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# An efficient regioselective bromination of activated aromatic compounds using 1,4-bis (triphenylphosphonium) butane peroxodisulfate

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## ABSTRACT

A mild, efûcient and highly chemo- and regioselective method for the bromination of electron rich aromatic molecules has been developed by electrophilic substitution of $Br^+$, which was generated in situ from $Br_2$ or KBr using 1,4-bis (triphenylphosphonium) butane peroxodisulfate (BTPPBPDS) as the oxidant. Free aromatic amines remained unaffected under the reaction conditions. 

## KEYWORDS

Bromination;
1,4-bis (triphenylphosphonium) butane peroxodisulfate (BTPPBPDS);
Chemo and regioselectivity;
Bromine;
Potassium bromide.

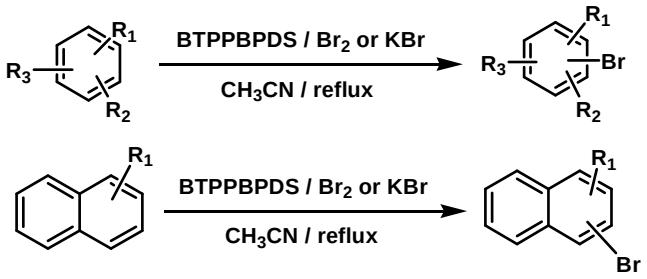
## INTRODUCTION

The bromination of aromatic substrates has received a great deal of interest in recent years owing to the commercial importance of brominated compounds in the synthesis of natural products, and in the manufacture of pharmaceuticals and agrochemicals. A variety of brominating reagents are available[1], and recent reports describe the use of NBS-sulfonic-acid-functionalized silica[2], NBS/$Al_2O_3$[3], NBS/$BF_3$–$H_2O$[4], NBS–$NH_4OAc$[5], NBS–TEAB[6], NBS– $Pd(OAc)_2$[7], NBS–DMF (or THF)[8], KBr–benzyltriphenyl- phosphonium peroxymonosulfate[9] or peroxodisulfate[10], 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide[11], $Br_2$ (for lithiated haloarenes)[12], a 2:1 bromide/bromated reagent as a source of HOBr[13], *N*-methylpyrrolidin-2-one hydrotribromide–$H_2O_2$[14], [Bmim]$Br_3$[15], hexamethylene- tetramine–$Br_2$[16], $Br_2$/$SO_2Cl_2$/zeolite[17], 1,2-dipyridiniumdi-tribromide-ethane[18e], alkylpyridinium tribromide[19], IBX amide resin-TEAB[20], poly(4-vinylpyridine)-supported bromate[21], tribromoisocyanuric acid[22], bromodichloroisocyanuric acid[23], polymer-supported organotin reagents[24], $NH_4VO_3$–$H_2O_2$–HBr[25], $CuBr_2$[26], etc. However, many of the reported methods are associated with one or more of the following drawbacks: (i) low yield, (ii) long reaction time, (iii) harsh reaction conditions, (iv) the use of toxic, corrosive or expensive, (v) the use of large amount of catalyst.

## RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods for the transformations in organic syn-

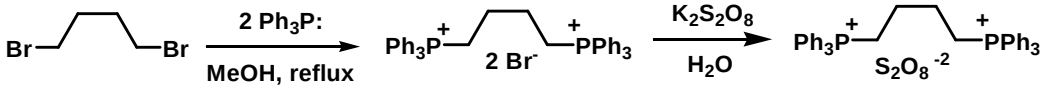
thesis using halogenating agents[27-30], herein we, in this article, are reporting the use of 1,4-bis (triphenylphosphonium) butane peroxodisulfate as a efûcient and highly chemo- and regioselective method for the bromination of electron rich aromatic molecules has been developed by electrophilic substitution of $Br^+$, which was generated in situ from $Br_2$ or KBr. (Scheme 1)




**Scheme 1**

BTPPBPDS was an easily prepared reagent, which was used recently for the bromination of aromatic compounds. The bromination of aromatic compounds with this reagent was investigated in $CH_3CN$ under reflux conditions. This reagent was easily prepared in a two step reaction. Thus treatment of two moles of triphenylphosphine with 1 mol of 1,4-dibromo butane at 64 °C afforded, after ûltration and puriûcation and ion exchanges with $K_2S_2O_8$, 1,4-bis(triphenyl phosphonium)butane peroxodisulfate in (57–96%) yield (Scheme 2).

To gain some preliminary information on this synthetically useful reaction, we studied the inûuence of different factors: solvent, molar ratio and temperature on the reaction kinetics. Thus, the effect of various solvents such as $CHCl_3$, $CH_2Cl_2$, $CCl_4$ and $CH_3CN$ on the reaction rate and yield were investigated. The experimental results showed that acetonitrile was the best choice for our procedure. Also our observations revealed that the molar ratio of 1.0:1.0:1.0 for aromatic substrate, bromine and oxidant, was the most effective, giving a short reaction times and clean products. (TABLE 1)




**BTPPBPDS**

**Scheme 2**

**TABLE 1 : The effect of amount of 1,4-bis (triphenylphosphonium) butane peroxodisulfate and various solvent on the reaction of bromination of *p*-methoxy benzene under reflux**

| Entry | aromatic substrate/ oxidant /$Br_2$ or KBr | Solvent | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | 1.0:0.5:1.0 | $CHCl_3$ | 90 | 53 |
| 2 | 1.0:1.0:1.0 | $CHCl_3$ | 60 | 68 |
| 3 | 1.0:1.5:1.0 | $CHCl_3$ | 60 | 68 |
| 4 | 1.0:0.5:1.0 | $CH_2Cl_2$ | 90 | 45 |
| 5 | 1.0:1.0:1.0 | $CH_2Cl_2$ | 70 | 59 |
| 6 | 1.0:1.5:1.0 | $CH_2Cl_2$ | 70 | 62 |
| 7 | 1.0:0.5:1.0 | $CH_3CN$ | 60 | 75 |
| 8 | 1.0:1.0:1.0 | $CH_3CN$ | 20 | 92 |
| 9 | 1.0:1.5:1.0 | $CH_3CN$ | 30 | 93 |
| 10 | 1.0:0.5:1.0 | $CCl_4$ | 120 | 38 |
| 11 | 1.0:1.0:1.0 | $CCl_4$ | 90 | 45 |
| 12 | 1.0:1.5:1.0 | $CCl_4$ | 90 | 46 |

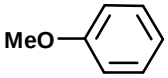
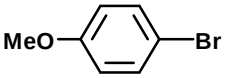
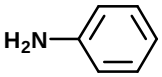
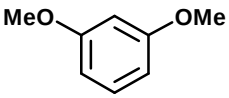
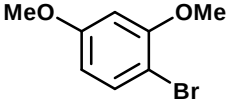
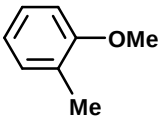
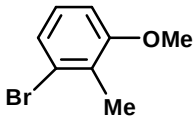
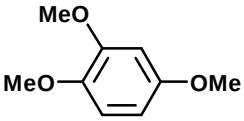
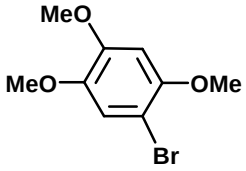
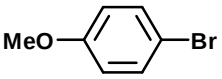
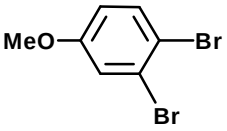
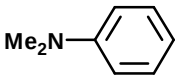
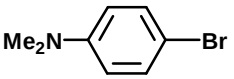
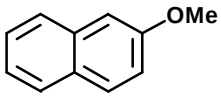
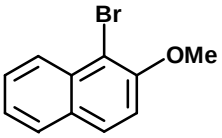
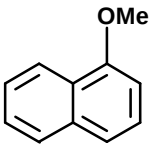
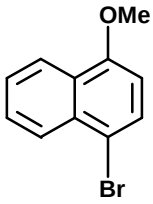
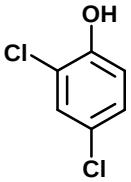
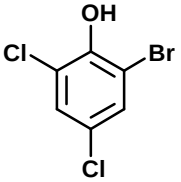
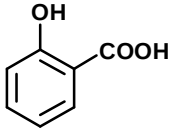
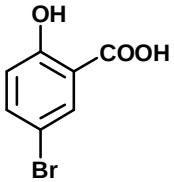
[a]Yields refer to the pure isolated products.

After optimizing these conditions using *p*-methoxy benzene as a model, various electron-rich aromatic compounds were brominated with bromine and KBr in the presence of 1,4-bis (triphenylphosphonium) butane peroxodisulfate in $CH_3CN$ under reflux condition to give brominated products with high regioselectivity. The results are summarized in TABLE 2.

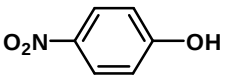
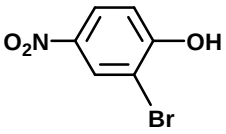
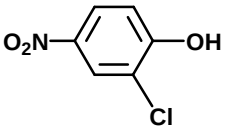
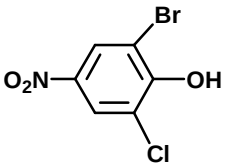
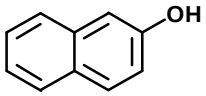
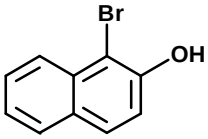
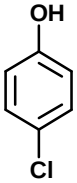
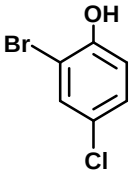
According to the results shown in the TABLE 2, the bromination of the substrates took place with high regioselectivity and only mono-bromination was found to occur. When a methoxy or an amine group was present on the aromatic ring (entries 1-9), bromination proceeded with high para-selectivity while ortho- bromination occurred when the para-position was blocked with a substituent other than a hydroxyl group. However, with the phenolic compounds (entries 10-16) the ortho-bromo compounds were the major products.

In conclusion, we have developed a very simple, mild and regioselective method for nuclear bromination of activated aromatic compounds using the 1,4-bis (triphenylphosphonium) butane peroxodisulfate (BTPPBPDS) reagent system with $Br_2$ or KBr as oxidant which is readily available, inexpensive and non-toxic.

**TABLE 2 : Bromination of some aromatic compounds with $Br_2$ and KBr in the presence of 1,4-bis (triphenylphosphonium) butane peroxodisulfate**

| Entry | Substrate | Product | Reagent | | | | M.p., °C (Lit.) |
|---|---|---|---|---|---|---|---|
| | | | $Br_2$ | | KBr | | |
| | | | Time (min) | Yield[b] (%) | Time (min) | Yield[b] (%) | |
| 1 |  |  | 20 | 97 | 35 | 92 | Liq (Liq)[18c] |
| 2 |  |  | 15 | 0 | 22 | 0 | ---- |
| 3 |  |  | 28 | 92 | 35 | 90 | 26-27 (25-26)[18c] |
| 4 |  |  | 31 | 89 | 40 | 87 | 67-69 (69-70)[18a] |
| 5 |  |  | 35 | 90 | 48 | 89 | 56-58 (54-55)[18a] |
| 6 |  |  | 30 | 89 | 39 | 90 | 61-62 (61-63)[18a] |
| 7 |  |  | 25 | 95 | 33 | 0 | 50-52 (52-54)[18a] |
| 8 |  |  | 28 | 89 | 37 | 93 | 53-55 (53-56)[18a] |
| 9 |  |  | 31 | 92 | 40 | 87 | 75-78 (78-81)[18a] |
| 10 |  |  | 15 | 84 | 27 | 89 | 85-87 (85-86)[18c] |
| 11 |  |  | 25 | 86 | 35 | 88 | 60-62 (58-62)[18c] |

Full Paper

| Entry | Substrate | Product | Reagent | | | | M.p., °C (Lit.) |
|---|---|---|---|---|---|---|---|
| | | | $Br_2$ | | KBr | | |
| | | | Time (min) | Yield[b] (%) | Time (min) | Yield[b] (%) | |
| 12 |  |  | 41 | 92 | 52 | 90 | 110-112 (111-115)[18a] |
| 13 |  |  | 45 | 93 | 55 | 89 | 96-98 (97-99)[18a] |
| 14 |  |  | 30 | 86 | 39 | 0 | 79-81 (78-81)[18a] |
| 15 |  |  | 15 | 90 | 30 | 91 | 91-93 (90-92)[18a] |

## EXPERIMENTAL

All products were characterized by comparison of their physical data, IR, $^1$H NMR and $^{13}$C NMR spectra with authentic samples[20-25]. The IR spectra were recorded on SP-HOO FT-IR spectrometer. $^1$H NMR and $^{13}$C NMR spectra were taken on a 500 MHz P-VV-COM spectrometer. 1,4-Bis(triphenylpho-sphonium)-2-butene Peroxodisulfate was prepared and other chemicals were purchased from the Merck chemical company Darmstadt, Germany. The purity determination of the products and reaction monitoring were accomplished by TLC on polygram SILG/UV 254 plates.

### Preparation of 1,4-bis(triphenylphosphonium) butane dibromide (1)

To a solution of 1,4-dibromobutane (0.215 g, 1 mmol) in $CH_3OH$ (10 mL) in a 50 mL round-bottomed ûask equipped with a magnetic stirrer and a reûux condenser was added triphenylphosphine (2 mmol). The reaction mixture was reûuxed for 3 h. The solution was cooled to room temperature and then diethyl ether was added drop wise until an oily product was separated. The ether was removed by decantation and methanol (20 mL) was added. Stirring the methanol solution for 20 min afforded a white precipitate which was ûltered, washed with methanol and then dried with yield (90%).

### Preparation of 1,4-bis(triphenylphosphonium)butane peroxodisulfate (2)

1,4-Bis(triphenyl phosphonium)butane dibromide (0.74 g, 1 mmol) was mixed with $H_2O$ (20 ml), the mixture was completely stirred to obtain a clear solution. Then, chloroform (2–3 ml) was added and the organic and aqueous phases were separated. The aqueous phase was ûltered. In other sections $K_2S_2O_8$ (0.037 g, 0.137 mmol) and $H_2O$ (10 ml) were added and completely stirred to obtain a clear solution. This solution was added to the aqueous phase (obtained in previous section) with stirring for 1 h to obtain a white powder, this powder was washed with $H_2O$ (4×10 ml) and then was dried in a desiccator. 1,4-Bis(triphenyl phosphonium)butane Peroxodisulfate (BTPPBPDS) was obtained in 85% yield. m.p. 130-132 °C (Scheme 1). $C_{40}H_{38}S_2O_8P_2^{+2}$: IR (KBr): $cm^{-1}$ 3053, 2985, 1681, 1585, 1472, 1437, 1100, 750, 724, 689, 556. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.2-2.3 (t, 2H, $CH_2$-), 3.6–3.8 (m, 2H, $CH_2$-P), 7.25-7.85 (m, 15H, $H_{ar}$). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 23, 27, 115, 137, 142.

### General procedure for bromination of aromatic compounds

To a solution of aromatic compound (1 mmol) in

$CH_3CN$ (5 mL) in a 50 mL round-bottomed ûask with a magnetic stirrer was added 1,4-bis(triphenylphosphonium)butane peroxodisulfate (1 mmol) and bromine (1 mmol) or potassium bromide (1 mmol, 0.12 gr).

The reaction mixture was stirred magnetically at ambient temperature under reflux for the appropriate time indicated in TABLE 1 & 2.

Progress of the reaction was monitored by TLC (Eluent: carbon tetrachloride/diethyl ether, 4 : 2, and carbon tetrachloride/n-hexane, 8 : 2) or GC (capillary column). The reaction mixture was cooled to room temperature and filtered. The excess bromine was removed from the filtrate by dropwise addition of sodium thiosulfate solution (1M).

Then dichloromethane (5 mL) was added, and the solution was transferred to a separatory funnel. The organic layer was separated and dried over magnesium sulfate or calcium chloride. Evaporation of the solvent followed by recrystallization or column chromatography on silica gel of the crude product gave the corresponding brominated compounds in good to excellent yields (TABLE 2).

The products were characterized on the basis of their physical and spectral analysis and by direct comparison with literature data[18a-c].

## REFERENCES


**[1]** **(a)** M.B.Smith, J.March; March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Edition, Wiley: New York, 698-705 **(2007)**; **(b)** R.C.Larock; Comprehensive Organic Transformations, 2nd Edition, Wiley-VCH: New York, 622-624 **(1999)**.

**[2]** B.Das, K.Venkateswarlu, M.Krishnaiah, H.Holla; Tetrahedron Lett., **47**, 8693 **(2006)**.

**[3]** G.K.Imanzadeh, M.R.Zamanloo, H.Eskandari, K.Shayesteh; J.Chem.Res.(S) 151 **(2006)**.

**[4]** G.K.S.Prakash, T.Mathew, D.Hoole, P.M.Esteves, Q.Wang, G.Rasul, G.A.Olah; J.Am.Chem.Soc., **126**, 15770 **(2004)**.

**[5]** B.Das, K.Venkateswarlu, A.Majhi, V.Siddaiah, K.R.Reddy; J.Mol.Catal.A: Chem., **267**, 30 **(2007)**.

**[6]** N.C.Ganguly, P.De, S.Dutta; Synthesis, 1103 **(2005)**.

**[7]** **(a)** D.Kalyani, A.R.Dick, W.Q.Anani, M.S.Sanford; Org.Lett., **12**, 2523 **(2006)**; **(b)** D.Kalyani, A.R.Dick, W.Q.Anani, M.S.Sanford; Tetrahedron, **62**, 11483 **(2007)**.

**[8]** D.Pla, F.Albericio, A.Lvarez; M.Eur.J.Org.Chem., 1921 **(2007)**.

**[9]** H.Adibi, A.R.Hajipour, M.Hashemi; Tetrahedron Lett., **48**, 1255 **(2007)**.

**[10]** H.Tajik, I.Mohammadpoor-Baltork, J.Albadi; Synth. Commun., **37**, 323 **(2007)**.

**[11]** A.R.Hajipour, S.A.Pourmousavi, A.E.Ruoho; Indian J.Chem B., **45**, 796 **(2006)**.

**[12]** K.Menzel, E.L.Fisher, L.DiMichele, D.E.Frantz, T.D.Nelson, M.H.Kress; J.Org.Chem., **71**, 2188 **(2006)**.

**[13]** S.Adimurthy, G.Ramachandraiah, A.V.Bedekar, S.Ghosh, B.C.Ranu, P.K.Ghosh; Green Chem., **8**, 916 **(2006)**.

**[14]** S.Singhal, S.L.Jain, B.Sain; J.Mol.Catal.A: Chem., **258**, 198 **(2006)**.

**[15]** **(a)** Z.G.Lee, Z.C.Chen, Q.G.Zheng; Chin.Chem. Lett., **16**, 1007 **(2005)**; **(b)** Z.G.Lee, Z.C.Chen, Q.G.Zheng; Synthesis, 2809 **(2004)**.

**[16]** M.M.Heravi, N.Abdolhosseini, H.A.Oskooie; Tetrahedron Lett., **46**, 8959 **(2005)**.

**[17]** J.M.Gnaim, R.A.Sheldon; Tetrahedron Lett., **46**, 4465 **(2005)**.

**[18]** **(a)** C.Galli; J.Org.Chem., **56**, 3238 **(1991)**; **(b)** C.Galli, S.Giammarino; J.Chem.Soc.Perkin.Trans.2, 1261 **(1994)**; **(c)** M.Fabbrini, C.Galli, P.Gentili, D.Macchitella, H.Petride; J.Chem.Soc.Perkin. Trans.2, 1516 **(2001)**; **(e)** V.Kavala, S.Naik, B.K.Patel; J.Org.Chem., **70**, 4267 **(2005)**.

**[19]** **(a)** G.Cerichelli, L.Luchetti, G.Mancini; Colloids Surf.A, **289**, 226 **(2006)**; **(b)** J.Salazar, R.Dorta; Synlett, 1318 **(2004)**.

**[20]** D.-K.Kim, W.-J.Chung, Y.-S.Lee; Synlett, 279 **(2005)**.

**[21]** H.Tajik, F.Shirini, P.Hassanzadeh, H.R.Rashtabadi; Synth.Commun., **35**, 1947 **(2005)**.

**[22]** L.S.De Almeida, P.M.Esteves, M.C.S.De Mattos; Synthesis, 221 **(2006)**.

**[23]** L.S.De Almeida, P.M.Esteves, M.C.S.De Mattos; Synlett, 1687 **(2007)**.

**[24]** J.-M.Chretien, F.Zammattio, E.Le Grognec, M.Paris, B.Cahingt, G.Montavon, J.-P.Quintard; J.Org.Chem., **70**, 2870 **(2005)**.

**[25]** T.Moriuchi, M.Yamaguchi, K.Kikushima, T.Hirao; Tetrahedron Lett., **48**, 2667 **(2007)**.

**[26]** S.Batt, S.K.Nayak; Synth.Commun., **37**, 1687 **(2007)**.

**[27]** **(a)** M.M.Lakouraj, M.Tajbakhsh, F.Ramzanian-Lehmali, K.Ghodrati; Monatsh.Chem., **139**, 537 **(2008)**; **(b)** M.M.Lakouraj, M.Tajbakhsh, F.Ramzanian-Lehmali; Phosphorus Sulfur and Silicon, **183**, 3388 **(2008)**; **(c)** H.Ghasemnejad-Bosra, M.Tajbakhsh, F.Ramzanian-Lehmali, M.Shabani-Mahali, M.A.Khalilzadeh; Phosphorus Sulfur and Silicon, **183**, 1496 **(2008)**; **(d)** M.Tajbakhsh, M.M.Lakouraj, F.Ramzanian-Lehmali; Synlett, **11**, 724 **(2006)**; **(e)** M.Tajbakhsh, I.Mohammadpoor-Baltork, F.Ramzanian-Lehmali; Phosphorus Sulfur and Silicon, **178**, 2621 **(2003)**; **(f)** M.Tajbakhsh, I.Mohammadpoor-Baltork, F.Ramzanian-Lehmali; J.Chem.Res.(s), 185 **(2001)**; **(g)** H.Ghasemnejad-Bosra, M.Faraje, S.Habibzadeh, F.Ramzanian-Lehmali; J.Serb.Chem.Soc., **75**, 299 **(2010)**.

**[28]** H.Ghasemnejad-Bosra, M.Faraje, S.Habibzadeh; Helv.Chim.Acta, **92**, 575 **(2009)**.

**[29]** H.Ghasemnejad-Bosra, M.Forouzani; Heterocycl. Commun., **17(1-2)**, 83 **(2011)**.

**[30]** H.Ghasemnejad-Bosra; Organic Chemistry: An Indian Journal, **8(8)**, 303 **(2012)**.

**[31]** P.V.Vyas, A.K.Bhatt, G.Ramachandraiah, A.V.Bedekar; Tetrahedron.Lett., **44**, 4085 **(2003)**.