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Selective electrochemical deprotection of cinnamyl ethers, esters, and carbamates

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Abstract—Electrochemical deprotection of the cinnamyl moiety from ethers, esters, and carbamates was studied with the focus on O- versus N- selectivity as well as selectivity over allyl or benzyl systems. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Although the use of the cinnamyl ether as an alcohol protecting group (with electrochemical cleavage) was initially reported in 1968, it has been used only infrequently.[1] It has also been used as a carboxylic acid protecting group.[2] The allyl group has been used more often, and many methods have been developed for its deprotection.[3] Among these are several that employ a palladium catalyst and a nucleophile[4] to trap the allyl group from the π allyl palladium intermediate. Another common approach to the deprotection of allylic protecting groups is isomerization of the double bond to a vinyl ether followed by acid hydrolysis.[5] Allyl and cinnamyl groups have also been removed electrochemically using a Pd catalyst.[6] We have previously reported the selective electrochemical deprotection of cinnamyl ethers in the presence of allyl ethers in conduritol-like systems.[7] The electrochemical method is remarkably selective in removing exocyclic cinnamyl groups over those in which the cinnamyl double double bond is contained in the ring. Allyl ethers are inert under such conditions.

The allyloxycarbonyl (Alloc) and cinnamyloxycarbonyl (COC) moieties are used as protecting groups for amines. In the case of the COC group, the protecting group is introduced via cinnamyloxycarbonylbenzotriazole (COC-OBT)[8] or cinnamyloxycarbonyl imidazole (COC-Im).[9] Removal of COC[9] or Alloc[3,10] groups is similar to removal of the ethers. To our knowledge no methods to deprotect selectively either the cinnamyl group or the allyl group in the presence of the other have been reported, save our earlier publication.[7]

Extending our work on selective electrochemical deprotection of cinnamyl ethers, we have investigated the selectivity of cinnamyl ethers in the presence of benzyl ethers (cinnamyl versus benzyl), cinnamyl ethers in the presence of cinnamoyl esters (cinnamyl versus cinnamoyl), cinnamyl ethers in the presence of cinnamyl amine (*O*-cinnamyl versus *N*-cinnamyl), and cinnamyl esters in the presence of cinnamyl amides (cinnamate versus cinnamide).

We studied the electrochemical deprotection of the cinnamyloxycarbonyl group with focus on cinnamyl versus allyl selectivity, and O- versus N- selectivity, as an alternative to chemical methods for COC deprotection, which require stoichiometric amounts of reagents. Finally, we achieved selective reduction of a vinyl bromide in the presence of a cinnamyl ether. Herein we report the results of these studies.

2. Results and discussion

2.1. Cinnamyl ethers and esters

The selectivity of electrochemical cinnamyl deprotection in the presence of allyl ethers[7] prompted us to investigate cinnamyl versus benzyl selectivity (Table 1). Cyclic voltammetry (CV) of benzyl ether **2** (for details of CV conditions see the Experimental section) exhibited a weak reduction wave at −3.1 V. CV of **1**, containing both benzyl and cinnamyl ethers, exhibited reduction waves at −2.8 and −3.1 V. We initially assumed that the wave at −2.8 V was due to the cinnamyl ether and the wave at −3.1 V was due to the benzyl ether. However, the CV of **3**, with only the

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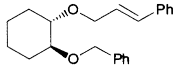
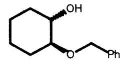
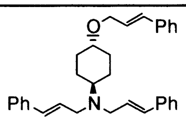
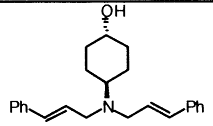
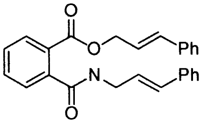
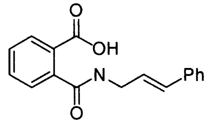
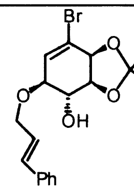
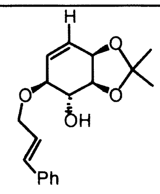
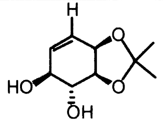
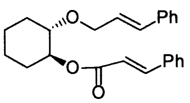
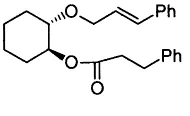
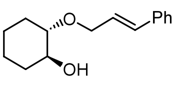
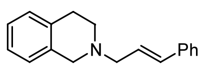
Table 1. Electrochemical cleavage of cinnamyl ethers

Entry	Substrate	Potential/Electrode	Product	Yield
1	 **1**	–3.10 V with 1.1 eq. cyclohexene Hg electrode	 **2**	64% (73% conversion)[11]
2	 **5**	–2.85 V Hg electrode	 **6**	56%
3	 **7**	–2.30 V Hg electrode	 **8**	71%
4	 **9**	–2.65 V RVC electrode	 **10**	66%
5	**9**	–2.65V Hg electrode	 **11**	73%
6	 **12**	–2.15V Hg electrode	 + **12** **13**	1:1 mixture 80%

cinnamyl ether, was identical to that of **1**. Electrochemical reduction of **1** (for details of electrolysis conditions see the Experimental section) at –2.85 V provided **2** cleanly with no evidence of reduction of the benzyl ether (Table 1). Indeed, the reduction could be performed even at –3.1 V with the benzyl ether unaffected. With the ability to deprotect cinnamyl ethers selectively to allyl and benzyl ethers, we turned our attention to nitrogen versus oxygen reactivity.

Electrochemical reduction of amine **4** provided only recovered starting material, which boded well for selective O-deprotection. Consequently, we investigated the reductive deprotection of ether–amine **5** and ester–amide **7**. The CV of **5** exhibited reduction waves at –2.95 and –3.15 V, similar to other cinnamyl ethers. As expected, **5** was selectively deprotected to afford alcohol **6**. The CV of **7** showed reduction waves for each cinnamyl group with waves at –1.84, –2.47, –2.99, and –3.13 V. Electrochemical reduction at –1.8 V produced only acid **8**. These initial findings demonstrate the selective removal of the cinnamyl group from oxygen over nitrogen in ethers and esters over amines and amides, as well as the selectivity over *O*-benzyl groups. Previous experiments[7]demonstrated that no selectivity can be expected when traditional methods such as dissolved metal reductions are used.


3


4

Previously we reported that electrolysis of compounds containing both cinnamyl ether and vinyl bromide moieties afforded products with both cinnamyl group removal and debromination.[7] Noting that the cinnamyl group is removed very sluggishly using a carbon electrode, we sought to selectively debrominate systems containing both functionalities with the cinnamyl ether intact. Thus, electrolysis of **9** at −2.6 V with a reticulated vitreous carbon (RVC) electrode provided **10** in 66% yield. Electrolysis of **9** with a mercury pool electrode resulted in both debromination and cinnamyl group removal as previously reported.[7] This is useful in reduction of vinyl bromides in the presence of other olefins or hydride sensitive groups.

Cyclic voltammetry of **12**, containing both a cinnamyl ether and a cinnamoyl ester, exhibited peaks at −2.18, −2.82 (broad), and −3.11 V. Based on the CV we expected that the ester might be selectively reduced preferentially to the ether. However, reduction of **12** at −2.15 V produced a small amount of cyclohexane diol (<10%) and a 1:1 mixture of **12** and **13**. This result indicates a selective hydrogenation of cinnamyol ester versus the cinnamyl ether.

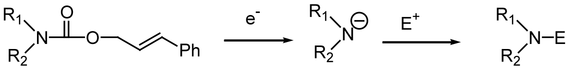
2.2. Cinnamyloxycarbonyldeprotection

The cinnamyl–oxycarbonyl group has been used to protect amines.[9] Typical deprotection conditions involve a Pd catalyst and ammonium formate. These conditions are also used for deprotection of the Alloc group making the selective deprotection of COC in the presence of Alloc unlikely. We wished to determine if the COC group could be selectively removed electrochemically in the presence of an Alloc group as well as to determine if *N*- versus *O*- selectivity could be achieved as with the cinnamyl group.

Substrates were prepared by reaction of the appropriate amine with cinnamyloxycarbonyl imidazole.[9] COC–protected tetrahydroisoquinoline (**14**) and morpholine (**16**) exhibited similar CV's with peaks at −2.48 V, −2.72 V and −3.08 V for **14** and −2.57 and −3.15 V for **16**. Electrochemical reduction at −2.45 V produced the corresponding amines in 80% and 54% isolated yields respectively (Table 2). The lower yield of morpholine is most likely related to the isolation of a volatile product rather than the total conversion. In both cases, TLC and NMR of the crude reaction mixture indicated the absence of starting material and little or no other products. Interestingly, when the reduction was performed in the absence of a proton source, products that appear to arise from the addition of the electrochemically generated nitrogen anion to acetonitrile were obtained (Scheme 1). This finding suggests that it might be possible to couple the electrochemical COC deprotection with subsequent trapping of the nitrogen anion by electrophiles in a base-free alkylation procedure.

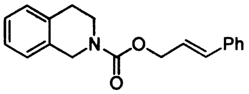
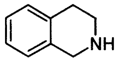
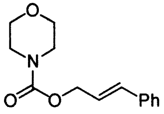
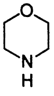
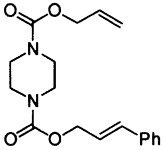
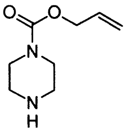
COC versus Alloc selectivity was tested with carbamate **18**. As with the cinnamyl versus allyl ethers,[7] only two reduction waves (−2.54 and −3.08 V), both attributable to the COC group, were observed in the CV. Electrochemical reduction of **18** produced **19** as the only isolated product in 79% yield (Table 2).

Finally, the question of N- versus O- selectivity was examined with **20**. Cyclic voltammetry showed a very broad reduction wave at −2.3 V and two more waves at −2.75 and −2.93 V. Electrochemical reduction at −2.3 V did not selectively remove the *O*-cinnamyloxycarbonyl group. Both cinnamyloxycarbonyl groups were removed, indicating that the driving force for the departure of the heteroatom is controlled at the site of cinnamyl connection, not at the carbamate or carbon-

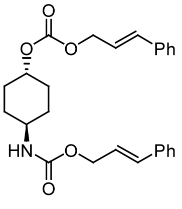


Scheme 1.

Table 2. Electrochemical cleavage of the cinnamyloxycarbonyl group

Entry	Substrate	Potential/Electrode	Product	Yield
1	 **14**	−2.45 V Hg electrode	 **15**	80%
2	 **16**	−2.45V Hg electrode	 **17**	54%
3	 **18**	−2.45 V Hg electrode	 **19**	79%

ate site and that lower basicity (i.e. alkoxide versus amide) controls the cleavage.



20

3. Conclusion

We have shown that cinnamyl and cinnamyloxycarbonyl groups are versatile protecting groups. Each group can be selectively removed in the presence of the corresponding allyl[7] or allyloxycarbonyl group. The cinnamyl group can also be removed in the presence of a benzyl ether. In both cases (cinnamyl and cinnamyloxycarbonyl), oxygen deprotection occurs selectively over nitrogen deprotection except in the case of carbonate/carbamate competition. Reaction setup up is simple and requires no special equipment other than a potentiostat. The only reagents that are used are phenol (as a proton source) and Et_4NBr (electrolyte), both of which can be recovered.[11]

4. Experimental

Cyclic voltammetry experiments were performed with 25–30 mg of sample in 10 mL of 0.15 M Et_4NBr in CH_3CN using a carbon cathode and platinum anode. An Ag/Ag^+ reference electrode was used (0.5785 V versus NHE). Sweep rates were typically 50 mV/s. Reported potentials are for peak maxima. Bulk electrolysis was performed in a 150-mL beaker with a Hg pool cathode and Ag/Ag^+ reference electrode. A Pt anode was place in a separate chamber divided from the rest of the cell by a fine glass frit. Sample (1.0 mmol) and phenol (2.0 mmol) were dissolved in 50 mL of 0.15 M Et_4NBr in acetonitrile electrolyte solution, placed in the beaker, and the solution was purged of oxygen bubbling argon through the solution for 10 minutes. Electrolyte solution (10 mL) was added to the anode chamber. Electrolysis was performed at the appropriate potential. The reaction was monitored by observing the drop in current, the Coulombs delivered, and by TLC. The reaction was judged complete when the current leveled off, the number of Coulombs exceeded 2 F per mole, and/or TLC indicated little or no remaining starting material. The solution was decanted into ether (150 mL) and filtered to remove the charge carrier. The filtrate was evaporated, and the product was isolated.

Acknowledgements

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11. When the reduction was conducted in the presence of 1.1 equiv. of cyclohexene, the yield improved to 64% although the conversion was slower (73%, 27% starting material). Apparently, removing bromine generated at the anode by scavenging it improves the yield. The authors are very grateful to the referee who suggested this experiment.