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Application of *N*-methylpyrrolidin-2-one hydrotribromide in organic synthesis

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Abstract. The review describes the broad applicability of a modern reagent, *N*-methylpyrrolidin-2-one hydrotribromide (MPHT), in organic synthesis. The methods for its preparation and use in the bromination reactions of different classes of organic compounds (alkenes, alcohols, ketones, *etc*.), in the oxidation and epoxide ring-opening reactions, in conversions of alkenes to aziridines are considered. Special attention is given to the environmentally friendly character of MPHT. The bibliography includes 186 references.

I. Introduction

Over the last few years, development of chemical products and processes that reduce or eliminate the use and generation of hazardous substances has become a challenging task in order to protect the environment and to support the sustainable organic synthesis.[1–4]

The bromination of organic compounds[5–7] is a valuable reaction, which finds extensive applications in the synthesis of many pesticides and pharmaceuticals.[8] Direct bromination using molecular bromine although being a simple approach,[9–11] utilizes only 50% of the bromine for bromination with the other half forming HBr waste. Thus, in a large scale synthesis millions of tonnes of acid waste are produced, which is rarely recycled for reuse in industry, as the additional step and the corrosiveness of HBr make it more expensive and cumbersome. Further, liquid bromine is hazardous, volatile by nature and requires extreme care in its production, transportation and utilization.[12]

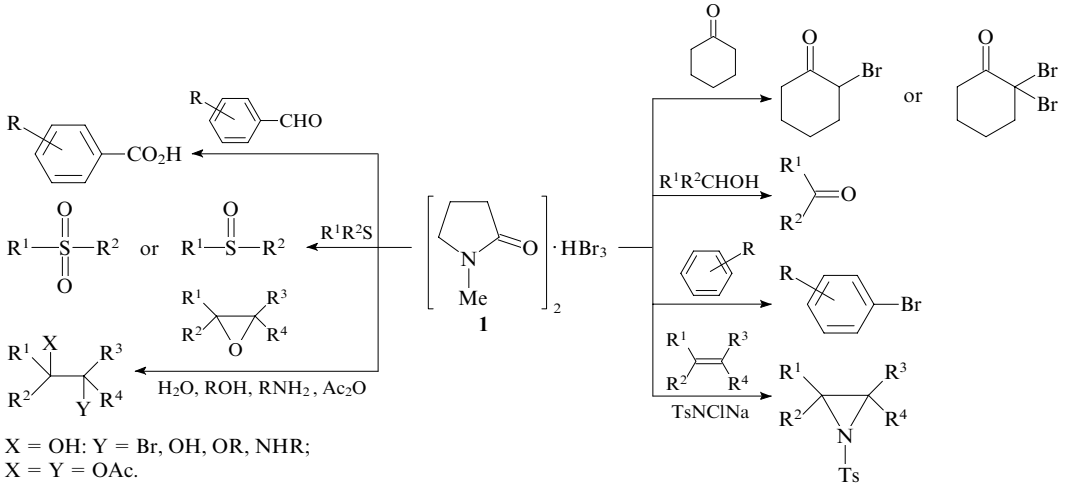
Crystalline organic ammonium tribromides (OATB) (or quaternary ammonium tribromides, QATB) also referred to as solid bromine[13–15] are promising and more desirable alternatives of liquid bromine because of their ease of handling, storage, transport and ability to maintain desired stoichiometry. Organic ammonium tribromides (OATB) are an important class of compounds, which find wide application in organic synthesis mainly as brominating agents,[16–18] oxidizing agents[19–21] and as bifunctional catalysts in the oxidative bromination of aromatic compounds[22–24] with aqueous hydrogen bromide/hydrogen peroxide and diastereoselective bromination of allyl glycosides.[25] In addition to this, they also have the ability to release bromine in a controlled manner; for example, in the oxidation of sulfides to sulfoxides,[26–28] the low concentration of bromine in the reaction mixture makes the procedures safer and minimizes the possibilities of over-oxidation of sulfides into sulfones and also prevent the undesired reactions of other functional groups, which is particularly important in the synthesis of biologically relevant sulfoxides.[29,30] Organic ammonium tribromides can also be used efficiently for the Hoffmann degradation of amides,[31] methoxybromination of styrene[32] and for the one-step synthesis of *N*-substituted acylureas and carbamates from amides.[33] A variety of organic tribromides have been reported in the literature including tetramethylammonium tribromide (TMATB),[34] benzyltrimethylammonium tribromide,[35–37] *N*-benzyl-1,4-diazabicyclo[2.2.2]octane (*N*-benzyl-DABCO) tribromide,[38] phenyltrimethylammonium tribromide (PTATB),[39–42] tetrabutylammonium tribromide (TBATB),[43–46] *p*-tolyltrimethylammonium tribromide,[47] cetyltrimethylammonium tribromide (CTMATB),[28] $\{[K\cdot 18\text{-crown-6}]Br_3\}_n$,[48] pyridinium hydrobromide perbromide ($PyHBr_3$),[49,50] *etc*. These reagents have been widely used as efficient brominating agents for the bromination of a variety of organic substrates[51–53] such as allylic alcohols, enones, alkenes, alkynes, activated aromatics such as anilines, phenols, polycyclic hydrocarbons such as anthracene and phenanthrene and sensitive substrates such as imidazole.

Further, a variety of reactions other than bromination such as oxidation using these reagents are reported in the literature, which expand the scope of these reagents in organic synthesis. For example, the oxidation of phosphorus(I) and (III) oxyacids by QATB leads to the corresponding phosphorus(III) and phosphorus(V) oxyacids, respectively.[54]

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Scheme 1



Generally, these reagents can be prepared by two methods, *viz*., by the reaction of organic bromides with molecular bromine and/or HBr or, alternatively, with aqueous H_2O_2 and KBr (or NH_4Br) in the presence of catalytic amounts of V_2O_5 (or H_2MoO_4).[55,56] However, this method generates some heavy metal as toxic waste, which makes its utility limited from environmental points of view.

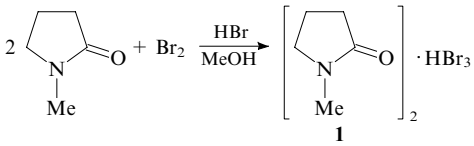
Recently, Berrien *et al*.[57] have reported an efficient brominating reagent, *viz*., *N*-methylpyrrolidin-2-one hydrotribromide (MPHT, $[NMP]_2 \cdot HBr_3$, **1**), which is easily accessible, crystalline in nature and remarkably stable towards air, moisture and therefore can be stored at room temperature without decomposition. MPHT acts as a source of bromonium ion in analogy with molecular bromine and any other brominating agent such as hypobromite,[58] *N*-bromosuccinimide,[59] bromine azide[60] and HBr.[61,62] In addition, MPHT has successfully been used as a highly active pre-catalyst for a variety of organic reactions probably due to its ability to generate *in situ* dry HBr in the reaction medium. Further, MPHT is not corrosive, less toxic and stable crystalline compound that is easier to handle than molecular bromine. Thus, MPHT is a novel promising reagent, which will surely open new avenues for its potential in organic synthesis.

N-Methylpyrrolidin-2-one hydrotribromide was reported[57] to serve as a reagent for the *anti*-addition of bromine to C=C double bonds with the reactivity comparable to that of molecular bromine, but with the additional benefits of facile handling, safety and stability. This led us interested towards the use of MPHT for organic reactions. We have explored the potential of this reagent for a variety of organic reactions including bromination, oxidation, aziridination, protection/deprotection of nucleophilic substrates, and ring opening of epoxides (Scheme 1).

The prime goal of this report is to focus on the applicability and versatility of MPHT for a variety of organic transformations, which will surely open new avenues for its potential in organic synthesis.

II. Preparation of *N*-methylpyrrolidin-2-one hydrotribromide

N-Methylpyrrolidin-2-one hydrotribromide (MPHT; $[NMP]_2HBr_3$) **1** is a crystalline orange compound, which can readily be prepared by the reaction of *N*-methylpyrrolidone with bromine and HBr solution (30% HBr in acetic acid) in 87% yield under mild reaction conditions.[57]



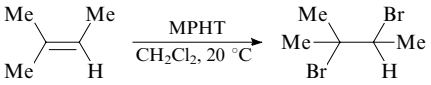
Its structure has been determined by single-crystal X-ray diffraction method.[63] The crystals are built of *N*-methylpyrrolidin-2-one molecules, *N*-methylpyrrolidin-2-onium cations and the anions Br_3^-. This complex is insensitive to moisture and showed a remarkable stability at room temperature: no free bromine could be detected when exposed to air for several months. Discoloration of the original orange solution could be observed during the bromination reactions as long as MPHT is consumed.

III. Applications of *N*-methylpyrrolidin-2-one hydrotribromide in organic synthesis

1. Bromination of alkenes

Bromination of organic molecules is an important task in synthetic organic chemistry. Previously, bromination of alkenes has been primarily performed by using molecular bromine as the reagent, mainly in chlorinated solvents to give vicinal dibromides.[64] However, to avoid the use of bromine due to its toxic, corrosive nature, during the last decade several new bromination methods have been developed in order to circumvent its hazardous potential.[51,65] Replacement of bromine with its promising alternatives has received particular interest in recent years. Thus bromination of alkenes with bromodimethylsulfonium bromide (BDMS)[66] and pentylpyridinium tribromide[67] was reported. However, these reagents have certain drawbacks: the synthesis of BDMS requires highly volatile dimethyl sulfide, which is difficult in handling, while pentylpyridinium tribromide involves the use of expensive organic ammonium cation. The key features such as accessibility, inexpensive nature and remarkable stability make the use of MPHT complex to be superior and promising tribromide reagent over existing ones.

The bromination of 2-methylbut-2-ene at room temperature using MPHT in dichloromethane as the brominating agent was documented.[57]

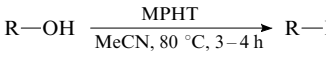


Discoloration of the original orange solution indicated the completion of the reaction and consumption of the MPHT. *N*-Methylpyrrolidin-2-one hydrobromide and *N*-methylpyrrolidin-2-one are by-products of the reaction and are removed by washing the organic layer with water.

2. Conversion of alcohols into the corresponding bromides

The conversion of alcohols into the corresponding bromides is an important synthetic transformation and in this context various methods including the use of HBr/H_2SO_4,[68] HBr in the presence of Bu_4NBr/Aliquat 336,[69] polymer-supported triphenylphosphine dibromide and polymer-supported triphenylphosphine and carbon tetrabromide[70] or *via O*-alkylisoureas[71] have been reported in the literature, However, most of the methods are associated with the limitations as they yield a mixture of products in the case of secondary alcohols due to isomerization. Thus, a method for the selective bromination of alcohols is desired. In this context, Furukawa *et al.*[72] recently reported the use of BDMS as an effective reagent for the conversion of alcohols into bromides in high yields. However, the drawbacks of BDMS have been mentioned.

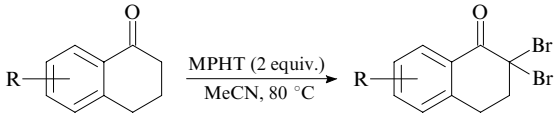
Thus, to overcome these limitations, we thought it would be worthwhile to use MPHT as a brominating agent. Bromination of a variety of aliphatic alcohols was studied; all the alcohols were selectively and efficiently converted to the corresponding bromides in high yields. They compare favourably with the recently reported BDMS.



R	Yield (%)		R	Yield (%)	
	MPHT	BDMS		MPHT	BDMS
Bn	72	–	Bu^n	80	73
n-C_5H_{11}	76	–	Bu^s	62	57

3. Preparation of α-bromo ketones

Bromination of carbonyl compounds is an important transformation, since the resulting α-brominated products find extensive applications as versatile intermediates in organic synthesis, such as for the synthesis of α-aryl ketones. Although a variety of reagents have been explored for the α-bromination of ketones,[73–75] however, very few reports are known for α,α-dibromination of carbonyl compounds. The most commonly used reagent for this transformation is elemental bromine.[76,77] A variety of alternative methods have been discovered in current years, which make use of $HBr-H_2O_2$,[78] 1,3-dibromo-5,5-dimethylhydantoin,[79] polymer-supported brominating reagents,[80] $KBr-KBrO_3$–Dowex[81] or dioxane dibromide–silica gel under microwave irradiation.[82] However, few of them are promising. It is now well established that organic ammonium tribromides are promising alternative. In fact, MPHT has recently been used as a soft brominating reagent for bromination of carbonyl compounds,[83] in particular, for the selective preparation of α,α-dibromotetralones, which are suitable substrates for the construction of substituted 2-bromo-1-naphtols. The reactivity of complex **1** was evaluated with several 1-tetralones in order to prepare the α,α-dibrominated compounds. The effect of various parameters on the reaction was also studied. Among the various solvents studied, CH_3CN was found to be the solvent of choice. The efficiency of the reaction increased with temperature, at 80 °C the complete conversion of the starting material is very fast to give high yields of the desired products.

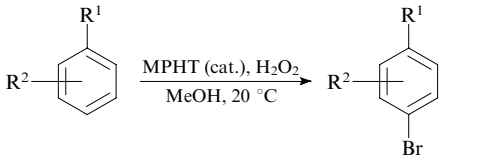


R = H, OMe, Br.

4. Bromination of aromatic compounds

Bromination of aromatic compounds is a fundamentally important synthetic transformation as brominated arenes are extensively used as precursors in the preparation of various bioactive molecules, pharmaceuticals and play vital roles in the metal-catalyzed coupling reactions.[84,85] A variety of methods using molecular bromine,[86,87] transition metal catalysts[88] and systems sodium periodate–alkali metal halides[89] have been reported in the literature. However, these methods are associated with the drawbacks such as the use of toxic and hazardous bromine, use of expensive transition metals and formation of polysubstituted and other side products. Therefore, in the recent years the main emphasis is being placed towards the use of transition metal-free systems in a view to develop environmentally benign synthetic methodologies.

In this context, several improved methodologies using *N*-bromosuccinimide,[90,91] systems Br_2/SO_2Cl_2 (Ref. 92) and Br_2/MnO_2,[93] *N*,*N*,*N*,*N*-tetrabromobenzene-1,3-disulfonamide[94] and a hexamethylenetetramine–Br_2 (Ref. 53) complex have recently been reported. During our research, we developed a simple yet efficient protocol for the regioselective bromination of aromatic compounds using *N*-methylpyrolidin-2-one hydrotribromide (MPHT) as a brominating agent in the presence of aqueous 30% hydrogen peroxide under very mild reaction conditions.[95]



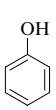
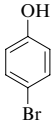
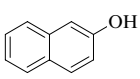
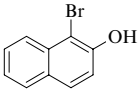
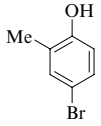
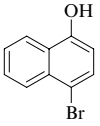
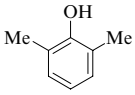
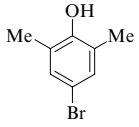
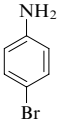
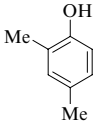
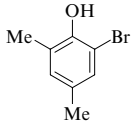
(92%–98%)

R^1 = OH, NH_2, OMe; R^2 = H, Me, OMe, Cl.

The merits of the present methodology are reflected from the fact that it provides better yields of monobrominated aromatics in shorter reaction times under milder reaction conditions as compared to the previously known methods using *N*-bromosuccinimide in tetrabutylammonium bromide as a brominating agent (Table 1).

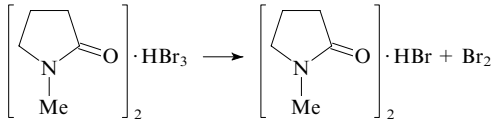
The halogenation of aromatic compounds using a system HHal (aq.)–H_2O_2 was reported.[96] The proposed reaction mechanism involved the *in situ* generation of HOHal, which subsequently affords a reactive species for the electrophilic substitution in the aromatic nucleus. In analogy with this, we assumed that the reaction involving MPHT might proceed *via* hypobromous acid formed in the reaction of

Table 1. A comparison of brominating systems based on MPHT and NBS.

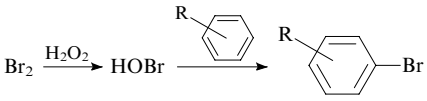
Substrate	Product	MPHT (Ref. 96)[a]		NBS (Ref. 90)[b]		Substrate	Product	MPHT (Ref. 96)[a]		NBS (Ref. 90)[b]	
		time /min	yield (%)	time /h	yield (%)			time /min	yield (%)	time /h	yield (%)
		< 1	96	2	90			< 1	94	–	–
		–	–	2	84			–	–	4	75
		10	85	–	–			10	90	4	88
		20	90	–	–						

Reaction conditions: [a] 0.5 mol MPHT and 1.0 mol of aqueous 30% H_2O_2 per mol of a substrate, 20 °C; [b] 1.0 mol NBS and 0.2 g per mol of a substrate, 100 °C.

MPHT with hydrogen peroxide, subsequent electrophilic attack of the reactive bromine species on the aromatic ring yielded the corresponding brominated product.



1



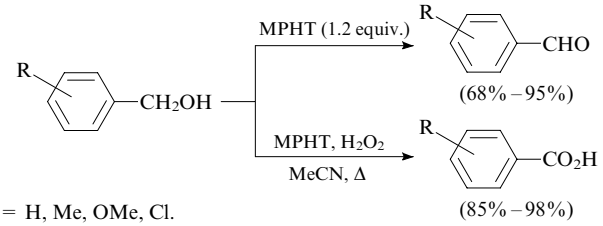
The use of MPHT alone as a brominating agent gave poor yields, while the addition of aqueous hydrogen peroxide enhanced the reaction rate and yielded brominated products in excellent yields in shorter reaction times.

5. Oxidation of organic compounds using MPHT as a catalyst

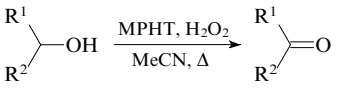
a. Oxidation of alcohols and *vic*-diols

The oxidation of alcohols to carbonyl compounds is an important synthetic transformation [97, 98] and in the recent years emphasis is being given towards the use of environmentally benign oxidants such as molecular oxygen and hydrogen peroxide with a view to develop green methodologies.[99, 100] Oxidation of alcohols to ketones with molecular oxygen in the presence of cobalt-,[101] palladium-(Ref. 102) and ruthenium-based catalysts [103] and cobalt complexes with 2-methylpropanal [104] as the sacrificial aldehyde has been reported in the literature. However, most of the existing methods are associated with one or more drawbacks such as use of expensive and toxic metals like ruthenium and palladium, oxidation of only activated alcohols such as benzylic and allylic alcohols, the need for auxiliary reagents and drastic reaction condition like high pressure. Although solid OATB have found wide applications in organic synthesis as substitute for molecular bromine, their use as catalysts for the oxidation with hydrogen peroxide has not been reported. For the first time we discovered the potential of MPHT as an oxidation catalyst in conjunction with H_2O_2 for the oxidation of alcohols to carbonyl compounds.[105] With the developed protocol, a variety of secondary alcohols, 1,2-diols and primary alcohols could selectively be oxidized in excellent yields to the corresponding ketones, 1,2-diketones and aldehydes with aqueous 30% hydrogen peroxide in refluxing acetonitrile in the presence of catalytic amounts of MPHT. The selective oxidation of primary alcohols to aldehydes is also an important and desirable synthetic transformation as susceptibility of aldehydes for further oxidation to carboxylic acids narrows the choice of the reagent.

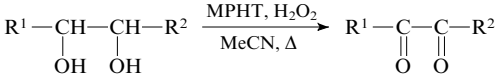
The oxidation of various primary alcohols was studied with aqueous 30% H_2O_2 in the presence of catalytic amounts of MPHT and stoichiometric amount of MPHT without H_2O_2 as the oxidation systems. While benzylic alcohols yielded the corresponding acids in refluxing acetonitrile using the former system, aliphatic primary alcohols were selectively converted to the corresponding aldehydes under these reaction conditions. When oxidation of benzylic alcohols was carried out with stoichiometric amounts of MPHT (in the absence of H_2O_2), it yielded the corresponding aldehydes selectively.



R = H, Me, OMe, Cl.



R^2 = Ph: R^1 = Me, Ph; R^1 = Et, R^2 = Bu^n;
$R^1-R^2 = (CH_2)_5$.



R^1 = R^2 = Ph, 4-$MeOC_6H_4$; R^1 = 4-$MeOC_6H_4$, R^2 = Ph.

Among the various benzylic alcohols studied, unsubstituted benzyl alcohol was found to be most prone to oxidation and those substituted with electron-donating groups were found to be more reactive than those bearing electron-withdrawing substituents.

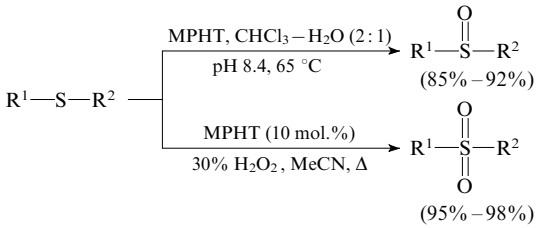
The effect of various solvents on the oxidation of alcohols was evaluated by an example of benzhydrol, its oxidation with hydrogen peroxide was carried out in different solvents under reflux using catalytic amounts of MPHT. Among the various solvents studied such as acetonitrile, 1,2-dichloroethane, THF and chloroform, acetonitrile was found to be the solvent of choice.

The exact mechanism of this reaction is not clear at this stage; the reaction probably proceeds *via* an intermediate [36] that is formed upon reaction of the alcoholic OH group with the tribromide ion. Subsequent abstraction of the hydrogen atom results in the corresponding carbonyl compound with elimination of HBr.

b. Oxidation of sulfides to sulfoxides and sulfones

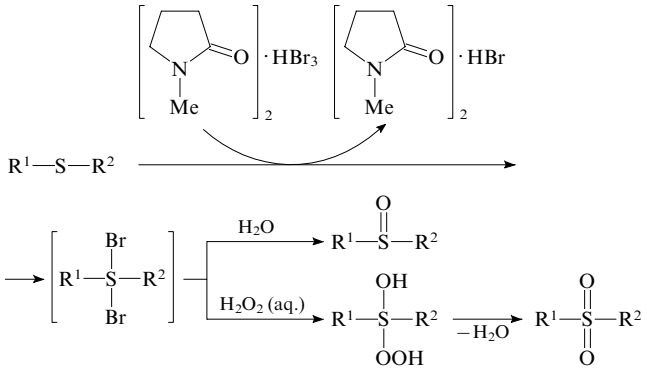
Oxidation of sulfides to sulfoxides and sulfones is an important reaction as these compounds are extensively being used in various areas of synthetic organic chemistry.[106, 107] For the oxidation of sulfides to sulfoxides and sulfones, a variety of reagents and methods have been explored.[108, 109] In a view of developing environmentally clean methodologies, diverse transition metal-based catalysts were proposed.[110–112] However, the inherent drawbacks are their expensive nature, toxicity and difficult synthesis of metal complexes. In this context, several metal-free methods for the oxidation of sulfides have been developed.[113, 114] Recently, the highly efficient aerobic oxidation of a wide range of sulfides utilizing a 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)/$NaNO_2$ and HBr/Bu^tONO catalytic system has been reported.[115] Despite their potential advantages such as low price, easy handling, commercial availability and relatively high stability, the formation of by-products such as sulfonic and sulfinic acids makes these methods of limited utility.

We studied for the first time the utility of MPHT as a selective oxidant of sulfides.[116] During this course with MPHT, the reactions were carried out in a 2:1 chloroform–water (pH 8.4) mixture at 65 °C. A variety of sulfides were selectively and efficiently oxidized to the corresponding sulfoxides in excellent yields without any evidence for the formation of sulfones or other by-products. Among the various substrates studied, dialkyl sulfides were found to be the most reactive, probably due to the electron-donating character of the alkyl groups. Similarly, alkyl aryl sulfides were found to be more reactive as compared to diaryl sulfides. In the oxidation of sulfides with aqueous 30% hydrogen peroxide in the presence of catalytic amounts of MPHT, the corresponding sulfones could be obtained as the only reaction products.



R^1 = R^2 = Ph, Pr^n, Pr^i, Bu^n; R^1 = Ph: R^2 = Me, Bn.

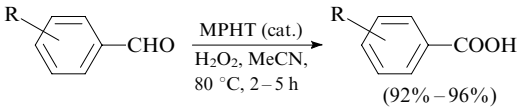
The effect of various parameters like temperature, solvent, amount of catalyst was also evaluated for the reaction. We assumed that an intermediate initially formed by the reaction of the sulfide with bromine released *in situ* from MPHT. In the next step, the intermediate would be converted either to sulfoxide or sulfone.



c. Oxidation of aldehydes

Subsequently, we have developed a simple methodology for the oxidation of aldehydes using MPHT as a catalyst. The oxidation of aldehydes to carboxylic acids is an important synthetic transformation and a variety of conventional oxidants notably Mn- and Cr-based are reported.[117, 118] These metal-containing reagents are used in stoichiometric quantities, which produce large amounts of inorganic wastes not acceptable from the environmental viewpoint. Environmentally friendly oxidants such as hydrogen peroxide in combination with transition-metal catalysts have been reported.[119, 120] However, the drawbacks of all the aforementioned reagents are the use of strong acidic/basic conditions, use of toxic and heavy metals, high cost, large excess of oxidants and low yields of the desired products. Therefore, some improved catalytic methods including the use of organocatalysts,[121] metal-free protocols [122] and solid-phase reagents [123] have been developed.

In continuation of our work on the development of metal-free synthetic methodologies for the oxidation reactions, we first used MPHT as a catalyst in conjunction with hydrogen peroxide for the oxidation of aromatic aldehydes to carboxylic acids.[124]



R = H, Me, OMe, Cl, NO_2, OH.

The oxidation of aromatic aldehydes to the corresponding acids could successfully be achieved by reacting the substrate (1 mmol) with hydrogen peroxide (2 mmol) in the presence of a catalytic amount of MPHT (10 mol.%) in acetonitrile. A variety of aldehydes were selectively and smoothly converted to the corresponding acids in excellent yields without any evidence for the formation of brominated compounds and other by-products. Other functional groups such as a hydroxyl group and other heteroatoms was found to be inert and aldehydes were selectively converted into acids without affecting these groups.

The effect of reaction parameters such as the catalyst concentration, the effect of the oxidant, temperature and solvent was also studied. In the absence of the oxidant, with MPHT alone, oxidation of benzaldehyde was found to be slow and gave intricate mixture of products. However, very high concentration of MPHT also adversely affected the reaction and gave the bromination products predominantly. Among various solvents studied, acetonitrile was found to be the solvent of choice for this transformation. Also, the introduction of hydrogen peroxide in one portion gave poor yield of the desired product while its dropwise addition gave maximum yield of the product in shorter reaction time.

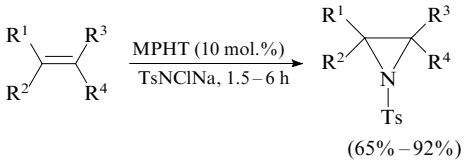
The plausible mechanism of this reaction may involve the formation of hypobromous acid by the reaction of hydrogen peroxide with MPHT, which then reacts with the aldehyde to afford an intermediate, which eliminates HBr to yield the corresponding acid.

6. Aziridination of alkenes using MPHT as a catalyst

Aziridines are attractive compounds exhibiting interesting properties due to the increased strain and unique reactivity of the three-membered ring. They are also used as electrophiles and as chiral auxiliaries/ligands in asymmetric synthesis and are present as substructures in various pharmaceuticals and natural products in which they exhibit potent and diverse biological activities,[125–127] including amino acids, β-lactams, antibiotics and alkaloids.[128] The formation of aziridines as a result of addition of thermally or photochemically generated nitrenes to alkenes is a well-known reaction, however it is characterized by low yields and competing hydrogen abstraction and insertion reactions.[129–131] Alkene-based aziridinations are of practical importance because the starting materials are readily available and inexpensive.

Catalytic aziridination of alkenes had drawn little attention before 1991 when a copper-catalyzed system for this transformation was reported.[132] Since then, various transition-metal complexes, *viz*., those containing rhodium,[133,134] copper,[135–137] ruthenium,[138,139] cobalt,[140] iron,[141] manganese,[142] nickel,[143] silver[144] and gold[145] as well as few non-metallic compounds[146–148] have been shown to catalyze this transformation. *N*-Tosyliminophenyliodinane (PhI=NTs)[149] is studied in detail as an efficient nitrene precursor, but its explosive nature, unstability, and commercial unavailability limit its wider utilization.[150] Other convenient nitrene sources like chloramine-T,[151–155] bromamine-T,[156] azides,[157,158] cyanoimido complexes,[159] and sulfonamides[160,161] have been explored for this transformation. At present, metal-free catalytic methodologies are gaining particular attention from synthetic as well as environmental viewpoints. In this context, metal-free protocols that make use of phenyltrimethylammonium tribromide,[162] pyridine hydrobromide perbromide($PyHBr_3$),[163] *N*-bromamides[164,165] have also been developed. However, inherent to these methods drawbacks include the formation of allylic amination products from reactive substrates such as cyclohexene and the use of toxic and volatile organic solvents.

We studied the use of MPHT, a non-metal catalyst for aziridination of alkenes with chloramine-T as a nitrene donor.[166]

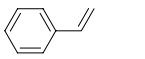
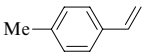
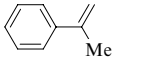


$R^1 = R^2 = R^3 = H$: R^4 = Ph, 4-MeC_6H_4, 4-ClC_6H_4; $R^1 = R^2 = H$, R^3 = Me: R^4 = Ph, CO_2Me; $R^1 = R^4 = H$, R^2 = Ph, $R^3 = CO_2Me$; $R^2 = R^4 = H$: $R^1 - R^3 = (CH_2)_4$, $(CH_2)_6$.

A variety of alkenes were selectively converted to the corresponding aziridines in very good yields using this procedure under solvent-free conditions. Among the alkenes studied, α-methyl styrene and its derivatives substituted with electron-donating groups in the benzene ring were found to be the most reactive, while methyl *trans*-cinnamate was found to be the least reactive.

Water and an ionic liquid were also tested as the reaction media for the aziridination of 4-methylstyrene. The reactions in water were very slow and yielded complex

Table 2. Comparison of efficiencies of catalytic systems in aziridination of alkenes.

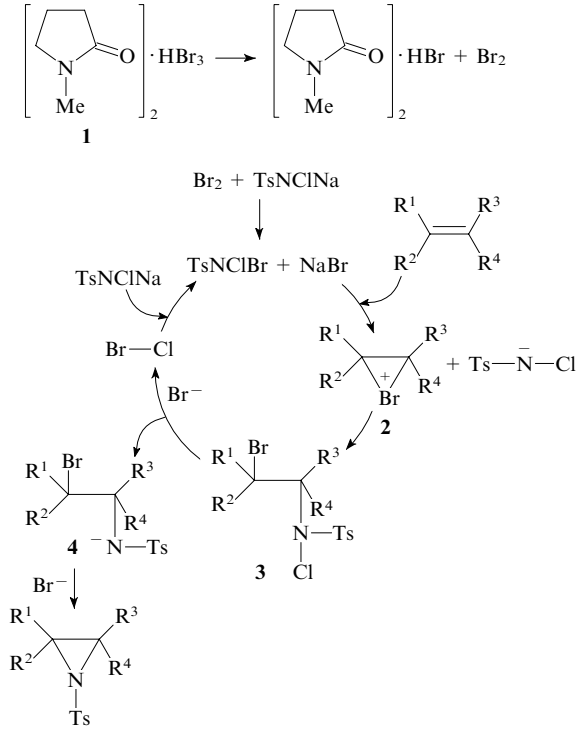
Substrate	MPHT (Ref. 166)[a]		$[PyH]Br_3$ (Ref. 163)[b]		H_2O_2–HBr (Ref. 167)[c]	
	time /h	yield (%)	time /h	yield (%)	time /h	yield (%)
	2.5	85	4	60	5.0	75
	2.0	90	–	–	3.5	86
	3.5	75	12	70	5.0	75
	1.5	92	–	–	2.5	92
	4.0	65	–	–	5.0	67
	–	–	6	65	–	–

Reaction conditions: [a] alkene (3 mmol), chloramine-T (1.1 mmol), MPHT(10 mol.%), 20 °C; [b] alkene (5 mmol), chloramine-T (1.1 mmol), $[PyH]Br_3$(10 mol.%), MeCN, 25 °C; [c] alkene (1 mmol), chloramine-T (1.2 mmol), 30% aqueous H_2O_2 (20 mol.%), 48% HBr (20 mol.%), MeCN, 25 °C.

mixtures of the products along with a small amount of aziridine, whereas in the case of an ionic liquid the reaction proceeded more efficiently and afforded higher product yield. The use of MPHT was found to be superior in terms of selectivity and yield of aziridines in comparison to the recently reported efficient catalytic systems such as pyridine hydrobromide perbromide ($PyHBr_3$) and H_2O_2/HBr (Table 2).

The exact mechanism of the reaction remains obscure. The reaction is probably initiated by generation of a reactive species from MPHT. This attacks the alkene to afford bromonium intermediate **2**, which undergoes ring opening by $Ts(Cl)N^-$ to give β-bromo-*N*-chloro-*p*-toluenesulfonamide **3**. The attack of the Br^- ion on the N—Cl group of the presumed intermediate **3** results in the anion **4**, which on cyclization yields the corresponding aziridine while the regenerated Br^- ion again reacts with chloramine-T to initiate another catalytic cycle (Scheme 2).

Scheme 2

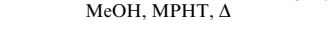


7. Chemoselective protection of nucleophilic functional groups

Chemoselective protection of functional groups such as OH, SH and NH_2 is an important and unavoidable step of organic synthesis, particularly in the preparation of multifunctional target molecules. Importantly, acetylation with acetic anhydride is the most fascinating and preferable approach due to its easy introduction, stability under mild acidic, basic conditions and easy deprotection. Various conventional methods for acetylation of alcohols, phenols, thiols and amines with acetic anhydride in the presence of bases such as triethylamine, DMAP [168] and tributylphosphine [169] (some of them are toxic, flammable and have unpleasant odour) have been reported; the catalytic methods make use of, *e.g.*, gadolinium triflate,[170] magnesium perchlorate,[171] Nafion,[172] zeolites,[173] iodine [174] and heterogeneous catalysts.[175] Development of metal-free catalytic methodologies is an area of current interest and importantly, these methods are particularly useful for the synthesis of the compounds that are sensitive to metal contamination such as pharmaceuticals.

Functional group manipulations using molecular bromine are one of the most common transformations in synthetic organic chemistry. Since bromine itself is hazardous compound, the replacement of bromine with its solid analogues has gained particular attention in recent years. In this context, an efficient methodology [176] for the acetylation of various functional groups with acetic anhydride using bromodimethylsulfonium bromide as a catalyst under solvent-free conditions can be mentioned. However, volatility and toxic nature of dimethyl sulfide is the major limitation.

The safe handling and high stability of MPHT inspired us to develop a new methodology for the protection of nucleophilic substrates by acetylation (as well as their regeneration to the parent compounds) using MPHT as a catalyst. Alcohols, thiols, phenols and amines were chemoselectively converted to the corresponding esters, thioesters and amides with acetic anhydride at room temperature under solvent-free conditions. Removal of the acetyl protecting group could successfully be effected by refluxing the acetate in methanol in the presence of catalytic amounts of MPHT. Studies of the effects of various parameters such as solvent, temperature, catalyst concentration and mechanistic studies are currently being carried out in our laboratory.



R = Alk, Ar, Bn, *etc.*; X = O, S, NH.

8. Regioselective ring opening of epoxides

Ring opening of epoxides with nucleophilic reagents is an important synthetic transformation as it offers a simple and straightforward regio- and stereoselective approach to the synthesis of several 1,2-difunctionalized products.[177, 178] β-Alkoxy alcohols, 1,2-diacetates, *vic*-diols and β-amino alcohols are important precursors, possess valuable synthetic utilities and find extensive applications in the preparation of pharmaceuticals as well as bioactive molecules.[179–182] The most common approach to the synthesis of these compounds involves the ring opening of epoxides with an appropriate nucleophile under strongly acidic or basic conditions.[183, 184] However, some of these processes possess drawbacks from synthetic and environmental viewpoints. Thus an excess of mineral acid such as H_2SO_4 or stoichiometric amounts of Lewis acid are to be used, undesirable side products are formed mainly due to di- or polymerization of epoxides, the product yields are low and the reactions are time-consuming. Several improved catalytic methodologies mainly using transition metal-based catalysts under homogeneous or heterogeneous conditions have been developed for this transformation to circumvent the drawbacks mentioned.[185] Although these methods generally lead to high yields with good regioselectivity, the use of toxic or expensive transition metals and formation of side products restrict their widespread applicability.[186]

In our studies on MPHT, we developed a simple and efficient solvent-free methodology for the regioselective ring opening of epoxides with alcohols, water, amines and acetic anhydride to afford the corresponding β-alkoxy alcohols, 1,2-diols, β-amino alcohols and 1,2-diacetates in the pres-

ence of catalytic amounts of *N*-methylpyrrolidine-2-one hydrotribromide at ambient temperature.

With equimolar amounts of MPHT (substrate : reagent = 1 : 1.2), epoxides smoothly underwent regioselective ring opening in acetonitrile (the solvent of choice) and afforded β-bromohydrins.

In both versions of the reaction, ring opening of 2-aryl-epoxides, for example, styrene oxide, occurred with the preferential attack at the benzylic position, probably due to formation of an intermediate stabilized benzylic cation. At the same time, in the case of 2-alkylepoxides ring opening products were formed as a result of cleavage at the terminal position with the preferential attack of a nucleophile from the less hindered side. Cycloalkene oxides such as cyclohexene oxide and cyclopentene oxide, efficiently reacted with MPHT and yielded the corresponding 2-bromocyclohexanol and 2-bromocyclopentanol, respectively, in high yields. Among the various solvents studied, acetonitrile was found to be the solvent of choice.

Alkylamines in general were found to be less reactive than anilines in terms of the reaction times and yields of the cleaved product.

Other studies, such as ring opening of aziridines and compatibility of the functional groups under the reaction conditions and its mechanism, are in progress.

IV. Conclusion

In the present article, we have demonstrated that *N*-methylpyrrolidin-2-one hydrotribromide is a versatile reagent, which can also be used as an efficient catalyst for a variety of reactions other than bromination and can be considered to be a safer alternative of hazardous molecular bromine in organic synthesis. Depending on the reaction conditions, MPHT can also act as a source of positively charged brominating species, dry HBr and molecular bromine. The unique features of MPHT are its ease of synthesis, high stability at room temperature and compatibility towards a number of functional groups. Varying the reaction condition, one can obtain different products from the same precursor. For example, sulfides can selectively be oxidized to either sulfoxides or sulfones. Keeping in view the reactivity, stability and versatility of MPHT, we believe that it will be emerged as a highly useful reagent in organic synthesis.

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