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Regioselective Aromatic Electrophilic Bromination with Dioxane Dibromide Under Solvent-Free Conditions

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Abstract: Highly regioselective ring bromination of aromatic compounds has been accomplished with high yields and good purity using dioxane dibromide (DD) under solvent-free conditions. Notable features of this methodology include operational simplicity, rapid reactions, excellent control over the degree of bromination, and tolerance of various functional groups during the reaction.

Keywords: electrophilic aromatic substitution, regioselectivity, solid-phase synthesis

Ring bromination^[1] of aromatic compounds is an important reaction in organic synthesis. Numerous methods have been developed, which include the classical use of molecular bromine^[2,3] in various organic (mainly halogenated) solvents. To prevent loss due to high volatility, an excess amount of bromine is often used during the reaction to drive the reaction to completion. The products of the reactions are generally complicated and contaminated with by-products^[1-3] due to poor regioselectivity, overbromination, and oxidative and polymeric transformations of the sensitive substrates and products. Toxicity, corrosive, lachrymatory, and the fuming nature are the most serious disadvantages of the conventional bromination methods. There are some reports^[4] of alternative bromination procedures, but most of them

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involve drastic reaction conditions, costly reagents, and organic solvents as reaction media. We report herein a mild, solvent-free protocol using dioxane dibromide (DD) for highly regioselective aromatic electrophilic bromination (Scheme 1); the results are furnished in Table 1.

As is evident from Table 1, the compounds underwent clean and regioselective ring bromination with good yields and high purity within a reasonable period of time. A notable feature of the present methodology was excellent control over the degree of bromination (entries 2, 4-7 in Table 1) by using duly weighed, calculated amounts of DD. This was rarely observed in the most of the earlier reports. Phenol (entry 5) and anisole (entry 7) were not overbrominated beyond 2,4-dibromo- derivatives despite the use of an excess amount of DD. So, the present method can serve as an efficient and relatively green protocol for the single-step preparation of commercially important 2,4-dibromoaromatics from easily accessible precursors. Sensitive moieties, such as methoxycarbonyl (entries 8, 9) and formyl (entries 10, 11), were also tolerant of this method. 3-Hydroxybenzaldehyde has been reported^[3b] to yield regioisomeric monobrominated products in various proportions when molecular bromine in different organic solvents is used as the brominating agent, but in the present method, 6-bromo-3-hydroxybenzaldehyde was obtained almost exclusively in high yield (entry 11) with minimal formation of isomeric by-products (by 300-MHz⁻¹H NMR). The more electron-rich aromatic ring underwent preferential bromination in phenyl benzoate (entry 12), which on hydrolysis led to the exclusive formation of 4-bromophenol. Bromination of 2-aminobenzoic acid led to 2-amino-3,5dibromobenzoic acid and 2,4,6-tribromoaniline in a 45:55 ratio (determined by ¹H NMR). Treatment of 2-hydroxybenzoic acid with a large excess amount of DD (greater than 6 equiv) led to the formation of a ternary mixture of 5-bromo-2-hydroxybenzoic acid, 3,5-dibromo-2-hydroxybenzoic acid, and 2,4,6-tribromophenol in a 23:61:16 ratio (determined by ¹H NMR). Hydroquinone, which is highly susceptible to oxidative transformations, also underwent clean bromination with DD to yield highly substituted 2,3,5-tribromo-1,4-dihydroxybenzene (characterized by ¹H NMR and ¹³C NMR of the corresponding acetate) in good yield (73%).

In conclusion, a good preparative method has been developed for synthetically and commercially important functionalized bromoaromatics with good yield, high purity, and excellent selectivity through operationally simple and relatively green procedures. Notable advantages of the methodology



Scheme 1.

Table 1. Selective bromination of aromatic compounds with dioxane dibromide under solvent-free conditions

Entry	Substrate	Mol. eqv. of DD	Product	Time (min)	Yield ^a (%)
1	NHCOMe	1.5	Br-O-NHCOMe	30	84 ^[2,5]
2	— NH ₂	1.2		15	75 ^[2,5]
3	Br-O-NH2	2.5		30	87 ^[2,5]
4	Юнон	1.2	Br - OH	10	61 (70 ^b) ^[2]
5	Юн	>4.0	ВгОН Вг	20	80 ^[2,5]
6	OMe	1.5	Br - OMe	15	85 ^[2,5]
7	OMe OMe	>4.0	Br - OMe Br	45	86 ^[2]
8		1.5		30	74
9	Он СООМе	1.5	Br OH COOMe	30	85
10	О -он сно	1.0		30	82
11	ОН СНО	1.1	Вг — ОН СНО	30	80 ^[3b]
12		1.5		30	75 ^[2]

"Yield refers to that of isolated pure products, characterized chemically and spectroscopically. ^bBy ¹H NMR, remainder 2,4-dibromophenol.

include 1) excellent control over the degree of bromination, 2) high regioselectivity, 3) minimization of organic solvents as reaction medium by carrying out the reactions under solvent-free conditions, 4) tolerance of sensitive functional groups, and 5) general applicability, accommodating a variety of substitution patterns.

EXPERIMENTAL

General Procedure for Bromination Using DD

DD (as required by the stoichiometry as in Table 1) was added in portions to the neat substrate (5 mmol, cooled at $0-5^{\circ}$ C in ice water) and well mixed. The mixture was allowed to attain the ambient temperature and left for the stipulated time period (as mentioned in Table 1). Crushed ice was then added to the reaction mixture and filtered (if the product was solid) or extracted with ether (for a semisolid or liquid mass), and it was washed successively with saturated aqueous sodium bicarbonate solution and water and dried to get the product in almost pure form. The products were further purified by crystallization, shortpath distillation, or filtration chromatography on a short column of silica gel using 5% ethyl acetate-petroleum ether, if needed.

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REFERENCES

- Smith, K. Advances in the synthesis and applications of organobromine compounds. In *Advances in Organobromine Chemistry II*; Desmurs, J.-R.; Gerard, B.; Goldstein, M. J., Eds.; Elsevier: New York, 1995, pp. 49–64.
- 2. Vogel, A. I. A Text Book of Practical Organic Chemistry, 5th ed.; 1989.
- (a) Eguchi, H.; Tokumoto, K.; Nishida, A.; Fujisaki, S. Regioselective bromination of phenols. In *Advances in Organobromine Chemistry II*; Desmurs, J.-R.; Gerard, B.; Goldstein, M. J., Eds.; Elsevier: New York, 1995, pp. 4–16; (b) Van Otterlo, W. A. L.; Michael, J. P.; Fernandes, M. A.; de Koning, C. B. Unforeseen formation of 2-bromo-3-hydroxybenzaldehyde by bromination of 3-hydroxybenzaldehyde. *Tetrahedron Lett.* **2004**, *45*, 5091–5094, and references cited therein.

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- 4. (a) Kajigaeshi, S.; Kakinami, T. Bromination and oxidation with benzyltrimethyl ammonium bromide. In Advances in Organobromine Chemistry II; Desmurs, J-R.; Gerard, B.; Goldstein, M. J., Eds.; Elsevier: New York, 1995, 29-48; (b) Ganguly, N. C.; De, P.; Dutta, S. Mild regioselective monobromination of activated aromatics and heteroaromatics with N-bromosuccinimide in tetrabutylammonium bromide. Synthesis 2005, 1103-1108; (c) Heravi, N. M.; Abdolhosseini, N.; Oskooie, H. A. Regioselective and high yielding bromination of aromatic compounds using hexamethylenetetramine-bromine. Tetrahedron Lett. 2005, 46, 8959-8963; (d) Gnaim, J. M.; Sheldon, R. A. Regioselective bromination of aromatic compounds with Br₂/SO₂Cl₂ over microporous catalyst. Tetrahedron Lett. 2005, 46, 4465-4468; (e) Ghorbani-Vaghei, R.; Jalili, H. Mild and regioselective bromination of aromatic compounds with N,N,N',N'-tetrabromobenzene-1,3-disulfonylamide (TBBDA) and poly (N-bromobenzene-1,3-disulfonylamide (PBBS). Synthesis 2005, 1099-1102; (f) Kim, D.-K.; Chung, W.-J.; Lee, Y.-S. Simple bromination of activated arenes by IBX amide resin and tetraethylammonium bromide. Synlett 2005, 279-282; (g) Kavala, V.; Naik, S.; Patel, V. K. A new recyclable ditribromide reagent for efficient bromination under solvent-free condition. J. Org. Chem. 2005, 70, 4267-4271.
- Aldrich Handbook of Fine Chemicals Laboratory Equipment; Aldrich Chemical Company: Bangalore, India, 2004–2005.