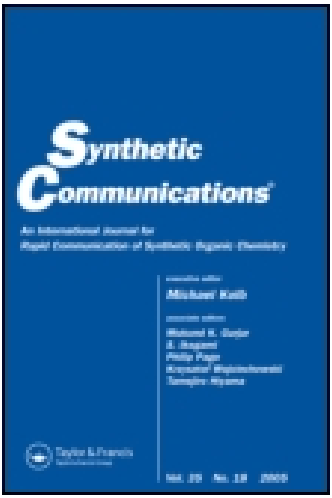

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

1-Benzyl-4-Aza-1-Azoniabicyclo[2 Tribromide as a Highly Reactive Brominating Agent for Aniline Derivatives

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Published online: 10 Jan 2011.

To cite this article: A. R. Hajipour , H. Imanieh & S. A. Pourmousavi (2004) 1-Benzyl-4-Aza-1-Azoniabicyclo[2.2.2]Octane Tribromide as a Highly Reactive Brominating Agent for Aniline Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:24, 4597-4604, DOI: 10.1081/SCC-200043274

To link to this article: http://dx.doi.org/10.1081/SCC-200043274

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 24, pp. 4597–4604, 2004

1-Benzyl-4-Aza-1-Azoniabicyclo[2.2.2] Octane Tribromide as a Highly Reactive Brominating Agent for Aniline Derivatives

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ABSTRACT

Reaction of anilines with 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide (3) in the presence of $CaCO_3$ in small amounts of methanol gave brominated aromatic amines in good yields at room temperature. The isolation of products is straightforward.

Key Words: Aniline; Bromination; Tribromide.

Bromination of organic substrates, particularly aromatic compounds, has received a significant amount of attention in recent years,[1–4] owing to the

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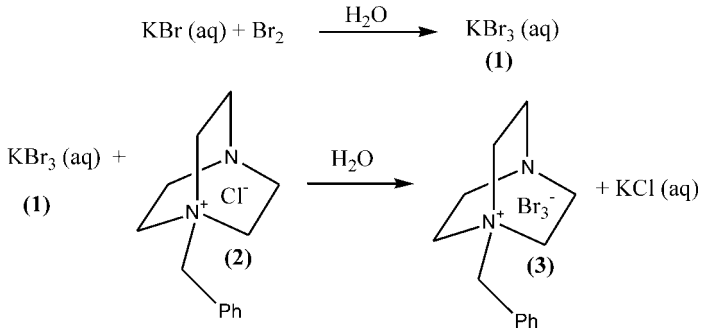
DOI: 10.1081/SCC-200043274 0039-7911 (Print); 1532-2432 (Online)

considerable commercial importance of such compounds as potent antitumor, antibacterial, antifungal, antineoplastic, antiviral, and antioxidizing agents[5] and also as industrial intermediates for the manufacture of pharmaceuticals, and agrichemicals. Unfortunately, the hazards associated with traditional bromination are not trivial and cannot be ignored. Environmental problems caused by the use of detrimental chemicals and solvents in classic bromination are some of the major concerns.[6]

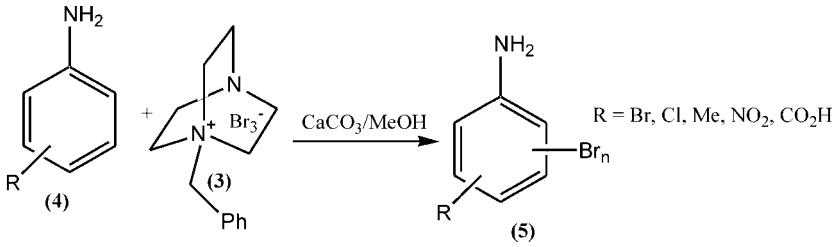
The use of stable solid crystalline brominated complexes have been reported in several cases,[7–9] but only a few reactions in bromination of aromatic amines giving some selective and controlled products in sequential reactions have been reported.[10] The topology of (3) and reactivity of diazonium ion encouraged us to investigate another brominating complex in order to have some selective brominated products. In continuation of our research to develop new reagents for iodination and bromination of aromatic compounds,[11] we wish to report here the preparation of (3) as an inexpensive starting material. This reagent was prepared straightforward by addition of an aqueous solution of KBr_3 to a solution of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride at room temperature. Stirring the yellowish solution for 30 min at room temperature resulted in an orange powder that showed an intense electronic absorbtion at 279 nm typical of tribromide,[12] and this reagent is soluble in methanol and dichloromethane and insoluble in water and carbon tetrachloride. Reagent (3) is a very stable compound and can be stored at bench for months without losing its activity (Sch. 1).

The reagent (3) is an efficient reagent for bromination of aniline derivatives in good to excellent yields. This reagent brominated activated and deactivated aromatic amines (Sch. 2).

We noticed that the presence of methanol markedly facilitated the bromination of **4**. In this case the main active species, which generate Br^+,



Scheme 1.



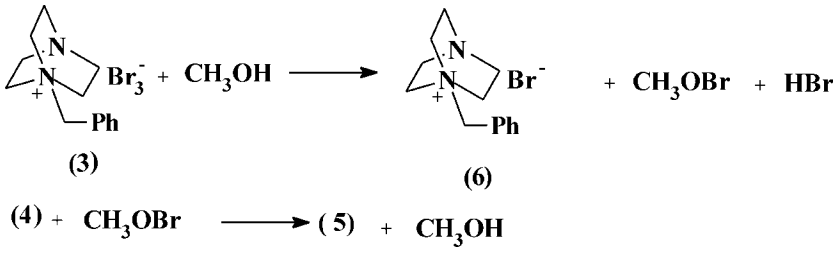
Scheme 2.

is probably methyl hypobromite, which was produced from the reaction of (3) with methanol, which can be employed repeatedly. The generated hydrogen bromide should be neutralized by additional calcium carbonate.[9] The probable mechanism is shown in Sch. 3.

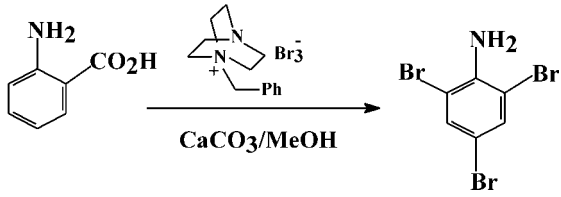
The reaction occurs under mild conditions in a few minutes. Interestingly, in the case of 2-aminobenzoic acid, we obtained 2,4,6-tribromoaniline instead of 2-amino-3,5-dibromobenzoic acid. This product showed that a carboxylic acid group can be replaced by bromine in good yield (Sch. 4, Table 1).

The tribromide (3), having advantages of stable solid crystalline, can be easily handled because of its solid character and availability to be treated quantitatively as compared with the commonly used liquid bromine. It is important that this reagent can be reproduced. After extraction of the bromoaromatic compounds, the aqueous layer was treated with a fresh bath of the aqueous Br_2 to regenerate the reagent **3** in quantitave yield. This means that the complex can be considered to be a Br_2 transfer agent.

In summary it is interesting to mention that this reaction needs only a few milliliters of inexpensive methanol, and the end-point of the reaction can be easily confirmed by decolorization of the orange-colored solution. Other advantages of this reaction are straightforward work-up of product by evaporation of methanol under vacuum and washing the residue with small



Scheme 3.



Scheme 4.

amounts of warm ether to isolate the pure products. Finally, we believe that the procedure for bromination of aromatic amines using Br_3^- is a highly useful method owing to its cost-effectiveness, simplicity, mildness, and good yields.

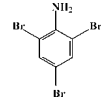
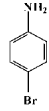
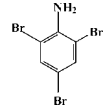
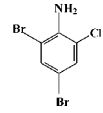
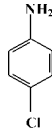
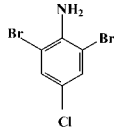
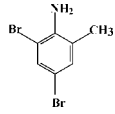
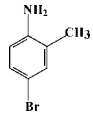
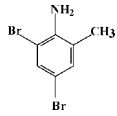
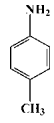
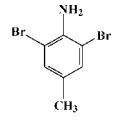
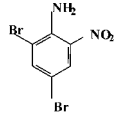
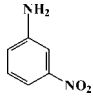
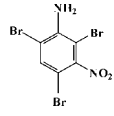
EXPERIMENTAL

All yields refer to isolated products after purification. All the products were confirmed by comparison with authentic samples (mp, TLC, and ^{1}H-NMR).[13–21] All melting points were taken on a Gallenkamp melting apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM-390 NMR spectrometer operating at 90 or 300 MHz. The spectra were measured in $CDCl_3$ (unless otherwise stated) relative to TMS.

Preparation of 1-Benzyl-4-Aza-1-Azoniabicyclo[2.2.2]Octane Tribromide (3)

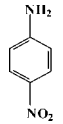
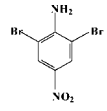
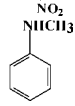
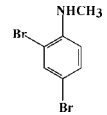
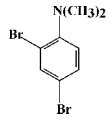
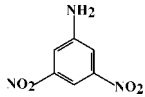
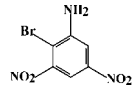
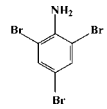
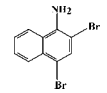
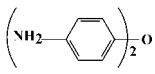
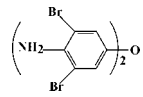
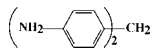
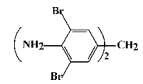
To a stirring solution of KBr (11.9 g, 0.1 mol) in water (200 mL) was added bromine dropwise (16.0 g, 0.1 mol) at room temperature. After 30 min the bromine color disappeared and KBr_3 was formed. To a solution of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (**2**)[22] (24.8 g, 0.1 mol) in water (200 mL) was added the KBr_3 solution dropwise until a yellow precipitate was formed. After stirring 30 min, the reaction mixture was filtered and washed with water (3 × 30 mL). The filtered cake was dried under vacuum and resulted in yellow crystals (40.0 g, 90% yield), which decomposed at 181–183°C to a dark-brown material. IR (KBr): $\upsilon = 3050$ (m), 1600 (s) 1460 (s), 1360 (s), 1040(m), 1210 (s), 840 (m), 800 (m) cm^{-1}, ^{1}H-NMR: δ 3.52–3.57 (t, 6H), 3.68–3.72 (t, 6H), 4.73 (s, 2H), 7.57 (s, 5H), ^{13}CNMR: δ 131.1, 128.9, 127.5, 124.7, 112.4, 48.8, 42.1. UV (CH_2Cl_2) λ_{max}: 279 nm, Anal. Calc. for $C_{13}H_{19}N_2Br_3$: C, 35.24; H, 4.32; N, 6.32%. Found: C, 35.55; H, 4.21; N, 6.53%.

Table 1. Bromination of anilines (**4**) by reagent (**3**).

Entry	Compounds **(4)**	Product (5)[a]	Molar ratio (3/4)	Time (min)	Yield (%)[b]	mp °C or bp °C/ mmHg (lit.)[13–21]
4a			3/1	10	94	121 (112)
4b			2/1	10	95	121 (122)
4c			2/1	15	90	101–102 (103–104)
4d			2/1	15	92	94–95 (95.5)
4e			2/1	5	90	38–40 (39–40)
4f			2/1	5	95	38–40 (39–40)
4g			2/1	25	90	77–78 (79)
4h			3/1	30	85	127 (127)
4i			2/1	45	80	119–121 (120.5)

(*continued*)

Table 1. Continued.

Entry	Compounds (4)	Product (5)[a]	Molar ratio (3/4)	Time (min)	Yield (%)[b]	mp °C or bp °C/ mmHg (lit.)[13–21]
4j			2/1	40	85	204–206 (206–207)
4k			2/1	15	85	48–49 (48–49)
4l			2/1	25	80	276/740 (275/740)
4m			3/1	60	80	178–179 (180)
4n			3/1	25	90	120–122 (122)
4o			2/1	15	90	116–117 (118–119)
4p			4/1	20	90	120–122
4q			4/1	20	85	162–165

[a]All isolated products are known and their spectra and physical data have been reported in literature.
[b]Pure product.

Bromination of Aniline Derivatives (4a–q)

A typical procedure: To a solution of aniline (**4a**) (0.19 g, 2 mmol) in methanol (10 mL) was added (**3**) (2.66 g, 6 mmol) and $CaCO_3$ (0.6 g, 6 mmol).

The reaction mixture was stirred for 10 min at room temperature; meanwhile, decolorization of orange solution took place. When TLC showed complete disappearance of aniline, the solvent was evaporated and the solid residue was washed with ether (4 × 40 mL) and filtered off. The combined organic layers were dried on $MgSO_4$ and evaporated under vacuum to give 2,4,6-tribromoaniline (**5a**), which was recrystallized in methanol/water (1 : 3) as colorless needles in 94% yield (0.62 g).

4,4′-diamino-3,5,3′5′-tetrabromo-diphenylether (4p): m.p. 120–122, ^{1}H-NMR: δ 3.7–3.9 (broad, 4H), 4.1(s-2H), 7.5 (s-4H).

4,4′-diamino-3,5,3′5′-tetrabromo-diphenylmethane (4q): m.p. 162–165, ^{1}H-NMR: δ 4.2–4.6 (broad, 4H), 7.3 (s, 4H).

Regeneration of Reagent (3)

After the residue was washed with ether and filtrated, the filtered cake was washed with water (3 × 20) to dissolve the 1-benzyl-4-aza-1-azoniabicyclo [2.2.2]octane bromide and separate the inorganic salt that is insoluble in water ($CaCO_3$) by filtration. Then, to the combined aqueous solution was added a batch of bromine solution (0.96 gr 6 mmol in 50 mL water) during 30 min to obtain (**3**) as yellow crystals (2.32 gr 90% yield).

ACKNOWLEDGMENT

Partial support of this work by the Isfahan University of Technology (IUT), Research Council is gratefully acknowledged. Further financial support from the Center of Excellency in Chemistry Research (IUT) is gratefully acknowledged.

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Received in UK August 7, 2004