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Research Article

ELECTROCATALYTIC OXIDATIVE SIDE CHAIN BROMINATION OF ALKYL ARYL KETONES

R. Jagatheesan[1*], K. Joseph Santhana Raj[1], S. Lawrence[2] and C. Christopher[3]

[1]Department of chemistry, St. Joseph's College, Tiruchirappalli-620 002, Tamil Nadu, India.
[2]Department of chemistry, Govt. Arts College, Ariyalur-621 713, Tamil Nadu, India.
[3]Department of chemistry, St. Xavier's College, Thirunelveli-627 002, Tamil Nadu, India.

ABSTRACT

Selective side chain bromination of alkyl aryl ketones transformation is reported, ammonium bromide was used as a greener and effective bromine source along with the catalytic amount of H_2SO_4 as supporting electrolyte in homogeneous medium. The reaction was carried out in single compartment cell outfitted with platinum anode and stainless steel cathode at ambient temperature. The effects of different electrodes are studied and reported. Various aryl alkyl ketones are proceeded to the respective α-monobrominated products in moderate to excellent yields.

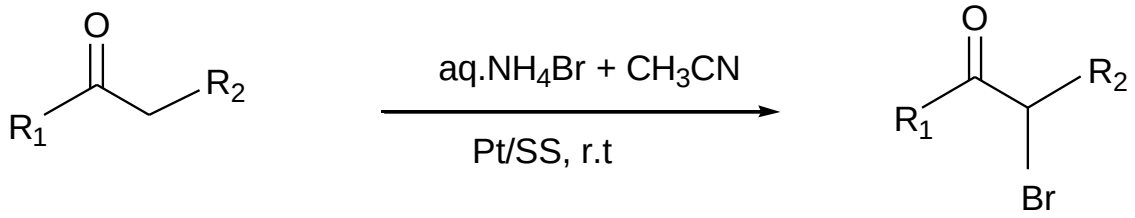
Keywords: HOBr, Undivided cell, In-situ, Homogeneous electrolysis, Electrocatalysis

1. INTRODUCTION

The α-halogenation of carbonyl compounds is an important transformation in synthetic organic chemistry. These important classes of compounds are useful synthetic intermediates for various transformations employed in organic and pharmaceutical synthesis.[1] Especially, α-bromo carbonyl compounds have become an important construction motif for the development of various biologically active compounds such as quinoxalines,[2] thiophene and thiazolidin-4-one,[3] imidazo[1,2-a][1,3,5]triazin,[4] cyclohexanone derivatives,[5] pyrazolo[1,5-α][1,3,5]triazine and thiadiazine,[6] triazolo[3,4-b][1,3,4]thiadiazine,[7] pyrazolines,[8] imidazo[2,1-b]benzothiazoles[9] and imidazoles.[10] Furthermore, they are versatile building blocks for the retro-synthesis of natural products.[11] Particularly, α-bromo acetophenone derivatives are reported to have active participation in the inhibition of protein tyrosine phosphatase such as SHP-1 and PTP1B.[12]

The side chain monobromination of carbonyl compounds has been a challenging task, because during the reaction a small amount of disubstituted product as an impurity is always accompanied with monosubstituted product.[13] Considerable efforts have been focused on the development of various useful reagents and procedures are reported for the synthesis of α-halo carbonyl compounds.[14] In general, α-bromoketones are synthesized from the reaction of ketones with liquid bromine. In addition to this, many alternative and efficient methods are also reported in various routes which includes organic and Inorganic brominating agents as follows; dioxane dibromide,[15] pyridinium bromochromate,[16] tribromoisocyanuric acid,[17] 1-butyl-3-methylimidazolium tribromide,[18] hexamethylenetetramine-bromine[19] and *N*-bromosuccinimide is one of the reagents often used for introduction of bromine into organic molecules with various catalysts.[20-23] Besides, inorganic brominating agents NH_4Br- oxone,[24] NH_4Br-$(NH_4)_2S_2O_8$,[25] KBr-H_2O_2,[26] H_2O_2–HBr,[27,28] copper(II) bromide,[29] magnesium bromide[30] and electrochemical bromination methods[31,32] have also been reported. Some of the reagents reported for bromination are often perilous, very toxic, expensive, not readily available, need to be freshly prepared, require drastic conditions or prolonged reaction times

and involve tedious work-ups. Consequently an amiable, selective, non-hazardous and inexpensive reagent is still in demand. In continuation of our earlier work on electrochemical selective side chain bromination,[33] now we wish to approach a competent and expeditious electrochemical method for the α-bromination of acetophenone and substituted acetophenone compounds to give the corresponding phenacyl bromides in very good yields by homogeneous electrolysis in an undivided cell as shown in Scheme 1.



R_1= aryl, substituted aryl; R_2= H (or) Methyl.
Scheme 1: Electrochemical side chain bromination of alkyl aryl ketones

The most convenient electrolytic cells are the undivided cell or single compartment cells. Divided cells are sometimes quite troubles, especially if the electrolysis medium is an emulsion or a suspension of fine solid particles. Sometimes electroosmotic forces cause liquid flow from one compartment to the other, especially if the compositions of the anolyte and catholyte are very different.[34]

2. EXPERIMENTAL

2.1 Representative Procedure for Electrochemical Bromination of Acetophenone

Acetophenone (10 mmol) was dissolved in acetonitrile (20 ml) and this solution transferred to a single compartment cell. To this cell, aqueous NH_4Br (80 ml of 60% solution) and 0.33M H_2SO_4 were added. Deionised water used for preparing ammonium bromide solution. A platinum anode and stainless steel cathode of 15 cm^2 area were inserted at a distance of 2 cm^2 into the homogeneous solution. The cell was introduced into the electrolytic circuit and 2F of electricity was passed galvanostatically at a current density of 100 mA cm^{-2} (Assuming a 2-electron process to occur, the quantity of the current required was calculated and the duration of the passage of the current was set in the instrument) at the ambient temperature and the whole solution was stirred constantly throughout the reaction. After passing 2F of electricity the current flow was stopped and the reaction mixture alone was stirred another 5 hours to allow the *in-situ* generated HOBr to react with the acetophenone completely under closed condition. After this additional stirring, the reaction mixture was extracted with ethyl acetate (3×25 mL). Finally the combined organic layer was washed with water (20 mL) and dried over anhydrous sodium sulfate. The product phenacyl bromide was obtained after evaporation of the solvent at reduced pressure and crystallized from a mixture of methanol and hexane.

The electrochemical reaction was monitored by Shimadzu HPLC with LC-8A column (250mm×4.6 mm) as stationary phase. The eluent consisted of acetonitrile/water (60:40) at a flow rate of 1 mL/min. Samples were analyzed at a wavelength of 254 nm with a UV detector coupled to a printer. Authentic samples were used to calculate the peak areas of the respective experimental products for yield calculation. HPLC analysis of the crude indicates the presence of 94 % phenacyl bromide. The product was analyzed and characterized by ^{1}H NMR, ^{13}C NMR, Fourier transform–infrared (FT-IR) spectra and HRMS.

3. RESULTS AND DISCUSSION

In broad sense all electrochemical reactions are catalytic reactions. In the primary step, the electron exchange occurred, so it is a catalytic phenomenon: the electrode plays the role of the catalyst, or more precisely, hence it termed here as the electrocatalyst. Since, it catalyzes the electron transfer reaction, Grubb called this phenomenon electrocatalysis.[35]

3.1 Effect of electrodes

To study the effect of electrodes on the α-bromination of ketones, we carried out a reaction with a solution of acetophenone, 60% NH_4Br and catalytic amount of H_2SO_4 using the following electrode combinations (Pt, SS, C, DSA and Zn) at ambient temperature. However a yield of the product 2-bromo-1-phenylethanone was obtained at only 2F/mole is reported (Table 1). Finding suitable anode for halogenations is not easy because nascent

halogens attack most materials. Graphite and platinum anode would be most suitable in most cases. From the table 1, it is observed that the Pt/SS electrode combinations were performed well in this condition. In some cases, especially in single compartment cells, nature of both anode and cathode may be of about equal importance. The most prudent way to select an electrode depends on its material and its surface morphology.

3.2 Achievement of reproducibility

Predominantly, reproducibility is one of the main principles of the scientific method. In order to ensure the scrutinized experimental condition that we carried out previously, here the same substrate with the same reaction conditions was performed to get the concordant yield. Moreover, the yield was obtained in all the attempts as good as desired (Table 2).

A possible mechanism for the electrochemical side chain bromination of aromatic ketones in homogeneous electrolysis is proposed in scheme 2

Table 1: Effect of electrode variation on selective bromination of acetophenone[a]

S. No	Electrode (anode/cathode)	Phenacyl bromide Yield (%)	Current efficiency (%)
1	Pt/Pt	80	80
2	Pt/SS	94	94
3	C/SS	78	78
4	DSA/SS	68	68
5	Zn/SS	16	16

[a]***Reaction mixture:*** 60% NH_4Br + 0.33 M H_2SO_4 + 10 mmol acetophenone + water 80% - acetonitrile 20%.
Cell: Undivided cell
Electrolysis conditions: Amount of electricity, 2F; Current density, 100 mA cm^{-2}; Temperature, 30 to 35 °C; Stirring time, 5 hours after electrolysis.

Table 2: Achievement of reproducibility on selective bromination of acetophenone[a]

S.No	Parameter	Attempts	Phenacyl bromide yield (%)	Current efficiency (%)
1	Reproducibility	1	94	94
2		2	94	94
3		3	93	93

[a]***Reaction mixture:*** 60% NH_4Br + 0.33 M H_2SO_4 + 10 mmol acetophenone + water 80% - acetonitrile 20%.
Cell: Undivided cell
Electrolysis conditions: Amount of electricity, 2F; Current density, 100 mA cm^{-2}; Electrodes, platinum/stainless steel; Temperature, 30 to 35 °C; Stirring time, 5 hours after electrolysis..

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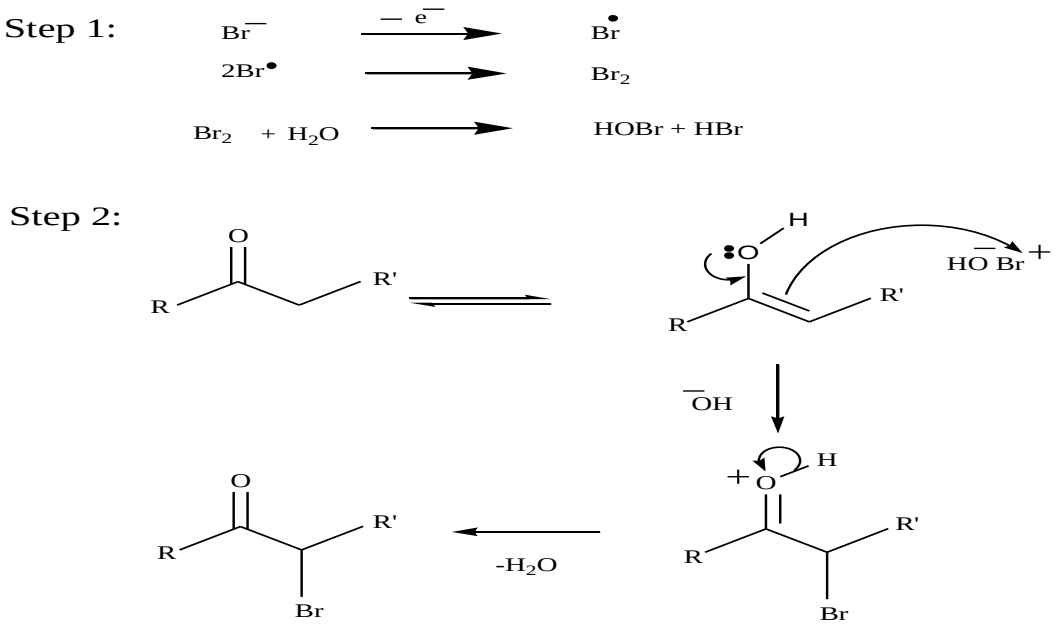


Scheme 2: Possible mechanism for the electrochemical side chain bromination of aromatic ketones.[33]

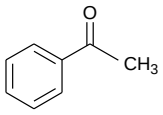
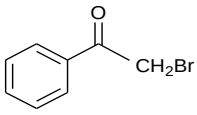
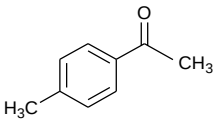
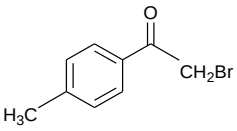
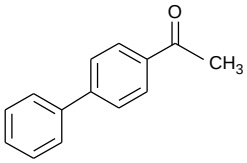
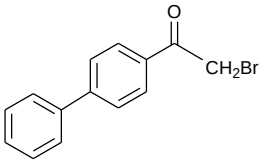
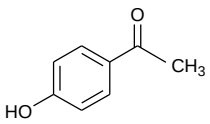
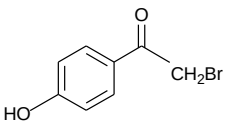
To evaluate the scope of this optimized condition, a variety of aralkyl ketones were subjected to the bromination reaction to test the generality of this method and the results are summarized in table 3.

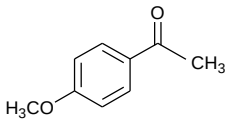
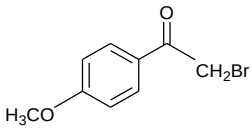
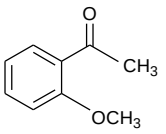
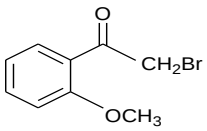
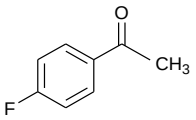
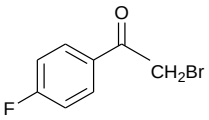
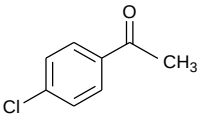
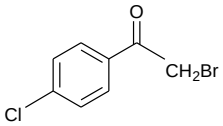
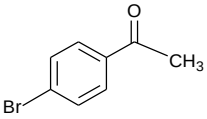
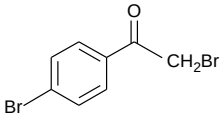
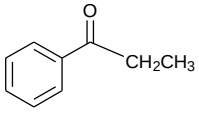
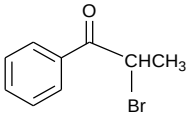
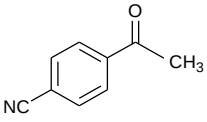
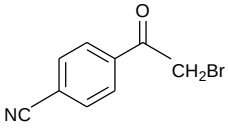
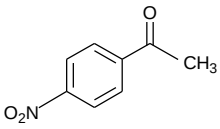
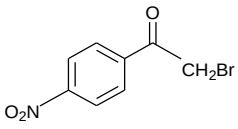
In the electrolysis of NH_4Br solution, at the first, bromide ion oxidized into radical and the formed radicals combined to form bromine molecule. The electrochemically generated bromine combines with water, giving one molecule of hypobromous acid (HOBr) and one molecule of HBr. The hypobromous acid is unstable due to its pronounced ionic nature and consequently can react with the enol form of the ketone to form α-bromo derivative. The electron withdrawing carbonyl group enhances the acidic strength of α-hydrogen and is thus replaced readily by halogens.

The bromination of a variety of alkyl aryl ketones proceeded efficiently, to afford the corresponding α-bromo ketones in moderate to good yields (Table 3). The chemical reactivity description of the substituted acetophenones is remarkable. Phenacyl bromide obtained from acetophenone in excellent yield (Table 3, entry 1). Fairly activating (Table 3, entry 2 and 3) and deactivating (Table 3, entry 7-9) groups present on the aromatic ring of acetophenone gave moderate to high yields of the corresponding α-bromo products. Even if, the aromatic ring of acetophenone (Table 3, entry 2) has methyl and acetyl group, the acetyl group preferentially brominated due to the electron withdrawing nature of carbonyl group. Highly activating (Table 3, entry 4-6) group present on the aromatic ring and its position on the ring also alter the product yield. Generally electron donating groups present on the aromatic ring direct the ring hologenation, whereas in this case α-bromination achieved in excellent yield without forming nuclear bromination product.[33]

Interestingly, propiophenone was brominated at the α-position, but it gave product in moderate yield at 2F and high yield at 4F (Table 3, entry 10). Furthermore, the presence of highly deactivating groups (Table 3, entry 11 and 12) on the aromatic ring of acetophenone gave reasonable yields of α-brominated product.

Table 3: Electrocatalytic α-bromination of alkyl aryl ketones[a]

Entry	Substrate	Product	Yield (%)	Current efficiency (%)
1			94	94
2			68	68
3			64	64
4			80	83*

5			74	76*
6			68	69*
7			87	87
8			97	97
9			94	94
10			64 83[b]	64 44
11			50	56*
12			24	24

[a] ***Reaction mixture:*** 60% NH_4Br + 0.33 M H_2SO_4 + 10 mmol substrate + water 80% - acetonitrile 20%. ***Cell***: Undivided cell. ***Electrolysis conditions:*** Charge passed, 2 F/mol; Current density, 100 mA cm^{-2}; Temperature, 30 to 35 °C; Electrodes, Platinum/Stainless Steel; Stirring time, 5 hours after electrolysis.
[b] Yield obtained at 4 F/mol
* Electricity utilized for the formation of both desired and undesired product.

4. CONCLUSION

There are many advantages associated with this electrochemical method. For example, the variables are easily controlled, no catalyst or mediator required and the cost of the equipment is generally not that high. The main fascination of the present method is that these reactive species could be formed *in situ* and greater product selectivity achieved at ambient temperature. In this case, it is an excellent dosage control (by simple current control) what is not easy in many classical methods. In the context of green chemistry, noncatalytic processes have attracted considerable attention, hence this procedure might be recommended as a superior one.

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