Selective C–H bond electro-oxidation of benzylic acetates and alcohols to benzaldehydes†

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A chemical oxidant-free and mediator-free, direct electro-oxidation of both benzylic alcohols and benzylic esters are reported. The scope of the reaction is explored as a function of both steric and electronic effects. Expansion of the scope to non-benzylic and heteroaryl substrates is investigated. Functionalisation of esters and alcohols selectively to the aldehyde oxidation level using a traceless electron approach is reported.

Introduction

The controlled and chemo-selective oxidation of primary alcohols to aldehydes and secondary alcohols to the corresponding ketones are fundamental reactions in organic synthesis.1 In turn, these aldehydes and ketones serve as precursors for a variety of complexity generating reactions.2 However, the controlled oxidation of primary alcohols to aldehydes can be problematic due to over-oxidation to the carboxylic acid oxidation state.3 There are a range of versatile chemical oxidants available to the academic and industrial chemist that enable this transformation to be performed on demand.4 However, the majority of these oxidation reactions are stoichiometric in nature and therefore suffer from the generation of quantities of chemical waste.5

Recently, the field of electrosynthesis has undergone a renaissance6 and has found application in a variety of organic synthetic transformations, such as: C–H bond activation,7 total synthesis,8 and the Diels–Alder reaction9 amongst others.10 A fundamental advantage of the electrosynthesis approach is the replacement of the need to use stoichiometric oxidants and instead the oxidation reaction is performed on the electrode surface via quantum mechanical tunelling11 or through a mediator in solution.12

To address the challenge of identifying a cleaner oxidation, we explored the use of electrosynthesis to replace the need for both a chemical oxidant and mediator in these Redox transformations. The simultaneous removal of oxidant and mediator would minimise chemical waste associated with the reaction. We have recently investigated the Shono-type oxidation of C–H bonds adjacent to a tertiary amide13 and our initial foray into this area began with attempting to expand the scope of the amide oxidation to esters (Fig. 1). It is known that the Shono electro-oxidation of amides proceeds through an N-acyl iminium species (A).14 It was therefore postulated that a transient O-acyloxonium species (B)15 could form under similar electro-oxidative conditions in esters bearing an α-methylene or methide group.

This unstable O-acyloxonium species (B) would in turn react further with adventitious water to form the aldehyde product and a carboxylic acid as a by-product via intermediate (C). Alternatively, an ester and aldehyde product could potentially form when conducted in an alcohol. To the best of our knowledge there are only limited reports of electro-oxidative cleavage of an ester group.16

![Fig. 1](https://example.com/fig1.png)

**Fig. 1.** Context: Expanding the scope of amide C–H bond functionalisation from amides (A) to esters (B).
Results and discussion

To probe whether this methodological leap was indeed feasible, a collection of benzyl acetates were prepared including the parent benzyl acetate 1a, a mild electron donating example 1b and a mild electron withdrawing example 1c (structures shown in Table 2). Cyclic voltammetry was recorded for 1a (Fig. 2).

Using a sensitive measurement of 10 mV s⁻¹ scan rate it was observed in both electrolyte systems (LiClO₄ and Bu₄NClO₄) that oxidation waves for all three substrates were observed with +1.0 V (1a), +1.2 V (1b) and +0.9 V (1c) oxidation potentials (relative to Ag/AgCl) and a slightly improved peak current (Ip) measurement in Bu₄NClO₄. On the basis of this positive oxidation result, screening of potential conditions to enable viable electro-oxidation of model benzyl acetate 1a was attempted (Table 1).

In the first instance, potentiostatic conditions were screened with 1a (entries 1–8) using both Bu₄NClO₄ and LiClO₄ as the electrolyte. The applied voltage was varied around the observed oxidation potential for 1a (cyclic voltammetry measurement, +1.0 V) with up to an extra 300 mV applied to compensate for expected iR drop across the electrode surface. In all cases, the reaction was performed until F mol⁻¹ equivalent to 4 electrons per mole of substrate was passed or starting material consumption was observed. Near the oxidation potential of 1a trace conversion to the desired aldehyde 2a was observed in both electrolyte systems (entries 3, 4 and 6, 7, respectively). However, at higher applied voltages degradation products were observed (entries 5 and 8, respectively), coupled with excessive time required for sufficient charge to be passed (24 h to 5 days), a controlled voltage approach was ruled out in this system early on. Switching to a galvanostatic approach, using the same electrolyte systems and reticulated vitreous carbon (RVC) electrodes produced more promising results (entries 9–15).

In particular, it was observed that a single solvent system gave higher yields than the previously optimized solvent system for the Shono oxidation, acetonitrile-methanol plus coupled with its ease of separation from the reaction products, was selected as the electrolyte. To probe whether additional water improved the reaction yield (entry 15) plus coupled with its ease of separation from the reaction products, was selected as the electrolyte. To probe whether additional water improved the reaction yield (entry 15) based on a postulated mechanism led to a reduced yield versus entry 14. Furthermore, passing no electrical current led to no reaction (entry 16). To test the hypothesis that C–H bond oxidation adjacent to an ester was possible, a collection of benzyl esters were prepared. Our initial results are detailed in Table 2. It was found using the optimised conditions, appreciable amounts of the desired aldehyde (2a–2e) were obtained from the benzylic acetates (1a–1c). To address, the mechanism issue identified in Fig. 1, a simple aqueous base wash removed the by-product. However, there were still limitations to this approach for example electro-oxidation of cyclic benzylic ester 1d or homologated ester 1e, did not
afford the aldehyde 2d and 2e, respectively. These limitations coupled with the use of an acyl ancillary group still did not meet our green chemistry standards due to the additional manipulation step required to prepare the acetate. We therefore considered whether a stabilising group on the heteroatom adjacent to the C–H bond was essential for successful electrooxidation. Promisingly, cyclic voltammetry measurements on benzyl alcohol 3a showed an oxidation wave at +1.2 V relative to Ag/AgCl. Using our previously optimised conditions for the ester electro-oxidation we explored the direct, mediator-free, oxidation on a range of commercially available alcohols (Table 3).

It was possible to cleanly convert benzyl alcohol (3a) to benzaldehyde (2a) under the mild conditions of lithium perchlorate in methanol in near quantitative yield and in improved yield compared to the chemical manipulation of forming the benzyl acetate (99% vs. 80%, respectively). The scope of this reaction was further investigated via exploration of the effects of electron withdrawing and donating group around the ring system and steric effects around the reacting centre. The use of a chlorine atom as an electron withdrawing group in the ortho- (2f, 81%), meta- (2g, 55%) and para- (2h, 86%) positions was well tolerated. The use of a methyl group as a mild electron donating group in the ortho- (2i, 66%), meta- (2j, 99%) and para- (2b, 83%) positions also afforded good to excellent yields of the aldehyde.

Intriguingly, a strong electron donating group para to the reacting centre (from para-methoxy benzyl alcohol) resulted in a greatly reduced yield of aldehyde 2k (27%). The relatively low yield of 2k compared with other benzaldehydes is likely to be due to the para-methoxy group stabilizing the carbon-centred benzylic radical leading to further unproductive reaction pathways and oxidative decomposition of 2k.

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Conclusion

The use of mediator-free, galvanostatic, direct electro-oxidation of benzylic alcohols and acetates shows scope on a range of substrates and offers an alternative and complementary approach to the preparation of valuable aldehydes. Mechanistic investigations to determine the sequence of electro-oxidation steps are now underway.

Experimental section

General methods

Reactions were carried out under nitrogen. Organic solutions were dried over MgSO₄. Starting materials were purchased from commercial suppliers and were used without further purification. Solvents were dried over molecular sieves (3–4 Å). Flash silica chromatography was performed using Sigma-Aldrich high-purity grade, pore size 60 Å, 200–400 mesh particle size silica gel. ¹H and ¹³C NMR spectra were recorded on a JEOL ECS 400 NMR Spectrometer at 400 MHz or Bruker AVIII 300 or 400 MHz spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0) and/or referenced to the solvent in which they were measured. All chemical shifts (δ) are reported in parts per million, and coupling constants (J) are reported in Hertz. Low and High-resolution mass spectrometry analysis were obtained using an Agilent 6450 LC-MS/MS system. Infrared (IR) spectra were recorded on a ThermoScientific Nicolet Impact-380 ATR-FTIR spectrometer. Electrolysis and cyclic voltammetry were performed using a Metrohm Autolab PGSTAT100N with a 10 Amp Booster (Metrohm Autolab, UK) with an undivided electrochemical cell. Data was processed using Autolab Nova software (version 2.0). The electrode system for electrolysis consisted of two reticulated vitreous carbon (RVC) electrodes (supplier: ERG Aerospace; specifications: 45 pores per inch (PPI); 800 square foot per cubic foot; size 20 × 11 × 5 mm) for galvanostatic reactions plus an additional pseudo Ag/AgCl reference electrode for potentiostatic reactions. Please see ref. 13 for further details and images of the reaction set-up.

General procedures and safety statements

Preparation of benzyl acetates. A round bottom flask equipped with a magnetic stirrer was charged with the appropriate benzyl alcohol (10.0 mmol) and acetic anhydride (15.0 mmol). The reaction mixture was refluxed (85 °C) for 15 h. Upon cooling to room temperature the reaction mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (30 mL). The combined organic phase was washed with 1 M aq HCl (30 mL), saturated aq NaHCO₃ (30 mL), water (30 mL), brine (30 mL), and dried (MgSO₄). The solvent was evaporated under reduced pressure to afford the title compound without further purification.

Electrosynthetic oxidation reactions. A sealable electrolytic cell equipped with a magnetic stirrer was added anhydrous methanol (10 mL), lithium perchlorate (0.53 g [0.50 M]) and the alcohol (0.5 mmol [0.05 M]) or the benzyl acetate (0.5 mmol [0.05 M]) under study. Two reticulated vitreous carbon (RVC) electrodes were inserted into the solution at a distance of approximately 0.5 cm from each other and the vial sealed. The solution was cooled to 0 °C (ice-bath) and degassed with nitrogen. A fixed current (10 mA) was passed through the solution in an ice bath until the desired charge (Q) was transferred (on average t = 5.5 h). Upon completion of the reaction, the solvent was evaporated (at 35 °C), the residual oil was partitioned between water (10 mL) and ethyl acetate (5 mL × 3). The combined organic extracts were dried (MgSO₄) and evaporated. Analytical quality sample of the aldehyde/ketone was obtained by column chromatography (SiO₂; cyclohexane–ethyl acetate) to afford the title compound.

Cyclic voltammetry studies. An undivided glass cell equipped with a rectangular reticulated vitreous carbon (RVC) anode (11 cm²) and rectangular RVC cathode (11 cm²), arranged opposite to one another at a distance of 3.0 mm with...
a Ag/AgCl pseudo reference electrode placed 1.0 mm from the working electrode. To this reaction vessel was added the analyte under study (5.0 mM) in the relevant organic solvent(s) (total volume 6.0 mL) and electrolyte (e.g. tetrabutylammonium perchlorate (0.5 M)). Scan rate was varied using the Autolab Nova 2.0 software.

**Caution: Perchlorates** – May intensify fire. In combination with flammable solvents, all sources of ignition should be avoided. During the concentration stage of the work-up, low temperature rotary evaporation with a suitable shield should be employed. The aqueous layer (after extraction) was treated with excess sodium sulphite prior to disposal.

**Caution: Passing an electrical current through flammable organic solvent** – The potentiostat and wiring should be regularly inspected for faults and pass all relevant electrical tests prior to use.

**Spectroscopic data**

**Benzyl acetate** (1a). The title compound was afforded as a clear oil (0.85 g, 56%) using general procedure A. 1H NMR (400 MHz, CDCl3) δ 7.42–7.29 (m, 5H), 5.12 (s, 2H), 2.11 (s, 3H) ppm; 13C NMR (100.1 MHz, CDCl3) δ 171.0, 136.0, 128.7, 128.4, 128.3, 66.4, 21.1 ppm; m/z (ESI) = 151 [M + H]⁺. Spectroscopic data are in accordance with literature.

**4-Methylbenzyl acetate** (1b). The title compound was afforded as a clear oil (0.98 g, 53%) using general procedure A. 1H NMR (300 MHz, CD3OD) δ 7.85 (m, 2H), 7.68 (m, 1H), 7.60 (m, 2H) ppm; 13C NMR (100.1 MHz, CDCl3) δ 190.8, 140.7, 134.5, 130.1, 129.2 ppm; m/z (ESI) = 187 [M + H]⁺. Spectroscopic data are in accordance with literature.

**Benzaldehyde** (2a).27 The title compound was afforded as a colourless oil (57 mg, 81%) using general procedure B (from 4-chlorobenzaldehyde, 3c). Alternatively, the title compound (48 mg, 68%) was prepared using general procedure A (from 4-chlorobenzaldehyde, 1c). 1H NMR (300 MHz, CDCl3) δ 7.99–7.78 (m, 2H), 7.71–7.43 (m, 2H) ppm; 13C NMR (100.1 MHz, CDCl3) δ 20.1 ppm; m/z (ESI) 121 [M + H]⁺. Spectroscopic data are in accordance with literature.

**4-Chlorobenzaldehyde** (2e).28 The title compound was afforded as a white powder (60 mg, 86%) using general procedure B (from 4-chlorobenzaldehyde, 3c). Alternatively, the title compound (48 mg, 68%) was prepared using general procedure A (from 4-chlorobenzaldehyde, 1c). 1H NMR (300 MHz, CDCl3) δ 7.99–7.78 (m, 2H), 7.71–7.43 (m, 2H) ppm; 13C NMR (100.1 MHz, CDCl3) δ 20.1 ppm; m/z (ESI) 121 [M + H]⁺. Spectroscopic data are in accordance with literature.
procedure B (from 4-methoxybenzyl alcohol). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 9.88 (s, 1H) 7.88–7.78 (m, 2H) 7.09–6.95 (m, 2H) 3.89 (s, 3H); $^{13}$C NMR (100.1 MHz, CDCl$_3$) δ 190.4, 164.3, 131.5, 129.8, 113.9, 55.6 ppm; m/z (ESI) 135 [M – H]$^-$; Hi-Res LC-MS (ESI) m/z calc for C$_8$H$_7$O$_2$ [M – H]$^-$; 135.0452, found 135.0454. Spectroscopic data are in accordance with literature.

Conflicts of interest

There are no conflicts to declare.

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