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A simple and improved regioselective brominations of aromatic compounds using *o*-xylylenebis (triphenylphosphonium) peroxodisulfate

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ABSTRACT

Direct bromination of a wide range of aromatic compounds with electron donating groups such as methoxy, hydroxy, or amino groups have been achieved with high regioselectivity and excellent yields with Br₂ in the presence of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate (OXTPPPODS) under mild reaction in acetonitrile. The use of lithium bromide as a bromination reagent afforded high yields of monobromo compounds with complete regioselectivity under neutral conditions in acetonitrile.

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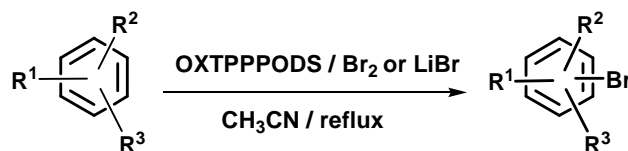
KEYWORDS

Bromination;
o-Xylylenebis
(triphenylphosphonium)
peroxodisulfate;
High regioselectivity;
Lithium bromide.

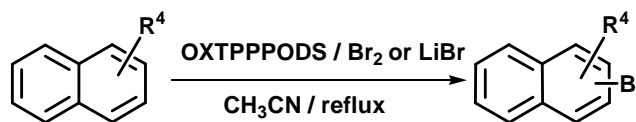
INTRODUCTION

Halogenated aromatic compounds have been used as intermediates for a number of natural products and bioactive materials^[1] and also proved as important and useful reagents in organic syntheses by functionalization through carbon-carbon bond formation of diarenes, ethylenic, or acetylenic condensations using transition metals.^[2] Especially during the past decade, numerous methods for the direct introduction of halogen atom into aromatic molecules have been intensively developed.^[2] Aryl bromides are often used in the syntheses of aryl esters, aryl olefins, and other useful compounds. There are many published cases. It is well known that bromine is more reactive than iodine in aromatic halogenation. But it

is difficult to control monobromination using elemental bromine which only depends on the reaction conditions^[3] especially for the electron-rich aromatic



R¹, R², R³ = H, OH, OMe, Cl,
NO₂, CH₃, N(CH₃)₂, COOH



R⁴ = OH, OMe

Scheme 1 : Bromination of aromatic compounds

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compounds. Thus, there have been numerous reported bromination reagents in the literature.^[4-13] However, many of them suffer from regioselectivity of bromination of activated aromatic compounds, so the control over the degree of bromination and the regioselectivity is still needed.

In recent years, we have reported several peroxodisulfate reagents for oxidative transformations under nonaqueous conditions,^[14] and we now report a new practical and regioselective bromination of activated aromatic compounds under mild reaction conditions as shown in (Scheme 1).

o-Xylylenebis (triphenylphosphonium) peroxodisulfate was obtained as follows: an aqueous solution of *o*-xylylenebis (triphenylphosphonium bromide) was added under stirring to a solution of potassium peroxodisulfate in water at room temperature. The products were successively washed with water and acetone and dried under reduced pressure. This reagent is stable white powder which could be stored for months without losing their activity.

EXPERIMENTAL

The reactions were monitored by TLC using silica gel plates and the products purified by flash column chromatography on silica gel (Merck; 230-400 mesh), and were identified by comparison of their spectra and physical data with those of the authentic samples. ¹HNMR spectra were measured at 90 MHz on a JEOL spectrometer with tetramethylsilane as an internal reference and CDCl₃ as the solvent. IR spectra were recorded on Pye-unicam SP 1100 spectrophotometer. Elemental analysis was performed on a LECO 250 instrument.

Typical procedure for the synthesis of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate

To an aqueous solution of 39.45 g *o*-xylylenebis (triphenylphosphonium bromide) (50 mmol) in 100 cm³ H₂O was added a solution of 13.51 g potassium peroxodisulfate (50 mmol) in 100 cm³ H₂O. The mixture was stirred at room temperature for 30 min. The precipitate formed was filtered, washed with cooled distilled water (50 cm³), and dried in a desiccators under vacuum over calcium chloride to afford a white

powder (92%), which decomposes at 181-183 °C to a white material. ¹H NMR (DMSO): 7.90-6.85 (m, Ar, 34H), 4.7 (d, 4H, CH₂P). Analysis: C₄₄H₃₈P₂O₈S₂. Calcd. C, 64.38 %; H, 4.66 %; S, 7.81 %, Found: C, 64.37 %; H, 4.64 %; S, 7.79 %.

Typical procedure for the bromination of aromatic compounds

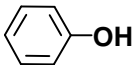
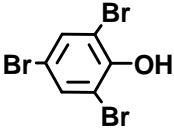
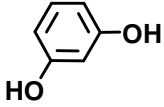
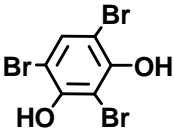
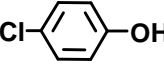
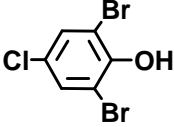
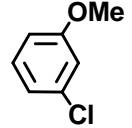
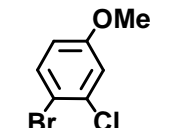
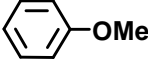
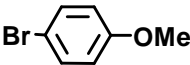
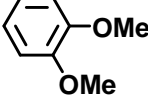
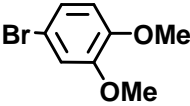
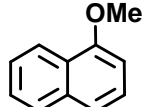
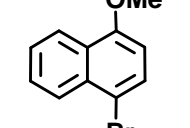
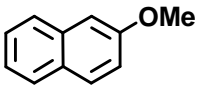
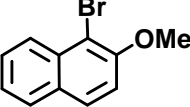
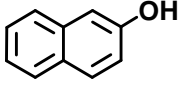
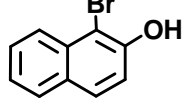
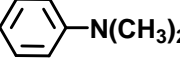
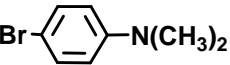
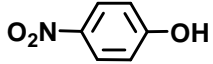
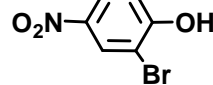
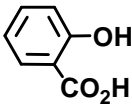
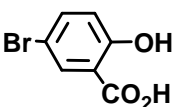
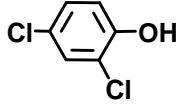
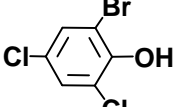
To a solution of aromatic compound (1 mmol) in acetonitrile (5 cm³), Br₂ (1.2 mmol) or LiBr (1.2 mmol) and *o*-xylylenebis (triphenylphosphonium) peroxodisulfate (1.2-1.2 mmol) were added and stirred (under room temperature for Br₂ and reflux temperature for LiBr). Progress of the reaction was monitored 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 (1 M). 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 1 and 2).

The products were characterized on the basis of their physical and spectral analysis (TABLE 1-3) and by direct comparison with literature data.

RESULTS AND DISCUSSION

In contrast to K₂S₂O₈, Na₂S₂O₈, or (NH₄)₂S₂O₈, *o*-xylylenebis (triphenylphosphonium) peroxodisulfate is easily soluble in various organic solvents such as acetonitrile, acetone, methanol, methylene chloride and therefore it can be easily used in general organic reactions. Various electron-rich aromatic compounds were brominated with bromine in the presence of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate at room temperature in CH₃CN to give brominated products with high regioselectivity. The results are summarized in TABLE 1.

TABLE 1 : Bromination of some aromatic compounds with Br₂ in the presence of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate.^a

Entry	Substrate	Product(s)	Oxidant/ Substrate/ Br ₂	Time,h	Yield, (%) ^b	M.p., °C	M.p. ^{lit.} , °C
1			1.2/1/1.2	0.3	94	90-94	90-94
2			1.2/1/1.2	0.3	90	108	108
3			1.2/1/1.2	0.5	78	91	91-92
4			1.2/1/1.2	0.5	85	Liq	Liq ^{18a}
5			1.2/1/1.2	0.3	97	Liq	Liq ^{18e}
6			1.2/1/1.2	0.3	83	Liq	Liq
7			1.2/1/1.2	0.4	75	64	63-65 ^{18a}
8			1.2/1/1.2	0.5	83	55	53-56 ^{18a}
9			1.2/1/1.2	0.4	90	79	78-81 ^{18a}
10			1.2/1/1.2	0.3	95	52-54	52-54
11			1.2/1/1.2	0.5	60	112	111-115 ^{18a}
12			1.2/1/1.2	0.4	78	60	58-62 ^{18a}
13			1.2/1/1.2	0.3	73	68	68

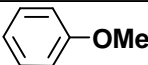
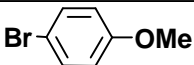
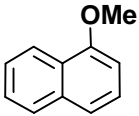
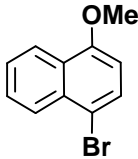
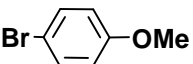
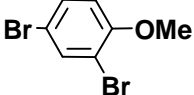
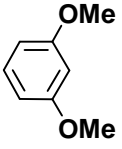
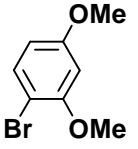
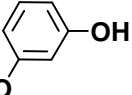
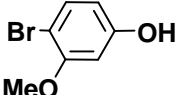
^a Reactions were carried out in CH₃CN at reflux temperature.^b All products were characterized spectroscopically (¹HNMR, IR) and showed physical and spectral. data in accordance with their expected structure and by comparison with authentic samples.

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Aromatic bromination with complete regioselectivity by preventing polybromination under mild conditions has been accomplished by lithium bromide in the pres-

ence of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate. The results obtained are reported herein in TABLE 2.

TABLE 2 : Bromination of some aromatic compounds with lithium bromide in the presence of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate.^a

Entry	Substrate	Product(s)	Oxidant/Substrate/LiBr	Time,h	Yield, (%) ^b	M.p., °C	M.p. ^{lit.} , °C
1			1.2/1/1.2	9	98	Liq	10-12 ^{18c}
2			1.2/1/1.2	21	87	64	63-65 ^{18a}
3			1.2/1/1.2	28	73	61	61-63
4			1.2/1/1.2	6	95	25-26	25
5			1.2/1/1.2	6	89	84	84

^a Reactions were carried out in CH₃CN at reflux temperature.

^b All products were characterized spectroscopically (¹HNMR, IR) and showed physical and spectral data in accordance with their expected structure and by comparison with authentic samples.

Monobrominations exclusively occurred at the *p*-position of methoxy or amino group (TABLE 1, entries 4-7 and 10). When *p*-position of methoxy group was blocked with a substituent, only *o*-bromination occurred (TABLE 1, entries 3, 8, 9, 11, 13 TABLE 2, and entry 3).

Complete regioselectivity of monobromination of compounds with bromine and *o*-xylylenebis (triphenylphosphonium) peroxodisulfate failed. To overcome this problem, a milder bromination system was designed using lithium bromide and *o*-xylylenebis (triphenylphosphonium) peroxodisulfate. The direct use of hazardous molecular bromine can be avoided by the use of neutral salt of LiBr. Various activated aromatic compounds reacted with lithium bromide in the presence of *o*-xylylenebis (triphenylphosphonium) peroxodisulfate in acetonitrile at reflux temperature to give the corresponding monobrominated products in excellent yields with complete regioselectivity. In a representative experimental, lithium bromide (104 mg, 1.2 mmol) and *o*-Xylylenebis (triphenylphosphonium) Peroxodisulfate (1.17 g, 1.2 mmol) were added to a solution of anisole (108 mg, 1.0

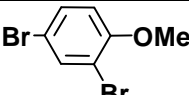
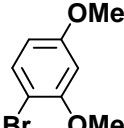
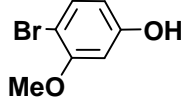
mmol, CH₃CN: 20mL) at reflux temperature with stirring. After complete disappearance of the starting material [monitored by TLC using ethyl acetate–*n*-hexane (1:10)], the solvent was removed from the reaction mixture on a rotary evaporator. The residue was then diluted with water (15 ml) and extracted with CHCl₃ (3 × 15 ml). The organic layer was separated, washed with brine and then dried over anhydrous MgSO₄. Removal of the solvent resulted in a solid which was chromatographed over silica gel using petroleum ether and an increasing proportion of ethyl acetate as eluent. ethyl acetate–*n*-hexane (1:10) eluent gave a solid which was purified by a silica gel column chromatography (silica gel 60: 0.040–0.063 mm, eluent: ethyl acetate/*n*-hexane 1/10, *p*-bromo anisole : 183 mg, 98%). The results obtained are summarized in TABLE 2.

In comparison with the system using bromine and *o*-xylylenebis (triphenylphosphonium) peroxodisulfate, the LiBr system needed longer reaction time but resulted in high yields and complete regioselectivity in monobrominations. *m*-Methoxyanisole (TABLE 2, en-

TABLE 3 : ¹H-NMR and ¹³C-NMR spectral data of the products

Entry	Product	¹ HNMR, ppm	¹³ CNMR, ppm
1		5.92 (1H,s,-OH), 7.62 (2H,s,Ar)	118.2(C2,6), 119.7(C4),135.1(C3,C5), 151.4(C1)
2		6.32 (2H,s,-OH), 7.59 (1H,s,Ar)	110.6(C2), 110.8(C4,C6),134.7(C5), 152.8(C1,C3)
3		5.91 (1H,s,-OH), 7.48 (2H,s,Ar)	117.2(C2,C6),131.3(C4), 132.9(C3,C5), 150.5(C1)
4		3.71 (3H,s,-OCH ₃), 6.64 (1H,dd,Ar), 6.77(1H,m, Ar), 7.35-7.37 (1H,dd, Ar),	55.76(-OCH ₃),101.33(C1), 103.07(C3),112.44(C5), 134.63(C6), 154.05(C2), 157.68(C4),
5		3.70 (3H,s,-OCH ₃), 6.57-6.61(2H,dd, Ar), 7.19-7.23(2H,dd, Ar)	56.15(-OCH ₃),108.60(C1), 111.90(C3,5), 129.00(C2,6), 156.91(C4),
6		3.72 (6H,s,-OCH ₃), 6.32(1H,dd, Ar), 6.83-6.88(2H,m, Ar)	56.2(-OCH ₃),114.9(C3), 115.2(C4), 123.1(C6), 124.9(C5), 148.8(C1), 150.2(C2)
7		3.20-3.43(1H, m,Ar), 3.61-3.86 (1H,m,Ar), 3.80 (3H,s,-OCH ₃), 5.71-5.76 (1H,m,Ar), 5.82-5.87 (1H,m,Ar), 6.60 (1H,m,-Ar), 7.19 (1H,mAr)	31.28(C8), 31.38(C5), 55.22(-OCH ₃),108.90(C2), 119.03(C3), 124.53(C9), 126.86(C10), 132.33(C7), 132.35(C6), 145.77(C4),149.59(C1)
8		3.15-3.37(1H, m,Ar), 3.62-3.85(1H, m,Ar), 3.78 (3H,s,-OCH ₃), 5.75-5.78 (1H,m,Ar), 5.83-5.87(1H, m,Ar), 6.71-6.73 (1H,m,-Ar), 7.05-7.08 (1H,mAr)	35.11(C5), 35.18(C8), 56.63(-OCH ₃),110.53(C3), 115.07(C1), 128.33(C10), 128.58(C4), 130.78(C7), 131.24(C6), 137.59(C9),156.86(C2)
9		5.47 (1H,s,-OH), 3.14-3.37 (1H,m,Ar), 3.62-3.85 (1H,m,Ar), 5.78 (1H,m,Ar),5.83(1H,m,Ar), 6.75(1H,m,Ar),7.05(1H,m,Ar),	35.11(C5), 37.17(C8), 115.43(C1), 116.47(C3), 128.14(C4), 128.93(C10), 130.78(C7), 131.24(C6), 135.43(C9),151.28(C2)
10		2.94 (6H,s,-NCH ₃), 6.60-6.62(2H,dd, Ar), 7.31-7.33(2H,dd, Ar)	40.2(-NCH ₃),116.2(C4), 116.5(C2,C6), 132.5(C3,C5), 150.1(C6),
11		5.60 (1H,s,-OH), 7.16-7.18 (1H,dd,Ar),7.80-7.82(1H,dd,Ar), 7.30 (1H,d,Ar),	107.04(C2), 119.80(C6), 122.91(C5), 127.62(C3), 142.04(C4), 157.63(C1),
12		11.45 (1H,s,-OH), 11.31 (1H,s,-COOH), 6.99-7.02(1H,dd,Ar), 7.57-7.59 (1H,dd,Ar), 7.77-7.78 (1H,dd,Ar),	100.46(C5),112.38(C1), 118.26(C3), 132.81(C4), 136.09(C6), 157.86(C2), 171.54(CO ₂ H),
13		5.94 (1H,s,-OH), 7.34 (1H,s,Ar), 7.44(1H,s,Ar)	116.6(C6), 127.8(C2), 129.9(C5), 130.5(C4),130.8(C3), 146.4(C1)

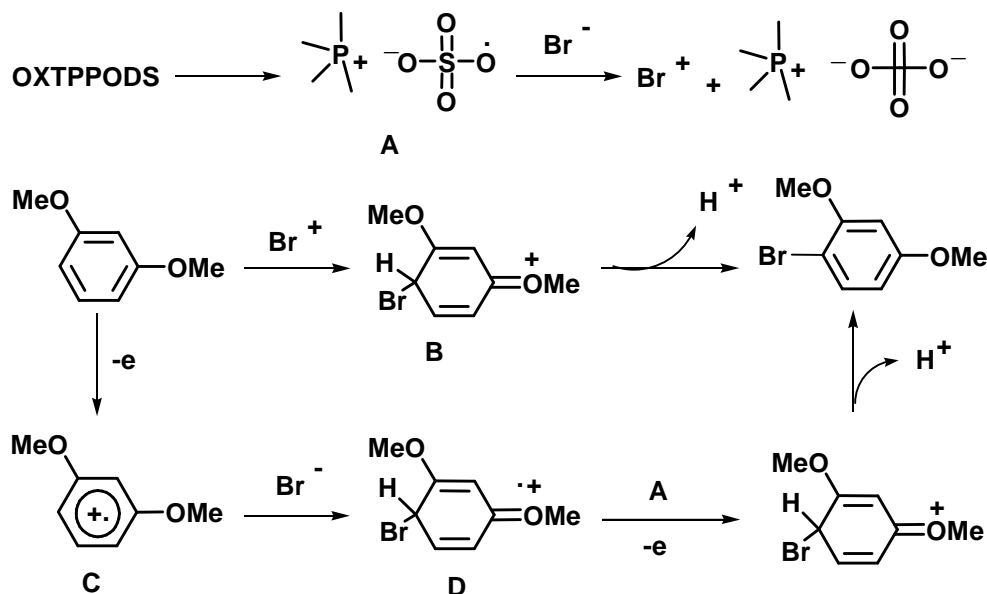
Full Paper

Entry	Product	¹ HNMR, ppm	¹³ CNMR, ppm
14		3.73 (3H,s,-OCH ₃), 6.55-6.59(1H,dd, Ar), 7.25-7.45 (2H,m, Ar)	55.8(-OCH ₃), 114.4(C2), 117.6(C4), 118.7(C6), 131.17(C5), 135.8(C3), 156.1(C1)
15		3.70 (3H,s,-OCH ₃), 3.83(3H,s, -O CH ₃), 6.45-6.50 (2H,m, Ar), 7.13(1H,dd,Ar)	55.87(-OCH ₃), 55.93(-OCH ₃), 115.35(C5), 116.27(C2), 118.70(C1), 125.66(C6), 148.84(C4), 149.78(C3),
16		3.83 (3H,s,-OCH ₃), 5.85(1H,s, -OH), 6.40-6.45 (1H,dd, Ar), 7.25-7.30(2H,m,Ar)	55.2(-OCH ₃), 104.2(C2), 104.8(C4), 119.4(C6), 134.1(C5), 158.4(C3), 158.5(C1)

try 4) gave *o*-bromo-*m*-methoxyanisole in quantitative yield (95%). The bromination occurred at only *p*-position of electron donating group: *o*-brominated isomers were not detected. In the case of *m*-methoxyphenol (TABLE 2, entry 5), only *p*-bromo-*m*-methoxyphenol (TABLE 2, entry 5, *p*-position was brominated toward OH group) was obtained.

Although the mechanism for the bromination with lithium bromide and OXTPPODS is not clear but the

reaction appears to be initiated via formation of phosphonium sulfate radical A by homolysis of OXTPPODS. The sulfate radical A may oxidize bromide anion to bromonium cation.^[4] The electrophilic attack of bromonium cation at *p*-position of activated aromatic compounds produces the intermediate B, which is readily converted to brominated product. However, there is an alternative possibility to form a radical cation C by one electron transfer, which may convert to a radi-



Scheme 2

cal intermediate D (Scheme 2).

CONCLUSION

We have developed a complete regioselective bromination of activated aromatic compounds under the mild conditions using OXTPPODS as an oxidant. The stable peroxydisulfate OXTPPODS can be readily

prepared, which can be handled easily and safely. Thus, it can be practically used for oxyhalogenation reaction. Bromination with bromine in the presence of OXTPPODS gave the mono and tribrominated products, respectively, in high to excellent yields as the major products in short reaction time. In contrast to using bromine, bromination with lithium bromide resulted in only monobrominated products with com-

plete regioselectivity in good to excellent yields under neutral and mild conditions. In this reaction, lithium bromide proves a better alternative to hazardous molecular bromine.

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