Chapter 3

Regioselective $\alpha$-bromination of alkyl aromatic compounds by two-phase electrolysis

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Regioselective $\alpha$-bromination of alkyl aromatic compounds by two-phase electrolysis

3.1 Introduction

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 chemicals including agrochemicals, flame retardants, disinfectants, antibacterial and antiviral drugs, precursor to a number of organometallic species and useful in the synthesis of natural products.

The bromination of aromatic hydrocarbon can occur either in a side chain or on the ring depending on the conditions. In the presence of sunlight alkyl benzenes are brominated predominantly in the side chain [1]. In the presence of Lewis acids, such as metal halide or iodine, aromatic hydrocarbons are halogenated on the aromatic ring [2]. Radical bromination on benzylic positions has been achieved using bromine [3-5] and N-bromosuccinimide [6,7]. In addition, the bromine complex of the styrene vinyl pyridine co-polymer [8] and bromotrichloroethane [9,10] and copper(II) bromide[11] have been reported to be effective for benzylic bromination. Side chain
bromination using sodium bromate and bromotrimethylsilane has also been reported [12] but in only low yields. Recently, trimethyl benzene was reacted with \( N \)-bromosuccinimide in \( \text{CCl}_4 \) solvent and obtained 1,3,5-tris-(tribromomethyl) benzene as product in 79 \% yield. 51\% yield of the above product was obtained when the reaction was carried out using benzene as solvent [13]. silica phosphine, \( \text{Br}_2 \) along with \( \text{PCl}_3\text{-SiO}_2 \) in acetonitrile solvent used for the conversion of alcohols and thiols to alkyl bromides in 97\% yield [14]. In presence of \( \text{MnO}_2 \) as oxidizing agent, toluene was brominated using liquid bromine and 100\% benzyl bromide was obtained as product [15]. Direct bromination of alcohols and their derivatives with tertiary butyl bromides in ionic liquid (bmim) were also reported under sonication condition. This novel, efficient and green methodology offered 80\% benzyl bromide at 20 °C [16].

Ning Shan et al. showed solid state regio-stereo selective benzylic bromination of Diquinoline compounds using \( N \)-bromosuccinimide [17]. Free radical bromination of benzylic proton by \( \text{H}_2\text{O}_2 - \text{HBr} \) system ‘on water’ was demonstrated by Jernej Iskra et al. [18]. \( \text{NaIO}_4 \) mediated selective bromination of alkyl aromatic compounds were carried out by A. Sudalai et al. using water as solvent [19]. Association of fluorous phase – vanishing method with visible light induced benzylic bromination by bromine liquid was also reported
Visible light induced ‘on water’ benzylic bromination with \(N\)-bromosuccinimide was reported by Adja. P. et al. [21]. Partial oxidation of p-t-butyl toluene catalysed by homogeneous cobalt and cerium acetate catalysts in the Br-/\(\text{H}_2\text{O}_2\)/Acetic acid system was reported. In this case benzyl bromide formed as intermediate product. The selectivity and its mechanistic aspects were discussed [22]. Magesh K. Lakshmanan studied the Structure/reactivity relationship in Benzophenanthrene skeleton by benzylic bromination using \(N\)-bromosuccinimide as brominating reagent [23].

Very recently benzylic bromination was carried out with \(N\)-bromosuccinimide in trifluoromethyl benzene as solvent by Diana snarez et al. [24]. Poly \((N,N'\text{-dibromo-} \ N\text{-ethyl –Benzene-1,3-disulfonamide})\)- \(N,N,N',N'\text{-tetrabromo-} \ N\text{-sulfonamide}\) and novel poly\((N,N'\text{-dibromo-}N\text{-phenylbenzene 1,3-disulfonamide})\) were used as a powerful reagent for benzylic bromination [25]. Radical brominations with \(\text{H}_2\text{O}_2\text{–HBr}\) and \(N\)-bromosuccinimide in an aqueous medium were used as a ‘green’ approach to electrophilic and radical bromination. Several activated and less activated aromatic molecules, phenyl substituted ketones and styrene were efficiently brominated ‘on water’ using both systems at ambient temperature and without an added metal or acid catalyst, whereas various non activated toluenes were functionalized at the benzyl position in the presence of visible light as
a radical activator. A comparison of reactivity and selectivity of both brominating systems reveals the H$_2$O$_2$–HBr system to be more reactive than NBS for benzyl bromination and for the bromination of ketones, while for electrophilic aromatic substitution of methoxy-substituted tetralone, it was higher for NBS. Also, higher yields of brominated aromatics were observed when using H$_2$O$_2$–HBr ‘on water’. Bromination of styrene reveals that not just the structure of the brominating reagent but the reaction conditions: amount of water, organic solvent, stirring rate and interface structure, play a key role in defining the outcome of bromination (dibromination vs bromohydroxylation).

In addition, mild reaction conditions, a straightforward isolation procedure, inexpensive reagents and a lower environment impact make aqueous brominating methods a possible alternative to other reported brominating protocols [26]. The majority of the above mentioned brominating agents require the presence of peroxide or another radical initiator. The reagents involved for benzylic bromination are costly and in some cases the yields are not very high. 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 homogenous electrolysis in practical electroorganic synthesis [27]. In the homogenous system less selectivity is observed due to oxidation of the substrate on the surface of the electrode giving mixtures of nucleus (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 regioselective products. After the completion of the electrolysis, separation and concentration of the organic layer affords the product.

Krishnan et al. attempted electrochemical chlorination of toluene in 10% HCl solution as electrolyte and they got ring brominated product \( o-,p- \) chlorotoluenes in a ratio of 66:33 respectively [28]. Similarly when we attempted chlorination of \( p \)-xylene, a mixture of \( 2-, 2,5 \)-dichloro \( p \)-xylene in 79% yield (nuclear chlorinated products) was obtained [29]. The electrodes used were ruthenium oxide coated over titanium metal as anode and graphite as cathode. In this case \( p \)-xylene was taken as a neat solution. As the density of \( p \)-xylene is less than 10% HCl, the organic layer was present as a top layer. While stirring, it formed as droplets in aqueous HCl solution. In another different experimental condition we obtained 81% of benzyl chloride.
i.e. the side chain halogenated product, rather than ring halogenated product [30]. In this case, 30% NaCl solution containing 5% sulphuric acid was used as electrolyte. Among the two phases the aqueous NaCl solution was present as top layer and chloroform containing toluene as bottom layer. While electrolysis proceeded the two layers were maintained by simply stirring the bottom chloroform layer alone and the electrodes were placed in the aqueous phase. As we got entirely different product from the same starting material, but at different conditions, we attempted to see the performance of the electrochemical bromination reaction at the same condition. Bromination occurs in a similar fashion but is slower and more selective manner because bromine atom is a less reactive hydrogen abstraction agent than chlorine atom as reflected by the higher bond energy of H-Cl than H-Br.

Electrochemical bromination was investigated in different solvents [31-38] and most of the work deals with ring brominated products. Side chain bromination has not been much explored. In this chapter 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 at 0 °C in a single compartment cell as shown in Scheme 3.1.
Scheme 3.1 Electrochemical bromination of toluene by two-phase electrolysis.

3.2 Experimental

3.2.1 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<sup>2</sup> area were used as the anode and the cathode. 50 ml of 50% 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 (Shimadzu) using a Shimpack ODS-18 column (125 mm x 4.5mm) as the stationary phase. The eluent consisted of methanol/ water (80:20) 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 confirm the product and 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 50% 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 did not touch the electrodes. The temperature of the electrochemical cell contents was monitored at 0 - 5 °C throughout the electrolysis. The electrolysis was conducted galvanostatically at a current density of 30 mA/cm² until the quantity of the current indicated in Table 3.1 was passed. An aliquot was drawn periodically from the organic phase and analysed by HPLC. After completion of the electrolysis, the lower organic phase was separated; washed with water (2 x 25 ml), dried over anhydrous Na₂SO₄ and the solvent was removed by distillation. HPLC analysis of the residue (1.1gm) indicated the presence of 95% benzyl bromide and 2% nuclear brominated toluene along with 3% unconverted toluene.
Fig. 3.1 Electrochemical cell for side chain bromination of alkyl aromatic compounds.
Fig. 3.2 The cell and instrumental arrangements for bromination alkyl aromatic compounds.
3.3 Results and Discussion

A number of alkyl aromatics and substituted alkyl aromatic compounds were subjected to side-chain bromination by two-phase electrolysis using an aqueous 50% NaBr solution as the supporting electrolyte containing a catalytic amount of HBr (5%). We observed smooth bromination at the $\alpha$-position of the side chain without the formation of any poly-brominated product.

The product distributions from the reactions are listed in Table 3.1. 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, alkyl naphthalene was brominated mainly on the aromatic ring. 2-methylnaphthalene, for example, gave 1-bromo-2-methylnaphthalene as the only isolated brominated product.

In the electrolysis of NaBr solution, the two electrodes reactions are the generation of Br$_2$ at the anode, the formation of hydroxide ion and H$_2$ at the cathode. If the products of both of these cell reactions are allowed to mix then the dissolved bromine undergo further reactions to form hypobromous acid which depends on the electrolyte concentration, pH and temperature.
Bromine oxides have been prepared but none has been fully characterized and all are unstable. The oxyacids of bromine are strong oxidants but they are unstable at ordinary temperature and stable only in solution [39]. There are some evidences about the formation of hypobromous acid (HOBr) [40]. Side chain bromination of toluene follows a free radical mechanism and the brominating species is dibromine monoxide (Br₂O) which is formed as shown in equations 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 Br₂O as the brominating species, which is extracted by the organic phase where the selective bromination occurs.

\[
\begin{align*}
\text{Br}_2 + \text{H}_2\text{O} & \rightarrow \text{HOBr} + \text{HBr} \quad \text{--------(1)} \\
2\text{HOBr} & \rightarrow \text{Br}_2\text{O} + \text{H}_2\text{O} \quad \text{--------(2)}
\end{align*}
\]

As the reactive species Br₂O is unstable, it is cleaved homolytically into Br⁻ and ·OBr. The more reactive ·OBr, abstracts 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 gave higher percentage of nuclear brominated product rather than side chain brominated products (entry 7 in Table 3.1). This is due to ring bromination of activated aromatics by the attack of Br⁺, which is generated from HOBr as shown in equation 3.

\[ \text{HOBr +H}^+ \rightarrow \text{H}_2\text{O} \ + \text{Br}^+ \quad \text{(3)} \]

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 formations of the products were confirmed by chemically generating HOBr as in equation 4 and toluene was brominated with that reagent.

\[ \text{HgO} + 2\text{Br}_2 +\text{H}_2\text{O} \rightarrow 2\text{HOBr} +\text{HgBr}_2 \quad \text{(4)} \]

Furthermore, dibromine monoxide was prepared chemically in CCl₄ as shown in equation 5 and the toluene was brominated at 0 -5 °C. The product obtained was benzyl bromide as a sole product.
\[
\text{HgO} + 2\text{Br}_2 \rightarrow 2\text{Br}_2 + \text{HgBr}_2 \tag{5}
\]

**Table 3.1** The ratio of reactants and products of the electrochemical bromination of toluene substituted toluenes and substituted naphthalene via two-phase electrolysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Product</th>
<th>Charge passed</th>
<th>Yield (%)</th>
<th>Current efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\text{\textsubscript{3}}\text{CH\textsubscript{2}}\text{Br}</td>
<td>CH\text{\textsubscript{3}}\text{CH\textsubscript{2}}\text{Br}</td>
<td>4.3 F/mole</td>
<td>95</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>CH\text{\textsubscript{3}}\text{Cl}</td>
<td>CH\text{\textsubscript{3}}\text{Cl}</td>
<td>5.0 F/mole</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>CH\text{\textsubscript{3}}\text{Br}</td>
<td>CH\text{\textsubscript{3}}\text{Br}</td>
<td>3.0 F/mole</td>
<td>89</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>CH\text{\textsubscript{2}}\text{CH\textsubscript{3}}</td>
<td>CH(\text{Br})\text{CH\textsubscript{3}}</td>
<td>4.5 F/mole</td>
<td>85</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>CH\text{\textsubscript{3}}\text{Cl}</td>
<td>CH\text{\textsubscript{3}}\text{Cl}</td>
<td>3.0 F/mole</td>
<td>62</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>CH\text{\textsubscript{3}}\text{Cl}</td>
<td>CH\text{\textsubscript{3}}\text{Cl}</td>
<td>4.0 F/mole</td>
<td>57\textsuperscript{a}</td>
<td>35</td>
</tr>
</tbody>
</table>
(a) benzal bromide 22% formed along with 10% recovered starting material
(b) 4-methylbenzyl bromide 45% formed along with 2% recovered starting material
3.4 Spectral data of benzyl bromides

1. Benzyl bromide, Liquid; b.p 198°C, IR(neat): ν=
3064,3031,2968,1951,1586,1496,1227,1069,758,698,606. cm⁻¹.
¹H NMR (400MHz, CDCl3): δ 4.5 (S, 2H), 7.2-7.4 (m, 5H).

2. 4-Chloro benzyl bromide: Solid, m.p:48°C, IR(neat): ν=
3088,3067,2957,2926,2853,1698,1578,1492,1464,1224,1092,1016,
840,591 cm⁻¹. ¹H NMR (400MHz, CDCl3): δ 4.45(s,2H),7.2-7.4(m,5H).

3. 1,4-Bis(bromomethyl)benzene, solid, m.p145°C, IR(neat): ν=
3753,3427,2970,2370,1920,1686,1509,1435,1416,1224,1195,1083,
846,747, 609,478 cm⁻¹. ¹H NMR (400MHz, CDCl3): δ 4.5(s,4H),
7.4(S,4H),

4. 4-Methyl benzylbromide: Liquid, b.p 218°C, IR (neat): ν=
3025,2966,2920,2862,2732,2293,1893,1657,1588,1484,1400,1068,
1009,798 cm⁻¹. ¹H NMR (400MHz, CDCl3): δ 2.34 (t, 3H), 4.5 (s,2H),
7.1-7.2(m, 2H), 7.26-7.3 (m, 2H).
Fig. 3.3 HPLC data of 4-bromo toluene.
Fig. 3.4 HPLC data of reaction mixture containing 4-bromo toluene (R.T=8.9 min.) and 4-bromo benzyl bromide (R.T=7.8 min.).
Fig. 3.5 HPLC data of reaction mixture containing 91% 4-bromo benzyl bromide (R.T=8.1 min.) as product.
Figure 3.6 $^1$HNMR data of 4-bromo benzyl bromide obtained by electrochemical bromination method.
Fig. 3.7 $^1$H NMR data of 1,4-Bis bromomethyl benzene in DMSO solvent (entry 7).
Fig. 3.8. $^{13}$C NMR data of 1,4-Bis bromomethyl benzene in DMSO solvent.
3.5 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. Electrochemical bromination reaction has been carried out in a single compartment cell with platinum electrodes at 0 ºC in chloroform using an aqueous sodium bromide solution (50%) containing a catalytic amount of HBr. Two–phase electrolysis resulted in high yields (60–95%) of monobromo compounds with very high regioselectivity (>95%). 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.
3.6 References


