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A convenient and regioselective oxidative bromination of electron-rich aromatic rings using potassium bromide and benzyltriphenylphosphonium peroxymonosulfate under nearly neutral reaction conditions

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Abstract—Regioselective oxidative bromination of electron-rich aromatic rings has been studied using potassium bromide as a bromine source in the presence of benzyltriphenylphosphonium peroxymonosulfate as oxidant under nearly neutral reaction conditions. In most cases we obtained monobrominated derivatives regioselectively and in good to high yields without the aid of strong acids.

Brominated aromatic compounds have gained increasing interest as versatile intermediates for the synthesis of biologically active compounds such as potent antitumour, antibacterial, antifungal, antiviral, and antioxidizing agents.[1] Conventional bromination methods typically use elemental bromine, generating toxic, and corrosive hydrogen bromide, leading to environmental pollution.[2] Traditional methods of aromatic bromination involve the use of nonselective hazardous acidic reagents such as mineral acids and metal halides, which can lead to separation difficulties and toxic and corrosive wastes. Examples of conventional and traditional methods include: Br_2–Lewis acids,[3] NBS–H_2SO_4–CF_3CO_2H,[4] NBS–PTSA,[5] NBS–NaOH,[6] NBS–SiO_2,[7] Br_2–Al_2O_3,[8] Br_2–Zeolite,[9] NBS–Amberlyst,[10] NBS-HZSM-5,[11] Clayzib,[12] *tert*-BuOOH– or H_2O_2–HBr,[13] and HBr–DMSO.[14] The replacement of such reagents with non-toxic and more selective reagents is very desirable and represents an important goal in the context of clean synthesis. The use of potassium bromide as brominating reagent in the presence of sodium tungstate or ammonium molybdate as catalyst using hydrogen peroxide or sodium perborate as an oxidant has been developed.[15] Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) is an inexpensive, water-soluble, and stable oxidizing reagent that is commercially available, however, this reagent is insoluble in organic solvents and buffering is needed due to its acidity.[16] Recently, sodium bromide or potassium bromide combined with Oxone® has been used as an effective reagent for the bromination of activated arenes.[17] Replacement of the potassium cation in potassium peroxymonosulfate with quaternary phosphonium is very desirable and increases its solubility in organic solvents.

Recently, we reported benzyltriphenylphosphonium peroxymonosulfate **BTPPMS** as a mild, inexpensive and efficient reagent in organic transformations.[18] Following our continued interest in **BTPPMS** and in the course of our studies on the halogenation of organic compounds,[19] we herein report highly efficient and selective bromination reactions of activated arenes employing potassium bromide as the bromine source and **BTPPMS** as the oxidant under non-aqueous conditions.

Keywords: Activated arenes; Benzyltriphenylphosphonium peroxymonosulfate; Oxidative bromination; Potassium bromide.
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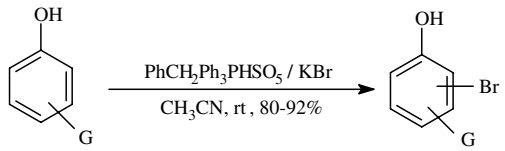
Thus, a series of electron-rich aromatics such as substituted phenols and anilines containing even numbers of electron-withdrawing substituents was subjected to bromination in acetonitrile at ambient temperature to furnish the corresponding bromoarenes. Aromatic amines were also examined as there is a possibility that they might be oxidized by this system rather than undergoing substitution.[20]

BTPPMS is a mild, efficient, stable, and cheap reagent, which is quite soluble in dichloromethane, chloroform, acetone, and acetonitrile but insoluble in non-polar solvents such as carbon tetrachloride, *n*-hexane, and diethyl ether. It is readily prepared by the dropwise addition of an aqueous solution of Oxone® to an aqueous solution of benzyltriphenylphosphonium chloride in a quantitative yield at room temperature and can be stored for months without losing its potency.[18] The amount of HSO_5^- in this reagent has been determined by iodometric titration[21] and the measurements are consistent with almost 99% by weight of active oxidizing agent.

We have reported a selective method for the bromination of phenols, affording bromophenols in good to high yields within short reaction periods. Our method is based on the in situ oxidation of potassium bromide using **BTPPMS** in acetonitrile. Simply by adding **BTPPMS** to a solution of phenol and potassium bromide in acetonitrile, rapid and selective bromination was achieved at room temperature. The products could be separated by a straightforward workup. The method has been applied successfully to a variety of phenols. Most of the reactions were regioselective and in those examples where both *ortho*- and *para*-substitution was possible, the *para*-substituted product was the only isomer isolated. *para*-Substituted aromatics were brominated in the *ortho*-position. Introduction of an electron-withdrawing group to the aromatic ring substantially decreased the rate of ring bromination while an electron donating group increased the rate (Scheme 1).

Initially, the bromination of 2,6-dimethylphenol **1g** as a model compound using potassium bromide and **BTPPMS** in various solvents was examined. The solvents examined were dichloromethane, chloroform, and acetonitrile. The reactions were carried out by stirring **1g** with **BTPPMS** and KBr (1:1) at room temperature. Dichloromethane and chloroform were inferior solvents compared to acetonitrile. Next, the effects of the amount of the oxidant **BTPPMS** and KBr were examined with **1g** (1 mmol) in acetonitrile. The optimum molar ratio of phenol to KBr to oxidant **BTPPMS** (1:1:1) was found to be ideal for complete conversion. The role of **BTPPMS** was confirmed by conducting a blank experiment where the formation of bromo compound was not observed even after 24 h. The products were isolated by filtering the reaction mixture and washing with acetonitrile, quenching the filtrate with aqueous sodium thiosulfate, drying over sodium sulfate and concentrating in vacuo. The residue was purified by column chromatography over silica gel or by crystallization in an appropriate solvent. The structure was confirmed by ^{1}H NMR, mass spectra, and melting point and elemental analysis for crystalline products. To evaluate the utility of this procedure for large scale bromination, a 10-fold scale reaction was carried out successfully for the bromination of 2-methoxynaphthalene **1c**, 1-bromo-2-methoxynaphthalene was obtained in 89% yield within 2 h[26] (Table 1).



G = H, Electron releasing or withdrawing substituent

Scheme 1. Oxidative bromination of phenols using **BTPPMS** and potassium bromide.

BTPPMS was also used to brominate anilines at ambient temperature. Various activated and deactivated anilines were brominated upon simple admixing with **BTPPMS** and potassium bromide. In most cases, the optimum mole ratio of aniline to KBr to oxidant **BTPPMS** was found to be 1:1:1 (Table 1). *N*,*N*-Dimethylaniline **1v** was selectively brominated at the *para*-position within 1 h to give the corresponding 4-bromo-*N*,*N*-dimethylaniline in a 80% yield. 2-Chloroaniline **1s**, 4-chloroaniline **1t**, and 4-bromo-2-methylaniline **1u** exhibited a similar reactivity leading to the corresponding brominated anilines in good to high yields with no detectable influence of the substituent. Bromination of acetanilide **1w** which is less reactive than aniline proceeded well and produced 4-bromoacetanilide in 90% yield in 4 h (Table 1). It is interesting to mention that this reaction only requires a few milliliters of acetonitrile and the end point of reaction is easily confirmed by the decolourization of the dark-brown solution. Finally, we believe that the procedure for the bromination of aromatic amines using **BTPPMS** is a highly useful method owing to its ease, mildness, and reaction under nearly neutral reaction conditions (Scheme 2).

Bromination of an aromatic compound in the presence of **BTPPMS** proceeds according to the stoichiometry of Equation 1. It is believed that the bromination proceeds via the formation of potassium hypobromous. Potassium hypobromous has a higher instability due to pronounced ionic nature and thus more reactivity towards the aromatic nucleus.

The other mechanism is proposed according to a radical pathway upon hemolytic cleavage of the O–O bond in the peroxymonosulfate anion (^-O_3S–O–OH) according to Equation 2. The absence of bromination of the side chain such as the ring methyl group is indicative of the electrophilic mechanism of the reaction rather than a radical pathway (Table 1). In the case of Oxone®, a similar mechanism has been proposed in the literature.[17c]

In conclusion, we have developed a novel system using **BTPPMS** as an interesting alternative to liquid oxidants such as hydrogen peroxide, *tert*-butylhydroperoxide, and dimethylsulfoxide for the oxidative bromination of