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Original scientific paper

Simple and improved regioselective brominations of aromatic compounds using *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate in the presence of potassium bromide under mild reactions conditions

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Abstract: A simple, efficient, and mild method for the selective bromination of some activated aromatic compounds using *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate in the presence of potassium bromide in non-aqueous solution is reported. The results obtained revealed good to excellent selectivity between the *ortho* and *para* positions of phenols and methoxyarenes.

Keyword: bromination; *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate; potassium bromide; phenols; methoxyarenes.

INTRODUCTION

Selective bromination of aromatic compounds is an important reaction in organic synthesis. Therefore, various methods have been developed for the bromination of aromatic rings using different reaction conditions. Direct treatment of aromatic compounds with molecular bromine normally results in a mixture of mono-, di-, and polysubstituted products. In addition, direct bromination of activated aromatic compounds by bromine generates hydrogen bromide, which is corrosive, toxic, and pollutes the environment.[1–4] To overcome these difficulties, numerous methods have been proposed to increase the selectivity and also the yields of the desired *para*-products.[5–14]

In recent years, several peroxodisulfate reagents for oxidative transformations under non-aqueous conditions have been reported.[15] As a part of a program related to the development of peroxodisulfate reagents, a new, simple, and general procedure is reported now for the bromination of a number of phenols and methoxyarenes using *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate

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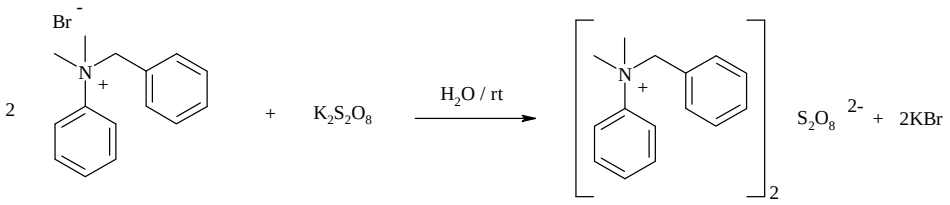
(DMBAPODS) in the presence of potassium bromide as the source of bromine. *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate was obtained as follows:[14] an aqueous solution of *N*-benzyl-*N*,*N*-dimethylanilinium bromide was added under stirring to a solution of potassium peroxodisulfate in water at room temperature. The products were successively washed with water and acetone and dried under reduced pressure. This reagent is a stable white powder which could be stored for months without losing its activity (Scheme 1).



DMBAPODS

Scheme 1. Synthesis of *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate.

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). The products were identified by comparison of their spectra and physical data with those of authentic samples. The ^{1}H-NMR spectra of the brominated compounds were measured at 90 MHz on a JEOL spectrometer with tetramethylsilane as the internal reference and $CDCl_3$ as the solvent. Elemental analysis was performed on a LECO 250 instrument.

Typical procedure for the synthesis of N-*benzyl*-N,N-*dimethylanilinium peroxodisulfate*

To an aqueous solution of 14.60 g *N*,*N*-dimethylanilinium bromide (50 mmol) in 100 mL H_2O was added a solution of 13.51 g potassium peroxodisulfate (50 mmol) in 100 mL H_2O. The mixture was stirred at room temperature for 30 min. The formed precipitate was filtered, washed with cooled distilled water (50 mL), and dried in a desiccator under vacuum over calcium chloride to afford a white powder (92 %), which decomposes at 181–183 °C to a dark brown material. Anal. Calcd. for: $C_{30}H_{36}N_2O_8S_2$: C, 58.43; H, 5.87; N, 4.54 %. Found: C, 58.46; H, 5.89; N, 4.56; ^{1}H-NMR (90 MHz, DMSO-d_6, δ / ppm): 6.9–8.2 (10H, *m*, C_6H_5), 5.8 (2H, *s*. CH_2), 3.95 (6H, *s*. CH_3).

Typical procedure for the bromination of aromatic compounds with potassium bromide in the presence of N-*benzyl*-N,N-*dimethylanilinium peroxodisulfate*

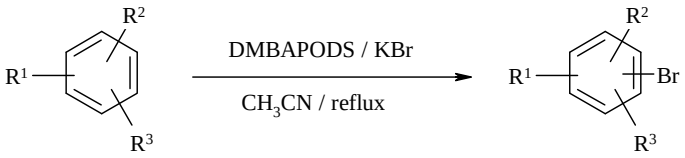
To a solution of aromatic compound (1 mmol) in acetonitrile (5 mL), KBr (1.2 mmol) and *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate (1–1.2 mmol) were added and the mixture heated under reflux for 1.5–9.5 h. The progress of the reaction was monitored by TLC (eluent: carbon tetrachloride/diethyl 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 the dropwise addition of a sodium thiosulfate solution (1 M). Then dichloromethane (5 mL) was added and the solution 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.

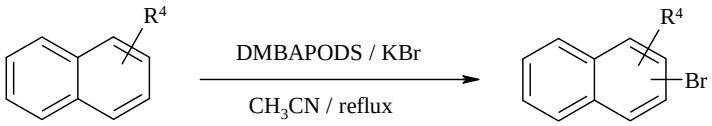
The products were characterized based on their physical and spectral analysis and by direct comparison with literature data (Supplementary Material).[16]

RESULTS AND DISCUSION

This article reports the use of potassium bromide as the source of bromine and *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate as the oxidizing agent in acetonitrile as solvent for the bromination of a number of phenols and methoxyarenes (Scheme 2). The results are given in Table I.



R^1, R^2, R^3 = H, OH, OMe, Cl, NO_2, CH_3, COOH



R^4 = OH, OMe

Scheme 2. General reaction for the bromination of aromatic compounds.

Thus, the methoxybenzenes were successfully reacted to afford the desired monobrominated products (Table I, entries **1**–**9**), except 2-methoxynaphthalene, which gave 1-bromo-2-methoxynaphthalene (Table I, entry **7**). Catechol, phenol, *ortho*-cholorophenol, *ortho*-cresol and *ortho*-methoxyphenol were quantitatively converted to the *para*-brominated products with respect to the hydroxyl groups (Table I, entries **10**–**14**). *para*-Nitrophenol and 2,4-dinitrophenol were also converted to the monobrominated products over longer reaction times (Table I, entries **15** and **16**). Resorcinol and *para*-methoxyphenol were quantitatively reacted to give the corresponding monobrominated products (Table I, entries **17** and **18**). Some other aromatic compounds, such as 1-naphthol and 2-naphthol, were also subjected to these reaction conditions, and the corresponding products were obtained in good yields (Table I, entries **20** and **21**). Salicylic acid and 2,4-dihydroxybezoic acid produced the brominated products over longer times and in low-

er yields compared to the other activated phenols and methoxyarenes (Table I, entries **19** and **22**).

TABLE I. Bromination of some aromatic compounds with potassium bromide in the presence of *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate (reactions were performed in CH_3CN at reflux temperature)

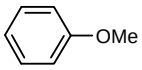
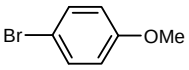
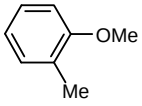
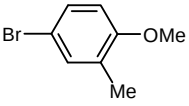
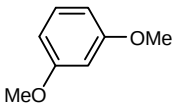
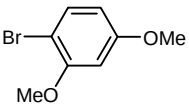
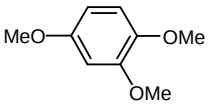
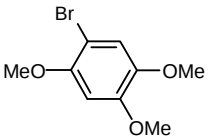
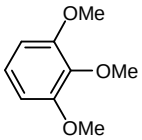
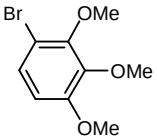
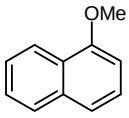
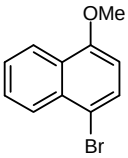
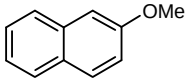
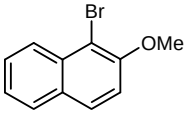
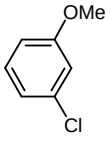
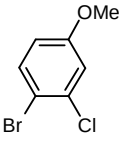
Entry	Substrate	Product(s)[a]	Oxidant/sub-strate/KBr	Time h	Yield %[b]	M.p. °C	M.p.[lit.] °C
1			1.2/1/1.2	3	91	Liq	Liq[18e]
2			1.2/1/1.2	3.5	95	69	69–70[18a]
3			1.2/1/1.2	4	93	25	25–26[18a]
4			1.2/1/1.2	3	94	55	54–55[18a]
5			1/1/1.2	2.5	92	Liq	Liq[18a]
6			1/1/1.2	7	84	64	63–65[18a]
7			1.2/1/1.2	6	90	55	53–56[18a]
8			1/1/1.2	5	89	Liq	Liq[18a]

TABLE I. Continued

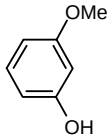
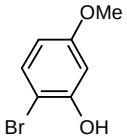
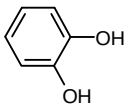
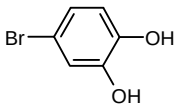
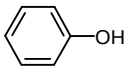
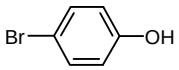
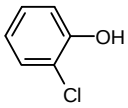
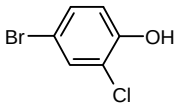
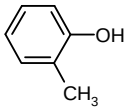
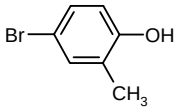
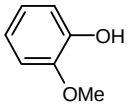
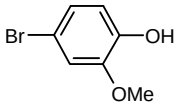
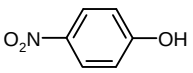
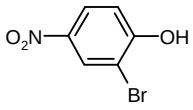
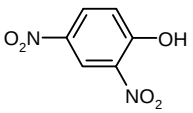
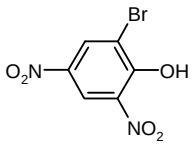
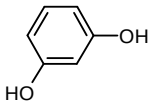
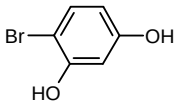
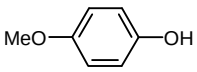
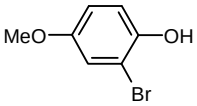
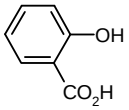
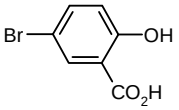
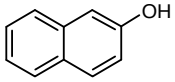
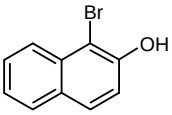
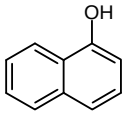
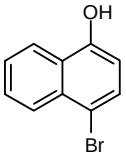
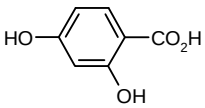
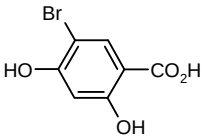
Entry	Substrate	Product(s)[a]	Oxidant/sub-strate/KBr	Time h	Yield %[b]	M.p. °C	M.p.[lit.] °C
9			1/1/1.2	3.5	96	152	152–154[18a]
10			1.2/1/1.2	3	95	87	87–89[18b]
11			1/1/1.2	4.5	96	63	61–64[18b]
12			1/1/1.2	1.5	97	51	49–50[18c]
13			1/1/1.2	4	93	57	58–59[18d]
14			1/1/1.2	3.5	96	34	34–37[18c]
15			1/1/1.2	8	97	112	111–115[18a]
16			1/1/1.2	9.5	91	99	97–99[18a]
17			1/1/1.2	2	94	104	103–105[18d]
18			1/1/1.2	4.5	95	45	44–45[18d]

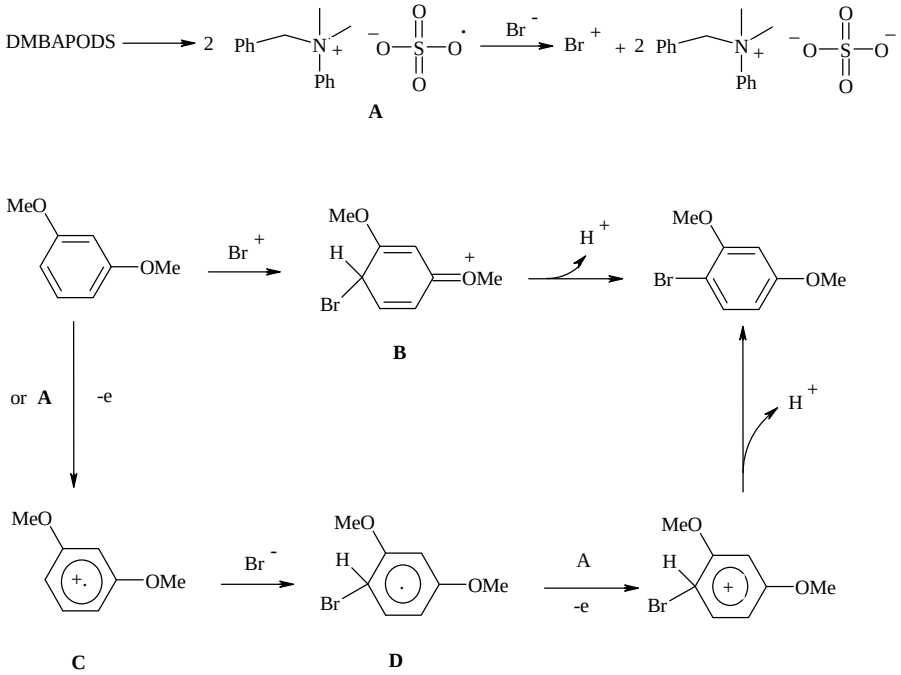
TABLE I. Continued

Entry	Substrate	Product(s)[a]	Oxidant/sub-strate/KBr	Time h	Yield %[b]	M.p. °C	M.p.[lit.] °C
19			1/1/1.2	6	79	60	58–62[18a]
20			1/1/1.2	5.5	90	79	78–81[18a]
21			1/1/1.2	5	91	129	129–131[18a]
22			1/1/1.2	6	73	165	165–167[18a]

[a]All products were characterized spectroscopically (^{1}H-NMR and IR) and showed physical and spectral data in accordance with their expected structure and by comparison with authentic samples;[16] [b]yields of isolated products

Although the mechanism for the bromination with lithium bromide and *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate is not clear, the reaction appears to be initiated *via* the formation of the *N*-benzyl-*N*,*N*-dimethylanilinium sulfate radical A by homolysis of *N*-benzyl-*N*,*N*-dimethylanilinium peroxodisulfate.[17] The sulfate radical A may oxidize the bromide anion to the bromonium cation. The electrophilic attack of the bromonium cation at the *p*-position of activated aromatic compounds produces the intermediate B, which is readily converted to the brominated product. However, there is an alternative possibility to form the radical cation C[18] by a one-electron transfer, which may convert to the radical intermediate D (Scheme 3).[4]

It is worth mentioning that the chemoselective conversion of methoxyaromatics to their *para*-substituted products was achieved in excellent yield. Another noteworthy advantage of this system lies in its ability to selectively brominate the *para vs*. the *ortho* position in catechol, phenol, *ortho*-chlorophenol, 2-methoxyphenol and *ortho*-cresol.



Scheme 3. Proposed mechanism for the synthesis of brominations of aromatic compounds.

CONCLUSIONS

The presented method represents an efficient, chemoselective and environmentally friendly synthesis methodology for the bromination of some activated aromatic compounds.

SUPPLEMENTARY MATERIAL

The ^{1}H-NMR and ^{13}C-NMR spectral data of the products are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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И З В О Д

РЕГИОСЕЛЕКТИВНО БРОМОВАЊЕ АРОМАТИЧНИХ ЈЕДИЊЕЊА ПОМОЋУ *N*-БЕНЗИЛ-*N*,*N*-ДИМЕТИЛАНИЛИНИЈУМ-ПЕРОКСОДИСУЛФАТА У ПРИСУСТВУ КАЛИЈУМ-БРОМИДА ПОД БЛАГИМ РЕАКЦИОНИМ УСЛОВИМА

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Описан је једноставан и ефикасан поступак селективног бромовања активираних ароматичних једињења помоћу *N*-бензил-*N*,*N*-диметиланилинијум-пероксодисулфата у при-

суству калијум-бромида у неводеним растварачима. Постигнута је добра селективност између *орто и пара* супституције фенола и метоксиарена.

(Примљено 16. марта, ревидирано 9. децембра 2010)

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