

Simple and Efficient Chlorination and Bromination of Aromatic Compounds With Aqueous TBHP (or H₂O₂) and a Hydrohalic Acid.

Nivrutti B. Barhate, Anil S. Gajare, Radhika D. Wakharkar*
and Ashutosh V. Bedekar*

*Division of Organic Chemistry: Technology
National Chemical Laboratory, Pune 411 008, India.*

Received 7 April 1998; accepted 23 June 1998

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. © 1998 Elsevier Science Ltd. All rights reserved.

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 H₂O₂ 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

H₂O₂/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	<i>N,N</i> -Dimethyl(2-methoxy)benzamide	TBHP (1.0 eq.), HCl (1.0 eq.)	<i>N,N</i> -Dimethyl(3-chloro-6-methoxy)benzamide	88
6	<i>N,N</i> -Dimethyl(3-methoxy)benzamide	TBHP (1.0 eq.), HBr (1.0 eq.)	<i>N,N</i> -Dimethyl(2-bromo-5-methoxy)benzamide	98
7	<i>N,N</i> -Dimethyl(2-methyl-3,4,5-trimethoxy)benzamide	TBHP (1.0 eq.), HCl (1.0 eq.)	<i>N,N</i> -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 ₂ O 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 ₂ O ₂ (4.0 eq.), HCl (4.0 eq.)	2,4-Dichloroanisole	75
13	<i>N,N</i> -Dimethyl(3,4,5-trimethoxy)benzamide	TBHP (4.0 eq.), HCl (4.0 eq.)	<i>N,N</i> -Dimethyl(2-chloro-3,4,5-trimethoxy)benzamide	70
14	<i>N,N</i> -Dimethyl(3,4,5-trimethoxy)benzamide	H ₂ O ₂ (4.0 eq.), HCl (4.0 eq.)	<i>N,N</i> -Dimethyl(2,6-dichloro-3,4,5-trimethoxy)benzamide	74

^aCharacterised by usual spectral and analytical methods; ^bisolated 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 C₁₀H₁₂BrNO₂; 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.

Acknowledgements: We wish to thank Dr. V.H. Deshpande for useful discussions and to CSIR, New Delhi for the award of Pool Officership to AVB and Senior Research Fellowship to NBB.

References:

- a) De la Mare PB, Electrophilic Halogenation. Cambridge: Cambridge University Press, 1976: Chap. 5. b) Larock RC, Comprehensive Organic Transformations. New York: VCH, 1989:315.
- C-Halogenation*: a) Clark BF. Chem. News. 1931;143:265. b) Walling C, Mintz MJ J. Am. Chem. Soc. 1967;89:1515. c) Moore HW, Gajipe G. Synthesis 1973:49. d) Watson WD. J. Org. Chem. 1974;39:1160. e) Smith K, Butters M, Paget WE, Nay B. Synthesis 1985:1155. f) Peake CJ, Strickland JH. Synth. Commun. 1986;16:763. g) Raja R, Ratnasamy P. J. Cat. 1997;170:244.
- N-Halogenation*: a) Baumgarten HE, Bower FA. J. Am. Chem. Soc. 1954;76:4561. b) Baumgarten HE, Petersen JM. Org. Synth. 1961; 41:82. c) Bucciarelli M, Forui A, Moretti I, Torre G. J. Org. Chem. 1983;48:2640.
- Oxidation*: a) Grob CA, Schmid HJ. Helv. Chim. Acta 1953;36:1763. b) Detty MR. J. Org. Chem. 1980;45:274. c) McGillivray G, Ten Krooden E, Beyers M. S. Afr. J. Chem. 1986;39:51. d) Milovanovic JN, Vasojevic M, Gojkovic S. J. Chem. Soc., Perkin. Trans. 2 1991:1231. e) Takeda T, Watanabe H, Kitahara T. Synlett. 1997:1149.
- a) Teeter HM, Bell EW. Org. Synth. Coll. Vol. 4, 1963:125. b) Mintz MJ, Walling C. Org. Synth. 1969;49: 9.
- Sharpless KB, Verhoeven TR. Aldrichimica Acta 1979;12:63.