Tetrahedron Letters 53 (2012) 3357–3360

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Mechanistic aspects of aldehyde and imine electro-reduction in a liquid–liquid carbon nanofiber membrane microreactor

John D. Watkins *, James E. Taylor, Steven D. Bull, Frank Marken

Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

ARTICLE INFO

Article history:
Received 20 February 2012
Revised 31 March 2012
Accepted 19 April 2012
Available online 27 April 2012

Keywords:
Hydrogenation
Electro-reduction
Electrosynthesis
Carbon nanofiber membrane
Microreactor

ABSTRACT

A simple and electrolyte-free ion-transfer electrosynthesis micro-reactor system (volume 100 μL, up to 10 mg batches) for processes at liquid–liquid interfaces is developed and demonstrated for the reduction of aldehydes and imines. These cathodic reactions occur at an amphiphilic carbon nanofiber membrane accompanied by proton cation transfer from an aqueous phase into an organic phase.

As a methodology in organic synthesis, electrosynthesis[1] offers a variety of benefits over other procedures. Reactions can be controlled with a potential bias, or conducted under mild conditions with strong acids or bases generated in situ.[2] Much attention has been paid to single phase electrosynthetic reactions where a considerable concentration of electrolyte is required in the organic media. Water is an ideal electrochemical medium due to its high dielectric constant, but is often dismissed as a potential solvent due to its incompatibility with many organic processes. However, electrochemical processes occurring in organic media in simultaneous contact to an aqueous electrolyte phase and an electrode (a 'triple phase boundary') provide an alternative approach to carrying out preparative electrosynthesis.[3] It has been found that redox processes can only occur at the contact line of both liquid phases and electrode and new approaches have been investigated to increase the size of the triple phase boundary reaction zone. Recent studies have extended the methodology to include a range of water immiscible carrier phases,[4] dual phase flow channels,[5–7] acoustic emulsions,[8,9] high shear force emulsions,[10] and most recently an amphiphilic carbon nanofiber membrane-based microreactor.[11] Another benefit of the triple phase boundary synthetic approach is similar to the biphasic approach used by Amemiya et al.[12,13] for biphasic systems. In the triple phase boundary process however, no electrolyte is required in the product phase leading to cleaner syntheses with no need for an electrolyte separation step.

Traditionally hydrogenation reactions have been carried out using molecular hydrogen and a suitable catalyst, or via transfer hydrogenation reactions.[14] Examples of the electro-reduction of unsaturated alkenes to their corresponding alkanes using a mediated approach[15] and single phase reactions have recently been reviewed.[16] The electro-reduction of aldehydes and ketones is also of considerable interest due to the possibility of using different experimental conditions and reactor design to control product distribution. The radical mechanism involved in these processes leads primarily to coupled diol products as found by Bian and Bai [17] although competing reaction pathways that lead to alcohol and/or condensation products also took place. Kise et al. reported the electro-reductive acylation of aromatic ketones using acylimidazoles and chlorotrimethylsilane to form α-trimethylsiloxy ketones and esters.[18] They have also demonstrated the inter- and intramolecular electro-reductive cyclization of dicarbonyl compounds to form *trans*-1,2-diols.[19] Atobe et al. have since shown that the use of acoustic emulsification can be used to change the diasteromeric selectivity of aldehyde reduction products.[20]

An alternative electrochemical strategy to the direct reduction of carbonyl compounds followed by the abstraction of hydrogen is the electrogeneration of hydrogen at an electrode surface prior to its addition to the carbonyl compound. The challenge in achieving good yields using this approach is to find an electrode material that is suitable for the efficient evolution of hydrogen that is also capable of catalyzing hydrogenation of the carbonyl group. Santana et al. reported the efficient hydrogenation of a range of alkene and carbonyl substrates using conditions that were optimized for hydrogen evolution at a nickel deposit on iron electrodes.[21]

---

* Corresponding author at present address: Frick Chemistry Laboratory, Princeton University, Princeton, NJ 08544, USA.

E-mail address: jdw4@princeton.edu (J.D. Watkins).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.092

In this study the bulk electrolysis of aromatic aldehydes and imines is reported in an amphiphilic carbon nanofiber microreactor.[22] Figure 1A shows a photograph of the 100 μL reactor in a glass capillary with the carbon nanofiber membrane held in place by silicone. Once immersed into the aqueous phase (see Fig. 1B) an organic liquid is added and a stable interface forms for triple phase boundary electrolysis. The inclusion of a high speed micro-propeller ensures effective mixing and transport within the organic phase.

In the triple phase boundary mechanism the redox active species is only reduced at the boundary between solid electrode, aqueous electrolyte, and organic carrier phases with the concerted insertion of one proton per electron to maintain charge neutrality (Fig. 1C). Initially, the electro-reduction reaction of benzaldehyde derivatives was undertaken under triple phase boundary conditions. Voltammetry experiments (not shown) were conducted for 160 mM benzaldehyde in acetonitrile in contact with a 1 M Na_2SO_4 + 0.1 M PBS pH7 aqueous phase and suggest that the onset of reduction was at ca. −1.0 V versus SCE with a broad peak at ca. −1.9 V versus SCE,[23] meaning that a preparative electrolysis was conducted at −1.9 V versus SCE.[24] When the products of the benzaldehyde reduction were analyzed by ^{1}H NMR spectroscopy, it was found that although the conversion from starting material was essentially 100%, two distinct products had been formed (see Table 1). These were assigned as benzhydrol (1B, 2-electron product) and the *meso*-pinacol (1A, 1-electron product) as reported previously by Bian and Bai.[17] When changing the benzaldehyde concentration from 320 to 80 to 40 mM the product ratio changed from 1.0:1.8 to 1.0:1.4 to 1.0 to 1.0 respectively, indicative of more dimerization occurring at higher concentrations. In an attempt to control the pinacol-to-alcohol ratio the pH of the aqueous phase was varied, however even in 1 M Na_2SO_4 + 1 M H_3PO_4 the pinacol-to-alcohol ratio only reached 1.4:1.0. Therefore, the composition and pH of the aqueous phase appear to have a surprisingly insignificant effect on the product ratio of this electro-reductive reaction. A similar experiment using toluene as solvent instead of acetonitrile gave very similar results in terms of yield and product distribution (see Table 1).

Further investigations were then carried out to determine the functional group compatibility of this electro-reduction reaction using various aromatic aldehydes as substrates (Table 1). The reduction of *para*-trifluoromethylbenzaldehyde proceeded well, giving complete conversion in favor of the 2-electron reduction product (2B) and with a lower reduction potential being required (Table 1, entry 2). Reduction of *para*-, *meta*-, and *ortho*-tolualdehyde required more negative potentials to proceed giving slightly reduced conversions in favor of their corresponding alcohol (3–5B) products (Table 1, entries 3–5). Pleasingly, the reduction also worked well in the presence of a chloroaryl-substituent, with no additional side products observed from competing chloro group reduction (Table 1, entry 6). However, the reduction potential required for *para*-methoxybenzaldehyde was found to be too negative to allow reduction to occur (Table 1, entry 7). It was also found that *para*-nitro and *para*-cyano substituents were incompatible with these electro-reductive conditions, affording a complex mixture of products.

Finally, the effect of the concentration of the inert supporting electrolyte in the aqueous phase was investigated. Increasing the concentration of Na_2SO_4 to 2 M was found to give a pinacol (A) to alcohol (B) ratio of 1.0:1.7, whilst decreasing the concentration down to 0.1 M Na_2SO_4 resulted in a reversal in product ratio (1.4:1.0) in favor of the pinacol product.

The electro-reduction of imines to amines or vicinal diamines in organic/aqueous biphasic media would provide a useful synthetic tool for the controlled reduction of hydrolytically stable imines. Therefore, electro-reductions of a small series of *para*-trifluoromethyl-benzalimines[25] were carried out, the results of which are presented in Table 1 (entries 9–11). It was found that the benzylimine underwent a selective 2-electron reduction to afford the corresponding amine, although only in 11% conversion after 2 h (Table 1, entry 9). The overall conversion could be improved to around 50% by increasing the reaction time to 4 h (Table 1, entry 10). A faster reaction was observed for the reduction of the isopropyl-imine derivative, with complete conversion into products observed within 4 h. However, this reduction was less selective, with the amine and diamine reduction products being formed in a 1:1 ratio (Table 1, entry 11).

The ratio of products produced in the aldehyde reduction reactions (pinacol (A) versus alcohol (B) products) was surprisingly independent of the composition and pH of the aqueous phase used. The reaction conditions within the carbon nanofiber membrane are likely to be dominated by the nature of the 'triple phase boundary' zone.[26] Based on the known solubilities of the organic reactants, the reaction should occur predominantly in the organic phase. However, in the region close to the interface, fast transport of protons is possible and the formation of the 2-electron product is more likely (see 'monomer zone' in Fig. 2). The 'proton availability' reflects the ability of protons to transfer from the aqueous phase into a thin zone within the organic liquid during the reduction. At distances further away from the triple phase boundary reaction zone, electrochemical reduction at the carbon nanofiber electrode is still possible, but the formation of a 1-electron dimer can compete and dominate (see 'dimer zone' in Fig. 2).

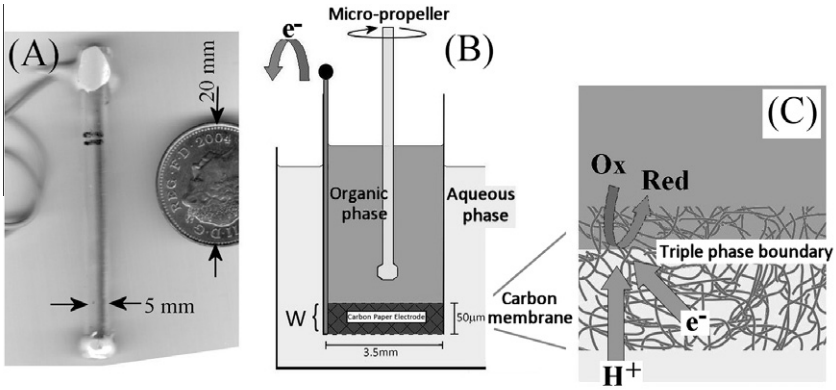
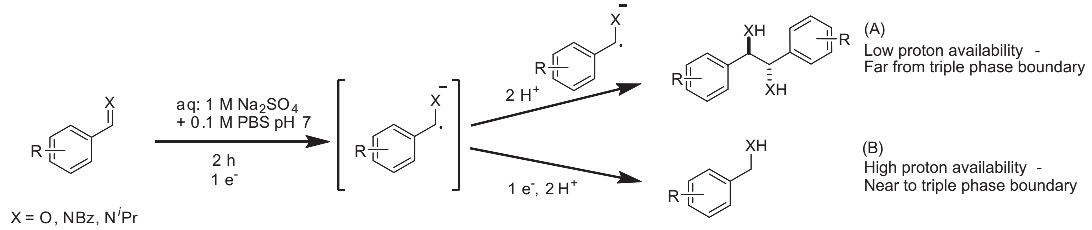
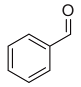
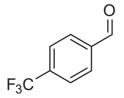
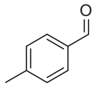
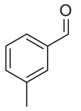
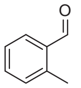
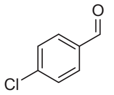
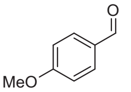
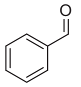
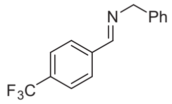
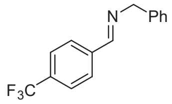
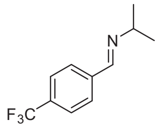


Figure 1. (A) Photograph of the tubular microreactor. (B) Schematic drawing of the microreactor capillary with organic phase and micro-propeller immersed with the amphiphilic carbon nanofiber membrane separating the aqueous electrolyte phase. (C) Schematic drawing of the overall interfacial process during reduction in the organic phase.

Table 1
Summary data for the reduction of substituted benzaldehydes (160 mM) in a liquid–liquid carbon membrane microreactor in an organic phase of 100 μL MeCN and an aqueous phase of 1 M Na_2SO_4 + 0.1 M PBS pH 7



Entry	Reactant	Conditions	Triple phase reduction potential versus SCE	Ratio[a] A:B	Conversion[b]
1		MeCN/2 h	−1.90 V	1.0:1.8	100%
2		MeCN/2 h	−1.80 V	1.0:1.7	100%
3		MeCN/2 h	−2.10 V	1.0:3.1	66%
4		MeCN/2 h	−2.10 V	1.0:1.8	94%
5		MeCN/2 h	−2.10 V	1.0:1.7	70%
6		MeCN/2 h	−2.10 V	1.0:1.8	99%
7		MeCN/2 h	−2.10 V	—	Negligible
8		Toluene/2 h	−1.85 V	1.0:1.6	100%
9		MeCN/2 h	−1.70 V	Amine only	11%
10		MeCN/4 h	−1.70 V	Amine only	50%
11		MeCN/4 h	−1.85 V	1.0:1.0	100%

The initial reduction current was found to decay rapidly to a limiting current of 1–1.5 mA giving ca. 7–11 C of charge flow in a 2 h electrolysis. This value represents an excess charge of 2 or 3 times compared to the required current for the 2 electron reduction of 160 mM of aldehyde or imine in 100 μL of solvent.

[a] Product distribution calculated from integration of resonances arising from diol (2H) and alcohol (2H) at ca. 4.75 and 4.6 ppm in their ^1H NMR spectra, respectively for aldehydes and from integration of resonances arising from diamine (2H) and amine (2H) at ca. 4.80 and 4.65 ppm in their ^1H NMR spectra, respectively for imines.

[b] Conversion calculated from comparison of integration of the aldehyde peak (1H) at ca. 10 ppm and the new singlet peaks for diol (2H) and alcohol (2H) at ca. 4.75 and 4.6 ppm in their ^1H NMR spectra, respectively for aldehydes or from comparison of integration of the imine peak (1H) at ca. 8.4 ppm and the new singlet peaks for diamine (2H) and amine (2H) at ca. 4.80 and 4.65 ppm in their ^1H NMR spectra, respectively for imines.

Based on this model, it appears that the pH of the aqueous phase is less important than the mobility of protons through the organic phase and this can explain the experimental observations. It was also found that the use of the organic soluble proton donor trifluoroacetic acid, did not change the product yields appreciably. In future we believe that further study of the conditions at the carbon nanofiber-supported liquid–liquid interface will be important for a wider range of electro-synthetic processes to be possible.

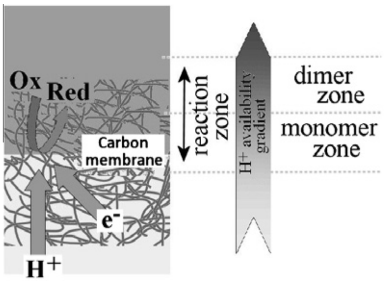


Figure 2. Schematic drawing of the extended triple phase boundary reaction zone and the reaction zone with a change in proton availability causing the formation of a mixture of monomer and dimer reduction products.

Particularly interesting will be the use of pulse-electrolysis where the diffusion time of reagents within the membrane electrode can be controlled to increase the yield of 2-electron product versus 1-electron product.

In conclusion, a microreactor system for hydrogenation and electro-reduction reactions has been developed based on a carbon nanofiber membrane that separates an aqueous electrolyte and an immiscible organic phase (toluene or acetonitrile). For aldehyde reduction and imine reduction processes good conversions and interesting selectivity effects have been observed. Although not isolated in this case, the use of this reactor for preparative reactions can yield up to 5 mg of products to be produced. This assumes a maximum concentration of 250 mM redox material can be effectively electrolyzed, as found in our previous study.[11] There is however potential for scale up through the use of continuous flow methods. The novel electro-reductive method described should be easily adapted to other related synthetic challenges.

Acknowledgements

J.D.W. gratefully acknowledges the EPSRC for funding support and J. E. T. thanks the University of Bath for the award of a Ph.D. Research Fellowship.

References and notes

1. Utley, J. *Chem. Soc. Rev.* **1997**, *26*, 157.
2. Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.
3. Marken, F.; Webster, R. D.; Bull, S. D.; Davies, S. G. *J. Electroanal. Chem.* **1997**, *437*, 209.
4. Scholz, F.; Komorsky-Lovric, S.; Lovric, M. *Electrochem. Commun.* **2000**, *2*, 112.
5. MacDonald, S. M.; Watkins, J. D.; Gu, Y.; Yunus, K.; Fisher, A. C.; Shul, G.; Opallo, M.; Marken, F. *Electrochem. Commun.* **2007**, *9*, 2105.
6. Watkins, J. D.; MacDonald, S. M.; Fordred, P. S.; Bull, S. D.; Gu, Y. F.; Yunus, K.; Fisher, A. C.; Bulman-Page, P. C.; Marken, F. *Electrochim. Acta* **2009**, *54*, 6908.
7. MacDonald, S. M.; Watkins, J. D.; Bull, S. D.; Davies, I. R.; Gu, Y.; Yunus, K.; Fisher, A. C.; Page, P. C. B.; Chan, Y.; Elliott, C.; Marken, F. *J. Phys. Org. Chem.* **2009**, *22*, 52.
8. Atobe, M.; Ikari, S.; Nakabayashi, K.; Amemiya, F.; Fuchigami, T. *Langmuir* **2010**, *26*, 9111.
9. Watkins, J. D.; Bull, S. D.; Marken, F. *J. Phys. Chem. C* **2009**, *113*, 15629.
10. Watkins, J. D.; Amemiya, F.; Atobe, M.; Bulman-Page, P. C.; Marken, F. *Electrochim. Acta* **2010**, *55*, 8808.
11. Watkins, J. D.; Ahn, S. D.; Taylor, J. E.; Bulman-Page, P. C.; Bull, S. D.; Marken, F. *Electrochim. Acta* **2011**, *56*, 6764–6770.
12. Amemiya, F.; Fuse, K.; Fuchigami, T.; Atobe, M. *Chem. Commun.* **2010**, *46*(16), 2730.
13. Amemiya, F.; Matsumoto, H.; Fuse, K.; Kashiwagi, T.; Kuroda, C.; Fuchigami, T.; Atobe, M. *Org. Biomol. Chem.* **2011**, *9*, 4256.
14. Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
15. da Silva, A. P.; Mota, S. D. C.; Bieber, L. W.; Navarro, M. *Tetrahedron* **2006**, *62*, 5435.
16. Popp, F. D.; Schultz, H. P. *Chem. Rev.* **1962**, *62*, 19.
17. Bian, Y. J.; Bai, D. S. *J. Indian Chem., Sect. B* **1890**, *2007*, 46.
18. Kise, N.; Agui, S.; Morimoto, S.; Ueda, N. *J. Org. Chem.* **2005**, *70*, 9407.
19. Kise, N.; Shiozawa, Y.; Ueda, N. *Tetrahedron* **2007**, *63*, 5415.
20. Atobe, M.; Tonoi, T.; Nonaka, T. *Electrochem. Commun.* **1999**, *1*, 593.
21. Santana, D. S.; Melo, G. O.; Lima, M. V. F.; Daniel, J. R. R.; Areias, M. C. C.; Navarro, M. *J. Electroanal. Chem.* **2004**, *569*, 71.
22. *Procedure for creation of the carbon membrane microreactor:* First a glass tube of internal diameter 3.5 mm and external diameter 5 mm was cut to be 50 mm in length. A strip, ca. 3 mm wide of graphite foil was cut to be 70 mm in length and attached to the inside of the glass tube by a chemically resistant silicon based adhesive and the ends of the foil folded around the top and bottom of the glass tube. A contact was formed at one end of the tube by the adhesion of a copper wire by silver epoxy. At the other end a carbon membrane disc was cut to 5 mm diameter and placed in contact with the foil. Silicon adhesive was used to seal the carbon to the tube with a circle of carbon ca. 3.5 mm exposed on both the inside and outside of the glass tube. Upon curing the silicon adhesive contracted and forced the carbon membrane and foil into a physical electrical contact suitable for electrochemical study.
23. Voltammetric experiments were performed using a microAutolab III system (Ecochemie, Netherlands) in staircase voltammetry mode, with the step potential maintained at approximately 1 mV. The counter and reference electrodes were platinum gauze and KCl-saturated calomel (SCE, Radiometer), respectively. The working electrode was a 4 mm diameter carbon nanofiber membrane disc ('Bucky paper', Nanolabs US, with low resistivity (~0.1 Ω cm) containing relatively low impurity levels (Fe 0.36, Si 0.31, Al 0.23, Na 0.32, S 0.23 at %) mounted with Ambersil silicone (Silicoset 151) on a glass capillary of 3.5 mm inner diameter and 5 mm outer diameter. The electrical contact was made with a 1 mm stripe of pyrolytic graphite film (Goodfellow, UK) inside of the glass capillary. Solutions were deaerated with argon (Pureshield, BOC). The pH was measured with a glass electrode (3505 pH meter, Jenway). All experiments were conducted at a temperature of 22 ± 2 °C.
24. *General procedure for electro-reduction reactions:* In order to perform a synthetic reduction in the microreactor the electrode was first placed ca. 20 mm deep in an aqueous solution containing electrolyte (Fig. 1). After visual inspection for leaking of aqueous phase into the tube, 100 μL of organic phase containing redox probe was added to the inside of the glass tube. The electrode was left to equilibrate for several minutes to confirm no leaking of either phase though the carbon membrane. A cyclic voltammogram was performed to ascertain the suitability of the electrode for synthesis and a suitable potential for potentiostatic reduction was chosen. Resistance variations were seen to change the voltammetric shape slightly between electrodes. The overhead stirrer was inserted into the glass tube to a depth of ca. 1 mm from the surface of the electrode and was engaged at a rotation speed of ca. 300 Hz while the potential was held at a value corresponding to a suitable reductive current (1–10 mA). After the synthesis was complete the overhead stirrer was removed and the internal organic solution separated by pipette as well as three washings of the inside of the glass tube by fresh acetonitrile. The electrode was then immersed in clean MeCN followed by 1 M H_3PO_4 followed by distilled water for about an hour each before reuse. The aqueous phase can be recycled immediately.
25. *General procedure for the synthesis of imines:* Both imines were produced by the same reaction process. To a solution of 4-trifluoromethylbenzaldehyde (3.8 mmol) in anhydrous MeCN (20 ml) was added (3.8 mmol) benzylamine under nitrogen and the mixture was stirred at room temperature for 24 h. In some cases a white precipitate formed due to the acid base pairing of oxidized aldehyde and amine but was removed by gravity filtration. The MeCN was removed by rotary evaporation and the residue analyzed by ^{1}H and ^{13}C NMR spectroscopy showing the imine product with no aldehyde being present. The sample was used without further purification.
26. Marken, F.; Watkins, J. D.; Collins, A. M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 10036.