

METABOLISM MIMICRY: AN ELECTROSYNTHETIC METHOD FOR THE SELECTIVE DEETHYLATION OF TERTIARY BENZAMIDES

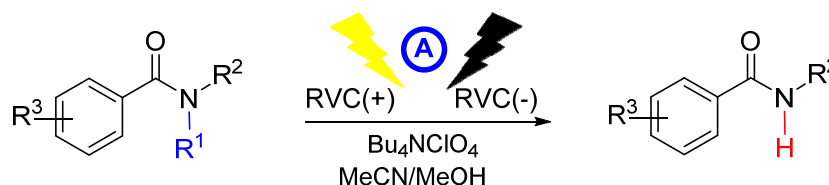
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Developments of electrochemical coupled mass spectrometry have given vast amount of *in situ* metabolite detection data but with few exceptions no physical sample of the metabolite.¹ A commonly encountered metabolism pathway is the *N*-dealkylation of a drug molecule, which occurs during phase I metabolism through an isoform of the hememediated cytochrome P450 enzyme (CYP450).² The electrochemical 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.

Inspired by nature's use of an *in situ* substrate specific oxidation site (cytochrome P450), we explored the use of electrochemistry for the selective removal of an ethyl group from a tertiary amide to afford secondary amide containing metabolites and compounds. The scope and limitations of the method were interrogated with 14 examples with the parent benzamide reaction optimised (86% yield) including scalable production of the major human metabolite of the insecticide DEET.³



Scheme 1: *N*-dealkylation of tertiary amides using electrochemical methods reported in this work.

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. The scalable production of the major human metabolite of the insecticide, DEET was achieved from the parent molecule in one-step.³ 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.

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[2] B. Bonn, C. M. Maimirembwa, Y. Aristei, I. Zamora, Drug Metab. Dispos. 2008, 36, 2199-2210

[3] M. K. Bal, C. E. Banks, A. M. Jones, ChemElectroChem, DOI: 10.1002/celc.201900028