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Regioselective Photochemical and Microwave Mediated Monobromination of Aromatic Compounds using 2,4,4,6-Tetrabromo-2,5-cyclohexadienone

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Abstract: Bromination of different aromatic substrates have been described using 2,4,4,6-tetrabromo-2,5-cyclohexadienone in conjunction with microwave and ultraviolet radiations. Important features of the work include high regioselectivity obtained in very short to moderate reaction time, atom economy, and recyclability of the reagent.

Keywords: bromination, microwave irradiation (MWI), regioselectivity, solvent free, 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD), ultraviolet radiation

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Brominated aromatic precursors are of paramount importance for the synthesis^[1] of various natural products, pharmaceuticals, and agrochemicals. Numerous industrially valuable products such as fire retardants, insecticides, herbicides, and pesticides are synthesized using different bromofunctionalities. Development of modern coupling reactions,^[2] such as the Stille–Suzuki, Tamao–Kumada, Heck, and Sonogashira reactions, has greatly increased the demand for brominated aromatic compounds.

The traditional bromination reaction involves the direct use of elemental bromine,^[3] which generates corroding hydrogen bromide as a side product, a substance that must be neutralized before it is discarded. Literature reports various reagents for monobromination of aromatic compounds, which does not make use of elemental bromine. N-bromosuccinamide (NBS),^[4] under different reaction conditions, has more often been used for allylic, benzylic, photochemical, and aromatic bromination reactions.1-Butyl-3-methylimida-zolium tribromide^[5] ([bmim]Br₃) has been used for the bromination of phenols. Alkali metal bromides have been oxidized by various oxidizing agents such as concentrated H₂SO₄^[6] and NaClO₂,^[7] along with different catalysts to get the monobrominated product of activated aromatic compounds. Benzenehexabromide^[8] and bromotrichloromethane^[9] have been used for the photochemical side-chain bromination of different alkylated aromatic substrates.

Most of the methods require hazardous conditions, prolonged reaction time, tedious workup, and expensive reagents. Thus, a milder, selective, inexpensive, and nonhazardous reagent that does not employ use of elemental bromine is still in demand, and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) provides a key to this. We sought to extend the TBCHD chemistry by a mild, selective, and straightforward reaction under solventfree conditions for different aromatic substrates. 2,4,4,6-Tetrabromo-2,5cyclohexadienone has earlier been used for the bromination of the aromatic ring for aniline^[10] and phenol^[11] derivatives. Moreover, it is also known for bromination of conjugated unsaturated ketones^[12] along with its use in other organic transformations such as preparation of azides^[13] and halides^[14] and deprotection of acetals and ketals.^[15] However, its use in photochemical reactions^[16] is very limited so far. Herein we report sidechain and nuclear bromination of various activated arenes by the use of TBCHD on solid support using photochemical and microwave energy for the first time.

Bromination of arenes and heteroarenes is often an unselective reaction resulting in a mixture of mono- and polybrominated derivatives with consequent tedious separation and poor atom economy. Therefore, selectivity and atom economy are the essential aspects in different synthetic endeavors, and use of TBCHD provides a key to control the aforementioned aspects. TBCHD was earlier prepared by the reaction of 2,4,6-tribromophenol^[11] with molecular bromine, which generates the corrosive hydrogen bromide, but now a new methodology has been devised for its preparation from

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phenol^[17] without using elemental bromine. Various advantages of the reagent are its easy recyclability, atom economy, selectivity, moderate to very short reaction time, and simple reaction setup.

Use of TBCHD in a photochemical reaction gives the monobrominated product, uncontaminated with poly bromo or ring-substituted derivatives, along with 2,4,6-tribromophenol as a side product, which can be recycled easily to regenerate the reagent. Side-chain bromination was carried out by adsorbing the reactants on silica and exposing them to ultraviolet light for 4 to 5 h (Scheme 1).

The reaction gives only the side-chain-substituted products, without the formation of any ring-substituted product, in excellent yields with simple workup. In the case of aromatic compounds containing both the alkyl group and activating group, such as the hydroxyl group, only ring-substituted products are formed. In the case of compounds with deactivating groups, such as the nitro group, no nuclear or side-chain substitution is observed. All the results have been tabulated (Table 1).

For the nuclear bromination of different aromatic compounds, reactants are adsorbed on solid support and exposed to microwave radiations for a few seconds (Scheme 2). Excellent yields are obtained for a range of activated aromatic and heteroaromatic compounds, in very short reaction time (Table 2). Results obtained are also compared with those of the conventional method. The introduction of the electron-withdrawing group, as well as moderate activating group, results in failure of the reaction.

The effect of a solid support during the nuclear bromination reaction was also investigated, and the best results are obtained by the use of silica and neutral alumina (Table 3). 2,4,6-Tribromophenol, the side product formed at the end of the reaction, was used for the regeneration of TBCHD after extracting it from the aqueous layer. Regenerated reagent was used three times with good yields for the bromination of toluene and anisole (side-chain and nuclear substitution, respectively). We also found that it has a long shelf life and works well even after 6 months if stored in a cool and dark place.

In conclusion, a new method for side-chain and nuclear bromination of activated aromatic compounds has been developed using TBCHD under simple reaction conditions. The methodology provides a key to control the selectivity by the use of microwave and ultraviolet energy, giving quantitative yields, very fast to moderate reaction rates, and atom economy.



Scheme 1.

S. No	Substrate	Product	Irradiation time (h)	Yield (%)
1	CH3	CH ₂ Br	4	95
2	CH3 CH3	CH ₂ Br	4.5	82
3	H ₃ C	H ₃ C	4.5	84
4	CH ₂ CH ₃	CHBrCH ₃	4	94
5		Br	4	92
6	CH ₃ NO ₂	_	14	—
7	НаС	H ₃ C OH Br	3	35

Table 1. Photochemical side-chain bromination of different alkylated arenes using 2,4,4,6-tetrabromo-2,5-cyclohexadienone

Note. All the compounds were characterized on the basis of ¹H NMR and IR spectral data, which were consistent with those reported in the literature.

EXPERIMENTAL

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General Procedure for Side-Chain Bromination

TBCHD (2 mmol) was ground with silica (2.5 g) followed by dropwise addition of substrate (2 mmol). It was ground well to be adsorbed uniformly on the silica. Reaction mixture was transferred to a conical (250-mL) container covered with a watch glass and exposed to ultraviolet radiation



Scheme 2.

Table 2. Nuclear bromination of different aromatic and heteroaromatic compounds using 2,4,4,6-tetrabromo-2,5-cyclohexadienone

			Stirring at rt		MWI (160 W)	
S. No	Substrate	Product	Time (h)	Yield (%)	Time (s)	Yield (%)
1	OCH3	OCH ₃	3	94	50	95
2	но	Br O O	2	68	120	74
3	NH ₂	NH ₂	3	92	50	95
4		Polymerises	2		40	
5	$\langle \rangle$		3	62	80	78
6		∠_s →_Br	3	75	80	85
7	NH2	OCH3 Hr NH2	3	52	50	56
8	$\bigcirc \bigcirc \bigcirc$	Br	4	42	150	72
9	CH3		12	_	240	_
10	NO ₂	—	12		300	_
11	\bigcirc	_	12	—	300	—

Notes. All the compounds were characterized on the basis of ¹H NMR and IR spectral data, which were consistent with those reported in the literature. Products 2 and 7 were identified on the basis of ¹³C NMR.

S. No	Solid support	Yield (%)
1	Acidic alumina	92
2	Basic alumina	94
3	Neutral alumina	96
4	K-10 clay	82
5	KSF clay	88
6	Silica	96

Table 3. Yields of 4-bromoanisol on different solid supports

for the time specified in Table 1. The resulting mixture was then shifted to a short column and eluted with dichloromethane $(3 \times 10 \text{ mL})$. The DCM layer was washed with 5M NaOH solution $(3 \times 15 \text{ mL})$, followed by water, and dried. Evaporation of the solvent under reduced pressure yielded the product in excellent yield. In the case of cresol, after irradiation, the resultant mixture was directly separated via column chromatography using hexane and ethyl acetate (9:1) as eluent.

General Procedure for Nuclear Bromination

TBCHD (2 mmol) was ground with silica (2.5 g) or neutral alumina (2.5 g) until a light yellow powder was formed, followed by dropwise addition of substrate (2 mmol). It was ground well and transferred to a conical (50-mL) container covered with a watch glass. The resulting mixture was irradiated with microwaves at 160 W for the time specified in Table 2 and worked up as previously except for 6-hydroxy-4-methyl-2*H*-chromen-2-one[substrate 2 (Table 2)]. To obtain the monobromo derivative of substrate 2, the resulting mixture was first eluted with DCM (3×10 mL) followed by ethanol (10 mL). The ethanol fraction was concentrated and left overnight to get needle-shaped crystals of 7-bromo-6-hydroxy-4-methyl-2*H*-chromen-2-one.

Recycling of the Reagent

The aqueous layer was neutralized by dil. hydrochloric acid. When the solution became slightly acidic, as indicated by pH paper, it was extracted with DCM. The organic layer was dried and evaporated to yield 2,4,6-tribro-mophenol (72%), which was used as such for preparing the reagent by the reported method.

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REFERENCES

- (a) Yue, E. W.; Gerdes, J. M.; Mathis, C. A. Synthesis of 2,3,-dimethoxy-5-iodobenzoic acid. J. Org. Chem. 1991, 56 (18), 5451; (b) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. Asymmetric synthesis of (-)-steganone. Further application of chiral biaryl syntheses. J. Amer. Chem. Soc. 1987, 109 (18), 5446; (c) Merour, J. Y.; Coadou, J. Y.; Tatibouet, F. Syntheses of 2(5)-substituted 1-acetyl-3-oxo-2,3-dihydroindoles, 3-acetoxy-1-acetylindoles, and of 2-methyl-5-methoxyindole-3-acetic acid. Synthesis 1982, 12, 1053; (d) Florvall, L.; Oegren, S. O. Potential neuroleptic agents. 2,6-Dialkoxybenzamide derivatives with potent dopamine receptor blocking activities. J. Med. Chem. 1982, 25 (11), 1280.
- (a) Diederich, F.; Stang, P. J. Metal Catalyzed Cross-Coupling Reactions; Wiley-VCH: Weinheim, Germany, 1998; (b) Li, J. J. Name Reactions: A Collection of Detailed Reaction Mechanisms, 2nd edn; Springer-Verlag: Berlin, 2003.
- 3. Taylor, R. Electrophilic Aromatic Substitution; Wiley: Chichester, UK, 1990.
- 4. (a) Lambert, F. L.; Ellis, W. D.; Parry, R. J. Halogenation of aromatic compounds by N-bromo- and N-chlorosuccinimide under ionic conditions. J. Org. Chem. 1965, 30 (1), 304; (b) Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. N-Bromosuccinimide-dibromodimethyllhydantoin aqueous base: a practical method for the bromination of activated benzoic acids. Tetrahedron. Lett. 1993, 34 (6), 931; (c) Rajagopal, R.; Jarikote, D. V.; Lahoti, R. J.; Daniel, T.; Srinivasan, K. V. Ionic liquid promoted regioselective monobromination of aromatic substrates with N-bromosuccinimide. Tetrahedron Lett. 2003, 44 (9), 1815; (d) Rajagopal, R.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Regioselective side-chain as well as nuclear monobromination of aromatic substrates with N-bromosuccinimide using phosphotungstic acid supported on zirconia as a heterogeneous catalyst. J. Mol. Catal. A: Chem. 2004, 210 (1-2), 165-169; (e) Mataka, S.; Kurisu, M.; Takahashi, K.; Tashiro, M. The bromination of methylarenes with NBS by irradiation using a tungsten lamp. Preparation of benzotribromides. Chem. Lett. 1984, 11, 1969.
- Le, Z.-G.; Chen, Z.-C.; Hu, Y. (bmim)Br₃ as a new reagent for regioselective monobromination of phenols and several activated aromatics under solvent-free conditions. *Chinese J. Chem.* **2005**, *23* (11), 1537.
- Myint, Y. Y.; Pasha, M. A. Oxidative monobromination of electron-rich arenes by concentrate H₂SO₄/alkali metal bromides. *J. Chem. Res.* 2004, *11*, 732.
- Masao, H.; Hiroyuki, M.; Shigetaka, Y.; Takashi, M. Halogenation of aromatic ethers with sodium chlorite, metal catalyst and kaolin. *Nippon Kagakkai Koen Yokoshu* 1999, 76 (2), 817.
- Aly, M. M.; Bolton, R.; Williams, G. H. Photochemical bromination by benzene hexabromide. J. Chem. Res., Synop. 1983, 1, 24.

- Baldwin, S. W.; O'Neil, T. H. Benzylic bromination with bromotrichloromethane. Synth. Commun. 1976, 6 (2), 109.
- 10. Calo, V.; Ciminale, F.; Lopez, L.; Todesco, P. E. A selective bromination of aromatic amines. J. Chem. Soc. (C) 1971, 3652.
- Toda, F.; Schmeyers, J. Selective solid state bromination of anilines and phenols. Green Chem. 2003, 5, 701.
- Calo, V.; Lopez, L.; Pesce, G.; Todesco, P. E. Bromination of conjugate unsaturated ketones. Synthesis of α,β-unsaturated bromo ketones. 1st. Chim. Org., Univ. Bari, Bari, Italy. *Tetrahedron* 1973, 29 (11), 1625–1628.
- Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. An efficient method for converting alcohols to azides with 2,4,4,6-tetrabromo-2,5-cyclohexadienone/PPh3/ Zn(N3)2.bul.2Py. *Tetrahedron Lett.* **1997**, *38* (22), 3955.
- (a) Tanaka, A.; Oritani, T. Direct transformation of sterically less hindered silyl ethers to the corresponding bromides with inversion of configuration. *Tetrahedron Lett.* 1997, 38 (41), 7223; (b) Tanaka, A.; Oritani, T. A mild and efficient method for converting alcohols and tetrahydropyranyl ethers to bromides with inversion of configuration. *Tetrahedron Lett.* 1997, 38 (11), 1955.
- Iranpoor, N.; Firouzabadi, H.; Shaterian, H. R. Catalytic and chemoselective deprotection of S,S- and S,O-acetals and ketals in the presence of their O,Oanalogs with electrophilic halogens under neutral conditions. *Tetrahedron Lett.* 2003, 44 (25), 4769.
- Lopez, L.; Calo, V. 2,4,4,6-Tetrabromocyclohexa-2,4-dienone: a new electron acceptor in the photosensitized oxidation of unsaturated substrates. J. Chem. Soc., Chem. Commun. 1984 (19), 1266.
- Bedekar, A. V.; Gadde, R.; Ghosh, P. K. Process for preparing 2,4,4,6-tetrabromo-2,5-cyclohexadienone. U.S. Patent Application 20040127750. Kind Code: Al, Serial No.: 335124. US Current Class: 568/362. US Class at Publication: 568/362.

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