An Environmentally Benign Synthesis of Organic Ammonium Tribromides (OATB) and Bromination of Selected Organic Substrates by Tetrabutylammonium Tribromide (TBATB)

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Abstract: Stable crystalline organic ammonium tribromides (OATB), like Me₄NBr₃, Et₄NBr₃, Bu₄NBr₃, cetyltrimethylammonium tribromide, PyHBr₃, can be readily synthesised from the reaction of the corresponding bromides with V₂O₅ and aqueous H₂O₂. Typically, TBATB, Bu₄NBr₃, brominates a variety of organic substrates rather easily under mild conditions. An activated aromatic ring is selectively brominated in the presence of an olefinic double bond. © 1998 Elsevier Science Ltd. All rights reserved.

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Bromination, especially of aromatic substrates, is usually carried out by elemental bromine, but organic ammonium tribromides (OATB) including pyridine hydrobromide perbromide (PyHBr₃) are preferable owing to hazards associated with bromine. The other advantages of OATB are that they are crystalline, easy to handle and maintain the desired stoichiometry. Several tribromides have been reported i.e., tetramethylammonium tribromide (TMATB), phenyltrimethylammonium tribromide (PTATB), cetyltrimethylammonium tribromide (CetTMATB), tetrabutylammonium tribromide (TBATB), 1,8-diazabicyclo[5,4,0]-tetrabutylammonium tribromide (DBUHBBr₃) and pyridine hydrobromide perbromide (PyHBr₃). However, their preparations invariably involve elemental bromine and in some cases HBr as well. This again causes an environmental concern. On the other hand, there is an obvious demand for brominated organic substrates due to their importance both as synthetic intermediates and as potent antitumor, antifungal, antibacterial, antineoplastic and antiviral compounds. It would be extremely useful to develop an environmentally benign alternative synthetic protocol for the synthesis of OATB. A new synthesis of OATB is reported in this communication with TBATB as a typical example. In the course of our investigation of the reactivity of peroxovanadium systems, the
oxidation of bromide leading to tribromide was noticed. Vanadium bromoperoxidase (VBrPO) related biomimetic oxidations of bromide have also been studied in solution by others. Consequently, it has become clear that a peroxovanadium(V) intermediate is capable of the catalytic oxidation of bromide. Based on this, our strategy was to isolate the ultimate oxidation product of bromide employing organic quaternary ammonium cations so that the organic ammonium tribromides (OATB) could be synthesised in an environmentally acceptable way. Thus, in a typical reaction 2.75 mmol of V$_2$O$_5$ was dissolved in 44.1 mmol of 30% H$_2$O$_2$, with stirring at ca 5°C. To the clear red solution 11 mmol of tetrabutyl ammonium bromide, dissolved in 7 mL of water, was added and the reaction was stirred at ambient temperature. The reaction took place readily and the solution became yellow with concurrent precipitation of yellow or orange yellow tetrabutylammonium tribromide (TBATB), Bu$_4$NBr$_3$. The product was isolated after 15-20 min, washed with water 2 or 3 times and dried in air or by pressing between the folds of a filter paper. The isolated yield$^{10}$ was 68%, m.p. 75°C (Lit$^4$ 76°C). TBATB can be recrystallised from acetonitrile. The compound showed an intense electronic absorption at 267 nm typical of tribromide (Br$_3$).$^{11}$ Importantly, the same methodology worked very well for TMATB, tetraethylammonium tribromide (TEATB), PTATB, CetTMATB and PyHBr$_3$ which were synthesised in very high isolated yields from the corresponding organic ammonium bromides and pyridinium hydrobromide, respectively. The involvement of peroxovanadate(V) as the active oxidant has been ascertained from the observance of the peroxovanadium charge-transfer (CT) band at ~430 nm (ε=300) in aqueous V$_2$O$_5$-H$_2$O$_2$ solution.

$$\text{Bu}_4\text{NBr} \underset{\text{V}_2\text{O}_5, \text{H}_2\text{O}_2}{\rightarrow} \text{Bu}_4\text{NBr}_3 \ (\text{TBATB})$$

As a typical example, the efficacy of TBATB obtained by the new protocol was ascertained. The results of room temperature bromination of aromatics including polycyclic hydrocarbons 1-5, sensitive substrates such as imidazole 6, allyl alcohol 7, alkenes 8-10 and ketone 11 are summarised in Table 1. Thus, TBATB brominates activated aromatics such as aniline 1 very smoothly to give bromoaniline in H$_2$O-DMF. Both p-bromo- and 2,4,6-tribromo aniline may be selectively synthesised depending on the molar ratio of the reagent that is used. Polycyclic aromatics such as anthracene 3 and phenanthrene 4 can be brominated in acetic acid. Here again, 9-bromo and 9,10-dibromo anthracene can be prepared selectively by setting the molar ratio between the substrate: TBATB at (1:1) or (1:2), respectively. Unreactive rings like benzene 5 were brominated to afford the corresponding bromide in good yield by treating the substrate with Ag$_2$SO$_4$ in H$_2$SO$_4$.$^{12}$ TBATB is also capable of brominating heteroaromatics sensitive to usual bromination, for instance, imidazole 6 in CH$_2$Cl$_2$: MeOH (1:1) mixture was brominated to 2,4,5-tribromimidazole in a high yield (68%). Treatment of allyl alcohol 7 with the reagent in CH$_2$Cl$_2$ afforded 2,3-dibromopropanol in 72% yield. Also TBATB allows easy double bond bromination 8-10 under mild reaction conditions. The reaction of acetophenone 11 with the reagent produced bromomethyl phenyl ketone.
Table 1. Bromination of Aromatic and Some Other Substrates with TBATB

<table>
<thead>
<tr>
<th>Substrate (Entry)</th>
<th>Solvent/Time in min.</th>
<th>Substrate : TBATB</th>
<th>Product(s) (^b)</th>
<th>% yield (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniline (1)</td>
<td>50% Aq DMF/15</td>
<td>1:1</td>
<td>p-bromoaniline</td>
<td>60</td>
</tr>
<tr>
<td>Aniline (1)</td>
<td>50% Aq DMF/15</td>
<td>1:3</td>
<td>2,4,6-tribromoaniline</td>
<td>65</td>
</tr>
<tr>
<td>Phenol (2)</td>
<td>CH(_2)Cl(_2)/MeOH(1:1), CaCO(_3)/60</td>
<td>1:3</td>
<td>2,4,6-tribromophenol</td>
<td>60</td>
</tr>
<tr>
<td>Anthracene (3)</td>
<td>Acetic acid/30</td>
<td>1:1</td>
<td>9-bromoanthracene</td>
<td>70</td>
</tr>
<tr>
<td>Anthracene (3)</td>
<td>Acetic acid/30</td>
<td>1:2</td>
<td>9,10-dibromoanthracene</td>
<td>55</td>
</tr>
<tr>
<td>Phenanthrene (4)</td>
<td>Acetic acid/30</td>
<td>1:1</td>
<td>9-bromophenanthrene</td>
<td>46</td>
</tr>
<tr>
<td>Benzene (5)</td>
<td>conc H(_2)SO(_4), Ag(_2)SO(_4)/30</td>
<td>1:1</td>
<td>bromobenzene</td>
<td>40</td>
</tr>
<tr>
<td>Imidazole (6)</td>
<td>CH(_2)Cl(_2)/MeOH(1:1), CaCO(_3)/60</td>
<td>1:3</td>
<td>2,4,5-tribromomidazole</td>
<td>68</td>
</tr>
<tr>
<td>Allyl alcohol (7)</td>
<td>CH(_2)Cl(_2)/60</td>
<td>1:2</td>
<td>2,3-dibromopropanol</td>
<td>72</td>
</tr>
<tr>
<td>Styrene (8)</td>
<td>CH(_2)Cl(_2)/60</td>
<td>1:2</td>
<td>vic-dibromostyrene</td>
<td>62</td>
</tr>
<tr>
<td>Chalcone (9)</td>
<td>CHCl(_3)/180</td>
<td>1:2</td>
<td>Threeo-dibromochalcone</td>
<td>65</td>
</tr>
<tr>
<td>Cinnamic acid (10)</td>
<td>CHCl(_3)/120</td>
<td>1:2</td>
<td>2,3-dibromo-3-phenyl propanoic acid</td>
<td>60</td>
</tr>
<tr>
<td>Acetophenone (11)</td>
<td>50% Aq DMF/30</td>
<td>1:1</td>
<td>bromomethyl phenyl ketone</td>
<td>46</td>
</tr>
</tbody>
</table>

\(^*\) Reactions were monitored by TLC, GC. \(^b\) Products were characterised by comparison with authentic pure samples. \(^c\) Isolated yields are reported.

Heretofore unprecedented is the selective bromination of an activated aromatic ring in the presence of an olefinic double bond by TBATB. For example substrate 12, an important synthetic precursor for naturally occurring flavonoids (c.f. Vitexin), on being reacted with an equimolar amount of TBATB gave 12a\(^14\) as the exclusive product, while a similar reaction when conducted with 12:TBATB at a molar ratio of 1:3 yielded 12b\(^14\) (Scheme 1).

Scheme-1

**Bromination of organic substrates**: The substrate (10 mmol) and TBATB (10, 20 or 30 mmol as indicated in Table 1) in 25 mL of the specified organic solvents, and 20 mmol of CaCO\(_3\) for phenol and imidazole, were vigorously stirred for the specified period of time. The reaction mixture was filtered \(\text{in vacuo}\), the filtrate was
diluted with 100-120 mL of water to completely precipitate the product. The product was then filtered in vacuo and washed with water. For the liquid product the aqueous layer was extracted with ether and the separated ether layer was washed with water, dried over anhydrous Na₂SO₄ and finally evaporated under reduced pressure.

For benzene, a mixture of the substrate (10 mmol), Ag₂SO₄ (15 mmol) and 25 mL of conc. H₂SO₄ was stirred at room temperature for ca. 10 min followed by the addition of TBATB (12 mmol). The reaction mixture was stirred for 30 min and then poured into 150 g of crushed ice. The precipitated AgBr was separated by suction filtration. The filtrate and the precipitate were separately extracted with ether and washed several times with water until they were free from acid. The combined ether extract was evaporated under reduced pressure.

In conclusion, we have found an environmentally favourable procedure for peroxovanadium(V)-mediated biomimetic oxidation of bromide leading to the synthesis of organic ammonium tribromides (OATB). Synthesised in this way the crystalline tribromides are stable, and no Br₂ and HBr was used. Using OATB bromination proceeded smoothly with a variety of substrates which afforded the corresponding bromoorganics in good yields. Furthermore, selective bromination of an activated aromatic ring in the presence of an olefinic double bond is possible with such a reagent.

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References and Notes

[10] The compound analysed correctly C₁₂H₂₀NBr₃: Calc. C, 39.85; H, 7.54; N, 2.91; Br, 49.71.
[14] Products 12a and 12b gave satisfactory analytical and spectral data 12a: ¹H NMR (CDCl₃, 300 MHz) δ: 3.98 (s, 6H), 5.11 (s, 2H), 6.04 (s, 1H), 6.98 (d, 1H), 7.36-7.56 (m, 9H), 7.77 (d, 1H), 14.97 (s, 1H).
[15] ¹H NMR (CDCl₃, 300 MHz) δ: 3.96 (s, 3H), 3.99 (s, 3H), 4.79 (d, 1H), 5.08 (s, 2H), 5.58 (d, 1H), 6.06 (s, 1H), 7.00-7.56 (m, 9H), 14.99 (s, 1H).