodologies were developed which did not require its use. For example, it is known that the first method of preparation of TBATB involved the use of bromine [15] but thereafter, Kajigaeshi *et al.* modified the synthetic procedure and synthesized TBATB using NaBrO$_3$ and HBr [25]. Hajipour *et al.* developed another synthetic methodology and synthesized 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide by treating an aqueous solution of potassium peroxomonosulfate to a solution of 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane bromide and KBr (*Scheme 3*) [26].



Scheme 3. Synthesis of 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide [26]

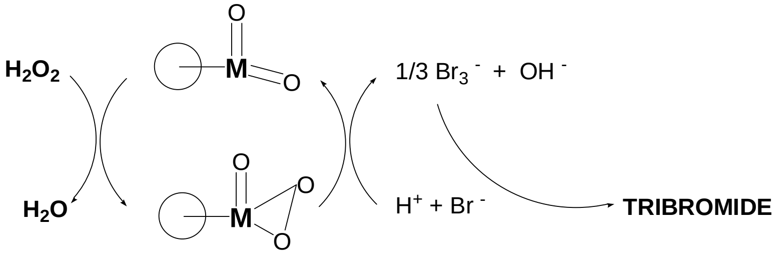
A ditribromide reagent, 1,2-dipyridiniumditribromide-ethane (DPTBE) or 1,1'-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) was synthesized by Patel *et al.* by refluxing pyridine (2 equiv) with dibromoethane (1 equiv). 1,2-dipyridiniumdibromide-ethane (DPDBE) or 1,1'-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB) so formed was treated with KBr (4.5 equiv) followed by oxidation of bromide to bromine using an aqueous solution of Oxone® (2 equiv) leading to the formation of an orange precipitate of DPTBE or EDPBT (*Scheme 4*) [18].



Scheme 4. Synthesis of 1,2-dipyridiniumtribromide-ethane [18]

Efforts to circumvent the use of bromine also led to the exploration of other oxidizing agents such as potassium permanganate (KMnO$_4$) [27], nitric acid (HNO$_3$) [28] and ammonium persulfate (NH$_4$)$_2$S$_2$O$_8$ [29] for successful oxidation of different quaternary ammonium bromides to the corresponding quaternary ammonium tribromides.

Peroxo-metal mediated synthesis of tribromides: In 1998 a new synthetic methodology was developed in our group by Chaudhuri *et al.*[30] which provided an economical and cleaner process for synthesis of quaternary ammonium tribromides [31]. This process was based on the principle of biomimetic oxidation of quaternary ammonium salts of bromide (Br^-) to tribromide (Br_3^-) using a peroxo-metal intermediate in an acidic medium (*Scheme 5*).



$$\textbf{QAB} \xrightarrow[H_2SO_4 / KBr]{V(V) \text{ or } Mo(VI) / H_2O_2} \textbf{QATB}$$

Scheme 5. Biomimetic method of tribromide synthesis [30]

Scheme 5 includes a graphical representation of some of the tribromides that could be developed using the peroxo-metal mediated pathway, and here QAB = quaternary ammonium bromide and QATB = quaternary ammonium tribromide in which QA = quaternary ammonium, *viz.*, tetramethylammonium (TMA), tetraethylammonium (TEA), tetrapropylammonium (TPA), tetrabutylammonium (TBA), benzyltrimethylammonium (BTMA), cetyltrimethylammonium (CTMA) and cetylpyridinium (CetPy) [7,19,20,30,31]. It may be mentioned in passing that this methodology has successfully worked on organic phosphonium compounds also, leading to the synthesis of ethyltriphenylphosphonium tribromide (ETPPTB) [32].

The strategy is based on preparing quaternary salts of tribromide wherein the bulky cationic moiety is an ammonium unit and the anionic portion is the tribromide portion. The reaction proceeds without the involvement of bromine or HBr and the quaternary bromide salt is itself the source of primary bromide. In the reaction, monobromide is oxidized to tribromide wherein 1/3 of the bromide is obtained from the quaternary bromide salt and remaining 2/3 of the bromide is obtained from an additional secondary source, which can be potassium bromide (KBr) or ammonium bromide (NH_4Br). The bromide oxidation reaction leading to the formation of tribromide is facilitated by the peroxo-metal intermediate that is prepared *in-situ* in the reaction medium itself. Highervalent metal catalysts such as V(V) and Mo(VI) are used in catalytic amounts for activation of hydrogen peroxide, however, any other metal capable of activating peroxide can also be used. An acidic medium created through the addition of 1 molar H_2SO_4 is needed to promote the reaction. The reaction does not require the use of organic solvent.

Sodium carbonate mediated method of tribromides synthesis: The peroxo-metal mediated reaction strategy that was described in the previous section has been accepted as the most environmentally benign method for synthesis of QATBs [7]. However, one drawback of the protocol is the use of heavy metal as catalyst for activation of hydrogen peroxide. While it cannot be denied that transition metals have an extremely important role as catalysts for numerous transformation reactions, but at the same time, the hazards caused by these metals cannot be denied either. Therefore, what is needed is catalysts for hydrogen peroxide activation that work as efficiently as peroxometal catalysts but are more innocuous in nature.

While continuing our effort to develop a benign method for synthesis of QATBs, our attention was drawn to peroxocarbonates as oxidizing agents, for bromide oxidation. It may be explained that there exist several reagents which have the capability of activating hydrogen peroxide and subsequently oxidizing bromide, however, since environmental benignity was our major concern, the oxidant that was being sought was one which was as innocuous as possible. In this context sodium carbonate was chosen, which in combination with hydrogen peroxide, exists as peroxocarbonate. There are a number of reports and reviews available on the use of sodium peroxocarbonate (SPC) as a functional group oxidant, usually for organic transformations [33]. Taking cues from this information, an attempt was now made to study the possibility of using percarbonate for bromide oxidation subsequently leading to the formation of tribromide [34]. Mechanistically, the principle involved remains essentially the same except for the avoidance in the use of heavy metal ions for hydrogen peroxide activation. In this metal-free synthetic protocol, in presence of an excess of hydrogen peroxide, sodium carbonate as well as sodium bicarbonate rapidly react into an equilibrium mixture of carbonate ions and peroxo carbonate ions. The peroxocarbonate ion reacts in a manner that is similar to any other peroxometallate, and thereby allows oxidation of bromide to tribromide, thereby affording the quaternary ammonium tribromides by a new metal-free synthetic pathway (*Scheme 6*) [34].

$$\mathbf{QAB} \xrightarrow[H_2SO_4\ /\ KBr]{Na_2CO_3/\ H_2O_2} \mathbf{QATB}$$

Scheme 6. Metal-free method of tribromide synthesis [34]

APPLICATIONS

Quaternary ammonium tribromides have become reagents of importance as bromine-alternatives for organic transformations. There are numerous reagents which have been prepared by several methodologies. This review, which may be the first one on the synthesis of QATBs gives a comprehensive account of the methods of preparation of some of these reagents. From green chemistry point of view, this review could be important as it traces the manner in which of the synthetic methodologies have been progressively developed resulting in more environmentally benign protocols.

CONCLUSIONS

Quaternary ammonium tribromides are a group of reagents which collectively are the most benign alternatives for the toxic reagent bromine, and are capable of facilitating a host of organic transformation reagents on a wide variety of substrates. Considering the importance of these reagents, over the years several methods of their synthesis have been developed. However, not all the methods of synthesis have been complementary to the tenets of green chemistry. This has therefore led to continued studies on the method of preparation of quaternary ammonium tribromides which this review traces, culminating in the latest report in which QATBs are prepared by a metal free method of synthesis which allows the synthesis by an inherently safer synthetic protocol.

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