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ANODIC ELECTROCHEMISTRY AND THE USE OF A 6-VOLT LANTERN BATTERY: A SIMPLE METHOD FOR ATTEMPTING ELECTROCHEMICALLY BASED SYNTHETIC TRANSFORMATIONS

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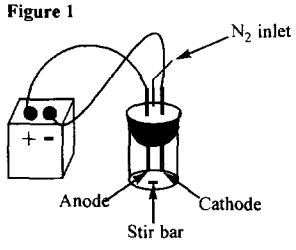
Abstract: A series of electrochemical transformations have been accomplished using a 6-volt lantern battery as a power supply. The reactions included both intramolecular anodic olefin coupling reactions and an anodic amide oxidation. In all cases, the reactions afforded preparatively useful amounts of product and demonstrated that electrochemical synthetic methods can be readily attempted without the need for specialized equipment.

Organic electrochemistry has long held promise as a method for organic synthesis.[1] This promise has been based upon the possibilities electrochemistry displays for oxidizing and reducing molecules at preset potentials and for generating reactive radical ion intermediates under neutral conditions. Yet while numerous synthetic methods have been developed,[2] organic electrochemistry has failed to excite the imagination of the majority of synthetic organic chemists. One of the principal reasons for this lack of interest has been the perception that electrochemical reactions require the use of expensive, specialized equipment. If such equipment is required, then it is simply not practical for a chemist to try an electrochemical step as part of a total synthesis effort. This is especially true if the electrochemical step is only one of several alternatives for accomplishing a given transformation. But is the use of specialized equipment really necessary for attempting an electrochemical reaction? For years proponents of electroorganic synthesis have argued that the specialized equipment is not necessary.[3] However, the vast majority of electrochemical synthetic methods reported (including ours) make use of commercial power supplies, potentiostats, and coulometers. While many of these electrochemical setups are reasonably priced,[4] most synthetic organic chemistry groups do not have such equipment. For this reason, we began an effort to identify simple, cost effective methods for initiating the electrochemical reactions that we have been studying. We report here that both intramolecular anodic olefin coupling reactions[5] and anodic amide oxidations[6] can be accomplished with the use of a 6-volt lantern battery as a power supply.[7] Other than the electrodes, no other electrochemical equipment was required.

Figure 1

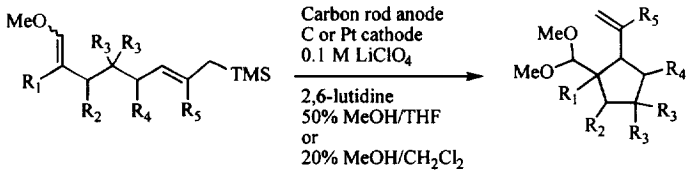


The setup for the reactions involved the use of the 6-volt lantern battery, two wires, and a vial fitted with a two-holed rubber stopper (Figure 1). The electrodes (normally carbon rods or a small piece of platinum wire sealed into a glass tube)[7] were passed through the holes in the rubber stopper. When a reticulated vitreous carbon (RVC) anode was needed, one end of a carbon

rod anode was sharpened in a pencil sharpener, the carbon rod pushed through one hole of the rubber stopper, and then the sharpened end pushed into a small piece of the RVC foam. In addition to the electrodes, a syringe needle was pushed through the stopper for use as a nitrogen inlet. The reactions were stirred using a magnetic stir bar. All of the reactions were monitored by TLC for the loss of starting material.

Initially, a trio of intramolecular anodic olefin coupling reactions was selected for study (Scheme 1). These

Scheme 1



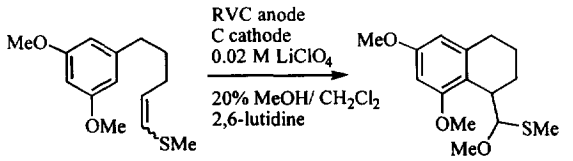
1a. R_3=R_5 = Me; R_1=R_2=R_4 = H
1b. R_4 = OTBDMS; R_5 = Me; R_1=R_2=R_3 = H
1c. R_1=R_2= -$(CH_2)_4$-; R_3=R_4=R_5 = H

2a. 78%
2b. 68%
2c. 51%

reactions were selected because they were known to smoothly afford cyclized products at low voltages ($E_{p/2}$ = +1.4 V vs. Ag/AgCl) and because there was little risk of overoxidizing the product. Several items concerning these reactions deserve comment. First, both the identity and stereochemistry of the products from these reactions were identical to those reported previously.[8] For the oxidation of **1a**, the reaction led to **2a** as a mixture of stereoisomers about the newly formed bond. For **1b**, the reaction led to **2b** as a pair of diastereomers that were both trans with respect to the alkoxy (R_4) and vinyl substituents. For **1c**, the reaction led to **2c** as a pair of diastereomers that both possesed a cis-ring juncture. Second, the reaction conditions used for all three oxidations (solvent, electrolyte, choice of electrodes) were nearly identical to those reported earlier for the procedures using conventional electrochemical equipment. Two minor changes were made. For all three reactions, a carbon rod anode was used in place of an RVC anode, and 2,6-lutidine was used as a proton scavanger in place of potassium carbonate. Finally, the yields of the reactions were not optimized. Instead, the reactions reported in Scheme 1 reflect a direct transposition of the conditions reported for the oxidations using conventional electrochemical equipment into the cell employing the battery as the power supply. While not quite as high as in the previous experiments (using conventional preparative electrolysis equipment, the yields for the oxidations orginating from **1a**, **1b**, and **1c** were 84%, 83%, and 70% respectively), it was clear that the battery experiments provided an excellent appraisal of the overall utility of the oxidative cyclization reactions.

Having succesfully determined that the 6-volt battery could initiate oxidative cyclization reactions, we turned our attention to a more sensitive cyclization reaction (Scheme 2). In the case of substrate **3**, the product generated (**4**) would also be susceptible to oxidation.[1b] In the past, overoxidation of the product was minimized with the use of a vinylsulfide initiating group and the use of very low current densities. The low current densities were accomplished by using a RVC anode and a small flow of current (11 mA for a 1.7 mmol scale reaction). These conditions served to optimize the selectivity of the constant current electrolysis by allowing for a high percentage of the starting material to be converted to product before the potential at the anode surface began to climb.

Scheme 2

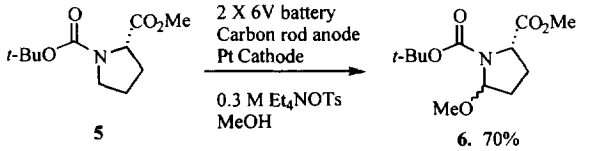


3 4. 57% (10% rec. SM)

A 72% yield of **4** was obtained without the formation of any products from overoxidation. Could such a careful electrolysis be mimicked with the use of a battery that forced a 6-volt potential drop accross the cell? An initial attempt at the oxidation using conditions identical to that reported previously (RVC anode, carbon cathode, 0.2 M $LiClO_4$ in 20% $MeOH/CH_2Cl_2$ electrolyte solution, and 2,6-lutidine as a proton scavanger)[1b] was not promising. The reaction was messy, clearly formed products from overoxidation, and led to only a 30% isolated yield of **4**. Fortunately, a ten-fold reduction in the concentration of the electrolyte led to a large improvement in the reaction. Using a 0.02 M solution of $LiClO_4$ in 20% $MeOH/CH_2Cl_2$, the reaction led to a 57% isolated yield of **4** along with a 10% yield of recovered starting material. No product from overoxidation was observed in the 300 MHz ^{1}H-NMR spectrum of the crude reaction mixture. The improvement in this reaction was attributed to a decrease in the current density at the anode surface. The use of a lower concentration of electrolyte led to an increase in the resistance of the cell and therefore a decrease in the total current flow. In short, even though the potential drop across the cell had to be a constant 6-volts due to the use of the battery, the current density at the electrode surface could be varied by controlling the electrolyte concentration. The use of the battery proved to be compatible with an intramolecular anodic olefin coupling reaction that was sensitive to overoxidation.

The anodic oxidation of *t*-Boc protected proline methyl ester (**5**) was also examined (Scheme 3). This

Scheme 3



5 6. 70%

reaction was selected because the functionalization of proline derivatives has played a key role in our construction of a number of conformationally restricted peptide analogs.[9] In addition, the oxidation of a carbamate represented a key challenge for the use of a battery as a power supply. Oxidations of carbamates ($E_{p/2}$ *ca.* +1.95 V vs. Ag/AgCl) and amides are often more difficult to accomplish than enol ether oxidations. In many cases, oxidation of the solvent competes with oxidation of a carbamate or amide substrate. Carbamate and amide oxidations often utilize high current densities in order to improve the efficiency of the process. It was not clear that a 6-volt battery would be a strong enough power supply to mimic these conditions. In fact, our first attempt to accomplish the oxidation of **5** with a 6-volt battery was not succesful. Only starting material was recoverd. With this in mind, two 6-volt batteries were hooked in series and then spliced into the reaction setup. This doubled the potential drop across the cell to 12-

volts. Using these conditions, the oxidation of **5** proceeded smoothly, and a 70% isolated yield of the methoxylated product **6** was obtained.

In conclusion, the feasibility of using a 6-volt lantern battery as a power supply for accomplishing electrochemically based synthetic methods was examined. The battery proved useful for initiating both intramolecular anodic olefin coupling reactions and anodic amide oxidations. Reactions requiring either low or high current densities could be conducted. The development of these electrolysis conditions should give synthetic chemists who don't have preparative electrochemical setups an opportunity to explore the utility of electrochemically based synthetic methods.

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3. See for example reference 1a page 216.
4. The preparative electrochemical setup we normally use is available from The Electrosynthesis Company, Inc. for *ca.* $2,000.
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7. A RAYOVAC model number 918, 6-volt lantern battery was used. Carbon electrodes were purchased from The Electrosynthesis Company, Inc. The platinum auxiliary electrode used for the oxidation of **1b** and **1c** can be purchased from the Electrosynthesis Company, Inc. or made easily from a glass tube, a short piece of platinum wire, a longer piece of copper wire, and some solder. In these reactions, little difference has been seen between the use of a either a carbon or platinum auxiliary electrode.
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