Journal of The Electrochemical Society, 2020 **167** 045502

The Role of Oxygen in the Electrochemical Reduction of Ethyl 2-(2-(Bromomethyl)phenoxy)acetate at Carbon Cathodes in Dimethylformamide

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Cyclic voltammetry (CV) and controlled-potential electrolysis (CPE) were employed to examine the direct reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate at carbon cathodes in dimethylformamide (DMF) containing tetramethylammonium tetrafluoroborate ($TMABF_4$) as the electrolyte. Cyclic voltammogram of the substrate exhibits a single irreversible cathodic wave with a peak potential of –1.75 V vs SCE, which is characteristic for the reduction of organic halides in aprotic solvents. Bulk electrolyses of ethyl 2-(2-(bromomethyl)phenoxy)acetate were carried out in the absence and presence of oxygen. The product distributions were obtained by gas chromatograph (GC) as well as gas chromatograph coupled to a mass spectrometer (GC−MS). Two bicyclic compounds, ethyl 2,3-dihydro-1-benzofuran-2-carboxylate and ethyl benzofuran-2-carboxylate, were found to be formed in a total yield of more than 40% in the presence of oxygen. The reaction mechanism, in which the oxygen plays a significant role, was proposed and discussed on the basis of this study.
 [DOI: 10.1149/1945-7111/ab72ef]

Manuscript submitted November 30, 2019; revised manuscript received January 21, 2020. Published February 17, 2020.

Many hetero-bicyclic compounds possess a variety of bioactivities and have broad applications in pharmaceuticals.[1–7] Some cyclic and bicyclic compounds have been synthesized by electrochemical means via direct reduction of organic halides involving carbanion intermediates, due to simplicity of the reaction procedures. For example, electrochemical cyclization of allylic α,ω-dibromides was accomplished for the synthesis of cycloalkadienes[8] while reduction of dimethyl α,α'-dibromoalkanedioates at platinum cathodes in DMF could produce dimethyl 1,2-cylcoalkanedicarboxylates in relatively high yields.[9] More interestingly, electrolyses of *o*-trichloroacetylanilides in acetonitrile at selected cathodic potentials would lead to different bicyclic products, depending upon the substituents on the imine group.[10] Nevertheless, electrochemical methods are limited for the synthesis of heterocyclic compounds by direct reduction of organic halides, mostly due to the low product yields. Some haloalkenes can also be reduced to radicals to form different cyclic species.[11,12] However, these processes often require various metal catalysts. A number of electrochemical cyclization reactions using organic halides as the starting materials have been reviewed by Little and Schwaebe.[13]

Benzyl halides and their derivatives can be directly reduced to benzylic anions at various cathodes in aprotic solvents.[14,15] Given a benzyl halide derivative with the appropriate structure and configuration, comparable intramolecular cyclization of carbanion intermediates could take place to make bicyclic products. Recently, our group investigated the reduction of methyl 2-bromomethylbenzoate at carbon cathodes in DMF and found that the corresponding benzylic anions were formed, which would undergo intramolecular cyclization reaction in the presence of water to generate phthalide.[16]

In this study, the direct electrochemical reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate at carbon cathodes in DMF was examined. It was expected that the two-electron reduction of the substrate should cause the cleavage of carbon−bromine bond to give the corresponding benzylic carbanion, which may undergo nucleophilic attack on the carbonyl and the addition-elimination reaction could lead to the formation of a bicyclic compound, chroman-3-one, via intramolecular cyclization (Scheme 1). Nevertheless, the electrolyses of the substrate carried out under inert conditions generated ethyl (2-methylphenoxy)acetate as the major product along with ethyl 2,3-dihydro-1-benzofuran-2-carboxylate in a yield of 20%. Interestingly, in the presence of oxygen, the reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate gave rise to the formation of ethyl benzofuran-2-carboxylate in a yield of more than 40%, in addition to a much smaller amount of ethyl 2,3-dihydro-1-benzofuran-2-carboxylate. The experimental results showed that oxygen played a significant role in the intramolecular cyclization of the substrate initiated by electrogenerated bases. The detailed reaction mechanism was proposed and discussed on the basis of cyclic voltammetry (CV) and controlled-potential electrolysis (CPE) data.

Experimental

Reagents.—Each of the following chemicals was purchased and used as received: DMF (Acros Organics, 99.8%, extra dry over molecular sieves), *o*-cresol (Sigma-Aldrich, >99%), ethyl chloroacetate (Sigma-Aldrich, 99%), ethyl acetate (Fisher, 99.9%), potassium carbonate (EM Science, 99%), 2,2′-azobisisobutyronitrile (AIBN, Sigma-Aldrich, 98%), *N*-bromosuccinimide (NBS, Alfa Aesar, 99%), chloroform (Fisher, 99.9%), anhydrous ethyl ether (Fisher, 99.9%), hexanes (Fisher, >99%), ethyl benzofuran-2-carboxylate (Sigma-Aldrich, 97%), sodium hydroxide (EMD Chemicals, 97%), sodium chloride (VWR, >99%), magnesium sulfate (Alfa Aesar, anhydrous, 99.5%), and *n*-tridecane (Alfa Aesar, 99%). $TMABF_4$ (Sigma-Aldrich, 97%), used as the supporting electrolyte, was stored in a vacuum oven at 60 °C prior to use. DMF was employed as the solvent for electrochemical experiments. All deaeration procedures were carried out with Airgas UHP argon. CD_3Cl (Sigma-Aldrich, 99.8% D) was utilized as the solvent in NMR spectrometry.

Ethyl (2-methylphenoxy)acetate and ethyl 2-(2-(bromomethyl)phenoxy)acetate were synthesized according to the literature methods. Ethyl (2-methylphenoxy)acetate was made from reacting *o*-cresol with ethyl chloroacetate in DMF followed by extraction using ethyl acetate.[17] Further bromination with AIBN and NBS in chloroform[18] gave the crude ethyl 2-(2-(bromomethyl)phenoxy)acetate, which was purified by flash column chromatography using 95% hexanes/5% ethyl ether as the eluent. The identity of each compound was confirmed with the aid of GC–MS (70 eV) and NMR (400 MHz): (a) for ethyl (2-methylphenoxy)acetate, GC–MS: *m/z* 194 (M^+, 66%), 165 (2%), 148 (10%), 121 (74%), 107 (81%), 91 (100%); ^{1}H NMR (CD_3Cl): δ 7.14−6.71 (m, 4H, ArH), 4.64 (s, 2H, $ArOC\underline{H}_2COOEt$), 4.28 (q, 2H, $ArOCH_2COOC\underline{H}_2CH_3$), 2.32 (s, 3H,

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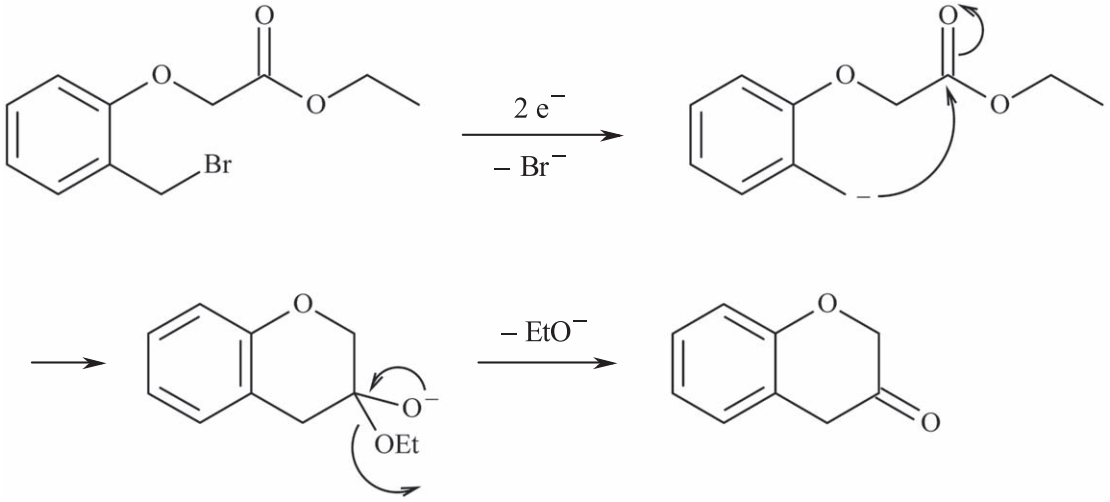


Scheme 1. A possible reaction mechanism for the electrochemical reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate.

$ArC\underline{H}_3$), 1.31 (t, 3H, $ArOCH_2COOCH_2C\underline{H}_3$); (b) for ethyl 2-(2-(bromomethyl)phenoxy)acetate, GC–MS: *m/z* 274 & 272 (M^+, 1%), 193 (100%), 201 & 199 (6%), 147 (2%), 121 (35%), 107 (49%), 91 (66%); ^{1}H NMR (CD_3Cl): δ 7.37−6.75 (m, 4H, Ar$\underline{H}$), 4.71 (s, 2H, $ArC\underline{H}_2Br$), 4.64 (s, 2H, $ArOC\underline{H}_2COOEt$), 4.26 (q, 2H, $ArO\underline{C}H_2COOC\underline{H}_2CH_3$), 1.29 (t, 3H, $ArOCH_2COOCH_2C\underline{H}_3$).

Cells and electrodes.—Cells for CV[19] and CPE[20] have been described previously. For CV experiments, a 3-mm-diameter glassy carbon working electrode (Part No. CHI104, CH Instruments) was used and a platinum wire was employed as the auxiliary electrode. Customized 2.4 cm diameter × 0.4 cm thick reticulated vitreous carbon disks (Duocel RVC 100 PPI, Energy Research and Generation) were used as working cathodes for CPE; these disks were cleaned and handled according to established procedures.[21] The reference electrode consists of a cadmium-saturated mercury amalgam in contact with DMF saturated with both cadmium chloride and sodium chloride[22,23] and it has a potential of −0.76 V vs SCE at 25 °C. Potentials are quoted with respect to SCE in this paper.

Instrumentation.—All CV and CPE experiments were carried out with a CH Instruments model 620B electrochemical analyzer. Electrolysis products were characterized and quantitated with the aid of an Agilent Technologies model 7890B gas chromatograph (GC) equipped with a flame ionization detector (FID) and a model 5977A mass-selective detector (MSD). The analytes were separated on Agilent Technologies 30 m × 0.25 mm capillary columns (HP-5MS) with a stationary phase (0.25 μm thickness) of 5% crosslinked phenylmethylsiloxane. ^{1}H NMR spectra were collected by a Bruker Avance III 400 MHz instrument.

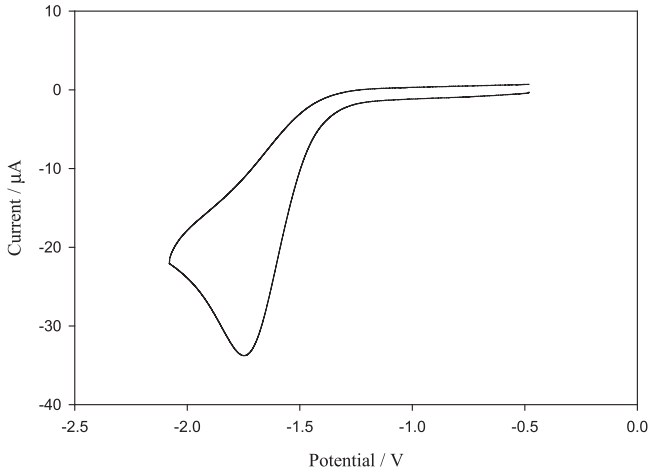


Figure 1. Cyclic voltammogram recorded with a glassy carbon electrode (3-mm-diameter) at 100 mV s^{-1} for 2.4 mM of ethyl 2-(2-(bromomethyl) phenoxy)acetate in DMF containing 0.050 M $TMABF_4$.

Separation, identification, and quantitation of products.—Electrolysis products were separated by GC and their identities were confirmed by comparing gas chromatographic retention times of suspected products with those of authentic compounds as well as by mass spectrometry (GC–MS, 70 eV): (a) for ethyl 2,3-dihydro-1-benzofuran-2-carboxylate, *m/z* 192 (M^+, 42%), 146 (34%), 119 (87%), 118 (46%), 91 (100%); (b) for ethyl benzofuran-2-carboxylate, *m/z* 190 (M^+, 70%), 162 (68%), 145 (100%), 118 (31%), 89 (45%). Quantitation of the products was accomplished by means of GC−FID using an internal standard method, which has been outlined elsewhere.[24] A known amount of *n*-tridecane was added as the electroinactive internal standard to each solution prior to electrolysis. Samples for gas chromatographic analysis were taken from the diethyl ether extracts of the electrolyzed solutions washed with brine. The GC response factors were determined experimentally with respect to *n*-tridecane for the electrolysis products and the product yields reported in this paper represent the absolute percentage of starting material incorporated into a particular species.

Results and Discussion

Cyclic voltammetry and controlled-potential electrolysis.—Figure 1 depicts the cyclic voltammogram for the reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate recorded at a scan rate of 100 mV s^{-1} with a glassy carbon electrode in DMF containing 0.050 M $TMABF_4$. One irreversible cathodic wave with a peak potential of −1.75 V, which corresponds to the two-electron reductive cleavage of the benzylic carbon−bromine bond, can be observed. This reduction peak potential is similar to that for benzyl bromide (−1.80 V).[15] The small difference is likely due to the presence of oxygen atom at *ortho* position in the substrate, which would make it slightly easier to break the benzylic carbon−bromine bond.

CPEs of ethyl 2-(2-(bromomethyl)phenoxy)acetate were first carried out under argon at −1.90 V, at which the electrochemical reduction of the substrate would be a two-electron process to give benzylic carbanion intermediates, according to previous studies.[14,16] Compiled in Table I are coulometric results and product yields for the electrolyses of the substrate at reticulated vitreous carbon cathodes in DMF containing 0.050 M $TMABF_4$ for duplicate experiments. In an inert environment, the reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate generates ethyl (2-methylphenoxy)

Table I. Coulometric data and product distributions for CPEs of ethyl 2-(2-(bromomethyl)phenoxy)acetate at −1.90 V in DMF containing 0.050 M $TMABF_4$ under different environments.

Substrate (mM)	Environment	*n*	Product Distribution (%)		
			1	2	3
11.1	Ar	1.24	60	19	trace
11.9	Ar	1.19	58	20	trace
11.0	O_2	NA[a)]	<1	2	43
11.1	O_2	NA	1	6	43

1 = ethyl (2-methylphenoxy)acetate; **2** = ethyl 2,3-dihydro-1-benzofuran-2-carboxylate; **3** = ethyl benzofuran-2-carboxylate. a) NA = not applicable.

acetate (**1**) and ethyl 2,3-dihydro-1-benzofuran-2-carboxylate (**2**) as the major products in the yield of approximately 60% and 20%, respectively. Trace amounts of ethyl benzofuran-2-carboxylate (**3**) are also found in the products and the coulometric *n* value is about 1.2, indicating that a portion of the substrate is consumed chemically instead of electrochemically.

The formation of ethyl benzofuran-2-carboxylate is likely due to the oxidation of ethyl 2,3-dihydro-1-benzofuran-2-carboxylate. Since usually the electrochemical cell is not perfectly sealed during electrolyses,[16,25,26] it is not surprising that adventitious oxygen may leak into the system and participate in various reactions. For comparison purpose, subsequent CPEs of ethyl 2-(2-(bromomethyl)phenoxy)acetate were conducted with the electrochemical cell opened to air and the results are also presented in Table I. As oxygen could be reduced at −1.90 V as well, the electrolyses were stopped after the cathodic current decayed to a plateau and the coulometric *n* value is not meaningful in this case. The observed product distribution changes significantly and ethyl benzofuran-2-carboxylate becomes the major product in a yield of more than 40%, while the amounts of ethyl 2,3-dihydro-1-benzofuran-2-carboxylate and ethyl (2-methylphenoxy)acetate are much less. In all cases (under either O_2 or Ar with adventitious O_2), the recovery of starting materials is less than 100%, mostly because benzyl bromide derivatives can be easily oxidized by oxygen during electrolyses to the corresponding anionic benzoate derivatives, which have been reported by other studies[16,26] and are not detectable by GC.

Cyclic voltammogram collected for the solution of ethyl 2-(2-(bromomethyl)phenoxy)acetate after electrolysis at −1.90 V under argon shows no electroactive species left while that electrolyzed in the presence of oxygen at −1.90 V exhibits a reversible redox couple at E_{pc} of −2.10 V and E_{pa} of −1.97 V (Fig. 2a). These CV features match well with those for authentic ethyl benzofuran-2-carboxylate, as revealed by Fig. 2b. Since the bicyclic structure in ethyl benzofuran-2-carboxylate is well conjugated, it is not surprising that it can undergo a reversible electrochemical reduction process. The CV results are also in agreement with those from CPE studies that ethyl benzofuran-2-carboxylate is generated when ethyl 2-(2-(bromomethyl)phenoxy)acetate is reduced in the presence of oxygen.

Mechanistic features and discussions.—The acidity of α-hydrogen in aldehydes and ketones is well known due to the high electron-withdrawing property of the carbonyl group and resonance stabilization of the conjugate base. Although the α-hydrogen in esters is typically less acidic than ketones, the presence of another oxygen atom next to the alpha position in the structure of ethyl 2-(2-(bromomethyl)phenoxy)acetate may likely increase that acidity. The deprotonation of the α-hydrogen would become the key step for the intramolecular cyclization reaction of the substrate. As shown in Scheme 2, the direct reduction of ethyl 2-(2-(bromomethyl)phenoxy) acetate under argon should be an overall two-electron process to give the corresponding benzylic anion, which can be protonated by DMF (the solvent, SH) to afford ethyl (2-methylphenoxy)acetate (**1**, reaction 1). Subsequently, the electrogenerated base (S^-) would deprotonate the α-hydrogen of the substrate to form the corresponding anion, which may undergo a S_N2 attack on the carbon−bromine bond to complete intramolecular cyclization and generate ethyl 2,3-dihydro-1-benzofuran-2-carboxylate (**2**, reaction 2). As previously mentioned, adventitious oxygen may further oxidize ethyl 2,3-dihydro-1-benzofuran-2-carboxylate to form trace amounts of ethyl benzofuran-2-carboxylate (**3**, reaction 3). Since a portion of the substrate could be consumed chemically due to reaction 2 and direct oxidation by oxygen, the coulometric *n* value is found to be approximately 1.2 instead of 2.

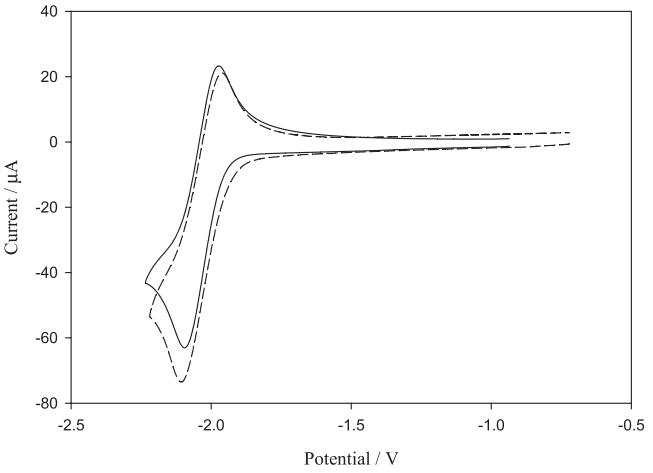
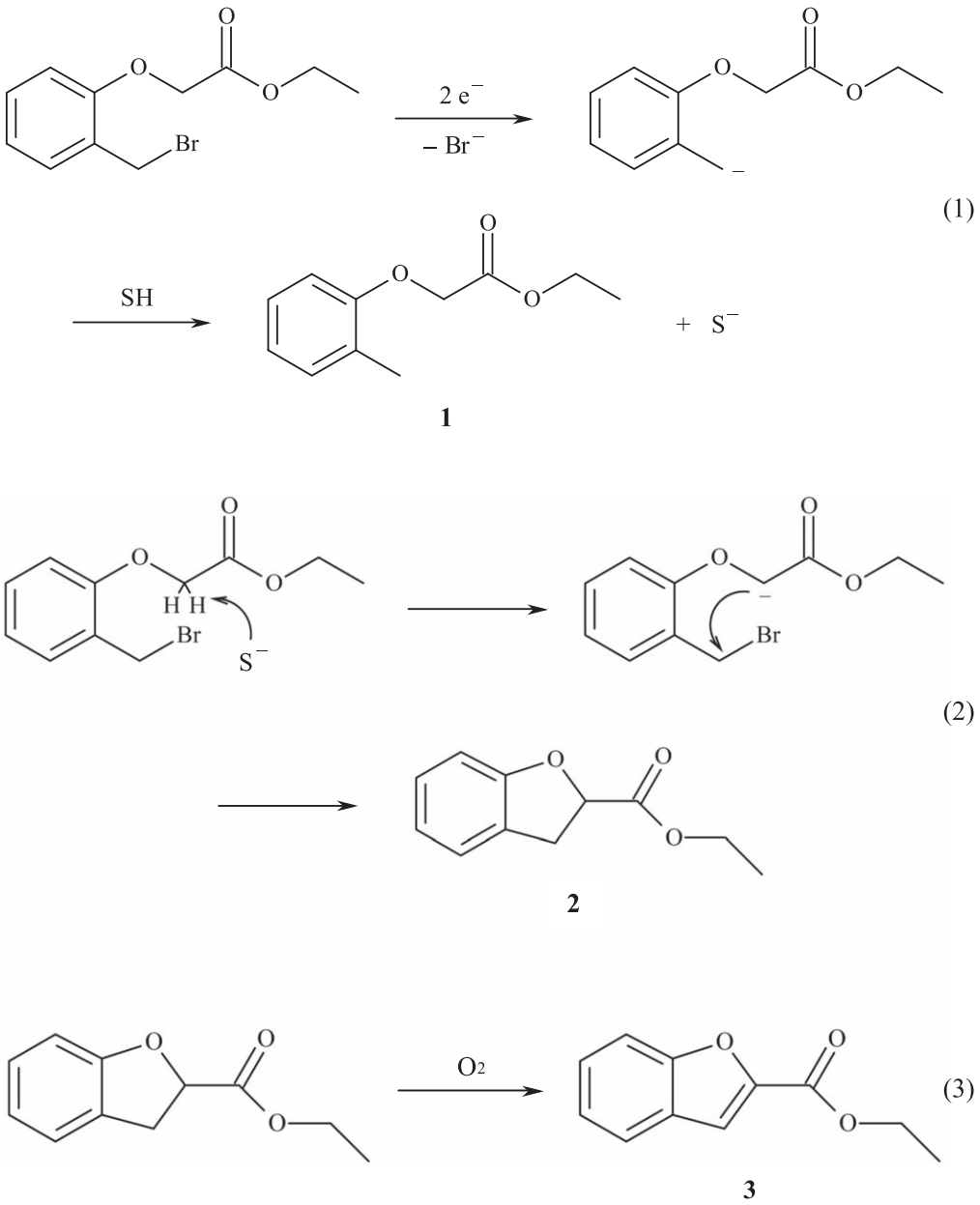


Figure 2. Cyclic voltammograms recorded with a glassy carbon electrode (3-mm-diameter) at 100 mV s^{-1} in DMF containing 0.050 M $TMABF_4$ for: (a) solution electrolyzed in the presence of oxygen at −1.90 V initially containing 11 mM of ethyl 2-(2-(bromomethyl)phenoxy)acetate (dash line) and (b) 3.8 mM of ethyl benzofuran-2-carboxylate (solid line).

When the electrolysis of ethyl 2-(2-(bromomethyl)phenoxy) acetate is carried out in the presence of oxygen (estimated to be between 2 and 3 mM by CV), the molecular oxygen can also undergo successive one-electron reductions to produce superoxide anion (reaction 4) and peroxide dianion (reaction 5, which is unlikely to take place in this study due to the much more negative reduction potential). The superoxide anion, as an electrogenerated base, has been proven to be a very powerful nucleophile in non-aqueous media[27] and it can even deprotonate water in DMF to form hydroperoxyl radical (reaction 6). Thus, it is expected that the deprotonation of the α-hydrogen in ethyl 2-(2-(bromomethyl)phenoxy)acetate by superoxide anion, similar to reaction 2, would become more predominant. Ultimately, the final product yield of ethyl benzofuran-2-carboxylate increases dramatically. Meanwhile, the direct reduction of substrate becomes insignificant, most likely due to the faster diffusion of oxygen molecule to the electrode surface.

$$O_2 + e^- \rightarrow O_2^{\cdot -} \quad [4]$$

$$O_2^{\cdot -} + e^- \rightarrow O_2^{2-} \quad [5]$$



Scheme 2. Proposed reaction mechanism for the electrochemical reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate.

$$O_2^{\cdot-} + H_2O \rightarrow HO_{2\cdot} + OH^- \quad [6]$$

To further confirm the reaction mechanism, solutions of ethyl 2-(2-(bromomethyl)phenoxy)acetate were electrolyzed at −1.20 V in the presence of oxygen. At this potential, the oxygen will be reduced to superoxide anion while the substrate is intact. The electrolyses products include both ethyl 2,3-dihydro-1-benzofuran-2-carboxylate and ethyl benzofuran-2-carboxylate, in the yield of 5% and 31%, respectively. The results show clearly that superoxide anion by itself, as the electrogenerated base from the reduction of oxygen, can initiate the intramolecular cyclization reaction of the substrate to give the hetero-bicyclic products. Another two compounds were also found by GC–MS among the products and both have a molecular ion peak at *m*/*z* 208 with similar retention times, indicating an extra mass of 18 is incorporated into the structure of ethyl benzofuran-2-carboxylate to form two isomers. It is possible for the alkene double bond in ethyl benzofuran-2-carboxylate to undergo slow hydrolysis with residual water in DMF to generate these two compounds, which have a combined yield of approximately 9%.

Conclusions

In summary, the electrochemical reduction of ethyl 2-(2-(bromomethyl)phenoxy)acetate at –1.90 V in DMF undergoes carbanion pathways. However, in the presence of oxygen, the reduction will cause the formation of superoxide anion which can greatly enhance the deprotonation of α-hydrogen in the substrate and chemically generate the bicyclic products in considerably higher yields. The study demonstrates that the reduction of oxygen could play a significant role in the electrochemical synthesis of benzofuran derivatives, which possess various bioactivities[28–32] including as antidepressants and anxiolytics.[33]

Acknowledgments

This work is financially supported by the National Science Foundation (Grant No. CHE-1757843). The authors would also thank Dr. Alexander Kornienko's research group for the help with flash column chromatography.

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