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An experimentalist's guide to electrosynthesis: the Shono oxidation

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ABSTRACT

Electrosynthesis is a powerful method to functionalise organic molecules without the need to use chemical reagents or protecting groups, yet it is not widely used in synthesis. In this study, we investigated the Shono oxidation of a tertiary amide (electrochemical functionalisation of a C–H bond adjacent to an amide nitrogen atom), demonstrating the value of performing cyclic voltammetry, varying voltage and charge per mole, selection of electrolyte and electrode material. We demystify the process to demonstrate a simple relationship between oxidation potential, and charge transfer required, which affords a high conversion to the desired alpha-methoxylated product using an undivided experimental cell.

Introduction

Electrochemistry meets all the criteria of green, sustainable chemistry for organic synthesis[1] and can be used for protecting group-free synthesis, CH activation chemistry and umpolung reaction centres, generating complex reaction products from simple starting materials.[2] In our laboratory, our interest has focused on the Shono oxidation,[3] which has the remarkable ability to transform C–H groups adjacent to tertiary amides via an *N*-acyl iminium intermediate, to C–X bonds, for example, C–O, C–C bonds. In light of the current interest in C–H activation chemistry,[4] we sought to demonstrate how this seminal reaction can be performed in a standard University laboratory set-up. In our recent review of the Shono reaction[5] we identified a paucity of literature on how to get the best results from this reaction. This can be off-putting to those organic chemists considering performing reactions using electrochemistry. The goal of this article is to demonstrate how a simple screen of three parameters can increase the likelihood of success in electrosynthesis, and make this exciting, emerging and enabling branch of synthesis more widely used by the organic community.

Results and discussion

We selected a simple tertiary amide **1** that meets the criteria of the Shono oxidation, yet has not been systematically investigated as far as we know in electrosynthesis. Although Eberson et al. reported[6] a one-off galvanostatic route to **2** in 1979, no spectra or characterisation was reported. This method required a high surface area graphitic rod (800 cm^2) and a stainless steel cathode placed 1 mm apart to reduce resistance. An applied voltage of between 20 and 26 V and a current of 50 A was passed through a solution of **1** in methanol with 0.01 M Bu_4NBF_4 as the electrolyte to afford **2** in a current yield of 63% and material yield of 76%. Clearly, this high voltage and current is not attainable in most chemical laboratories and the choice of reaction conditions was not understood nor justified.

The goal of this study will be to show how model compound **1** can be anodically (electrochemical oxidation) methoxylated to give **2** (Scheme 1) using a simple parameter screen and enabling this sustainable chemistry to be used in synthetic labs, more generally. For comparison, Weinreb and co-workers reported an alternative synthetic route[7] for the preparation of **2** from **3** using a chemical oxidant and transition metal co-additive (Scheme 1). Of note, Weinreb's route suffered from a dealkylation side reaction due to adventitious water.

Amide **1** was prepared in 85% yield using previously reported chemistry.[8] Prior to performing electrosynthesis we wished to determine the oxidation potential of **1** in methanol using cyclic voltammetry, however the oxidation peak for **1** to **2** was masked

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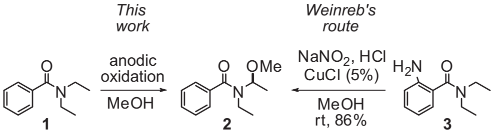

Scheme 1. Anodic oxidative methoxylation of **1** to **2** and Weinreb's route to **2** from **3**.

by the oxidation of the solvent beginning at +1.6 V (cyclic voltammograms are located in ESI S1–S4). Therefore, we switched to a solvent with a wider potential window, namely, acetonitrile containing 10% methanol as the co-solvent. Using the relatively cheap electrode material with a large electrode surface area, reticulated vitreous carbon (RVC), as both the working electrode and counter electrode and a silver wire as the reference (see ESI S5 for an example electrode set-up) we obtained typical cyclic voltammograms that exhibited a distinct oxidation peak for **1** which was well resolved prior to the onset of solvent breakdown (Fig. 1).

A scan rate study, as shown in Figure 1b, is a useful voltammetric approach to try and understand the process in hand. In this case, the voltammetry is conducted over a range of scan rates. A plot of peak current (I_p) against scan rate υ, and an additional plot of peak current against the square-root of the scan rate allows one to determine if the process is diffusional (since $I_p \sim \upsilon^{1/2}$) or adsorbed in nature ($I_p \sim \upsilon$) where the plot with the most linear response indicates the dominant process.[9] In our case, analysis of the data presented in Figure 1 showed a linear response ($I_p/A = 5.16 \times 10^{-4}\ A/(\upsilon s^{-1})^{1/2} + 4.34 \times 10^{-6} A;\ N = 5;\ R^2 = 0.999$) indicating a diffusional process. Therefore, due to the unique voltammetric signature presented in Figure 1, the appropriate equation for the case of a fully irreversible electron transfer process (not stirred) the Randles–Ševčik equation is as follows:

$$I_p = \pm 0.496(\alpha n')nFAC(FD\upsilon/RT)^{1/2}$$

where A is the geometric area of the electrode (cm^2), α is the transfer coefficient (usually assumed to be close to 0.5), n is the total number of electrons transferred per molecule in the electrochemical process, n' is the number of electrons transferred before the rate determining step, F is the Faraday constant, R is the universal gas constant and T is the temperature at which the electrochemical process is performed. This equation clearly shows that temperature, voltammetric scan rate, the diffusion coefficient and concentration of the analyte under investigation and the electrode area all significantly affect the observed voltammetric signal (I_p). Note that current density (A/m^2) is frequently mentioned in various publications, which from inspection of the units is simply the current (A) divided by the electrode area (m^2), and allows a comparison between experimentalists and represents the current density of the active electrode surface.

In an electrosynthetic experiment, the potential needs to be fixed at a suitable value chosen by the experimentalist. In the literature, we sometimes find cyclic voltammetry exhibits a useful voltammetric signal at +1.5V but then the electrosynthesis is held at an extreme potential of +4.5 V[10] or not using the oxidation potential to enhance selectivity.[11] *The question is why?* In addition, how was this value deduced and what are the implications? If we return to our exemplar Shono electrosynthesis, a key experiment to undertake is a blank voltammogram (Fig. 1a). This is required to understand the exact solvent window (the point in which there is no solvent breakdown) and to ensure that the voltammetric peak of interest is not located in this region, since in addition to the main desired electrochemical process underway; the degradation of the solvent will also occur thus convoluting the electrochemical and electrosynthetic processes (see later). Note the second peak in the voltammogram presented in Figure 1b was due to the electrochemical oxidation of the electrolyte as was evident from comparison of the blank voltammogram (Fig. 1a). With the knowledge that **1** cleanly oxidises at +1.65 V based on the cyclic voltammetry shown in Figure 1b with no interference from solvent degradation, we considered the effect of increasing the potential at which the electrosynthesis was conducted.

Once the voltammetric potential has been carefully chosen, the electrosynthetic reaction (also known as bulk electrolysis) is conducted by holding the reaction at the chosen potential. A common approach is to use chronocoulometry where the total charge (Q) that passes during the time following a potential step is measured as a function of time. Q can be obtained by integrating the current during the applied potential step. In order for the electrosynthetic reaction to go to completion, the amount of charge (C) passed is given by:

$$Q = (m_A/RMM)nF$$

where Q is the charge required to drive the reaction to completion, m_A is the mass (g) of the electroactive analyte, RMM is the relative molecular mass (g mol^{-1}), F is the Faraday constant and n is the

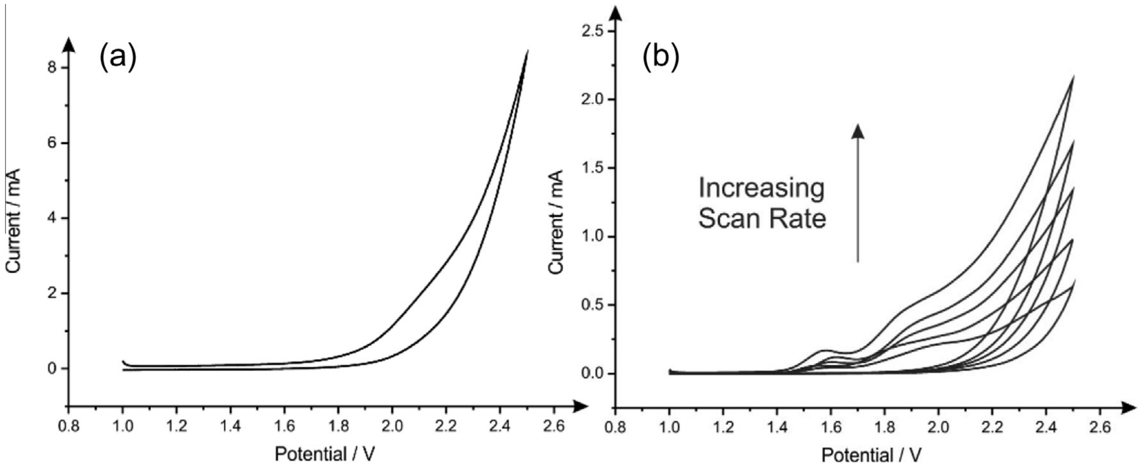

Figure 1. (a): Cyclic voltammetric profile for the blank in MeCN/MeOH (10:1) with 0.47 M TBAP as electrolyte at rates 5 mV/s, 10 mV/s, 25 mV/s, 50 mV/s, 100 mV/s and 250 mV/s at 0 °C. (b): Cyclic voltammograms for **1** in MeCN/MeOH (10:1) with 0.47 M TBAP as electrolyte and 4.7 mM of compound **1** at scan rates of 5 mV/s, 10 mV/s, 25 mV/s, 50 mV/s, 100 mV/s and 250 mV/s at 0 °C.