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Chemoselective Chemical and Electrochemical Deprotections of Aromatic Esters

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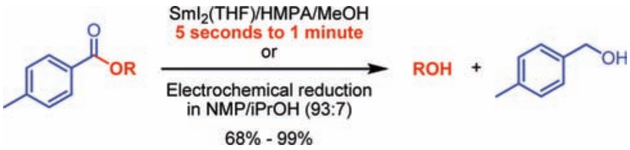
ABSTRACT



Alcohols can be easily and chemoselectively deprotected from the corresponding aromatic esters by using either SmI_2/HMPA or by electrolysis in the presence of a proton source.

To be effective, protecting groups must fulfill several requirements such as easy availability of the reagents, efficient preparation of the protected function and a high yielding (ideally quantitative) deprotection step under mild and orthogonal conditions.[1] Aromatic esters such as benzoates fulfill the first requirement since they can be easily generated by an improved procedure.[2] Unfortunately, they are difficult to hydrolyze due to their enhanced stability.[3] Apart from the classical acidic and basic methods of ester deprotection, single electron transfer appears to be an attractive alternative since aromatic esters have a lower reduction potential than aliphatic esters.[4] While such reductions have been reported previously in the literature using dissolving metals,[5] they proceed with negligible chemoselectivity. Organic electrosynthesis offers an obvious solution to this problem since the reducing power of an electrode can be easily controlled during electrolysis. During their pioneering work in this field, Horner and Neumann showed that benzoate esters could be converted to benzyl alcohols by electrolysis.[6] However, the electrolyses were carried out only on primary aromatic esters, and they required the use of a mercury cathode. Moreover, a tetramethylammonium salt had to be added to produce the highly reactive Hg(Me_4N) amalgam, which is the true reactant.[7] The occurrence of this organomercurial derivative prevented any control over the reduction potential.

Recently, we have developed a chemical[8] and an electrochemical method for the reduction[9] of toluate esters **1**, which generates initially the radical anion **2**. Subsequent fragmentation of **2** leads to the production of the radical **3** and toluate anion **4**. While attempting to optimize this process, we have serendipitously discovered that the addition of a protic source to the reduction medium completely altered the fate of the reaction. Instead of the deoxygenated product, the alcohol **5**, generated by selective cleavage of the toluoyl fragment, was obtained in high yield. In this article, we disclose a new and efficient way to deprotect toluate esters chemoselectively in the presence of other sensitive functional

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(1) (a) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: New-York, 2005. (b) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2007.

(2) Sano, T.; Ohashi, K.; Oriyama, T. *Synthesis* **1999**, *7*, 1141.

(3) Yoshimoto, K.; Kawabata, H.; Nakamichi, N.; Hayashi, M. *Chem. Lett.* **2001**, *9*, 934.

(4) Cankar, P.; Dubas, D.; Banfield, S. C.; Chahma, M.; Hudlicky, T. *Tetrahedron Lett.* **2005**, *46*, 6851.

(5) (a) Pinnick, H.; Fernandez, E. *J. Org. Chem.* **1979**, *15*, 2810. (b) Belhoul, C.; Guijarro, D.; Yus, M. *Synthesis* **2006**, *2*, 308.

(6) Horner, L.; Neumann, H. *Chem. Ber* **1965**, *98*, 3462.

(7) Southworth, B. C.; Osteryoung, R.; Fleischer, K. D.; Nachod, F. C. *Anal. Chem.* **1961**, *33*, 208.

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

(9) Lam, K.; Markó, I. E. *Chem. Commun.* **2009**, 95.

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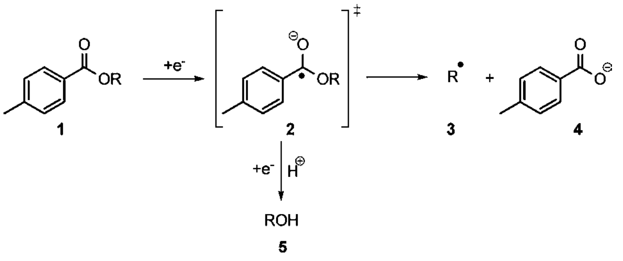
and protecting groups. Since the implementation of the methods of electroorganic chemistry in most synthetic laboratories suffers from a high activation barrier,[10] we have also developed, in parallel to the electrochemical method, a chemical deprotection protocol employing the SmI_2/HMPA system.

Scheme 1. Decomposition Pathway of the Toluate Radical Anion



Preliminary electrochemical investigations using cyclic voltammetry revealed that the addition of an alcohol to the electrolytic reaction medium quenched the in situ generated radical anion **2** and completely suppressed the reversibility of the reduction process (Figure 1, dotted curve). With this information in hand, the reduction of fluorenylmethyl toluate **6** by the SmI_2/HMPA system in the presence of methanol[11] was investigated. We were delighted to find that the deprotection proceeded within seconds and in almost quantitative yield.

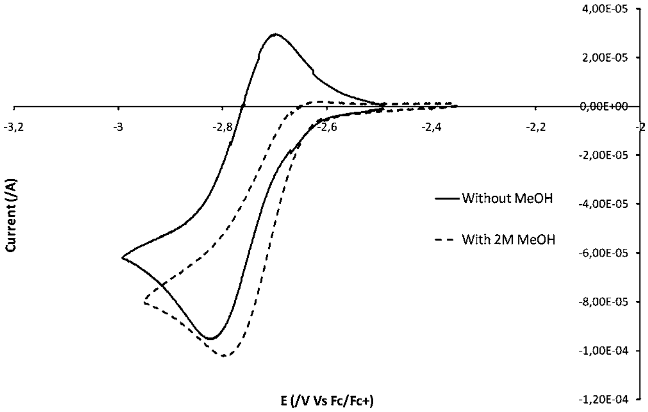
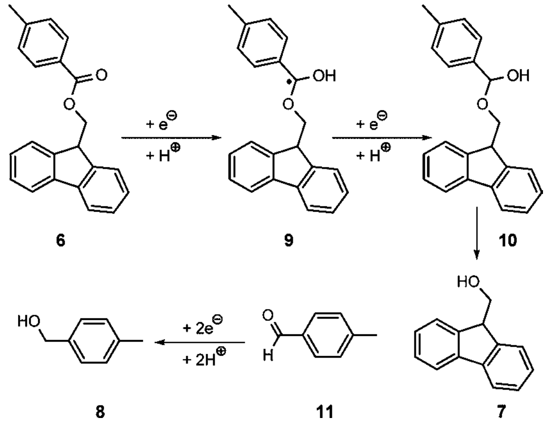


Figure 1. Influence of the addition of methanol on the reduction of ethyl toluate (10^{-3} M in NMP containing 0.1 M NBu_4BF_4. Glassy carbon working electrode/Platinum foil counter electrode/Reference electrode: Pt wire/Sweeping rate 150 mV/s).

The use of a large excess of SmI_2 led to the isolation of *p*-methylbenzyl alcohol **8** as a byproduct and enabled us to propose a tentative mechanistic rationale (Scheme 2).

Scheme 2. Possible Mechanism



We believe that the in situ generated radical anion **6** (similar to **2**) is rapidly protonated by the alcohol, affording the radical **9**, which is transformed into the hemiketal **10** by a second electron-transfer/protonation sequence. Spontaneous collapse of **10** into the corresponding alcohol **7** and aldehyde **11** is followed by its subsequent reduction into the benzylic alcohol **8**.

During our optimization studies, other proton sources, such as water or acetic acid, were tested, alas to no avail. Even the triethylamine/water system proved to be fruitless.[12] Moreover, heating the solution is essential since, at room temperature, only 20% of the desired alcohol was obtained after 12 h; the rest were mainly degradation products.

Growing ecological concerns enticed us to investigate an electrolysis process to replace the samarium iodide and the HMPA. At the onset of our work, we have employed the electrochemical system developed previously for the deoxygenation reaction.[13] This device consists of a divided H-Cell fitted with carbon graphite electrodes.[14] The deoxygenations were typically performed in NMP.[15] Various parameters, such as the proton source, the temperature, and the presence or absence of oxygen, were then screened. Some of the salient results are collected in Table 1.

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(10) Frey, D. A.; Wu, N.; Moeller, K. *Tetrahedron Lett.* **2001**, *37*, 8317.

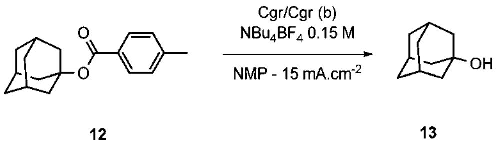
(11) Standard reduction procedure: In a 100 mL flame-dried three necked flask, maintained under argon and equipped with a condenser and a magnetic stirrer, 2.3 mL (13.4 mmol, 20 equiv) of HMPA are added to 33.5 mL (3.4 mmol, 5 equiv) of SmI2 (0.1 M in THF). The solution turns immediately into a purple color. Finally, 0.55 mL of methanol (13.4 mmol, 20 equiv) are added. The solution is then heated at reflux and 210 mg (0.67 mmol, 1 equiv) of the 9-fluorenylmethyl toluate, dissolved in a minimum of THF, is quickly added. The reaction is followed by TLC (the reaction is usually finished within 5 seconds to 1 minute). After completion, the mixture is quenched by the addition of 10 mL of saturated aqueous NH_4Cl. The aqueous layer is extracted three times with 10 mL of dichloromethane and the organic phases are pooled, washed twice with a saturated solution of sodium carbonate and then dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure and the crude product is purified by silica gel column chromatography using ether/hexane (1:1) as eluent ($R_f = 0.4$). The title compound is obtained as a white powder in 99% yield. This material proved to be identical to an authentic sample of fluorenemethanol.

(12) Dahlén, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123.

(13) Lam, K.; Markó, I. E. *Chem. Commun.* **2009**, 95.

(14) Lund, H.; Hammerich, O. *Organic Electrochemistry*, 4th ed.; Marcel Dekker Inc: New York, 2001.

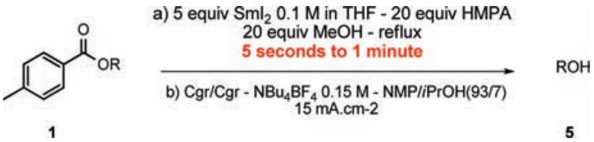
Table 1. Optimizing the Electrolysis

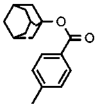
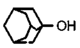
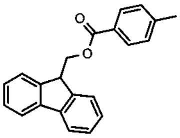
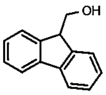
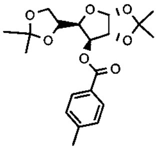
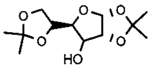
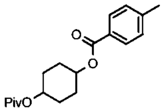
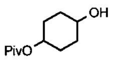
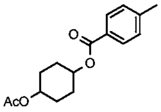
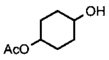
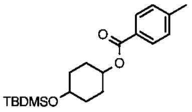
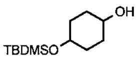
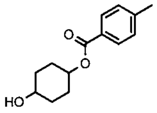
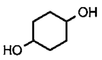
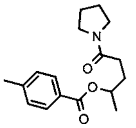
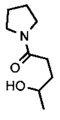


entry	temperature	degassed	additive	yield[a] %
1	25 °C	Yes	2 M H_2O	0
2	90 °C	Yes	2 M H_2O	12
3	90 °C	Yes	2 M MeOH	21
4	90 °C	Yes	2 M EtOH	73
5	90 °C	Yes	2 M *i*PrOH	95
6	25 °C	Yes	2 M *i*PrOH	0
7	90 °C	No	2 M *i*PrOH	13
8	90 °C	Yes	1 M AcOH	51
9	90 °C	Yes	2 M AcOH	44

[a] All yields were determined by GC. [b] Cgr: carbon graphite electrode.

Table 2. Chemoselective Deprotection of Toluates



entry	toluate		product		yield % (a)	yield % (b)
1		**12**		**13**	89	95
2		**6**		**7**	99	81
3		**14**		**15**	87	0
4		**16**		**17**	90	76
5		**18**		**19**	90	83
6		**20**		**21**	89	72
7		**22**		**23**	98	68
8		**24**		**25**	83	89

[a] Using SmI_2. [b] Using electrolysis. All yields are for isolated, pure compounds.

Examination of Table 1 clearly reveals the superiority of *i*PrOH as the proton donor. A gradual increase in yield is observed when going from H_2O to MeOH, EtOH and, finally, *i*PrOH (entries 2−5). Interestingly, this order is opposite to the pK_a of the alcohol. The use of acetic acid resulted in only modest yields (entries 8−9) and no reaction took place at 25 °C (entries 1 and 6). Careful degassing is also required and the presence of oxygen results in essentially complete inhibition of the transformation (entry 7).

Having delineated two different sets of conditions for the deprotection of toluate esters, we then applied them to a variety of substrates to determine the scope and limitations of the method (Table 2). As can be seen in Table 2, high yields of free alcohols are obtained throughout. Primary, secondary and tertiary toluates are deprotected with equal efficiency (entries 1, 2 and 4), indicating again that the toluate is the electro-active part of the substrate. Interestingly, both methods tolerate other ester functions (entries 4 and 5), silyl ethers (entry 6) and amide moieties (entry 8). While acetals and ketals are compatible with the SmI_2/HMPA protocol, decomposition of substrate **14** occurs under electrochemical conditions. Finally, free alcohol functions remain untouched (entry 7). In view of the notorious inertia of aromatic esters toward basic and acidic conditions, the mild, efficient and fully chemoselective deprotections reported in Table 2 are quite unique.

These exciting results prompted us to examine if aromatic esters could be chemoselectively deprotected according to their reduction potential. Indeed, the reduction potential of an aromatic ester can be easily modulated by altering the nature and the number of substituents on the aromatic ring. For such a selective transformation to proceed, electrolysis at a specific potential is required. To test this hypothesis, substrate **26**, bearing a toluate and a *p*-trifluoromethylbenzoate esters, was readily assembled and its cyclic voltammogram recorded (Figure 2). This voltammogram clearly displays two reduction waves. The first one at −2.0 V corresponds to the radical anion of the trifluorobenzoyl

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(15) Standard constant current electrolysis procedure: An H-type cell, with two compartments of 100 mL, 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 stirring bar. Both compartments were then flushed with argon during 10 minutes. After filling them with 5 g of NBu_4BF_4 and with 100 mL of a mixture of NMP/*i*PrOH (93:7), 210 mg (0.668 mmol) of fluorenylmethyl toluate **6**, dissolved in a little NMP, were added to the cathodic compartment and the solution was heated to 90 °C. Then, the intensity of the current was fixed at 90 mA and the mixture was electrolysed until completion of the reaction, as shown by TLC or by GC. The cell was then cooled to room temperature and the catholyte was carefully diluted with 100 mL of 4N HCl. The resulting solution was extracted 4 times with 30 mL of ether. The organic phases were pooled, dried over sodium sulphate and the solvent was removed under reduced pressure. Finally, the crude product was purified by chromatography on silica gel, using ether/hexane (1:1) as eluent (R_f = 0.4), affording the title compound as a white powder in 81% yield. This material proved to be identical to an authentic sample of fluorenemethanol.

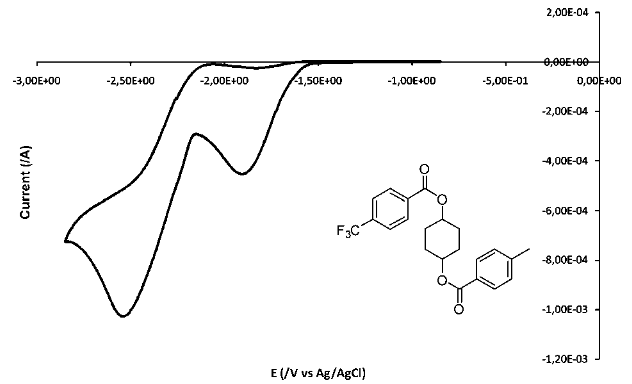
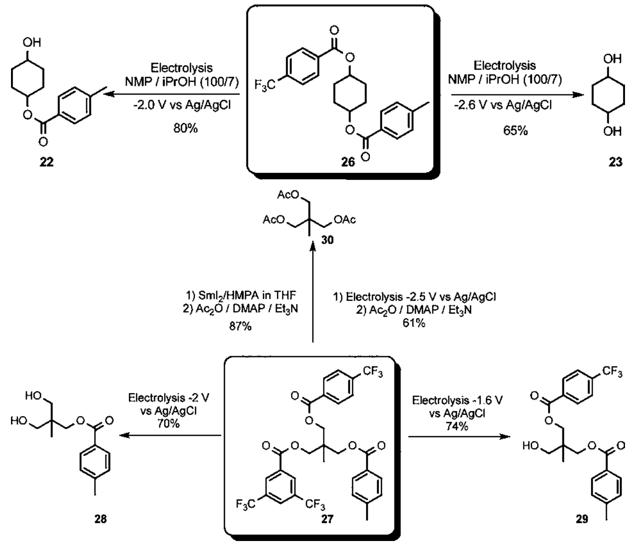


Figure 2. Cyclic voltammogram of **26** (10^{-3} M in a mixture of NMP/*i*PrOH 93:7 containing 0.1 M NBu_4BF_4. Glassy carbon working electrode/Platinum foil counter electrode/Reference electrode: Ag/AgCl in EtOH sat LiCl/Sweeping rate 150 mV/s).

Scheme 3. Selective Deprotections



substituent while the second maximum at −2.6 V has been attributed to the radical anion of the toluate group and to the dianion of the trifluorobenzoate. By setting the potential at −2.0 V, only the trifluorotoluate should be deprotected.

In the event, substrate **26** was submitted to the electrolysis conditions, using a controlled potential fixed at −2.0 V versus Ag/AgCl.[16] Gratifyingly, only the monodeprotected ester **22** was obtained in 80% yield (Scheme 3). Double deprotection was realized at −2.6 V, in up to 65% yield.

Finally, double chemoselective deprotection and triple hydrolysis could be performed efficiently by simply adjusting the reduction potential. Remarkably, while the electrochemical protocol can be made completely chemoselective, the SmI_2/HMPA procedure unravels all the protecting groups without any discrimination whatsoever.

In summary, we have developed a chemical and an electrochemical method for the mild, efficient, and chemoselective deprotection of aromatic esters. Our new methods tolerate a wide range of other functional groups and protecting groups such as aliphatic esters, amides, alcohols, silyl ethers, acetals, and ketals. Upon the basis of their respective reduction potential, unmasking of differently substituted aromatic esters can be smoothly performed, with full control of the chemoselectivity of the transformation.

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Supporting Information Available: Experimental procedure with description of ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Standard fixed potential electrolysis procedure: An H-type cell, with two compartments of 100 mL, 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 stirring bar. Both compartments were then flushed with argon during 10 minutes. After filling them with 5 g of NBu_4BF_4 and with 100 mL of a mixture of NMP/*i*PrOH (93:7), a reference electrode (Ag/AgCl saturated with LiCl in EtOH) was introduced through a salt bridge containing the solvent and the supporting electrolyte. Then 200 mg (0.5 mmol) of the diester **26**, dissolved in a little NMP, were added to the cathodic compartment and the solution was stirred and heated to 90 °C. The intensity of the potential was fixed at −2.0 V and the mixture was electrolysed until completion of the reaction, as indicated by TLC, GC and the drop of the current. The cell was then cooled to room temperature and the catholyte was carefully diluted with 100 mL of 4N HCl. The resulting solution was extracted 4 times with 30 mL of ether. The organic phases were pooled, dried over sodium sulphate and the solvent was removed under reduced pressure. Finally, the crude product was purified by chromatography on silica gel, using ethyl acetate/hexane (1:1) as eluent ($R_f = 0.3$), affording the title compound as a thick oil in 80% yield.