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Bal, Mandeep; Banks, Craig; Jones, Alan M

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Metabolism mimicry: An electrosynthetic method for the selective deethylation of tertiary benzamides

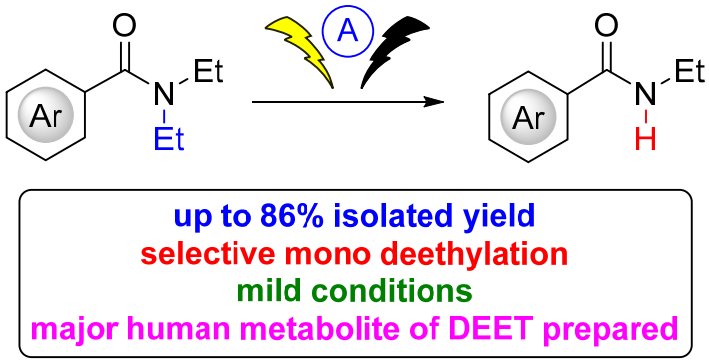
Ms. Mandeep K. Bal[a], Prof. Craig E. Banks[a], and Dr. Alan M. Jones[b]*

[a] Faculty of Science and Engineering, Manchester Metropolitan University, Chester Street, Manchester, M1 5GD, United Kingdom.

[b] School of Pharmacy, University of Birmingham, Edgbaston, B15 2TT, United Kingdom.

* Corresponding author: a.m.jones.2@bham.ac.uk; +44(0)121-414-7288

Graphical Abstract



Abstract

The electrosynthetic deethylation of tertiary amides, commonly encountered moieties in pharmaceuticals and agrochemicals, is an analogue of the function of cytochrome P450 enzymes, a major oxidant metabolic pathway for xenobiotics. The ability to tractably synthesise in a late stage manner, drug metabolites from the parent drug is currently unsolved. We report the first study, mechanistic rationale, and synthetic scope of an *undivided controlled current* electrosynthetic method that selectively mono deethylates tertiary amides without over-reaction. An optimisation survey found that changing the electron input from controlled voltage to controlled

current conditions led to deethylation rather than the expected dehydrogenative coupling. The scope and limitations of the method were interrogated with 14 examples with the parent benzamide reaction optimised (86% yield), and the scalable production of the major human metabolite of the insecticide, DEET was achieved from the parent molecule in one step.

Key words

Deethylation, dealkylation, electrosynthesis, tertiary amide, metabolite, P450, DEET.

Introduction

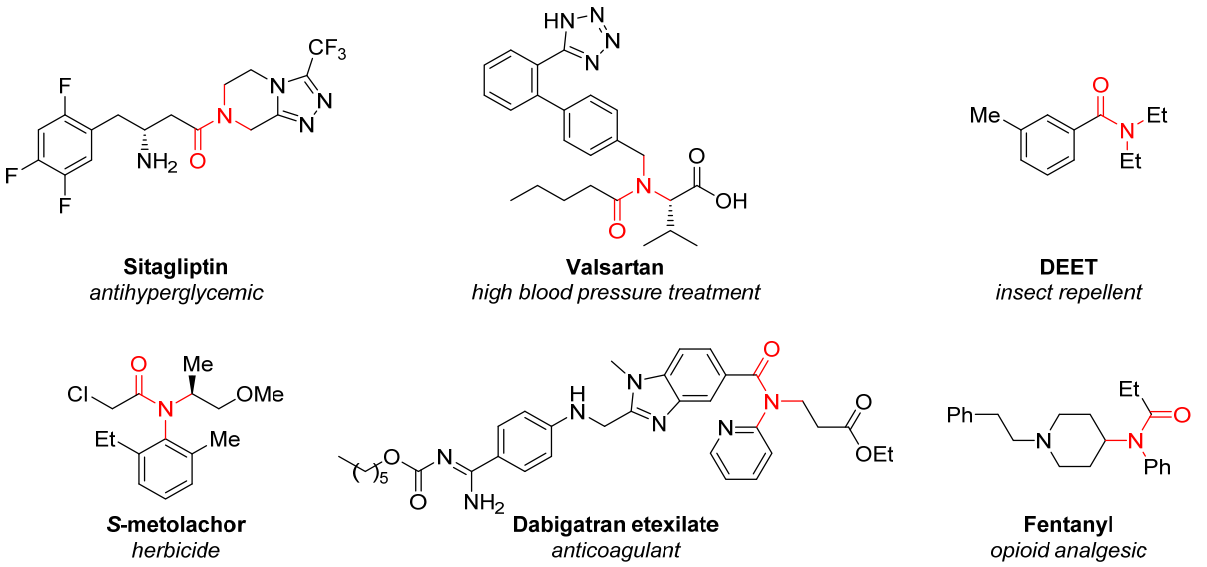
Understanding the metabolic products of a new chemical entity (NCE) in the pharmaceutical and related industries is of paramount importance as it dictates the toxicology, half-life of the NCE and clearance amongst many others.[1] Conventional methods of studying drug metabolism rely on *in vitro* approaches, including supersomes, microsomes, cytosol, S9 fraction, cell lines, primary hepatocytes, liver slices and perfused liver, or an electrochemical reactor connected to an in-line mass-spectrometry.[2] Developments of electrochemical coupled mass spectrometry have given vast amount of *in situ* metabolite detection data but with few exceptions no physical sample of the metabolite.[3]

It is a requirement of the FDA [4] that all detectable metabolites of a new drug entity are prepared for rigorous toxicological studies which necessitates currently their *de novo* synthesis, which although is not insurmountable, can require tremendous intellectual and practical effort to achieve.[5]

A commonly encountered metabolism pathway is the *N*-dealkylation of a drug molecule which occurs during phase I metabolism through an isoform of the heme-mediated cytochrome P450 enzyme (CYP450).[6] This transformation increases the

polarity of the drug molecule and alongside subsequent phase II conjugation enables the drug to be eliminated from the body.

Figure 1. Examples of pharmaceuticals and agrochemicals that contain a tertiary amide



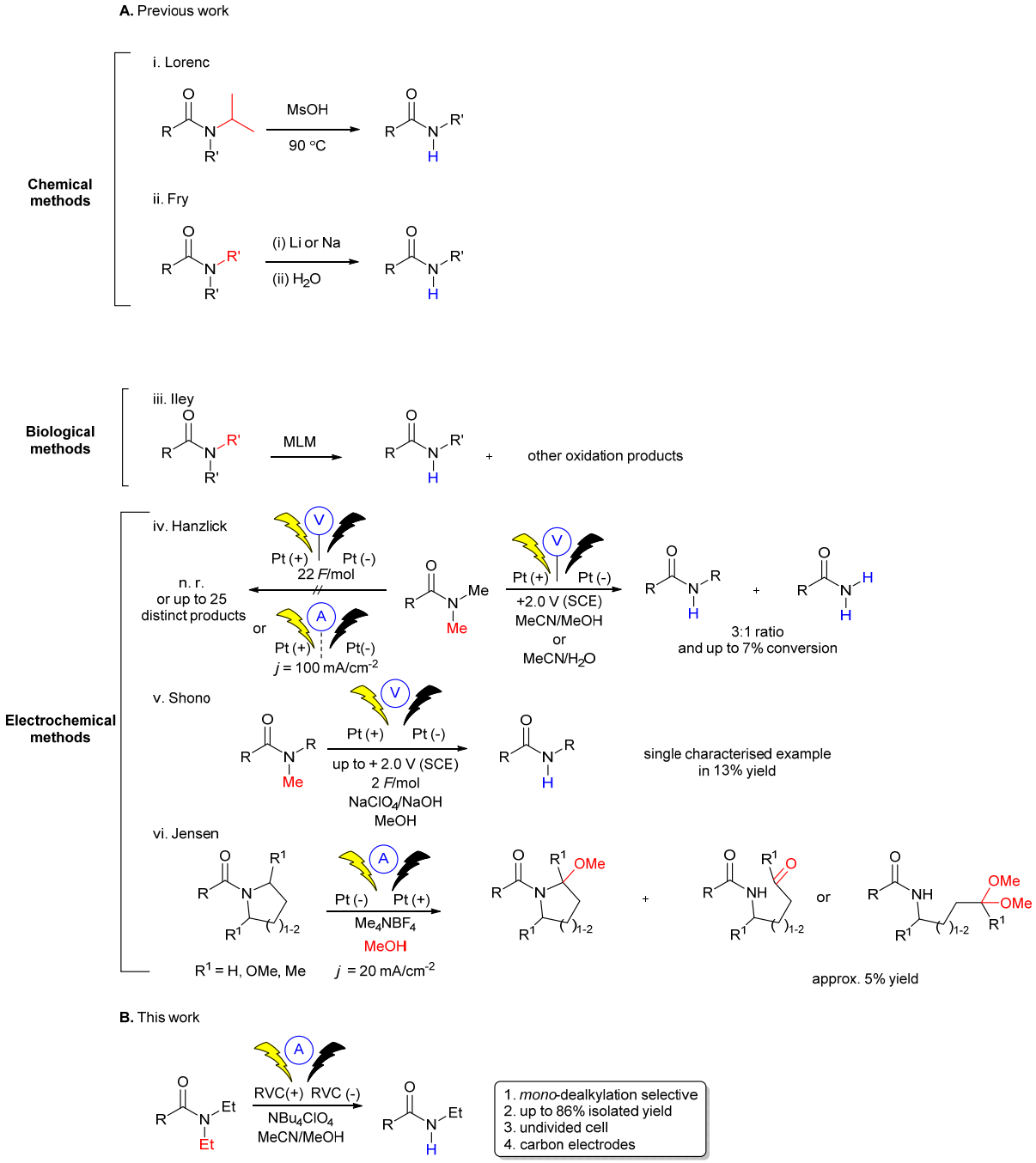
The ubiquitous nature of the amide bond found both in nature; agrochemicals and drug molecules (**Figure 1**) necessitated the development of a late-stage electrosynthetic *N*-dealkylation method described herein. The Shono-type oxidation manifold of amides[7] coupled with the reported *in situ* collapse of α-oxidised intermediaries[8] in the oxa-Shono reaction prompted us to consider the generality of this reaction manifold for tertiary amide *N*-dealkylation.

To the best of our knowledge, only three examples of electrosynthetic amide dealkylation have been reported. Hanzlick and co-workers[9] (**Scheme 1 A (iv)**) reported a *divided* cell controlled voltage method of a benzamide that included mono and double dealkylation products in a 3:1 ratio. This provided insight into the mechanism of cytochrome P-450 dealkylation through kinetic isotope studies. Although an *undivided* galvanostatic method was attempted this led to 25 distinct product peaks and a *divided* method still produced a complex mixture. Secondly, Shono and co-workers[10] (**Scheme 1 A (v)**) have compared potentiostatic electrochemical *N*-demethylation of amides with their microsomal metabolism

counterparts with the only reported yield being 13% of *des*methylation. Significantly, Hanzlick reported they were unable to replicate Shono's conditions for dealkylation. Thirdly, Jensen and colleagues[11] observed in selected cyclic amide examples (where an R^1 group was already α to the tertiary amide), a trace quantity (~5%) but isolable dealkylation side-product alongside the expected dehydrogenative coupling (**Scheme 1 A (vi)**). A mechanism was proposed to account for the formation of an ester, ketone or aldehyde-level product, involving the formation of an acetal intermediate which ring opened with methanol, followed by water mediated hydrolysis to afford carbonyl containing by-products. A high current density of 20 $mAcm^{-2}$ and an average cell potential of 28.9 V was used.

There are limited direct chemical methods by comparison e.g. alkali metal induced[12a], or use of a strong acid when a stabilised carbocation is the leaving group.[12b] Therefore, *N*-dealkylation not only for metabolism[13] but for its synthetic utility would be a good candidate for a direct electrosynthetic method without the need to use stoichiometric chemical oxidants under mild conditions.[14]

Scheme 1. Previous methods to *N*-dealkylation of tertiary amides and the new route disclosed.



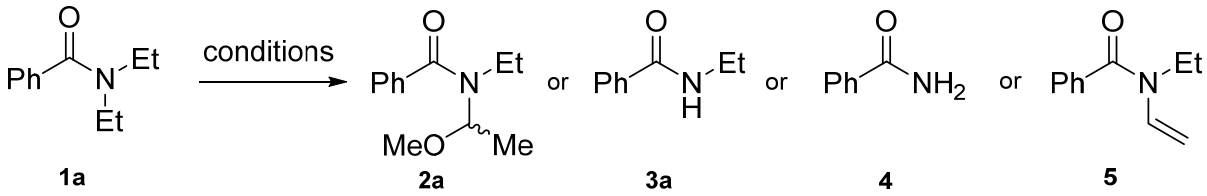
More recently, Roth and co-workers have reported an electrochemical method to convert methylene and thioethers in four drug molecules to the corresponding carbonyl and sulfoxide containing-metabolites, respectively.[15] Taylor and co-workers[16] have developed a specific electrochemical method to dealkylate a tertiary amine found in *Festoterodine*, an anti-muscarinic drug. Inspired by these pertinent recent successes in the use of electrosynthesis applied to metabolite preparation, and

combined with the paucity of mild, direct chemical methods in the literature we sought to address a timely issue with electrosynthetic *N*-dealkylation of amides.

Results and discussion

To probe the feasibility of developing an electrochemical *N*-dealkylation of tertiary amides, a model system, of structural similarity to the insecticide, DEET was selected **1a** (**Figure 2**). Our original results with **1a** under potentiostatic conditions[7b] afforded in high conversion, 95%, the expected α-methoxylated Shono product (**2a**) with a trace amount of the enamide (**5**). More recently efficient methods to prepare Shono-type products have been reported under controlled current conditions.[17] Switching the electron input control from controlled voltage to controlled current (I = 5.0 mA, and current density, j = 0.71 mA/cm^2) delivered a dealkylated product (**3a**) in an appreciable conversion (78%) without by-products (99% b.r.s.m.). Under these as yet unoptimised conditions, there was no evidence of over-reaction to the primary amide (**4**). In an unrelated system, Becker and co-workers have observed similar alterations in the product profile between controlled potential and controlled current syntheses.[18]

Figure 2. Comparison of products resulting from electrosynthesis of **1a** under controlled current and controlled voltage conditions (% conversion).



Conditions	2a	3a	4	5
controlled current I = 5.0 mA j = 0.71 mA/cm^2	0	78	0	0
controlled potential V = + 1800 mV	95	0	0	<5

These preliminary results led us to survey the optimisation of the *N*-dealkylation of **1a** to deliver **3a** (**Table 1**).

Entry	Electrical input	*j* (mA/cm^2)	Q (*F*mol^{-1})	Solvent	Additive	Atmos.	T (°C)	Bu_4NClO_4 [M]	Isolated yield of **3a** (%)
1	5.0 mA	0.71	4.0	MeCN	MeOH	air	0	0.10	0
2	5.0 mA	0.71	4.0	MeCN	MeOH	air	0	0.20	22
3	5.0 mA	0.71	4.0	MeCN	MeOH	air	0	0.30	31
4	5.0 mA	0.71	4.0	MeCN	MeOH	air	0	0.40	85
5	5.0 mA	0.71	4.0	MeCN	MeOH	air	0	0.50	86
6	1.0 mA	0.14	4.0	MeCN	MeOH	air	0	0.50	11
7	3.0 mA	0.43	4.0	MeCN	MeOH	air	0	0.50	32
8	10 mA	1.42	4.0	MeCN	MeOH	air	0	0.50	15
9	20 mA	2.84	4.0	MeCN	MeOH	air	0	0.50	24
10	30 mA	4.26	4.0	MeCN	MeOH	air	0	0.50	22
11	40 mA	5.68	4.0	MeCN	MeOH	air	0	0.50	20
12	50 mA	7.10	4.0	MeCN	MeOH	air	0	0.50	16
13	-	-	-	MeCN	MeOH	air	0	0.50	0
14	+1800 mV	0.0073	4.0	MeCN	MeOH	air	0	0.47	0[a]
15	+1500 mV - +2200 mV	-	2.0-4.0	MeCN	MeOH	air	0	0.47	0[b]
16	5.0 mA	0.71	4.0	MeCN	H_2O	air	0	0.50	0
17	5.0 mA	0.71	4.0	MeCN	MeOH NaOH	air	0	0.50	9
18	5.0 mA	0.71	4.0	MeCN	MeOH	N_2	0	0.50	<5[c]
19	5.0 mA	0.71	4.0	MeCN	MeOH H_2O	N_2	0	0.50	42

Table 1. Survey of conditions for the transformation of **1a** to **3a**. Key: [a] 95% conversion to **2**; [b] n.r to 99% conversion to **2**; [c] exclusion of moisture.

Initial optimisation began with determining the required concentration of electrolyte for efficient conversion (**Table 1**, entries 1-5). A relatively high loading of electrolyte 0.50 M of Bu_4NClO_4 was required to reduce cell resistance in the solvent medium (entry 5). Next, we explored varying current (*I*) and current density (*j*) in entries 5-12 (**Table 1**). It was determined that *I* = 5.0 mA (*j* = 0.71 mA/cm^2, entry 5) gave a clear maxima for the formation of **3a** compared to lower and higher currents (and current densities). Generally, a lower *j* should be preferred (entries 6-7) to enable reaction

selectivity and is only increased with increases in mass of substrate, thus operating the cell with $I_{opt} > I_{cell}$ (optimal current (I_{opt}) from Faraday's laws) will not adversely affect selectivity but led to lower conversion. Use of a higher I_{cell} (entries 8-12) than I_{opt} lowers current efficiency and leads to oxidation/reduction of solvent/electrolyte, giving potential side reactions and at high currents unproductive *Joule* heating.[19]

During the constant current method, the cell potential varied throughout the transfer time (as the resistance of the cell changes, $V=I\cdot R$). The observed average cell potential is generally lower, with lower applied currents, than when compared to higher currents, this correlates with the higher conversion (and isolated yield of **3**a observed, in entry 5 vs entries 6-12). This can be explained by the cell potential being closer to the oxidation potential of **1a**, relative to that observed at higher applied currents.† Our observations of fluctuations of cell potential during the controlled current experiments are in line with previous reports in other systems.[20]

Entry 13 demonstrates that electricity is essential for the conversion of **1a** to **3a** with no concomitant background reaction with the perchlorate electrolyte.

We have previously surveyed a variety of solvents, electrolytes, and electrode materials and have not observed dealkylation under potentiostatic conditions.[7b] Highlights are presented in entries 14-15 (**Table 1**) demonstrating that potentiostatic conditions delivered dehydrogenative coupling to **2a**, not dealkylation to **3a**. Very low current densities (entry 14) were observed leading to long reaction times. Furthermore, controlled current is operationally simpler than controlled voltage in terms of reaction set-up, although controlled voltage is usually a milder, more selective method.[21]

We next considered, using galvanostatic conditions, the effects of methanol, base and water on the conversion of **1a** to **3a** (**Table 1**, entries 16-19). Entry 16 shows that methanol is essential for reactivity, suggesting that a Shono-type reaction sequence is invoked in the dealkylation pathway,[22] the addition of external base (entry 17) gave

a reduced conversion to **3a**. Under rigorously dried conditions (entry 18) trace conversion to **3a** was observed, however, injection of H_2O (1.0 mL) to this previously anhydrous conditions (entry 19) recovered the reaction to **3a** in a 42% isolated yield. Taken together with reaction scope data in **Table 2**, potential reaction pathways are shown in **Scheme 2**.

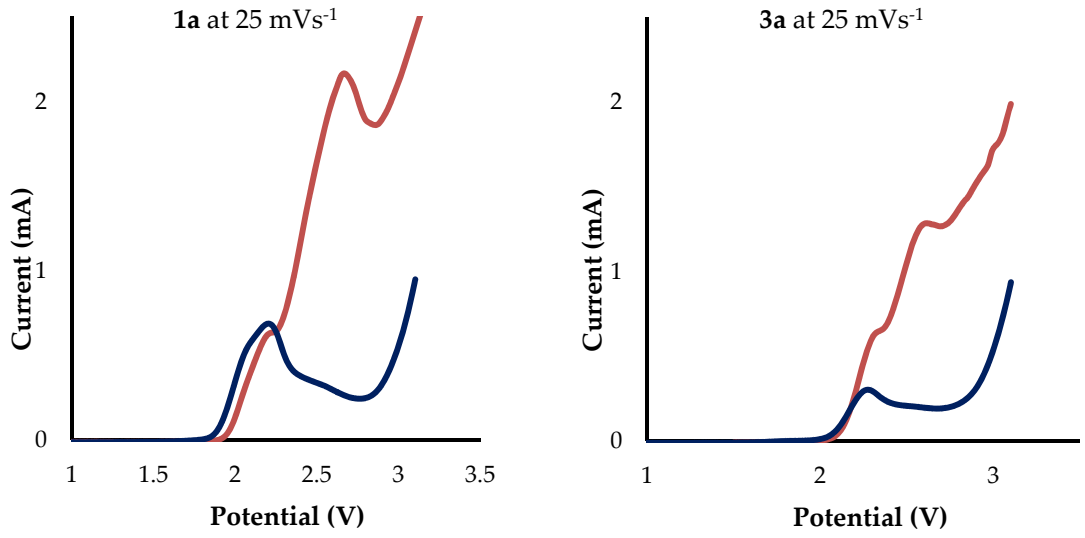


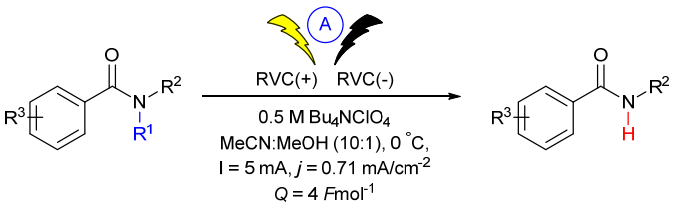
Figure 3. Linear sweep voltammetric oxidative response from surveying the scan rate of **1a** and **3a**. Conditions: MeCN/MeOH or H_2O (10:1), 500 mM Bu_4NClO_4, 22.0 mM of analyte, W.E. = GC, C.E. = Pt wire, R.E. = Ag^+/Ag (-0.057 V versus Fc^+/Fc), ν = 5-250 mVs^{-1}. Data for ν = 25 mVs^{-1} shown for clarity.† Solvent system: **Red** = MeCN/MeOH, **Blue** = MeCN/H_2O.

We next sought to explain why under controlled current conditions the dealkylation terminated after a single ethyl group was removed. To address this we performed linear sweep voltammetry scan-rate surveys of **1a** and **3a**.† As shown in **Figure 3** two ill-defined oxidation waves for **1a** occur at E_p^{ox} +2.20 V and 2.67 V *versus* E_p^{ox} +2.32 and 2.61 V for **3a** in MeCN/MeOH. Changing the solvent system to MeCN/H_2O led to a single broad oxidation wave for **1a** (E_p^{ox} = 2.25 V) and **3a** (E_p^{ox} = 2.37 V), respectively. Although methanol compresses the useable voltammetric window (vs. MeCN/H_2O), methanol enables a modest -50 mV reduction in the onset of the first oxidation response of **1a** and **3a**, respectively. Comparing **1a** and **3a** it is clear that **1a** has a lower oxidation potential (-112 mV) compared to **3a**, suggesting that **1a** would

be more readily oxidised than **3a**. This is in concurrence with previous reports that tertiary amides have a lower oxidation potential compared to secondary amides.[23] The data obtained using Ag^{+}/Ag was standardised by comparison to Fc^{+}/Fc to minimise reference electrode potential drift.[24]

There is less electron density on the nitrogen in **3a** than in **1a** meaning a higher applied voltage is required to adjust the Fermi level of the electrode to match the energy level of **3a**. Therefore, the reaction of **3a** becomes unfavourable until higher over potentials are applied, (e.g. after consumption of the lower E_p^{ox} substrate, **1a**) providing insight into the observed selectivity profile of mono dealkylation over double dealkylation. To further validate this hypothesis, an authentic synthesised sample of **3a** was re-subjected to the reaction conditions for a further 4.0 Fmol^{-1} at 5.0 mA and no evidence of **4** was observed, only recovery of unreacted **3a**. It is likely that unproductive electron pathways are in operation when the cell adjusts to the potential of **3a** as it is in competition with methanol for redox processes on the electrode surfaces due to the higher E_p^{ox} for **3a** than **1a**.

We next investigated the scope of this novel dealkylation procedure with a range of benzamide and alkylamide analogues to probe effects of electron donating/withdrawing groups, steric effects and changes to the alkyl group on the reaction (**Table 2**).



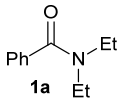
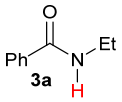
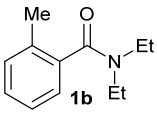
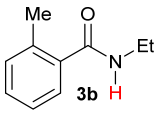
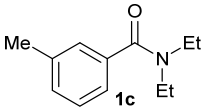
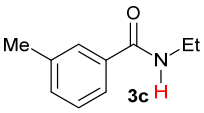
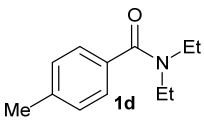
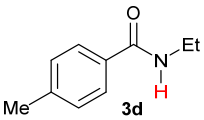
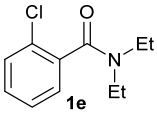
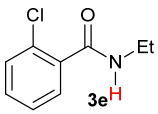
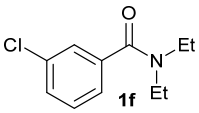
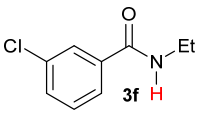
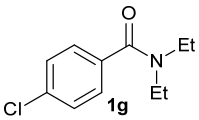
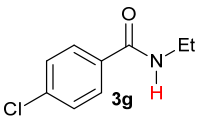
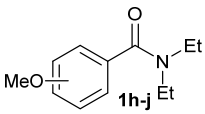
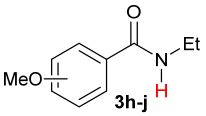
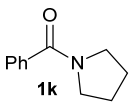
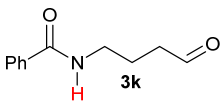
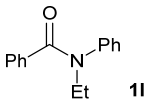
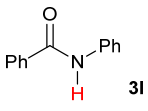
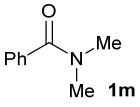
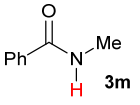
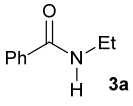
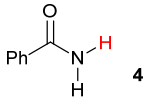
Entry	Substrate	Product	Isolated yield (%)
1	 **1a**	 **3a**	86
2	 **1b**	 **3b**	54
3	 **1c**	 **3c**	52
4	 **1d**	 **3d**	0[a]
5	 **1e**	 **3e**	15[b]
6	 **1f**	 **3f**	60[b]
7	 **1g**	 **3g**	70
8	 **1h-j**	 **3h-j**	**3h** *o* (rsm) **3i** *m* (rsm)[c] **3j** *p* (rsm)
9	 **1k**	 **3k**	<5
10	 **1l**	 **3l**	0 (rsm)
11	 **1m**	 **3m**	0 (rsm)
12	 **3a**	 **4**	0 (rsm)

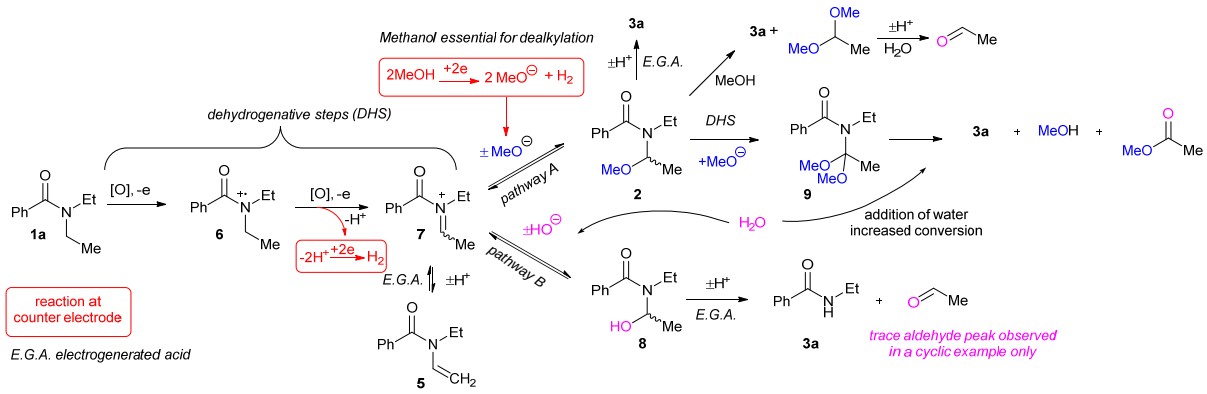
Table 2. Exploring the scope of the electrochemical dealkylation reaction. Key: [a] complex mixture formed (n = 3); [b] I = 10 mA; [c] under divided conditions the formation of **1a** was observed; *r.s.m.* = recovered starting material.

Using the optimised procedure from **Table 1** the isolated yield for the *N*-deethylation of the parent benzamide was increased to 86% (entry 1, **Table 2**). In contrast, (entries 2-3) which contain an inductively electron rich aryl system in the *ortho* and *meta* positions were detrimental to the isolated yield but proved tractable with the methodology. Surprisingly, the highest yield was observed with the *ortho*-methyl group (entry 2), when compared with the similar electronics observed in the *para*-methyl system (entry 4) which afforded a complex mixture, it is logical to assume that the deviation of the aryl ring from planarity is sufficient to temper the effect of the methyl group upon the *N*-centred radical.[25] Gratifyingly, no observation of benzylic methyl hydroxylation was observed under the reaction conditions.

Changing the methyl group to chlorine was used to probe a modest electron withdrawing functionality on the adjacent tertiary amide (entries 5-7). Comparable yields to the placement of a methyl group were observed, apart from with the *ortho*-chloro example (entry 5), this may be due to the larger twist applied to the adjacent amide carbonyl system.[26] It was noted for entries 5 and 6, a modestly increased current (and density) afforded an improved isolated yield.

Placement of a strong electron donating group in the *ortho*, *meta* or *para* positions (entry 8), led to the recovery of starting material in all cases. A reason for this may be due to the formation of a methoxy radical[8, 27] (in preference to tertiary amide oxidation) which may redox shuttle unproductively at the working and counter electrodes.[28] To test this hypothesis, **1i** (*m*-OMe) was subjected to analogous reaction conditions in a sintered glass frit divided H-cell.[29] † Intriguingly, **1i** now reacted productively to give a mixture of products, with the detection of demethoxylated **1a** as the major product as identified by ^{1}H NMR spectroscopy.[30]

The use of a cyclic tertiary amide (entry 9, **1k**, **Table 2**) produced a complex mixture of products, however, an aldehyde peak was observed within the crude ^{1}H NMR spectrum, giving mechanistic insight (**Scheme 2**). Placing a nitrogen radical stabilising[25] phenyl group on the amide resulted in no reaction (entry 10, **Table 2**). Intriguingly, only deethylation was observed, the use of *N*,*N*-dimethylbenzamide did not undergo the analogous demethylation reaction (entry 11, **Table 1**). The use of non-benzamide tertiary amides, such as *N*,*N*-dimethylacetamide and *N*-methylpyrrolidinone (not shown) did not undergo any reaction under these conditions.



Scheme 2 Possible reaction mechanisms for the formation of **3a**.

Scheme 2 shows several potential routes to the observed deethylation of **1a**. Initially, **1a** undergoes Shono-type dehydrogenative steps (DHS) to radical cation (**6**) via single electron transfer (SET) and onwards to *N*-acyl iminium (**7**) via a combined SET and hydrogen atom transfer (HAT). In accordance with the Shono mechanism for the initial steps, we observed the formation of gas bubbles (H_2) at the cathode.[31] It is known for intermediate **7** to equilibrate under the electrogenerated acidic (EGA) conditions with enamide **5**.[7b] At this point the reaction mechanism could depart into two major pathways (A: methanol mediated and B: water mediated). MeOH and H_2O are both suitable nucleophilic traps for the *N*-acyl iminium (**7**) that are reduced to methoxide and hydroxide, respectively at the counter electrode.

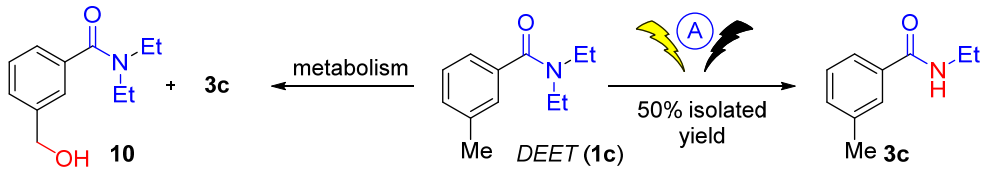
Pathway A begins with the commonly encountered reaction of **7** with methoxide to generate **2**. At this point three potential sub-pathways are possible: i) electrogenerated acid mediated decomposition of the hemiaminal to **3a**; ii) direct attack of **2** with methanol or methoxide would deliver **3a** and an aldehyde oxidation state level by-product; or iii) subsequent DHS to prepare acetal, **9** and in a similar manner to pathway A (ii) collapse or water mediated cleavage would afford **3a**. In support of pathway A (routes ii and iii), Mitzlaff and co-workers[11] observed a trace amount of dealkylation in cyclic tertiary amides *via* α-methoxy or α,α-dimethoxy intermediates involving methanol-mediated ring opening and water hydrolysis.

Pathway B begins with the rare interception of **7** with water to generate **8** directly. One of the few reports of the direct α-hydroxylation of (cyclic) tertiary amides was by Mori and co-workers using an MeCN/H_2O (20:1) system, unfortunately the product was not characterised as the reaction was telescoped but provides evidence for the dehydrogenative coupling without methanol.[32] In our hands (**Table 1**, entry 16) we were unable to replicate a direct α-hydroxylation of **1a**. However, if **2** so formed, under EGA conditions, the collapse of the hemiaminal would deliver **3a** and an aldehyde oxidation state by-product. In one example (**Table 2**, entry 9) an aldehyde by-product was observed in the crude ^{1}H NMR spectroscopy but equally could be derived from pathway A (i or ii).

In summary, based on previous literature reports and our findings within, it appears most likely that Pathway A dominates via the typical Shono α-methoxylation initiation. Key new findings are that (i) methanol is essential for the reaction; and (ii) trace quantity of water are required to assist the reaction, through electro-generation of acid and to react with the acetal by-products via hydrolysis.[33]

Intriguingly, example **1c** in **Table 2** produced an authentic multi milligram sample of the major human metabolite of the commonly encountered insect repellent, diethyltoluamide (DEET), sufficient for biological evaluation. The major human metabolites of DEET are hydroxylation of the *meta*-methyl group and deethylation of

the tertiary amide (**1c**) using microsomes (**Scheme 3**).[34] As a test of our electrochemical methodology; it delivered a tractable synthesis of an authentic sample of the deethylated human metabolite in an isolated 50% yield. Although the mechanistic steps involved between electrochemical oxidation and *in vivo* metabolism differ in the initiation stages, single electron transfer (SET) versus hydrogen atom transfer (HAT), respectively[13] the outcome was hypothesised to be identical in this case. Furthermore, this work demonstrates the promise of the approach to prepare human metabolites of tertiary amide containing molecules. Excitingly, the approach does not cause oxidation at adjacent potentially electroactive side groups such as the benzene ring or the methyl group.



Scheme 3. Application of the methodology to the tractable preparation of the human metabolites of an insect repellent (DEET).

Conclusions

Inspired by nature's use of an *in situ* substrate specific oxidation site (cytochrome P450) we explored the use of electrosynthesis for the selective removal of an ethyl group from a tertiary amide to afford secondary amide containing metabolites and compounds. We have detailed a new method to switch the reaction outcome of an electrochemical reaction by changing the electron input and investigated the solvent's role in the observed dealkylation. This reaction holds potential to dial-in alternative reactivity to the system under study. Furthermore, our methodology allows a complementary method to prepare *N*-deethylated metabolites in tractable quantities. Further tests are ongoing to establish the generality of the disclosed methodology in drug scaffolds.

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† Further experimental details, voltammetry data and NMR spectra can be found in the accompanying electronic supporting information.

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Table of Contents

An electrochemical method that mimics cytochrome P450-mediated dealkylation is reported. Changing from controlled potential to controlled current conditions gave dealkylation over the expected dehydrogenative coupling. The method is operationally straightforward and solely affords *mono* deethylation products. Application of the electrochemical method to the insecticide, *DEET*, affords on a preparative scale the major human metabolite in a single step.