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A simple and regioselective α-bromination of alkyl aromatic compounds by two-phase electrolysis

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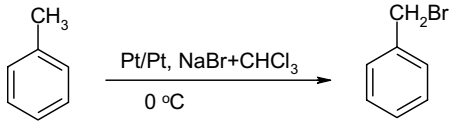
Abstract—Electrochemical bromination of toluene and substituted toluenes by two-phase electrolysis yields the corresponding α-brominated products. The reaction has been carried out in a single compartment cell with platinum electrodes at 0 °C in chloroform using an aqueous sodium bromide solution (60%) containing a catalytic amount of HBr. Two-phase electrolysis results in high yields (60–95%) of monobromo compounds with very high regioselectivity (>95%).

Substitution of C–H bonds in alkyl aromatic compounds by radical halogenation is one of the most important reactions for functionalisation of alkyl aromatics. Benzyl bromides and substituted benzyl bromides are primarily used as synthetic intermediates in the pharmaceutical and other fine chemical industries.

Radical bromination on benzylic positions has been achieved using bromine[1–3] and *N*-bromosuccinimide.[4,5] In addition, the bromine complex of the styrene vinylpyridine co-polymer[6] and bromotrichloroethane[7,8] and copper(II) bromide[9] have been reported to be effective for benzylic bromination. The majority of brominating agents require the presence of a peroxide or another radical initiator. Side-chain bromination using sodium bromate and bromotrimethylsilane has also been reported[10] but in only low yields. By using electrochemical technology, it is possible to carry out a desired reaction via a two-phase electrolytic reaction, resulting in high yields and selectivity.

Two-phase electrolysis has a distinct advantage over conventional homogeneous electrolysis in practical electro-organic synthesis.[11] In the homogeneous system, less selectivity is observed due to oxidation of the substrate on the surface of the electrode giving mixtures of nuclear (*ortho* and *para* isomers) and side-chain brominated products. In a two-phase electrolysis system, the reactive species formed by the electrolytic oxidation of a halide ion in the aqueous phase can be taken continuously into the organic layer and then reacted with the substrate to give the products regioselectively. After the completion of the electrolysis, separation and concentration of the organic layer affords the product.

Electrochemical bromination has been investigated in different solvents[12–19] and most of the work deals with ring brominated products. Side-chain bromination has not been much explored. In continuation of our earlier work on electrochemical halogenation of aromatic compounds, we present a simple and regioselective electrochemical method for the α-bromination of toluene and substituted toluenes to give the corresponding benzyl bromides in very good yields by two-phase electrolysis[20] at 0 °C in a single compartment cell as shown in Scheme 1. We observed smooth bromination at the α-position of the side-chain without the formation of any poly-brominated product. A number of alkyl aromatics and substituted alkyl aromatic compounds were subjected to side-chain bromination by two-phase electrolysis using an aqueous 60% NaBr solution as the supporting



Scheme 1. Electrochemical bromination of toluene by two-phase electrolysis.

Keywords: Electrochemical bromination; Two-phase electrolysis; α-Brominated products; Regioselectivity.
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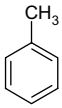
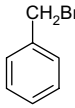
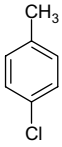
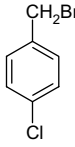
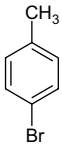
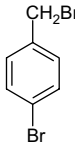
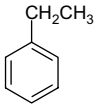
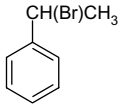
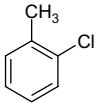
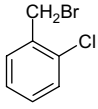
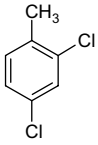
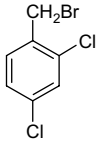
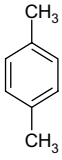
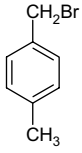
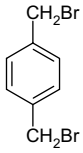
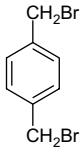
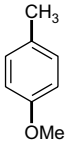
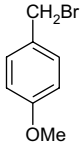
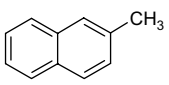
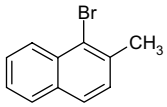
Table 1. The ratio of reactants and products of the electrochemical bromination of toluene, substituted toluenes and substituted naphthalenes via two-phase electrolysis

Entry	Reactant	Product	Charge passed (F/mol)	Yield (%)	Current efficiency (%)
1			4.5	91	44
2			5.0	90	40
3			3.0	89	44
4			4.5	85	37
5			3.0	62	25
6			4.0	57[a]	35
7			3.0	50	33
			6.0	48[b]	32
			9.0	90	41
8			6.0	12[c]	5
9			6.0	80	26

[a] Benzal bromide 22% formed along with 10% recovered starting material.
[b] 4-Methylbenzyl bromide 45% formed along with 2% recovered starting material.
[c] 3-Bromo-4-methoxytoluene 39% and 2-bromo-4-methoxytoluene 37% were formed together with 12% recovered starting material.

electrolyte containing a catalytic amount of HBr (5%). The product distributions from the reactions are listed in Table 1. The reaction proceeds under mild conditions and in an efficient way in the presence of a less hazardous brominating agent than Br_2, *N*-bromosuccinimide and pyridinium tribromide. In contrast to the exclusive benzylic bromination of alkyl benzenes, an alkyl naphthalene was brominated mainly on the ring. 2-Methylnaphthalene, for example, gave 1-bromo-2-methylnaphthalene as the only isolated brominated product.

Side-chain bromination of toluene follows a free radical mechanism and the brominating species is dibromine monoxide (Br_2O), which is formed as shown in Eqs. 1 and 2. In the first step, electrochemically generated bromine is combined with water giving hypobromous acid and hydrogen bromide. In presence of HBr, one molecule of water is removed from two molecules of hypobromous acid as a hydronium ion resulting in the formation of Br_2O as the brominating species, which is extracted by the organic phase, where the selective bromination occurs.

$$Br_2 + H_2O \rightarrow HOBr + HBr \quad (1)$$

$$2HOBr \rightarrow Br_2O + H_2O \quad (2)$$

As the reactive species Br_2O is unstable, it is cleaved homolytically into $Br^{\bullet}$ and $^{\bullet}OBr$. The more reactive $^{\bullet}OBr$, abstracts a benzylic hydrogen to form HOBr. Subsequently, the bromine radical attacks the benzyl radical and benzyl bromide is formed as the product. This explains the fact that the isolated product is only benzyl bromide. Although dibromine monoxide is exceptionally reactive in the bromination of non-activated and deactivated alkyl aromatic compounds, an activated compound like 4-methoxytoluene gives a higher percentage of nuclear brominated product rather than side-chain brominated products (entry 7 in Table 1). This is due to ring bromination of activated aromatics by the attack of Br^+, which is generated from HOBr as shown in Eq. 3.

$$HOBr + H^+ \rightarrow H_2O + Br^+ \quad (3)$$

If HOBr alone was present as the brominating agent in the absence of HBr, then the product obtained from toluene was a mixture of side-chain brominated (54%) and nuclear brominated (47%) products [a mixture of 22% *o*-bromotoluene and 25% *p*-bromotoluene]. The formation of these products was confirmed by chemically generating HOBr as in Eq. 4; the toluene being brominated by the usual method.

$$HgO + 2Br_2 + H_2O \rightarrow 2HOBr + HgBr_2 \quad (4)$$

Furthermore, dibromine monoxide was prepared chemically in CCl_4 as shown in Eq. 5 and toluene was brominated at 0 °C. The product obtained was benzyl bromide as the sole product.

$$HgO + 2Br_2 \rightarrow Br_2O + HgBr_2 \quad (5)$$

In conclusion, the electrochemical method for side-chain bromination of toluene to yield benzyl bromide by two-phase electrolysis constitutes a novel and an efficient alternative procedure. Studies were carried out on the electrochemical synthesis of benzyl bromide and substituted benzyl bromides [α-brominated products] from substituted toluenes in high yields. Reactions were carried out under mild conditions using very simple electrochemical apparatus. This method has several advantages such as the absence of secondary products, low cost, selective bromination, high rate of conversion and high yields.

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20. Representative electrochemical procedure: Deionised water was used for preparing sodium bromide solution. An Aplab power source was used as the direct current source for the electrolysis. A beaker type glass cell (120 ml capacity) equipped with a magnetic stirrer was used for the electrolysis and two platinum sheets of 10 cm^2 area were used as the anode and the cathode. Fifty milliliters of 60% sodium bromide solution containing a catalytic amount of hydrobromic acid (5%) was used as the electrolyte and the bromine source. The reaction was monitored by HPLC using a Shimpack ODS-18 column (125 mm × 4.5 mm) as the stationary phase. The eluent consisted of methanol/water (70:30) at a flow rate of 1 ml/min. Samples were analysed at a wavelength of 254 nm with a UV detector. Authentic samples of benzyl bromide and substituted benzyl bromides were used to calculate the peak areas of the corresponding experimental products for yield calculation.
    Toluene (610 mg, 6.6 mmol) was dissolved in chloroform (25 ml) and the solution was transferred to a single compartment electrolytic cell. A 60% solution of aqueous

NaBr (50 ml) containing 5% HBr was added. The aqueous upper phase acted as the supporting electrolyte and also as the bromine source. Two platinum electrodes were placed in the aqueous phase without touching the organic phase but very close to the interphase. 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 monitored at 0–2 °C throughout the electrolysis. The electrolysis was conducted galvanostatically at a current density of 30 mA/cm^2 until the quantity of the current indicated in Table 1 was passed. An aliquot was drawn periodically from the organic phase and analysed by HPLC. After the completion of the electrolysis, the lower organic phase was separated; washed with water (2×25 ml), dried over anhydrous Na_2SO_4 and the solvent was removed by distillation. HPLC analysis of the residue indicated the presence of 91% benzyl bromide and 5% nuclear brominated toluene along with 4% unconverted toluene.