Short communication

Synthesis of Benzyl Triethyl Ammonium Tribromide and Its Application as a Highly Efficient and Regioselective Reagent for the Bromination of Activated Aromatic Compounds

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Abstract

Benzyl triethyl ammonium tribromide was prepared by oxidation of bromide ion with HNO_3. The resulted tribromide was used as an efficient, regioselective, and recoverable reagent for the bromination of anilines, phenols and anisoles in good to excellent yields at room temperature.

Keyword: Regioselective bromination, anilines, phenols, anisols, benzyl triethyl ammonium tribromide, activated aromatic compounds.

1. Introduction

Halogenated aromatic compounds are an important class of molecules in the synthetic organic chemistry. They are key intermediates in the preparation of organometallic reagents[1] and play vital roles in transition metal mediated coupling reactions.[2–5]

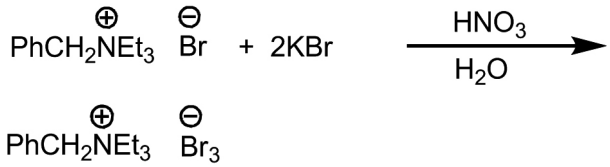
A variety of methods have been reported in the literature for the bromination of organic compounds.[6] Some examples of the reagents and catalysts that have been developed for this purpose include NBS-sulfonic acid functionalized silica,[7] KBr–benzyltriphenylphosphonium peroxymonosulfate,[8] Br_2 (for lithiated haloarenes),[9] bromide/bromated reagent,[10] hexamethylenetetramine–Br_2,[11] $CuBr_2$,[12] $ZrBr_4$/diazene,[13] polymer-supported triorganotin bromide,[14] peroxodisulfate,[15] IBX amide resin-TEAB,[16] Br_2/SO_2Cl_2/zeolite,[17] NBS–TEAB,[18] bromodichloroisocyanuric acid,[19] NBS–$Pd(OAc)_2$,[20] NBS/Al_2O_3,[21] NBS–NH_4OAc,[22] and NBS–DMF (or THF).[23] However, the use of these methods is associated with the drawbacks such as a) the use of toxic and hazardous bromine, which is very difficult to handle and cause severe burns in contact with skin, b) the use of expensive heavy transition metals, and c) formation of polysubstituted and other side products.

Recently bromine-free bromination with stable crystalline organic ammonium tribromide like 1,2-dipyridiniumditribromide-ethane,[24] and alkylpyridinium tribromide[25] has gained considerable interest. Tribromides are more suitable than the liquid bromine because of their crystalline nature, easy storage and transport, and maintenance of desired stoichiometry. Preparations of these reagents in most cases involve organic ammonium bromide and molecular bromine, avoiding direct use of the toxic molecular bromine. Recently, organic ammonium tribromides have been prepared in an environmentally benign way by the reaction of V_2O_5, aqueous H_2O_2 and KBr.[26] However, this method generates some heavy metal as toxic waste. Therefore, the search for new methods of preparation of ammonium tribromide has evoked great contemporary interest.

2. Results and Discussion

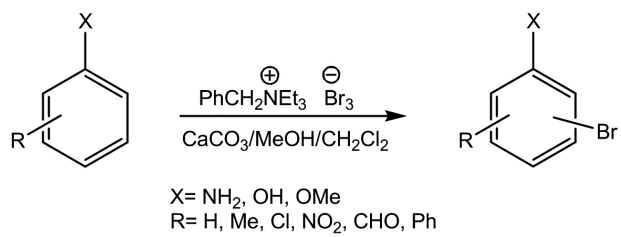
In continuation of our program to develop environmentally benign methods for the preparation of tribromide salts and for bromination of aromatic compounds,[27–28] we report here a new and environmentally benign alternative protocol for the preparation of benzyl triethyl ammonium

tribromide (BTEAT) as a new and recoverable reagent, and its application in efficient and selective bromination of aromatic compounds. The preparation of BTEAT is based on the oxidation of bromide ion to tribromide ion (Br_3^-) by nitric acid as an inexpensive oxidant followed, by precipitation with the benzyl triethyl ammonium cation (Scheme 1). The BTEAT showed an intense UV absorption at 267 nm, typical for tribromide ion (Br_3^-).[26]



Scheme 1

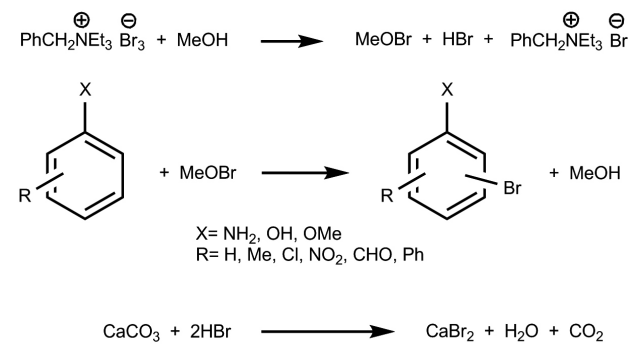
BTEAT is a regioselective brominating agent in the presence of a solvent mixture of methanol/dichloromethane, and calcium carbonate at room temperature. Monobrominated products were formed in excellent yields and could be easely separated by straightforward workup (Scheme 2). Among the various studied substrates substituted anilines, phenols and anisoles were found to be the most reactive**.** The reaction times were short and some of the phenols and anilines underwent the conversion immediately (Table 1, entries 2–4, 15). Alkyl, halogen, carbonyl, methoxy and nitro groups remained unaffected in the bromination reaction. Deactivated aromatic compounds such as benzonitrile (Table 1, entry 20) could not be brominated under investigated reaction conditions.



Scheme 2

Most of the reactions were regioselective and in those examples where both, *ortho*- and *para*-substitutions were possible, the *para*-substituted product was the only isolated isomer. *para*-Substituted aromatics were brominated on *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 (see Table 1).

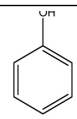
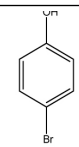
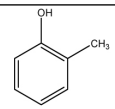
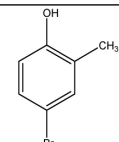
We noticed that the presence of methanol markedly facilitated the bromination reaction. The main active species, which generate Br^+, is probably the methyl hypobromite (MeOBr), which was produced from the reaction of BTEAT with methanol, and can be employed repeatedly. The reaction could be facilitated by addition of calcium carbonate powder to neutralize the generating hydrogen bromide (Scheme 3). In absence of calcium carbonate, aromatic amines did not brominate at given reaction conditions. This is probably due to the formation of a salt of the free amine with the produced hydrogen bromide, which makes the aromatic ring electron deficient.

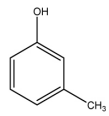
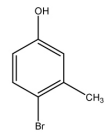
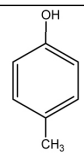
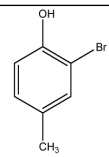
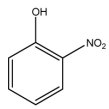
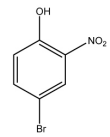
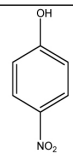
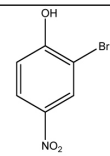
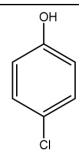
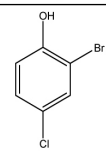
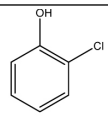
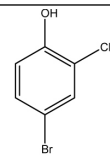
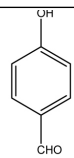
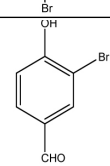
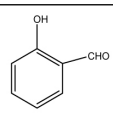
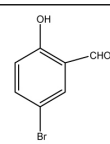
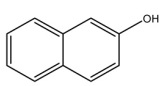
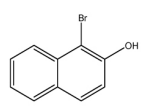
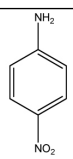
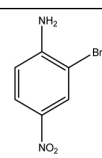
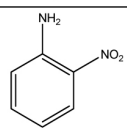
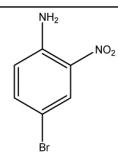


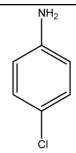
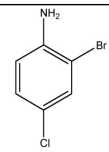
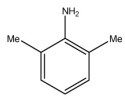
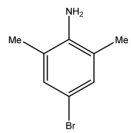
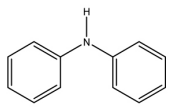
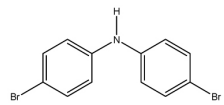
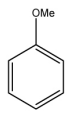
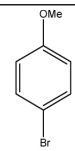
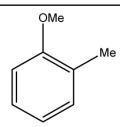
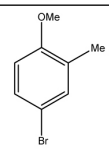
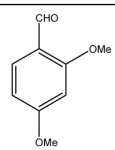
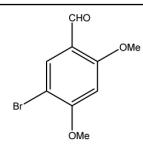
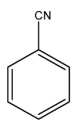
Scheme 3

After extraction of the bromoaromatic products, the aqueous layer was treated with a fresh aqueous KBr and HNO_3 to regenerate the BTEAT in quantitave yield. The recovered reagent is identical with the parent reagent,

Table 1: Regioselective bromination of aromatic compounds by BTEAT in the presence of $CaCO_3$ and $MeOH/CH_2Cl_2$ at room temperature.[a, b]

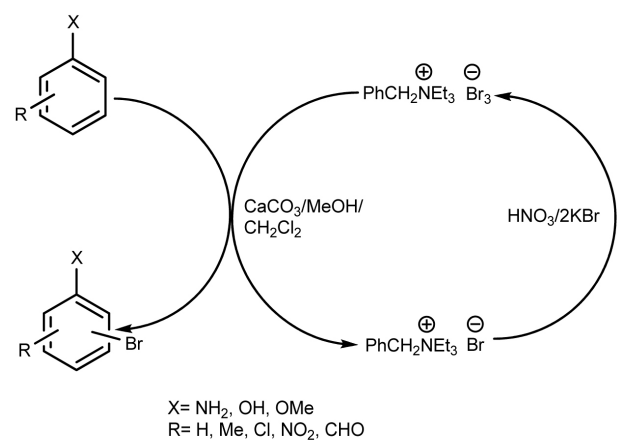
Entry	Substrate	Product	Time (min)	Yield (%)	m.p. (°C) found	m.p. (°C) reported	Ref
1			2	91	64–66	68–69	29
2			Immediately	95	63–64	63–64	29

Entry	Substrate	Product	Time (min)	Yield (%)	m.p. (°C) found	m.p. (°C) reported	Ref
3			Immediately	90	58–60	59	29
4			Immediately	93	Liq.	Liq.	29
5			20	85	90	91–93	29
6			50	86	114–115	114–115	8
7			10	95	32–34	32–34	8
8			15	90	49–50	49–50	8
9			10	75	129–130	130–132	30
10			15	90	103–104	102–103	30
11			5	92	83–85	84	29
12			10	93	105	104.5	29
13			50	85	109–111	110–112	11

Entry	Substrate	Product	Time (min)	Yield (%)	m.p. (°C) found	m.p. (°C) reported	Ref
14			10	90	64–66	66–68	11
15			Immediately	95	47–49	46–48	11
16[c]			5	85	104–106	105–108	31
17			100	95	Liq.	Liq.	32
18			80	90	65–67	66–69	32
19			5	95	139	134–138	33
20		–	24 h	–	–	–	–

[a] Refers to isolated yield.
[b] All products are known compounds and were characterized by their melting points, and IR and ^{1}H NMR spectroscopy.
[c] The reaction was carried out with 2 equivalents of BTEAT.

which means that BTEAT can be considered as a Br_2 transfer agent (Scheme 4).



Scheme 4

3. Experimental

Starting materials were purchased from Fluka, Merck and Aldrich. Reactions were monitored by TLC using silica gel plates. Products were characterized by comparison with authentic samples (IR, ^{1}H NMR spectroscopy, CHN analysis, melting point and TLC analysis). Melting points were measured on a Gallenkamp melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 300 NMR spectrometer in $CDCl_3$ and CD_3COCD_3 as solvents, relative to the

tetrametylsilane as internal standard. IR spectra were recorded on a FT-IR Perkin Elmer-RXI spectrophotometer. IR spectra of solids were performed using KBr pellets.

3. 1. Synthesis of BTEAT by Oxidation of Potassium Bromide

To a stirred solution of benzyl triethyl ammonium bromide (6.25 g, 23 mmol) and potassium bromide (5.47 g, 46 mmol) in distilled water (30 mL) the solution of nitric acid (63%, 5.129 mL, 115 mmol) was added dropvisely. A yellow-orange precipitate was formed, and the resulting mixture was stirred for 1h. The precipitate was isolated by filtration and washed with distilled water (3 × 10 mL). The filter cake was dried and recryctalized from $CHCl_3$ to afford BTEAT as yellow crystals (7.4 g, 76% yield). Mp 99–101 °C, IR (KBr): ν 3050 (m), 1600 (s) 1460 (s), 1360 (s),1040(m), 1210 (s), 840 (m), 800 (m) cm^{-1}, ^{1}H–NMR: δ 1.50 (t, 9H), 3.55 (q, 6H), 4.85 (s, 2H), 7.48–7.80 (m, 5H) ppm, ^{13}C NMR: δ 133.1, 130.9, 129.5, 126.7, 62.4, 52.4, and 7.5 ppm, UV (CH_2Cl_2); λ_{max} 267nm, Anal. Calc. for $C_{13}H_{22}NBr_3$: C, 36.11; H, 5.1; N, 3.24%. Found: C, 36.2; H, 5.2; N, 3.34%.

3. 2. Typical procedure for bromination of phenols by BTEAT

BTEAT (0.862 g, 2 mmol) was added to a slurry of $CaCO_3$ (0.6 g, 6mmol) and phenol (0.18 g, 2 mmol) in 5 mL solution of methanol/CH_2Cl_2 (3:2) and the mixture stirred for 2 min at room temperature. After disappearance of the starting material (monitored by TLC) the solvent was removed under reduced pressure and the solid residue was washed with ether (4 × 20 mL) and filtered off. The combined organic layers were dried over magnesium sulfate, and solvent evaporated under vacuum to give 4-bromophenol which was recrystallized from methanol/water (1:3) as a colorless needles in 91% yield (0. 31 g).

3. 3. General Procedure for Regeneration of BTEAT

After extraction of brominated aromatic compounds from reaction mixture, the residue was washed with water (3 × 20 mL), and separated from solid residue by filtration. To the combined water solution containing benzyl triethyl ammonium bromide (2 mmol) and bromide ion (2 mmol) was added a solution of KBr (0.24 g, 2 mmol). Additional drop wise addition of HNO_3 solution (63%, 0.45 mL, 10 mmol) in 10 mL of water during 30 min produce BTEAT as yellow crystals (0.604 g, 70% yield). The recovered reagent is identical in all respects with the parent BTEAT.

4. Conclusions

We have developed a simple and an environmentally favorable procedure for the oxidation of ammonium bromide leading to the synthesis of BTEAT. The crystalline tribromide BTEAT is stable and can be easily handled because of its solid character and availability to be treated quantitatively. On the other hand, no Br_2 or HBr is used for the production of this reagent. Regioselective monobromination of several activated aromatic compounds with BTEAT was demonstrated to be efficiently performed which would be a highly useful method because of its simplicity, high selectivity, excellent yields, and environmental benignity. BTEAT as brominating reagent can be easily recycled; therefore, the process is economically viable for large-scale reaction.

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6. References

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Povzetek

V prispevku avtorji obravnavajo pripravo benzil trietil amonijevega tribromida z oksidacijo bromidnega iona s HNO_3. Nastali tribromid so uporabili kot učinkovit, regioselektiven in obnovljiv reagent za bromiranje anilinov, fenolov in anizolov z dobrimi izkoristki že pri sobni temperatruri.