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Regioselective Bromination of Organic Substrates by Tetrabutylammonium Bromide Promoted by V_2O_5–H_2O_2: An Environmentally Favorable Synthetic Protocol

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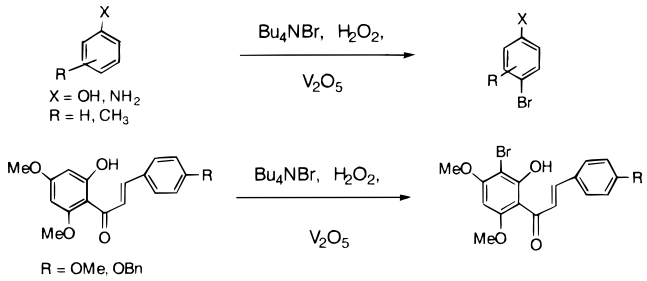
ABSTRACT



Vanadium pentoxide very effectively promotes the bromination of organic substrates, including selective bromination of some aromatics, by tetrabutylammonium bromide in the presence of hydrogen peroxide; mild conditions, high selectivity, yield, and reaction rate, and redundancy of bromine and hydrobromic acid are some of the major advantages of the synthetic protocol.

Bromination of organic substrates, particularly aromatics, has garnered a significant amount of attention in recent years[1−8] owing to the considerable commercial importance of such compounds as potent antitumor, antibacterial, antifungal, antineoplastic, antiviral, and antioxidizing agents[9] and also as industrial intermediates for the manufacture of speciality chemicals, pharmaceuticals, and agrochemicals. Unfortunately, the hazards associated with traditional bromination are not trivial and cannot be ignored.[7] Environmental problems caused by the use of detrimental chemicals and solvents[10] in classical bromination and the anticipated legislations against their use are some of the major concerns. Consequently, what is needed is a methodology that would be environmentally friendly and clean and yet efficient, site-selective, operationally simple, and cost-effective. Selective bromination of aromatics, which is of great commercial importance, has also been a case in point.

Taking cues from the knowledge of the activity of vanadium bromoperoxidase (VBrPO),[11] which catalyses bromination of marine natural products, as well as our earlier

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Table 1. Bromination[a] of Aromatics and Some Other Substrates with Tetrabutylammonium bromide (TBAB) and V_2O_5−H_2O_2

substrate	*t*/h	product	yield (%)[b]
aniline (**1**)	0.5	4-bromoaniline[c]	82
acetanilide (**2**)	2	4-bromoacetanilide	92
o-cresol (**3**)	1.5	4-bromo-*o*-cresol	92
m-cresol (**4**)	0.5	4-bromo-*m*-cresol	60
phenol (**5**)	1	2,4,6-tribromophenol[d]	98
β-naphthol (**6**)	1	1-bromo-*β*-naphthol	76
anthracene (**7**)	1	9,10-dibromoanthracene[d]	93
cyclohexene (**8**)	2	1,2-dibromocyclohexane	70
crotyl alcohol (**9**)	2	2,3-dibromo-1-butanol	60
2-butyne-1,4-diol (**10**)	1.5	2,3-dibromo-2-butene-1,4-diol	46
cyclohexanone (**11**)	2	2-bromocyclohexanone	52
4-hydroxycoumarin (**12**)	1	α,α-dibromo-*o*-hydroxy acetophenone (**15**)	55
4-benzyloxy-4′,6′-dimethoxy-2′-hydroxychalcone (**13**)	1	4-benzyloxy-3′-bromo-4′,6′-dimethoxy-2′-hydroxychalcone (**16**)	72
2′-hydroxy-4,4′,6′-trimethoxy-chalcone (**14**)	1	3′-bromo-4,4′,6′-trimethoxy-2′-hydroxy-chalcone (**17**)	70

[a] Reactions were monitored by TLC and GC. [b] Isolated yields. [c] Isolated as an acetyl or a benzoyl derivative. [d] Using substrate:TBAB at 1:1, *p*-bromophenol and 9-bromoanthracene are obtained as ca. 20% and ca. 30% yields, respectively.

experience of the reactivity of peroxovanadium systems,[12] we have now developed an environmentally acceptable bromination protocol involving V_2O_5 as a promoter and hydrogen peroxide and tetrabutylammonium bromide (TBAB) as the sources of active oxygen and bromide, respectively. The solvent of choice is CH_3CN/H_2O. The promoter (V_2O_5) and the oxidant (H_2O_2) are both environmentally acceptable chemicals.

The methodology is based on (i) activation of dioxygen by the interaction of H_2O_2 with vanadium(V) leading to the formation of peroxovanadium(V) species ($\lambda = 430$ nm) in solution followed by (ii) oxidation of bromide by the peroxovanadium(V) intermediate ultimately leading to the formation of Br_3^- ($\tilde{\lambda} = 266$ nm) as the active brominating agent, and finally (iii) bromination of organic substrates to afford bromoorganics (Figure 1). The wavelengths listed in

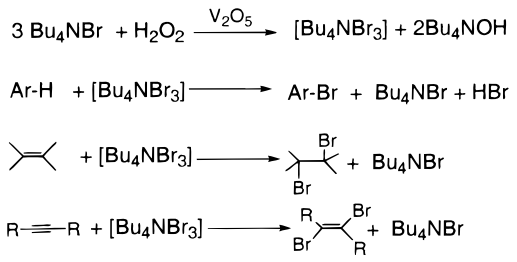

Figure 1. Generation of TBATB and bromination of organic substrates.

parentheses were used experimentally to characterize the species present in the methodology, lending credence to the contention.

Various conditions were sampled, with the result that a 1:3:0.5:16 substrate to tetrabutylammonium bromide to V_2O_5 to H_2O_2 stoichiometry appeared optimal (ostensibly to speed conversion to products with high yields) and that CH_3CN/H_2O (1:1, 8 mL/mmol of TBAB) solvent gave very good yields. The bromination reaction was conducted at ca. 5 °C with stirring for the time period shown for each substrate in Table 1. The desired products have been obtained in high to very high yields as reported (Table 1). Notably, the reaction may be conducted using a substrate:V_2O_5 molar ratio of 1:0.1 or 0.2; however, conversion to product is rather slow. Importantly, no extra addition of acid is required by this method. The reaction pH was, however, found to be ca. 2.1. Incidentally, the intrinsic acidity of the reaction originating from dissolution of V_2O_5 in hydrogen peroxide solution not only neutralizes the hydroxide in Figure 1 but also maintains the acidic reaction medium. The pH values recorded at the beginning and after completion of the reaction were ca. 2.0 and ca. 2.2, respectively. It appears that sufficient acid could be generated in the process from the use of 0.5 molar equiv of V_2O_5 to allow for bromide oxidation by the peroxovanadium(V) species formed in the reaction. The methodology is capable of being made catalytic with KBr as the consumable source.

Quite intriguing is the regioselective bromination of activated aromatics such as aniline (**1**), acetanilide (**2**), *o*-cresol (**3**), and *m*-cresol (**4**) exclusively to the corresponding *p*-bromo derivatives. In the latter two cases the -OH group seems to have a stronger influence than the $-CH_3$ group. Under similar experimental conditions, phenol (**5**) and *β*-naphthol (**6**) produced 2,4,6-tribromophenol and 1-bromo-

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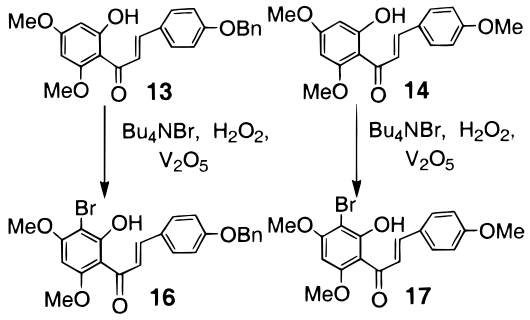
β-naphthol, respectively, in very high yields. A polycyclic aromatic, anthracene (**7**), is capable of being brominated to 9,10-dibromoanthracene. Notable in this context is that by setting the molar ratio between the substrate and TBAB at 1:1, phenol (**5**) and antharacene (**7**) can be brominated to yield *p*-bromophenol (ca. 20%) and 9-bromoanthracene (ca. 30%) in addition to the tribromo and dibromo derivatives, respectively, if desired.

The efficacy of the methodology lies also in the bromination of alkene and alkyne systems as exemplified by the facile bromination of cyclohexene (**8**), crotyl alcohol (**9**), and 2-butyne-1,4-diol (**10**), respectively. The conversion of cyclohexanone (**11**) to the corresponding 2-bromocyclohexanone in high yield might be a paradigm for the synthesis of α-bromoketone. Quite interesting is the transformation of 4-hydroxycoumarin (**12**) to α,α-dibromo-*o*-hydroxyacetophenone (**15**).[13] Indeed α,α-dibromination of the enol form of β-ketolactone (cf. **12**) is, to the best of our knowledge, unprecedented. Also important is the selective bromination of the activated aromatic ring in the presence of an enone by the present methodology. Thus, for instance, the activated aromatic ring of 4-benzyloxy-4′,6′-dimethoxy-2′-hydroxychalcone (**13**) and 2′-hydroxy-4,4′,6′-trimethoxychalcone (**14**) were selectively brominated, in the presence of an enone, to produce 4-benzyloxy-3′-bromo-4′,6′-dimethoxy-2′-hydroxychalcone (**16**) and 3′-bromo-4,4′,6′-trimethoxy-2′-hydroxychalcone (**17**),[14] respectively, in very high yields.



The products (**16** and **17**) are important precursors for the synthesis of the flavonoids (cf. vitexin).[15] Control experiments conducted by adjusting the pH to 2.1 with 0.01 M H_2SO_4, separately without involving either V_2O_5 or H_2O_2, did not bring about any change in the substrates so far examined.

In summary, we have shown that various brominated organic compounds can be prepared via the treatment of organic substrates including aromatics typically with tetrabutylammonium bromide promoted by hydrogen peroxide and V_2O_5. We have evidence showing that the methodology may work as well with other organic bromides such as tetraethylammonium bromide, cetyltrimethylammonium bromide, and pyridinium bromide, for instance. This methodology represents an efficient, straightforward, and safer alternative to the rather hazardous classical bromination protocols, opening an opportunity to gain easy access to a variety of bromoorganics. Its synthetic applications as well as the reaction mechanism are currently under investigation.

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Supporting Information Available: Detailed experimental procedures for bromination of *o*-cresol (**3**) to 4-bromo-*o*-cresol and 4-benzyloxy-4′,6′-dimethoxy-2′-hydroxychalcone (**13**) to 4-benzyloxy-3′-bromo-4′,6′-dimethoxy-2′-hydroxychalcone (**16**) and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) **Selected data for 15:** δ_H ($CDCl_3$) 6.78 (s, 1H, -C*H* Br_2), 6.95 (t, J = 6 Hz, 1H, Ar*H*), 7.50 (d, J = 9 Hz, 1H, Ar*H*), 7.56 (t, J = 6 Hz, 1H, Ar*H*), 7.84 (d, J = 9 Hz, 1H, Ar*H*), 11.46 (s, 1H, O*H*, D_2O exchangeable); δ_C($CDCl_3$) 38.59, 114.21, 119.74 (2C), 130.38, 138.54, 164.43, 191.39.

(14) **Selected data for 17:** δ_H ($CDCl_3$) 3.84 (s, 3H, OC*H*$_3$), 3.97 (s, 3H, OC*H*$_3$), 3.98 (s, 3H, OC*H*$_3$), 6.03 (s, 1H, 5′*H*), 6.92 (d, J = 9 Hz, 2H, Ar*H*), 7.54 (d, J = 12 Hz, 2H, Ar*H*), 7.74 (d, J = 15 Hz, 1H, olefinic *H*), 7.83 (d, J = 15 Hz, 1H, olefinic *H*), 14.98 (s, 1H, O*H*, D_2O exchangeable), δ_C ($CDCl_3$) 55.82, 56.50, 56.72, 87.61, 92.42, 114.83, 122.05, 124.91, 128.47, 130.68, 143.91, 162.03, 162.17, 162.61, 163.63, 193.08.

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