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Electrochemical Benzylic Oxidation of C-H Bonds

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Oxidized products have become increasingly valuable as building blocks for a wide variety of different processes and fine chemistry, especially in the benzylic position. We report herein a sustainable protocol for this transformation through C-H functionalization and is performed using electrochemistry as the main power source and *tert*-butyl hydroperoxide as the radical source for the C-H abstraction. The temperature conditions reported here do not increase above 50^{O}C and use an aqueous-based medium. A broad substrate scope is explored, along with bioactive molecules, to give comparable and increased product yields when compared to prior reported literature without the use of electrochemistry.

Introduction

Over the past few decades, the late-stage oxidation of organic molecules via direct C-H activation has attracted substantial interest among synthetic organic chemists.[1-6] Methods using environmentally friendly, cost-effective reagents and solvents for transformations, especially regarding complex molecules, have been in high demand.[7-9] Among the many C-H functionalization processes,[10] the direct benzylic oxidation of alkylarenes and heteroarenes is an important protocol to provide the corresponding ketone compounds for uses as key intermediates with a variety of commercial applications, such as the synthesis of pharmaceuticals, flavor compounds, polyester fibers, and agrochemicals.[11-12]

Although numerous methods have been developed for the benzylic oxidation of C-H bonds, most of these methods suffer from limitations. Traditional benzylic oxidation methods require the use of stoichiometric amounts of toxic reagents, including Cr(VI),[13] Mn(IV)[14] and Se(IV),[15-16] and can also be achieved by using transition metal catalysts, such as Bi,[17] Rh,[18] Ru,[19] Mn,[20] Co,[21] and Pd[22] in combination with excess amounts of oxidants. However, most of these transition metal catalyzed benzylic oxidation reactions do not tolerate heterocycles due to the strong coordination of heteroatoms to the metal catalysts. Furthermore, a relatively high temperature is usually required to initiate this transformation due to the inertness of benzylic C-H bonds[23-24] Other studies of benzylic oxidation have also suffered from a narrow substrate scope.[25-26] Due to the importance of benzylic C-H oxidation reactions and the limitation of current protocols, a general method that can selectively oxidize benzylic C-H bonds of substrates bearing various heterocycles using environmentally friendly solvents and reagents is highly desirable.

The use of electrochemistry in organic chemistry has provided new avenues for synthetic transformation outside the ability of the traditional methods. During electrochemistry, organic molecules are able to gain or lose electrons upon interaction with the electrodes, thus easily producing reactive reaction intermediates. Consequently, electrochemical methods are inherently selective and sustainable for the functionalization of organic molecules. Therefore, electrochemical approaches are conceivably able to overcome these limitations that their traditional counterparts have and provide “greener” ways for direct benzylic oxidation.

The past few years have witnessed the resurrection of electrochemistry in organic synthesis,[27-38] especially electrochemical C-H activation.[39-41] For example, the Baran group has reported efficient and scalable protocols for allylic C-H oxidation[39] and, more recently, unactivated $C_{sp}{}^{3}$-H bonds through electrochemical methods, with the use of organic mediators.[40] Stahl *et al*. have also recently developed electrochemical benzylic oxidation reaction using NHPI as the mediator[41] in organic solvents, using pyridinium perchlorate as the electrolyte and a high temperature of 100°C. Compared to traditional synthetic methods, electrochemical methods generally have higher overall energy efficiency and offers the ability for milder conditions as well as the generation of less toxic waste.[42-44] Electrochemistry also allows the regulation of the chemoselectivity by controlling the applied current or potential.

Since one of our long-term goals is to develop efficient electrochemical approaches for organic synthesis and energy catalysis,[45] we report herein an electrochemical method for direct oxidation of benzylic C-H bonds via the formation of the *tert*-butyl peroxyl radical in aqueous conditions using an inexpensive electrolyte and at relatively mild temperatures. Substrates containing common heterocycles, such as pyridines,

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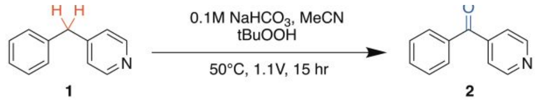
Electronic Supplementary Information (ESI) available: General reaction procedures, photographic guides of divided and undivided cells, supplemental figures and NMR spectroscopic identification of products. See DOI: 10.1039/x0xx00000x benzimidazoles and thiophenes are explored and their benzylic ketone products are obtained in modest-to-excellent yields.

Results and Discussion

Peroxyl radicals have long been known to be reactive and capable of abstracting moderately strong C-H bonds,[46-50] as the O-H BDE of tBuOOH is approximately 89 kcal/mol.[51] Traditional methods for the generation of peroxyl radicals involve transition metal initiation and thermal heating.[50,52-53] We hypothesize that the use of electrochemistry could serve as alternate methods for the generation of such a reactive species, allowing the C-H abstraction to occur in a controllable fashion. To test this hypothesis, we studied the electrochemical oxidation of a model substrate, 4-benzylpyridine, **1**, to phenyl-4-pyridinyl-methanone, **2**, using *tert*-butyl hydroperoxide as the oxidant in a divided cell (Table 1). The first condition optimized was the applied voltage where four different voltages were tested: 0.7-1.0 V (entry 2-5) and compared to 1.1V (entry 1, 64%) used in the development stage. None of the lower voltages afforded a higher yield, (49%, 53%, 59%, 59%, respectively) when compared to 1.1V and any voltages above 1.1V were not explored in keeping with our goal of making this reaction green and environmentally friendly, as well as the risk and possibility of over oxidation. The amount of *t*BuOOH that could be used was also explored during the development, as ratios of 0.5, 1, 2 and 3 equivalents of *t*BuOOH-to-substrate were explored (entries 6-9) and compared to 6 equivalents (entry 1, 64%). The smaller ratios did effect the overall product yield (27%, 47%, 60%, 62%, respectively, thus 6 equivalents were chosen as the desired ratio.

Table 1 Optimized Reaction Conditions[a]

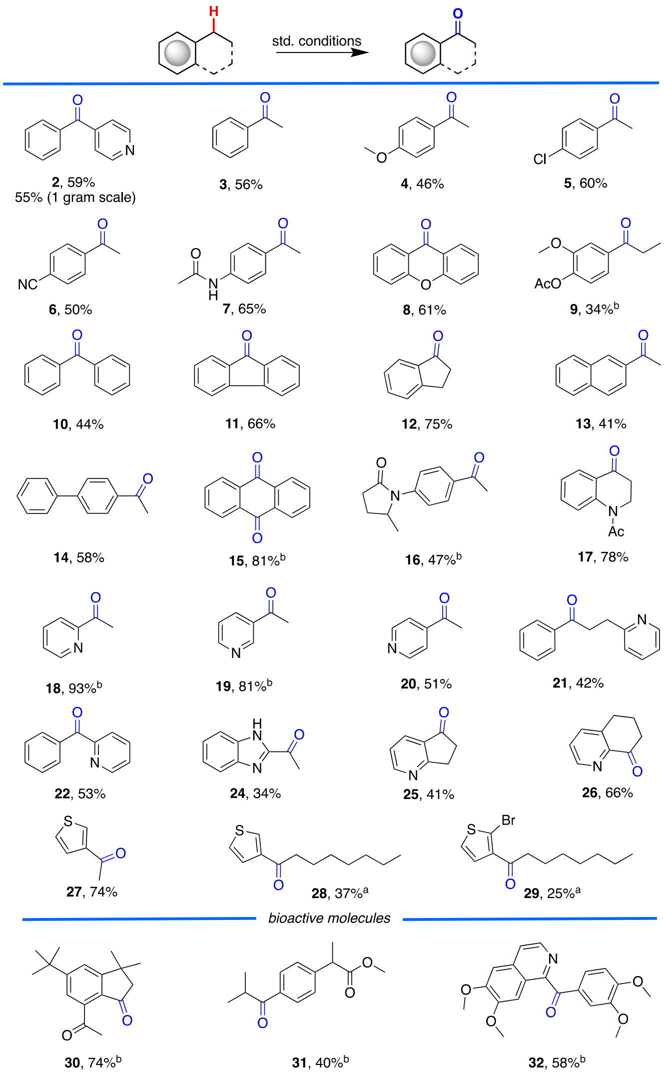


Entry	tBuOOH (equivs)	Potential (V)[b]	Temperature °C	Yield (%)[c]
1	**6**	**1.1V**	**50°C**	**64%**
2	6	1.0V	50°C	59%
3	6	0.9V	50°C	59%
4	6	0.8V	50°C	53%
5	6	0.7V	50°C	49%
6	3	1.1V	50°C	62%
7	2	1.1V	50°C	60%
8	1	1.1V	50°C	47%
9	0.5	1.1V	50°C	27%

[a]Reactions were run at 2 mmol scale using RVC working and counter electrodes; [b]*vs* Ag/AgCl reference electrode. [c]Yields are determined by GC/MS using dodecane as the internal standard.

Additionally, conversion to acetophenone, **3** (Fig. S1), was tested and at pH = 8, a $NaHCO_3$ solution in a combination of CH_3CN and water was found to be the optimal electrolyte while subsequent pHs with different electrolytes were found to be detrimental to the oxygenation reaction (entries 4-7). The electrochemical oxidation reaction can also be conducted at room temperature albeit with a lower yield (entry 3) and furthermore, trace amounts of products were observed when the reactions were conducted in the absence of *tert*-butyl hydroperoxide or without electricity (entry 1 and 2).

There were also a few other conditions taken into account during the optimization that included the type of electrode used and the type of reaction cell. All of the products and yields presented here were obtained using 100 PPI Reticulated Vitreous Carbon (RVC) electrodes as both the working and counter electrode. Other working electrodes tested included glassy carbon and graphite, with platinum counter electrodes. However, not only were product yields considerably lower with the use of the different types of electrodes, but also the use of a precious metal, such as platinum, does not support our goal of being sustainable. Additionally, much lower yields were observed when the reactions were conducted in an un-divided cell. For example, the yield drops to 42 % when the oxidation of **1** was conducted in an undivided cell. (Photographic guides for the set-up of both divided and undivided cells are located in the SI.)



Scheme 1 Substrate scope of the electrochemical benzylic C-H oxidation reaction. Isolated yields. [a]Reactions were run on 2 mmol scale with 1:1 $NaHCO_3$:MeCN. [b]Reactions were run on 0.5 mmol scale with 1:1 $NaHCO_3$:MeCN

With the optimized reaction conditions in hand, we then explored the substrate scope of this benzylic C-H oxidation reaction, with a particular focus on pharmaceutically relevant structural features (Scheme 1). In general, compounds containing different heterocycles, **2, 4-10**, are well tolerated with moderate-to-excellent yields for all oxidized products. Molecules containing different electron-donating, **11** and **12**, and electron-withdrawing groups, **13** and **14**, in the *para* position to the benzylic C-H were all successfully oxidized. One result of particular note is in relation to the size of the cyclohexane ring, when fused to a pyridine, and where the oxidation, and thus the ketone, would be observed. With a cyclopentane ring, **9**, the ketone was observed on the benzylic carbon opposite from the nitrogen within the pyridine. However, when a cyclohexane ring is present, **10**, the ketone is observed on the benzylic carbon directly adjacent to the nitrogen in the pyridine. (Spectral data is provided in the Supplemental Information.) This electrochemical benzylic oxidation reaction has also been applied for the late-stage functionalization of bioactive molecules. For example, celestolide **29,** ibuprofen methyl ester **30**, and papaverine **31** were able to be oxidized at the benzylic position without affecting other functional groups found in the molecules with synthetic useful yields. Finally, when the oxidation of **1** was conducted on a gram scale, compound **2** was obtained at a similar yield (55%), thereby supporting the possibility of large-scale use.

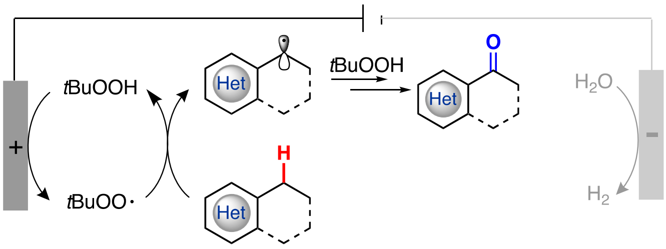
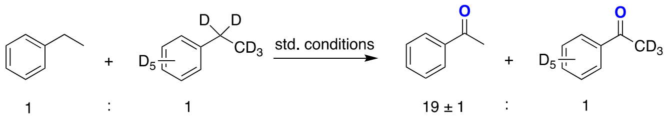


Fig. 1 Proposed Mechanism for the *t*BuOOH-mediated electrochemical oxidation of benzylic C-H bonds.

A possible mechanism (Fig. 1) can be proposed where the electrochemical oxidation of tBuOOH on the anode results in the formation of a *tert*-butyl peroxyl radical, which performs the C-H abstraction in the benzylic position of the substrate, thereby resulting the formation a benzylic radical. This radical then reacts with *t*BuOOH yielding the corresponding oxygenated products with *tert*-butanol as a side product. A few studies were then conducted to understand the mechanism of this reaction, especially the involvement of the *tert*-butyl peroxyl radical.

To further investigate the probability of this proposed mechanism, a kinetic isotope effect study was performed under standard reaction conditions with **1** and its deuterated isotopolgue (d^{10}- ethyl benzene). The k_H/k_D was found to be 19.1 ± 1 (Scheme 2) and the magnitude of this KIE suggests that the C-H abstraction is the rate-limiting step in the mechanism, which supports our proposed mechanism. The k_H/k_D reported here matches closely to the isotope effect reported by Howard et al. of 14 ± 5 for the C-H abstraction by a *tert*-butyl peroxyl radical.[54]



Scheme 2 Kinetic Isotope Effect Study using a mixture of ethylbenzene and ethylbenzene-d$_{10}$

Cyclic voltammetry was also performed to understand the electrochemical behavior of *t*BuOOH (Fig. 2 and Fig. S2). When the system only contains the solvents (blue line) and ethylbenzene (green line), near zero current is observed until approximately 1.15V, where water oxidation occurs. Interestingly, in the presence of *t*BuOOH, oxidation current was observed starting at ~0.7 V *vs* Ag/AgCl (red and yellow line). The irreversibility of the CV suggests the formation of a reactive species, presumably the *tert*-butyl peroxyl radical.

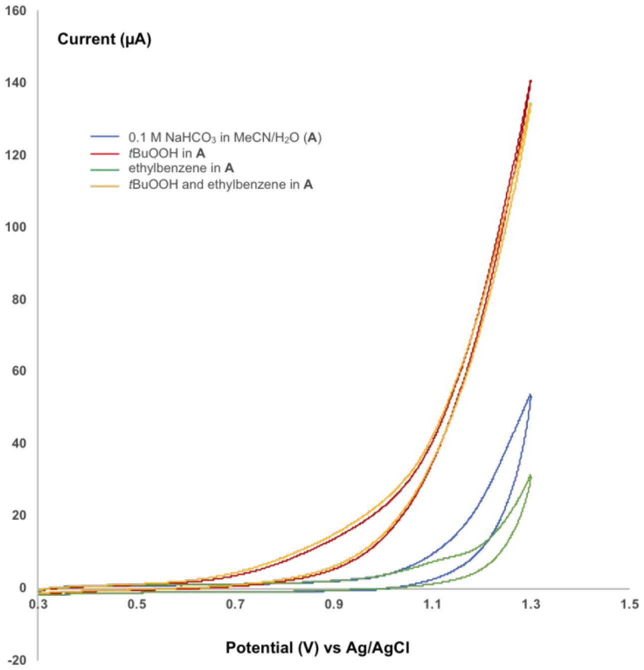


Fig. 2 Cyclic Voltammetry experiments. Glassy carbon as the working electrode; Scan rate: 100mV/s; 1mM tBuOOH and 0.17 mM ethylbenzne

A comparison of the optimized electrochemical reaction conditions reported here with previously reported benzylic oxidization, which used heavy metals and other conditions, is shown in Table S1. In these reported methods, the use of heavy metal oxidants such as iron chloride,[55] chromium (VI) oxide,[56] cobalt (II) perchlorate,[57] bismuth,[17] Co/NHPI-mediated[41] and provided yields that either underperformed or were comparable to the yields obtained through this method. This comparison not only highlights the potential utility of the new conditions discussed here by providing comparable yields, but also providing a more sustainable way to perform this transformation. Additionally, through the use of an aqueous solvent, a non-toxic electrolyte, sodium bicarbonate, was able to be used, thus decreasing the carbon footprint that this method would leave.

Conclusions

The results described here show the development of a general method for benzylic C-H activation and oxidation. This reaction is performed using mild reaction temperatures, aqueous-based solvents and electrochemistry to initiate formation of the *tert*-butyl peroxyl radical to perform the C-H activation step, which is shown as the rate-limiting step in the proposed mechanism based on its KIE value. The broadness of the substrate scope highlights the practicality of this method to be adapted and employed for large-scale synthesis. Additionally, by showing the effectiveness of this method on bioactive molecules, this method may be adaptable by medicinal chemists to generate oxidized analogues and allow for the evaluation in a clinical setting.

Conflicts of interest

There are no conflicts to declare

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