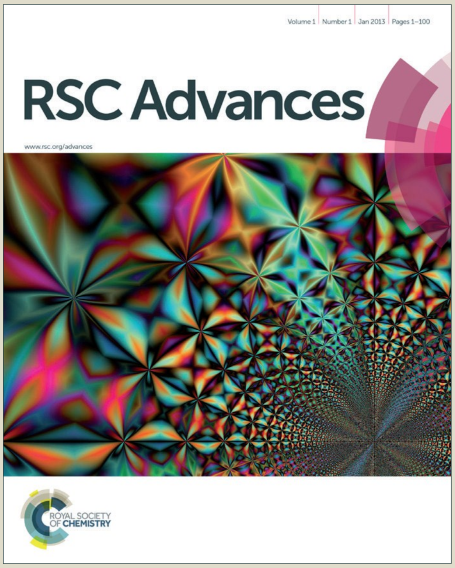
RSC Advances

This article can be cited before page numbers have been issued, to do this please use: A. Subbarayappa and V. Pappula, *RSC Adv.*, 2016, DOI: 10.1039/C6RA13680J.



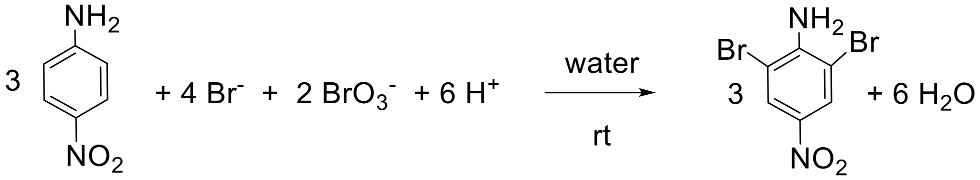
View Article Online
DOI: 10.1039/C6RA13680J

Green Process Development for the Preparation of 2, 6-Dibromo-4-nitroaniline from 4-Nitroaniline Using Bromide-Bromate Salts in Aqueous Acidic Medium

Venkatanarayana Pappula and Subbarayappa Adimurthy*

Academy of Scientific & Innovative Research, CSIR–Central Salt & Marine Chemicals Research Institute, G.B. Marg, Bhavnagar-364 002. Gujarat (INDIA).
E-mail: adimurthy@csmcri.org

Abstract: Organic solvent-free process for the preparation of 2, 6-dibromo-4-nitroaniline, (important intermediate in the synthesis of azo disperse dye) from 4-nitroaniline using 2:1 bromide-bromate salts under aqueous acidic medium at ambient conditions has been developed. The 2:1 bromide-bromate couple could be obtained by mixing pure $NaBr/NaBrO_3$ salts or by adjusting the 5:1 mole ratio of $NaBr/NaBrO_3$ (obtained in aqueous solution as intermediate from bromine manufacture industry by cold process) to 2:1 by the addition of suitable oxidant. After completion of the reaction the product was purified by simple filtration and washing with water. The aqueous acidic filtrate was recycled up to five times without loss of purity and yield of the product. The method was extended to other aromatic substrates.



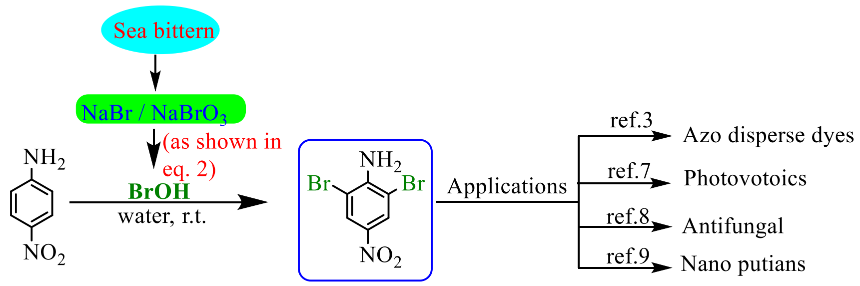
Bromination of aromatic substrates is a fundamental reaction in organic chemistry[1] due to the importance of the resultant bromo-products which are used as intermediates in the synthesis of various pharmaceutical industries[2] azo-disperse dyes,[3] flame retardants,[4] pesticides[5] and herbicides.[6] Particularly, 2,6-dibromo-4-nitroaniline (DBPNA) is a very important intermediate in azo-disperse dye industry and in the synthesis of star polyfluorenes which are useful in photovoltaic applications.[7] In addition to the above industrial applications, the antifungal behaviour of this molecule made it pharmaceutically important product.[8] DBPNA is a main building block in the synthesis of Nanoputians.[9] Due to the important applications of bromocompounds, a number of brominating reagents have been developed by

View Article Online
DOI: 10.1039/C6RA13680J

various groups. Among those reagents, liquid bromine is a very classical reagent for industrial production of desired bromo compounds despite its hazardous nature. To overcome the hazardness and handling problems associated with liquid bromine at large scale, we have introduced a new concept of using liquid bromine intermediate, which consists an aqueous solution of 5:1 bromide-bromate mole ratios during the liquid bromine recovery by cold process.[10] This 5:1 mole ratio of Br^-/BrO_3^- could be used for various bromination reactions in combination of mineral acids and suitable oxidants as desirable. Alternately, the 5:1 Br^-/BrO_3^- could be converted to 2:1 mole ratios using oxidants like sodium hypochlorite and can be used for aromatic substitution reactions under aqueous conditions (Scheme 1).[11] During the bromination process of organic substrates, the addition of any mineral acids to the aqueous solution containing 2:1 Br^-/BrO_3^- salts generates hypobromous acid (BrOH) which is accountable for electrophilic substitution reactions.

$$5\ NaBr + NaBrO_3 + 3\ NaOCl \longrightarrow 4\ NaBr + 2\ NaBrO_3 + 3\ NaCl \quad \text{(eq. 1)}$$

$$2\ NaBr + NaBrO_3 + 3\ H^+ \longrightarrow 3\ BrOH + 3\ Na^+ \quad \text{(eq. 2)}$$



Scheme 1. Bromination of PNA and its applications.

Based on our published reports, one of the textile dye manufacturing industry in India[12] approached us to develop a process for the preparation of the dye intermediate 2, 6-dibromo-4-nitroaniline from *para*-nitroaniline (PNA) using our concept of environment-friendly bromination process to dispense the problems associated with liquid bromine. Accordingly, we undertook the process development of the desired molecule, and performed the reactions using alkaline intermediate as well as constituted bromide-bromate salts to achieve the desired yield, purity, product colour and its effluent recyclability which are discussed in this report.

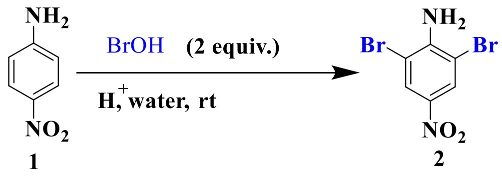
Initially, we performed the reactions with bromide-bromate salts and different mineral acids, solvents at lab scale (1-2 g of PNA) experiments (see Table S1, in the supporting information for details). After screening of different conditions, we found that, the good yield of the desired

View Article Online
DOI: 10.1039/C6RA13680J

product could be obtained by the addition of brominating reagent solution slowly to the aqueous acidic PNA slurry, rather than addition of acid to the solution containing PNA and aqueous brominating solution. This mode of addition was also advantageous for the recycling of the acidic filtrate after collecting the product by filtration under organic solvent-free conditions. Then, we tested the reaction with brominating reagent prepared from aqueous alkaline intermediate. The alkaline bromine intermediate solution which contains 5:1 mole ratio of $NaBr/NaBrO_3$ was selectively oxidized to 2:1 ratio of $NaBr/NaBrO_3$ by the controlled addition with NaOCl solution (Scheme 1, eq. 1). These 2:1 ($NaBr/NaBrO_3$) aqueous solution and constituted bromide-bromate salts were used for the bromination of PNA at 10.0 gram scale and the results are discussed in Table 1.

As the product DBPNA was obtained in 95% yield with 100% purity by GC, by conducting the reaction only in water, without any column separation but, by simple filtration and washing with water (Table S1). Then we scaled up the reaction to 10.0 g starting substrate (PNA) to check the feasibility of the reaction (Table 1). The reaction of PNA with 2:1 ratio of $NaBr/NaBrO_3$ and three equivalents of hydrochloric acid (w.r.t. PNA), 84% yield of DBPNA was obtained with 94% purity (Table 1, entry 1). The same reaction with nitric acid gave 85% yield with reduced purity (Table 1, entry 2). However, with two equivalents of sulfuric acid H_2SO_4 the reaction gave 94% yield with 100% purity (Table 1, entry 3). By decreasing the

Table 1. Preparation of DBPNA from PNA[a].



entry	**BrOH** used	H^+ source (equiv.)	yield of **2** (%)	GC-purity (%)
1	$NaBr/NaBrO_3$(2:1)	HCl (3)	85	93
2	$NaBr/NaBrO_3$(2:1)	HNO_3 (3)	84	86
3	$NaBr/NaBrO_3$(2:1)	H_2SO_4 (2)	94	100
4	$NaBr/NaBrO_3$(2:1)	H_2SO_4 (1.5)	95	100(96.8)[b]
5	$NaBr/NaBrO_3$(2:1)	H_2SO_4 (1)	86	85
6	Alkaline bromine(2:1)	H_2SO_4 (1.5)	95	100
7[c]	Alkaline bromine(2:1)	H_2SO_4 (1.5)	91	100 (90.3)[b]

[a] Reaction conditions unless otherwise noted: The reactions were carried out at 10 g PNA, aqueous brominating reagent solution, at room temperature, 4 h. [b] Purity by HPLC assessed by colourtex industry. [c] Reaction performed at 100 g scale of PNA.

View Article Online
DOI: 10.1039/C6RA13680J

amount of acid to 1.5 equivalents also the same yield of the product was obtained with same purity (Table 1, entry 4). A sample of this product was also tested and evaluated by the colourtex industry to meet their requirements.[13] Further, reducing the H_2SO_4 to one equivalents, both the yield and purity was dropped to 86% and 85% respectively (Table 1, entry 5). Maintaining the H_2SO_4 at 1.5 equivalents (w.r.t. PNA), the same reaction was performed with the brominating reagent prepared from the alkaline bromine intermediate, the similar yield of DBPNA was obtained (Table 1, entry 6). To validate the method, batch scale experiment was conducted at 100 g of PNA. At large scale, small amount of mono bromo product was observed with 91% yield of the desired product.[14]

As stated the product was obtained in a required purity by filtration, and washing, the filtrate was acidic in nature (as 0.5 equivalent acid was used for the reaction to obtain good yield of the product) and not suitable to dispose as such. Hence the filtrate containing 0.5 equivalents of acid was collected after filtration of solid product and it was recycled in the following cycle by the addition of one equivalent of acid along with the required quantities of NaBr and $NaBrO_3$ with minimum amount of water to dissolve the salts. In this way we performed up to five such recycles of the filtrate and the results are presented in fig 1. As can be seen from the fig 1, the similar yield of DBPNA and purity was obtained up to five cycles.

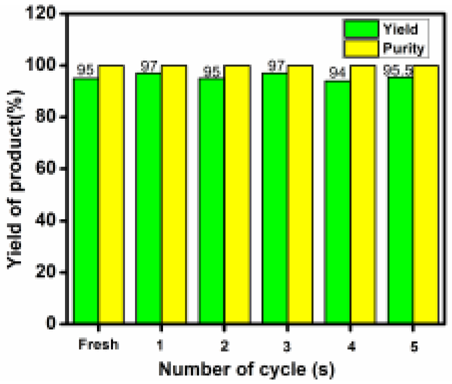


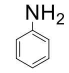
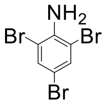
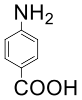
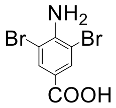
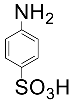
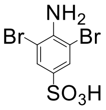
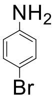
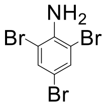
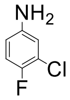
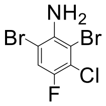
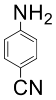
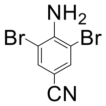
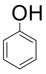
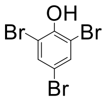
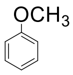
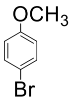
Fig 1. Recyclable study

After filtration of the reaction mixture the filtrate containing excess acid is collected and reused for the next cycle. H_2SO_4 required for the synthesis of dibromo-*para*-nitroaniline is 1.5 equivalents in fresh cycle. Excess of 0.5 equivalents of H_2SO_4 was recycled along with aqueous effluent for next recycles. The yield and purity of the product doesn't affect up to 5 continuous recycles of the aqueous effluent.1 equiv. of H_2SO_4 only used for up to five recycles. By recycling the acidic filtrate not only reduces the acid requirement, but also minimize the effluent discharge which contains hazardous waste into the environment.

View Article Online
DOI: 10.1039/C6RA13680J

The same bromination procedure was extended to other representative industrially aromatic substrates (Table 2). Bromination of aniline with three equivalents of aqueous brominating reagent gave 94% of tribromoaniline by simple filtration and washing with water (Table 2, entry 1). Similarly, the bromination of other aniline derivatives were performed with two equivalents of brominating reagent, and obtained the corresponding dibromo derivatives in good yields (91-95%) (Table 2, entries 2-6). Tribromination of phenol and mono bromination of anisole were obtained in 90% and 95% yields respectively (Table 2, entries 7 and 8).

Table 2. Bromination of other aromatic substrates[a]

entry	substrate	product	yield(%)	purity(%)[b]
1			94	100
2			95	100
3			94	100
4			94	100
5			92	100
6			93	100
7			90	100
8[c]			95	100

[a] Reaction conditions unless otherwise stated: All the reactions were performed at 5.0 mmol scale, at room temperature, 4h reaction time, for entries 1 and 7, three equivalents of BrOH & two equivalents of H_2SO_4, for entries 2-6, two equivalents of BrOH & 1.5 equivalents of H_2SO_4 and for entry 8, one equivalent of each BrOH and H_2SO_4 were employed, yields of crude product obtained after filtration and washing with water without column separation. [b] Purity based on area % by GC. [c] Product extracted with DCM.

View Article Online
DOI: 10.1039/C6RA13680J

General procedure for the preparation of 2,6-dibromo 4-nitro aniline from 4-nitro aniline using NaBr and $NaBrO_3$ salts: To a one liter two necked round bottomed flask fitted with overhead stirrer and addition funnel was charged with 4-nitro aniline PNA (10 g, 72.5 mmoles) and aqueous H_2SO_4 solution [prepared by dissolving 10. 86 g; 110.8 mmol in 60 mL water (i.e. 1:10 v/v)]. The contents were stirred for 5 minutes to get homogeneous slurry of PNA. To the above mixture, an aqueous solution containing 11.59 g of total bromide (10.0 g; 97.0 mmol NaBr and 7.21 g; 47.7 mmol $NaBrO_3$ dissolved in 100 mL of water) was added slowly dropwise through additional funnel during a period of 2 h at room temperature. After complete addition of the brominating solution, stirring was continued for another 2 h at the same temperature. The reaction mixture completely turns to yellowish, then the reaction mixture was filtered by using Buckner funnel connected to vacuum pump. The filtrate (mother liquor) was collected for recycle in the following batch. The residue containing product was washed with water (3x50 mL). The yellowish solid product obtained was oven dried at 100° C for 1 hour. After drying product DBPNA 95 % (20.30 g, 68.6 mmol) was obtained it was further characterized by ^{1}H & ^{13}C NMR, GCMS, LCMS, IR and melting point.

For recycling reactions, to the filtrate collected in the first batch was added another one equivalent of H_2SO_4, (7.24 g; 73.9 mmol), fresh 10.g of PNA, stirred for five minutes. Then the same quantities of aqueous brominating reagent solution as indicated above was added and the same procedure was followed up to five cycles. The yields and purity of recycled are indicated in fig 1.

Preparation of 2,6-dibromo 4-nitro aniline from 4-nitro aniline using alkaline brominating reagent:[15] To a ten liter glass reactor connected and equipped with a mechanical stirrer, cooling condenser and additional funnel facility, was charged with 4-nitro aniline PNA (100 g, 0.725 moles) and aqueous H_2SO_4 solution [prepared by dissolving 106.5 g; 1.08 mol in 600 mL water (i.e. 1:10 v/v)]. The contents were stirred for 5 minutes to get homogeneous slurry of PNA. To the above mixture, an aqueous solution (2.0 L) containing 116.0 g of total bromide (prepared from the original alkaline bromine solution)[15] was added during a period of 2.0 h at room temperature. Stirring was continued for further 2.0 h. The reaction mixture was treated with 5% $Na_2S_2O_3$ solution (to reduce the excess bromine). Filtered the product under vacuum, and the residue was washed with water (3x1000 mL), and the product was dried as indicated in the above general procedure to get 91% yield (Table 1, entry 7).

Conclusions:

In conclusion, we have developed a convenient procedure for the quantitative preparation of 2,6-dibromo 4-nitro aniline from 4-nitroaniline using NaBr and $NaBrO_3$ salts in aqueous acidic medium under ambient conditions without use of organic solvent in the process. The pure product could be obtained by simple filtration and washing with water, which will meets the requirement of industrial applications as a dye intermediate. We suggest the mode of addition of brominating reagent to the aqueous acidic 4-nitroaniline solution to get better yield and it helps to recycle the acidic filtrate. During the recycle of filtrate, the dilution of water in the process does not affect either on the yield or the purity of the product. The same procedure was extended for the preparation of other industrially important aromatic bromoproducts.

Acknowledgement:

CSIR-CSMCRI Communication No. 024/2016. We thank colourtex Industry, Surat, India for showing initial interest and for the product analysis. V.P. is thankful to UGC, New Delhi, India for his fellowship. We thank CSIR-Indus Magic (CSC-0123) for financial assistance. We are also thankful to Dr. P. K. Ghosh for initial discussions.

Supporting information available: ^1H and ^{13}C NMR spectra, optimization reactions and product analysis data by Colourtex Industry.

Notes and References

1 J. E. McMurry and E. E. Simanek, *Fundamentals of Organic Chemis*try, 6th Edition, 2006.

2 G. W. Gordon, *Chem. Soc. Rev.*, 1999, **28**, 335.

3 A. T. Peters, *J. Soc. Dyers Colourists*, 1988**, 104**, 344.

4 D. Ioffe and A. Kampf, "*Bromine, Organic Compounds*" *Kirk-Othmer Encyclopedia of Chemical Technology* , John Wiley & Sons, 2002.

5 M. J. Dagani, H. J. Barda, T. J. Benya and D. C.Sanders, Ullmann's *Encyclopedia of Industrial Chemistry: Bromine Compounds; Wiley-VCH: Weinheim*, 2002.

6 M. A. Cutulle, G. R. Armel, J.T. Brosnan, M. D. Best, D. A. Kopsell, B. D. Bruce, H. E. Bostic and D. S. Layton, *J. Agric. Food Chem*., 2014, **62**, 329.

7 Ch. Chakraborty, A.Layek, P .P. Ray and S. Malik, *European Polymer Journal*, 2014**, 52**, 181.

8 H. Gershon, M. W. McNeil, R. Parmegiani and P. K. Godfrey, *Appl. Microbiol.*, 1971, **22**, 438.

View Article Online
DOI: 10.1039/C6RA13680J

9 S. H. Chanteau and J.M. Tour, *J. Org. Chem*., 2003, **68**, 8750.

10 (a) G. Ramachandraiah, P. K. Ghosh, A. S. Mehta, S. Adimurthy, A. D. Jethva and S. S. Vaghela *US Patent* 6740253, 2004; (b) G. Ramachandraiah, P. K. Ghosh, S.Adimurthy, A. V. Bedekar and D. B. Shukla, *US Patent* 7459139, 2008.

11 (a) S. Adimurthy, G. Ramachandraiah, A. V. Bedekar, S. Ghosh, B. C. Ranu and P. K. Ghosh, *Green Chem*., 2006, **8**, 916; (b) S. Adimurthy, S. Ghosh, P. U. Patoliya, G. Ramachandraiah, M. K. Agrawal, M. R. Gandhi, S. C. Upadhyay, P. K. Ghosh and B. C Ranu, *Green Chem*., 2008, **10**, 232; (c) M. K. Agrawal, S. Adimurthy, B. Ganguly and P. K. Ghosh, *Tetrahedron,* 2009, **65**, 2791; (d) R. D. Patil, G. Joshi, S. Adimurthy and B. C. Ranu, *Tetrahedron Lett.*, 2009, **50**, 2529; (e) R. D. Patil, G. Joshi and S. Adimurthy, *Ind. Eng. Chem. Res.*, 2010, **49**, 8100; (f) G. Joshi and S.Adimurthy, *Ind. Eng. Chem. Res.*, 2011, **50**, 12271; (g) M. Dinda, M. K. Agrawal, M. R. Gandhi, S. C. Upadhyay, S. Adimurthy, S. Chakraborty and P. K. Ghosh, *RSC- Advances* 2012, **2**, 6645; (h) S. Adimurthy, G. Ramachandraiah, G. Joshi, R. D. Patil, M. R. Gandhi, M. Subbareddy and P. Maiti, *US Patent* 8957239, 2015.

12 Colourtex Industries Ltd. Surat, Gujarat – 395 023, INDIA.

13 For details of analysis please see the Table S2 in the supporting information.

14 When the bromination of PNA was performed with the brominating reagent prepared from alkaline bromine intermediate under the conditions studied, small amount of corresponding chloro derivative was observed. This may be due to the presence of NaCl present in the reagent (Please see ref 10 for details).

15 The alkaline bromine solution obtained from the bromine manufacture industry contains 5:1 mole ratio of NaBr/$NaBrO_3$ (total bromide content of the alkaline solution is 0.20 g/ml) was converted to 2:1 ratio of NaBr/$NaBrO_3$ by the controlled oxidation of bromide to bromate using 4% NaOCl solution and this aqueous solution was used in the present procedure. For the recycling experiments the constituted NaBr and $NaBrO_3$ salts were used unless otherwise indicated. For 100.0 g of PNA, 116 g of total bromine is required. Hence 579.5 mL of original alkaline bromine solution was treated with 1350 mL of NaOCl (4% w/v) solution and used for the reaction.

View Article Online
DOI: 10.1039/C6RA13680J

Green Process Development for the Preparation of 2, 6-Dibromo-4-nitroaniline from 4-Nitroaniline Using Bromide-Bromate Salts in Aqueous Acidic Medium

Venkatanarayana Pappula and Subbarayappa Adimurthy*

Academy of Scientific & Innovative Research, CSIR–Central Salt & Marine Chemicals Research Institute, G.B. Marg, Bhavnagar-364 002. Gujarat (INDIA).

E-mail: adimurthy@csmcri.org

Abstract: Organic solvent-free process for the preparation of 2, 6-dibromo-4-nitroaniline, from 4-nitroaniline using 2:1 bromide-bromate salts under aqueous acidic medium at ambient conditions has been developed. The product was purified by simple filtration and washing with water.