A Direct and Simplistic Bromination of Commercially Important Organic Compounds in Aqueous Media by Eco-friendly AlBr$_3$-Br$_2$ Reagent System

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Abstract A facile, simplistic, highly efficient, environmentally safe, regioselective, controllable and economical method for the bromination of organic compounds using aqueous AlBr$_3$-Br$_2$ reagent system.

Keywords Halogenation, Oxidative-Bromination, Molecular Bromine, Aqueous Medium, New Reagent System

1. Introduction

To date, available research on bromination of organic aromatic compounds in aqueous medium is very few and far between, except only few examples. Ganchegui et al. described the oxybromination of phenol (C$_6$H$_5$OH) and aniline C$_6$H$_5$NH$_2$ subsidiary products using NaBr-H$_2$O$_2$ in H$_2$O/scCO$_2$ (water/supercritical carbon dioxide) biphasic system, however low conversion rate, high temperature (40 °C), longer duration (from 4 to 20 h) and use of surplus amount of reagent (substrate : NaBr : H$_2$O ; 1 : 3 : 3) are some of the concomitant inadequacies. Furthermore, experiments using dense gases must only be conducted in appropriate equipment and under apposite safety precautions. In recent times, Padgorsek et al. defined an interesting oxidative bromination of triggered arenes using H$_2$O$_2$-HBr/”on water” system is advantageous since water is the only by-product; though, a very high reaction time (from 8 hr to 28 hr) and the several threats associated with H$_2$O$_2$ make the process of limited industrial utility. The highly lethal 48 per cent aqueous HBr reacts aggressively with many metals with the generation of extremely flammable hydrogen gas, which may burst, which further limits its usage. Other described—on water || and —in water || brominating system are limited only to the synthesis of bromohydrins, α-bromoketones, iodination and benzylic bromination.

Factually hundreds of Br$_2$-based and oxidative bromination reagents have been described for the bromination of organic compounds, some latest reports are given in Table no. 5. For Bromine (Br$_2$) there are several other reagent systems that have been established as a substitute, but not restricted to, NBS/[Bmim]Br, ZrBr$_4$/diazene, [k.18-crown-6]Br$_3$, [BMPy]Br$_3$ [Hmim] Br$_3$, [Bmim] Br$_3$,53f poly(4-vinylpyridinium tribromide), DABCO-bromine, pentapyridinium tribromide, ethylene bis(N- methylimidazolium) ditribromide. The bromination of polymer latex has been carried out using bromine emulsion which is prepared by liquefying bromine (Br$_2$) into an aq. solution of wetting agent/surfactant.

On the other hand, nothing like such reagent commercialized till date, because of its costly nature, very bad retrieval and recycling of used reagent/agent, waste treatment for large quantities of HBr-byproduct and poor stability of reagents and storage challenges in long period; therefore they are suitable for laboratory-scale requirements only with narrow application range. In the Previous section of the chapter, we have described aq. Al Br$_3$- Br$_2$ system in acetonitrile (MeCN) as a highly effective brominating agent which provided a rapid bromination of industrially important compounds in outstanding yields and pureness. The method is advantageous due to the cost-effective nature of the brominating reagent and high pureness of the wanted products, whereas the usage of organic solvents acetonitrile (MeCN) and the further utility. Consequently, to make the system more industrially-oriented and environmentally-approachable, we tried the bromination of liquid substrates using aq. Al Br$_3$- Br$_2$ can diffuse through the dews of aniline leading to bromination. During the reaction process the bromine (Br$_2$) color vanished instantly resulting the instantaneous synthesis of 2,4,6-tribromoaniline in 96 per cent yield (HPLC pureness 99.7 per cent) within 15 min of reaction time (Table no. 7, entry 19). This result heartened us to brominate the solid substrate (4-nitroaniline) under the similar conditions. As we noticed an instantaneous loss of reddish-brown hue in the round bottom flask and whole Br$_2$
get used within 2-3 minutes of magnificent signifying a prompt interface between the Br₂ and 4-nitroaniline has occurred in the aqueous system. Yellow color crystalline powder in 98 per cent yield of 2,6-dibromo-4-nitroaniline (HPLC purity of 99.08 per cent) was achieved (Table no. 7, entry 16). Cheered by the above resulted outcomes, the bromination of industrially-important compounds using aqueous Al Br₃-Br₂ solution under aqueous conditions at room temperature without using any organic solvent before and after the completion of reaction, the reaction have successfully been performed.

While bromination was carried out in water using aq. Al Br₃ system, it offers the following benefits:

1. Absence retrieval step and loss of solvent during the recycling procedure that makes the present reaction more appropriate, (2) no addition of water is obligatory after completion of reaction as the brominated product too is insoluble in water in case of acetonitrile solvent, 15 ml water has to be added for 10 ml acetonitrile (MeCN) solvent to separate the precipitated product. This upsurges the overall volume of filtrate thereby upturn the cost of recovery of Al Br₃ from the aq. medium at the completion of reaction, (3) the reaction is functionally-easy and friendly which don’t requires heating or cooling, (4) the brominated compound and Al Br₃ recuperated at the end of reaction are in unadulterated form as there is no organic solvent in the reaction mixture for their adulteration and also the only HBr byproduct present in the aqueous filtrate has to be transformed to Al Br₃ (5) the present method leads to zero waste discharge to the surroundings, since from the three components of the reagent, i.e., Al Br₃, Br₂ and water; one atom of Br₂ was shifted to organic substrate and the other half-forming HBr is again employed back to Al Br₃ by its neutralization with Ca(OH)₂.

The Al Br₃ of the fresh reaction and additional Al Br₃ produced from HBr nullification was recovered as a crystalline solid by concentrating the aqueous filtrate (14 g Al Br₃ in 20 ml H₂O similar to collected works procedure). The recovered Al Br₃ has possible industrial value in different sectors i.e; Pharmaceuticals, preservers, and fire retardants etc. have also been employed effectively to rejuvenate the brominating reagent for bromination in consequent batches without any substantial loss of reactivity. Henceforward, at the end of the reaction we have nonentity to dispose to the environment which is justified in view of green chemistry.

Bromination of substituted aromatics compounds using aqueous Al Br₃-Br₂ system

2. Objective

Clean and green reaction methods that do not use dangerous organic solvents are reinvigorated and are in excessive demand now. A modern report on “green solvents” determined that the use of solvents like dioxane, acetonitrile, 1-butanol, propanol, acids, acetone, ethyl, formaldehyde and THF are not suggested from an environmental viewpoint. Water, on the other hand, is an auspicious solvent because it is readily available, non-flammable, non-toxic and can give the easy split-up of catalysts or reagents from many aromatic products. To date, water is rarely used in accessible research on bromination of aromatic compounds, which is very limited except few examples. Factually hundreds of Br₂-based and oxidative bromination reagents have been described for the bromination of organic compounds. On the other hand, no such commercial reagent is available till date, due to their costly nature, poor retrieval and recycling of used reagent, waste treatment for large quantities of HBr-byproduct and poor stability of reagents and storage challenge in long periods; therefore they are suitable for laboratory-scale requirements only with narrow application range. The usage of aqueous AlBr₃-Br₂ system as the most inexpensive brominating agent and H₂O as a reaction media exemplifies the most logical and reasonable choice of brominating reagent to fulfill the need of inexpensive, cleaner and most effective system. In simple words, H₂O fulfills all the requirements in direct synthesis of commercially- important brominated aromatic compounds. In current study, we are presenting, for the first time, a simple and direct bromination of C₆H₅OH and C₆H₅NH₂ subsidiary products with strong electron-withdrawing groups (EWG) such as carboxylic (-COOH), nitro (-NO₂) and formyl (-CHO) as examples of pharmaceutical reaction intermediates under absolutely aqueous conditions.

3. Experimental

i) Reagents and analytics

Reagents and initial material were procured from across, Aldrich and Merck and were used as usual. Only fine powdered form substrates were used during complete reaction process, granulated and scaly substrates were grinded and transformed into fine powder prior to reactions to improve the dissolution factor. Twice as distilled water was used during the complete study, Water model no. 2695 instrument with PDA detector was used for HPLC analysis purpose, column C18 (250mm × 4.6× 5 μ ) , solvent scheme of 70 per cent CH3OH + 30 per cent H2O, and 1 mL/minute flow rate. HPLC purity is represented by area per cent. Bruker Avance II 400 NMR spectrometer was used for NMR studies and chemical shifts were described by δ ppm; spectra were recorded in DMSO and CDC13, 1H NMR (comparative to TMS referenced as 0.00 ppm) and 13C NMR (comparative to DMSO referenced as 39.50 ppm). GCMS studies were performed by using “Agilent GC-5893” with chromatation software; HP5-MS-column, with specification 30m × 0.25mm × 0.25µ; constant flow of- 2 ml/minutes; mass-director; mass range- 14 to 650 amu; detector temp- 290°C; injector temp- 280°C; injected sample volume- 1 microliter of 5 per cent solution in methanol. Mass spectroscopical (MS) data were documented on “Micromass Quattro Micro API triple quadrupole MS” which was...
equipped with a Bunchner funnel, and then washed-off with Na₂S₂O₃ solution (10 per cent, 10 ml × 3) and dried out in vacuum drying oven at 100 °C. The product was achieved as yellow powder (2.90 g, 98 per cent yield, and 99.03 per cent HPLC of 2, 6-dibromo-4-nitroaniline (DBNA) and the desired melting point of 206-208 °C, which is not actually as per the required specifications. Further reduction in mole ratio of Br₂/4-NA from 1.8 to 1.65, decrease the yield percentage of under-brominated product from 93-88 per cent, which melts at 102-103 °C, correspondingly (melting point of 2-bromo-4-nitroaniline is 102-103 °C), at the mole ratio of 1.5 and 1.25.

iii) The effect on yield and melting point of DBNA by mole ration of Br₂

The excellence of the end product is strongly reliant on the mole ratio of Br₂/4-NA which also has been confirmed by recent studies. It also been initiated that the optimal yield (98 per cent) of 2, 6-dibromo-4- nitroaniline (DBNA) and the desired melting point of 206°C (literature, 206-208°C) are achieved at 2:1 mole ratio of Br₂/4-NA in the bromination of 4-NA by aqueous AlBr₃ solution as effective brominating agent. Further, if we increase the mole ratio of Br₂/4-NA from 2.0 to 2.2, yield of end product becomes stagnant. If we reduce the mole ratio from 2.0 to 1.8, the end product yield drops 98-93 per cent with a reduction in melting point 198-200 °C, which is not actually as per the required specifications. Further reduction in mole ratio of Br₂/4-NA from 1.8 to 1.65, decrease the yield percentage of under-brominated product from 93-88 per cent, which melts at 160-170°C. The monobrominated 4-nitroaniline were achieved that melt at 102°C and 100-101°C, correspondingly (melting point of 2-bromo-4-nitroaniline is 104°C), at the mole ratio of 1.5 and 1.25.

iv) The Route for Recycle/Reutilize 2, 3 and 4

Analogous to the above typical method of Reutilize 1, Br₂ (3.2 g, 20 mmol) was added to the aq. solution containing recycled aluminium tribromide (AlBr₃) achieved after the separation of 2, 6-dibromo-4-nitroaniline (Br₂C₆H₄(NO₂)NH₂) and the reaction proceeded in a similar reaction pattern with 4- nitroaniline, C₆H₄N₂O₂ (1.3726 g, 10 mmol) for every reaction cycle.

4. Result & Discussion

i) Reaction conditions screening

The dibromination of para-substituted substrate decreases the possible complex mixture of mono- and dibrominated species, thus in order to abridge the analytics, 4- nitroaniline (4-NA) was castoff as a typical substrate in a first-screening in a first-screening for appropriate reaction conditions. To optimize the yield and pureness, the bromine (Br₂) and (AlBr₃) concentration effects on the end product yield and Melting point are achieved. With increase in mole ratio of Br₂/4-NA from 0.25 to 2.0, yield of end product becomes stagnate. If we increase the mole ratio from 2.0 to 2.2, yield of end product becomes stagnant. If we reduce the mole ratio from 2.0 to 1.8, the end product yield drops 98-93 per cent with a reduction in melting point 198-200 °C, which is not actually as per the required specifications. Further reduction in mole ratio of Br₂/4-NA from 1.8 to 1.65, decrease the yield percentage of under-brominated product from 93-88 per cent, which melts at 160-170°C. The monobrominated 4-nitroaniline were achieved that melt at 102°C and 100-101°C, correspondingly (melting point of 2-bromo-4-nitroaniline is 104°C), at the mole ratio of 1.5 and 1.25.

ii) Procedure for recycling of Hydrogen Bromide as AlBr₃ and reformation of brominating reagent (Recycle 1)

The neutralization of filtrate originated from above reaction done by Al(OH)₃ (0.7401 g, 10 mmol) to convert hydrogen bromide into AlBr₃. Consequently, (3.23 g, 20 mmol) Br₂ was added to the aq. solution containing recycled aluminium tribromide solution was then added fine powder of 4-nitroaniline (1.3813 g, 10 mmol) quickly within 5 minutes taken in a round-bottom flask (100 ml) equipped with a pressure-equalizing funnel and magnetic stirring bar. The thick yellowish precipitates of 2, 6-dibromo-4-nitroaniline were attained within 20 minutes at room temperature immediately after adding Br₂ color disappeared. By using vacuum filtration the end product was separated from the mother liquor (solution left over after crystallization) and then washed-off with sodium thiosulfate (Na₂S₂O₃) solution (10 per cent, 10 ml × 3) and dried out in vacuum drying oven at 100°C. A high purity (99 per cent) 2, 6-dibromo-4-nitroaniline yellow powder was achieved in 2.82 g (98.08 per cent) yield with melting point 206°C. The distinguishing data was documented for the isolated product and found similar as given in the above distinctive method.

The hydrogen bromide evolved was again nullified and the aqueous solution was uninterruptedly recycled in the next run with an additional amount of Br₂.

2.82 g (98.08 per cent) yield with melting point 206-208°C. The product was achieved as yellow powder (2.90 g, 98 per cent yield, and 99.03 per cent HPLC of 2, 6-dibromo-4-nitroaniline (DBNA) and the desired melting point of 206°C (literature, 206-208°C) are achieved at 2:1 mole ratio of Br₂/4-NA in the bromination of 4-NA by aqueous AlBr₃ solution as an effective brominating agent. Further, if we increase the mole ratio of Br₂/4-NA from 2.0 to 2.2, yield of end product becomes stagnant. If we reduce the mole ratio from 2.0 to 1.8, the end product yield drops 98-93 per cent with a reduction in melting point 198-200 °C, which is not actually as per the required specifications. Further reduction in mole ratio of Br₂/4-NA from 1.8 to 1.65, decrease the yield percentage of under-brominated product from 93-88 per cent, which melts at 160-170°C. The monobrominated 4-nitroaniline were achieved that melt at 102°C and 100-101°C, correspondingly (melting point of 2-bromo-4-nitroaniline is 104°C), at the mole ratio of 1.5 and 1.25.

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iii) Influence of AlBr₃/Br₂ mole ratio on yield and melting point of 2, 6-dibromo-4- nitroaniline (DBNA)

Available literature shows an identical pattern in the bromination of 4-NA using aqueous AlBr₃ solution as brominating agent because of increase in mole ratio of AlBr₃/4-NA from 0.25 -2.0; at mole ratio 2:1 ideal yield and preferred melting point are achieved. With increase in mole ratio of AlBr₃/4-NA from 0.25 to 2.0, melting point does not change significantly but the yield of the product upturns.
(from 91 to 98 per cent. The function of aluminium tribromide (AlBr₃) was defensible by performing a blank reaction for 1 h at 25°C using molecular bromine as a brominating agent which resulted in a composite fusion of under-brominated species that melt from 160 to 190°C. Thus, the result drawn in to conclusion that the optimal mole ratio 1:2:2 of 4-NA to AlBr₃ to Br₂ was establish to be best for the dibromination of 4-NA.

iv) Stirring

For mixing the hydrophobic aromatic substrate with the aqueous inorganic medium and for preventing local high concentrations of active bromo species, as the reaction was prompt, a proficient/effective stirring (750 rpm or higher) was required. The common applicability of this method was recognized when bromination of structurally-different activated aromatic compounds substituted with electron-withdrawing groups were analyzed (Table 2). It is the revolution of the present bromination reagent (aq. AlBr₃-Br₂ solution) over a newly reported brominating system (NBS/[Bmim]Br or dioxane) that C₆H₅OH and C₆H₅NH₂ byproducts with strong electron-withdrawing groups (EWG) such as -COOH, -NO₂ and -CHO were promptly brominated regioselectively in outstanding yields and pureness. The same reported system, however, yields a combination mix of mono- and dibromo products. In the present system, salicylic acid 1 and 4-hydroxybenzoic acid 2 were transformed with quantitative conversion resulting in clean synthesis of 3,5- dibromosalicylic acid (92 per cent yield; 96.2 per cent HPLC purity) and 3,5-dibromo-4-hydroxybenzoic acid (94 per cent yield; 99.2 per cent HPLC purity) after 20 min and 15 min, respectively. Pharmacuetically-important aromatic aldehydes (Table 3, entries 3, 4, 5) were also instantaneously synthesized using aq. AlBr₃-Br₂ system in excellent yields. Under these conditions, acetaniline 6 and benzaniline 7 were regioselectively transformed to their mono-brominated products in very good yields. The regioselectivity witnessed in these reactions matches to that predictable for an electrophilic bromination path modulated by steric effects. We observed that oxine (8) and sulfanilamide (9) could also be efficiently brominated affording pharmaceutically-important 5, 7-dibromooxine (96 per cent yield; 99.67 per cent HPLC pureness) and 3,5-dibromosulfanilamide (94 per cent yield; 96.6 per cent HPLC pureness) within 15 minutes. Another antibacterial compound, 2, 4-dibromo-6-nitrophenol was isolated in excellent yield within 20 minutes from 2-nitrophenol (Table no. 6, entry 10). With the poor reactivity 4-nitrophenol (11) shows outstanding reactivity resulting 2,6-dibromo-4-nitrophenol (94 per cent yield; 97.5 per cent HPLC pureness) within 30 minutes using two equivalent of reagent. Bromination of the same substrate with H₂O₂-HBr/‘on water, gave 2, 6-dibromo-4-nitrophenol over a period of 24 hr. The advantages of the present system is a regioselective, effective, facile, and fast bromination of deactivated anilines (Table no. 6, entries 12 to 16) in outstanding end product yields at 25°C upon simple admixing with aq. CaBr₂-Br₂ solution which is slightly challenging by other methodologies. 1-Bromo-2- naphthol 17 (92 per cent yield; 96.2 per cent HPLC pureness) was promptly obtained under undistinguishable reaction conditions in excellent yield within 10 minutes of reaction time while for 1,6-dibromo-2-naphthol 18 (97 per cent yield; 96.5 per cent HPLC purity), within 25 minutes and 2 equivalents of aqueous AlBr₃-Br₂ solution were necessary. Which represents the position of the electrophilic attack and the number of inflowing Br₂ atoms during reaction process can be structured by controlling the ratio of substrate: aqueous AlBr₃-Br₂ solution, i.e., 1/1 mono-, 1/2 for di-, and 1/3 for tribromination of aromatic compounds.
Table 1. A comparison of the results of present system (aq. AlBr$_3$-Br$_2$ solution) with the literature precedents of some recently published brominating systems in the synthesis of pharmaceutical intermediates

| Entry | Substrate | Product | aq AlBr$_3$-Br$_2$ (present system) | Recently published brominating systems |
|-------|-----------|---------|-------------------------------------|---------------------------------------|
| 1.    | $\text{NH}_2\text{NO}_2$ | $\text{Br}\text{NH}_2\text{NO}_2$ | 92 per cent, 15 min, 25°C(99.2 per cent)$^b$ | NH$_3$/H$_2$O$_2$/AcOH 73 per cent, 4h, rt HBr/H$_2$O$_2$/MeOH 99 per cent, 12h, 0°C to rt, NBS/SO$_3$/H-functionalized silica 91 per cent, 3h, rt. |
| 2.    | $\text{NHCOCH}_3$ | $\text{BrNHCOCH}_3$ | 96 per cent, 15 min, 25°C(99.9 per cent)$^b$ | LiBr/CAN/MeCN 99 per cent, 1h, rt, KBr/BTPPMS/MeCN 90 per cent, 4h, rt, TEATB/H$_2$O-DMF 65 per cent, 1h, rt, KBr/ H$_2$O$_2$/CuPcF$_{16}$-APSG/MeCN 87 per cent, 2.2h, 60°C |
| 3.    | $\text{HCOCH}_3$ | $\text{HO-CH}_3\text{CHO}$ | 93 per cent, 20 min, 25°C(96.6 per cent)$^b$ | NBS/MeCN/h$_2$O 89 per cent, 1h, rt NBS/MeCN/h$_2$O 89 per cent, 1h, 32°C |
| 4.    | $\text{HCOCH}_3$ | $\text{HO-CH}_3\text{CHO}$ | 93 per cent, 15 min, 25°C(96.2 per cent)$^b$ | Hexaminethylene tetraminebromine/CH$_2$Cl$_2$ 30 per cent, 5 min, rt |
| 5.    | | | 96 per cent, 15 min, 25°C(99.67 per cent)$^b$ | HBr/iso-amyl nitrite/ CH$_2$Cl$_2$ 100 per cent, 16h, rt |
| 6.    | $\text{O}_2\text{N-CH}_2\text{OH}$ | $\text{O}_2\text{N-CH}_2\text{OH}$ | 94 per cent, 15 min, 25°C(97.5 per cent)$^b$ | H$_2$O$_2$/HBr/`on water` 95 per cent, 24h, rt |
| 7.    | $\text{NH}_2\text{NH}_2$ | $\text{NH}_2\text{NH}_2$ | 96 per cent, 15 min, 25°C(99.7 per cent)$^b$ | HBr/ H$_2$O$_2$/MeOH 96 per cent, 8h, 0°C to rt TEATB/H$_2$O-DMF 63 per cent, 1.5h, rt TEATB/50 per cent aq DMF 65 per cent, 15 min, rt |
| 8.    | | | 97 per cent, 25 min, 25°C(96.5 per cent)$^b$ | HBr/ H$_2$O$_2$/MeOH 84 per cent, 20h, rt |
| 9.    | | | 92 per cent, 10 min, 25°C(96.23 per cent)$^b$ | HBr/ H$_2$O$_2$/MeOH 93 per cent, 15h, rt KBr/ H$_2$O$_2$/AcOH/Zoelite 45 per cent, 5h, rt KBr/BTPPMS/MeCN 92 per cent, 2h, rt KBr/ H$_2$O$_2$/CuPcF$_{16}$-APSG/MeCN 75 per cent, 2h, 60°C H$_2$O$_2$/HBr/`on water` 90 per cent, 8h, rt |
| 10.   | $\text{OH}$ | $\text{OH}$ | 98 per cent, 20 min, 25°C(99.03 per cent)$^b$ | HBr/ H$_2$O$_2$/MeOH 95 per cent, 10h, 0°C to rt H$_2$O$_2$/HBr/`on water` 95 per cent, 28h, rt |

The use of aqueous AlBr$_3$-Br$_2$ system as the most economical brominating agent and H$_2$O as a solvent/reaction medium denotes the most logical choice as a brominating reagent to fulfill the need of inexpensive, cleaner and most effective system for the instantaneous synthesis of commercially-significant brominated compounds. A comparative study of the brominating capability of the aqueous AlBr$_3$-Br$_2$ system with the recently circulated methods is testified in Table 5 which clearly indicates the benefits of the present system over obtainable methods. In this present study, we are presenting, an effective reagent system for electron-withdrawing groups (EWG) like; -COOH, NO$_2$ and -CHO as examples of pharmaceutical reaction intermediates under purely aqueous conditions.
**Table 2.** Bromination by using aqueous AlBr$_3$-Br$_2$ system for several aromatic compounds

| Entry | Substrate | Product | Solvent system | Mp/°C (lit.) | Application |
|-------|-----------|---------|----------------|-------------|-------------|
|       |           |         | Water$^a$       | Acetonitrile$^a$ |             |
|       |           |         | Time/min | Yield$^d$ (per cent) | Time/min | Yield$^d$ (per cent) |             |
| 1.    |          |         |           |             |             |             | Antibacterial, antifungal |
| 2.    |          |         |           |             |             |             | Antibacterial, antifungal and anthelmintic |
| 3.    |          |         |           |             |             |             | Intermediate for agrochemicals and pharmaceuticals |
| 4.    |          |         |           |             |             |             | Intermediate for dyestuffs |
| 5.    |          |         |           |             |             |             | A potent antifungal, in the preparation of diazonium |
| 6.    |          |         |           |             |             |             | Fine organic and custom intermediate |
| 7.    |          |         |           |             |             |             | Fine organic and custom intermediate |
| 8.    |          |         |           |             |             |             | Precursor for substituted thiazoles used as fungicides |
| 9.    |          |         |           |             |             |             | Pharmaceutic-al intermediate |
| 10.   |          |         |           |             |             |             | Anthelmintic |
Underneath these reaction conditions, the deactivated substrate like nitrobenzene and benzoic acid did not show any transformation at all. Table no. 2 discloses that the yield and the reaction time for several brominated products are comparable in H₂O and acetonitrile (ACN) as solvents, correspondingly. The only limitation associated with the reaction using water as a solvent is that granular and scaly substrates have to be crushed and ground proceeding to reactions to convert them into fine powders. Since the reaction operates entirely in water and generates absolute zero discharge; it seems very effective valuable from environmental safety point of view to extend this system for other commercially-important compounds. Subsequent, a desirable greener approach to the present study is following by an environmental friendly recycling procedure. The nonexistence of organic waste and organic solvents in the reaction process supported simple separation procedure comprised of filtration of solid phase brominated compounds and the addition of calcium hydroxide powdered form (Ca(OH)₂) to the filtrate for the neutralization of hydrogen bromide waste so that the bromine of hydrogen bromide thus fixed as Aluminum bromide. The aqueous filtrate was reclaimed in the next cycle and the reinforced brominating agent was then used to brominate the substrate successively in the next run.

**Table 3. Reprocessing experiments for the dibromination of 4-nitroaniline**

| Recycle | Appearance | Yield (per) | Mp°C (lit., °C) | Purity |
|---------|------------|-------------|----------------|--------|
| Newbatch | Yellow Powder | 98.2 | 206 | 99.20 |
| Reprocess 1 | Yellow Powder | 98.0 | 206 | 98.98 |
| Reprocess 2 | Yellow Powder | 97.6 | 204-206 | 98.57 |
| Reprocess 3 | Yellow Powder | 97.3 | 205-206 | 98.26 |
| Reprocess 4 | Yellow Powder | 97.4 | 204-206 | 98.84 |

*Surroundings: 10mmol 4-NA, 20mmolBr₂(4-NAandBr₂ moles charged in every reaction cycle) and 20mmolAlBr₃ (charged for fresh batch only) at room temperature (25°C) for 20 minutes (each cycle).

*** Inaccessible Yields  ** Purity determined by HPLC
By this methodology, very productively and effectively the dibromination of 4-nitroaniline has been carried out for 4 cycles after the fresh batch using 4-NA: Br₂ (1: 2) mole ratio in each run without adding of the fresh aluminium tribromide (AlBr₃) to give 2, 6-dibromo-4-nitroaniline within 20 minutes at room temperature. Reprocessing experiments (Table no. 7) shows that for at least 4 cycles followed by the fresh batch, there is no substantial loss of reactivity of the rejuvenated brominating reagent. When the concentration of aluminium tribromide (AlBr₃) upturns in the filtrate, then through vaporization process filtrate was concentrated which causes precipitation of AlBr₃ as a crystalline solid and an added amount of AlBr₃ (7 mol) was recuperated after fresh batch + 4 cycles: resulted 1 mol of aluminium tribromide (AlBr₃) produced likewise in every cycle by the neutralization of hydrogen bromide by adding Al(OH)₃. Therefore, starting with 1 mol of 4-NA wrt 2 mol of Aluminium tribromide in the fresh batch, at the end of reaction process we achieved 7 mol of AlBr₃. Consequently, effectively the byproduct hydrogen bromide has been utilized, and at the end of reaction, process generates zero discharge of organic waste and effluent to the surroundings.

**Figure 8.** 1H-NMR spectra of 3,5-dibromosalicylic acid (1)
Figure 9. IR spectra of 3,5-dibromosulfanilamide (9)

Figure 1. \(^1\)H-NMR spectra of 4-bromoacetanilide (6)
A Direct and Simplistic Bromination of Commercially Important Organic Compounds in Aqueous Media by Eco-friendly AlBr₃-Br₂ Reagent System

Figure 10. GC-MS of 3,5-dibromosulfanilamide (9)
Figure 11. GC-MS of 2,4-dibromo-6-nitrophenol (10)
Figure 12. LC/MS of 2,6-dibromo-4-nitroaniline (Br₂C₆H₂(NO₂)NH₂) (16)
Figure 13. 1H and 13C-NMR of 2,6-dibromo-4-nitroaniline (16)
5. Conclusions

We have testified a rapid, mild, cost effective and facile method for the effective and selective synthesis of pharmaceutically-important brominated intermediates using aq. AlBr3-Br2 system as an instantaneous brominating agent under aqueous conditions. The green features of this practice include no use of organic solvent and an operative utilization of HBr byproduct which lead to zero organic waste and zero waste discharge to the environment, consequently applicable for large scale bromination.

The categorization data (1H NMR, Infrared and Mass Spectroscopy) achieved for various representative compounds are given below:

3,5-Dibromo-4-hydroxybenzoic acid (2): White fine crystalline powder; 1H NMR (400 MHz, Dimethyl Sulfoxide”DMSO”): δ 8.02 (2H, ArH, s), 11 (1H, OH, s), 13 (1H, COOH, s); Infrared (KBr): 3450, 3081, 2976, 2652, 2530, 1798, 1690, 1588, 1482, 1420, 1340, 1305, 1275, 1205, 1169, 1137, 903, 893, 766, 738, 718, 671, 520, 470 cm⁻¹; MS m/z (mass-to-charge ratio) calcd. for C7H4Br2O3: 329.816, found 328.8.

1H NMR (400 MHz, Trichloroacetonitrile “CDCl3”): δ: 7.5 (2H, s, Ar), 4.54 (2H, br. S, NH2). Infrared (KBr): 3436, 3288, 1468, 1392, 1274, 1238, 1057, 849, 736, 712, 666, 542, 478 cm⁻1 MS Atmospheric Pressure Chemical Ionization (APCI) m/z (mass-to-charge ratio) calcd. for C6H4Br3N: 329.816, found 328.8.

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