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Simple and Efficient Chlorination and Bromination of Aromatic Compounds With Aqueous TBHP (or H_2O_2) and a Hydrohalic Acid.

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Abstract:

A combination of aqueous *tert*-butylhydroperoxide (70%) or hydrogen peroxide (34%) and a hydrohalic acid was found effective in chlorination and bromination of aromatic compounds.

Keywords: Aryl halides; oxyhalogenation.

Halogenated aromatic compounds are a useful class of intermediates as they are precursors to a number of organometallic species useful in the synthesis of natural products and pharmaceutically important compounds. Many of the available methods [1] of direct halogenation of aromatic systems involve the use of potentially hazardous elemental halogen or expensive transition metal based catalysts.

The use of *tert*-butylhypohalite and hypohalous acid for the halogenation [2,3] and oxidation [4] of various organic compounds is widely explored. The preparation of *tert*-butylhypochlorite has been reported [5] but it is known to pose handling problems due to its hazardous nature. In this communication we wish to present the use of a combination of aqueous *tert*-butylhydroperoxide (TBHP) or hydrogen peroxide with a hydrohalic acid for the halogenation of aromatic compounds. We observed smooth halogenation in boiling methanol without any catalyst for both of these oxidants.

A number of different aromatic substrates were subjected to the halogenation reaction to test the generality of this method and the results are summarized in Table-1. Efficient halogenation of aromatic substrates with good yields and regioselectivity with TBHP and hydrohalic acids (CAUTION! [6]) is presented in Table-1 (entries-1 to 8). The chlorination of 1,4-dimethoxybenzene (entry–9) with an excess of TBHP and HCl (4 eq. each) afforded 2-chloro-1,4-dimethoxybenzene in 71% yield without the formation of a detectable amount of the dichloro compound, whereas H_2O_2 furnished 2,5-dichloro-1,4-dimethoxybenzene (entry-10) as the single product in 73 % yield. This interesting difference between the oxidants was confirmed using anisole and *N,N*-dimethyl(3,4,5-trimethoxy)benzamide (entry-11 to 14). It is believed that the chlorination proceeds *via* the formation of *tert*-butylhypochlorite when TBHP/HCl is used while *via* hypochlorous acid when

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H_2O_2/HCl is used. The similar selectivity for bromination could not be observed probably because of the much higher reactivity of the bromonium ion.

Table-1: Halogenation of aromatic compounds:

Entry	Aromatic nucleus	Reaction condition	Product[a]	% Yield[b]
1	Anisole	TBHP (1.0 eq.), HBr (1.0 eq.)	4-Bromoanisole	76
2	1,4-Dimethoxybenzene	TBHP (1.0 eq.), HBr (1.0 eq.)	2-Bromo-1,4-dimethoxybenzene	89
3	4-Methylphenol	TBHP (1.0 eq.), HBr (1.0 eq.)	2-Bromo-4-methyl phenol	74
4	Methy 3-methoxybenzoate	TBHP (1.0 eq.), HBr (1.0 eq.)	2-Bromo-5-methoxy methylbenzoate	73
5	*N*,*N*-Dimethyl(2-methoxy)benzamide	TBHP (1.0 eq.), HCl (1.0 eq.)	*N*,*N*-Dimethyl(3-chloro-6-methoxy)benzamide	88
6	*N*,*N*-Dimethyl(3-methoxy)benzamide	TBHP (1.0 eq.), HBr (1.0 eq.)	*N*,*N*-Dimethyl(2-bromo-5-methoxy)benzamide	98
7	*N*,*N*-Dimethyl(2-methyl-3,4,5-trimethoxy)benzamide	TBHP (1.0 eq.), HCl (1.0 eq.)	*N*,*N*-Dimethyl(2-chloro-3,4,5-trimethoxy-6-methyl)benzamide	70
8	1,4-Dimethoxybenzene	TBHP (4.0 eq.), HBr (4.0 eq.)	2,5-Dibromo-1,4-dimethoxybenzene	98
9	1,4-Dimethoxybenzene	TBHP (4.0 eq.), HCl (4.0 eq.)	2-Chloro-1,4-dimethoxybenzene	71
10	1,4-Dimethoxybenzene	H_2O_2 (4.0 eq.), HCl (4.0 eq.)	2,5-Dichloro-1,4-dimethoxybenzene	73
11	Anisole	TBHP (4.0 eq.), HCl (4.0 eq.)	2-Chloroanisole:4-Chloroanisole (35:65)	50
12	Anisole	H_2O_2 (4.0 eq.), HCl (4.0 eq.)	2,4-Dichloroanisole	75
13	*N*,*N*-Dimethyl(3,4,5-trimethoxy)benzamide	TBHP (4.0 eq.), HCl (4.0 eq.)	*N*,*N*-Dimethyl(2-chloro-3,4,5-trimethoxy)benzamide	70
14	*N*,*N*-Dimethyl(3,4,5-trimethoxy)benzamide	H_2O_2 (4.0 eq.), HCl (4.0 eq.)	*N*,*N*-Dimethyl(2,6-dichloro-3,4,5-trimethoxy)benzamide	74

[a]*Characterised by usual spectral and analytical methods;* [b]*isolated yield.*

Standard reaction procedure:

N,N-dimethyl(2-bromo-5-methoxy)benzamide (Table-1; entry-6): A solution of TBHP (70 % aq.; 0.15 mL; 1.17 mmol) was added to a cooled mixture of HBr (48 % aq.; 0.20 mL; 1.17 mmol) in methanol (5 mL) and the mixture stirred for 5 min. To this cold solution, *N*,*N*-dimethyl(3-methoxy)benzamide (0.21 g; 1.17 mmol) was added, and the mixture stirred for 30 min. and then refluxed for 6 h. The product was purified by flash column chromatography over silica gel to afford pure product (0.28 g; 98 %). δ_H 2.85 (s, 3H), 3.10 (s, 3H), 3.80 (s, 3H), 6.80 (m, 2H), 7.45 (m, 1H). δ_C 35.0, 39.0, 56.0, 110.0, 113.0, 117.0, 134.0, 139.0, 159.0, 169.0. MS m/z (%) 259 (M^++2, 31), 258 (34), 257 (M^+, 35), 256 (M^+-1, 38), 215 (85), 213 (100), 187 (23), 185 (28), 172 (15), 170 (17). Microanalysis: Calc. for $C_{10}H_{12}BrNO_2$; C: 46.51; H: 4.65; N: 5.43; Br: 31.39 %, Found, C: 46.34; H: 4.60; N: 5.22; Br: 31.62 %.

Thus we report our preliminary results on the simple and efficient aromatic chlorination and bromination with positive halogen reagents generated *in situ* by the oxidation of aqueous hydrohalic acid. We observed a selective monochlorination with hydrochloric acid and *tert*-butylhydroperoxide as oxidant while exclusive dichlorination **was** observed with hydrogen peroxide and hydrochloric acid.

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