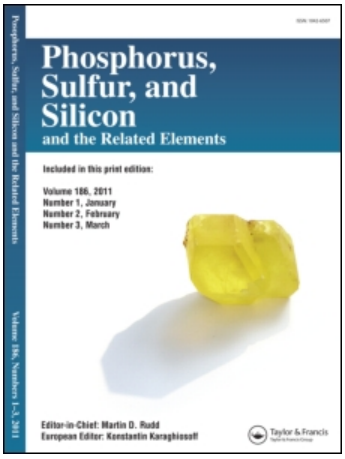


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Practical and Regioselective Halogenations of Aromatic Compounds Using Tetrabutylammonium Peroxydisulfate

Yong Hae Kim[a]; Min Young Park[a]; Seung Gak Yang[a]
[a] School of Molecular Science, Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejon, Korea

To cite this Article Kim, Yong Hae , Park, Min Young and Yang, Seung Gak(2005) 'Practical and Regioselective Halogenations of Aromatic Compounds Using Tetrabutylammonium Peroxydisulfate', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 5, 1235 — 1240
To link to this Article: DOI: 10.1080/10426500590911395
URL: http://dx.doi.org/10.1080/10426500590911395

Phosphorus, Sulfur, and Silicon, 180:1235–1240, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500590911395

Taylor & Francis
Taylor & Francis Group

Practical and Regioselective Halogenations of Aromatic Compounds Using Tetrabutylammonium Peroxydisulfate

Min Young Park
Seung Gak Yang
Yong Hae Kim
School of Molecular Science, Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejon, Korea

*The halogenated aromatic compounds have been important intermediates for various synthetic methods. Electron-rich aromatic compounds were easily iodinated using tetrabutylammonium peroxydisulfate (**1**) and iodine in mild conditions with excellent yields. Bromination was achieved using **1** and bromine, and regioselective bromination of highly activated aromatic compounds was also achieved using **1** and lithium bromide in mild conditions with excellent yields.*

Keywords Bromination; iodination; regioselective halogenation; tetrabutylammonium peroxydisulfate

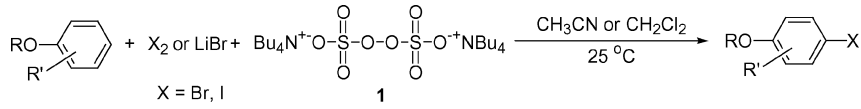
INTRODUCTION

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 and ethylenic or acetylenic condensations using transition metals.[2] Especially during the past decade, numerous methods for the direct introduction of halogen atoms into aromatic molecules have been intensively developed. Iodination of aromatic compounds needs additives to activate the less-reactive iodine sources such as iodine, NaI, and KI. Various methods have been investigated and reported.[3] However, because most of these methods require a hazardous or toxic reagent, or high reaction temperature for a long reaction time, it is difficult to control the regioselectivity of iodination. Aryl bromides often are also used in syntheses of aryl esters, aryl olefins, and other useful classes of compounds.

Received July 9, 2004; accepted October 5, 2004.
Address correspondence to Yong Hae Kim, School of Molecular Science of M. O. E., Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejon, 305-701, Korea. E-mail: Kimyh@kaist.ac.kr

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 mono bromination using elemental bromine only, especially for the electron rich aromatic compounds. There have been numerous bromination reagents reported.[4] However, many of them suffer from regioselectivity of bromination of activated aromatic compounds, so the control over the degree of bromination and the regioselectivity still has been needed.

Recently, we have reported an efficient iodination system for activated aromatic compounds using iodine and tetrabutylammonium peroxydisulfate [$(n\text{-}Bu_4N)_2S_2O_8$] **1**.[5] Here we describe a new practical and regioselective iodination and bromination of activated aromatic and heterocyclic compounds under mild reaction conditions as shown in Scheme 1.



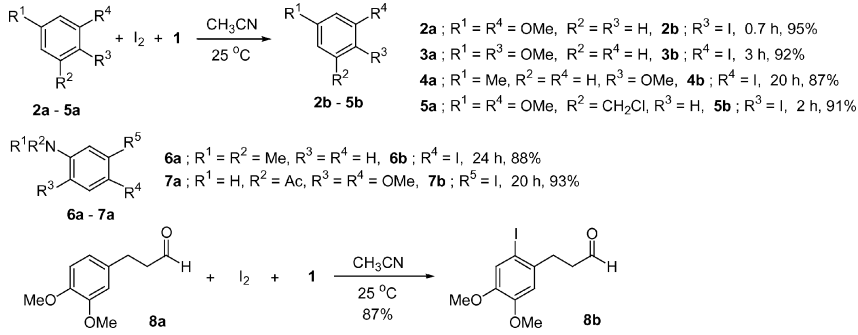
SCHEME 1 Halogenation of aromatic compounds with tetrabutylammonium peroxydisulfate as an oxidant.

The peroxide **1** turned out to be a useful source of the tetrabutylammonium sulfate radical, which shows oxidizing ability and can be readily converted to sulfate anion by one electron transfer from substrate.[6] In contrast to $K_2S_2O_8$, $Na_2S_2O_8$, or $(NH_4)_2S_2O_8$, **1** is easily soluble in various organic solvents such as acetonitrile, acetone, methanol, and methylene chloride and therefore it can be easily used in general organic reactions. Regioselective iodination of various aromatic compounds can be successfully achieved using **1** and iodine. To prevent polybromination, aromatic bromination with complete regioselectivity has been achieved using lithium bromide and **1** under mild conditions. The results obtained are reported herein.

RESULTS

The compound **1** was successfully prepared by mixing two equivalent of tetrabutylammonium hydrogensulfate and potassium persulfate in water. After stirring for 30 min at 25°C, the desired product was extracted with methylene chloride, washed with distilled water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the pure precipitate solid, which met elemental analysis.[6a] The white solid **1** is stable for a couple months at 25°C and can be stored in the refrigerator almost permanently.

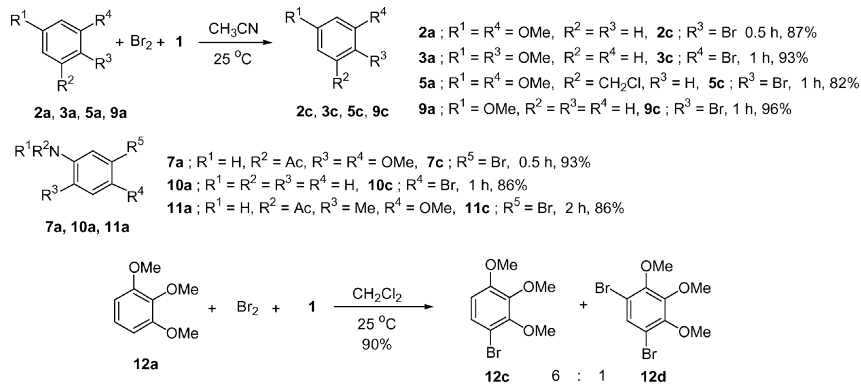
In order to check the regioselectivity in the iodination reaction, a variety of methoxy arenes and aniline derivatives were iodinated. Various activated aromatic compounds were reacted with iodine in the presence of **1** at room temperature in acetonitrile or methylene chloride to give mono iodinated products. The products obtained showed the complete regioselective *p*-oriented iodination with respect to electron donating group of –OMe or —$N(Me)_2$. The results obtained are summarized in Scheme 2.



SCHEME 2 Iodination reaction of aromatic compounds with iodine and tetrabutylammonium peroxydisulfate.

The regioselectivity can be deduced from the results that iodination occurred at a more electron-rich and less sterically hindered position. Methoxybenzenes were iodinated with selectivity of *p*-position, whereas *o*-iodination only occurred when the *p*-position was blocked with a substituent (**3b**). Although the iodination of aniline derivatives (**6a** and **7a**) is slower as compared to dimethoxybenzenes, only *p*-iodinated products were obtained in excellent yields under the same mild conditions. It is noteworthy that an aromatic compound **8a** bearing aldehyde moiety, which can be readily oxidized, was iodinated at *p*-position with regioselectivity in high yield (87%) without oxidizing aldehyde moiety. It was observed that there was no iodination of aromatic compounds bearing electron-withdrawing substituents, such as nitrobenzene and acetophenone, under the same reaction conditions: starting material was recovered almost quantitatively.

We applied this oxyhalogenation reaction to the bromination of electron-rich aromatic compounds. Various electron-rich aromatic compounds were brominated with bromine in the presence of **1** at 25°C in methylene chloride to give mono brominated products with high regioselectivity. The results obtained are summarized in Scheme 3. Mono brominations exclusively occurred at the *p*-position of methoxy

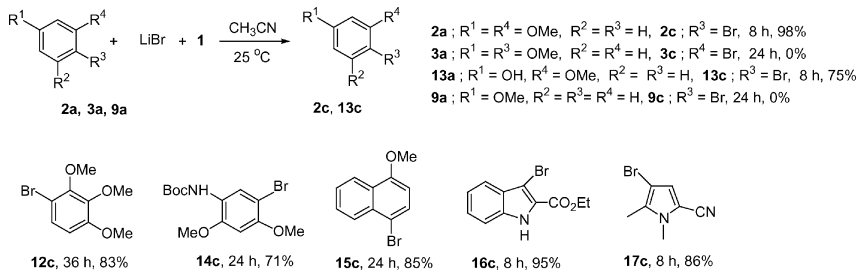


SCHEME 3 Bromination reaction of aromatic compounds with bromine and tetrabutylammonium peroxydisulfate.

or amino group. When *p*-position of methoxy group was blocked with a substituent, *o*-bromination occurred only. Because bromination of aniline and methoxybenzene proceeded more slowly as compared with that of dimethoxybenzene, the reaction appears to be related to the electron density of the aromatic compounds.

Complete regioselectivity of mono bromination of 1,2,3-trimethoxybenzene (**12a**) with bromine and **1** failed: a mixture of mono- and dibrominated products was obtained in the ratio of 6:1. The elongated reaction time (6 h) with **2a** also caused the formation of small amount of dibrominated product (monobrominated **2c**: approximately 90%, dibrominated product: approximately 10%). To overcome this problem, a milder bromination system was designed using lithium bromide and **1**. The direct use of hazardous molecular bromine can be avoided by the use of the neutral salt of LiBr. Various activated aromatic compounds reacted with lithium bromide and **1** in acetonitrile at 25°C to give the corresponding monobrominated products in excellent yields with complete regioselectivity. The results obtained are summarized in Scheme 4.

In comparison to the system using bromine and **1**, this system needed longer reaction time but resulted in high yields and complete regioselectivity in monobrominations. *m*-Methoxyanisole (**2a**) gave *o*-bromo-*m*-methoxyanisole **(2c)** in quantitative yield (98%). A large-scale bromination reaction (**12a**: 4.33 g, 25.7 mmol; **1**: 43.5 g, 64.2 mmol; LiBr: 5.6 g, 64.2 mmol) was performed for the practical purpose of giving **12c** in high yield (82%). The bromination occurred at only the *p*-position of the electron-donating group: *o*-brominated isomers were not detected. In the case of *m*-methoxyphenol (**13a**), only *p*-bromo-*m*-methoxyphenol



SCHEME 4 Bromination reaction of aromatic compounds with LiBr and tetrabutylammonium peroxydisulfate.

(**13c**, *p*-position was brominated toward OH group) was obtained. Some heterocycles (**16a** and **17a**) were also successfully brominated with lithium bromide and **1** at 25°C in acetonitrile in high yields. However, less-activated aromatic compounds such as anisole or toluene did not give brominated products under the same reaction conditions.

We have developed highly regioselective iodination and bromination of activated aromatic compounds under the mild conditions using **1** as an oxidant. The stable peroxydisulfate **1** can be readily prepared and can be handled easily and safely. Thus, it can be practically used for oxyhalogenation reaction. Bromination and iodination with bromine and iodine in the presence of **1** gave the monobrominated and iodinated products, respectively, in high to excellent yields as the major products in short reaction time. In contrast to using bromine, bromination with lithium bromide and **1** resulted in only monobrominated products with complete regioselectivity in good to excellent yields under neutral and mild conditions. In this reaction, lithium bromide proves to be a better alternative than hazardous molecular bromine.

REFERENCES

[1] a) A. Butler and J. V. Walker, *Chem. Rev.*, **93,** 1937 (1993); b) R. H. Seevers and R. E. Counsell, *Chem. Rev.*, **82,** 575 (1982); c) K. C. Nicolau, *Angew. Chem., Int. Ed. Eng.*, **32,** 1377 (1993).

[2] a) E. B. Merkushev, *Synthesis*, 923 (1988); b) R. F. Heck, *Org. React.*, **27,** 345 (1982); c) J. K. Stille, *Angew. Chem., Int. Ed. Eng.*, **25,** 508 (1986); d) A. Suzuki, *Pure Appl. Chem.*, **63,** 419 (1991).

[3] a) Y. Noda and M. Kashima, *Tetrahedron Lett.*, **38,** 6225 (1997); b) M. C. Carreno, J. L. G. Ruano, G. Sanz, M. A. Toledo, and A. Urbano, *Tetrahedron Lett.*, **37,** 4081 (1996); c) L. C. Brazdil and C. J. Curtler, *J. Org. Chem.*, **61,** 9621 (1996); d) K. Orito, T. Hatakeyama, M. Takeo, and H. Suginome, *Synthesis*, 1273 (1995); e) S. M. Hubig, W. Jung, and J. K. Kochi, *J. Org. Chem.*, **59,** 6233 (1994); f) J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, **58,** 2058

(1993); g) K. J. Edgar and S. N. Falling, *J. Org. Chem.*, **55,** 5287 (1990); h) K. Elbs and A. Jaroslawzew, *J. Prakt. Chem./Chem.-Ztg.*, **88,** 92 (1913); i) A. R. Hajipour, M. Arbabian, and A. E. Ruoho, *J. Org. Chem.*, **67,** 8622 (2002); j) N. Narender, P. Srinvasu, S. J. Kulkarni, and K. V. Raghavan, *Synth. Commun.*, **32,** 2319 (2002).

[4] a) M. C. Carreño, J. L. García Ruano, G. Sanz, M. A. Toledo, and A. Urbano, *Synlett*, 1241 (1997); b) N. B. Barhate, A. S. Gajare, R. D. Wakharkar, and A. V. Bedekar, *Tetrahedron*, **55,** 11127 (1999); c) U. Bora, G. Bose, M. K. Chaudhuri, S. S. Dhar, R. Gopinath, A. T. Khan, and B. K. Patel, *Org. Lett.*, **2,** 247 (2000); d) W. P. Reeves, C. V. Lu, B. Schulmeier, L. Jonas, and O. Hatlevik, *Synth. Commun.*, **28,** 499 (1998); e) D. Roche, K. Prasad, O. Repic, and T. J. Blacklock, *Tetrahedron Lett.*, **41,** 2083 (2000); f) S. C. Roy, C. Guin, K. K. Rana, and G. Maiti, *Tetrahedron Lett.*, **42,** 6941 (2001); g) A. R. Hajipour, S. E. Mallakpour, H. Imanieh, and S. A. Pourmousavi, *J. Chem. Res., (S),* 272 (2002); h) P. Bovicelli, E. Mincione, R. Antonioletti, R. Bernini, and M. Colombari, *Synth. Commun.*, **31,** 2955 (2001); i) A. P. Deshmukh, K. J. Padiya, V. K. Jadhav, and M. M. Salunkhe, *J. Chem. Res. (S)*, 828 (1998).

[5] S. G. Yang and Y. H. Kim, *Tetrahedron Lett.*, **40,** 6051 (1999).

[6] a) J. C. Jung, H. C. Choi, and Y. H. Kim, *Tetrahedron Lett.*, **34,** 3581 (1993); b) H. C. Choi and Y. H. Kim, *Synth. Commun.*, **24,** 2307 (1994); c) H. C. Choi, K. I. Cho, and Y. H. Kim, *Synlett*, 207 (1995); d) S. G. Yang, D. H. Lee, and Y. H. Kim, *Heteroat. Chem.*, **8,** 435 (1997); e) J. P. Hwang, S. G. Yang, and Y. H. Kim, *J. Chem. Soc., Chem. Commun.*, 1355 (1997); f) Y. H. Kim, J. P. Hwang, and S. G. Yang, *Tetrahedron Lett.*, **38,** 3009 (1997).