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Novel Electrochemical Deoxygenation Reaction Using Diphenylphosphinates

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ABSTRACT

The electrochemical reduction of diphenylphosphinate esters leads smoothly and in high yields to the corresponding deoxygenated products. In comparison with the previously developed methodologies, the electrolysis could be performed at lower temperature and with a higher current density, resulting in a shorter reaction time.

The removal of a hydroxyl group to form the corresponding alkane is typically achieved by using the well-known Barton−McCombie reaction[1] or one of its less toxic variants.[2] Unfortunately, this transformation suffers from a serious drawback which is the need to prepare the heat and light sensitive xanthate.[3] One alternative to this procedure is the direct deoxygenation of the hydroxyl group by using a strong Lewis acid in combination with a hydride source.[4] However, this protocol is only effective if the molecule does not bear sensitive functionalities. On the other hand, growing ecological and economical concerns are driving chemists toward the discovery of new and nontoxic reactions that employ inexpensive reagents. With this objective in mind, we have recently reported some of our results on the electrochemical reduction of toluates as an alternative to classical deoxygenations. Indeed, electrochemical synthesis usually avoids the use of toxic metallic reagents, solvents, or additives, and it represents the cheapest and most readily available source of electrons. Unfortunately, the reduction of aromatic esters requires either the use of the toxic samarium(II) iodide/HMPA system[5] or that the electroreduction be carried out at high temperature with a low current density. These conditions, while highly successful, tend to require a long electrolysis time and give only modest yields of deoxygenated products when primary alcohol derivatives are employed.[6]

Diphenylphosphinates usually behave as leaving groups when they are activated by a Lewis acid.[7] They have also been used as mild activating agents in peptide coupling processes.[8] Surprisingly, and to the best of our knowledge, there are only a few records in the literature about the electrochemical behavior of phosphorus esters and their use in organic electrosynthesis.[9] In this communication, we wish to disclose that the electrochemical reduction of diphe-

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(2) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Spiegel, D. A.; Wiberg, K.; Schacherer, L.; Medeiros, M.; Wood, J. *J. Am. Chem. Soc.* **2005**, *127*, 12513. (c) Postigo, A.; Kopsov, S.; Ferreri, C.; Chatgilialoglu, C. *Org. Lett.* **2007**, *9*, 5159.

(3) Zard, Z. S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672.

(4) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741.

(5) Lam, K.; Markó, I. E. *Org. Lett.* **2008**, *10*, 2773.

(6) (a) Lam, K.; Markó, I. E. *Chem. Commun.* **2009**, 95. (b) Lam, K.; Markó, I. E. *Tetrahedron.* **2009**, *65*, 10930.

(7) (a) Kobayashi, Y.; Minowa, T.; Mukaiyama, T. *Chem. Lett.* **2004**, *33*, 1362. (b) McCallum, J. S.; Sterbenz, J. T.; Liebeskind, L. S. *Organometallics* **1993**, *12*, 927.

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(9) (a) For an excellent review, see: Kargin, Y. M.; Budnikova, Y. G. *Russ. J. Gen. Chem.* **2001**, *71*, 1393. (b) Ohmori, H.; Maeda, H.; Kikuoaka, M.; Maki, T.; Masui, M. *Tetrahedron* **1991**, *47*, 767. (c) Maeda, H.; Maki, T.; Ohmori, H. *Tetrahedron Lett.* **1992**, *33*, 1347. (d) Maeda, H.; Ohmori, H. *Acc. Chem. Res.* **1999**, *32*, 72.

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nylphosphinic esters leads to major improvements in our previously reported electrochemical methodology for the deoxygenation of alcohols.

At the onset of our studies, it was decided that the mechanism of reduction of phosphinic esters would be investigated by using cyclic voltammetry (Figure 1).

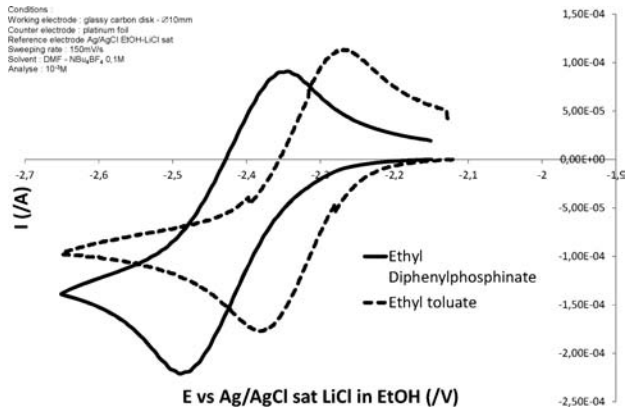
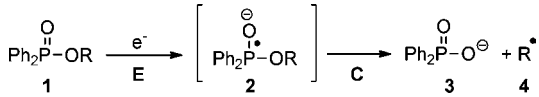


Figure 1. Cyclic voltammogram of ethyldiphenylphosphinate (plain line) and ethyl toluate (dotted line). Glassy carbon working electrode, Pt rod counter electrode, $Ag/AgCl_{sat}$ in LiCl in EtOH as reference electrode. 0.001 M in DMF containing 0.1 M in NBu_4BF_4. Sweeping rate: 150 mV/s.

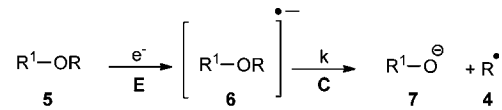
An interesting observation, that could be extracted from the cyclic voltammogram, is the reversible electrochemical behavior of ethyldiphenylphosphinate, indicating that the reduced product (most probably the corresponding radical anion) does not decompose immediately but possesses a long enough lifetime to enable its oxidation back to the starting phosphinate. The reduction potential of ethyl diphenylphosphinate is only slightly more negative than the corresponding toluate: −2.4 V vs Ag/AgCl. Next, the number of electrons exchanged during this redox process has been determined by using standard coulometric techniques. The number of faradays consumed per mole of ethyldiphenylphosphinate was found to be equal to one. These observations strongly suggest that the reduction of diphenylphosphinates follows an EC type mechanism. Hence, the diphenylphosphinate ester **1** is initially reduced into the corresponding radical-anion **2** (E, Electrochemical step) which decomposes subsequently into diphenylphosphonic acid (**3**) and into the radical of the alkyl part (**4**) (C, Chemical step) (Scheme 1).

Scheme 1. Probable Decomposition Pathway



The main driving force of this reaction would be the formation of the phosphorus−oxygen double bond when the phosphorus(IV) intermediate **2** decomposes into the phosphorus(V) species **3**. With the reduction process being reversible, we were able to use the Shain and Nicholson's technique,[10] refined with DigitalSimulation,[11] to determine the rate of decomposition of the radical-anion **2** as a function of the nature of the alkyl substituent R. Various diphenylphosphinates were synthesized,[12] and the rate constants for the dissociation of their radical anions were determined. These results are summarized in Table 1.

Table 1. Decomposition Rate of Toluate and Phosphinate-Derived Radical Anions



R^1 = *p*-$CH_3C_6H_4CO$, $(Ph)_2PO$

entry	R	*k*, *p*-$CH_3C_6H_4CO$	*k*, $(Ph)_2PO$
1	Ethyl	0.091	0.19
2	Cyclohexyl	0.097	0.33
3	1-Adamantyl	0.20	0.70
4	Allyl	6460[a]	Too fast to be mesured.[b]

[a] All mesures were realized in DMF containing 0.1 M NBu_4BF_4 using the same setup as mentioned previously[5] except for allyl toluate which was recorded at 4000 V/s using an ultramicroelectrode. [b] Even at 100 000 V/s, reversible behavior could not be observed.

As in the case of the reduction of aromatic esters,[13] the nature of the alkyl group R has a dramatic effect. The decomposition rate can be directly correlated to the stability of the produced radical **4**. Indeed, the more stable the radical **4**, the faster the decomposition of the radical-anion **6**. It is also noteworthy that the diphenylphosphinate radical-anion **2** tends to decompose 2 to 3 times faster than the corresponding toluate radical anion. From a synthetic point of view, a high decomposition rate is a much appreciated advantage, since it will help in minimizing undesired side reactions that could otherwise arise from the radical-anion **2**.

With this information in hand, 1-adamantyldiphenylphosphinate **8** was submitted to a preparative electrochemical reduction. For our initial experiment, the electrolysis was performed in a simple electrochemical system consisting of an undivided cell fitted with carbon graphite electrodes.[14] Several solvents like DMF, NMP, CH_3CN, and various supporting electrolytes such as $LiClO_4$, NBu_4BF_4, and NBu_4PF_6 were screened. Unfortunately, and despite all our efforts, no trace of adamantane **9** could be detected in these reactions. However, when the reduction was conducted in a divided cell, moderate yields of adamantane could be obtained.

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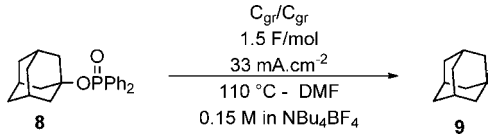
(11) http://www.elchsoft.com.
(12) McCallum, J. S.; Liebeskind, L. S. *Synthesis* **1993**, *8*, 819.
(13) Wagenknecht, J. H.; Goodin, R.; Kinlen, P.; Woodard, F. E. *J. Electrochem. Soc.* **1984**, *131*, 1559.
(14) Peltier, D.; Le Guyader, M.; Tacussel, J. *Bull. Soc. Chim. Fr.* **1963**, 2609.

In order to optimize this process, the influence of the solvent was initially studied. Some relevant results are collected in Table 2.

Table 2. Influence of the Solvent



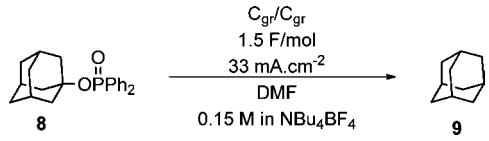
entry	solvent	yield[a]
1	DMSO	0 %[b]
2	CH_3CN	0 %[b]
4	NMP	43 %
5	DMF	44 %

[a] All yields are for pure, isolated products. [b] Decomposition of the starting material.

As can be seen from Table 2, NMP and DMF are suitable solvents for the electroreduction, while, in DMSO and acetonitrile, numerous byproducts were formed which, unfortunately, could not be easily identified.

Since the temperature of the electrolysis was playing a crucial role in the electroreduction of toluates, it was decided that its impact on the electrochemically mediated cleavage of diphenylphosphinates would be investigated. Some pertinent results are collected in Table 3.

Table 3. Influence of the Temperature



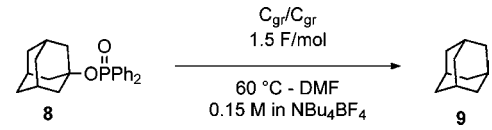
entry	temperature	yield[a]
1	-20 °C	0 %
2	0 °C	0 %
3	5 °C	9 %
4	60 °C	90 %
5	110 °C	44 %

[a] All yields are for pure, isolated products.

As can be seen from Table 3, the optimal temperature appears to lie around 60 °C. Lowering the temperature or increasing it beyond 60 °C results in a dramatic reduction in the yields of adamantane **9**. It is interesting to note that this behavior stands in sharp contrast to the reduction of the corresponding toluates that required up to 130 °C to proceed efficiently and in good yields. Next, the effect of the current density was investigated (Table 4).

From Table 4, the optimal current density was found to be 100 mA·cm^{-2}; higher current densities result in lower yields, fast degradation of the surface of the carbon graphite

Table 4. Influence of the Current Density



entry	current density	yield[a]
1	33 mA.cm^{-2}	90 %
2	60 mA.cm^{-2}	90 %
3	100 mA.cm^{-2}	92 %
4	150 mA.cm^{-2}	87 %
5	200 mA.cm^{-2}	32 %

[a] All yields are for pure, isolated products.

electrodes, and formation of side products originating from the electrodegradation of the solvent.[15] Finally, the supporting electrolytes and the nature of the electrodes were found to have little influence on the reaction rate even though carbon graphite electrodes offer the advantage of being cheap and easily renewable.

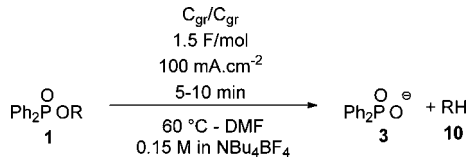
Having delineated the best conditions to successfully perform the electrochemically mediated removal of the oxygen function present in 1-adamantanol, the scope and limitations of our methodology for the reductive deoxygenation of alcohols were explored. Some significant results are collected in Table 5.

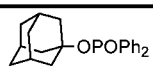
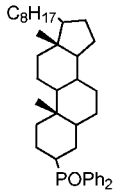
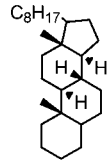
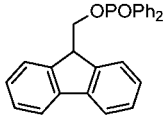
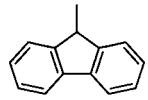
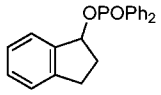
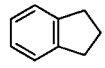
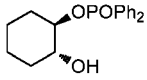
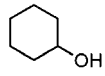
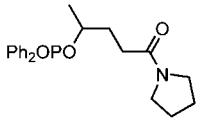
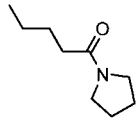
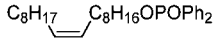
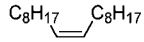
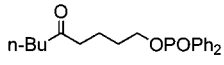
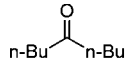
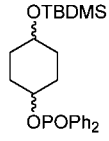
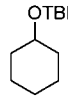
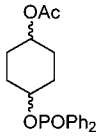
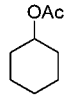
As can be seen from Table 5, primary, secondary, and tertiary (1°, 2°, and 3°) phosphinates smoothly undergo the reductive deoxygenation, leading to the corresponding saturated products in good to excellent yields. Especially noteworthy are the yields obtained for the primary phosphinates (entries 3, 7, and 8). These results contrast sharply with those reported previously for the corresponding toluates that not only reacted at much higher temperature (130 °C) but also provided the desired products in poorer yields (around 30%). It is interesting to note that, a wide variety of functionalities are tolerated under those conditions, such as alkenes (entry 7), amides (entry 6), ketones (entry 8), silylated ethers (entry 9), esters (entry 10), and even free alcohols (entry 5). This last experiment strongly suggested

(15) When the electrolysis was carried out at a constant potential of −2.4 V vs Ag/AgCl, only traces of deoxygenated product were isolated.

(16) **Standard electrolysis procedure**: An H-type cell, fitted with two compartments of 100 mL capacity, and separated by a sintered glass with a porosity of 40 μm, was dried during one night at 200 °C. Then, each cell was equipped with a graphite electrode of 6 cm^2 and a magnetic stir bar. Both compartments were then flushed with argon during 10 min. After filling them with 5 g of NBu_4BF_4 and with 100 mL of DMF, freshly distilled under argon, 600 mg (1.7 mmol) of 1-adamantyldiphenylphosphinate, dissolved in a little DMF, were added to the cathodic compartment and the solution was stirred at 60 °C. Then, the intensity of the current was fixed at 600 mA by using a potentiostat in galvanostatic mode, and the mixture was electrolyzed until completion of the reaction, as shown by TLC or by GC. The cell was then cooled down to room temperature, and the catholyte was carefully diluted with 100 mL of 4 N HCl. The resulting solution was extracted 4 times with 30 mL of ether. The organic phases were pooled and dried over sodium sulphate, and the solvent was removed under reduced pressure. Finally, the crude product was purified by chromatography on silica gel, using pentane as eluent, affording the title compound as a white powder in 92% yield. This material proved to be identical to an authentic sample of adamantane.

Table 5. Electrochemical Deoxygenation of Alcohols through Phosphinate Esters[16]

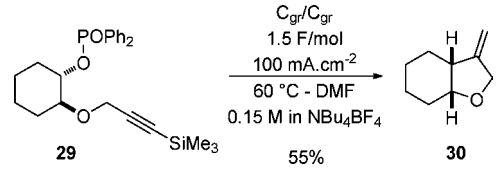


entry	esters		product		yield[a]
1		**8**		**9**	92 %
2		**11**		**12**	95 %
3		**13**		**14**	70 %
4		**15**		**16**	78 %
5		**17**		**18**	81 %
6		**19**		**20**	78 %
7		**21**		**22**	67 %
8		**23**		**24**	62 %
9		**25**		**26**	90 %
10		**27**		**28**	74 %

[a] All yields are for isolated, pure products.

that a radical pathway, rather than an ionic mechanism, was operating. In order to strenghten this proposal and to determine if the deoxygenation was going through a radical pathway, compound **29** was synthesized and submitted to the electrolysis. Gratifyingly, adduct **30**, resulting from a radical-mediated five exodig cyclization on the pendant alkyne side chain, could be isolated in good yield, thus reinforcing our proposed radical-based mechanism (Scheme 2).

Scheme 2. Radical Cyclization[a]



[a] The compound was identified by NMR, but the yield was determined by capillary gas chromatography due to the volatility of the product.

Interestingly, the final adduct **30** contains no silicon substituent; desilylation takes place during the reaction by an, as yet, unclear mechanism.[17] More experiments are currently being performed to understand the origin of the desilylation.

In summary, we have developed a new, efficient, and versatile methodology for the deoxygenation of 1°, 2°, and 3° alcohols that possesses a broad scope and proceeds under mild conditions. The method uses simple, commercially available diphenylphosphinoyl chloride and the cheapest source of electrons: electricity. Ongoing efforts are now directed toward a deeper understanding of the mechanism of this reaction, its transposition to purely chemical reduction, and its application to the total synthesis of relevant natural products.

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Supporting Information Available: Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The corresponding toluate led to the silylated cyclized product.