Electrochemical Deoxygenation of Primary Alcohols

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Abstract: Direct electrolysis of primary alcohols, in the presence of methyl toluate, leads smoothly to the formation of the corresponding deoxygenated product in high yield.

Key words: deoxygenation, electrochemical, esters, reduction, free radicals

The conversion of a hydroxyl group into the corresponding alkane is often a delicate process. For years, the Barton–McCombie reaction has been considered as the acme of such transformation.¹ Unfortunately, this reaction requires the prior derivatization of the alcohol into a heatand light-sensitive xanthate² and often suffers from the use of toxic reducing agents such as tin hydride. Whilst this drawback can be partially overcome by the use of less toxic systems, such as borane/air³ or phosphites,⁴ this reaction is such as difficult to perform on multigrams scale.⁵

Recently, our laboratory has been involved in the monoelectronic reduction of aromatic esters. Our investigations in that field prompted us to develop a chemical⁶ and electrochemical⁷ deoxygenation reaction using aromatic esters as benign radical precursors (Scheme 1).



Scheme 1 Deoxygenation of aromatic esters

Compared to most of the classical chemical deoxygenation reactions, the electrochemical reduction method that we developed has the advantage of avoiding the use of toxic reagents or co-solvents. Moreover, it employs the cheapest source of electrons: the electric current itself. Whilst this process proved to be efficient for the deoxygenation of secondary and tertiary derivatives,⁸ primary esters usually gave poor yields of deoxygenated product when subjected to the reductive conditions.⁹ Previous works by Nakajima, who developed an electrochemical benzoylation protocol¹⁰ and by Utley, who reported on an electrochemical transesterification–reduction system for oxalate esters,¹¹ prompted us to consider a similar sequence for the deoxygenation of alcohols without the need to esterify them prior to electrolysis. The basic principle

SYNLETT 2012, 23, 1235–1239 Advanced online publication: 26.04.2012 DOI: 10.1055/s-0031-1290778; Art ID: ST-2012-D0052-L © Georg Thieme Verlag Stuttgart · New York would involve the electrolysis of the desired alcohol, in the presence of an excess of methyl toluate, in a solution containing a tetrabutylammonium electrolyte (Figure 1).

Figure 1 Electrotransesterification–Deoxygenation

In the first step, the alcohol **4** would be deprotonated at the cathode to generate hydrogen gas and a highly nucleophilic tetrabutylammonium alkoxide **5**.¹² This alkoxide would then undergo transesterification with methyl toluate, leading to the in situ formation of **6**, the corresponding toluate of the starting alcohol **4**. Finally, toluate **6** could be electroreduced into the corresponding alkane **3**. Alternatively, **6** could be deprotected leading back to the initial tetrabutylammonium alkoxide **5**. Indeed, we have shown previously that the reduction of aromatic esters, in the presence of a proton source, such as an alcohol, leads to their chemoselective deprotection.^{6,7}

In this case, such a side reaction will be of minor importance since the alkoxide can undergo a new transesterification–deoxygenation sequence. This cycle can then be repeated until full conversion is reached.

Since some of the methyl toluate will also be directly electrolyzed before being able to serve as a transesterification



agent, the electrolysis process actually requires an excess of this methyl ester.

In a first attempt, the easiest electrolysis setting was used: an undivided cell, containing 3 mmol of docosanol and 10 equivalents of methyl toluate, dissolved in a DMF solution containing NBu_4BF_4 as supporting electrolyte, and equipped with two 6 cm² carbon graphite electrodes. Unfortunately, even after varying temperatures and the current densities, no traces of docosane were observed. However, much to our delight, when the same experiment was carried out in a divided cell, using conditions similar to those employed for our previous electrochemical deoxygenation methodology, docosanol was completely consumed after 12 hours and docosane was identified as the main product of the electrolysis (Scheme 2).

	C _{gr} //C _{gr} methyl toluate (10 equiv)	
~	NBu₄BF₄ (0.15 M in DMF) 15mA⋅cm ⁻² , 130 °C, 12 h	0 H M-
C ₂₁ H ₄₃ OH 3 mmol	yield: 67% current efficiency: 10%	С ₂₁ н ₄₃ —ме 7



This encouraging result prompted us to modify several electrolysis parameters in order to determine their respective impact on the deoxygenation process.

Table 1 Influenc	e of the Temperature
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C ₂₁ H ₄₃ 3 mm 6	C methyl toli NBu ₄ BF ₄ (i 15 mA OH	^{igr//Cgr} uate (10 equiv) 0.15 M in DMF) ⋅cm ⁻² , 12 h	S₂1H₄3─Me 7
Entry	Temp	Yield of 7 ^a	Current efficiency
1	−10 °C	0%	0%
2	0 °C	0%	0%
3	25 °C	0%	0%
4	40 °C	21%	3%
5	60 °C	87%	13%
6	100 °C	85%	13%
7	130 °C	67%	10%

^a All yields are for pure and isolated product.

As demonstrated before, the temperature plays a key role in the electrochemical reduction process. For the transesterification–deoxygenation reaction, the optimal temperature appears to lie between 60 °C and 100 °C (Table 1). As a second important parameter, the influence of the solvent was investigated (Table 2). Only DMF or NMP could be employed as solvent for the formation of the desired deoxygenated product. The use of acetonitrile or DMSO led to the formation of various degradation products, originating presumably from the electroreduction of the solvent and no docosane was formed in this process.

C ₂₁ H ₄₃ OH 3 mmol	C _{gr} //0 methyl toluate NBu ₄ BF ₄ (0.15 15 mA·cm ⁻² , 6	C _{gr} ∌ (10 equiv) M in solvent) 60 °C, 12 h → C	₂₁ Н ₄₃ —Ме
6			7
Entry	Solvent	Yield of 7 ^a	Current efficiency
1	DMF	87%	13%
2	NMP	85%	13%
3	MeCN	0%	0%
4	DMSO	0%	0%

^a All yields are for pure and isolated product.

Table 3 shows the influence of the current density. Increasing the current density higher than 35 mA.cm⁻² appears to have little impact on the yield of docosane. However, current densities greater than 200 mA.cm⁻² tend to decompose the carbon graphite electrodes during the electrolysis. Surprisingly, the time required to reach total conversion of the starting material is not directly proportional to either the current density or the amount of starting material. This could be partially explained by the presence of side reactions, such as the electroreduction of the solvent or the Hoffman degradation of the tetrabutylammonium salt. Electrolysis at a fixed potential of -2.4 V vs. Ag/AgCl_{sat}, which is selective for the reduction of toluate ester, was also conducted in order to avoid degradation of the solvent. Unfortunately, this time, the starting alcohol remained untouched, in stark contrast to methyl toluate which was totally electroreduced.

Since the electrolysis had to be performed at 60 °C, a possible way to avoid the Hoffman degradation would be to replace the tetraalkylammonium salt by an inorganic material like lithium perchlorate. As shown in Table 4, no docosane was obtained when LiClO₄ was used as the supporting electrolyte (entry 5), presumably because the intermediate lithium alkoxide might not be nucleophilic enough to perform the desired transesterification. Tetraalkylammonium salts with hydrophobic anions like BF₄⁻ or PF₆⁻ gave higher yields of deoxygenated products (entries 1, 2 and 6) than the corresponding halides (entries 3 and 4). These latter salts not only afforded lower yields of docosane but also produced significant amounts of bromine or iodine in the anodic compartment.

Table 3 Influence of the Current Density

Entry	Cumont donaitu	T. 3	Viald	Cumont
3 mi 6	mol		7	
C ₂₁ H ₄₃	∼он		C ₂₁ H ₄₃ —M	е
	NBu ₄ BF ₄ (0.	15 M in DMF)		
	methyl tolua	ate (10 equiv)		

			of 7 ^b	efficiency
1	5 mA·cm ⁻²	48 h	12%	1%
2	15 mA·cm ⁻²	12 h	87%	13%
3	$35 \text{ mA} \cdot \text{cm}^{-2}$	8 h	89%	8%
4	$50 \text{ mA} \cdot \text{cm}^{-2}$	6 h	90%	8%
5	100 mA·cm ⁻²	6 h	92%	4%
6	$200 \text{ mA} \cdot \text{cm}^{-2}$	6 h	92%	2%
7	300 mA⋅cm ⁻²	6 h	90%°	1%

^a Electrolysis time for the total consumption of docosanol.

^b All yields are for pure and isolated product.

^c Amount of docosanol electrolyzed was 10 g.

 Table 4
 Influence of Supporting Electrolyte

С ₂₁ Н ₄₃ ОН 3 mmol 6	C _{gr} //C _{gr} methyl toluate (10 equiv electrolyte (0.15 M in DM 100 mA·cm ⁻² , 60 °C, 6 h) F) ⁿ → C ₂₁ H ₄₃ −N 7	1e
Entry	Supporting electrolyte (0.15 M)	Yield of 7 ^a	Current efficiency
1	NBu_4BF_4	92%	4%
2	NBu ₄ PF ₆	91%	4%
3	NBu ₄ Br	87%	4%
4	NBu_4I	86%	4%
5	LiClO ₄	0%	0%
6	Et_4BF_4	91%	4%

^a All yields are for pure and isolated product.

The influence of cathodic material was also investigated, as shown in Table 5. Surprisingly, replacing carbon graphite by platinum or lead did not decrease the required electrolysis time even though those materials are known to have low hydrogen overpotential and should therefore deprotonate alcohols more readily than carbon graphite (entries 2 and 3). Even worse, they led to lower yields of docosane. Copper tended also to give poor yield of the desired product and led to the apparition of several unidentifiable by-products (entry 4). This might be due to the difficulty to have an oxide-free surface on the copper cathode.

Table 5 Influence of the Nature of the Cathode

C ₂₁ H ₄₃ 3 mmc 6	methyl NBu₄BF 100 m⁄ OH ────	$M//C_{gr}$ toluate (10 equiv) F_4 (0.15 M in DMF) $A \cdot cm^{-2}$, 60 °C, 6 h	► C ₂₁ H ₄₃ —M 7	1e
Entry	Cathode (6 cm ²)	Electrolysis time ^a	Yield of 7 ^b	Current efficiency
1	graphite	6 h	92%	4%
2	platinum	6 h	51%	2%
3	lead	6 h	50%	2%
4	copper	6 h	21%	1%

^a Electrolysis time for the total consumption of docosanol.

^b All yields are for pure and isolated product.

Table 6 shows the optimization of the number of equivalents of methyl toluate that have to be added. With three equivalents, a maximum of 92% yield was reached. Higher concentrations in methyl toluate did not increase the yield of docosane but usually rendered the purification of the final compound more difficult.

 Table 6
 Influence of the Number of Equivalents of Methyl Toluate

С ₂₁ Н ₄₃ ОН 3 mmol 6	M//C _{gr} methyl toluate NBu₄BF₄ (0.15 M in 100 mA⋅cm ⁻² , 60 °C	DMF) 2, 6 h → C ₂₁ H ₄₃	—Me 7
Entry	Methyl toluate (equiv)	Yield of 7 ^a	Current efficiency
1	1	25%	1%
2	2	68%	3%
3	3	92%	4%
4	4	92%	4%
5	6	92%	4%
6	10	92%	4%
7	15	92%	4%

^a All yields are for pure and isolated product.

If an excess of methyl toluate is not advisable, Wang resin toluate could be used instead of methyl toluate (Scheme 3). However the reaction time was longer and the yield of deoxygenated product was slightly lower. As Fuchigami

has reported, supported reagents are not electrolyzed even if they are electroactive. However, they can react with electrogenerated product in solution.¹³



Scheme 3 Electrolysis using Wang resin's toluate

With an optimized set of conditions in hand, the scope and limitations of this methodology were determined (Table 7). While the methodology gives excellent results for primary alcohols (Table 7, entries 1-8), secondary and tertiary alcohols remain essentially unaffected by the electrochemical process. This is certainly due to their respective steric hindrance which prohibits the transesterification process to occur (Table 7, entries 9 and 10). Moreover, the process tolerates several functional groups, such as carbon–carbon double bonds (Table 7, entry 2), chloride (Table 7, entry 3), esters (Table 7, entry 4), silyl ethers (Table 7, entry 5), amides (Table 7, entry 7) and aromatic groups (Table 7, entry 8). Furthermore, the process is not limited to small scale. Indeed, it can easily be used for the deoxygenation on a multigram scale without any significant drop in yield (Table 7, entry 1).

Table 7 Deoxygenation of various Alcono	able 7 Deoxygenation of Various Ale	cohol
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ROH 3 mmol 4	C _{gr} //C _{gr} methyl toluate (3 equiv) NBu₄BF₄ (0.15 M in DMF) 100 mA·cm ⁻² , 60 °C, 6 h		
Entry	Alcohol	Yield of RH ^a	Current efficiency
1	С ₂₁ Н ₄₃ ОН 6	92% ^b	4%
2	C ₈ H ₁₇ OH	90%	4%
3	CI OH	91%	4%
4	AcO OH	89%	4%
5	TBDMSO OH	90%	4%

Table 7 Deoxygenation of Various Alcohols (continued)

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^a All yields are for pure and isolated product.

^b A yield of 90% was obtained when 10 g of docosanol were electrolvzed

^c Determined by capillary gas chromatography.

In summary, we have developed a new one-pot electrotransesterification-electrodeoxygenation process that enables the deoxygenation of primary alcohols without the need for any prior derivatization.¹⁴ The methodology gives uniformly high yields of deoxygenated product, tolerates a wide range of functional and protecting groups and has proven to be efficient on small scale as well as on multigrams scale. Finally, this new deoxygenation process represents a greener and a cheaper alternative to classical chemical deoxygenation methods. Ongoing efforts are now directed towards a deeper elucidation of the exact mechanism of this reaction, by means of electroanalytical

techniques, and towards the improvement of the faradic yield.

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- (14) Typical Experimental Procedure: An H-type cell, with two compartments of 100 mL, separated by a sintered glass with a porosity of 40 µm, was dried for one night at 200 °C. Then, each cell was equipped with graphite electrode of 6 cm² and a magnetic stir bar. Both compartments were then flushed with argon for 10 min. After filling them with NBu₄BF₄ (5 g) and with DMF (100 mL; freshly distilled under argon), primary alcohol (1 equiv) and methyl toluate (3 equiv) were added to the cathodic compartment and the solution was stirred and heated to 60 °C. Then, the intensity of the current was fixed at 600 mA and the mixture was electrolyzed until completion of the reaction, as shown by TLC or by GC (usually 6 h). The cell was then cooled to r.t. and the catholyte was carefully diluted with 4 M HCl (100 mL). The resulting solution was extracted with Et_2O (4 × 30 mL). The organic phases were collected, dried over Na₂SO₄ and the solvent was removed under reduced pressure. Finally, the crude product was purified by chromatography over silica gel to yield the desired deoxygenated product.

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