Eco-Friendly Bromination and Oxybromination of Diverse Organic Molecules

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By

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PREFACE

The primary focus of this book is to introduce and make people aware of the eco-friendly brominating reagents available for graduate students, postgraduate students, and academic researchers and for the industrial community. We hope that it will help early researchers who would like to pursue their career in the field of chemistry, particularly in synthetic chemistry, as organobromo products are the key starting substrates in the diverse fields of chemistry such as natural products, pharmaceuticals, agriculture, fine chemicals and modern material chemistry. We have covered almost all brominating reagents available for the bromination of variety of organic substrates under various conditions.

The organization of the book is traditional. We have been able to cover topics around bromination by aromatic reactions (phenols, anilines, aromatic hydrocarbons, and heteroaromatics) and aliphatic substitution reactions (benzylic & active methylene compounds). Addition reactions across the double and triple bonds including styrenes and cyclic olefins are also covered. The oxidation of alcohols to carbonyl compounds, oxybrominations and oxidative esterifications using eco-friendly brominating reagents are included. In addition, the preparation of versatile bromo intermediates such as bromobenzene, N-bromosuccinimide, tetrabromobisphenol-A, bromoxynil, 4-nitrobenzyl bromide and 2,6-dibromo nitro aniline are described using eco-friendly brominating reagents.

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support for undertaking the works on the preparation of eco-friendly brominating reagents and their utility in the bromination of diverse organic substrates.

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Dr. Subbarayappa Adimurthy,
Dr. Chitrakar Ravi,
Dr. Rajendra D. Patil.

CHAPTER 1

INTRODUCTION

C. RAVI, R.D. PATIL, S. ADIMURTHY

1.1 Brief description of the bromination process and bromoproducts

Bromine is one of the fundamental elements of the periodic table, and the bromination of organic substances is an important type of reaction that is central to modern synthetic chemistry through the generation of active, stable and transformative intermediates in the production of agrochemicals and pharmaceuticals.[1] A wide range of bromo-organic compounds are starting substrates for a broad range of functional group interconversions and complex molecules syntheses used in pharmaceutical industries. Organobromides are also found naturally through photochemical

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[1] (a) Ioffe, D.; Kampf, A. Bromine, Organic Compounds. Kirk-Othmer Encyclopedia of Chemical Technology, 5th ed.; John Wiley & Sons, Inc.: New York, 2004, Vol. 4, pp 340−345.
(b) Turner, D. L. Determination of Brominated Vegetable Oil Concentrations in Soft Drinks using a Specific Ion Electrode. J. Food Sci. 1972, 37, 791−792.
(c) Laskowski, D. A. Physical and Chemical Properties of Pyrethroids. Rev. Environ. Contam. Toxicol. 2002, 174, 49−170.
(d) Green, J. Mechanisms for Flame Retardancy and Smoke Suppression - A Review. J. Fire Sci. 1996, 14, 426−442.
(e) Gribble, G. W. The Diversity of Naturally Occurring Organobromine Compounds. Chem. Soc. Rev. 1999, 28, 335−346.
(f) Decanio, S. J.; Norman, C. S. Economics of the “Critical Use” of Methyl Bromide under the Montreal Protocol. Contemp. Econ. Policy 2005, 23, 376−393.
(g) Kaspersma, J.; Doumen, C.; Munro, S.; Prins, A.-M. Fire Retardant Mechanism of Aliphatic Bromine Compounds in Polystyrene and Polypropylene. Polym. Degrad. Stab. 2002, 77, 325−331.

reactions, geothermal events, and metabolic pathways.[2] Bromination of organic substrates is of special interest due to its stability and active nature towards the conversion of complex molecules synthesis. Most small-molecule active pharmaceutical ingredients (APIs) include bromination as a crucial step in their synthetic pathway, indicating the easily-unnoticed significance of bromination reactions.[3]

The crucial bromination pathways are substitution reactions (aromatics bromination), addition reactions, where the bromine is added to unsaturated double and triple bonds (unsaturated organic brominations), and the free radical process for saturated hydrocarbon brominations. Whether the brominating process is named radical or ionic depends on the types of substrates used.[4]

Molecular bromine is an adaptable brominating agent. Generally, most of the organic compounds are brominated using elemental bromine through electrophilic addition, and are generally used for determination of unsaturation with a bromonium ion or bromocarbocation as the key intermediate; for aromatic and heterocyclic compounds and for the aliphatic C−H bonds the bromination reaction proceeds through electrophilic substitution. Numerous efforts have been pursued with elemental bromine in academia, industrial fields, and agriculture. However, its use should now be discouraged due to its hazardousness. Bromine is toxic, requires care in handling and is a strong irritant. The

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2 (a) Herrmann, H.; Majdik, Z.; Ervens, B.; Weise, D. Halogen Production from Aqueous Tropospheric Particles. Chemosphere 2003, 52, 485−502.
(b) Rasmussen, R. A.; Khalil, M. A. K.; Dalluge, R. W.; Penkett, S. A.; Jones, B. A Somewhat Forgotten Physicist. Science 1982, 215, 655− 656.
(c) Butler, A.; Sandy, M. Mechanistic Considerations of Halogenating Enzymes. Nature 2009, 460, 848.
3 (a) McGrath, N.A.; Brichacek, M.; Njardarson, J.T. J. Chem. Educ. 2010, 87, 1348–1349.
(b) Ponomaryov, Y.; Krasikova, V.; Lebedev, A.; Chernyak, D.; Varacheva, L.; Chernobroviy, A. Chem. Heterocycl. Compd. 2015, 51, 133–138.
(c) Yuan, J.; Liu, K.; Li, L.; Yuan, Y.; Liu, X.; Li, Y., Molecules 2014, 19, 14999–15004.
(d) Radl, S.; Stach, J.; Piša, O.; Cinibulk, J.; Havliček, J.; Zajicova, M.; Pekarek, T.; Heterocycl. J. Chem. 2016, 53, 1738–1749.
[4] Saikia, I.; Borah, A.J.; Phukan, P. Chem. Rev. 2016, 116, 6837–7042.

bromine vapor can directly affect breathing and damage the respiratory system. Elemental bromine is not selective in some cases and needs a catalyst to promote the brominations.[5] Therefore, various effective and selective brominating reagents have been developed as alternatives to liquid bromine. N-Bromosuccinimide (NBS), discovered by Ziegler, is a good alternative brominating agent. NBS is used for the bromination of a wide variety of unsaturated and aromatic compounds and allylic and benzylic positions under mild reaction conditions.[6] In addition, many brominating reagents have been discovered for the bromination of diverse organic substrates.

1.2 Different brominating reagents available for bromination reactions

In recent decades, several brominating agents have been introduced for the preparation of various bromo intermediates, and these intermediates have been employed for the synthesis of bioactive molecules. Herein, we describe the various reported brominating reagents employed for specific organic brominations.

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[5] (a) Kaszas, G. Rubber Chem. Technol. 2000, 73, 356–365. (b) Grigoruk, Z.G.; Orlov, Y.N.; Levanova, S.V.; Abramova, N.V. Russ. Chem. 2010, 83, 1880–1882. (c) Choudary, B.M.; Someshwar, T.; Reddy, C.V.; Kantam, M.L.; Ratnam, K.J.; Sivaji, L.V. Appl. Catal. 2003, 251, 397–409. (d) Datta, R.L.; Chatterjee, N.R. J. Am. Chem. Soc. 1916, 38, 2545–2552.

[6] (a) Wohl, A. Bromination of Unsaturated Compounds with N-Bromoacetamide: A Contribution to the Study of the Course of Chemical Processes. Ber. Dtsch. Chem. Ges. B 1919, 52B, 51−63.
(b) Koval’, I. V. N-Halo Reagents. N-Halosuccinimides in Organic Synthesis and in Chemistry of Natural Compounds. Russ. J. Org. Chem. 2002, 38, 301−337.

1	N-Bromobenzamide[7]	phenol to tribromophenol
2	Bromonitromethane[8]	benzene to bromobenzene
3	1,3-Dibromo-5,5-dimethylhydantoin (DBH or DBDMH)[9,10]	A variety of aromatic, heteroaromatic substrates and flavones
4	Tribromo-*m*-cresol bromide[11]	2,4,6-tribromo-*m*-cresol from m-cresol
5	Sodium Monobromoisocyanurate[12]	2-bromo-phenol from phenol
6	Dibromoisocyanuric Acid[13,14]	bromination of aromatic, active and aliphatic amines
7	Tribromoisocyanuric Acid (TBCA)[15,16,17]	arenes to monobromoarenes, and the vicinal dihalogenation of alkenes and mono and di-bromination of dicarbonyl compounds

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[7] Moore, F. J.; Cederholm, A. M. Benzoyl-p-Bromphenylurea: A By-Product in the Preparation of Benzbromamide. J. Am. Chem. Soc. 1906, 28, 1190−1198.

[8] Sherrill, M. L. The Reaction of Bromonitromethane with Aromatic Compounds in the Presence of Aluminum Chloride. J. Am. Chem. Soc. 1924, 46, 2753−2758.

[9] (a) Salellas, J. F.; Orazi, O. O. Nuclear Halogenation with 1,3-Dibromo-5,5-Dimethylhydantoin. III. Polycyclic Aromatic Hydrocarbons. An. Asoc. Quim. Argent. 1951, 39, 175−183.

(b) Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. N-Bromosuccinimide/Dibromodimethylhydantoin in Aqueous Base: A Practical Method for The Bromination of Activated Benzoic Acids. Tetrahedron Lett. 1993, 34, 931−934.

[10] Zhao, P.-L.; Wu, Q.-Y.; Zhou, Z.-Z.; Yang, G.-F. Microwave- Assisted Synthesis of 3-Bromoflavone using 1,3-Dibromo-5,5-dimethyl- imidazolidine-2,4-dione as Brominating Agent. Chin. J. Org. Chem. 2006, 26, 694−697.

[11] Goldhahn, H. Tribromo-m-Cresol Bromide. Oesterr. Chem.-Ztg. 1941, 44, 244−247.

[12] Okada, Y.; Yokozawa, M.; Akiba, M.; Oishi, K.; O-kawa, K.; Akeboshi, T.; Kawamura, Y.; Inokuma, S.; Nakamura, Y.; Nishimura, J. Bromination by Means of Sodium Monobromoisocyanurate (SMBI). Org. Biomol. Chem. 2003, 1, 2506−2511.

[13] Roeger, C.; Wuerthner, F. Core-Tetrasubstituted Naphthalene Diimides: Synthesis, Optical Properties, and Redox Characteristics. J. Org. Chem. 2007, 72, 8070−8075.

[14] Cheng, K.-M.; Wu, J. B.; Lin, H.-C.; Huang, J.-J.; Huang, Y.- Y.; Lin, S.-K.; Lin, T.-P.; Wong, F. F. Dibromination of 5-Pyrazolones and 5-Hydroxypyrazoles via Dibromoisocyanuric Acid. J. Heterocycl. Chem. 2010, 47, 1153−1156.

8	Bromodichloroisocyanuric Acid[18]	bromination of activated arenes
9	TetramethylammoniumTribromide (TMATB)[19,20,21]	nuclear bromination of aromatic hydrocarbons, di-bromination of allylic alcohols and benzylic bromination
10	TetraethylammoniumTribromide (TEATB)[22,23]	bromination of activated aromatic compounds and a variety of flavones
11	CetyltrimethylammoniumTribromide, C16H33- (CH3)3N+Br3 (CTMATB)[24,25]	bromination of a wide range of aromatic compounds, such as anilines, phenols, anthracene, imidazoles, cresols, phluroglucinol, methyl 3-phenyl-2-propenoate, etc., and bromination of conjugated double bonds

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[15] de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. A New Regioselective Bromination of Activated Aromatic Rings. Synthesis 2006, 2, 221−223.

[16] Tozetti, S. D. F.; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. Trihaloisocyanuric Acids/Nax. An Environmentally Friendly System for Vicinal Dihalogenation of Alkenes without using Molecular Halogen. J. Braz. Chem. Soc. 2007, 18, 675−677.

[17] Mendonca, G. F.; Sindra, H. C.; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. Trihaloisocyanuric Acids as Convenient Reagents for Regioselective Halogenation of β-Dicarbonyl Compounds. Tetrahedron Lett. 2009, 50, 473−475.

[18] de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S. Efficient Electrophilic Cobromination of Alkenes and Bromination of Activated Arenes with Bromodichloroisocyanuric Acid under Mild Conditions. Synlett 2007, 11, 1687−1690.

[19] Avramoff, M.; Weiss, J.; Schaechter, O. The Brominating Properties of TetramethylammoniumTribromide. J. Org. Chem. 1963, 28, 3256−3258.

[20] Farkas, L.; Schächter, O. Brominations with Tetramethylammonium Bromide-Bromine Mixtures. J. Am. Chem. Soc. 1949, 71, 2252−2253.

[21] Avramoff, M.; Weiss, J.; Schaechter, O. The Brominating Properties of TetramethylammoniumTribromide. J. Org. Chem. 1963, 28, 3256−3258.

[22] Rho, H. S.; Ko, B. S.; Kim, H. K.; Ju, Y.-S. Synthesis of 3- Bromo Derivatives of Flavones. Synth. Commun. 2002, 32, 1303−1310.

[23] Borah, R.; Thakur, A. J. Green Synthesis of TetraalkylammoniumTribromide using Cerium(Iv) Ammonium Nitrate (CAN) As Oxidant. Synth. Commun. 2007, 37, 933−939.

12	BenzyltriethylammoniumTribromide [26]	bromination of aromatic compounds
13	Tetrabutylammonium Bromide (TBAB)[27]	regioselective bromination of activated aromatics and bromination of a variety of substituted acetophenones
14	Dioxane Dibromide[28,29]	bromination of a variety of aromatic compounds and bromination of a variety of substituted acetophenones
15	$MeNBr_2$ and Me_2NBr[30]	di-bromination of various phenols
16	N-bromosaccharin (NBSac)[31]	bromination of electron-rich aromatic compounds
17	Bis(dimethylacetamide) Hydrogen Dibromobromate[32]	bromination of anilines and phenols

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[24] Bora, U.; Chaudhuri, M. K.; Dey, D.; Dhar, S. S. Peroxometal- Mediated Environmentally Favorable Route to Brominating Agents and Protocols for Bromination of Organics. Pure Appl. Chem. 2001, 73, 93−102.

[25] Bora, U.; Chaudhuri, M. K.; Dey, D.; Dhar, S. S. Peroxometal- Mediated Environmentally Favorable Route to Brominating Agents and Protocols for Bromination of Organics. Pure Appl. Chem. 2001, 73, 93−102.

[26] Pourmousavi, S. A.; Salehi, P. Synthesis of Benzyl Triethyl Ammonium Tribromide and its Application as a Highly Efficient and Regioselective Reagent for the Bromination of Activated Aromatic Compounds. ActaChim. Slov. 2009, 56, 734−739.

[27] Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. Regioselective Bromination of Organic Substrates by Tetrabutylammonium Bromide Promoted by V2O5- H2O2: An Environmentally Favorable Synthetic Protocol. Org. Lett. 2000, 2, 247−249.

[28] Yanovskaya, L. A.; Terentyev, A. P.; Belenky, L. I. Bromination with Dioxane Dibromide. I. Bromination of Phenols. J. Gen. Chem. USSR (Engl. Transl.) 1952, 22, 1594−1598.

[29] Pasaribu, S. J.; Williams, L. R. Selective Bromination of Substituted Acetophenones with Dioxan Dibromide. Aust. J. Chem. 1973, 26, 1327−1331.

[30] Schmitz, E.; Pagenkopf, I. Ortho Specific Bromination of Phenols. J. Prakt. Chem. 1985, 327, 998−1006.

[31] de Souza, S. P. L.; da Silva, J. F. M.; de Mattos, M. C. S. NChloro- and N-Bromosaccharins: Valuable Reagents for Halogenatio of Electron Rich Aromatics and Halohydroxylation of Alkenes. J. Braz. Chem. Soc. 2003, 14, 832−835.

18	1,8-Diazobicyclo[5.4.0]undec-7-ene HydrobromidePerbromide (DBUH)Br_3[33]	Polycyclic aromatic compounds such as naphthalene, anthracene, and phenanthrene
19	TetraalkylammoniumDichlorobromate, Bu_4NBrCl_2[34]	bromination of phenols and naphthols
20	1-Benzyl-4-aza-1-azoniabicyclo[2.2.2]octane Tribromide[35]	bromination of both activated and deactivated aromatic amines as well as phenolic compounds
21	N, N-Dibromo-p-toluenesulfonamide (Dibromoamine-T)[36]	rapid bromination of activated aromatic compounds such as phenols, anisole, and anilines
22	N,N-Dibromo-N,N-1,2-ethylenebis(4-methylbenzenesulfonamide)[37]	bromination of various aromatic compounds

---

[32] Rodygin, M. Y.; Mikhailov, V. A.; Savelova, V. A.; Chernovol, P. A. Bis(Dimethylacetamide)Hydrogen Dibromobromate: New Brominating Agent. Zh. Org. Khim. 1992, 28, 1926−1927.

[33] Muathen, H. A. 1,8-Diazabicyclo[5.4.0]Undec-7-Ene HydrobromidePerbromide: A New Mild Stable Brominating Agent For Aromatic Compounds. J. Org. Chem. 1992, 57, 2740−2741.

[34] (a) Negoro, T.; Wada, M.; Someya, M. Bromination of Phenols with TetraalkylammoniumDichlorobromate(1-). II. Bull. Fac. Educ., Wakayama Univ. Nat. Sci. 1999, 49, 47−55.

(b) Negoro, T.; Wada, M.; Someya, M. Bromination of Phenols with TetraalkylammoniumDichlorobromate(1-). I. Wakayama DaigakuKyoikugakubu Kiyo, Shizen Kagaku 1998, 48, 1−7.

[35] (a) Hajipour, A. R.; Imanieh, H.; Pourmousavi, S. A. 1-Benzyl-4- Aza-1-Azoniabicyclo[2.2.2]Octane Tribromide as A Highly Reactive Brominating Agent for Aniline Derivatives. Synth. Commun. 2004, 34, 4597−4604.

(b) Hajipour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. 1- Benzyl-4- Aza-1-Azoniabicyclo[2.2.2]Octane Tribromide as A Regenerable and useful Reagent for Bromination of Phenols under Mild Conditions. Indian J. Chem. 2006, 45B, 796−800.

[36] Saikia, I.; Chakraborty, P.; Sarma, M. J.; Goswami, M.; Phukan, P. Rapid and Total Bromination of Aromatic Compounds using TsNBr2 Without any Catalyst. Synth. Commun. 2015, 45, 211−217.

23	[[K·18-crown-6]Br3]n[38]	bromination of aromatic substrates
24	N-OctylquinoliniumTribromide[39]	bromination of all phenols, aromatic amines, alkenes, and alkynes
25	Silica-Supported QuinoliniumTribromide[40]	monobromination of aromatic amines
26	DABCO−Bromine (Bisbromine−1,4-diazabicyclo[2.2.2]octane Complex)[41]	bromination of activated aromatic substrates
27	Tetrabromo Hydrogenated Cardanol or 2,4,4,6- Tetrabromo-3-(n-pentadecyl)-2,5-cyclohexadienone[42]	bromination of various aromatic amines and phenols, and α- naphthol
28	1-Butyl-3-methylimidazolium Tribromide ([Bmim]Br_3)[43,44]	monobromination of various amines and phenols and regioselective monobrominating agent of various alkanones

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[37] Khazaei, A.; Manesh, A. A.; Safi, V. R.; Vaghei, R. G. Regioselective Bromination of Aromatic Compounds using N,N′-Dibromo-N,N′-1,2-Ethylene Bis(4-Methyl Benzene Sulfonamide). Asian J. Chem. 2005, 17, 2509−2512.

[38] Zolfigol, M. A.; Chehardoli, G.; Salehzadeh, S.; Adams, H.; Ward, M. D. {[K.18-Crown-6]Br3}N: A Unique Tribromide-Type and Columnar Nanotube-Like Structure for the Oxidative Coupling of Thiols and Bromination of Some Aromatic Compounds. Tetrahedron Lett. 2007, 48, 7969−7973.

[39] Kaushik, M. P.;Polshettiwar, V. N-OctylquinoliniumTribromide: A Task Specific Quinoline Based Ionic Liquid as a New Brominating Reagent. Indian J. Chem. 2006, 45B, 2542−2545.

[40] Li, Z.; Sun, X.; Wang, L.; Li, Y.; Ma, Y. Silica-Supported QuinoliniumTribromide: A Recoverable Solid Brominating Reagent for Regioselective Monobromination of Aromatic Amines. J. Braz. Chem. Soc. 2010, 21, 496−501

[41] Heravi, M. M.; Derikvand, F.; Ghassemzadeh, M. Tetrameric DABCO-Bromine: An Efficient and Versatile Reagent for Bromination of Various Organic Compounds. S. Afr. J. Chem. 2006, 59, 125−128.

[42] Attanasi, O. A.; Berretta, S.; Favi, G.; Filippone, P.; Mele, G.; Moscatelli, G.; Saladino, R. Tetrabromo Hydrogenated Cardanol: Efficient and Renewable Brominating Agent. Org. Lett. 2006, 8, 4291−4293.

[43] Le, Z.-G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. [bmim]Br3 as A New Reagent for Regioselective Mono-Bromination of Activated Aromatics under Solvent-Free Conditions. Chin. Chem. Lett. 2005, 16, 1007−1009.

29	BenzalkoniumTribromide (Benzal−Br3)[45]	bromination of phenols
30	1,2-Dipyridinium Ditribromide−Ethane[46]	*p*-brominating agent for acetanilides, phenols and anilines
31	1-Butyl-3-methylpyridinium Tribromide[47]	monobromination of anilines and phenols
32	(tert-Butylamino)triphenylphosphoniumTribromide[48]	bromination of various phenol derivatives
33	Ethylenebis(N-methylimidazolium) Ditribromide[49,50]	bromination of phenol and aniline and monobromination of 1,3- diketones and β-keto esters
34	4,4-Dibromo-3-methylpyrazol-5-	selective para-bromination of phenols and anilines

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[44] (a) Zhang, S. J.; Le, Z.-G. A Simple and Selective Procedure for α-Bromination of Alkanones with [bmim]Br3 as A Promoter Under Solvent-Free Conditions. Chin. Chem. Lett. 2005, 16, 1590−1592.
(b) Zhang, S.-J.; Le, Z.-G. Selective α-Monobromination of Ketones with [bmim]Br3. Chin. J. Org. Chem. 2006, 26, 236−238.

[45] Kavala, V.; Naik, S.; Patel, B. K. A New Recyclable Ditribromide Reagent for Efficient Bromination under Solvent Free Condition. J. Org. Chem. 2005, 70, 4267−4271.

[46] Kavala, V.; Naik, S.; Patel, B. K. A New Recyclable Ditribromide Reagent for Efficient Bromination under Solvent Free Condition. J. Org. Chem. 2005, 70, 4267−4271.

[47] Borikar, S. P.; Daniel, T.; Paul, V. An Efficient, Rapid, and Regioselective Bromination of Anilines and Phenols With 1-Butyl-3-MethylpyridiniumTribromide as a New Reagent/Solvent Under Mild Conditions. Tetrahedron Lett. 2009, 50, 1007−1009.

[48] Amer, A.; Mayer, A.; Conroy, G. M.; Zimmer, H. N-SubstitutedAminotriphenylphosphoniumTribromides as Novel Brominating Agents. Phosphorus, Sulfur Silicon Relat. Elem. 1996, 108, 245−248.

[49] Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Lasemi, Z. Efficient and Regioselective Bromination of Aromatic Compounds with Ethylenebis(N-Methylimidazolium) Ditribromide (EBMIDTB). Synth. Commun. 2010, 40, 868−876.

[50] Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Lasemi Z. Ethylenebis(N-Methylimidazolium) Ditribromide (EBMIDTB): An Efficient Reagent for the Monobromination of 1,3-Diketones and β- Ketoesters. Monatsh. Chem. 2009, 140, 57−60.

	one[51]	
35	CetylpyridiniumTribromide[52]	selective reagent for the bromination of phenols, anilines, anthracene, chalcone, etc.
36	N-Bromophthalimide[53]	selective para-bromination of substituted benzenes
37	PyridiniumBromochromate[54]	bromination of N-phenylbenzamides
38	QuinoliniumBromochromate[55]	bromination of anisole and acetanilide
39	PyridiniumDichlorobromate[56]	bromination of a variety of aromatic compounds
40	QuinoxaliniumBromochromate[57]	bromination aromatic compounds
41	HOBr[58]	bromination of benzoic acid
42	Phosphorus Oxybromide[59]	bromination of hydroxypyrimidines

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[51] Mashraqui, S. H.; Mudaliar, C. D.; Hariharasubrahmanian, H. 4,4-Dibromo-3-Methylpyrazol-5-One: New Applications for Selective Monobromination of Phenols and Oxidation of Sulfides to Sulfoxides. Tetrahedron Lett. 1997, 38, 4865−4868.

[52] Kumar, A.; Jamir, A.; Jamir, L.; Sinha, D.; Sinha, U. B. CetylpyridiniumTribromide, An Environmentally Benign Reagent for Organic Brominations and Acetylations. Org. Commun. 2011, 4, 1−8.

[53] Khazaei, A.; Manesh, A. A.; Safi, V. R. Regioselective Synthesis of para-Bromo Aromatic Compounds. J. Chin. Chem. Soc. 2005, 52, 559−562.

[54] Narayanan, N.; Balasubramanian, T. R. PyridiniumBromochromate - A New Reagent for Bromination and Oxidation. Indian J. Chem. 1986, 25B, 228−229.

[55] Özgün, B.; Degirmenbaşi, N. QuinoliniumBromochromate-A New Reagent for Bromination and Oxidation. Synth. Commun. 1996, 26, 3601−3606.

[56] Muathen, H. A. PyridiniumDichlorobromate: A New Stable Brominating Agent for Aromatic Compounds. Synthesis 2002, 169−171.

[57] Değirmenbaş, N.; Özgün, B. QuinoxaliniumBromochromate- A New and Efficient Reagent for Oxidation of Alcohols and Bromination of Aromatic Compounds. G. U. J. Sci. 2006, 19, 9−13.

[58] Derbyshire, D. H.; Waters, W. A. The Bromine Cation, Br+ and its Reactions. Nature 1949, 164, 446−447.

[59] Golding, D. R. V.; Senear, A. E. Phosphorus Oxybromide as a Brominating Agent. Bromopyrimidines. J. Org. Chem. 1947, 12, 293− 294.

43	Triphasic System of $Bu_4N^+HSO_4^-$, NaBr, and NaOCl[60]	bromination of cyclohexene
44	Ammonium Bromide[61]	monobromination of anilines and anisoles
45	Iodine Monobromide[62]	bromination of α-naphthol
46	Bromine Chloride[63]	bromination of various aromatic compounds
47	Bromine Fluoride[64]	bromination of m-dinitrobenzene
48	Bromine Triflouride[65]	bromination of deactivated aromatic compounds
49	PyridiniumHydrobromidePerbromide. (PyHBr3)[66]	selective bromination of double bonds
50	PyridiniumPerbromide[67]	bromination of cyclohexene, styrene, and vitamin C
51	Pyridine Sulfate Dibromide[68]	olefinic monomers bromination

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[60] Correia, J. A Triphasic Brominating/Oxidizing System. J. Org. Chem. 1992, 57, 4555−4557.

[61] Krishna Mohan, K. V. V; Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. Novel Bromination Method for Anilines and Anisoles using NH4Br/H2O2 in CH3COOH. Synth. Commun. 2004, 34, 2143−2152.

[62] Militzer, W. Brominations with Iodine Monobromide. J. Am. Chem. Soc. 1938, 60, 256−257.

[63] Schulek, E.; Burger, K. Substitutive Halogenation of Aromatic Compounds in Aqueous Solutions by Interhaloids-I: Halogenating Effect of Iodine Monochloride, Iodine Monobromide and Bromine Monochloride. Talanta 1958, 1, 147−152.

[64] Rozen, S.; Brand, M. Novel Aromatic Bromination using BrF Prepared Directly from the Corresponding Elements. J. Chem. Soc., Chem. Commun. 1987, 10, 752−753.

[65] Lerman, O.; Rozen, S. Bromine Trifluoride as a Bromination Agent for Deactivated Aromatic Compounds. J. Fluorine Chem. 1989, 45, 104.

[66] Starostenko, N. E.; Avdeeva, N. O.; Zeiberlikh, F. N.; Kurkovskaya, L. N.; Suvorov, N. N. Indole Derivatives. 129. Reaction of 5-Vinylindole with Brominating Agents. Chem. Heterocycl. Compd. 1987, 23, 271−274.

[67] Hoeurhold, H. H.; Drefahl, G.; Hindersin, P. Bromination of cis- and trans-3-Hexene with PyridiniumPerbromide as a Model for the Halogenation of Poly(cis-and trans-1,4-butadiene). Z. Chem. 1967, 7, 459−460.

52	Tetrabromo-o-benzoquinone [69]	bromination of chalcones
53	PyrrolidinoneHydrotribromide[70]	bromination of cyclohexene
54	Tetrabutylammoniumtribromide (TBATB)[71]	bromination of substituted alkenes
55	BenzyltrimethylammoniumTribromide[72]	brominating agent for the anti-stereospecific addition of alkenes
56	N-Bromoacetamide[73]	dibromination of numerous unsaturated compounds
57	3-(2,2,2-Trimethylhydrazinium)propionate Perbromide[74]	dibromination of methyl acrylate

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[68] Dey, N. C.; Borah, L.; Ghosh, A. C. Determination of the Purity of Monomers by a Catalytic Bromination Method. Analyst 1996, 121, 987−990.

[69] Latif, N.; ElBayouki, K. Tetrabromo-O-Benzoquinone. New Brominating Agent of Chalcones. Chem. Ind. 1975, 7, 316.

[70] Awang, D. V. C.; Wolfe, S. The Crystal Structure of Tetraphenylcyclobutadiene Molybdenum Dicarbonyl Bromide. Can. J. Chem. 1969, 47, 706−709.

[71] (a) Berthelot, J.; Fournier, M. A Simple, Safe, and Easy Bromination of Alkene using TBABr3: An Organic Laboratory Experiment. J. Chem. Educ. 1986, 63, 1011.

(b) Bellucci, G.; Chiappe, F.; Marioni, C. Evidence for a Reversible Electrophilic Step in Olefin Bromination. The Case of Stilbenes. J. Am. Chem. Soc. 1987, 109, 515−522.

[72] Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Fujisaki, S.; Tashiro, M. Bromination of Alkenes and Related Compounds by Use of BenzyltrimethylammoniumTribromide in Aprotic and Protic Solvents. Rep. Inst. Adv. Mater. Study 1988, 2, 87−94.

[73] (a) Wohl, A.; Jaschinowski, K. Further Experiments on the Bromination of Unsaturated Compounds with N-Bromoacetamide. Ber. Dtsch. Chem. Ges. B 1921, 54B, 476−484.

(b) Buckles, R. E. The Addition of Bromine to Olefinic Double Bonds. N-Bromoacetamide as a Source of Bromine. J. Am. Chem. Soc. 1949, 71, 1157−1159.

[74] Bremanis, G.; Kalvins, I.; Lukevics, E.; Liepins, E. Hydrazinecarboxylic Acid Derivatives. II. 3-(2,2,2-Trimethylhydrazinium) Propionic Acid, its Methyl Ester, and 3-(2,2,2-Trimethylhydrazinium)

58	Crown Ether Complexes of Molecular Bromine[75]	bromination of trans-β-methylstyrene
59	3-Bromo-3-(ethoxycarbonyl)-2,4-dioxo-1,2,3,4- tetrahydroquinones[76]	transbromination of cyclohexene
60	1,8-Diazabicyclo[5.4.0]undecene-7-bromotrichloromethane(DBU−$BrCCl_3$)[77,78]	bromination of active methylene compounds and bromination of active methylene compounds
61	Diethyl N,N Dibromophosphoroamidate[79]	bromination of alkenes and cycloalkenes
62	3-Bromo-5,5-dimethylhydantoin[80]	bromination of allylic and benzylic

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Propionate Perbromides as Novel Brominating Agents. Latv. PSR Zinat. Akad. Vestis, Kim. Ser. 1986, 5, 591−595.

[75] Pannell, K. H.; Mayr, A. Crown Ether Complexes of Molecular Bromine as Stereoselective Brominating Agents. J. Chem. Soc., Chem. Commun. 1979, 132−133.

[76] Ukrainets, I. V.; Sidorenko, L. V.; Golovchenko, O. S. 4- Hydroxy-2-Quinolones. Part 125. Ethyl 3-Bromo-2,4-Dioxo-1,2,3,4-Tetrahydroquinoline-3-Carboxylates as Potential Brominating Agents. Chem. Heterocycl. Compd. 2007, 43, 1008−1013.

[77] Hori, Y.; Nagano, Y.; Uchiyama, H.; Yamada, Y.; Taniguchi, H. Bromination of Active Hydrogen Compounds by Bromotrichloromethane and 1,8-Diazabicyclo[5.4.0]Undecene-7. A Convenient Synthesis for Bromides and Olefins. Chem. Lett. 1978, 73−76.

[78] Hori, Y.; Nagano, Y.; Uchiyama, H.; Yamada, Y.; Taniguchi, H. Bromination of Active Hydrogen Compounds by Bromotrichloromethane and 1,8-Diazabicyclo[5.4.0]Undecene-7. A Convenient Synthesis for Bromides and Olefins. Chem. Lett. 1978, 73−76.

[79] Osowska-Pacewocka, K.; Zwierzak, A. N,N-Dihalophosphoramides- XVI1: Ionic Addition of Diethyl N,N-Dibromophosphoroamidate (DBPA) to Alkenes and Cycloalkenes. Tetrahedron 1985, 41, 4717−4725.

[80] (a) Orazi, O. O.; Meseri, J. Halogenation with 3-Bromo-5,5- Dimethylhydantoin. An. Asoc. Quim. Argent. 1949, 37, 192−196.
(b) Domnin, N. A.; Larionova, M. A. Unsaturated Cyclic Hydrocarbons and their Derivatives. XIX. Synthesis of 1,2,3-Tribromocyclohexane and its Reaction with Quinoline. Russ. J. Gen. Chem. 1956, 26, 1398−1400.

63	2,2-Dibromo-2-cyano-N,N-dimethylacetamide[81]	α-monobromination of ketones
64	2-Bromo-2-cyano-N,N-dimethylacetamide[82]	bromination of α-carbon ketones
65	5,5-Dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane[83]	bromination of saturated and α,β-unsaturated carbonyl compounds
66	3-Bromo-4,4-dimethyl-2-oxazolidinone (NBDMO)[84]	allylic bromination
67	o-Polybromoquinone[85]	bromination of both aromatic[86] as well as selective α-bromination of α,β-unsaturated ketones
68	PhenyltrimethylammoniumTribromide[87]	bromination of carbonyl compounds

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[81] Vyas, S. G.; Kulkarni, A. B. 2,2-Dibromo-2-Cyano-N,NDimethylacetamide as a New Brominating Agent. Indian J. Chem. 1979, 17B, 305−306.

[82] Sekiya, M.; Ito, K.; Suzuki, K. 2-Bromo-2-Cyano-N,N-Dimethylacetamide as a New Brominating Agent. Tetrahedron 1975, 31, 231−233.

[83] Bloch, R. 5,5-Dibromo-2,2-Dimethyl-4,6-Dioxo-1,3-Dioxane; A New Brominating Agent for Saturated and α,β-Unsaturated Carbonyl Compounds. Synthesis 1978, 140−142.

[84] Gottardi, W. Dibromamin: Acylderivate. Monatsh. Chem. 1973, 104, 421−432.

[85] Calo', V.; Lopez, L.; Pesce, G.; Todesco, P. E. Contribution to the Bromination of Conjugate Unsaturated Ketones: Synthesis of α,β- Unsaturated Bromo Ketones. Tetrahedron 1973, 29, 1625−1628.

[86] (a) Calo, V.; Ciminale, F.; Lopez, L.; Todesco, P. E. A Selective Bromination of Aromatic Amines. J. Chem. Soc. C 1971, 3652−3653. (b) Fox, G. J.; Hepworth, J. D.; Hallas, G. Bromination of 3- Amino- And 3-Dimethylamino-Pyridine. J. Chem. Soc., Perkin Trans. 1 1973, 68−69.

[87] Sawa, M.; Mizuno, K.; Harada, H.; Tateishi, H.; Arai, Y.; Suzuki, S.; Oue, M.; Tsujiuchi, H.; Furutani, Y.; Kato, S. Tryptamine-Based Human β3-Adrenergic Receptor Agonists. Part 3: Improved Oral Bioavailability via Modification of the Sulfonamide Moiety. Bioorg. Med. Chem. Lett. 2005, 15, 1061−1064.

69	N-Bromo-tert-butylamine[88]	bromination of allylic position of cyclohexene
70	4-(Dimethylamino)pyridinium Bromide Perbromide[89]	bromination of acetophenones
71	Tribromoacetic Acid[90]	α-mono or α-dibromination of ketones
72	2,4-Diamino-1,3-thiazole Hydrotribromide[91]	bromination of aryl and styryl methylene ketones
73	1,2-Dibromoethane[92]	bromination of tertiary carbon
74	N,N-Dibromobenzenesulfonamide (Dibromoamine- B)[93]	bromination of β-diketones and β-keto esters
75	N,N′-Dibromo-N,N′-1,2-ethanediylbis[{(2,5-dimethylphenyl) sulfonyl}amine][94]	bromination of allylic positions
76	N-Methylpyrrolidin-2-one Hydrotribromide (MPHT)[95]	α,α-dibromination of tetralones

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[88] Boozer, C. E.; Moncrief, J. W. Allylic Bromination by NBromo- T-Butylamine. J. Org. Chem. 1962, 27, 623−624.

[89] Arrieta, A.; Ganboa, I.; Palomo, C. Reagents and Synthetic Methods. 38. 4-(Dimethylamino)Pyridinium Bromide Perbromide as A New Brominating Agent for Organic Compounds. Synth. Commun. 1984, 14, 939−945

[90] Stanovnik, B.; Tišler, M.; Jurgec, M.; Ručman, R. Bromination of α-Ergocryptine and Other Ergot Alkaloids with 3-Bromo-6-chloro- 2-methylimidazo[1,2-b]pyrimidazine-Bromine Complex as a New Brominating Agent. Heterocycles 1981, 16, 741−745.

[91] Forlani, L. 2,4-Diamino- 1,3-thiazole Hydrotribromide; A New Brominating Agent. Synthesis 1980, 6, 487−489.

[92] Ibarzo, J.; Ortuno, R. M. 1,2-Dibromoethane in the Synthesis of 2-Bromoesters: Bromination vs Alkylation. Tetrahedron 1994, 50, 9825−9830.

[93] Tajbakhsh, M.; Khazaei, A.; Mahalli, M. S.; Vaghi, R. G. N,NDibromobenzenesulfonamide: A Useful Regenrable Reagent for Bromination of Various Carbanionic Substrates. Phosphorus, Sulfur Silicon Relat. Elem. 2004, 179, 1159−1163.

[94] Khazaei, A.; Vaghei, R. G.; Karkhanei, E. Bromination of Organic Allylic Compounds by Using N,N′-Dibromo-N,N′-1,2-Ethane DiylBis(2,5-Dimethyl Benzene Sulphonyl)Amine. Synth. Commun. 2002, 32, 2107−2113.

77	N,N,N′,N′-Tetrabromobenzene-1,3-disulfonamide[96]	monobromination of benzylic positions
78	BenzimidazoliumBromochromate[97]	bromination of fluorene
79	Boron Tribromide[98]	selective benzylic bromination
80	Thionyl Bromide[99]	bromination of active methylenes
81	Bromoiodinanes[100]	bromination of toluene or cyclohexene

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[95] Bekaert, A.; Provot, O.; Rasolojaona, O.; Alami, M.; Brion, J.-D. N-Methylpyrrolidin-2-One Hydrotribromide (MPHT) A Mild Reagent For Selective Bromination of Carbonyl Compounds: Synthesis of Substituted 2-Bromo-1-Naphtols. Tetrahedron Lett. 2005, 46, 4187−4191.

[96] Ghorbani-Vaghei, R.; Chegini, M.; Veisi, H.; Karimi-Tabar, M. Poly(N,N′-Dibromo-N-Ethyl-Benzene-1,3-Disulfonamide), N,N,N′,N′-Tetrabromobenzene-1,3-Disulfonamide and Novel Poly(N,N-Dibromo-N-Phenylbenzene-1,3-Disulfonamide) as Powerful Reagents for Benzylic Bromination. Tetrahedron Lett. 2009, 50, 1861−1865.

[97] Özgün, B.; Degirmenbaşi, N. BenzimidazoliumBromochromate- A New Reagent for Bromination and Oxidation. Synth. Commun. 1999, 29, 763−766.

[98] Chen, H.; Shen, L.; Lin, Y. Benzylic Bromination of Toluene Derivatives with Boron Tribromide. Synth. Commun. 2010, 40, 998−1003.

[99] Al-Mousawi, S. M.; Bhatti, I.; Saraf, S. D. Reaction of Thionyl Bromide with Ketones. Org. Prep. Proced. Int. 1992, 24, 60−63.

[100] Amey, R. L.; Martin, J. C. Synthesis and Reaction of Substituted Arylalkoxyiodinanes: Formation of Stable Bromoarylalkoxy and Aryldialkoxy Heterocyclic Derivatives of TricoordinateOrganoiodine(III). J. Org. Chem. 1979, 44, 1779−1784.

1.3 Miscellaneous brominating reagents

1	Cyanogen Bromide[101]	bromination of amino enones
2	Dibromoisocyanuric Acid (DBI)[102]	bromination of melamine
3	Imidazo[1,2-b]pyridazine−Bromine[103]	bromination of alkenes, ketones, N-heterocyclic compounds, etc.
4	Trimethylsilyl Bromide (TMSBr)[104]	bromination of anomeric esters
5	Bromodimethylsulfonium bromide[105]	bromination of epoxides
6	Hexabromoacetone[106]	bromination of carboxylic acids
7	Ethyl Tribromoacetate[107]	bromination of carboxylic acids

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[101] Alberola, A.; Andres, C.; Ortega, A. G.; Pedrosa, R.; Vicente, M. Cyanogen Bromide as a Useful Brominating Agent, Synthesis of α- Bromo-β-Aminoenones. Synth. Commun. 1986, 16, 1161−1165.

[102] Gottardi, W. Hexabrommelamin. Monatsh. Chem. 1972, 103, 878−882.

[103] Stanovnik, B.; Tišler, M.; Drnovšek, I. 3-Bromoimidazo[1,2-b]pyridazine-Bromine and 3-Bromo-6-chloroimidazo [1,2-b]pyridazine- Bromine Complexes; New Brominating Agents for Organic Compounds. Synthesis 1981, 12, 987−989.

[104] Gillard, J. W.; Israel, M. Trimethylsilyl Bromide as A Mild, Stereoselective Anomeric Brominating Agent. Tetrahedron Lett. 1981, 22, 513−516.

[105] Olah, G. A.; Vankar, Y. D.; Arvanaghi, M. A New Synthesis of Cyclobutanones using Methyl Methylthiomethyl Sulfoxide. Tetrahedron Lett. 1979, 20, 3653−3656.

[106] Chavasiri, W.; Tongkate, P. Hexabromoacetone: A New and Efficient Brominating Agent for Synthesis of Alkyl and Acyl Bromides. Abstracts of Papers, 238th ACS National Meeting, Washington, DC, Aug 16−20, 2009; American Chemical Society: Washington, DC, 2009; ORGN-463.

[107] Kang, D. H.; Joo, T. Y.; Lee, E. H.; Chaysripongkul, S.; Chavasiri, W.; Jang, D. O. A Mild and Efficient Reaction for Conversion of Carboxylic Acids into Acid Bromides with Ethyl Tribromoacetate/Triphenylphosphine under Acid-Free Conditions. Tetrahedron Lett. 2006, 47, 5693−5696.

8	PentylpyridiniumTribromide[108]	bromination of a range of ketones, aromatics, alkenes and alkynes
9	HBr[109]	bromination of a range of alkenes, alkynes and aromatic compounds

1.4 Description of eco-friendly brominating reagent

Although, various brominating agents have been explored for the brominations, the production of bromo-intermediates themselves still holds importance. Further, while a lot of efforts have been made in both the academic and industrial fields to adopt the greenness process, the use of various hazardous reagents remains and generates large amounts of waste. Hence, it is necessary to develop sustainable reagents, particularly for bromination reactions. Recently, an eco-friendly brominating reagent was developed from an intermediate of the bromine manufacturing process that contains a 5:1 molar ratio of NaBr–$NaBrO_3$ (designated as BR-A). Upon acidification, BR-A releases bromine (Br_2) *in-situ* and is accountable for the addition across the variety of unsaturated substrates such as alkenes and alkynes to produce corresponding dibromo-derivatives with high atom efficiency and functional group tolerance (CO_2Et, OAc, OMe, carbonyl, methylenedioxy, Cl and NO_2).[110] Further, BR-A, when treated with NaOCl, affords another composition comprising of a 2:1 mole ratio of NaBr–$NaBrO_3$, which upon acidification generates BrOH, which is responsible for the bromination of a wide range of organic

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[108] Salazar, J.; Dorta, R. PentylpyridiniumTribromide: A Vapor Pressure-Free Room Temperature Ionic Liquid Analogue of Bromine. Synlett 2004, 1318−1320.

[109] (a) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. Simple and Practical Halogenation of Arenes, Alkenes and Alkynes with Hydrohalic Acid/H_2O_2 (or TBHP). Tetrahedron 1999, 55, 11127−11142. (b) Espenson, J. H.; Zhu, Z.; Zauche, T. H. Bromide Ions and Methyltrioxorhenium as Cocatalysts for Hydrogen Peroxide Oxidations and Brominations. J. Org. Chem. 1999, 64, 1191−1196.

[110] Adimurthy, S.; Ramachandraiah, G.; Bedekar, A.V.; Ghosh, S.; Ranu, B.C.; Ghosh, P.K. Eco-friendly and versatile brominating reagent prepared from liquid bromine precursor. Green Chem. 2006, 8, 916–922.

substrates, including aromatic substitutions and active methylene compounds such as benzylic and α-ketone brominations.[111] The details will be discussed in the proceeding chapters on eco-friendly brominating reagents and their applications.

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[111] Adimurthy, S.; Ghosh, S.; Patoliya, P.U.; Ramachandraiah, G.; Manoj Agrawal, M.R.; Gandhi, S.; Upadhyay, C.; Ghosh P.K.; Ranu, B.C. An Alternative Method for the Regio- and Stereoselective Bromination of Alkenes, Alkynes, Toluene Derivatives and Ketones Using a Bromide/Bromate Couple. Green Chem. 2008, 10, 232-237.

CHAPTER 2

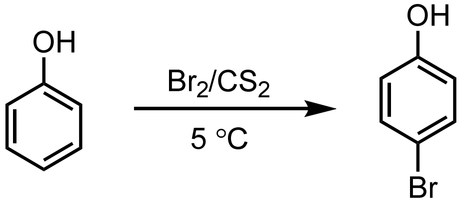
AROMATIC BROMINATIONS THROUGH SUBSTITUTION REACTIONS

C. RAVI, R.D. PATIL, S. ADIMURTHY

2.1 Bromination of phenols and napththols

2.1.1 Bromination of phenols using the Br_2/CS_2 system

In 1921, Adams and Marvel studied the bromination of phenol using elemental bromine for the preparation of *p*-bromophenol. They found that through the portionwise addition of bromine at a low temperature (5 °C) to the solution of phenol in carbon disulfide, *p*-bromophenol was obtained selectively with an excellent yield (**Scheme 1**).[1]



Scheme 1. Bromination of phenols using the Br_2/CS_2 system

Nishigaki *et al*. explored the same *p*-bromophenol preparation regioselectively through the bromination of phenols in a mixture of acetic acid and water in the presence of tetramethylammonium bromide at 25 °C for 2 h.[2] Heller *et al*. investigated the action of bromine on acetamidohydroxybenzoic acids

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[1] Adams, R.; Marvel, C. S. p-Bromophenol. Org. Synth. 1921, 1, 39.

[2] Nishigaki, J. Preparation of 4-Bromophenols by Regioselective Bromination of Phenols. Jpn. Kokai Tokkyo Koho JP 08127543 A 19960521, 1996.

and acetamidophenols. In particular, acetamido-2-hydroxybenzoic acid produced selectively the monobrominated product with molecular bromine with or without heating on a water bath.[3] Further, Takechi and Fukai regioselectively prepared *p*-bromophenols in 1,2-dimethoxyethane through the bromination of phenols at room temperature for 5 h in excellent yields.[4] Becker *et al.* developed a high positional synthesis of *p*-bromophenol through the bromination of phenols at −20 to +50 °C. The solvent selection plays a vital role in the selectivity.[5] Tishchenko *et al.* developed a simple procedure for the preparation of *p*-bromophenol from phenol using elemental bromine in an aqueous solution.[6]

Rajaram *et al.* used iodine and anhydrous aluminum chloride as catalysts for the preparation of *p*-bromophenol.[7] Chalabiev *et al.* reported dibromophenol synthesis via the bromination of phenol using bromine, with 16−25% aqueous sodium hypochlorite or 25−30% aqueous hydrogen peroxide as the oxidizing agents.[8] Becker *et al.* have developed a selective synthesis of *p*-bromophenol from phenol in different esters as solvents with bromine at −20 to +50 °C; they observed the crucial role of the solvent in the reaction system.[9] Avdeenko *et al.* reported the synthesis of *N*-acyl-2-bromo-4-aminophenols, *N*-acyl-2,6-dibromo-4-aminophenols, *N*-acyl-2,3,6-tribromo-4-aminophenols, and *N*-acyl-2,3,5,6-tetrabromo-1,4-benzoquinone benzoquinone imines from *N*-acyl derivatives of *p*-

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[3] Heller, G. Action of Bromine on Acetamidohydroxybenzoic Acids and Acetamidophenols. J. Prakt. Chem. (Leipzig) 1931, 129, 257−267.

[4] Takechi, N.; Fukai, Y. Preparation of p-Bromophenols by Regioselective Bromination of Phenols. Jpn. Kokai Tokkyo Koho JP 2000309555 A 20001107, 2000.

[5] Becker, A.; Kornberg, N.; Croitoru, B. Process for Preparing p-Bromophenol and Related Compounds. Ger. Offen. Patent Appl. DE 3742515 A1 19880714, 1988.

[6] Tishchenko, D. V. The Halogenation of Aromatics in Aqueous Solutions. J. Russ. Phys.-Chem. Soc. 1928, 60, 153−162.

[7] Rajaram, J.; Kuriacose, J. C. Bromination of p-bromophenol. II. Catalysis by Iodine and anhydrous Aluminium Chloride. Aust. J. Chem. 1969, 22, 1193−1198.

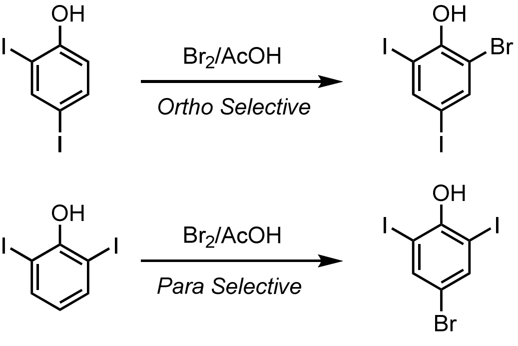
[8] Becker, A.; Kornberg, N.; Croitoru, B. Process for Preparing p- Bromophenol and Related Compounds. Ger. Offen. Patent Appl. DE 3742515 A1 19880714, 1988.

[9] Chalabiev, C. A.; Sadygov, O. A.; Gurbanov, M. S.; Shtejnberg, B. Y. Method of Dibromophenol Synthesis. U.S.S.R. Patent Appl. SU 1768574 A1 19921015, 1992.

aminophenols, 4-amino-1-naphthols, and *p*-phenylenediamines based on the solvent, temperature, and molar ratio of the starting material to the molecular bromine.[10]

2.1.2 Bromination of phenols using Br_2/acid system

Bromination of organic compounds is generally achieved with the equimolar addition of bromine with the substrates. The produced HBr is used in the preparation of value added brominated products either by the addition of oxidants and reagents or is disposed of as waste, causing serious environmental problems. Oxidizing reagents have been used to recycle HBr through the oxidation and subsequent bromination of the organic compounds. The Br_2/AcOH system is a good source for the bromination of aromatic and hetero aromatic compounds. The bromination of 1,4- and 2,6-diiodophenol was reported by Brenans *et al.* with bromine in acetic acid (Br_2/AcOH) to get 6-bromo-2,4-diiodophenol and 4-bromo-2,6-diiodophenol, respectively (**Scheme 2**).[11]



Scheme 2. Bromination using the Br_2/Acid system

Chumachenko *et al.* developed a procedure for the preparation of 3,5-dibromo-4- hydroxybenzoic acid from *p*-hydroxybenzoic acid using 2.5

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[10] Avdeenko, A. P.; Marchenko, I. L.; Kostygova, N. V. Bromination of N-acyl Derivatives of p-Aminophenols, 4-Amino-1- naphthols, and p-Phenylenediamines. Ukr. Khim. Zh. 2001, 67, 43−49.

[11] Brenans, P.; Yeu, K. Bromodiiodophenols, Symmetrical Trihalogeno Compounds. Compt. Rend. 1930, 190, 1560−1561.