



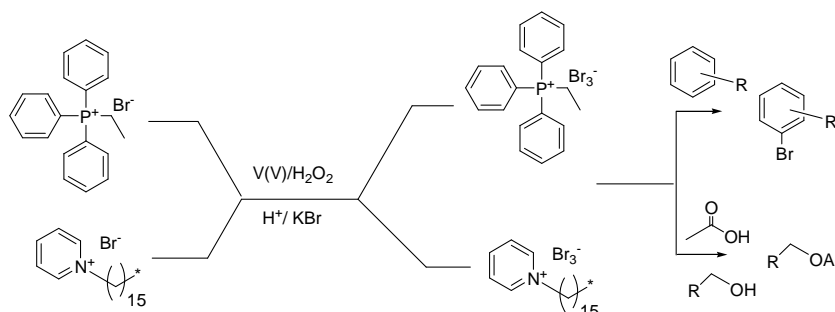
A comparative study of synthesis and reactivity of nitrogen and phosphorus based organic tribromide reagents

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ABSTRACT

Organic tribromides have become an important group of reagents in recent years because of their versatility and long shelf life. However, the reagents that have become most popular are the alkyl quaternary ammonium tribromides. Considering the diverse uses of these reagents and their widespread commercial applications it becomes important to incorporate newer tribromides into the existing series, and then comparatively assess their ease of synthesis and reactivity. In an effort to bring focus on the lesser known phosphorus based and pyridinium based reagents, this paper presents two reagents, viz., ethyltriphenyl phosphonium tribromide (ETPPTB) which is a phosphorus-based reagent and cetylpyridinium tribromide (CetPyTB), which is a pyridinium-based reagent, with focus on their methods of synthesis and their efficiencies in bromination and acylation reactions.



Keywords: tribromide, pyridinium, phosphonium, bromination, acylation.

INTRODUCTION

In current times, organic ammonium tribromides are becoming a small yet important group of reagents for organic transformations.[1-19] Because of their ease of formation, mildness, environmental benignity and immense versatility, these reagents have become quite popular and a number of reports are available discussing the importance of these reagents in various types of organic transformations. Citing a few examples, the reagents have been found to be efficient in bromination reactions,[1-10] acylations,[11-14] sulfide oxidations,[15-16] among others. Considering their versatility, design and development of newer, alternative synthetic protocols for organic ammonium tribromides has assumed a relevance of its own.

Organic phosphonium tribromides are the structural analogs of organic ammonium tribromides, with expectedly similar properties.[20-22] However, while organic ammonium tribromides have become very popular in recent years and a number of reports are available discussing the importance of these reagents in various types of organic transformations, unfortunately the phosphonium tribromides do not seem to have received a similar kind of attention

as yet. Nevertheless, these reagents merit an amount of investigation, especially because they are reported to have milder reactivity than organic ammonium tribromides. [23-25]

This paper reports the results of a comparative analysis which was done on the syntheses of phosphorus based and pyridinium based reagent and their reactivity profiles with respect to bromination and acetylation reactions. The reagents chosen for this study were two recently developed reagents, cetylpyridinium tribromide (CetPyTB) [19] and ethyltriphenyl phosphonium tribromide (ETPPTB) [25].

MATERIALS AND METHODS

All reagents of highest purity were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using Merck silica gel 60 F254 (0.25mm) with detection by UV or iodine. Chromatography was performed using Merck silica gel (60-120) mesh size with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Melting points were recorded on Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Nicolet Impact 410 spectrophotometer and UV/Vis Spectra were recorded in Perkin Elmer Lambda 25 spectrophotometer using acetonitrile as solvent.

Crystal data were collected with a Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoK α radiation ($\lambda=71073\text{\AA}$) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically.

Preparation of the Reagents:

Preparation of Ethyl Triphenyl Phosphonium Tribromide (ETPPTB)

An amount of V₂O₅ (10 mg, 0.1 mmol) was added to 30% H₂O₂ (9mL, 79.74 mmol) and stirred in a precooled beaker at 0–4°C until V₂O₅ completely dissolved and the solution attained a clear reddish brown color. To this content, 110mL of water were added. Then, a solution of ETPPB (5 g, 13 mmol) and potassium bromide (KBr) (3.57 g, 30 mmol) in 100mL of water was added. Later, 40mL of 1M H₂SO₄ was added in small portions, and the mixture was stirred for another 3h. ETPPTB precipitated out as fine yellow microcrystals, which were filtered under suction using Whatman 40 filter paper and dried in a vacuum desiccator using self-indicating coarse silica gel. It was further recrystallized in ethyl acetate : hexane (99:1%). The yield was 92%.

Preparation of Cetyl Pyridinium Tribromide (CetPyTB)

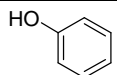
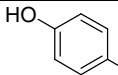
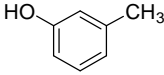
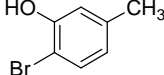
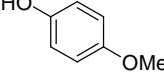
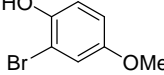
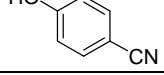
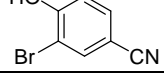
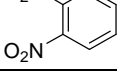
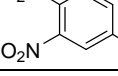
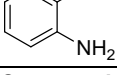
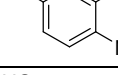
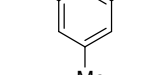
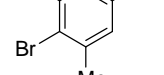
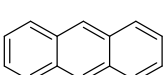
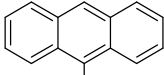
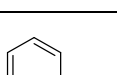
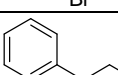
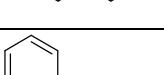
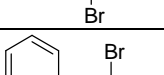
An amount of 0.06 g (0.34 mmol) of vanadium pentoxide (V₂O₅) was added to 5 mL (44.12 mmol) of 30% hydrogen peroxide (H₂O₂) taken in a pre-cooled 250 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V₂O₅ and H₂O₂ is exothermic*). The reaction mixture was stirred at 0–5°C temperature in an ice-water bath till all the V₂O₅ dissolved and the solution became reddish-brown. To it was added a solution of 4.89 g (41.07 mmol) of potassium bromide (KBr) and 5.28 g (13.74 mmol) of cetylpyridinium bromide (CetPyB), dissolved in 35 mL of water. To this, 50 mL of 1M sulphuric acid (H₂SO₄) was added in small portions. Magnetic stirring was continued for a further period of 2h at ice-water temperature. The yellow product thus formed was isolated by suction filtration using Whatman 1 filter paper. (Scheme2) The compound was then dried in a vacuum desiccator using anhydrous calcium chloride (CaCl₂) as desiccant. A deep orange yellow product was obtained on recrystallisation with acetonitrile. The yield of the recrystallised product was 6.60 g (88.3 %).

Bromination Reactions

Brominations using Ethyl Triphenyl Phosphonium Tribromide (ETPPTB)

In a typical reaction, the phenol (**1**, Table 1) (282 mg, 3 mmol) was taken in acetonitrile (3mL) and ETPPTB (1.59 g, 3 mmol), and dissolved acetonitrile (5 mL) was added dropwise with constant stirring at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was worked up to remove the spent reagent. The crude product thus obtained was concentrated and then subjected to column chromatography over a pad of silica gel to get 78% of the product.

Table 1: Bromination reactions using ETPPTB^a

Entry	Substrate	Time (min)	Product ^b	Yield ^c
1.		20		78
2.		15		81
3.		15		84
4.		15		61
5.		35		73
6.		25		76
7.		35		58
8.		15		68
9.		20		76
10.		45		65

^aReactions were monitored by TLC. ^bProducts were characterized by IR, ¹H NMR and ¹³C NMR. ^cIsolated yields are reported.

Brominations using Cetyl Pyridinium Tribromide (CetPyTB)

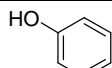
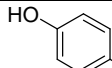
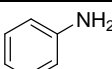
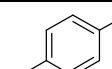
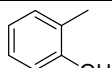
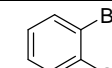
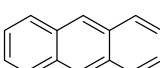
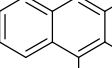

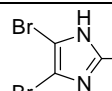
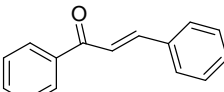
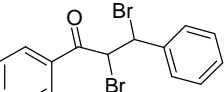
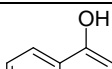
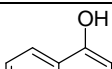
In a typical reaction, 188 mg (2 mmol) of phenol (**1**, Table 2) dissolved in 3 mL acetonitrile was taken in a 50 mL round bottomed flask and 2 mmol of CetPyTB, dissolved in 5 mL acetonitrile was added drop-wise with constant stirring at room temperature. The progress of the reaction was monitored by Thin Layer Chromatography (TLC) on silica gel 60 F₂₅₄ (0.25 mm). After completion of the reaction, the reaction mixture was subjected to column chromatography over a short pad of silica gel to afford the corresponding product in 73% yield. The details of bromination reaction profile have been shown in Table 2.

Acetylation Reactions

Acetylations using Ethyl Triphenyl Phosphonium Tribromide (ETPPTB)

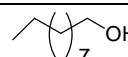
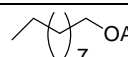
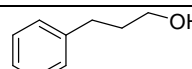
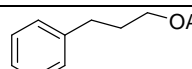
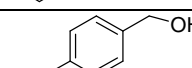
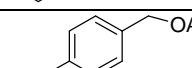
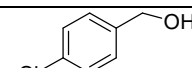
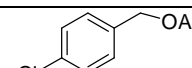
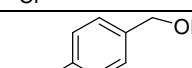
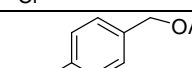
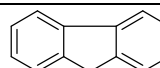
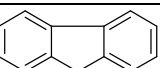
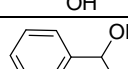
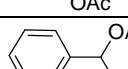
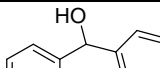
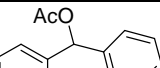
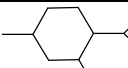
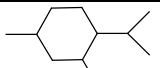
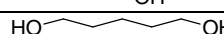
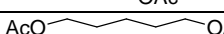
ETPPTB (159 mg, 0.3 mmol) was added to a solution of octadecyl alcohol (**1**, Table 3) (810 mg, 3 mmol) in acetic acid (3mL). The reaction mixture was refluxed, and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into a saturated solution of NaHCO₃ (15 mL) and then extracted with ethyl acetate (2-15mL). The organic layer was separated and dried over anhydrous Na₂SO₃, and the crude product was isolated. Further purification was achieved by passing the compound through a short column of silica gel. The product yield was 82%.

Table 2: Brominations using CetPyTB^a

Entry	Substrate	Time (min)	Product ^b	Yield ^c
1.		25		73
2.		30		72
3.		25		65
4.		15		92
5.		65		63
6.		35		75
7.		30		78

^aReactions were monitored by TLC. ^bProducts were characterized by IR, ¹H NMR and ¹³C NMR. ^cIsolated yields are reported.

Table 3: Acetylations using ETPPTB^a

Entry	Substrate	Time (min)	Product ^b	Yield ^c
1.		15		82
2.		15		78
3.		25		75
4.		15		79
5.		15		80
6.		45		73
7.		45		70
8.		55		67
9.		50		74
10.		10		69

^aReactions were monitored by TLC. ^bProducts were characterized by IR, ¹H NMR and ¹³C NMR. ^cIsolated yields are reported.

Acetylations using Cetyl Pyridinium Tribromide (CetPyTB)

To a solution of 558 mg (3mmol) dodecyl alcohol (**1**, Table 4) in 3mL acetic acid, an amount of 163 mg (0.3mmol) CetPyTB was added. The reaction mixture was refluxed and the progress of the reaction monitored by TLC. After completion of the reaction, the reaction mixture was poured into a saturated solution of NaHCO₃ (15mL) and then extracted with ethyl acetate (2x15mL). The organic layer was separated, dried over anhydrous Na₂SO₃ and the crude product isolated. Further purification was achieved by passing the compound through a short column of silica gel. The product yield was found to be 78%.

Table 4: Acetylations using CetPyTB^a

Entry	Substrate	Time (min)	Product ^b	Yield ^c
1.		15		78
2.		15		73
3.		15		84
4.		40		69
5.		55		65
6.		15		70

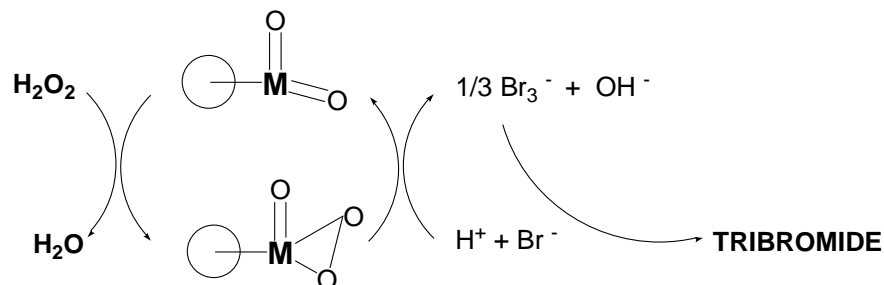
^aReactions were monitored by TLC. ^bProducts were characterized by IR, ¹H NMR and ¹³C NMR. ^cIsolated yields are reported.

RESULTS AND DISCUSSION

Two new reagents, cetylpyridinium tribromide (CetPyTB) and ethyltriphenylphosphonium tribromide (ETPPTB) have been prepared by using a similar strategy of bromide oxidation. Accordingly, the strategy is based on preparing quaternary salts of tribromide wherein, the bulky cationic moiety is either an ammonium (as pyridinium) or phosphonium 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 used as a source of primary bromide.

The bromide oxidation is conducted under mild conditions and the oxidant used is hydrogen peroxide. V(V) has been used as catalyst for activation of hydrogen peroxide, however, other similar higher valent transition metal catalysts which is capable of activating hydrogen peroxide can also be used. An acidic medium is required as promoter for bromide oxidation.

In the reaction, monobromide is converted to tribromide and 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 is KBr in the present case. The reaction does not require the use of organic solvent.

**Figure 1: Mechanism for Tribromide Formation**

Ethyl triphenylphosphine tribromide (ETPPTB), molecular formula C₂₀H₂₀PBr₃, is a deep orange, solid crystalline compound that melts at 135°C. It is soluble in polar aprotic solvents such as acetonitrile and dimethylformamide (DMF) as well as nonpolar aprotic solvents such as chloroform and dichloromethane (DCM) and is sparingly soluble in polar protic solvents such as ethanol and methanol. It is non-hygroscopic, air stable, and has a prolonged

shelf life at room temperature without loss of activity. The crystal structure of the compound reveals a monoclinic structure with space group $P2(1)=n$ and an independent, nearly symmetric, and linear tribromide ion and an independent ethyltriphenylphosphonium ion. The tribromide ion has bond lengths of 2.525\AA ($\text{Br}_1\text{-Br}_2$) and 2.563\AA ($\text{Br}_1\text{-Br}_3$) and a bond angle of 178.43° (Fig. 2).[25]

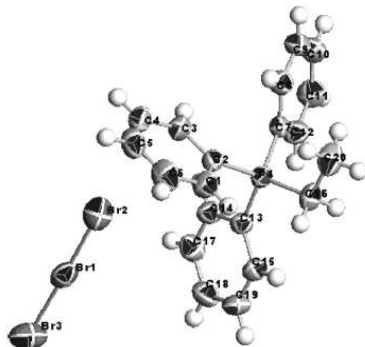


Figure 2: ORTEP view of ETPPTB with atom numbering scheme

Cetylpyridinium tribromide (CetPyTB), having molecular formula $\text{C}_{21}\text{H}_{38}\text{NBr}_3$ is a deep orange yellow solid microcrystalline compound which melts at $60\text{-}62^\circ\text{C}$. The existence of Br_3^- was ascertained using electronic spectroscopy. The reagent shows strong absorption at 279.84 nm ($\epsilon\ 15847$) which is a characteristic of tribromide (Figure 3).

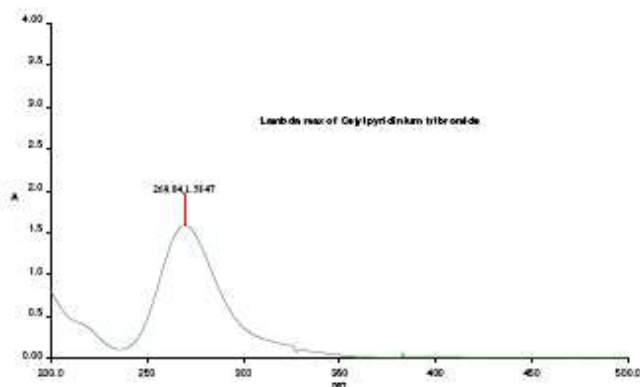


Figure 3: Electronic spectrum of Cetylpyridinium tribromide

The reagent is soluble in water and polar solvents like acetonitrile, methanol and ethanol. The active bromine content per molecule of cetylpyridinium tribromide was found to be 44.01% as per elemental analysis. CetPyTB is hygroscopic in nature and needs to be stored in air sealed containers. When stored in sealed sample vials the reagent has a long shelf life. The stability was ascertained by the determination of bromine contents periodically and re-recording of melting point from time to time.[19]

Bromination chemistry is an important area of research in organic chemistry because of the significance of bromoorganic compounds.[26-28] To study the versatility of the reagents as brominating agents, representative examples of different types of organic substrates were taken (Tables 1 and 2). The products were identified by comparison of their melting points, infrared (IR) absorption, and NMR spectra with the authentic samples. It was observed that bromination reactions were quite facile in both the cases, with ETPPTB having a slight edge over CetPyTB.

In addition to its efficiency as a brominating agent, we wanted to check the efficacy of the new reagent as a producer of in-situ HBr for acetylation reactions, a reactivity which is characteristic of tribromides. Acylations of protic nucleophiles such as alcohols, amines, and thiols are important in synthetic organic chemistry because the resulting esters, amides, and thioesters serve as important functional components and/or intermediates in synthetic chemistry.[29-32] Thus, some acylation reactions were attempted (Tables 3 and 4). The results were encouraging, revealing that both ETPPTB and CetPyTB can act equally well as acylating reagent.

CONCLUSION

As the need to bring in more and more reagents into the realm of newer reagents for organic transformations continues, there is an ongoing effort to design and develop newer reagents. In this context, the two new reagents, viz., ethyltriphenyl phosphonium tribromide (ETPPTB) and cetylpyridinium tribromide (CetPyTB) have been synthesized in high yields by easy, environmentally benign methods. The compounds have proved to be efficient in bromination and acetylation reagents, thus proving that they can be important additions to the existing array of tribromide reagents.

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