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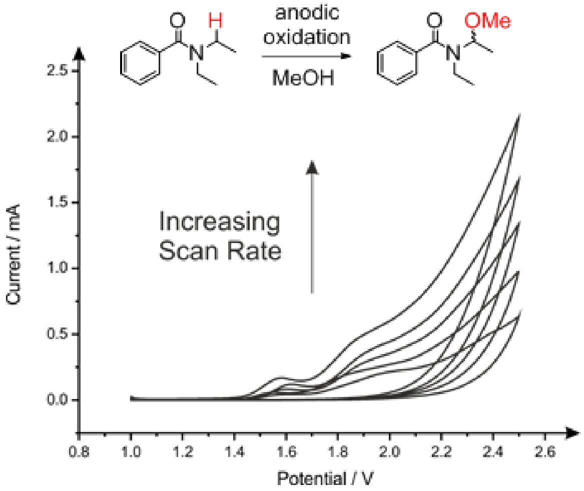
Graphical Abstract



An Experimentalists Guide to Electrosynthesis: The Shono Oxidation

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Keywords

Electrochemistry; Electrosynthesis; Shono oxidation; Anodic methoxylation; Potentiometry; Cyclic voltammetry.

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.

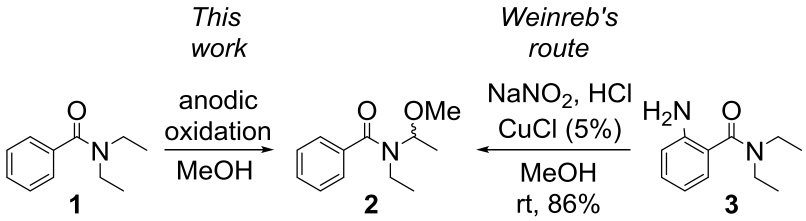
Introduction

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 e.g. 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 of-putting to those intrepid 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 and co-workers 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 20-26 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 not understood nor justified.



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

The goal of this study will be to show how model compound **1** can be anodically (electrochemical oxidation) methoxylated to **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 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 chemical reagent. 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 the of solvent breakdown (Figure 1).

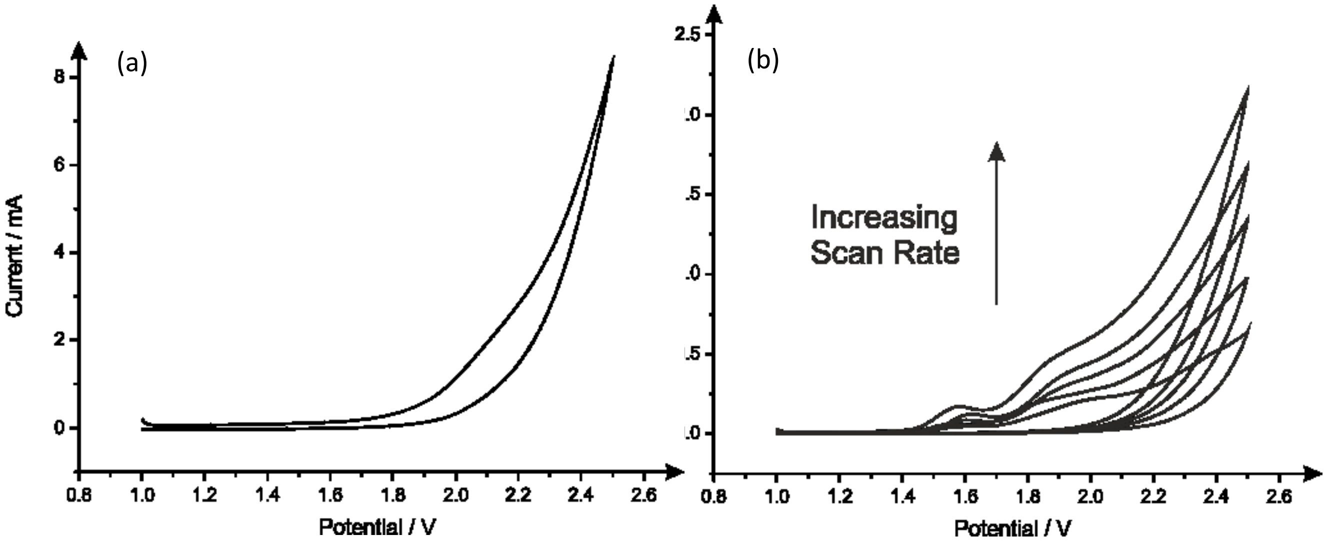


Figure 1(a): Cyclic voltammetric profile for the blank in MeCN : MeOH (10:1) with 0.47 M/l TBAP as electrolyte at rates 5 mV/s, 10 mV/s, 25 mV/s, 50 mV/s, 100 mV/s and 250 mV/s at 0° C; **Fig. 1(b):** Cyclic voltammograms for **1** in MeCN : MeOH (10:1) with 0.47 M/l TBAP as electrolyte and 4.7 mM/l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

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 ($I_p / A = 5.16x10^{-4}\ A/(\upsilon s^{-1})^{1/2} + 4.34x10^{-6}A;\ N = 5;\ R^2=0.999$) 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–Ševćik 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 per moles before the rate determining step, F is the Faraday constant, R is the universal gas constant and T is the temperature the electrochemical process is performed at. 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 the 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 (Figure 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 electro synthetic 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 (Figure 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 ($gmol^{-1}$), F is the Faraday constant and n is the total number of electrons passed in the electrochemical reaction. Once the amount of charge (C/mol) is known, the chronocoulometry experiment can be performed. Through monitoring the charge, one can determine how long the reaction will take to go to completion. In order to decrease this time, large surface area electrodes and mechanical stirring of the solution is typically employed.

Table 1 demonstrates the percentage conversions obtained for **1** to **2** using a range of voltages (+1.5 to +2.4 V) around the known oxidation potential (+1.65 V). In all cases the temperature was fixed at 0 °C, 4 *F*/mole was used and identical surface area electrodes were used. All reactions were performed on the same scale and upon reaction completion, the solvent was evaporated and the residue was dissolved in 0.60 mL d_6-DMSO (with TMS as the 0.0 ppm internal reference).[12]

Entry	Voltage (V)	*F*/mole	Time (h)	Normalised % conversion to **2**[a]
1	+1.5	4	2.6	0
2	+1.6	4	2.0	26
3	+1.7	4	3.2	93
3	+1.8	4	2.2	95
4	+1.9	4	2.3	100
5	+2.0	4	1.7	99

6	+2.1	4	0.9	77
7	+2.2	4	1.4	75
8	+2.4	4	0.2	n.d.[b]

Table 1. Variation of potential at a fixed *F*/mole on the percentage conversion of **1** to **2**. [a] The maximal integration of the diagnostic proton at 4.8 ppm is 0.75H due to the existence of rotamers around the amide bond accentuated by unsymmetrical methoxylation of one of the ethyl chains; [b] New aromatic protons were observed in the ^{1}H NMR spectrum suggesting formation of enamide **5** amongst other side products; n.d. = not determined.

It was found that as the voltage of the electrosynthesis reaction increased from +1.5 V to +2.4 V a clear maxima was observed at +1.9 V and above. However, discoloration of the electrodes (from black to grey and then blue) suggested over reaction and deposition on the electrode surface at this potential which would require replacement of the electrode materials for every reaction, limiting the green potential of this method. As the potential (V) was increased, the potential approaches and becomes outside of the potential window at which point solvent decomposition/degradation occurs. In this instance, the electrosynthetic process becomes complicated by solvent degradation products which affect the efficiency of the formation of the desired product **2**.

In conclusion, based on modification of the voltage parameter, as shown above (Table 1) it is pertinent to hold the potential for the electrosynthetic reaction at +1.9 V. Therefore, a simple formula based on cyclic voltammetry can be proposed for this example: Potentiostat voltage = CV oxidation potential (E/V) + a suitably applied over potential voltage (E/V). However, for the following experiments we decided to use +1.8 V for the following variation of the *F*/mole to reduce electrode attrition and reduce the severity of solvent degradation.

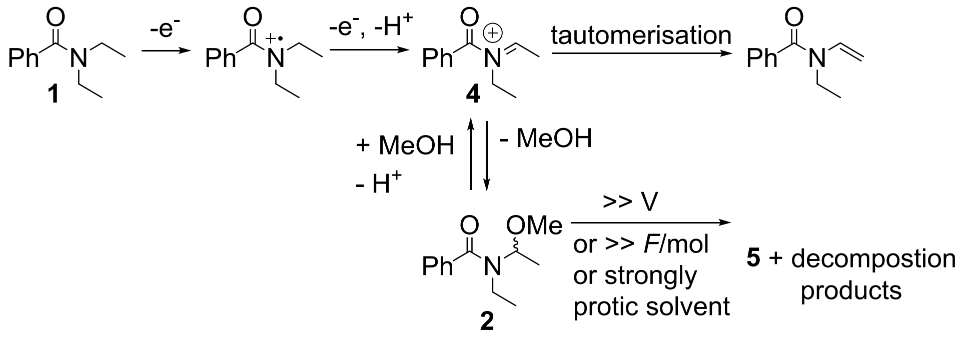
The Shono two-electron process should only necessitate the use of 2 *F*/mole, however the use of an excess, often 4 *F*/mole is used. We next investigated whether the reaction can indeed be performed at a lower charge (Table 2).

Entry	*F*/mole	Time (min)	Normalised % conversion to **2**
1	2	17	29
2	3	23	36
3	4	36	95

4	5	43	n.d.[a]

Table 2. The effect of varying *F*/mole. Potential held at +1.8V in all cases. [a] Decomposition was observed in the ^{1}H NMR spectrum, indicative of over-reaction to **5** amongst other side products; n.d. = not determined.

It was evident from Table 2 that 4 *F*/mole was optimal to achieve the highest conversion. The exact reason as to why this experimental value was twice that required theoretically (see Scheme 2 for formation of the intermediate *N*-acyliminium ion **4**) is not fully understood but could possibly be due to the concomitant oxidation of solvent breakdown and/or over-reaction; the exact reason will be considered in future reactions. Scheme 2 highlights this issue.



Scheme 2. Postulated mechanism to form **2** via *N*-acyliminium intermediate **4** and possible routes to the side-reaction product, enamide **5** amongst others.

Removal of a single electron from the lone pair of the amide nitrogen atom generates an unstable radical cation. Removal of the second electron *via* the concomitant expulsion of a proton generates the *N*-acyliminium ion **4** which can be intercepted by methanol to yield **2**. As expected in an acidic environment it is possible for **2** to revert to **4** *via* an E$_2$ mechanism. *N*-acyliminium **4** may also tautomerise to enamide **5** and *via* either **2**, **4** or **5** to give a variety of other decomposition products. It was noted that the presence of compounds other than amide **1** or the desired oxidation product **2** could be influenced *via* increasing the protic strength of the solvent and/or electrolyte (see later), increased charge or the over-voltage applied to the reaction system.

We next considered whether the choice of electrolyte influenced the outcome of the reaction (Table 3). Interestingly, the originally selected electrolyte, tetrabutylammonium perchlorate (TBAP),[13] afforded the highest conversion and yield despite using the same conditions of charge and voltage. Of note, it was found that changing both the electrolyte and solvent resulted in a quantitative conversion to enamide **5** (comparison with reference[14]) in 100% MeOH. Enamide **5** was not isolated due to instability on silica gel chromatography.

Entry	Electrolyte	Time (min)	Normalised % conversion to **2**
1	Bu_4NClO_4 (TBAP)	36	99%
2	Me_4NClO_4 (TMAP)	-	Not soluble
3a	Et_4NOTs	60	20%
3b	Et_4NOTs^a	218	0% (99% **5**)
4	$NaBF_4$	-	Limited solubility
5	$NaOSO_2Ph$	-	Not soluble
6	Bu_4NI (TBAI)	-	Not soluble

Table 3. Changing the electrolyte based on the optimal +1.8 Voltage and 4 *F*/mole conditions using MeCN : MeOH; (10:1) unless otherwise stated to convert **1** to **2**; [a] using 100% MeOH as solvent.

At this point, it was considered whether the perchlorate counter ion accelerated or caused a background chemical oxidation event independent of the electrical voltage applied. It could be seen both from entry 1 in Table 1 and from a control experiment of **1** in TBAP at 0 °C, that this caused no detectable change to **2**. Therefore, we next sought to optimise the concentration of TBAP employed (Table 4).

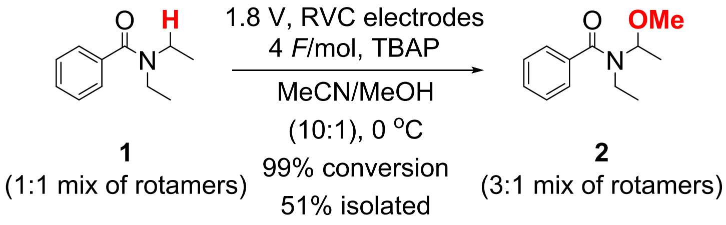
Entry	Electrolyte concentration (M)	Charge (C)	Time (min)
1	0.47	11	36
2	0.24	11.25	67
3	0.12	3.3	188

Table 4. Effect of changing the concentration of TBAP using the optimised V and *F* conditions for the conversion of **1** to **2**.

It was found, that in all cases, conversion of **1** to **2** was achieved but halving the concentration resulted in doubling the time required. Entry 3 was stopped early due to the excessive time required and a spike in the observed resistivity. It appears due to the high levels of resistance encountered in organic media necessitates the use of a high concentration of electrolyte to achieve the reaction in a reasonable time frame.

Taken together, the optimal conditions[15] of electrolyte choice, electrolyte concentration, voltage and Faradays used yielded a preparative conversion of **1** to **2** on a reasonable timescale, without resorting to very large currents and voltages that are only achievable in specialised labs.

The previously optimised conditions were used to convert **1** to **2** in 99% conversion relative to the reference and after extraction and purification by silica gel column chromatography afforded **2** (51% yield) without the need to use transition metals, chemical oxidants or harsh reaction conditions (Scheme 3).



Scheme 3. Optimised electrosynthesis of **2**.

During the course of our analysis of the ^{1}H NMR spectra associated with **2** and in comparison to Weinreb's spectral data,[7] a different rotamermeric ratio of **2** was observed ranging from a 1:1 mix[7] (generated via a 1,5-H atom radical transfer route) to a 3:1 mixture of rotamers using our alpha-methoxylation route (Table 5).

Original Assignment[7] of **2** in $CDCl_3$	Our Assignment of **2** in $CDCl_3$
7.38-7.27 (m, 5H)	7.36-7.28 (m, 5H)
4.82 and 3.65 (rotamers, 2 bs, 1H)	4.78 (s, 0.75H),
-	3.58 (s, 0.75 H),
3.35-3.26 (m, 2H)	3.32-3.26 (m, 1.5H),
3.04 (br s, 3H)	3.00 (s, 2.5H),
1.40-1.38 (d, *J* = 6.0 Hz, 3H)	1.35 (d, *J* = 6.0 Hz, 3H)
1.32-1.27 (m, 3H)	1.28-1.23 (m, 3H)

Table 5. Re-interpretation of the rotamers produced by alpha-methoxylation of **1** to **2** as measured by ^{1}H NMR spectroscopy.

Conclusions

In conclusion, we have demonstrated that from a rapid cyclic voltammogram measurement an electrosynthetic experiment can be undertaken which generates quantitative conversion and isolable amounts of the desired product. This reaction mitigates the use of chemical oxidants and transition group metals to achieve the selective reaction of a C-H bond to a C-O bond using "traceless" electrons. This work highlights the various factors that the electrosynthetic chemist needs to take into consideration. The selection and nature of electrolyte and counter ion are currently under study in our laboratory and will be reported in due course. Together, these results should encourage those wishing to quickly determine whether an electrosynthetic reaction may work in their organic synthesis and not be a method of last resort. Simply tuning the oxidation potential allows the dial-up of compounds **2** or **5** from amide **1**. It was also found that increased charge or potential led to degradation products from over-reaction, solvent breakdown and tautomerisation of intermediate **4**.

Acknowledgements

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12. It was envisioned to monitor the diagnostic 4.8 ppm peak for **2** using $CDCl_3$ but due to overlap of the $CHCl_3$ un-deuterated reference proton with the phenyl ring in **1** and **2**, d_6-DMSO was used for all the other reactions. The data obtained for all the reactions compared favourably either in $CDCl_3$ or d_6-DMSO (ESI **S6**).

13. (a) CAUTION: Tetrabutylammonium perchlorate (TBAP) may intensify fire and is an oxidiser (EU hazard code: H272). Although the safety data sheet for this perchlorate indicates incompatability with organic materials, sensible precautions allow for the safe use of this material on a preparative scale. For instance, heating may cause an explosion, therefore reactions and work-up are performed at room temperature or below; (b) We thank reviewer 1 for suggesting a control experiment with $TBABF_4$ (as in reference [6]) as a safer electrolyte, however due to limited solubility in acetonitrile a reproducible comparison was not achievable; (c) Organic Electrochemistry: Fourth Edition, Revised and Expanded, Lund, H.; Hammerich, O., eds, Marcel Dekker, Inc., New York, **2001**.

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15. Representative experimental procedure for the electrosynthesis of **1** to generate *N*-ethyl-*N*-(1-methoxyethyl)benzamide **2**: To an undivided glass cell (20 cm^3) equipped with a magnetic stirrer along with a rectangular reticulated vitreous carbon (RVC) anode (11 cm^2) and rectangular RVC cathode (11 cm^2), arranged opposite to one another at a distance of 3.0 mm with a silver wire reference electrode placed 1.0 mm from the working electrode. To the reaction vessel was added **1** (20 mg, 4.73 mM) in acetonitrile (21.6 mL), methanol (2.2 mL) and tetrabutylammonium perchlorate (3.84 g, 0.47 M). The electrolysis was carried out with stirring at a potential of 1.8 V (producing a current density of 7.3 $\mu A/mm^3$ at 0 °C) until a charge of 4.0 $Fmol^{-1}$ had passed. An average current of 5.05 mA passed through the electrodes. The solvent was evaporated under reduced pressure, and the product was isolated by column chromatography (ethyl acetate : petroleum ether, 10:90 to 15:85) to afford the title compound **2** as a yellow oil, (9.3 mg, 51%). ν_{max}/cm^{-1} 2963, 2913, 2859, 1763, 1738, 1646 and 1550; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.28 (m, 5H), 4.78 (s, 0.75H), 3.58 (s, 0.75 H), 3.32-3.26 (m, 1.5H), 3.00 (s, 2.5H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.28-1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 136.9, 129.5, 128.6, 126.7, 86.5, 54.7, 34.3, 20.2, 14.4; *m/z* (ESI) 208 (M+H); Hi-Res LC-MS (ESI) *m/z* calcd for $C_{12}H_{18}NO_2$ (M+H) 208.1338, found 208.1325.

Supplementary Material Spectroscopic and analytical data including ^1H and ^{13}C NMR spectra and cyclic voltammetry of all compounds are provided in the electronic supporting information, available at: xxx