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Site directed nuclear bromination of aromatic compounds by an electrochemical method

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Abstract—Direct bromination of a wide range of aromatic compounds possessing electron-donating groups, such as methoxy, hydroxy or amino groups, have been carried out by two-phase electrolysis. This electrochemical method results in high yields (70–98%) of monobromo compounds and usually with high regioselectivity (>95%) for the para position.

1. Introduction

Brominated aromatic compounds are valuable intermediates in organic synthesis and they have been used widely in industrially important products,[1] and biologically active substrates as antitumor, antifungal, antibacterial, antineoplastic and antiviral compounds.[2] The need for isomerically pure bromoaromatics has led to investigations into more selective brominating agents, and several methods have been reported in the literature. Reactions making use of organic ammonium tribromides (OATB) such as tetrabutylammonium tribromide (TBATB),[3,4] 1,8-diazabicyclo[5,4,0]-tetrabutylammonium tribromide[5] and pyridine hydrobromide perbromide,[6] together with methods employing anodic brominations in organic solvents[7] and bromine trifluoride[8] have been fully investigated. Various methods for oxidative nuclear bromination of aromatic molecules have been developed including KBr–H_2O_2 using metal-oxo catalysts,[9] KBr–$NaBO_3{\cdot}4H_2O$,[10] *t*-BuOBr–zeolite,[11] LiBr–$(NH_4)_2Ce(NO_3)_6$ and oxone–NaBr.[12] Firouzabadi and co-workers have reported heteropoly-acid cesium salt/cetyltrimethylammonium bromide as a catalytic heterogeneous system which allows highly regioselective bromination of aromatic compounds with bromine.[13] Quite recently, tetrabutylammonium peroxydisulfate,[14] *N*,*N*,N^1,N^1-tetrabromobenzene-1,3-disulfonylamide, poly(*N*-bromobenzene-1,3-disulfonylamide),[15] and *N*-bromosuccinimide, either alone[16] or with (i) ionic liquids[17] or (ii) tetrabutylammonium bromide,[18] have been used for the selective monobromination of aromatic compounds. Some of the reagents reported for bromination are often hazardous, very toxic, expensive, not readily available, need to be freshly prepared, require drastic conditions or prolonged reaction times and involve tedious work-ups. Thus a milder, selective, non-hazardous and inexpensive reagent is still in demand.

Recently, we reported the regioselective α-bromination of alkyl aromatic compounds by two-phase electrolysis.[19] In this work, it was observed that while most of the alkyl aromatic compounds studied underwent selective side-chain bromination, some were brominated solely on the aromatic ring. This prompted us to investigate the bromination potential of a two-phase electrolytic system for nuclear bromination of aromatic compounds. Herein, we report a mild and efficient method for the nuclear bromination of activated aromatic compounds by two-phase electrolysis using anodic oxidation of bromide ions as the bromine source (Scheme 1).[20] Thus, a series of aromatic compounds were subjected to nuclear bromination by two-phase electrolysis at 0 °C using a platinum sheet as electrodes to furnish the corresponding monobromo arenes, and the results are summarised in Table 1.

The two-phase electrochemical bromination reaction was conducted in an undivided cell. The electrolyte

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Keywords: Electrochemical bromination; Two-phase electrolysis; Site directed bromination; Regioselectivity.

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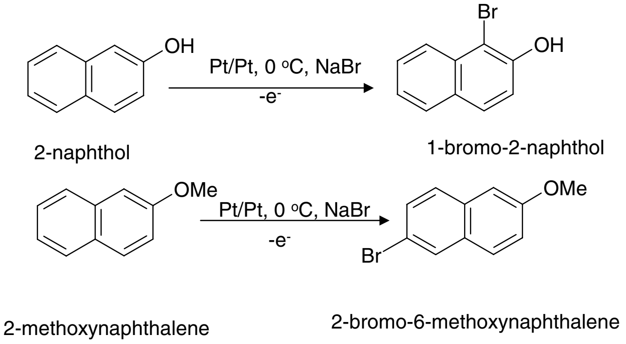
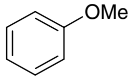
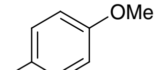
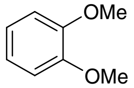
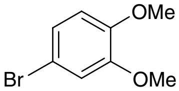
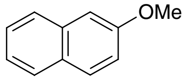
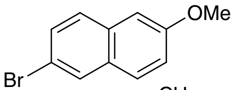
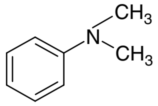
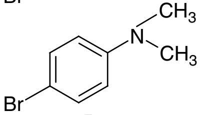
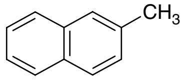
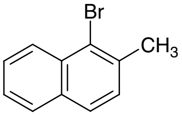
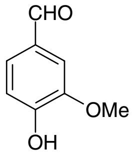
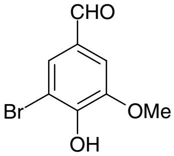
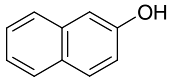
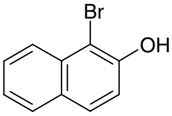
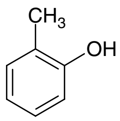
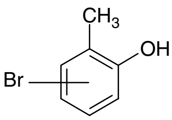
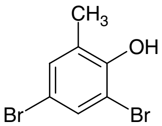
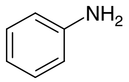
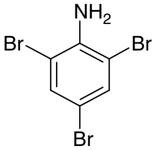


Scheme 1.

containing 50–60% aqueous NaBr with 5% HBr acting as the upper phase was used as the bromine source. The substrate, dissolved in chloroform, acted as the lower phase. The cell was composed of a jacketed glass cell provided with a coolant inlet and outlet facility. Deionised water was used for preparing sodium bromide solutions. A DC power source (Aplab) was used as the direct current source for constant current electrolysis. The cell used for the electrolysis was equipped with a magnetic stirrer, and two platinum sheets (10 cm^2) were used as the anode and the cathode, respectively. The reaction was conducted galvanostatically and was monitored by HPLC using a Shimpack ODS-18 column (125 mm × 4.5 mm) as the stationary phase. The eluent

Table 1. Electrochemical bromination of aromatic compounds by two-phase electrolysis

Entry	Substrate	Product[a]	Charge passed (F/mol)	Yield[b] (%)	Current efficiency (%)
1			2.3	92	87
2			2.1	95	95
3			4.0	98	50
4			1.9	86	85
5			4.0	80	50
6			2.2	95	90
7			2.0	94	94
8		 [3:3:3][c]	2.0	60	60
			4.0	92[d]	92
9			6.0	98	98

[a] Characterised by NMR spectroscopy.

[b] Isolated yield.

[c] Ratio of unconverted/*o*-/*p*-brominated products.

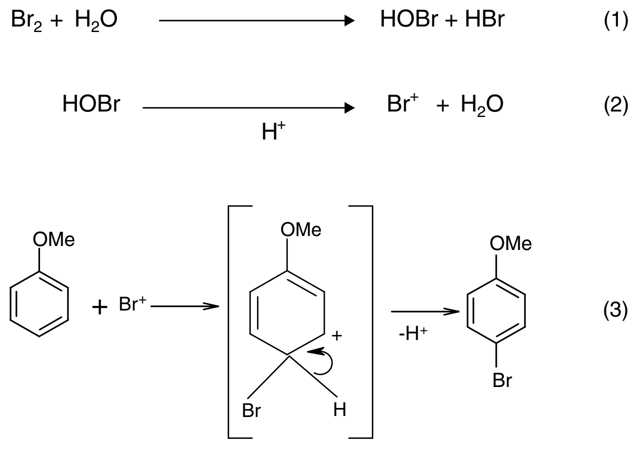
[d] 98% Conversion.

consisted of methanol: water (70:30) at a flow rate of 1 ml/min. Samples were analysed using a UV detector at a wavelength of 254 nm.

It is believed that electrochemically generated bromine combines with water, giving one molecule of hypobromous acid and one molecule of HBr. The hypobromous acid is unstable due to its pronounced ionic nature and thus in the presence of hydrobromic acid, one molecule of water is removed from hypobromous acid giving Br^+, which attacks the electron rich aromatic ring, and the product obtained under these conditions is exclusively the *p*-ring-brominated product and no trace of other regioisomers or dibromo products were detected (Scheme 2). When benzylic positions were present in the starting materials, no benzylic bromides were detected as products in the crude reaction mixture. Although the protected aromatic amine and phenol were *p*-brominated in excellent yields, aniline and phenol-like aromatic substrates furnished a mixture of *o*- and *p*-isomers (*o*-cresol gave 30% *o*- and 30% *p*-bromo isomers along with 40% of returned starting material) after passing the theoretical charge, while highly deactivated compounds, such as nitrobenzene and chlorobenzene, did not undergo bromination even on prolonged reaction. In the case of bromination of 2-naphthol, the *o*-brominated material was the sole product when the –OH group was unprotected. When protected with a methyl group, the *p*-brominated product was formed exclusively.

It is notable that following electrolysis, the brominated aromatic compound was easily isolated simply by separation of the organic layer with the remaining bromide salt available for further use in anodic bromination by adding calculated amount of HBr (based on the amount of current passed) to compensate the electrochemically depleted bromide and hydrogen ions. Thus a completely 'spent reagent'-free electroorganic synthesis can be demonstrated using two-phase electrolysis.

In conclusion, we have developed a new, mild and efficient method to brominate aromatic compounds selectively at the *p*-position by simple constant current two-phase electrolysis. The amount of bromine generated can be controlled precisely by simply switching off the electricity, thereby eliminating the problems of handling, transporting and storage of liquid bromine. The simple reaction set-up, cheap and environmentally friendly reagents, excellent yields of regioselective monobrominated products and simple work-up make this method valuable from a preparative point of view.



Scheme 2.

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20. Representative procedure for electrochemical bromination: A solution of 2-naphthol (10 mmol) in 25 ml of chloroform was taken in an undivided jacketed cell. To the above solution, a 50–60% aqueous sodium bromide solution (50 ml) containing 5 ml of HBr (46% solution,

30 mmol) was added. Two platinum electrodes (10 cm^2) were placed in the upper layer of the aqueous phase. The organic phase alone was stirred with a magnetic stirrer at a rate of 40 rpm in such a way that the organic layer does not touch the electrodes. The temperature of the electrochemical cell contents was maintained at 0 °C throughout the electrolysis. The electrolysis was conducted galvanostatically at a current density of 30 mA/cm^2 until the quantity of charge indicated in Table 1 was passed. During the electrolysis, the reaction was monitored by HPLC. After completion of electrolysis, the lower organic phase was separated, washed with water (2 × 25 ml), dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting mixture was analysed by HPLC, showing the presence of 94% of 1-bromo-2-naphthol along with 2% of the starting material and some minor impurities. The crude product was passed through a column of silica gel (60–120 mesh) and eluted with a mixture of ethyl acetate:*n*-hexane (1:9) to afford the pure brominated product (2.0 g; 94%). 1-Bromo-2-napthol, (entry 7) mp 78 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, 1H, $J = 8.1$ Hz), 7.72–7.74 (m, 2H), 7.56 (t, 1H, $J = 8.2$ Hz), 7.41 (t, 1H, $J = 8.2$ Hz), 7.28 (d, 1H, $J = 8.1$ Hz).