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Cetylpyridinium tribromide-An environmentally benign reagent for organic brominations and acetylations

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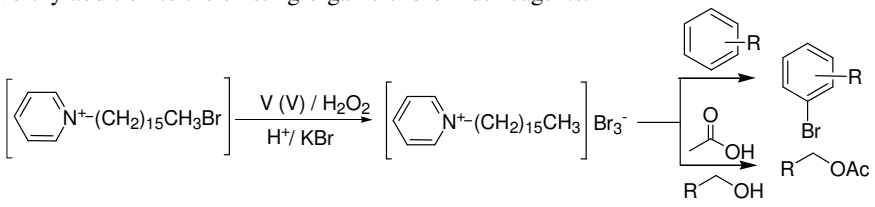
Abstract: Cetylpyridinium tribromide (CetPyTB) has been synthesized by a new environmentally benign protocol and its reactivity studied. Results show that the reagent shows efficiency as a brominating agent for electron-rich aromatic compounds as well as an efficient catalyst for acetylation of the alcohols, thus proving it to be a note-worthy addition to the existing organic tribromide reagents.



Keywords: Tribromides; bromination; acetylation; pyridinium.

1. Introduction

In current times, organic ammonium tribromides are becoming a small yet important group of reagents for organic transformations. 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.[1-19] 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.[1-7,15] As case in point, cetylpyridinium tribromide (CetPyTB) had been earlier reported in the context of aniline bromination.[20,21] However, the procedure reported for the synthesis of the reagent involved the use of elemental bromine which is a very toxic chemical, thus rendering the synthetic protocol of the reagent to be environmentally malevolent.

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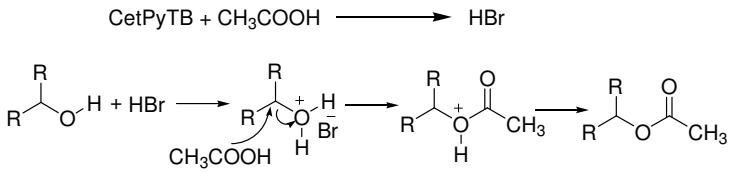
We have been putting our efforts towards the design and development of tribromides.[4,6,15,19] In this context it has been experimentally observed that among the tribromides, synthesis of pyridinium tribromides is relatively more difficult because the tribromide moiety sometimes converts to polybromide of indefinite composition. Realizing the fact that cetylpyridinium tribromide may have potential to be another important organic ammonium tribromide an alternative, environmentally benign method of synthesis was designed, involving a peroxo-metal intermediate. This paper reports the details of the synthetic protocol of the reagent and its catalytic efficacy in reactions like organic brominations and acetylation.

2. Results and Discussion

Cetylpyridinium tribromide (CetPyTB), having molecular formula $C_{21}H_{38}NBr_3$ is a deep orange yellow solid microcrystalline compound which melts at 60-62°C (Lit. 57-59°C)[22]. The existence of Br_3^- was ascertained using electronic spectroscopy. The reagent shows strong absorption at 279.84 nm (ε 15847) which is a characteristic of tribromide.[23-24] 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 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.

Bromination chemistry is an important area of research in organic chemistry because of the significance of bromoorganic compounds.[25] In order to study the versatility of CetPyTB as brominating agent, representative examples of different types of organic substrates were taken and reactions conducted. It was observed that bromination reactions were quite facile and the products were obtained in moderate to high yields. The results have been summarized in Table 2. The products were identified by comparison of their melting points, IR absorption and NMR spectra with the authentic samples.[1,9,13,26]

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. Acetylation 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.[27-28] Thus some acetylation reactions were attempted as shown in Table 3. The results of acetylation reactions of alcohols reveal that cetylpyridinium tribromide (CetPyTB) can act well as an acetylating reagent. Proposed mechanism for acetylation has been represented in Scheme 1.



Scheme 1. Mechanism for acetylation of alcohols

3. Conclusion

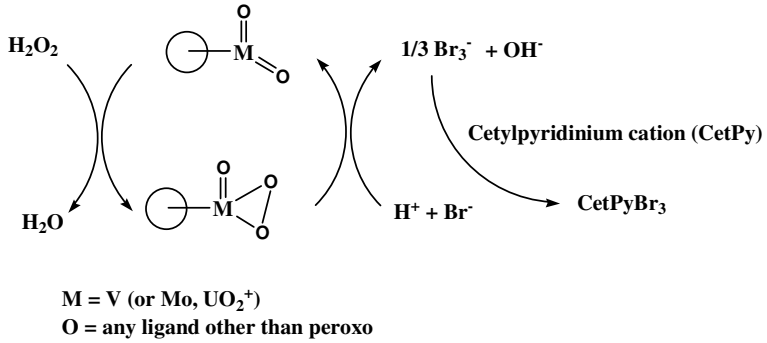
Cetylpyridinium Tribromide has been synthesized and its reactivity studied. Its easy method of preparation, mildness and efficacy in organic reactions such as brominations and acetylations shows that the reagent could be a useful addition to the existing lot of reagents.

4. Experimental

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 F_{254} (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.

4.1. Procedure for Preparation of Cetylpyridinium Tribromide

An amount of 0.06 g (0.34 mmol) of vanadium pentoxide (V_2O_5) was added to 5 mL (44.12 mmol) of 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic*). The reaction mixture was stirred at 0– 5 °C temperature in an ice-water bath till all the V_2O_5 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 (H_2SO_4) 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)



Scheme 2. Mechanistic Pathway for CetPyTB Synthesis

The compound was then dried in a vacuum desiccator using anhydrous calcium chloride ($CaCl_2$) 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 %).

4.2. Optimization of Synthetic Protocol of the Reagent

A number of reactions were carried out to arrive at the optimum amount of all the reagents used. Table 1 gives the optimal ratio of the chemicals required for the synthesis of the reagent:

Table 1. Optimized stoichiometry for the Synthesis of **CetPyTB**

CetPyB(g)	$V_2O_{5\ (g)}$	30% H_2O_2 (mL)	KBr (g)	1 M H_2SO_4 (mL)
13.74	0.34	44.1	41.07	50

One of the most reliable and rapid ways of characterization of tribromides is by recording their electronic absorption spectra. Br_3^- reveals characteristic signatures at *ca.* 265 nm with a shoulder at *ca.* 385 nm due to the transitions σ - σ^* and π - π^*, respectively.[23-24] The σ - σ^* and π - π^* transitions for the compound under discussion gave value 269.8 nm with a low intensity shoulder at 385 nm, (Fig.1) confirming the identity of the reagent as tribromide.

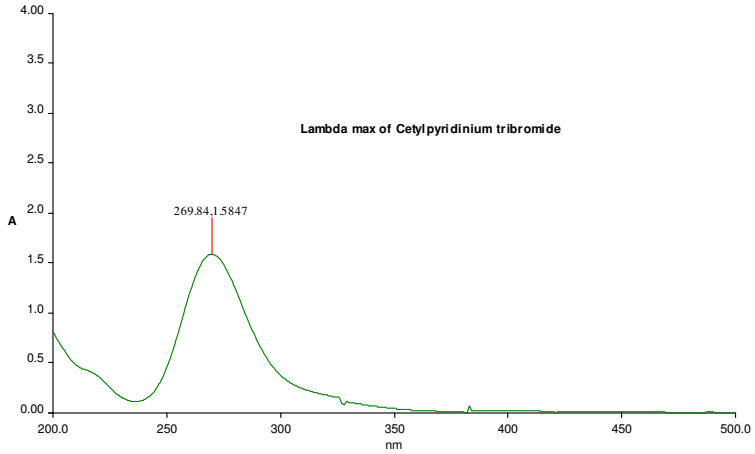
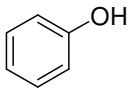
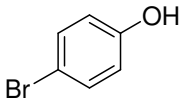
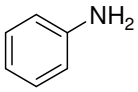
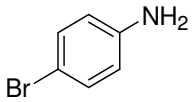
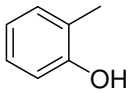
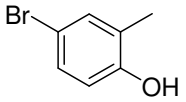
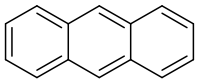
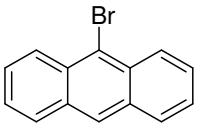
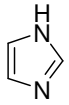
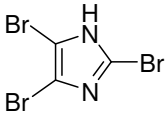
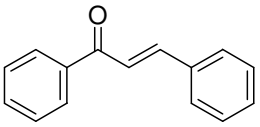
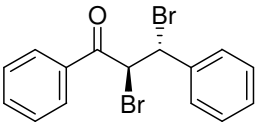
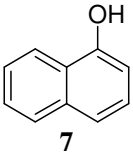
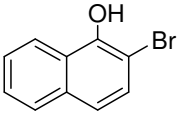


Figure 1. Electronic spectrum of Cetylpyridinium tribromide

4.3. Typical procedure for bromination reactions

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 F_{254} (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 products **1a** in 73% yield. The details of bromination reaction profile have been shown in Table 2.

Table 2. Bromination of organic substrates using CetPyTB[a]

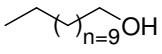
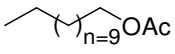
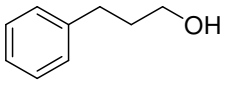
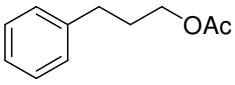
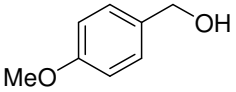
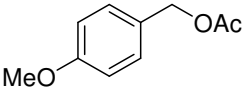
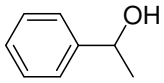
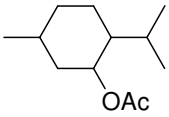
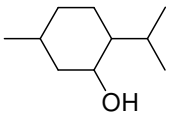
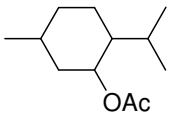
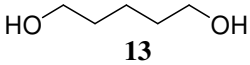
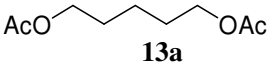
Substrate	Reaction Time (min)	Product[b]	% Yield[c]
 **1**	25	 **1a**	73
 **2**	20	 **2a**	72
 **3**	25	 **3a**	65
 **4**	15	 **4a**	92
 **5**	65	 **5a**	63
 **6**	35	 **6a**	75
 **7**	30	 **7a**	78

[a]Reactions were monitored by TLC. [b]Products were characterized by IR, ^{1}H NMR and ^{13}C NMR. [c]Isolated yields are reported.

4.4. Typical procedure for acetylation reactions

To a solution of 558 mg (3mmol) dodecyl alcohol (**8,** table 3) 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 $NaHCO_3$ (15mL) and then extracted with ethyl acetate (2x15mL). The organic layer was separated, dried over anhydrous Na_2SO_3 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 3. Acetylation of alcohols with Cetyl pyridinium tribromide[a]

Substrate	Reaction Time (min)	Product[b]	% Yield[c]
 **8**	15	 **8a**	78
 **9**	15	 **9a**	73
 **10**	15	 **10a**	84
 **11**	40	 **11a**	69
 **12**	55	 **12a**	65
 **13**	15	 **13a**	70

[a]Reactions were monitored by TLC. [b]Products were characterized by IR, ^{1}H NMR and ^{13}C NMR.. [c]Isolated yields are reported.

Melting points were determined using a Stuart Scientific SMP1 melting point apparatus and were uncorrected. The IR spectra were recorded in KBr pellets on a Perkin-Elmer FTIR Paragon 1000 spectrometer. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100.6 MHz) were run in DMSO- d6 on a Bruker Avance II spectrometer. Chemical shifts are given in ppm relative to TMS as internal standard. The positive-mode electrospray ionisation (ESI) mass spectra were recorded on a Perkin-

Elmer SCIEX API 300 spectrometer. The elemental analysis data were performed on a Thermo Electron Flash EA 1112. Chemicals were purchased from Aldrich and Acros Organics and used without further purification.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/OC

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