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 Me_4NBr_3, Et_4NBr_3, Bu_4NBr_3, cetyltrimethylammonium tribromide, $PyHBr_3$, can be readily synthesised from the reaction of the corresponding bromides with V_2O_5 and aqueous H_2O_2. Typically, TBATB, Bu_4NBr_3, 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.
Key words: Brominating reagents; Halogenation; Biologically active compounds

Bromination, especially of aromatic substrates, is usually carried out by elemental bromine,[1] but organic ammonium tribromides (OATB) including pyridine hydrobromide perbromide ($PyHBr_3$) 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),[2] phenyltrimethylammonium tribromide (PTATB),[3] cetyltrimethylammonium tribromide (CetTMATB), tetrabutylammonium tribromide (TBATB),[4] 1,8-diazabicyclo[5,4,0]-tetrabutylammonium tribromide (DBUHBr₃)[5] and pyridine hydrobromide perbromide ($PyHBr_3$).[6] 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.[7] 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,[8] 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.[9] 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_2O_5 was dissolved in 44.1 mmol of 30% H_2O_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_4NBr_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 PyHBr3 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 ($\varepsilon=300$) in aqueous V_2O_5-H_2O_2 solution.

$$Bu_4NBr \xrightarrow{\quad V_2O_5, H_2O_2 \quad} Bu_4NBr_3 \ (TBATB)$$
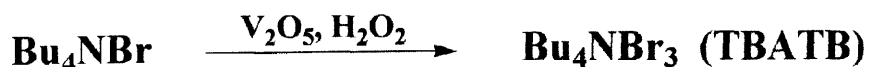
As a typical example, the efficacy of TBATB obtained by the new protocol was ascertained. The results of room temperature bromination of aromatics including polycyclic hydrocarbons 1-5, sensitive substrates such as imidazole 6, allyl alcohol 7, alkenes 8-10 and ketone 11 are summarised in Table 1. Thus, TBATB brominates activated aromatics such as aniline 1 very smoothly to give bromoaniline in H_2O-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_2SO_4 in H_2SO_4.[12] TBATB is also capable of brominating heteroaromatics sensitive to usual bromination, for instance, imidazole 6 in CH_2Cl_2: MeOH (1:1) mixture was brominated to 2,4,5-tribromoimidazole in a high yield (68%). Treatment of allyl alcohol 7 with the reagent in CH_2Cl_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

Substrate(Entry)	Solvent/Time in min.[a]	Substrate :TBATB	Product(s)[b]	% yield[c]
Aniline (1)	50% Aq DMF/ 15	1:1	p-bromoaniline	60
Aniline (1)	50% Aq DMF/ 15	1:3	2,4,6-tribromoaniline	65
Phenol (2)	CH_2Cl_2/MeOH(1:1),$CaCO_3$/ 60	1:3	2,4,6-tribromophenol	60
Anthracene (3)	Acetic acid/ 30	1:1	9-bromoanthracene	70
Anthracene (3)	Acetic acid/ 30	1:2	9,10-dibromoanthracene	55
Phenanthrene (4)	Acetic acid/ 30	1:1	9-bromophenanthrene	46
Benzene (5)	conc.H_2SO_4, Ag_2SO_4/ 30	1:1	bromobenzene	40
Imidazole (6)	CH_2Cl_2/MeOH(1:1),$CaCO_3$/ 60	1:3	2,4,5-tribromoimidazole	68
Allyl alcohol (7)	CH_2Cl_2/ 60	1:2	2,3-dibromopropanol	72
Styrene (8)	CH_2Cl_2/ 60	1:2	vic-dibromostyrene	62
Chalcone (9)	$CHCl_3$/ 180	1:2	Threo-dibromochalcone	65
Cinnamic acid (10)	$CHCl_3$/ 120	1:2	2,3-dibromo-3-phenyl propanoic acid	60
Acetophenone (11)	50% Aq DMF/ 30	1:1	bromomethyl phenyl ketone	46

[a] Reactions were monitored by TLC, GC. [b] Products were characterised by comparision 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 occuring flavonoids (c.f. Vitexin),[13] 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).
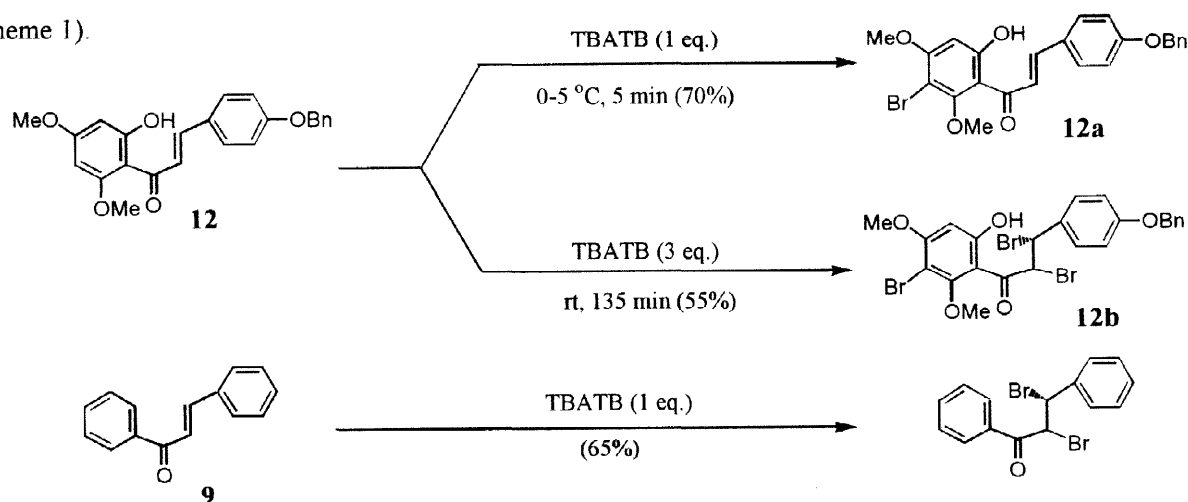
Scheme-1

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 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 Na_2SO_4 and finally evaporated under reduced pressure.

For benzene, a mixture of the substrate (10 mmol), Ag_2SO_4 (15 mmol) and 25 mL of conc. H_2SO_4 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 Br_2 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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[10]   The compound analysed correctly $C_{16}H_{36}NBr_3$: Calc. C, 39.85; H, 7.54; N, 2.91; Br, 49.71.
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[14]   Products **12a** and **12b** gave satisfactory analytical and spectral data **12a**: ^{1}H NMR ($CDCl_3$, 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).
       12b: ^{1}H NMR ($CDCl_3$, 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), 14.09 (s, 1H).