

Halogenations of Aromatic Compounds with Halide Anions in the
Presence of Nitrobenzenesulfonyl Peroxides.

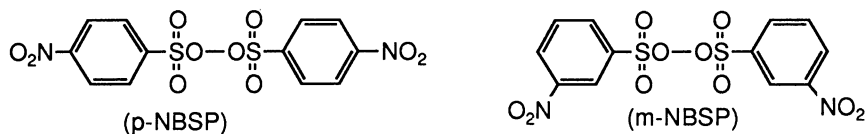
A Novel Method for the Formation of Positive Halogens

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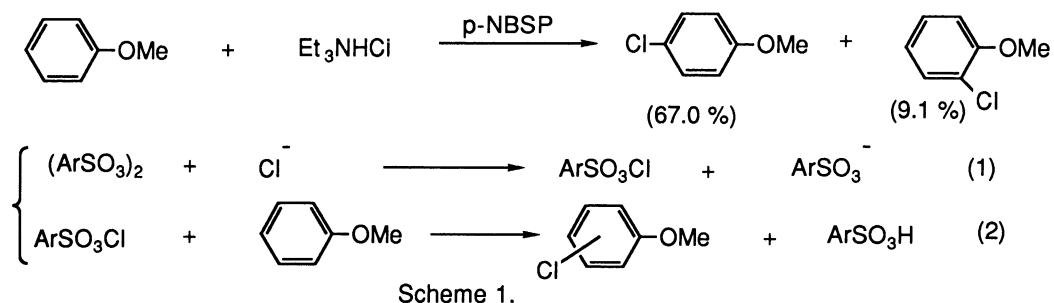
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A novel type of positive halogens, sulfonyl hypochlorite or sulfonyl hypobromite was formed in the reactions of halide anions with nitrobenzenesulfonyl peroxides; these hypohalites could be used as effective reagents for halogenation of aromatic rings.

We have been studying the novel methods for the introductions of functional groups into aromatic rings using peroxides.¹⁾ In the course of our studies, we found that the chlorination and bromination of aromatic rings by halide anion proceeded in the presence of nitrobenzenesulfonyl peroxides (NBSP),²⁾ and the results will be described herein.



p-NBSP (0.5 mmol) and triethylamine hydrogen chloride (Et_3NHCl : 0.75 mmol) were allowed to react at 0 °C in acetonitrile for 15 min, and to the resulting solution anisole (0.75 mmol) was added. The reaction mixture was stirred at 0 °C for additional 2 h, then methylene chloride was added. The solution was washed with water three times and the organic layer was analyzed by GC-MS. In this reaction, o- and p-chloroanisoles were formed but not m-chloroanisole, although anisyl p-nitrobenzenesulfonates, which are known to be main products in the reaction of p-NBSP and anisole in the absence of chloride anion,³⁾ were not formed. The isomer distribution in chloroanisoles suggests the electrophilic aromatic chlorinations; probably chloride anion was oxidized by NBSP to afford a positive chlorine compound. The plausible mechanism is shown in Scheme 1.



Generally, peroxides react as electrophiles in the presence of electron-donors;⁴⁾ especially, strong electron-withdrawing groups lower the energy level of O-O antibonding orbital of peroxides. Thus, p-NBSP should react as a good electrophile; e.g. chloride anion may react with p-NBSP to produce sulfonyl hypochlorite as shown in Scheme 1 (Eq. 1).⁵⁾ In the sulfonyl hypochlorite, the chlorine group should be charged positively owing to the effect of strong electron-withdrawing sulfonyloxy group and may react as an electrophile to be introduced into anisole. The halogenations of anisole under various conditions were also studied, and the results are summarized in Table 1.

Table 1. Halogenation of Anisole with halide anions in the presence of peroxides^{a)}

Peroxide	Solvent	Salt ^{b)}	Yield of ArX / % ^{c)}	Isomer ratio para / ortho
p-NBSP	CH ₃ CN	Et ₃ NHCl	76.1	88 / 12
m-NBSP	CH ₃ CN	Et ₃ NHCl	62.3	87 / 13
p-NBSP	CH ₂ Cl ₂	Et ₃ NHCl	49.1	96 / 4
m-NBSP	CH ₂ Cl ₂	Et ₃ NHCl	58.0	93 / 7
p-NBSP	CH ₃ CN	KCl ^{d)}	42.9	88 / 12
m-NBSP	CH ₃ CN	KCl ^{d)}	59.6	83 / 17
p-NBSP	CH ₃ CN	Et ₃ NHBr	76.0	100 / 0
m-NBSP	CH ₃ CN	Et ₃ NHBr	73.8	96 / 4
p-NBSP	CH ₂ Cl ₂	Et ₃ NHBr	66.0	91 / 9
m-NBSP	CH ₂ Cl ₂	Et ₃ NHBr	69.5	90 / 10
m-CPBA	CH ₃ CN	Et ₃ NHCl	none	
BPO	CH ₃ CN	Et ₃ NHCl	none	

a) 0.5 mmol of peroxide and 0.75 mmol of anisole were reacted at 0 °C.

b) 0.75 mmol of Et₃NHX or 1.5 mmol of KX were used. c) Determined by GC based on the peroxide. d) 0.025 mmol of 18-Crown-6 was added.

As an anion source, potassium chloride, which is stable and easy to handle, in the presence of 18-crown-6 could be also used. Not only chlorination but also bromination could be achieved in good yields, but iodination did not occur. In the reaction of iodide anion with NBSP, iodine was liberated. The reactions proceeded in both methylene chloride and acetonitrile but not in a nonpolar solvent, such as Freon-113 or hexane. m-Chloroperbenzoic acid (m-CPBA) or benzoyl peroxide (BPO) could not be applied to this method. Recently, the halogenation of very electron-rich benzenes, such as resorcinol dimethyl ethers, with potassium halides using m-chloroperbenzoic acid was reported, and the formation of m-chlorobenzoyl hypochlorite was also proposed.⁶⁾ However, the sulfonyl hypohalites should have higher potential as effective and versatile sources of positive halogen than acyl hypohalites, because m- and p-nitrobenzenesulfonates are very stable and act as very good leaving groups.⁷⁾

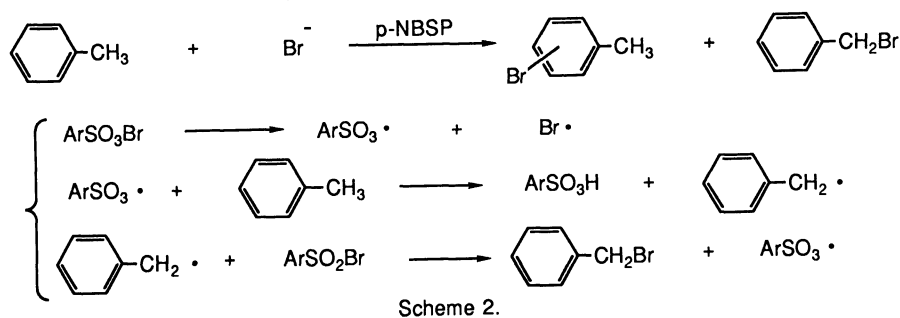
Table 2. Halogenation of toluene, benzene or thiophene with halide anion in the presence of NBSP^{a)}

Run	Substrate	Peroxide	Salt	Solvent	Temp ° C	Reaction time /h	Yield of ArX / % ^{b)}	Isomer ratio para/ortho
1	toluene	p-NBSP	Et ₃ NHCl	CH ₃ CN	0	24	77.6	58 / 42
2	toluene	m-NBSP	Et ₃ NHCl	CH ₃ CN	0	24	54.3	57 / 43
3	toluene	p-NBSP	Et ₃ NHCl	CH ₂ Cl ₂	0	48	31.4	55 / 45
4	toluene	p-NBSP	Et ₃ NHBr	CH ₃ CN	0	24	16.3 (32.3) ^{c)}	69 / 31
5	toluene	p-NBSP	Et ₃ NHBr	CH ₃ CN	-20	24	27.7 (11.4) ^{c)}	
6	toluene	p-NBSP	Et ₃ NHBr	CH ₃ CN	RT	1	7.7 (32.0) ^{c)}	
7	toluene ^{d)}	p-NBSP	Et ₃ NHBr	CH ₃ CN	0	24	57.6 (none) ^{c)}	40 / 60
8	benzene	p-NBSP	Et ₃ NHCl	CH ₃ CN	0	7 d	trace	
9	benzene ^{d)}	p-NBSP	Et ₃ NHCl	CH ₃ CN	RT	1	25.4	
10	thiophene	m-NBSP	Et ₃ NHCl	CH ₃ CN	0	0.25	56.2 ^{e)}	
11	thiophene	m-NBSP	Et ₃ NHBr	CH ₃ CN	0	0.25	46.4 ^{e)}	

a) 0.75 mmol of aromatic substrate, 0.5 mmol of NBSP, 0.75 mmol of triethylamine hydrogen halide, and 5 ml of solvent were typically used. b) Determined by GC based on NBSP. c) The yield of benzyl bromide was shown in parenthesis. d) 2.5 ml of substrate was used. e) 2-Substituted thiophene was solely produced.

The halogenations of toluene, benzene, and thiophene were also examined. The results are summarized in Table 2.

NBSP (0.5 mmol) and triethylamine hydrogen halide (0.75 mmol) were reacted in 5 ml of solvent, and then to the resulting solution 0.75 mmol of toluene was added. The chlorination of toluene proceeded in good yield, although the longer reaction time was required than that of anisole. In chlorination of toluene, the effects of peroxides (m-NBSP or p-NBSP) and solvents (acetonitrile or methylene chloride) on the yield or the reaction time were remarkable (Table 2, runs 1 - 3). In the reaction of bromide anion with toluene in the presence of NBSP, not only bromotoluene but also benzyl bromide were formed. The formation of benzyl bromide suggests the generation of radical species during the reaction; the unimolecular homolysis of sulfonyl hypobromite may occur competitively with bimolecular electrophilic aromatic substitution. The yield of benzyl bromide was increased when the reaction temperature was elevated (Table 2, runs 4 - 6); the homolytic cleavage of the hypobromite was probably accelerated. When a large excess of toluene was used in order to promote the bimolecular reaction, bromotoluenes were solely produced (Table 2, run 7).



The reaction with benzene was very slow and little chlorobenzene was formed when the reaction was performed under the typical reaction conditions for the chlorination of toluene (Table 2, run 8). Chlorobenzene was obtained in 25.4% yield when a large excess of benzene (2.5 ml) was reacted at room temperature with hypochlorite which was formed in the reaction of NBS (0.5 mmol) with triethylamine hydrogen chloride in 2.5 ml of acetonitrile (Table 2, run 9).

The reactivity of thiophene to electrophilic substitution is very high, and considerable amounts of dihalogenated thiophenes were produced when thiophene was added to the reaction mixture of NBS with triethylamine hydrogen halide. Monohalogenated thiophenes were selectively formed by the following procedure; NBS (0.5 mmol) was reacted with triethylamine hydrogen halide (0.75 mmol) in acetonitrile (2.5 ml) and the resulting solution was added drop by drop to thiophene (0.75 mmol) in 2.5 ml acetonitrile at 0 °C (Table 2, runs 10, 11). Since thiophene is unstable and easily polymerizes under acidic conditions, strict conditions are usually required for the halogenations of thiophene. In the present method, the chlorination or bromination of thiophene could be achieved in moderate yields.

The method for the formation of positive halogen described herein is very attractive and potentially useful in organic synthesis, since halide anions, which are stable and facile to handle, could be readily converted into very reactive and versatile positive halogens.

References

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