Chemistry International 1(3) (2015) 107-117

International Scientific Organization
http://iscientific.org/
Chemistry International
www.bosaljournals.com/chemint/

A direct and simplistic bromination of commercially important organic compounds in aqueous media by eco-friendly $AlBr_3$-Br_2 reagent system

Sushil Kumar Sharma* and D. D Agarwal

Department of Chemistry, JJTU, Rajasthan, India
*Corresponding author's E. mail: drsharmasushil@gmail.com

A R T I C L E I N F O

Article type:
Research article
Article history:
Received February 2015
Accepted May 2015
July 2015 Issue
Keywords:
Halogenation
Oxidative-bromination
Molecular Bromine
Aqueous Medium
New reagent system
Eco-friendly synthesis
Bromination

A B S T R A C T

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 was investigated.

© 2015 International Scientific Organization: All rights reserved.

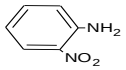
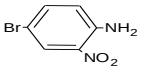
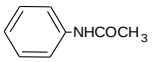
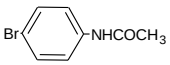
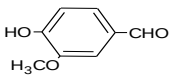
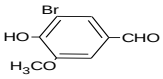
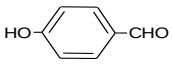
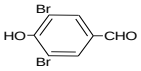
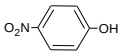
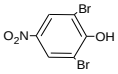
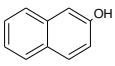
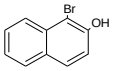
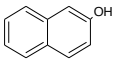
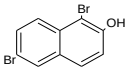
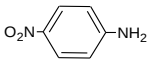
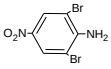
Capsule Summary: Bromination of substituted aromatics compounds using aqueous $AlBr_3$-Br_2 system is versatile technique for the synthesis of different brominated compounds.

Cite This Article As: Sushil Kumar Sharma and D. D Agarwal. A Direct and simplistic Bromination of commercially important organic compounds in aqueous media by eco-friendly $AlBr_3$-Br_2 reagent system. Chemistry International 1(3) (2015) 107-117.

INTRODUCTION

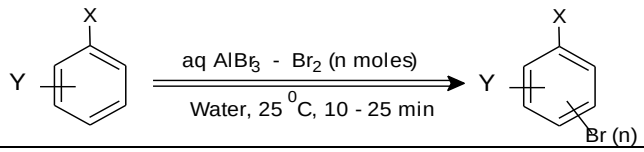
To date, available research on bromination of organic aromatic compounds in aqueous medium is very few and far between, except only few examples. Ganchegui et al. described the oxybromination of phenol (C_6H_5OH) and aniline $C_6H_5NH_2$ subsidiary products using NaBr-H_2O_2 in H_2O/$scCO_2$ (water/supercritical carbon dioxide) biphasic system, howbeit low conversion rate, high temperature (40 ^oC), longer duration (from 4 to 20 h) and use of surplus amount of reagent (substrate: NaBr : H_2O; 1 : 3 : 3) are some of the concomitant inadequacies (Bedekar et al., 2005; Surine et al., 1968). 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_2O_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_2O_2 make the process of limited industrial utility (Beckmann et al., 2013). 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 systems are limited only to the synthesis of bromohydrins, α-bromoketones, iodination and benzylic bromination.

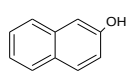
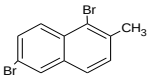
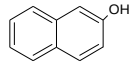
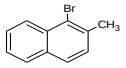
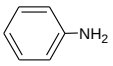
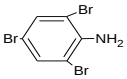
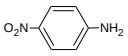
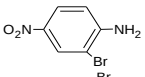
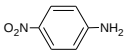
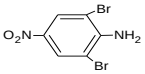
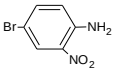
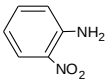
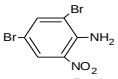
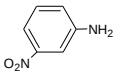
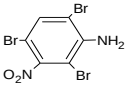
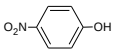
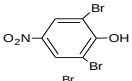
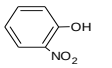
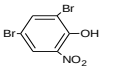
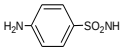
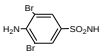
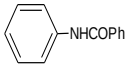
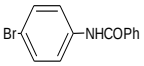
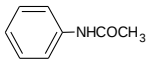
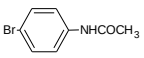
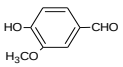
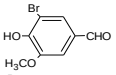
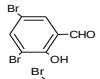
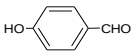
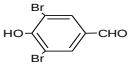
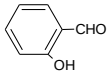
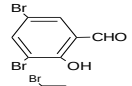
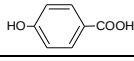
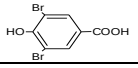
Table 1: A comparison of the results of present system (aq. $AlBr_3$-Br_2 solution) with the literature precedents of some recently published brominating systems in the synthesis of pharmaceutical intermediates

Entry	Substrate	Product	aq $AlBr_3$-Br_2 (present system)[a]	Recently published brominating systems
1.			92%,, 15 min, 25°C(99.2%)[b]	NH_4Br/H_2O_2/AcOH 73%, 4h, rt HBr/H_2O_2/MeOH 99% ,12h, 0°C to rt, NBS/SO_3H-functionalized silica 91%, 3h, rt.
2.			96%, 15 min, 25°C(99.9%)[b]	LiBr/CAN/MeCN 99%, 1h, rt, KBr/BTPPMS/MeCN 90%, 4h, rt, TEATB/H2O-DMF 65%, 1h, rt, KBr/ H_2O_2/$CuPcF_{16}$-APSG/AcOH 87%, 2.2h, 60 °C
3.			93%, 20 min, 25°C(96.6%)[b]	NBS/NH_4OAc/MeCN 89%, 1h, rt NBS/MeCN/hυ 88%, 30 min, 32°C NBS/SO_3- functionalized silica 73%, 3h, rt.
4.			93%, 15 min, 25°C(96.2%)[b]	Hexaminethylene tetraminebromine/CH_2Cl_2 30%, 5 min, rt
5.			96%, 15 min, 25°C(99.67%)[b]	HBr/iso-amyl nitrite/ CH_2Cl_2 100%, 16h, rt
6.			94%, 15 min, 25°C(97.5%)[b]	H_2O_2-HBr/`on water` 95%, 24h, rt
7.			96%, 15 min, 25°C(99.7%)[b]	HBr/ H_2O_2/MeOH 96%, 8h, 0°C to rt TEATB/H_2O-DMF 63%, 1.5h, rt TEATB/50% aq DMF 65%, 15 min, rt
8.			97%, 25 min, 25°C(96.5%)[b]	HBr/ H_2O_2/MeOH 84%, 20h, rt
9.			92%, 10 min, 25°C(96.23%)[b]	HBr/ H_2O_2/MeOH 93per cent, 15h, rt KBr/ H_2O_2/AcOH/Zeolite 45per cent, 5h, rt KBr/BTPPMS/MeCN 92per cent, 2h, rt KBr/ H2O2/$CuPcF_{16}$-APSG/AcOH 75per cent, 2h, 60°C H_2O_2-HBr/`on water` 90per cent, 8h, rt
10.			98%, 20 min, 25°C(99.03%)[b]	HBr/ H_2O_2/MeOH 95per cent, 10h, 0°C to rt H_2O_2-HBr/`on water` 95per cent, 28h, rt

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 1. 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

Table 2: 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	Solvent system				M. Point (^{0}C)	Applications
			Water		Acetonitrile			
			Time/min	Yield	Time/min	Yield		
1			20	96	25	97	103-104 (105-107)	Antibacterial, antifungal
2			15	93	10	96	83-84 (84)	Antibacterial, antifungal and anthelmintic
3			18	95	8	96	120 (120-121)	Intermediate for agrochemical-s and pharmaceuticals
4			20	93	20	94	104(102-104	Intermediate for dyestuffs
5			20	98	10	98	206(206-208	A potent antifungal, in the preparation of diazonium
6			18	91	15	90	108(110-113	Fine organic and custom intermediate
7			18	96	15	96	127(128-129	Fine organic and custom intermediate
8			15	96	15	95	101(101-103	Precursor for substituted thiazoles used as fungicides
9			30	94	28	95	145(145-147	Pharmaceutic-al intermediate
10			18	91	25	96	114(116-117	Anthelmintic
11			20	95	20	94	235(235-237	Pharmaceutic-al intermediate
12			15	96	15	95	200(198-200	A potent antifungal antiamoebic
13			18	97	20	95	200-202 (202)	Pharmaceutic-al intermediate
14			15	95	12	98	166(165-169	Analgesic, Antipyretic
15			25	92	35	96	163(164-166	In pharmaceutical flavor
16			25	95	15	93	82(80-84	Pharmaceutic-ally acceptable salt as inhibitor
17			20	92	20	96	183(181-185	Pharmaceutic-al intermediate
18			20	91	20	90	226(226-229	Bactericide when incorporated in to topical ointments
19			20	95	---	---	270(271-274	Medical intermediate

[Hmim]Br_3, [Bmim]Br_3, poly(4-vinylpyridinium tribromide), DABCO-bromine, pentypyridinium tribromide, ethylene bis(N-methylimidazolium) ditribromide. The bromination of polymer latex has been carried out using bromine emulsion which is

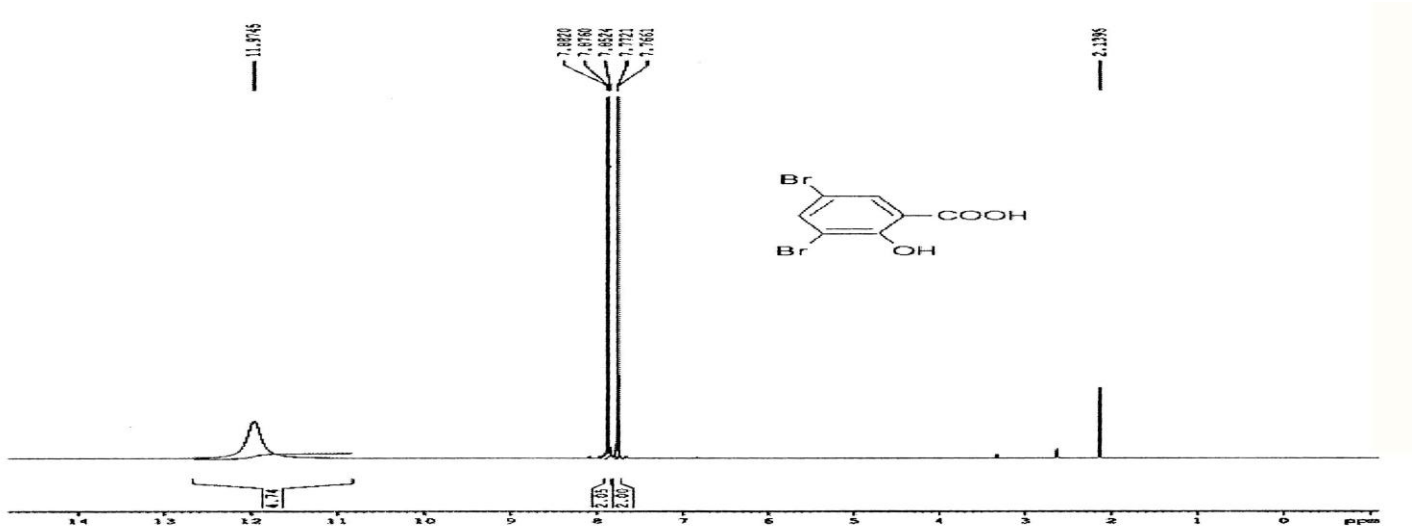


Fig. 1a: ^{1}H -NMR spectra of 3,5-dibromosalicylic acid

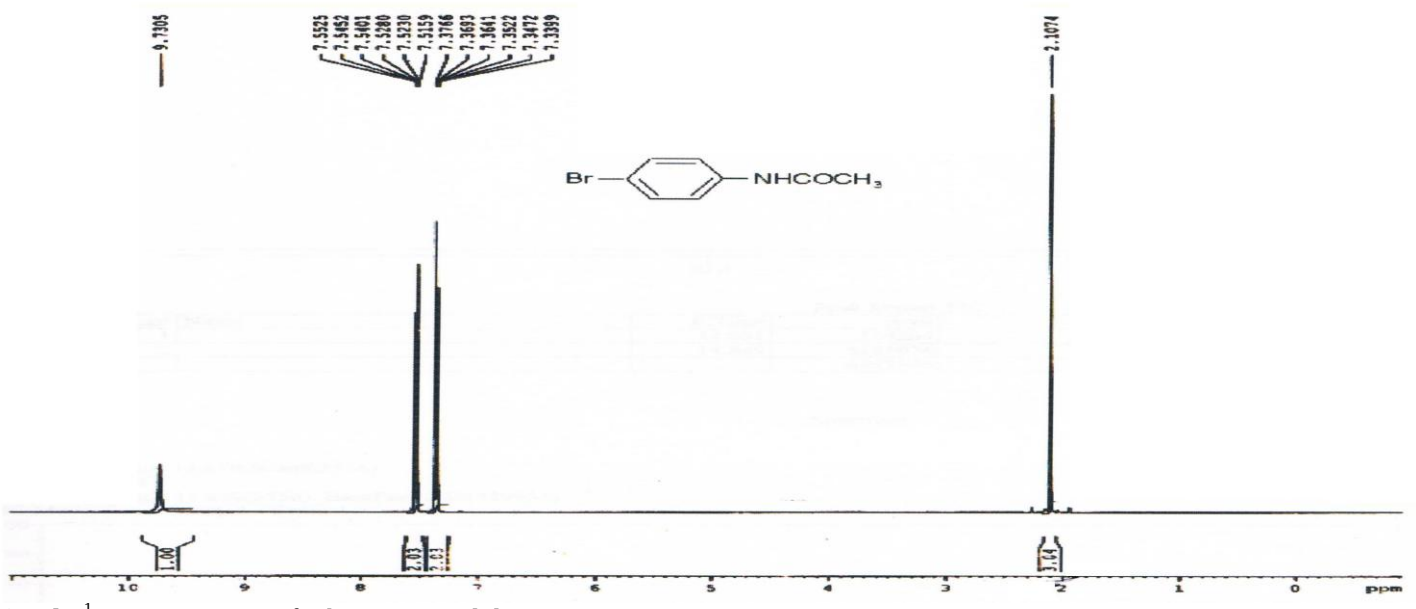


Fig. 1b: ^{1}H -NMR spectra of 4-bromoacetanilide

prepared by liquefying Br_2 into an aq. solution of wetting agent/surfactant (Beckmann et al., 2013; Benitez et al., 2011).

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. $AlBr_3$-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. $AlBr_3$-Br_2 can diffuse through the dews of aniline leading to bromination. During the reaction process the 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 2, 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 Br_2 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 2, entry 16). Cheered by the above resulted outcomes,the bromination of industrially-important compounds using aqueous $AlBr_3$-Br_2 solution under aqueous conditions at room temperature woitout

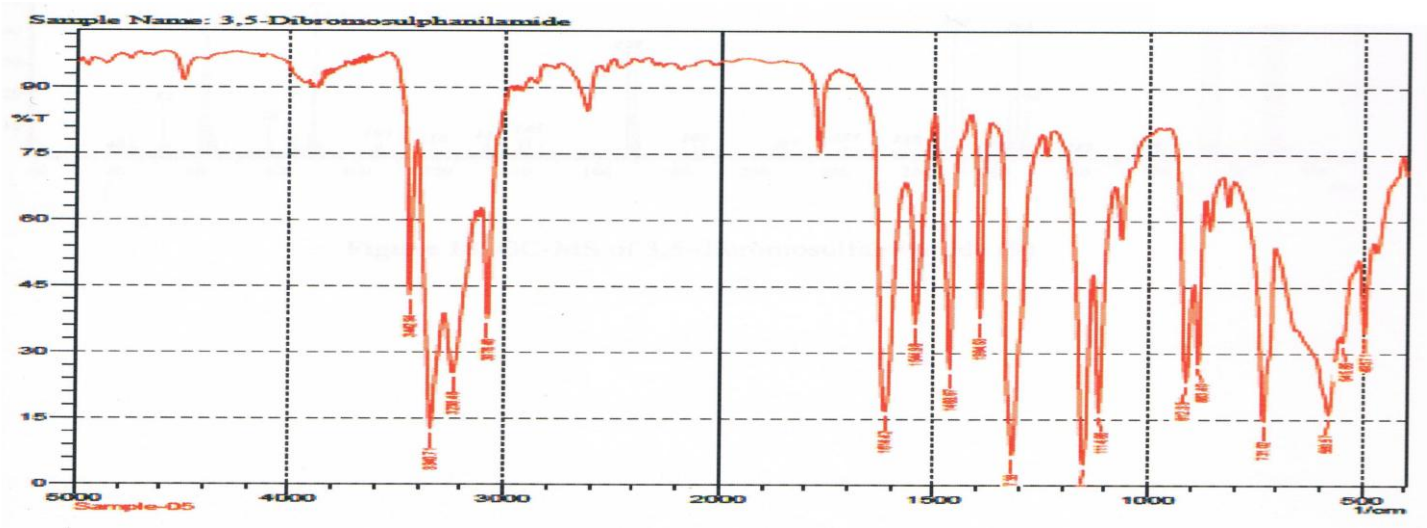


Fig. 2: IR spectra of 3,5-dibromosulfanilamide (9)

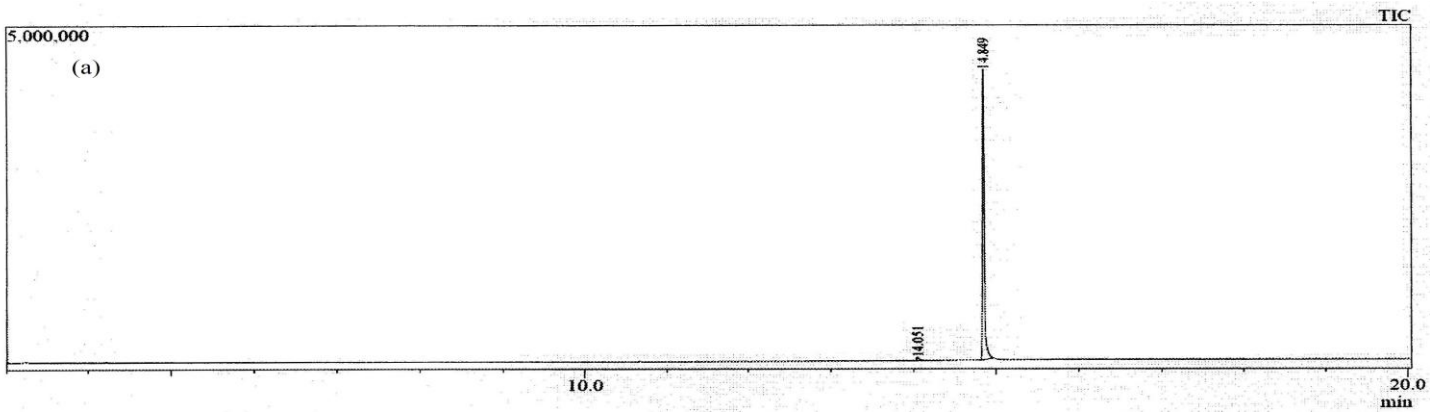


Fig. 3a: GC-MS Chromatogram of 3,5-dibromosulfanilamide with peak report

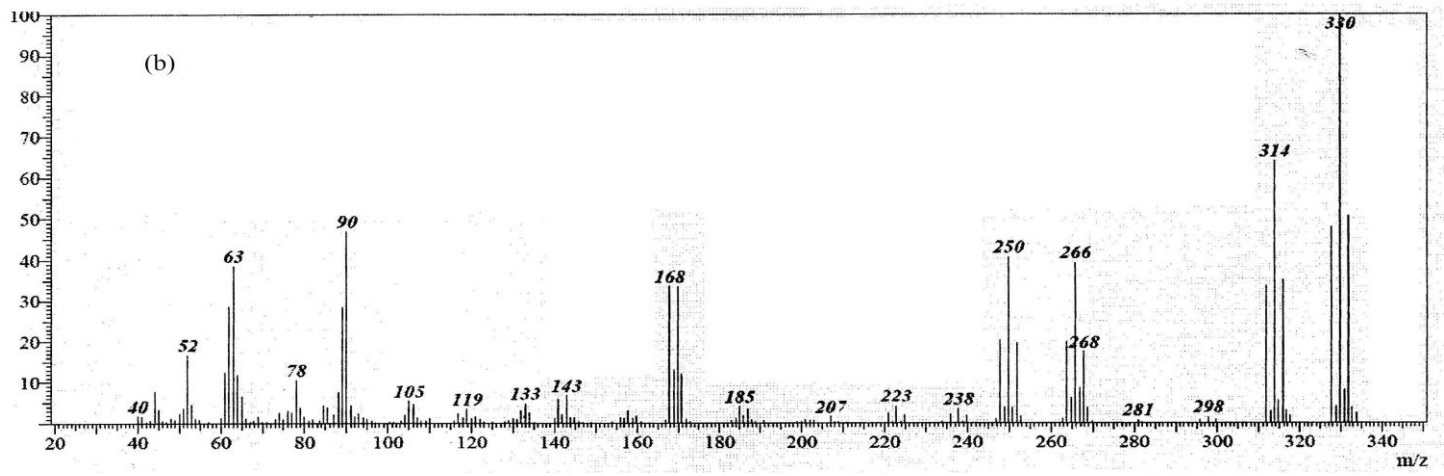


Fig. 3b: GC-MS spectra of 3,5-dibromosulfanilamide

using any organic solvent before and after the completion of reaction, the reaction heve successfully been performed (Borikar et al., 2009). While bromination was carried out in water using aq. $AlBr_3$ 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 AlBr3 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 $AlBr_3$ 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 $AlBr_3$ (5) the present method leads to zero waste discharge to the surroundings, since from the three components of the reagent, i.e., $AlBr_3$, Br_2 and water; one atom of Br2 was shifted to organic substrate and the other half-forming HBr is again employed back to $AlBr_3$ by its neutralization with Ca(OH)2.

The $AlBr_3$ of the fresh reaction and additional $AlBr_3$ produced from HBr nullification was recovered as a crystalline solid by concentrating the aq. filtrate (14 g $AlBr_3$ in 20 mL H_2O similar to collected works procedure). The recovered $AlBr_3$ 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 (Chinnagolla et al., 2013; Chiu et al., 2011).

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 a 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 Br_2-based and oxidative bromination reagents have been described for the synthesis brominated of organic compounds (Chiu et al., 2011). 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 $AlBr_3$-Br_2 system as the most inexpensive agent and H_2O 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 for the synthesis of diverse compounds (Asif et al., 2015abc; Kousar et al., 2015; Bhuvana and Madhurambal, 2015). In simple words, H_2O 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 C_6H_5OH and $C_6H_5NH_2$ subsidiary products with strong electron-withdrawing groups (EWG) such as carboxylic (-COOH), nitro (-NO_2) and formyl (-CHO) as examples of pharmaceutical reaction intermediates under absolutely aqueous conditions (Ganchegui et al., 2007; Podgorsek et al., 2009).

EXPERIMENTAL

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 CH_3OH + 30 per cent H_2O, 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 $CDCI_3$, 1H NMR (comparative to TMS referenced as 0.00 ppm) and ^{13}C NMR (comparative to DMSO referenced as 39.50 ppm). GCMS studies were performed by using "Agilent GC-5893" with chemstation 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 ^{0}C; injector temp- 280 oC; 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 ordinary APCI ion source. Infrared spectra studies were carried out on a Shimadzu Prestize 21 FT-IR Instrument (KBr, 3400-430 cm-1). Isolated compounds were acknowledged on the basis of physical determination and spectroscopic data (^{13}C NMR, ^1H NMR, Infrared and Mass Spectroscopy) (Adimurthy et al., 2006; Zolfigol et al., 2007).

A typical synthesis path of 2, 6-dibromo-4-nitroaniline (16)

A solution was prepared using $AlBr_3$ (3.95 g, 20 mmol) in aqueous media (10 mL) and was added to Br_2 (3.25 g, 20 mmol), the resultant mixture was stirred continuously at room temperature till it give clear dark pale yellow solution. Immediately this solution was added to a fine powdered form of 4-nitroaniline (1.3733 g, 10 mmol) booked in a round-bottom flask (100 mL capacity) equipped with a magnetic stirrer using a pressure-equalizing funnel within 2 -3 minutes of time. The bromine color vanished immediately and 2,6-dibromo-4-nitroaniline was achieved (yellowish thick precipitates) within 20 minutes (Monitored by Thin Layer Chromatography) at room temperature. The filtration of precipitated mass was done by vacuum filtration method using Bunchner funnel, and then washed-off with $Na_2S_2O_3$ solution and dehydrated in oven at 100 oC. The filtrate was saved for the Later runs. The product was achieved as yellow powder (2.90 g, 98% yield, and 99.03% HPLC area pureness). Melting point: 206 ^{o}C (literature,23b 206-208 oC). ^1H NMR (400 MHz, DMSO): δ value 8.25 (s, 2H, ArH), 6.85 (s, 2H, NH2); ^{13}C NMR (100 MHz, DMSO): 144.36, 135.69, 122.49, 109.44; IR (KBr): 3450, 3366, 3184, 2798, 2659, 2363, 1642, 1515, 1488, 1348, 1298, 1270, 1154, 953, 879, 816, 747, 669, 584, 543, 464 cm-1; MS, Atmospheric Pressure Chemical Ionization (APCI) m/z (mass-to-charge ratio) called. for $C_6H_4Br_2N_2O_2$:295.9; found 295.2.

Procedure for recycling of Hydrogen Bromide as $AlBr_3$ 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 $AlBr_3$. Consequently, (3.23 g, 20 mmol) Br_2 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[18]. The thick yellowish precipitates of 2, 6-dibromo-4-nitroaniline were attained within 20 minutes at room temperature immediately after adding Br_2 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 ($Na_2S_2O_3$) solution (10%, 10 mL × 3) and dried out in vacuum drying oven at 100 ^oC. A high purity (99%) 2, 6-dibromo-4-nitroaniline yellow powder was achieved in 2.82 g (98.08%) yield with melting point 206 ^oC. The distinguishing data was documented for the isolated product and found similar as given in the above distinctive method. The hudrogen bromide evolved was again nullified and the aqueous solution was uninterruptedly recycled in the next run with an additional amount of Br_2.

The Route for Recycle/Reutilize 2,3 and 4

Analogous to the above typical method of Reutilize 1, Br_2 (3.2 g, 20 mmol) was added to the aq. solution containing recycled aluminium tribromide ($AlBr_3$) achieved after the separation of 2,6-dibromo-4-nitroaniline ($Br_2C_6H_2(NO_2)NH_2$) and the reaction proceeded in a similar reaction pattern with 4- nitroaniline, $C_6H_6N_2O_2$ (1.3726 g, 10 mmol) for every reaction cycle.

RESULTS AND DISCUSSION

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 16 (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 (Br_2) and ($AlBr_3$) concentration effects on the end product yield and Mp of 2, 6-dibromo-4-nitroaniline (DBNA) were studied in the dibromination of 4-NA.

The effect on yield and melting point of DBNA by mole ration of Br_2

The excellence of the end product is strongly reliant on the mole ratio of Br_2/4-NA which also has been confirmed by recent studies. It also been initiated that the optimal yield (98%) of 2, 6-dibromo-4- nitroaniline (DBNA) and the desired melting point of 206 ^oC (literature, 206-208 ^oC) are achieved at 2:1 mole ratio of Br_2/4-NA in the bromination of 4-NA by aqueous $AlBr_3$-Br_2 solution as a effective brominating agent. Further, if we increase the mole ratio of Br_2/4- 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 ^oC, which is not actually as per the required specifications[18-21]. Further reduction in mole ratio of Br_2/4- 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 ^oC. The monobrominated 4-nitroaniline were achieved that melt at 102 ^oC and 100-101 ^0C, correspondingly (melting point of 2-bromo-4-nitroaniline is 104 ^oC), at the mole ratio of 1.5 and 1.25.

Influence of $AlBr_3$-Br_2 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 $AlBr_3$ solution as brominating agent because of increase in mole ratio of $AlBr_3$/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 $AlBr_3$/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 ($AlBr_3$) was defensible by performing a blank reaction for 1 h at 25 ^oC using molecular bromine as a brominating agent which resulted in a composite fusion of under-brominated species that melt from 160 to 190 oC. Thus, the result drawn in to conclusion that the optimal mole rato 1:2:2 of 4-NA to $AlBr_3$ to Br_2 was establish to be best for the dibromination of 4-NA.

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. $AlBr_3$-Br_2 solution) over a newly reported brominating system (NBS/[Bmim]Br or dioxane) that C_6H_5OH and $C_6H_5NH_2$ 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% yield; 96.2% HPLC purity) and 3,5-dibromo-4- hydroxybenzoic acid (94% yield; 99.2% HPLC purity) after 20 min and 15 min, respectively. Pharmaceutically-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 (Do et al., 2008). 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% HPLC pureness) and 3,5-dibromosulfanilamide (94 per cent yield; 96.6% 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 6, entry 10). With the poor reactivity 4-

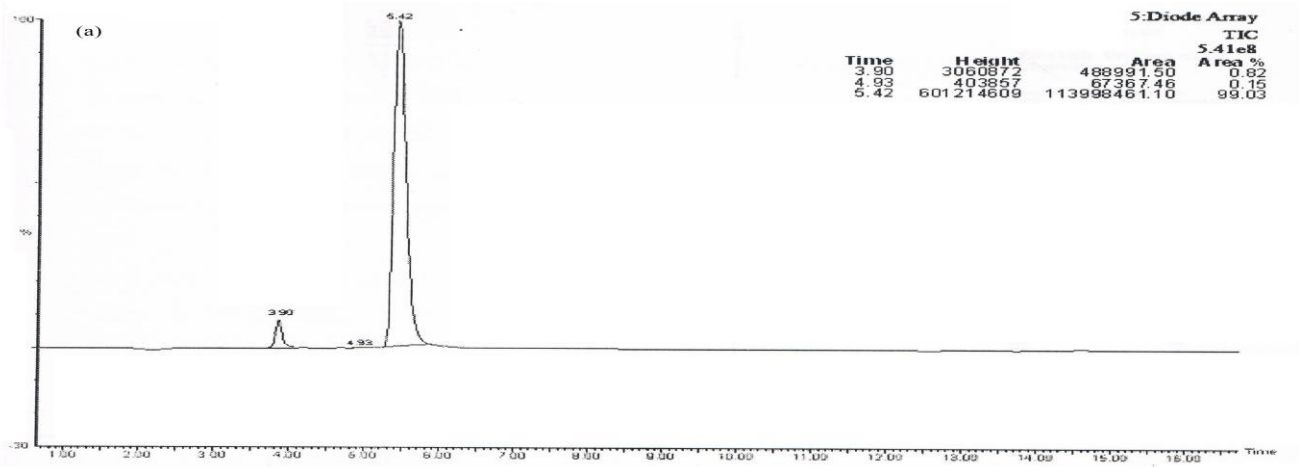


Fig. 5a: LC/MS of 2,6-dibromo-4-nitroaniline ($Br_2C_6H_2(NO_2)NH_2$) (Diode Array)

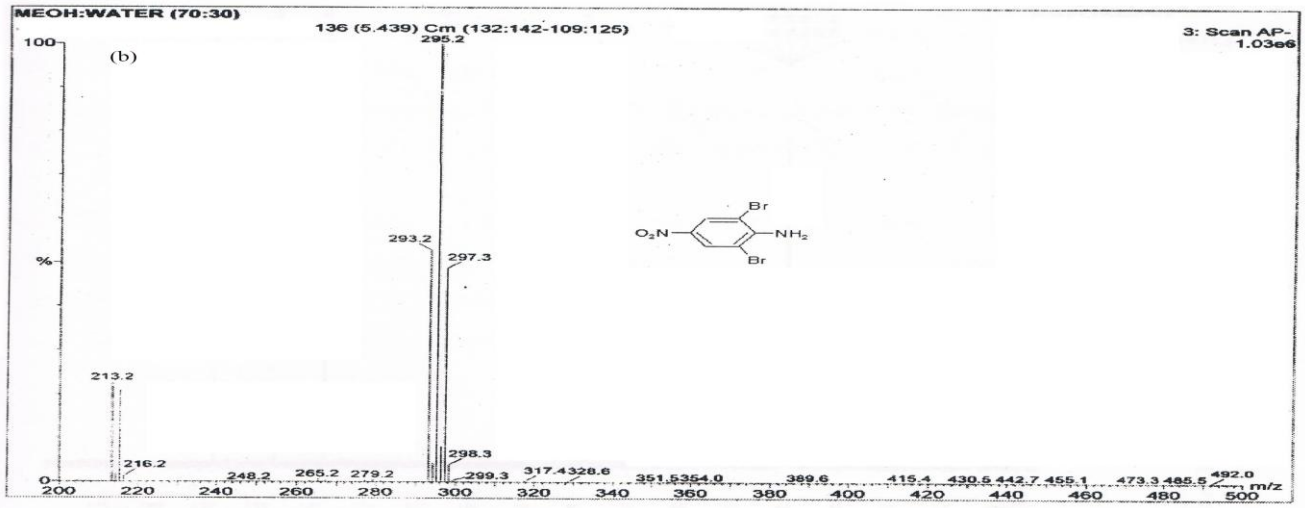


Fig. 5b: LC/MS of 2,6-dibromo-4-nitroaniline ($Br_2C_6H_2(NO_2)NH_2$) (Scan AP-1.03)

nitrophenol (**11)** shows outstanding reactivity resulting 2,6-dibromo-4-nitrophenol (94% yield; 97.5% HPLC pureness) within 30 minutes using two equivalent of reagent. Bromination of the same substrate with H_2O_2-HBr/'on water, gave 2, 6-dibromo-4-nitrophenol over a period of 24 hr. The advantages of the present system is an regioselective, effective, facilie, and fast bromination of deactivated anilines (Table. 2, entries 03 to 08) in outstanding end product yields at 25 °C upon simple admixing with aq. $CaBr_2$-Br_2 solution which is slightly challenging by other methodologies. 1-Bromo-2- naphthol **17** (92 per cent yield; 96.2% 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% yield; 96.5% HPLC pureness), within 25 minutes and 2 equivalents of aqueous $AlBr_3$-Br_2 solution were necessary. Which represents the position of the electrophilic attack and the number of inflowing Br_2 atoms during reaction process can be structured by controlling the ratio of substrate: aqueous $AlBr_3$-Br_2 solution, i.e., 1/1 mono-, 1/2 for di-, and 1/3 for tribromination of aromatic compounds.

The use of aqueous $AlBr_3$-Br_2 system as the most economical brominating agent and H_2O 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 2 which clearly indicates the benefits of the present system over obtainable methods. In this present study, we are presenting, a effective reagent system for electron-withdrawing groups (EWG) like; -COOH, NO_2 and -CHO as examples of pharmaceutical reaction intermediates under purely aqueous conditions (Eberlin et al., 2002; Edwards et al., 2009; Fong et al., 2009).

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 H_2O and acetonitrile (ACN) as solvents, correspondingly[25]. 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

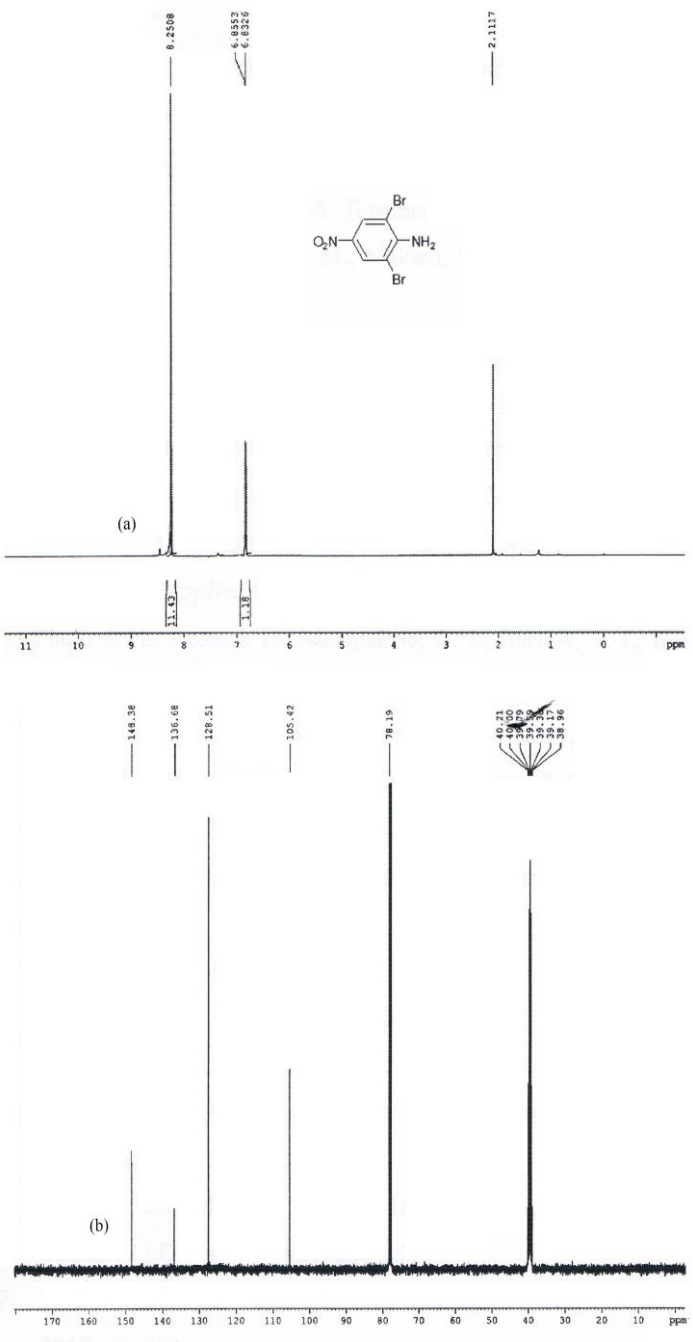


Fig. 6: ^{1}H and ^{13}C-NMR of 2,6-dibromo-4-nitroaniline **(16)**

valuable from environmental safety point of view to extend this system for other commercially-important compounds. Subsequent, a desireable 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 nutralization of hydrogen bromide waste so that the bromine of hydrogen bromide thus fixed as Aluminum bromide (Gavara et al., 2008). 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.

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: Br_2 (1: 2) mole rato in each run without adding of the fresh $AlBr_3$ to give 2, 6-dibromo-4-nitroaniline within 20 minutes at room temperature. Reprocessing experiments (Table 1) 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 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 $AlBr_3$ (7 mol) was recuperated after fresh batch + 4 cycles: resulted 1 mol of aluminium tribromide ($AlBr_3$) 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 $AlBr_3$. Consequently, effectively the byproduct HBr has been utilized, and at the end of reaction, process generates zero discharge of organic waste and effluent to the surroundings (Hajipour et al., 2006; Sharma et al., 2014ab; Sharma, 2015).

CONCLUSION

We have testified a rapid, mild, cost effective and facile method for the effective and selective synthesis of pharmaceutically-important brominated intermediates using aq. $AlBr_3$-Br_2 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 (^{1}H 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 (^{1}H, OH, s), 13 (1H, COOH, s); Infrared (KBr): 3450, 3081, 2976, 2652, 2530, 1798, 1690, 1588, 1482, 1420, 1404, 1340, 1305, 1275, 1205, 1169, 1137, 903, 893, 766, 738, 718, 671, 520, 470 cm^{-1}; MS m/z (mass-to-charge ratio) calculated (calcd) for $C_7H_4Br_2O_3$: 295.9, found 295.

5-Bromovanillin (5): Slightly-brown powder; IR (KBr): 3318, 3103, 3074, 3009, 2976, 2943, 2851, 2746, 1725, 1592, 1502, 1464, 1448, 1425, 1355, 1293, 1192, 1148, 1047, 973, 855, 796, 681, 602, 592, 538, 527 cm^{-1}; MS m/z (mass-to-charge ratio) calcd. For $C_8H_7BrO_3$: 231, found 235.

4-Bromoacetanilide (6): White crystals, ^{1}H NMR (400 MHz, Dimethyl Sulfoxide"DMSO"): δ 2.1 (s, 3H, CH3), 7.41 (d, J = 2.96 Hz, 2H, Ar), 7.64 (d, j = 2.89 Hz, 2H, Ar), 9.71 (s, 1H, NH). IR (Potassium Bromide): 3288, 3261, 3157, 3128, 3045, 1684, 1656, 1594, 1576, 1544, 1478, 1388, 1312, 1280, 1246, 1002, 845, 824, 754, 678, 508 cm^{-1}. MS Atmospheric Pressure Chemical Ionization (APCI) m/z (mass-to-charge ratio) calcd. For C_8H_8BrNO: 216.07, found 216.

Table 3: Reprocessing experiments for the dibromination of 4-nitroaniline[a]

Recycle	Appearance	Yield[b] (%)	Mp/°C(lit., 206-208 °C	Purity [c] (%)
New batch	Yellow Powder	98.2	206	99.2
Reprocess 1	Yellow Powder	98	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

[a]Surroundings: 10 mmol 4-NA, 20 mmol Br2 (4-NA and Br2 moles charged in every reaction cycle) and 20 mmol AlBr3 (charged for fresh batch only) at room temperature (25°C) for 20 minutes (each cycle), [b]Inaccessible Yields and [c]Pureness determined by HPLC

5,7-Dibromo-8-hydroxuquinoline (8): Light buff colored powder; ^{1}H NMR (400 MHz, Trichlorodeuteromethane "CDCl3"): δ value 7.446 (d, J = 0.514 Hz, ^{1}H), 8.465 (ddd, J = 8.803, J = 1.836, J = 0.514 Hz, ^{1}H), 7.223 (dd, J = 8.778, J = 4.681 Hz, ^{1}H), 8.839 (dd, J = 4.687, J = 1.834 Hz, ^{1}H). IR (KBr): 3087, 1742, 1576, 1489, 1464, 1387, 1374, 1266, 1212, 1156, 1043, 947, 884, 815, 782, 736, 672, 643, 614, 589, 559, 500 cm-1.MS Atmospheric Pressure Chemical Ionization (APCI) m/z (mass-to-charge ratio) calcd. For $C_9H_5Br_2NO$: 302.95, found 302.2.

3,5-Dibromosulphanilamide (9): Shining-white crystalline powder; ^{1}H NMR (400 MHz, Trichlorodeuteromethane "CDCl3"): δ : 5.74 (2H, s, NH2), 6.76 (s, 2H, SO_2NH_2), 7.92 (s, 2H, Ar); IR (KBr): 3443, 3341, 3238, 3076, 1614, 1545, 1464, 1395, 1317, 1151, 1114, 912, 883, 731, 580, 546, 496 cm^{-1}; MS Atmospheric Pressure Chemical Ionization (APCI) m/z (mass-to-charge ratio) calcd. for $C_6H_6Br_2N_2O_2S$: 330, found 330.

2,4,6-Tribromoaniline (19): Shining white fine needles; 1H NMR (400 MHz, Trichlorodeuteromethane "$CDCl_3$"): δ: 7.5 (2H, s, Ar), 4.54 (2H, br. S, NH_2). 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 $C_6H_4Br_3N$: 329.816, found 328.8.

ACKNOWLEDGEMENT

Dr. Ekta Sharma, Arnavi Sharma, Prof. (Dr.) D.D Agarwal.

REFERENCES

Adimurthy, S., Ramachandraiah, G., Bedekar, A.V., Ghosh, S., Ranu, B.C., Ghosh, P.K., 2006. Eco-friendly and versatile brominating reagent prepared from a liquid bromine precursor. Green Chemistry 8, 916–922.

Asif, M., 2015c. Antivral and antiparasitic activities of various substituted triazole derivatives: A mini review. Chemistry International 1(2), 71 -80.

Asif. M., 2015a. Pharmacologically potentials of different substituted coumarin derivatives. Chemistry International 1(1), 1-11.

Asif. M., 2015b. Chemistry and antioxidant activity of plants containing some phenolic compounds. Chemistry International 1(1), 35-52.

Beckmann, J., Bolsinger, J., Duthie, A., Finke, P., 2013. Diarylhalotelluronium(IV) cations [(8-$Me_2NC_{10}H_6$)2TeX]+ (X = Cl, Br, I) stabilized by intramolecularly coordinating N-donor substituents. Dalton Trans. 10, 1039.

Bedekar, A.V., Gadde, R., Ghosh, P.K., 2005. Process for preparing 2,4,4,6-tetrabromo-2, 5-cycloyhexadienone. U.S. Patent 6, 838, 582.

Benitez, F. J., Acero, J.L., Real, F.J., Roldan, G., Casas, F., 2011. Bromination of selected pharmaceuticals in water matrices. Chemosphere 85, 1430-1437.

Bhuvana, J., Madhurambal, G., 2015. Effect of trytophan as dopant on potassium acid phthalate single crystals. Chemistry International 1(2), 87-91.

Borikar, S.P., Daniel, T., Paul, V., 2009. Tetrahedron Letters 50, 1007.

Chinnagolla, R.K., Pimparkar, S., Jeganmohan, M., 2013. Ruthenium-catalyzed intramolecular selective halogenation of O-methylbenzohydroximoyl halides: a new route to halogenated aromatic nitriles. Chem. Commun 49, 3146-3148.

Chiu, Y., (Denville, NJ); Cottrell, S.A., (Baton Rouge, LA); Tung, H. S. (Getzville, NY); `Kopkalli, H.(Staten Island, NY) and Cerri, G.(Parsippany, NJ). , 2011. Process for the Manufacture of Fluorinated Olefins. U.S. Class: 570/175; Serial No.: 402,372.

Do, H.Q., Daugulis, O., 2008. A Simple Base-Mediated Halogenationof Acidic sp2 C-H Bonds under Noncryogenic Conditions. Organic Letters 11, 421-423.

Eberlin, A., Williams, D.L.H., 2002. Halogenation of enol tautomers of 2- cyanoacetamide and malonamic acid. Journal of Chem. Soc., Perkin Transactions 2, 1316–1319.

Edwards, J., Palermo, D., Analgesic, J., 2009. Anti-inflammatory composition. U.S. Patent 7, 510, 732.

Fong, H.L. (Sugar Land, TX); Johnson, T.H. (Houston, TX)., Semple, T.C. (Friendswood,TX)., 2009. Conversion of Alkylhalides in to Alcohol Alkoxylates. Current U.S. Class: 568/671. Serial No.: 887194.

Ganchegui, B., Leitner, W., 2007. Green Chemistry 9, 26.

Gavara, L., Boisse, T., Riogo, B., Henichart, J.P., 2008. Tetrahedron 64, 4999.

Hai, T.T., Nelson, D.J., 1991. Phamaceutical grade 3,5-dibromosalicylic acid and method for synthesizing same. U.S. Patent 5,013,866.

Kousar, N., Ali, S., Shahzadi, S., Rukh, L., Ramzan, S., Shahid, M., Sharma, S.K., Qanungo, K., 2015. Synthesis, characterization and antimicrobial activities of organotin(IV) complexes with ethylthioglycolate. Chemistry International 1(2), 92-98.

Podgorsek, A., Stavber, S., Zupan, M., Iskra., 2009. Journal Tetrahendron 65, 4429.

Sharma, S., Agarwal, D.D., 2014a. NH_4Br-Br_2 catalyzed oxidative bromination of aromatic compounds. Journal of Agriculture and Life Sciences 1, 65-81.

Sharma, S., Agarwal, D.D., 2014b. Oxidative Chlorination of aromatic compounds in aqueous media. Journal of Agriculture and Life Sciences 1, 146-164.

Sharma, S.K., 2015. Eco-friendly and fast bromination of industrially-important aromatic compounds in water using recyclable $AlBr_3$-Br_2 system. Chemistry International 1(1), 60-70.

Sharma, S.K., Agarwal, D.D., 2015. A Direct and simplistic Bromination of commercially important organic compounds in aqueous media by eco-friendly $AlBr_3$-Br_2 reagent system. Chemistry International 1(3), 106-115.

Surine, W.R., Majewski, T.E., 1968. Preparation of 3,5-dibromosalicylic acid. U.S. Patent 3, 381, 032.

Zolfigol, M.A., Chehardoli, G., Salehzadesh, S., Adams, H., Ward, M. D., 2007. Tetrahendron Letters 48, 7969.

Visit us at: http://bosaljournals.com/chemint/

Submissions are accepted at: editorci@bosaljournals.com