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Communication

Electrochemical synthesis of α,α-dihaloacetophenones from terminal alkyne derivatives

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ABSTRACT

By virtue of electrochemistry, a series of α,α-dihaloacetophenones were easily obtained with good to excellent yields. This electrochemical procedure was taken in a divided cell with constant current in aqueous media. The reaction can be carried out smoothly at room temperature under metal and oxidant free condition, which provides an eco-friendly synthesis for the α,α-dihaloacetophenone derivatives.

Halogenated organic compounds are of great importance in modern organic and organometellic synthesis, which have been attracting the synthetic chemists' attention. Of them, α,α-dihaloalkyl derivatives have been obtained much interest not only for their applications in pharmaceutical molecules [1], but also for their crucial roles in the synthesis of various intermediates [[2]]. For example, α,α-dihaloketones can be the starting material for the synthesis of cyclopropanes [2a,2e], α-keto amides [2b] or esters [2c], heterocycles [2d], unsaturated aldehydes [2f] or ketones [2g], *etc.*

General methods to prepare α,α-dihaloketones mainly include the dihalogenation of ketones [[3]] and the oxyhalogenation of alkynes [4]. In these traditional methods, excessive halogenation reagents were usually used, such as *N*-halosuccinimide [3a], trichloroisocyanuric acid [3b], molecular chlorine [3c] or bromine [3d,3e] and 1,3-dichloro-5,5-dimethylhydantoin [3f,3g]. In the case of oxyhalogenation of alkynes, some of the dihalogenation reagents of ketones can be adopted [4]. Sometimes additional oxidants were employed to generate the halogen or halogen equivalents from halides *in situ* [[5]]. Oxone [5a], Selectfluor [5b], $PhI(OAc)_2$ [5c], O_2 [5d] and $K_2S_2O_8$ [5e] can be used as oxidants. However these kinds of reagents were often required in stoichiometric quantity and some of them were toxic and expensive. Therefore the alternative methods were also reported. In 2006, for instance, Moises *et al.* [6] used trichloromethyl compounds as substrates, which can be dechlorinated in the presence of PPh_3-MeOH to give the dichloromethyl derivatives. In 2017, Rafael and coworkers [7] achieved dihalogenation of sulfoxonium ylides to prepare gem-dihalogenated haloketones.

Electrochemical method represents a powerful and efficient tool in organic synthesis, which can meet the requirement of environmental protection and sustainable development because electron is a green redox media [8]. We assumed that the oxyhalogenation reagent can be generated *in situ* slowly from halogen source by electrochemical method. The α,α-dihaloketones can be obtained from alkyne derivatives in the anodic reaction. Herein we report an electrochemical alkyne oxyhalogenation methodology to prepare α,α-dihaloketone derivatives.

In the preliminary experiments, phenylalkyne was chosen as the model substrate and the electrochemical process was carried out in an undivided cell (Table S1, Fig. S2 in Supporting information). However, in this case, α,α-dichloroacetophenone was easy to be dechlorinated in the cathodic reduction, resulting in the formation of acetophenone as a byproduct. This caused poor reaction yield and brought trouble in product isolation. In order to solve this problem, a divided cell was chosen as the reaction device (Fig. S1 in Supporting information) (Scheme 1).

According to the previous reports, 0.5 mmol of phenylalkyne was added in the anodic compartment of the electrolysis cell,

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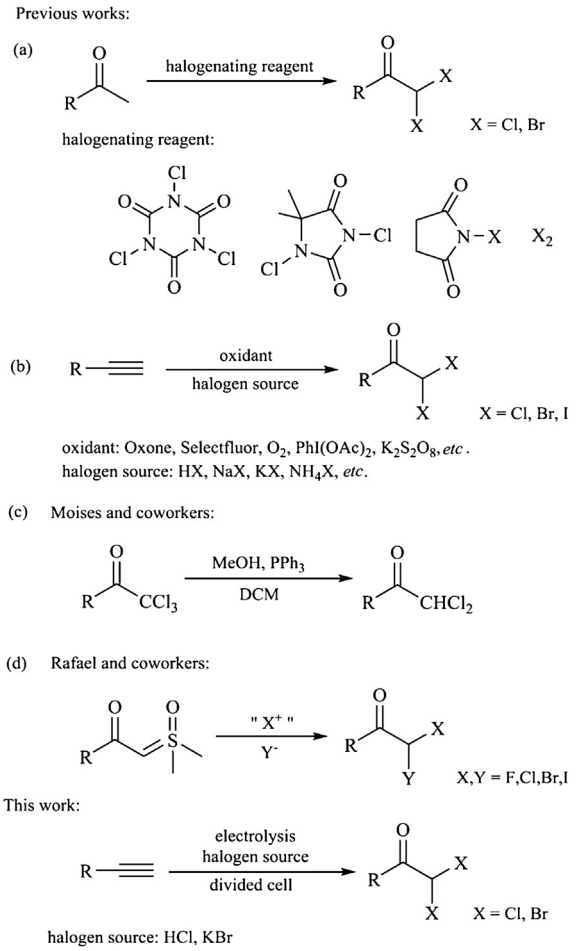
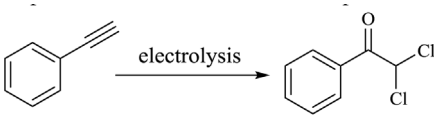


Scheme 1. Synthesis of α,α-dihaloketones.

which contained 6 mL of MeCN and 2 mL of HCl (1.2 mol/L, aq.) as solvent. The cathodic compartment was filled with 8 mL of H_2SO_4 (0.6 mol/L). Then 0.5 mmol of $LiClO_4$ was added as electrolyte in both electrolysis compartments. The two cells were separated by a membrane which can be selectively permeable for the positive ions (TRJCM Type, 1.5 × 1.5 cm^2).

Initially, the reaction was carried out with a 10 mA/cm^2 Pt-Pt electrode system at room temperature. As expected, 77% of the desired product was obtained (Table 1, entry 1). When NaCl, NH_4Cl or KCl was employed to replace HCl (1.2 mol/L) as chlorine source, the yield of the desired product was decreased, giving the reaction yield 65%, 54% and 60%, respectively (entries 2–4). This indicated that acidic environment at the anode favored the reaction. Then various ammonium salt electrolytes were examined in place of $LiClO_4$. The experimental results showed that the reaction still proceeded smoothly in spite of a slight decrease in the reaction yields (entries 5–7). Either the increase or decrease in the current density can result in the lower yields (entries 8 and 9). The electrode optimization showed that Pt-Pt electrode couple was the optimal for the reaction, while the Pt electrode was replaced by a graphite rod would lead to poor yield (entries 10–12). On the other hand, the solvent in anodic compartment had a significant effect on the reaction (entries 13–16). For instance, the reaction yield achieved 93% when the ratio of MeCN and HCl (1.2 mol/L) was 4:1 (total volume 10 mL) in the anodic compartment (entry 13). The higher or lower of this ratio would result in the low yield (entries 15 and 16). The addition of MeCN was necessary since a trace amount of the desired product was generated when water was the only solvent (entry 14). To extend the scope of the reaction

Table 1
The optimization of α,α-dichloroacetophenone.[a]



1 a **2 a**

Entry	Variation from standard condition	Yield (%)[b]
1	None	77
2	NaCl as chlorine source	65
3	NH_4Cl as chlorine source	54
4	KCl as chlorine source	60
5	$^nBu_4NBF_4$ as electrolyte	70
6	$^nBu_4NHSO_4$ as electrolyte	72
7	$^nBu_4NPF_6$ as electrolyte	68
8	10 mA as electric current	72
9	20 mA as electric current	54
10	Pt (+)-C (−) as electrode system	70
11	C (+)-Pt (−) as electrode system	61
12	C (+)-C (−) as electrode system	58
13[c]	8 mL MeCN, 2 mL HCl (1.2 mol/L, aq.)	93(92)[d]
14[c]	10 mL HCl (1.2 mol/L, aq.)	trace
15[c]	7 mL MeCN, 3 mL HCl (1.2 mol/L, aq.)	74
16[c]	9 mL MeCN, 1 mL HCl (1.2 mol/L, aq.)	82

[a] 0.5 mmol phenylacetylene, 0.5 mmol $LiClO_4$, 2 mL HCl (1.2 mol/L, aq.), 6 mL MeCN were added in the anodic compartment of the electrolysis cell; 0.5 mmol $LiClO_4$, 8 mL H_2SO_4 (0.6 mol/L) were added in the cathodic compartment of the electrolysis cell, r.t., 15 mA, Pt-Pt.
[b] ^{1}HNMR yield, $MeNO_2$ as internal standard.
[c] Variation of anodic compartment, while 10 mL H_2SO_4 (0.6 mol/L) in the cathodic compartment.
[d] Isolated yield.

substrate, α,α-dibromoacetophenone was tried to be obtained under the optimized condition (entry 13). However, only less than 30% of the desired product was obtained and 1,2-dibromophenylethylene was generated as the major product. The oxybromolation can also be carried out smoothly to give the corresponding product with moderate to good yields. Nevertheless, the solvent MeCN disfavored this oxybromolation while water promoted this transformation. After optimization, it was found that the acidic water solution was benefit to this oxybromolation. For instance, α,α-dibromoacetophenone can be obtained with the yield of 53% when MeCN:H_2SO_4 (0.6 mol/L, total volume 10 mL) was 1:1, while the reaction yield achieved 63% when the ratio was changed to 1:9. In order to avoid the interference of Cl^-, H_2SO_4 (0.6 mol/L) was used as the acid. Ultimately 10 mL of H_2SO_4 (0.6 mol/L) was chosen as the solvent in the anodic compartment, and KBr was added as the source of bromine (Table S2 in Supporting information). Under this modified conditions, the yield of α,α-dibromoacetophenone can reach 83%.

With the optimized conditions in hand, the scope of the reaction substrates was investigated, as shown in Scheme 2. The results showed that a variety of alkyne derivatives were suitable for this electrochemical transformation, affording the α,α-dichloroacetophenones with the yields of 31%–96% except for **2m**, which only generated in trace amount. This phenomenon was probably due to the steric effect. Similar result was also observed when diphenylacetylene was used as the reaction substrate. Compared with **2d** and **2f**, **2e** was obtained in lower yield, which maybe resulted from the steric effect. When the phenyl group was replaced by substituted phenyl, such as F-, Cl-, Br-phenyl (**2b-2f**), the reaction still afforded satisfied results. Similarly, 4-cyanophenylacetylene can be converted to **2l** successfully. Except for **2p**, either electron-donating groups (**2g-2k**) or electron-withdrawing groups (**2n** and **2o**) had little influence on the reaction yields (65%–94%). The lower yields of **2j** and **2k** (74% and 65%) were probably due to the existence of methylene groups, which tended to occur

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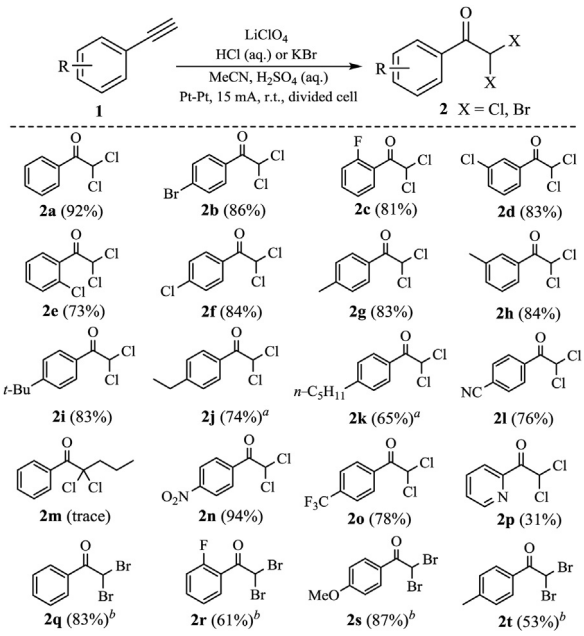
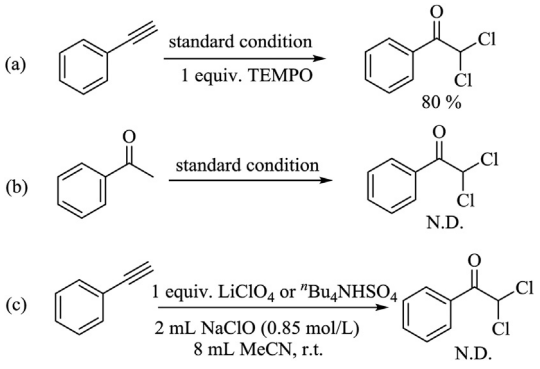


Scheme 2. The extension of the scope of the reaction substrates. [a] 0.5 mmol substrate, 0.5 mmol $LiClO_4$, 1.5 mL HCl (1.2 mol/L, aq.), 8.5 mL MeCN were added in the anodic compartment of the electrolysis cell; 0.5 mmol $LiClO_4$, 10 mL H_2SO_4 (0.6 mol/L) were added in the cathodic compartment of the electrolysis cell, rt, 15 mA, Pt-Pt. [b] 1.5 mmol KBr, 10 mL H_2SO_4 (0.6 mol/L) were added in the anodic compartment of the electrolysis cell.



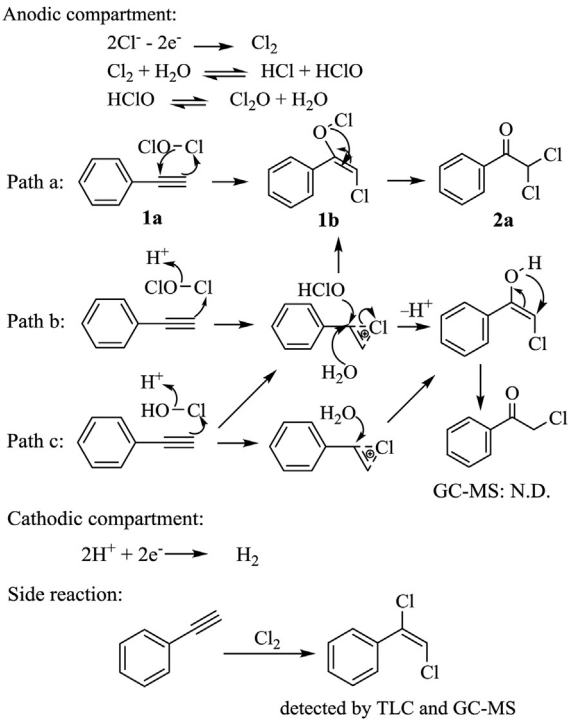
Scheme 3. The control experiments.

side reactions under the reaction conditions. For the synthesis of α, α-dibromoacetophenones, several substrates were examined in the reaction, affording the desired products with the yields from 53% to 87% (**2q**-**2t**).

Some control experiments were carried out to investigate the reaction mechanism. When 1.0 equiv. of radical inhibitor (TEMPO) was added in the reaction mixture (Scheme 3a), little influence on the **2a** yield was observed, which implied that this electrolysis process did not involve a free radical. The desired product could not be detected when acetophenone was used as the substrate (Scheme 3b). When NaClO (aq.) was employed as the chlorine source as well as the oxidant, no any α,α-dichloroacetophenone was observed either, as shown in Scheme 3c.

On the other hand, neither α-monochloroacetophenone nor acetophenone was detected by GC–MS under standard condition.

According to the facts of the experiments, the results of cyclic voltammetry (Fig. S3 in Supporting information) and the reported literature [4a], a possible mechanism was proposed in Scheme 4.



Scheme 4. The proposed mechanism.

Under the electrolysis condition, Cl^- will be oxidized to Cl_2 at the anode and reacts with H_2O to give HClO, which is eventually converted into the corresponding anhydride Cl_2O in equilibrium [9]. Cl_2O reacts with **1a** instead of HClO in a concerted process (Path a) since Cl_2O is a more reactive species to the substrate [10]. Eventually **2a** is generated from the tautomerization of **1b.** Path b and Path c would lead to the formation of α-chloroacetophenone, which was not detected by GC–MS, indicated that both of them are not the reaction pathways. On the other hand, Cl_2 can react with **1a** to generate the α,β-dichlorostyrene as a byproduct (detected by GC–MS), while at the cathode H^+ can gain electron to release H_2.

In summary, we developed an efficient and convenient electrochemical approach for the oxyhalogenation of alkyne derivatives. This method avoids the use of additional oxidants in the traditional process of dihalogenation of ketones and the oxyhalogenation of alkynes, which represents a green and practicable electrochemical methodology for the synthesis of α, α-dihaloacetophenone derivatives.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.02.030.

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