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Selectivity in the electrochemical deprotection of cinnamyl groups from oxygen and nitrogen functionalities: carbonates versus carbamates

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Abstract—Several cinnamyloxy carbamates and carbonates were subjected to electrochemical reduction, and the reductive fate of the cinnamyl group was investigated. Complete selectivity was observed in the removal of the cinnamyl group from oxygen versus nitrogen.

1. Introduction

The cinnamyl group has been shown to be easily and selectively removed by electrochemical reduction from oxygen and nitrogen atoms in preference to all other allylic systems.[1] We have shown that such reductions are also selective toward removal of cinnamyl groups in which the double bond is not further substituted or contained within a ring. Such selectivity is unusual compared to other methods of reduction (dissolved metal, and palladium-[2–5] or ruthenium-[6]mediated processes). Further study led to investigations of selectivity in electrochemical reductions of cinnamyl groups from ethers versus esters, ethers versus amines, cinnamyl ethers versus benzyl ethers, and cinnamyl versus allyl carbamates.[7] We have shown that reduction of cinnamyl groups from oxygen occurs in preference to their removal from nitrogen and that the cinnamyloxycarbonyl (COC) is reduced with complete selectivity in preference to allyloxycarbonyl (Alloc), which is usually removed via palladium catalysis, as shown in Figure 1.

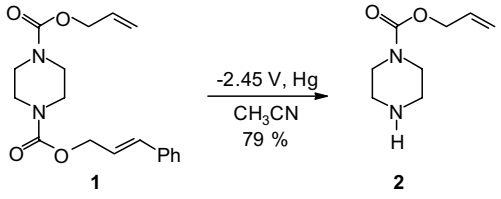

Figure 1. Electrochemical reduction of cinnamyl versus allyl carbamates.

In this letter, we report the outcome of electrochemical reductions of cinnamyl carbamates and cinnamyl carbonates and note the difference in the mechanism of reduction of the cinnamyl groups from these two functionalities, as opposed to the fate of their removal from esters and ethers.

2. Results and discussion

In an earlier letter,[7] we reported the electrochemical behavior of **3**, the linear sweep voltammogram (LSV) of which exhibited three waves (−2.30, −2.73, and −2.93 V vs AgCl/Ag). Reduction at −2.30 V furnished aminoalcohol **4** with apparent lack of selectivity, as shown in Figure 2. Reinvestigation of these results under slightly different conditions (absence of phenol as proton source) revealed three waves at −2.68, −2.79,

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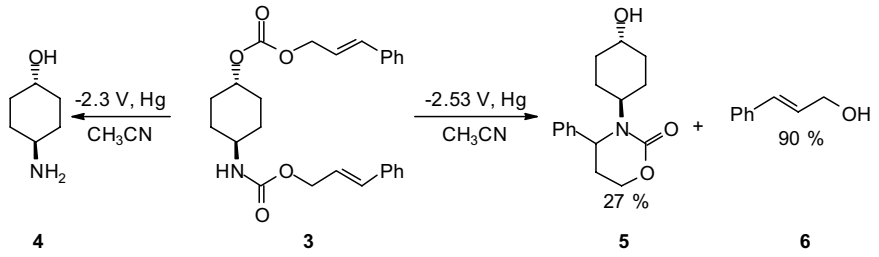

Figure 2. Electrochemical reduction of carbonate versus carbamate.

Table 1. Substrate reduction peak potentials with CH_3CN

Substrate	$Ep^1(V)$[a]	$Ep^2(V)$[a]	$Ep^3(V)$[a]
3	−2.680	−2.790	−3.080
6	—	−2.950	−3.080
9	−2.690	—	−3.080
11	—	—	−3.020
13	−2.680	−2.770	−3.100
14	—	−2.780	−3.080
19	—	−2.760	−3.080

[a] Versus $AgNO_3$/Ag.

and −3.09 V versus $AgNO_3$ (0.1 M MeCN)/Ag (Table 1).[8] By the comparison of the cyclic voltammogram (CV) of **3** with that of substrates **6, 9**, and **19**, the first wave was shown to correspond to the reduction of the carbonate, the second resulted from the reduction of the carbamate, and the third wave was due to cinnamyl alcohol, produced in the electrochemical reductions that occurred at the first and second waves. Accordingly, in the LSV of compound **3** the reductive cleavage of the carbonate group should occur at −2.68 V. As the reduction waves of the carbonate and carbamate are so close, the electrochemical reduction was performed at −2.53 V potential with 2 F/mol delivered. Surprisingly, alcohol **5** was isolated along with an equivalent of cinnamyl alcohol **6**. Thus, the previously reported[7] non-selective reduction of **3** to **4** was proven to be erroneous.

The reductive cleavage of the carbonate group clearly occurred selectively in preference to the carbamate whose further reduction led to the intramolecular cyclization. This result supported previously observed selectivity in the removal of the cinnamyl group from oxygen in preference to nitrogen but at the same time raised two additional questions: (1) Why did the carbonate yield cinnamyl alcohol and not 1-phenylpropene as in the reductions of esters (ethers)? (2) Is the secondary carbamate less prone to reductive cleavage than the more substituted case of **1**? To answer the first question we analyzed the products from the reduction of ether **7**, ester **8**, and carbonate **9**. Ether **7** was reduced at a mercury cathode at −2.82 V to afford 1,2,3,4-tetrahydro-2-naphthol (**10**) and 1-phenylpropene (**11**), which was detected by GC–MS. No cinnamyl alcohol (**6**) was detected. The electrochemical reduction of ester **8** afforded cyclohexanecarboxylic acid and a mixture of cinnamyl alcohol (**6**) and 1-phenylpropene (**11**) in a 1:2 ratio. The electrochemical reduction of carbonate **9** furnished tetrahydronaphthol **10** and cinnamyl alcohol (**6**), as shown in Figure 3. These results indicate that the first reductive event in cinnamyloxycarbonyl substrates occurs at the carbonyl group and not at the cinnamyl moiety. The observation that carbonates are reduced to yield only cinnamyl alcohol (and carbon monoxide) is consistent with the greater stability of radical anions derived from carbonate compared to those originating in esters. In esters such as **8**, the tendency to form an radical anion at the carbonyl versus the styrene unit is similar, and therefore both reduction products are observed.

We also investigated the reduction of **13** and **14** to determine the influence of substitution on the reduction of

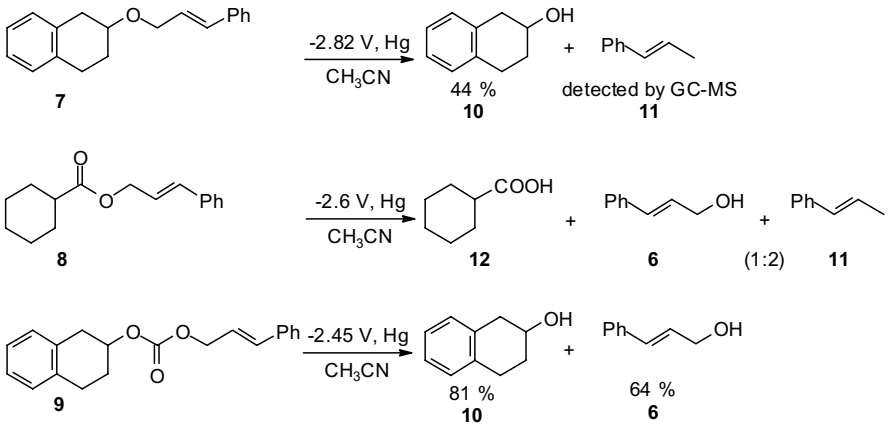

Figure 3. Reductive fate of cinnamyl ether, ester, and carbonate.

carbamates. Compound **13** was prepared directly from 4-hydroxypiperidine and cinnamyloxycarbonylimidazole in the presence of sodium hydride in dry dioxane. The preparation of the bis-protected 4-aminopiperidine **14** was performed in a similar way by treatment of 4-aminopiperidine with cinnamyloxycarbonylimidazole in dichloromethane. The LSV of compound **13** revealed three waves at −2.55, −2.90 and −3.05 V. Electrochemical reduction at a mercury cathode at −2.55 V furnished alcohol **15** and cinnamyl alcohol (**6**) in high yield reflecting full selectivity of the reduction. When carbamate **15** was subjected to identical reduction conditions in the presence of 2 equiv of phenol as a proton source, complete deprotection was observed to provide 4-hydroxypiperidine (**16**). Compound **14** showed two waves at −2.62 and −3.05 V. After the electrochemical reduction at −2.62 V at the mercury cathode (with and without the 2 equiv of phenol as a proton source) the cyclic carbamate **17** was isolated in a low yield and a mixture of 1-phenylpropene (**11**) and cinnamyl alcohol (**6**) were detected by GC–MS in a ratio 2.5/1. When the cyclic carbamate **17** was subjected to an additional 4 F/mol in the presence of phenol, complete deprotection was observed to the secondary amine **18** and 1-phenylpropene (**11**). The isolated yields reported for the reductions have not been optimized.[9] In the case of

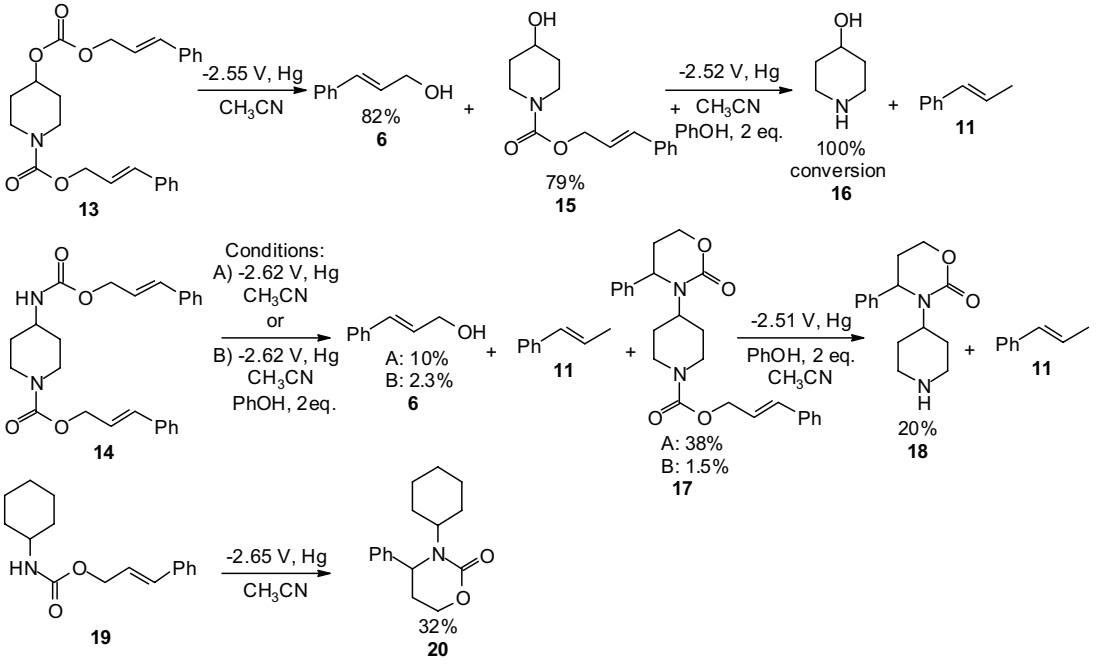

Figure 4. Results of the reductions of carbonate versus tertiary carbamate (in **13**), secondary versus tertiary carbamate (in **14**), and a secondary carbamate **19**.

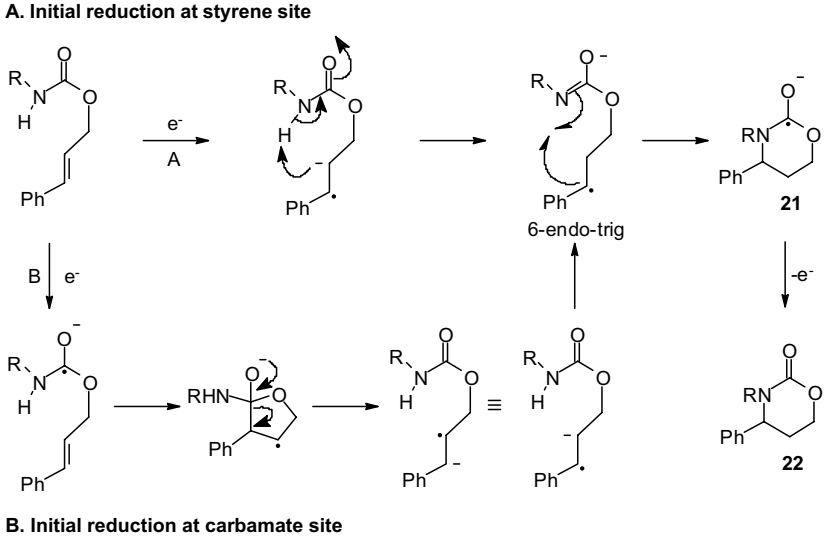

Figure 5. Proposed mechanistic options for electrocyclization of secondary carbamates.

secondary carbamate **19**, electrochemical reduction at −2.65 V at the mercury cathode afforded the cyclic carbamate **20** without any formation of cinnamyl alcohol or 1-phenylpropene (Fig. 4).

3. Conclusions

The electrochemical reduction of carbonates versus carbamates proceeds with complete selectivity with the carbonate moiety reduced in preference to carbamate. In the absence of a proton source, tertiary carbamates are not reduced and secondary carbamates cyclize via one of the possible pathways proposed in Figure 5. In carbamates, the tendency to form the ketyl versus styryl radical anion may be similar (as in esters). We offer an initial speculation regarding two options that may be possible: one involving the proton transfer as in pathway A (Fig. 5), the other proceeding through the ketyl cyclization as in pathway B. Both pathways would lead to the same product, **22**, after a loss of an electron from ketyl **21.**

In the presence of a proton source, tertiary carbamates are fully reduced to amines and cinnamyl alcohol. Secondary carbamates are prone to cyclization following the first electron transfer and are not further reduced. The selectivity of removal of the cinnamyl group favors the less basic atom (oxygen), in agreement with previously reported observations for ethers versus amines.[7] The mechanism of the observed electrocyclization will be investigated in detail, and the results as well as potential applications in synthesis will be reported in due course.

Acknowledgements

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8. Experimental procedure: Cyclic voltammetry experiments were performed with 15–30 mg of substrate in 30 mL of CH_3CN containing 0.15 M Et_4NBr (or 0.1 M *n*-Bu_4NPF_6 for values reported in Table 1). Glassy carbon was used as the working electrode. Platinum and $AgNO_3$/Ag (0.1 M CH_3CN) were used as counter and references electrodes, respectively. The working and counter electrodes were polished on alumina before use. *iR* compensations were applied for all experiments for potential measurements. Sweep rates were typically 100 mV/s. The reported potentials are for peak maxima. The electrolyses were performed at controlled potential in a cell with two compartments. The cathode was a mercury pool and the anode was platinum. The reactions were monitored by observing the drop in the current and by TLC. The solution was decanted into ether and filtered to remove the electrolyte. The filtrate was concentrated and the products isolated by column chromatography.
9. The conversions of substrates to products were complete (vide TLC analysis). Isolation and purification of products at the scale at which the initial experiments were performed (0.2–0.7 mM) were complicated by the large amount of electrolyte used. Optimized larger scale procedures will obviate these problems.