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A direct and simplistic bromination of commercially important organic compounds in aqueous media by eco-friendly $\text{AlBr}_3\text{-Br}_2$ 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 $\text{AlBr}_3\text{-Br}_2$ reagent system was investigated. As synthesized brominated organic compounds were characterized using advanced techniques. The yield of all synthesized brominated organic compounds was excellent with high purity. Results revealed that this direct and simple bromination of commercially important organic compounds in aqueous media in the presence of recycle of $\text{AlBr}_3\text{-Br}_2$ reagent system is an efficient method and could possibly be extended for the synthesis of other organic compounds.

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Capsule Summary: Bromination of substituted aromatic compounds using aqueous $\text{AlBr}_3\text{-Br}_2$ system is a versatile technique for the synthesis of different brominated compounds.

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INTRODUCTION

To date, available research on bromination of organic aromatic compounds in aqueous medium is very few and far between, except only a few examples. Ganchegui et al. described the oxybromination of phenol ($\text{C}_6\text{H}_5\text{OH}$) and aniline $\text{C}_6\text{H}_5\text{NH}_2$ subsidiary products using $\text{NaBr-H}_2\text{O}_2$ in $\text{H}_2\text{O}/\text{scCO}_2$ (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: $\text{NaBr} : \text{H}_2\text{O} : 1 : 3 : 3$) 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 appropriate safety precautions. In recent times, padgorsek et al.

defined an interesting oxidative bromination of triggered arenes using $\text{H}_2\text{O}_2\text{-HBr}/\text{on water}$ 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.

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

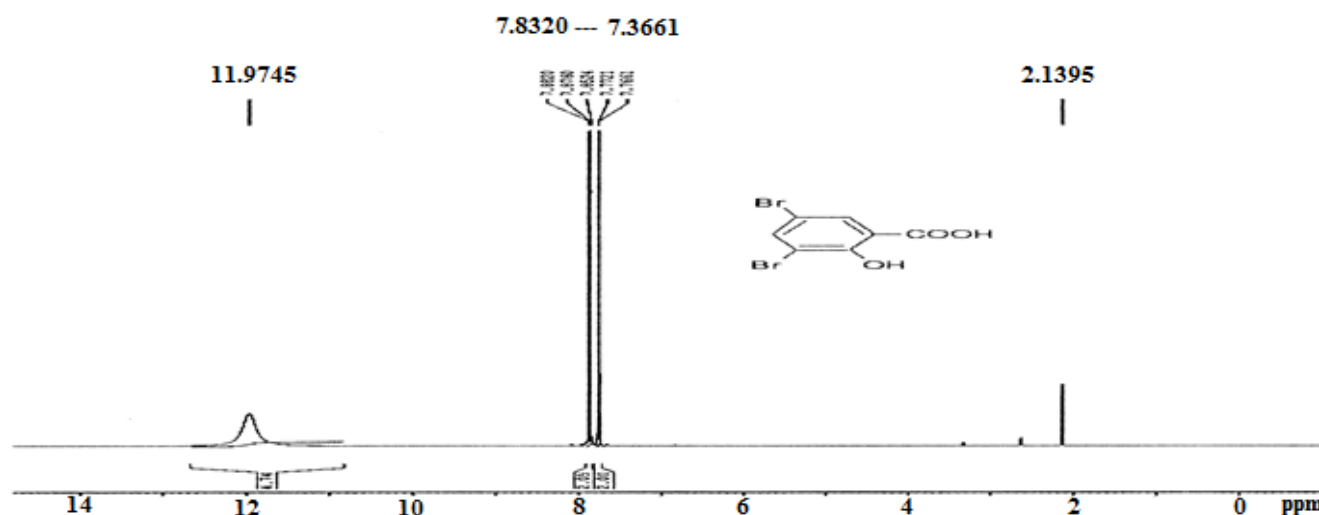


Fig. 1a: ^1H -NMR spectra of 3,5-dibromosalicylic acid

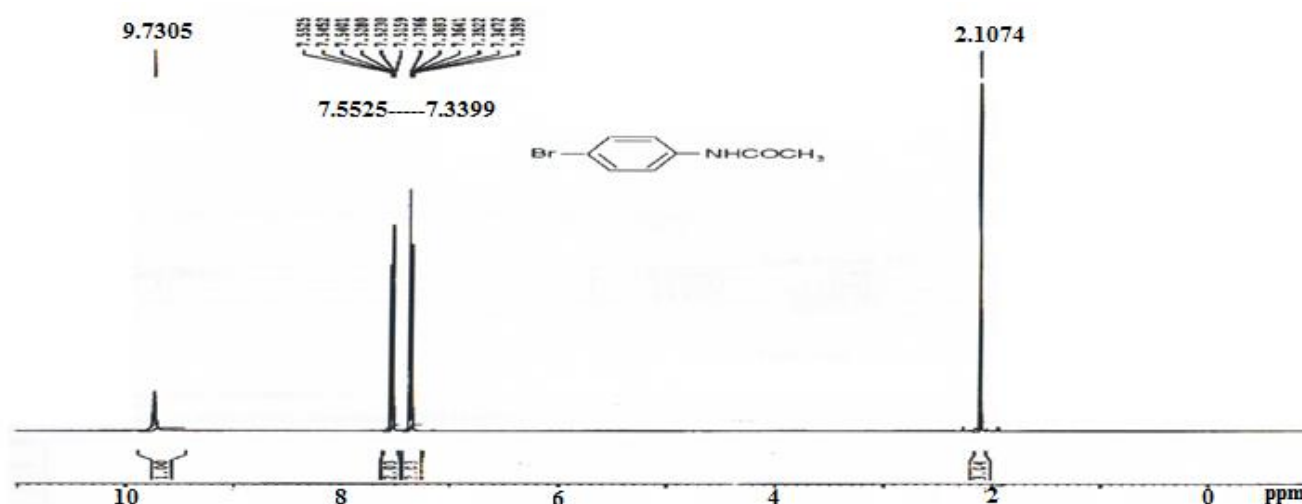


Fig. 1b: ^1H -NMR spectra of 4-bromoacetanilide

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 , 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 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 dewes 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.

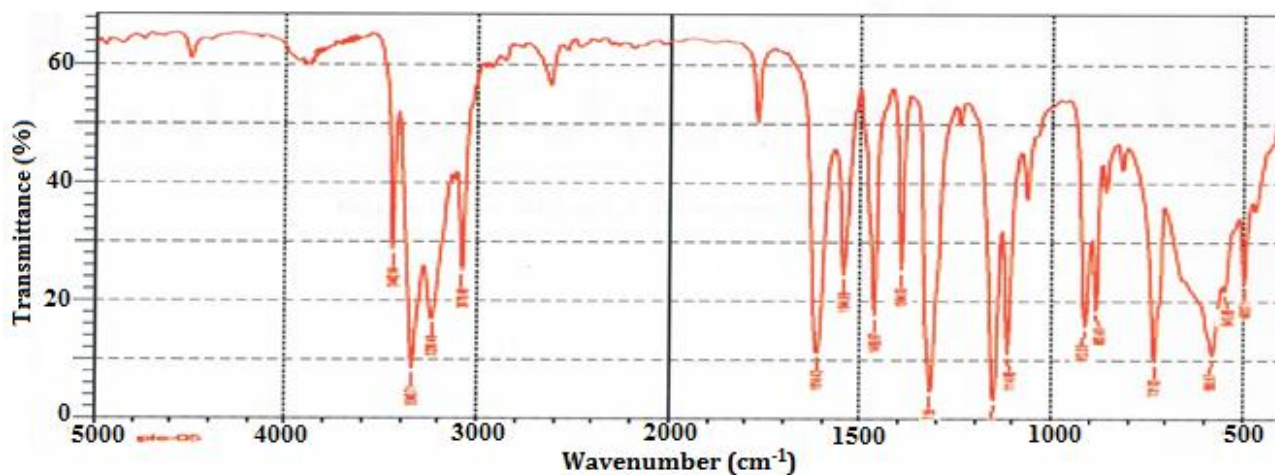


Fig. 2: IR spectra of 3,5-dibromosulfanilamide (9)

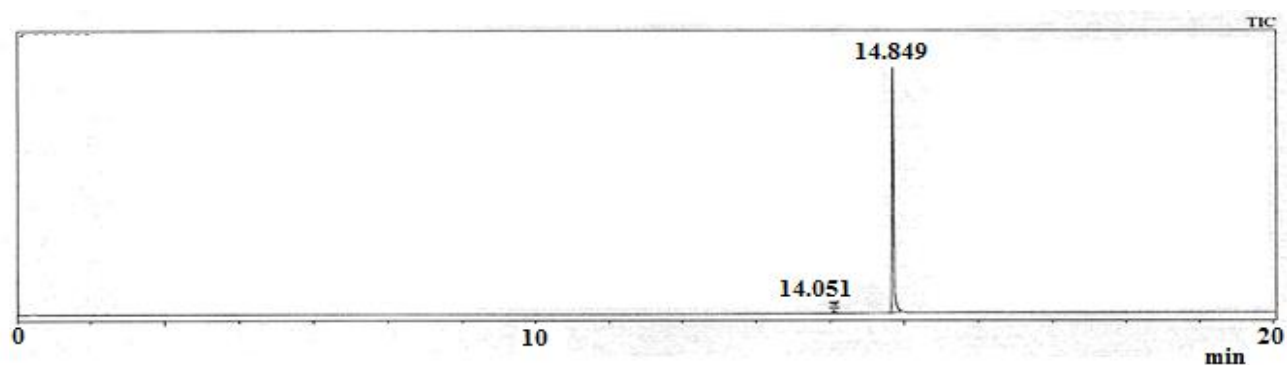


Fig. 3a: GC-MS Chromatogram of 3,5-dibromosulfanilamide with peak report

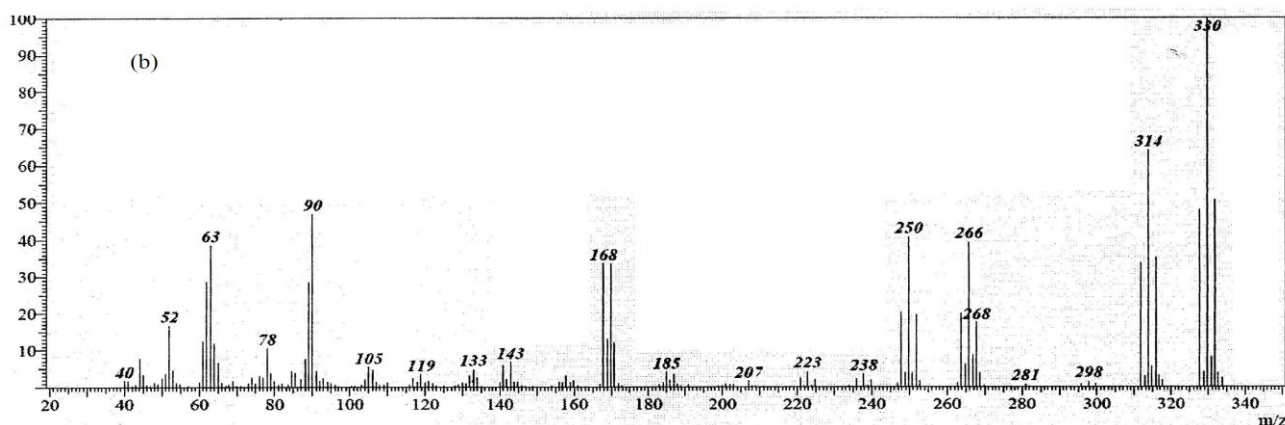


Fig. 3b: GC-MS spectra of 3,5-dibromosulfanilamide

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 $\text{AlBr}_3\text{-Br}_2$ 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 (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 AlBr_3 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 Br_2 was shifted to organic substrate and the other half-forming HBr is again employed back to AlBr_3 by its neutralization with $\text{Ca}(\text{OH})_2$.

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 $\text{C}_6\text{H}_5\text{OH}$ and $\text{C}_6\text{H}_5\text{NH}_2$ subsidiary products with strong electron-withdrawing groups (EWG) such as carboxylic ($-\text{COOH}$), nitro ($-\text{NO}_2$) and formyl ($-\text{CHO}$) as examples of pharmaceutical reaction intermediates under absolutely aqueous conditions (Ganchegui et al., 2007; Podgorsek et al., 2009).

MATERIAL AND METHODS

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 \times 4.6 \times 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 CDCl_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 \times 0.25mm \times 0.25 μ ; constant flow of- 2 ml/minutes; mass-director; mass range- 14 to 650 amu; detector temp- 290 $^\circ\text{C}$; injector temp- 280 $^\circ\text{C}$; 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 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).

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.

Table 1: A comparison of the results of present system (aq. AlBr₃-Br₂ 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 ₄ Br/H ₂ O ₂ /AcOH 73%, 4h, rt HBr/H ₂ O ₂ /MeOH 99%, 12h, 0°C to rt, NBS/SO ₃ H-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/H ₂ O-DMF 65%, 1h, rt, KBr/ H ₂ O ₂ /CuPcF ₁₆ -APSG/AcOH 87%, 2.2h, 60 °C
3.			93%, 20 min, 25°C(96.6%) ^b	NBS/NH ₄ OAc/MeCN 89%, 1h, rt NBS/MeCN/hv 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 ₂ Cl ₂ 30%, 5 min, rt
5.			96%, 15 min, 25°C(99.67%) ^b	HBr/iso-amyl nitrite/ CH ₂ Cl ₂ 100%, 16h, rt
6.			94%, 15 min, 25°C(97.5%) ^b	H ₂ O ₂ -HBr/ on water` 95%, 24h, rt
7.			96%, 15 min, 25°C(99.7%) ^b	HBr/ H ₂ O ₂ /MeOH 96%, 8h, 0°C to rt TEATB/H ₂ O-DMF 63%, 1.5h, rt TEATB/50% aq DMF 65%, 15 min, rt
8.			97%, 25 min, 25°C(96.5%) ^b	HBr/ H ₂ O ₂ /MeOH 84%, 20h, rt
9.			92%, 10 min, 25°C(96.23%) ^b	HBr/ H ₂ O ₂ /MeOH 93per cent, 15h, rt KBr/ H ₂ O ₂ /AcOH/Zeolite 45per cent, 5h, rt KBr/BTPPMS/MeCN 92per cent, 2h, rt KBr/ H ₂ O ₂ /CuPcF ₁₆ -APSG/AcOH 75per cent, 2h, 60°C H ₂ O ₂ -HBr/ on water` 90per cent, 8h, rt
10.			98%, 20 min, 25°C(99.03%) ^b	HBr/ H ₂ O ₂ /MeOH 95per cent, 10h, 0°C to rt H ₂ O ₂ -HBr/ on water` 95per cent, 28h, rt

Table 2: A comparison of the results of present system (aq. AlBr₃-Br₂ solution) with the literature precedents of some recently published brominating systems in the synthesis of pharmaceutical intermediates

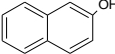
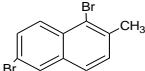
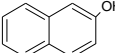
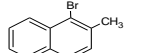
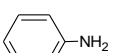
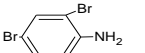
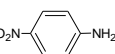
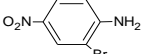
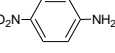
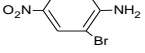
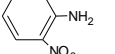
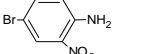
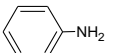
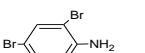
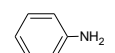
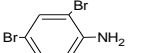
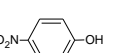
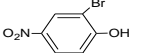
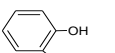
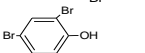
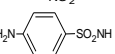
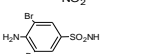
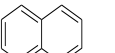
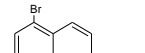
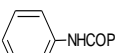
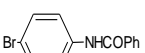
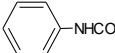
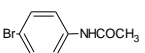
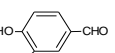
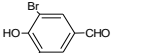
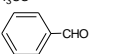
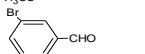
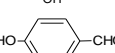
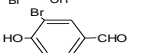
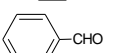
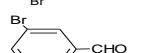
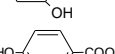
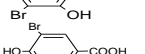
$ \begin{array}{c} \text{X} \\ \\ \text{Y} - \text{C}_6\text{H}_5 \xrightarrow[\text{Water, 25 } ^\circ\text{C, 10 - 25 min}]{\text{aq AlBr}_3 - \text{Br}_2 \text{ (n moles)}} \text{Y} - \text{C}_6\text{H}_4(\text{Br})_n \end{array} $						
Entry	Substrate	Product	Solvent system		M. Point (°C)	Applications
			Water	Acetonitrile		
			Time/min	Yield	Time/min	Yield
1			20	96	25	97
2			15	93	10	96
3			18	95	8	96
4			20	93	20	94
5			20	98	10	98
6			18	91	15	90
7			18	96	15	96
8			15	96	15	95
9			30	94	28	95
10			18	91	25	96
11			20	95	20	94
12			15	96	15	95
13			18	97	20	95
14			15	95	12	98
15			25	92	35	96
16			25	95	15	93
17			20	92	20	96
18			20	91	20	90
19			20	95	---	---

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

^aSurroundings: 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), ^bInaccessible Yields and ^cPureness determined by HPLC

The filtration of precipitated mass was done by vacuum filtration method using Bunchner funnel, and then washed-off with Na₂S₂O₃ solution and dehydrated in oven at 100 °C. 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 °C (literature, 23b 206-208 °C). ¹H NMR (400 MHz, DMSO): δ value 8.25 (s, 2H, ArH), 6.85 (s, 2H, NH₂); ¹³C 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 C₆H₄Br₂N₂O₂: 295.9; found 295.2.

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 bar¹⁸. 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%, 10 mL × 3) and dried out in vacuum drying oven at 100 °C. A high purity (99%) 2, 6-dibromo-4-nitroaniline yellow powder was achieved in 2.82 g (98.08%) 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.

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 (Br₂C₆H₂(NO₂)NH₂) and the reaction proceeded in a similar reaction pattern with 4- nitroaniline, C₆H₅N₂O₂ (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 (Br₂) and (AlBr₃) 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 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%) 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-Br₂ solution as a 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 specifications¹⁸⁻²¹. 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.

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 $\text{AlBr}_3/4\text{-NA}$ from 0.25 -2.0; at mole ratio 2:1 ideal yield and preferred melting point are achieved. With increase in mole ratio of $\text{AlBr}_3/4\text{-NA}$ 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 °C 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 ratio 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. $\text{AlBr}_3\text{-Br}_2$ solution) over a newly reported brominating system (NBS/[Bmim]Br or dioxane) that $\text{C}_6\text{H}_5\text{OH}$ and $\text{C}_6\text{H}_5\text{NH}_2$ byproducts with strong electron-withdrawing groups (EWG) such as $-\text{COOH}$, $-\text{NO}_2$ and $-\text{CHO}$ 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. $\text{AlBr}_3\text{-Br}_2$ 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-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 $\text{H}_2\text{O}_2\text{-HBr}/\text{on water}$, gave 2, 6-dibromo-

4-nitrophenol over a period of 24 hr. The advantages of the present system is an regioselective, effective, facile, 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. $\text{CaBr}_2\text{-Br}_2$ 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 $\text{AlBr}_3\text{-Br}_2$ 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 $\text{AlBr}_3\text{-Br}_2$ solution, i.e., 1/1 mono-, 1/2 for di-, and 1/3 for tribromination of aromatic compounds.

The use of aqueous $\text{AlBr}_3\text{-Br}_2$ 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 $\text{AlBr}_3\text{-Br}_2$ 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; $-\text{COOH}$, NO_2 and $-\text{CHO}$ 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, correspondingly²⁵. 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 (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.

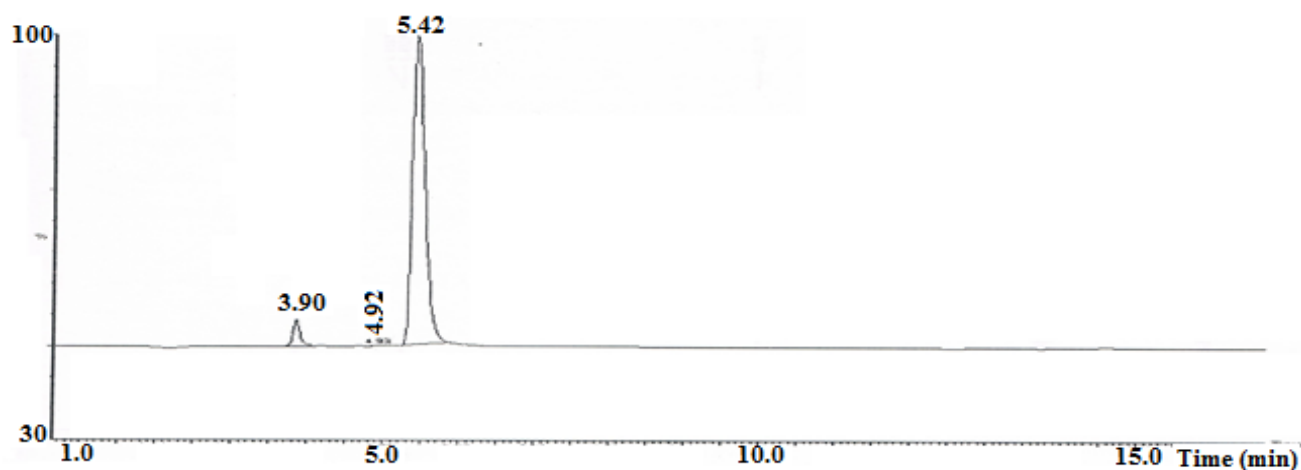


Fig. 5a: LC/MS of 2,6-dibromo-4-nitroaniline ($\text{Br}_2\text{C}_6\text{H}_2(\text{NO}_2)\text{NH}_2$) (Diode Array)

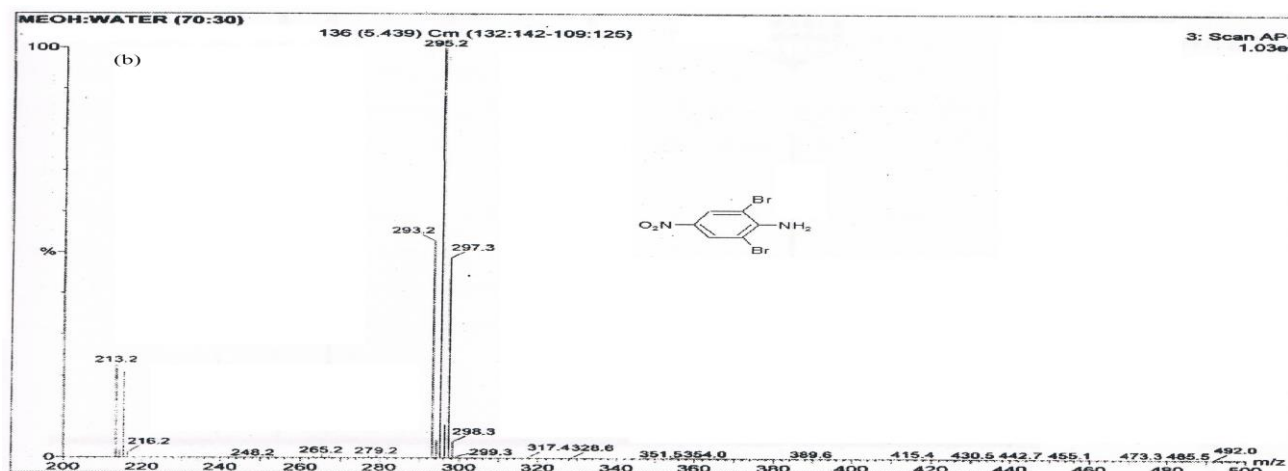


Fig. 5b: LC/MS of 2,6-dibromo-4-nitroaniline ($\text{Br}_2\text{C}_6\text{H}_2(\text{NO}_2)\text{NH}_2$) (Scan AP-1.03)

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 ratio 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 AlBr_3 upturns in the filtrate, then through vaporization process filtrate was concentrated which causes precipitation of AlBr_3 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 $\text{Al}(\text{OH})_3$. 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).

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. 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 (^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,

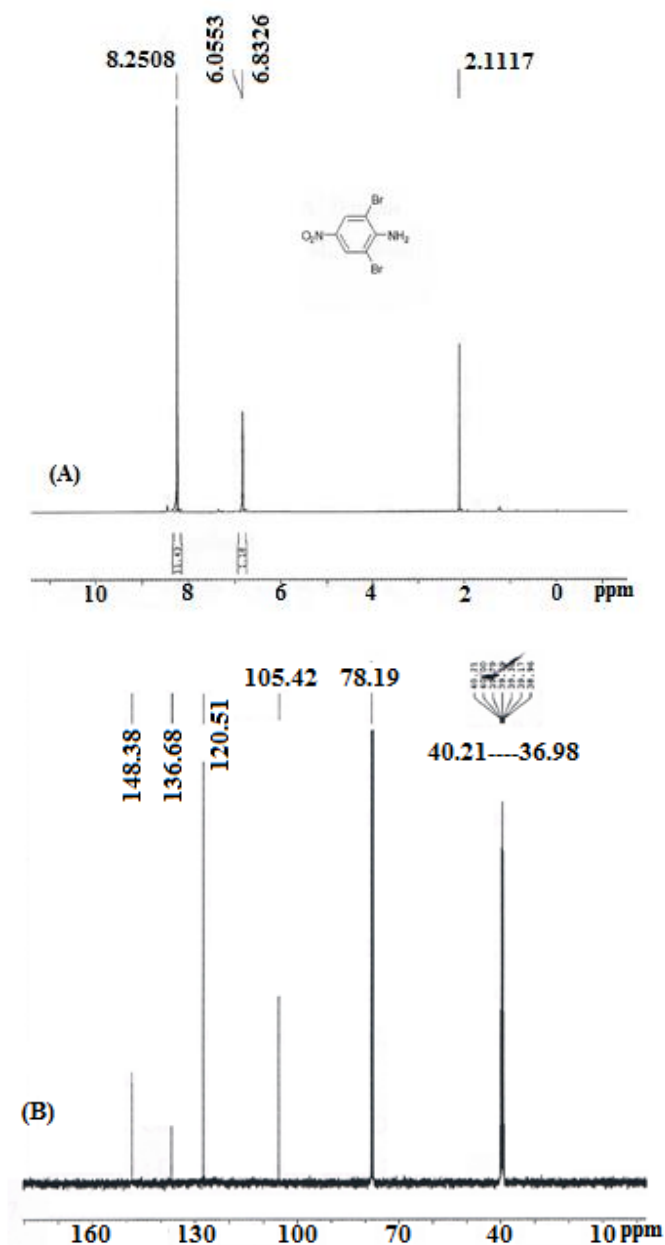


Fig. 6: ^1H and ^{13}C -NMR of 2,6-dibromo-4-nitroaniline (16)

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 $\text{C}_7\text{H}_4\text{Br}_2\text{O}_3$: 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 $\text{C}_8\text{H}_7\text{BrO}_3$: 231, found 235.

4-Bromoacetanilide (6): White crystals, ^1H NMR (400 MHz, Dimethyl Sulfoxide "DMSO"): δ 2.1 (s, 3H, CH_3), 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 $\text{C}_8\text{H}_8\text{BrNO}$: 216.07, found 216.

5,7-Dibromo-8-hydroxyquinoline (8): Light buff colored powder; ^1H NMR (400 MHz, Trichlorodeuteromethane " CDCl_3 "): δ value 7.446 (d, J = 0.514 Hz, ^1H), 8.465 (ddd, J = 8.803, J = 1.836, J = 0.514 Hz, ^1H), 7.223 (dd, J = 8.778, J = 4.681 Hz, ^1H), 8.839 (dd, J = 4.687, J = 1.834 Hz, ^1H). 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 $\text{C}_9\text{H}_5\text{Br}_2\text{NO}$: 302.95, found 302.2.

3,5-Dibromosulphanilamide (9): Shining-white crystalline powder; ^1H NMR (400 MHz, Trichlorodeuteromethane " CDCl_3 "): δ : 5.74 (2H, s, NH_2), 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 $\text{C}_6\text{H}_6\text{Br}_2\text{N}_2\text{O}_2\text{S}$: 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 $\text{C}_6\text{H}_4\text{Br}_3\text{N}$: 329.816, found 328.8.

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