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A New Recyclable Ditribromide Reagent for Efficient Bromination under Solvent Free Condition

Veerababurao Kavala, Sarala Naik, and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India

patel@iitg.ernet.in

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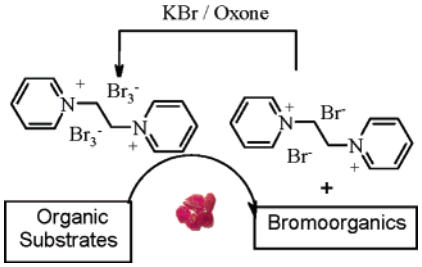

1,2-Dipyridiniumditribromide−ethane (DPTBE) has been synthesized and explored as a new efficient brominating agent. The crystalline ditribromide reagent is stable for months and acts as a safe source of bromine requiring just 0.5 equiv for complete bromination. It has high active bromine content per molecule and shows a remarkable reactivity compared to other tribromide reagents toward various substrates by just grinding the reagent and substrates in a porcelain mortar at room temperature. No organic solvent has been used during any stage of the reaction for substrates giving product as solid. Product can easily be isolated by just washing the highly water soluble 1,2-dipyridiniumdibromide−ethane (DPDBE) from the brominated product. The spent reagent can be recovered, regenerated, and reused without any significant loss.

Introduction

Bromination of aromatic substrates has received significant interest in recent years[1] owing to the increasing commercial importance of bromoorganics in the synthesis of a large number of natural products as well as in the manufacture of pharmaceuticals, intermediates for agrochemicals, and other specialty chemicals. Numerous industrially valuable products such as pesticides, insectides, herbicides, fire retardants, and other new materials carry bromo functionality.[2] These halides also undergo carbon−carbon bond formation via cross-coupling reactions such as Stille−Suzuki,[3] Heck,[4] and Sonogashira[5] or carbon−heteroatom bond formation via aromatic functionalization protocols.[6]

Traditional methods of bromination involve the direct or indirect use of elemental bromine under harsh reaction conditions.[7] To achieve higher efficiency and selectivity, the conventional reagent bromine has been employed with a variety of new techniques including phase vanishing methodology and fluorous solvent.[8] However, handling of bromine is cumbersome due to its hazardous nature, thus special care is required for its storage and transport. Moreover, bromination of aromatic substrates with elemental bromine involving an electrophilic aromatic substitution reaction with the formation of HBr as a byproduct effectively reduces the atom efficiency to 50%. The generated HBr waste must be neutralized before it can be discharged as an effluent. To overcome

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these problems some environmentally safer procedures has been envisioned to involve the in situ preparation of positive bromonium species by oxidation of bromide ion with suitable oxidants under various homogeneous and heterogeneous reaction conditions.[9]

Results and Discussion

Bromine free bromination with stable crystalline organic ammonium tribromide like tetrabutyl,[10] tetramethyl,[11b] cetyl,[9g] benzyltrimethyl,[9g,12] pentylpyridinium,[13] pyridinium,[14] and DBU[15] has gained considerable interest. Tribromides are more suitable than the liquid bromine because of their crystalline nature, hence easy for their storage, transport, and maintenance of desired stoichiometry. Preparations of these reagents involve organic ammonium bromide and molecular bromine in most cases, thus an indirect use of toxic molecular bromine. Recently, organic ammonium tribromide has been prepared in an environmentally benign way by the reaction of V_2O_5, aqueous H_2O_2, and KBr.[9g] However, this method generates some heavy metal as toxic waste.[9g] Other problems associated with these reagents are the use of expensive organic ammonium cations and the use of 1/3 of its total bromine for an aromatic electrophilic substitution type reaction and 2/3 of its bromine toward addition to C−C multiple bonds. Some of the organic ammonium tribromides have phase transfer properties, hence a substantial amount gets extracted along with the organic products in an organic solvent during workup, thereby making the purification tedious and the method expensive for large-scale reaction. Recovery and recycling of expensive organic ammonium cations is also poor after the reaction. Pyridinium tribromide or pyridinium hydrobromide perbromide is not so stable compared to other organic ammonium tribromides and is reported to have three different bromine compositions with different melting points.[14d] To overcome the problems of phase transfer properties, poor stability, regio- and stereoselectivity, recovery, and recycling of the spent reagent, we have synthesized a novel ditribromide reagent. The new reagent has higher bromine content per molecule, better bromination efficiency and selectivity and is devoid of phase transfer property, and the spent reagent can be recovered and regenerated easily. In this paper we wished to report the preparation of a new ditribromide reagent, development of a solvent, metal and ionic-liquid free bromination protocol, and recovery of the reagent.

The reagent was prepared by refluxing pyridine (2 equiv) with 1,2-dibromoethane (1 equiv). The resultant 1,2-dipyridiniumdibromide−ethane (DPDBE) solid was treated with KBr (4.5 equiv) followed by oxidation of bromide to bromine, using an aqueous solution of Oxone (1 equiv). The standard electrode potential ($E°$) of Oxone being −1.44 V is high enough for the oxidation of bromide to bromine. Oxone has been utilized for the oxidative bromination of aromatic compounds with NH_4Br.[9k] The orange precipitate of 1,2-dipyridiniumditribromide−ethane (DPTBE) was filtered (88% yield) and was recrystallized in acetonitrile to obtain large crystals as shown in Figure 1. The compound has been characterized by spectral and analytical data. This crystalline compound (Figure 1) is stable for several months at room temperature without loss of its activity.

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FIGURE 1. Crystals of 1,2-dipyridiniumditribromide−ethane (DPTBE).

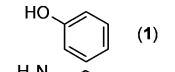
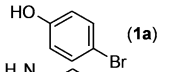
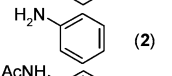
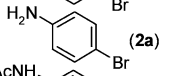
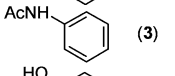
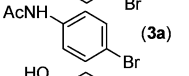
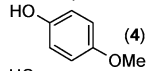
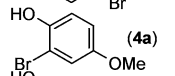
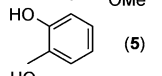
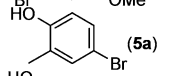
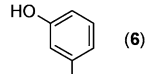
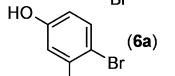
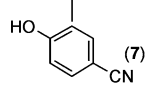
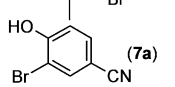
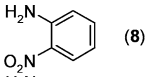
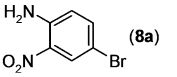
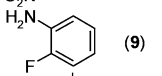
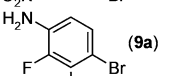
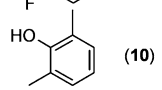
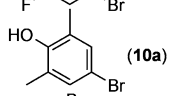
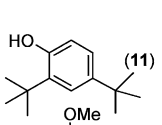
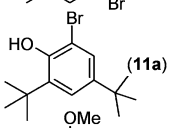
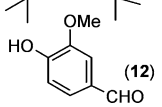
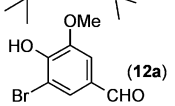
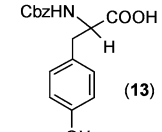
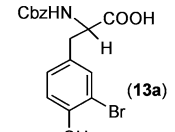
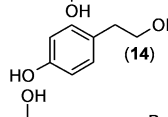
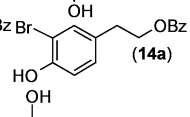
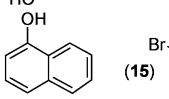
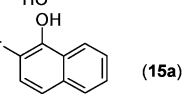
This new reagent, 1,2-dipyridiniumditribromide−ethane (DPTBE) is soluble in polar aprotic solvents (acetonitrile, DMSO, DMF, etc.), sparingly soluble in polar protic solvents (methanol, ethanol, acetic acid, etc.), but insoluble in nonpolar aprotic solvents (dichloromethane, chloroform, ethyl acetate, toluene, etc.). On the other hand, its precursor 1,2-dipyridiniumdibromide−ethane (DPDBE) is insoluble in most organic solvents but is highly soluble in water, indicating the absence of phase transfer property, thus facilitating efficient recovery of 1,2-dipyridiniumdibromide−ethane (DPDBE) and the separation of brominated products. This property attests the superiority of this reagent, which other known organic ammonium tribromides lack. It may be noted that bromination of organic compounds is usually effected by using equimolar ratios of bromine or tribromide with the substrate. To test the bromination efficiency of this new reagent, 2.5 equiv of the reagent 1,2-dipyridiniumditribromide−ethane (DPTBE) was added to 5 equiv of acetanilide **3** in acetonitrile (25 mL). The reaction was completed within 0.5 h precipitating out the colorless DPDBE in nearly quantitative amounts leaving the solution of *p*-bromoacetanilide **3a** in acetonitrile. DPDBE was filtered and recovered; *p*-bromoacetanilide **3a** was obtained in 95% yield on concentrating the acetonitrile. Thus, 1,2-dipyridiniumdibromide−ethane (DPDBE) efficiently delivers the bromine to the reaction medium and itself gets recovered quantitatively, thereby acting as the perfect bromine carrier. This procedure worked successfully for a number of substrates. Even though acetonitrile is a green solvent we wanted to develop a methodology devoid of any organic solvent not only because reaction rates are accelerated under solvent free conditions but also from the green chemistry point of view. To compare the efficacy of the reagent under solvent free conditions, acetanilide **3** (5 mmol) and 1,2-dipyridiniumditribromide−ethane (DPTBE) (2.5 mmol) were ground in a mortar and pestle at room temperature. The reaction was complete in less than 0.5 h as indicated by GC. Water (10 mL) was added to the reaction paste, the suspended *p*-bromoacetanilide **3a** was filtered, and the residue was washed with water (4 × 5 mL) giving a 95% yield of the product.

When this solvent free methodology was applied to phenol **1** and aniline **2** both gave regioselectively *p*-bromophenol **1a** and *p*-bromoaniline **2a**, respectively, which is otherwise difficult to achieve with other reagents. Regioselective bromination of phenol and aniline is an important protocol in organic synthesis because of their versatile synthetic intermediates for a considerable number of useful transformations. In an aromatic electrophilic substitution reaction para-orientation is favored over ortho-orientation due to stereoelectronic effects. Exclusive regioselective bromination of phenol (**1**) and aniline (**2**) has been achieved with supported reagents,[8c,i] in solid-phase reaction,[13a] under controlled in situ generation of electrophilic bromonium ion,[9f,r,10a] or by using special reagents and conditions.[8d,9x] The reagent DPTBE is an excellent bromine carrier and releases bromine only in contact with the substrate. Moreover, due to use of the reagent in a stoichiometric amount (0.5 equiv), no polybromination occurred with DPTBE. It may be noted here that some acidic fumes evolved during reaction with aromatic phenols and amines, which can, however, be suppressed by addition of 2 equiv of $NaHCO_3$. Regioselectivity remained unaltered even in the presence of $NaHCO_3$.

One of the salient features of this methodology is the exclusive regioselective bromination for the majority of the substrates (Table 1). Acetanilide **3** gave exclusively its para-derivative **3a**. When two *o*,*p*-directing groups are present in an aromatic ring, substituents having higher *o*,*p*-directing power influence the incoming bromo group to its para position and if the para position is blocked then to its ortho position as shown for substrates **4**−**6**. As expected in the presence of both a meta substituent and *o*,*p*-directing substituents in the same aromatic ring, the *o*,*p*-directing group controls the incoming bromo group to its para-position and if the para-position is blocked the bromination takes place in the ortho of the *o*,*p*-directing group as demonstrated for *p*-hydroxybenzonitrile **7**. However, using molecular bromine, a mixture of ortho and para products are obtained for *o*-cresol **5** and *m*-cresol **6**.[9q] Regioselective bromination has been demonstrated with substrates **7**−**12** bearing various combinations of functional groups. Phenolic substrates bearing benzyloxy carbonyl **13** and benzoyl group **14** survived under the described conditions giving corresponding *o*-bromo products **13a** and **14a**, respectively. The fused ring phenolic compound α-naphthol **15** afforded the expected 2-bromo-α-naphthol **15a**.

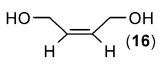
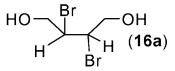
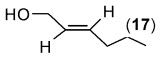
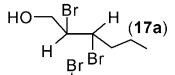
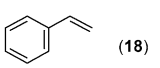
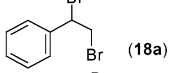
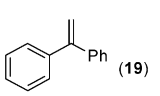
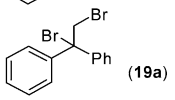
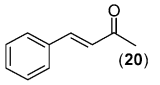
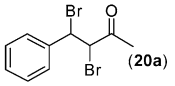
The versatility of the methodology also lies in the fact that apart from aromatic electrophilic bromination of aromatic amines and phenols in Table 1, this reagent also brominated several other functionalities such as ethylenic, acetylinic, and carbonyl functions efficiently (Table 2). For example, but-2-ene-1,4-diol **16**, hex-2-ene-1-ol **17**, vinyl benzene **18**, and 1,1-diphenylethene **19** containing ethylenic functionality were all brominated to corresponding *trans*-dibromo compounds with just 0.5 equiv of the reagent by simply grinding the substrate and the reagent in a mortar. The efficacy of the methodology was demonstrated by carrying out bromination of α,*β*-unsaturated ketones such as 4-phenylbut-3-en-2-one **20** and 1,3-diphenylpropenone **21**. Both substrates gave exclusively corresponding *erythro*-dibromo products **20a** and **21a**, respectively. Cinnamaldehyde diacylate **22** gave corresponding *erythro*-dibromo product in excellent yield without affecting the acylal functionality under the described conditions. It is also possible to achieve perfect chemoselective bromination of one double bond in a substrate containing two symmetrical double bonds as demonstrated for dibenzylidine acetone **23** with 0.5 equiv

TABLE 1. Bromination[a] of Organic Substrates with DPTBE under Solvent Free Condition

substrate	product	time (min)	yield[b]
 (**1**)	 (**1a**)	30	85
 (**2**)	 (**2a**)	30	85
 (**3**)	 (**3a**)	30	95
 (**4**)	 (**4a**)	30	92
 (**5**)	 (**5a**)	30	93
 (**6**)	 (**6a**)	30	92
 (**7**)	 (**7a**)	30	93
 (**8**)	 (**8a**)	30	96
 (**9**)	 (**9a**)	30	92
 (**10**)	 (**10a**)	30	95
 (**11**)	 (**11a**)	30	95
 (**12**)	 (**12a**)	30	94
 (**13**)	 (**13a**)	30	93
 (**14**)	 (**14a**)	30	94
 (**15**)	 (**15a**)	30	95

[a] Reactions were monitored by TLC. [b] Isolated yields.

TABLE 2. Bromination[a] of Organic Substrates with DPTBE under Solvent Free Condition

substrate	product	time (min)	yield[b]
 (**16**)	 (**16a**)	25	91
 (**17**)	 (**17a**)	30	88
 (**18**)	 (**18a**)	30	93
 (**19**)	 (**19a**)	25	87
 (**20**)	 (**20a**)	25	95
(**21**)	(**21a**)	30	92
(**22**)	(**22a**)	25	96
(**23**)	(**23a**)	20	87
(**24**)	(**24a**)	25	89
(**25**)	(**25a**)	35	84
(**26**)	(**26a**)	60	80
(**27**)	(**27a**)	60	85

[a] Reactions were monitored by TLC. [b] Isolated yields.

TABLE 3. Regioselectivity of Phenol, Aniline, *o*-Cresol, and *m*-Cresol with Different Tribromides

reagent/ condition	% of *p*-product (isolated yields/GC yields)			
	phenol (**1**)	aniline (**2**)	*o*-cresol (**5**)	*m*-cresol (**6**)
DPTBE/CH_3CN	84/88	84/89	93/96	91/95
DPTBE/solid	85/89	85/90	93/96	92/96
TEATB/solid	80/86	80/89	90/95	89/95
BTMATB/solid	80/87	80/87	90/96	88/96
CTMATB/solid	75/85	75/88	76/93	78/93
TBATB/solid	72/87	72/87	78/94	76/94

of the reagent. Substrates **24** and **25** containing acetylinic functionality could also be efficiently brominated with this reagent in excellent yields. However, terminal acetylinic substrate **25** gave a mixture of trans and cis product in the ratio 80:20 as obtained from the GC mass analysis. Finally, successful α-bromination of ketones such as cyclohexanone **26** and acetophenone **27** has been demonstrated with this reagent.

The superiority of this reagent and the methodology with respect to other organic ammonium tribromides has been shown by a highly efficient and regioselective bromination of phenol **1**, aniline **2**, *o*-cresol **5**, and *m*-cresol **6**. The results are summarized in the Table 3. As can be seen from Table 3, similar reactivity and regioselectivity was found for DPTBE both in solution (CH_3CN) and in the solid phase. Considering green chemistry aspects, the solid phase method is superior as no organic solvent is used in the first stage of the reaction and due to high water solubility of DPDBE only a small amount of organic solvent is required for product extraction. It may be noted here that for substrates giving solid products no organic solvent is used at any stage of the reaction. Other organic ammonium tribromides such as tetraethyl (TEATB), benzyltrimethyl (BTMATB), cetyltrimethyl (CTMATB), and tetrabutylammonium (TBATB) are equally effective as far as the chemical conversion is concerned, as monitored by GC. However, excess water washings are required during workup for reactions involving TEATB, BTMATB, CTMATB, and TBATB due to their phase transfer property, thereby reducing the

overall isolated yields. Sometime even after repeated washings, the product is invariably contaminated with organic ammonium cations, particularly for CTMATB and TBATB, requiring further chromatographic purification for all liquid products thereby loss of products as well as ammonium cations. On the other hand, due to high water solubility of DPDBE the product obtained with DPTBE is completely free from any contamination of cations, which can be recovered and regenerated efficiently without any significant loss. The active bromine content per molecule of DPTBE is 48%, which is higher compared to that of some of the other known tribromides, TEATB (43%), BTMATB (41%), CTMATB (30.5%) and TBATB (33%).

The most interesting feature of this reagent is that it can be regenerated. To regenerate the reagent from reaction of the type aromatic electrophilic substitution and α-bromination of ketones where exclusive monobromo products were obtained, 1.25 equiv of bromide (KBr) and 2 equiv of Oxone was added to the aqueous layer containing 1,2-dipyridiniumdibromide−ethane (DPDBE) and 2 equiv of spent bromide. To regenerate the reagent from the aqueous layer obtained from the bromination of ethylenic and acetylinic compounds, where only DPDBE is present, 2 equiv of KBr was added along with 2 equiv of Oxone. The recovered reagent is identical in all respects with the parent DPTBE reagent.

In summary, we have for the first time reported a ditribromide reagent with high active bromine content per molecule, which acts as an excellent bromine carrier capable of brominating 1 equiv of the substrate with just 0.5 equiv of the reagent. The reaction is carried out under a solvent free condition. Selectivities and reactivities were shown to be far superior to any of the reported reagents and methodologies. It has unique features of providing enhanced yields, a reduction in synthesis temperatures, shorter process times, and an environmentally friendly process. The spent reagent DPDBE can be easily recycled hence the process is economically viable for large-scale reaction. In addition to bromination it can be used for several other organic transformations as has been achieved by us with tetrabutylammonium tribromide.[16]

Experimental Section

Preparation of 1,2-Dipyridiniumditribromide−Ethane (DPTBE). Pyridine (9 mL, 100 mmol) and 1,2-dibromoethane (4.3 mL, 50 mmol) were refluxed for 0.5 h. The resultant solid, 1,2-dipyridiniumdibromide−ethane (DPDBE), was washed with ether (2 × 20 mL) and dissolved in water (50 mL). To this was added KBr (267 g, 225 mmol) followed by an aqueous solution of Oxone (122.8 g, 100 mmol dissolved in 80 mL of water) over a period of 10 min. The orange precipitate was filtered, dried in a vacuum desiccator, and recrystallized from acetonitrile to yield 58.6 g (88% yield) of 1,2-dipyridiniumditribromide−ethane (DPTBE). Mp 136−138 °C. UV (CH_3CN) 267 nm. IR (KBr) 3129, 3083, 3053, 3027, 2966, 2853, 1634, 1491, 1189, 958, 779, 677, 492 cm^{-1}. ^1H NMR (400 MHz, CD_3CN) δ 5.20 (s, 4H), 8.15 (m, 4H), 8.65 (m, 2H), 8.81 (m, 4H). ^{13}C NMR (100 MHz, CD_3CN) δ 59.6, 129.1, 145.1, 147.3. Elemental Anal. Calcd for $C_{12}H_{14}N_2Br_6$: C, 21.6; H, 2.11; N, 4.20; Br, 72.02. Found: C, 20.8; H, 2.18; N, 3.98; Br, 71.06.

General Experimental Procedure: Bromination of Phenol (1) to *p*-Bromophenol (1a). A mixture of phenol (**1**) (440 μL, 5 mmol) and 1,2-dipyridiniumditribromide−ethane (1.66 g, 2.5 mmol) was ground in a mortar by a pestle at room temperature. After disappearance of the starting material (monitored by TLC by taking a small amount of the mixture and dissolving it in ethyl acetate), the reaction mixture was transferred into a separatory funnel, admixed with ethyl acetate (20 mL), and washed with water (5 × 5 mL). Organic layer was dried over anhydrous Na_2SO_4 and filtered and solvent was concentrated in a rotary evaporator. The compound was sufficiently pure but for analytical data it was purified by passing it over a short column of silica gel, using a mixture of hexane and ethyl acetate as the eluent, to yield 740 mg (85%) of *p*-bromophenol (**1a**). This procedure is applicable to all substrates giving products as liquid. Alternatively 10 equiv of $NaHCO_3$ can be mixed in the reaction mixture for aromatic phenols and amines to prevent liberation of acidic fumes.

Bromination of Acetanilide (3) to *p*-Bromoacetanilide (3a). A mixture of acetanilide (**3**) (0.675 g, 5 mmol) and 1,2-dipyridiniumditribromide−ethane (1.66 g, 2.5 mmol) was ground in a mortar by a pestle at room temperature. After disappearance of the starting material (monitored by TLC by taking a small amount of the mixture and dissolving it in ethyl acetate), the reaction mixture was transferred into a G_3 sintered funnel and washed with water (5 × 5 mL), and the solid was dried to yield 1021 mg (95%) of *p*-bromoacetanilide (**3a**). This procedure is applicable to all substrates giving products as a solid.

Regeneration of 1,2-Dipyridiniumditribromide (from the reaction of aromatic electrophilic substitution and α-bromination of ketones where monobromo products were obtained). The aqueous layer originating from the above reaction containing 1,2-dipyridiniumdibromide−ethane (DPDBE) (1 equiv) and 2 equiv of bromide ion was concentrated to 5 mL and extracted with ethyl acetate (10 mL) to get rid of organic contaminants. To the aqueous layer was added KBr (354 mg, 3 equiv) followed by a pinch of Oxone (1.228 g, 2 equiv) with stirring. The precipitated orange solid was filtered to yield 1.17 g (88%) of 1,2-dipyridiniumditribromide. The recovered reagent is identical in all respect with the parent DPTBE reagent.

In principle aqueous layers of several reactions were combined and kept for several days to allow the water to evaporate and proportionate amounts of KBr and Oxone were added to regenerate the reagent.

Regeneration of 1,2-Dipyridiniumditribromide (from the reaction of addition to C−C multiple bonds). Identical to the above, except 2 equiv of additional KBr was added.

The following bromo compounds have been reported in the literature: **1a**, **2a**, and **3a**[9l] **4a**,[18] **5a** and **6a**,[9q] **7a**,[19] **8a** and **9a**,[9f] **12a** and **15a**,[17] **18a** and **19a**,[14d] **20a**,[4d] **21a**, **25a**, and **27a**,[13a]and **24a** and **26a**.[10a]

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Supporting Information Available: ^1H and ^{13}C NMR spectral data and spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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