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Efficient Electrochemical Deprotection of Carboxylic and Amino Acids from Their 2-(Hydroxymethyl)-1,3-dithiane (Dim) Esters

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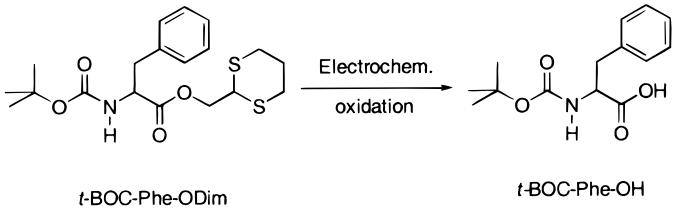
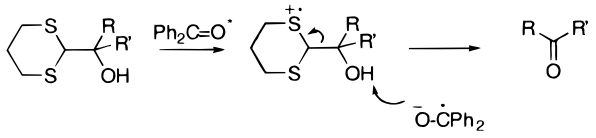
ABSTRACT



Carboxylic acids and amino acids are electrochemically deprotected from their 2-(hydroxymethyl)-1,3-dithiane (Dim) esters.

Earlier we found that photoinduced single-electron transfer in Corey−Seebach dithiane−carbonyl adducts[1] leads to efficient C−C bond cleavage:[2]



Our attempts to electrochemically induce this reaction in the adducts carrying alkyl substituents (R,R′ = H, Alk) led to partial dehydration, furnishing 2-alkylidene-substituted 1,3-dithianes instead. This facile elimination prompted us to explore the possibility of utilizing 2-(hydroxymethyl)-1,3-dithiane esters (Dim esters) as *electrochemically* removable protecting groups for carboxylic acids in general and, specifically, amino acids.

We first synthesized the Dim esters of simple carboxylic acids, phenylacetic (**1**), norbornylacetic (**2**) and benzoic (**3**), and were able to deprotect them via electrolysis in a divided cell[3] (isolated yields of the deprotected acids are shown in parentheses in Figure 1).

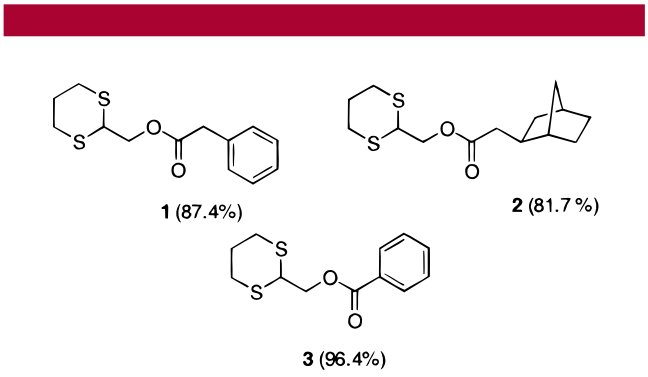


Figure 1.

Our mechanistic rationale includes the elimination of carboxylic acid from the initially formed dithiane cation radical (Scheme 1).

(1) For a review see: Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.
(2) McHale, W. A.; Kutateladze, A. G. *J. Org. Chem.* **1998**, *63*, 9924.

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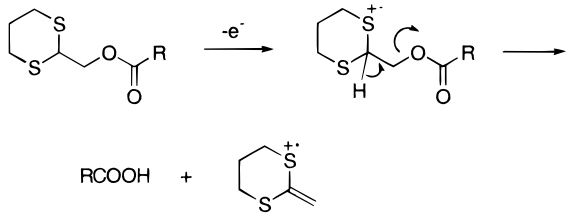
Scheme 1



It is well-known that cation radicals in acetonitrile are generally superacids. For example, Arnold reported the pK_a of the toluene cation radical to be −12.[4] It is therefore plausible that the proton at position *2* of the dithiane ring is eliminated, prompting the departure of the carboxylate. We did not identify the final product of the dithiane ring degradation, although it is known from the literature that the end products of anodic oxidations of various substituted dithianes are 1,2-dithiolane 1-oxides.[5]

We also considered the possibility of an intramolecular elimination of carboxylic acid from the cation radical, similar to pyrolysis of acetates. To this end we carried out ab initio computations at the MP2/6-31G(d) level of theory. For computational simplicity we utilized the Dim ester of *formic* acid. After full geometry optimization of the starting cation radical, we located the transition state and found the ZPE-corrected barrier to be only 22.7 kcal/mol (Figure 2). Thus,

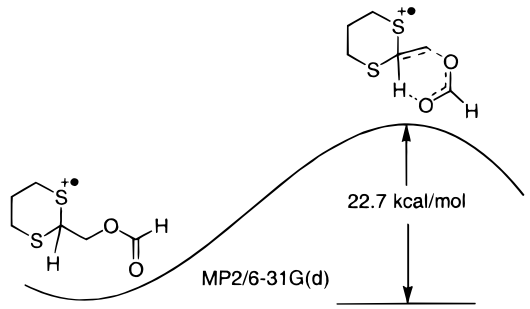
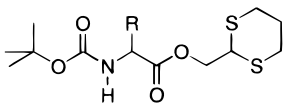


Figure 2.

it is conceivable that the reaction proceeds via this elimination mechanism.

We then proceeded to the primary goal of this project—to develop electrochemically removable protection for amino acids.

Kunz and Waldmann,[6] who originally introduced the Dim ester protecting group, utilized quite a drastic wet chemistry method for deprotection: complete oxidation of the dithiane ring into disulfone with hydrogen peroxide catalyzed by ammonium molybdate, followed by base-catalyzed elimination. In view of our results, we envisioned that a controlled electrochemical oxidation could prove a more delicate technique for amino acid deprotection. In this study we synthesized the Dim esters of *t*-BOC-protected phenylalanine (**4**), valine, (**5**), and leucine (**6**) via the DCC/4-pyrrolidi-



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nopyridine mediated esterification with 2-(hydroxymethyl)-1,3-dithiane.[7,8] Electrolytic deprotection was carried out in a 85% acetonitrile−15% 50 mM aqueous sodium acetate solution. We utilized a divided electrolytic cell with two 5 cm^2 platinum electrodes at a constant current of 3 mA.[9] The reaction progress was monitored by reversed-phase (C18) HPLC using the same 85:15 acetonitrile−50 mM aqueous sodium acetate buffer. The proton NMR of the reaction mixture at 100% conversion showed complete deprotection of the C terminus, leaving the *t*-BOC-protected N-terminus intact. The isolated yields were also determined (Table 1).

Table 1

	yield, %	
ester	esterification	deprotection[a]
4, R = CH_2Ph	90	74
5, R = $CH(CH_3)_2$	84	65
6, R = $CH_2CH(CH_3)_2$	98	67

[a] Isolated yields.

Although 100% deprotection was achieved in 3 h, extended (e.g., overnight) electrolysis did not cause any overoxidation of the deprotected amino acids, conceivably

(3) Electrolysis conditions: 5 cm^2 Pt cathode and anode, 20 °C, acetonitrile, 9 mM Dim ester, 0.1 M $LiClO_4$, under constant current (3 mA) conditions. Workup included evaporation of the solvent, addition of 10% aqueous KOH, ether extraction of organic side products, and acidification with hydrochloric acid followed by ethereal extraction of the acid.

(4) Nicholas, A. M. d. P.; Arnold, D. R. *Can. J. Chem.* **1982**, *60*, 2165.

(5) Glass, R. S.; Petsom, A.; Wilson, G. S. *J. Org. Chem.* **1986**, *51*, 4337.

(6) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 62. Waldmann, H.; Kunz, H. *J. Org. Chem.* **1988**, *53*, 4172.

(7) General procedure for esterification with DCC/4-aminopyridines: Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *46*, 4475−4478.

(8) A note about the stability of Dim esters: Kunz and Waldmann[6] reported that in acidic media the Dim esters were stable enough to allow selective deprotection of the t-BOC-protected N-termini. We also tested the stability of Dim esters under basic conditions. For example, an ethereal solution of **3** was shaken vigorously with 10% KOH. The layers were separated. The organic layer contained pure starting material. The aqueous layer was acidified with HCl and extracted with ether. No benzoic acid was detected, attesting to the stability of Dim esters to bases.

(9) For example: 82.6 mg of *t*-BOC-Phe-O-Dim (**4**) was dissolved in 20 mL of 85:15 acetonitrile−50 mM aqueous NaOAc. This solution was added to the cathode chamber of the divided cell; the anode chamber was filled solely with the acetonitrile buffer solution. A current of 3 mA was maintained for 3 h. HPLC monitoring showed that all starting material disappeared at this point. Solvent was removed, and the residue was worked up with 20 mL of 10% KOH/10 mL of ether. The aqueous layer was separated, acidified with hydrochloric acid, extracted with 2 × 15 mL of ether, and dried over Na_2SO_4. Ether was removed to give 41 mg (74%) of faintly yellow oil. Both NMR and HPLC confirmed pure N-*t*-BOC-Phe-OH.

due to the effect of an "electrochemical buffer". For instance, the generated 1,2-dithiolane 1-oxide, while not interfering with dithiane oxidation, may have prevented other potential side reactions.

In summary, we have developed an experimentally simple electrochemical deprotection technique for carboxylic acids. The approach may prove particularly valuable for amino acids, allowing selective protection/deprotection at the C-terminus.

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Supporting Information Available: GC-MS, HPLC, and ^{1}H NMR data and the results of the ab initio computation. This material is available free of charge via the Internet at http://pubs.acs.org.

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