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Asymmetric electrochemical carboxylation of prochiral acetophenone: An efficient route to optically active atrolactic acid via selective fixation of carbon dioxide

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ABSTRACT

A novel method of selective fixation of carbon dioxide was developed in this work. In an undivided cell the pharmaceutically active intermediate 2-hydroxy-2-phenylpropionic acid (atrolactic acid) has been produced from prochiral acetophenone in the presence of two kinds of chiral alkaloids, cinchonidine and cinchonine, acting as the inductors which were inclined to afford R and S products, respectively. Since the alkaloid has a strong tendency to adsorb to the surface of the cathode, three different cathode materials (stainless steel, platinum and copper) were applied in the process of asymmetric electrochemical carboxylation. Eventually, very distinct results were obtained. When the stainless steel was used as the cathode, a highest enantiomeric excess (ee) of 29.8% was achieved with an electrocarboxylation yield of 24.5%. Using cinchonidine and cinchonine as the inductors, the ee value of the aimed 2-hydroxy-2-phenylpropionic acid was also measured as a function of the concentration ratio of the alkaloid to the cocatalyst of butanol, supporting electrolyte, temperature, charge passed, current density and solvent. In particular, the butanol may play a critical role of helping to accomplish the asymmetric electrocarboxylation induction. From further analysis of cyclic voltammograms of acetophenone before and after addition of the alkaloid and butanol, a possible induction mechanism was put forward accordingly.

1. Introduction

Asymmetric electrochemical carboxylation has been challenging for many years due to the difficulty in selective fixation of the small molecule of carbon dioxide since it has been known that enantioselective electron transfer is not possible in principle and the electron cannot possess chirality [1]. In an attempt to achieve asymmetric induction, there are some prevalent methodologies such as the use of chiral solvents [2], chiral supporting electrolytes [3,4], chiral electrodes [5–12], chiral catalytic systems [13] or the intrinsic optical conformation of the substrate [14–17]. Using these methods to provide a chiral environment, there have been some reports about asymmetric electrochemical hydrogenation of various unsaturated organic compounds in a protic solvent. Usually, chiral solvents and supporting electrolytes need large amounts of optically active materials inherently. By contrast, only catalytic amounts of chiral materials are necessary when chiral electrodes are used as the chiral auxiliary [12]. As reported [6], optically active pyridylethanols have been produced from asymmetric reduction of 2- and 4-acetylpyridine on mercury electrodes when catalytic concentrations of certain alkaloids were present which could have a strong adsorption on the cathode. The use of chiral poly (pyrroles) coated electrode was also investigated [12]. Those authors realized the stereoselective electroreduction of 4-methylbenzophenone and acetophenone with up to 17% optical purity of the corresponding alcohols.

On the other hand, with the development of asymmetric electrochemical hydrogenation becoming more and more mature in recent years, only a few asymmetric electrochemical carboxylation was reported. Based on the own induction ability of the optically active substrate, Orsini et al. [15] once produced chiral 2-phenyl succinic ester derivatives by electrochemical reduction of chiral cinnamic acid derivatives under a CO_2 atmosphere. Another example was asymmetric electrocarboxylation of chiral *N*-(2-bromoacyl) oxazolidin-2-ones [16]. The presence of the Evan's chiral auxiliary permitted the resolution of the mixture of alkylmalonic ester derivatives. However, the optically active substrates should be cautiously chosen only leading to limited products accordingly. Besides, the chiral substrates were usually exorbitant. Thus there exists a need to explore asymmetric electrocarboxylation reaction from low-cost optically inactive prochiral substrates to synthesize more important optical pharmaceutical intermediates. To our best knowledge, however, asymmetric electrochemical carboxylation of common organic compounds such as prochiral aromatic ketones providing corresponding optically active α-hydroxy acids has never been reported.

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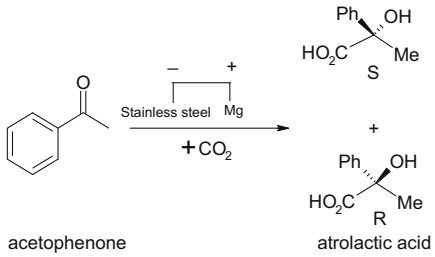

Scheme 1.

The purpose of this work is to establish a novel method of asymmetric electrochemical carboxylation of prochiral acetophenone by the induction of two kinds of chiral alkaloids, cinchonidine (**1**) and cinchonine (**2**) whose structures were shown below in Scheme 3, under neutral and mild conditions (Scheme 1). The optically active 2-phenyl-2-phenylpropionic acid (atrolactic acid) as the main product has been widely used as the anti-inflammatory agents intermediate. It is fortuitous that the alkaloid which is available from natural sources in optically active forms can also be electrosorbed to impart electrocarboxylation asymmetry on the electrode surface. This is in agreement to its electrosorbed role on mercury cathode to induce some asymmetric hydrogenation [6]. Actually, chiral atrolactic acid has been obtained by Schuster et al. [17] via asymmetric organic synthesis. Those authors studied addition of several organozinc reagents to α-keto esters on polymer supported chiral auxiliary. It was a pity that the result of corresponding (R)-2-hydroxy-2-phenylpropanoic acid was not very satisfying with a ratio of S to R enantiomer at 65:35. The α-hydroxyacids were also ever synthesized through enantioselective oxidation of terminal alkenes with AD-mix/TEMPO [18]. However, these methodologies for chiral 2-arylpropanoic acid involved hazardous organic reagents, costly chiral auxiliaries with the whole reaction system usually long and complex.

As regards to be benign to the environment, the cheap and abundant carbon dioxide was used as the possible source of carbon in our work. Carbon dioxide is the largest contributor to the greenhouse effect, which increases the average temperature of the earth to such a value that it may cause catastrophic events. Therefore, great efforts have ever been placed toward the fixation of CO_2 at atmospheric loading since CO_2 can be proposed as C1 building block in organic synthesis. In our previous work, electrochemical fixation of CO_2 providing access to organic compounds including organic carbonates, α-hydroxyacids and carboxylated acids in organic solvents and ionic liquids has been extensively studied and satisfying results were obtained [19–23]. Thereinto, the racemic atrolactic acid was also obtained via symmetrical electrochemical carboxylation of acetophenone in MeCN [23].

For the asymmetric electrochemical hydrogenation induced by the alkaloid in the protic solvent, existed proton source was very helpful to achieve the induction [8]. Likewise, the role of butanol used as the proton-donator was also investigated in our work of asymmetric electrocarboxylation of prochiral acetophenone in aprotic media. In order to elucidate the role of the alkaloid, the electroanalytical experiment was carried out in the three-electrode system. After contrastive analysis of cyclic voltammograms of acetophenone in the absence and presence of cinchonidine and butanol, the possible mechanism of asymmetric induction was proposed.

2. Experimental

2.1. Chemicals

The *N,N*-dimethylformamide (DMF) and acetonitrile (MeCN) of an analytical pure were dried over 4 A molecular sieves prior to use. Tetrabutylammonium iodine (TBAI) and acetophenone were purchased from Sinopharm Chemical Reagent Company and used as received. Tetraethylammonium tetrafluoroborate ($TEABF_4$) was synthesized according to the literature [24]. Two kinds of alkaloids, cinchonidine (CD) and cinchonine (CN) were used as received and preserved in the desiccator.

2.2. Electroanalytical procedure

The electroanalytical experiments were carried out in DMF with 0.1 M $TEABF_4$ as the supporting electrolyte, a glassy carbon as the working electrode (d = 2 mm), a platinum spiral (Pt) as the counter electrode and Ag/AgI/0.1 M TBAI in DMF as the reference electrode. Voltammetric measurements were performed by a CHI 650C electrochemical station (Shanghai Chenhua Instruments Company). Before the experiment, the oxygen was removed by continuous bubbling with nitrogen.

2.3. Typical electrolysis procedure

Current controlled electrolysis was performed in an undivided tank glass cell with cylindrical geometry equipped with a gas inlet and outlet. The volume of the electrolytic solution was 10 mL. The sacrificial magnesium rod anode was placed down the middle of a ringed reticulate stainless steel cathode (area ≈ 10 cm^2). Prior to every experiment, the solution was bubbled with carbon dioxide for 30 min to be saturated. Continuous CO_2 flow was maintained throughout the duration of the whole electrolysis process. A definite concentration of alkaloid was added to the electrolyte solution before the electrolysis started. At the end of each set of experiment, the DMF was distilled off in vacuo, leaving a viscous residue. After acidification with 2 M aqueous HCl, the acidified residue was extracted three times with diethyl ether. Then ether extracts were collected and washed with deionized water and 3 M hydroxide solution in succession. A second acidification and extraction followed by washing with saturated brine and drying over anhydrous $MgSO_4$ gave an almost pure 2-hydroxy-2-phenylpropionic acid.

The apparatus used to supply electric power in preparative scale experiments was a dc regulated power supply QJ 12001X (1 A, 120 V). Identification of products was performed using high performance liquid chromatography (HPLC). An HPLC instrument (Alltech 426 HPLC Pump) equipped with a UV (Linear UVIS 200) detector and chiralpak AD-H column was employed with the eluent of hexane/2-propanol/trifluoroacetic acid (TFA) mixed solution. The enantiomeric excess was calculated from HPLC and the carboxylation yield was based on the starting material.

3. Results and discussion

3.1. Electroanalytical results

In the absence of the alkaloid, the electrochemical behavior of acetophenone in DMF at glassy carbon electrode was studied when the scan range was restricted from −1.0 V to −2.5 V using $TEABF_4$ as the supporting electrolyte. The cyclic voltammograms of acetophenone at varied scan rates from 0.1 to 0.5 V s^{-1} were shown in Fig. 1. Two successive one-electron reduction peaks at −1.81 V and −2.25 V were observed at the scan rate of 0.1 V s^{-1}, which was greatly consistent with some previously studied electroreduction behavior of acetophenone [25]. The first electron uptake yielded a partially stable ketyl radical anion which was further reduced to a dianion at the second more negative potential. By increasing the scan rate, the first reduction peak shifted to more negative place, and the peak current increased concomitantly. Plotting the peak current as a function of square root of scan rate