Tetrahedron Vol 44, No 22, pp 6807 to 6810, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + 00

ELECTROREDUCTION OF 2-OXAZOLINES

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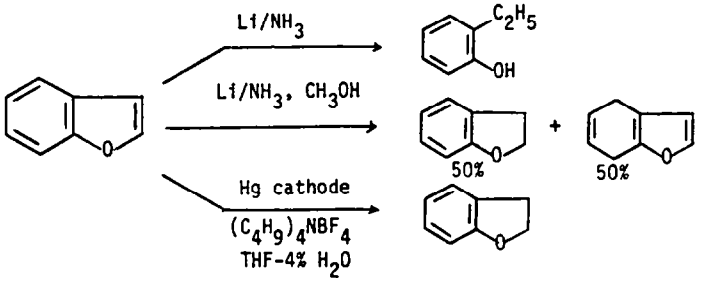
(*Received in USA* 26 *May* 1988)

Abstract - The cathodic behavior of 2-phenyl-4,4-dimethyl-2-oxazoline (4), 2,4,4-trimethyl-2-oxazoline (7) and 2-(1,1-dimethylethyl)-4,4-dimethyl-2-oxazoline (8) at Hg electrodes was investigated. A reduction peak for 4 at -2.49V(SCE), was observed by cyclic voltammetry (CV). Preparative reduction of 4 at a mercury pool yielded exclusively N-benzyl-2-amino-2-methylpropanol (6) in a high yield (91%). The electrolysis procedure was simple utilizing constant current and an undivided cell, and the pH remained neutral throughout the reaction. The 2-oxazolines 7 and 8 did not exhibit CV reduction peaks and were recovered after attempts of preparative electrolysis. CV and nmr measurements indicate that the reduction of 4 involves initial formation of the corresponding oxazolidine 5 followed by ring cleavage to the easily reducible tautomeric imine 5a which reacts to give 6.

Recently we have investigated the electrochemical reduction of difficult to reduce aromatic compounds[1]. In these studies it was shown that cathodic reduction at Hg in the presence of a tetrabutylammonium [$(C_4H_9)_4N^+$] electrolyte can lead to selective double bond reduction[1c]. This selectivity contrasts with the results obtained by reducing the same compounds with alkali metal in liquid ammonia with or without an added proton donor. As can be seen by the example of benzofuran reaction (scheme 1), alkali metal reduction is less selective and ring cleavage occurs in the absence of a proton donor.

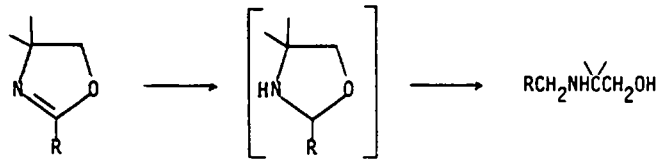


Scheme 1

Instances of over-reduction and ring cleavage during reduction are common. One example is the reduction of 2-oxazolines. Interest in these compounds stems from their synthetic utility and ability to act as protecting groups for carboxylic acids. They have been used[2] as precursors for a variety of organic compounds including aldehydes, lactones, amino acids, thiiranes, and olefins. Their inertness to reagents such as lithium aluminum hydride, chromate, Grignard reagents, mild acid and alkali, as well as the ease of their removal, make 2-oxazolines desirable protecting groups for carboxylic acids.

Meyers[2b] and co-workers have investigated the reduction of 2-aryl-2-oxazolines, as a means for aldehyde synthesis. Using DIBAL or alkali metal in liquid ammonia with a variety of reactants 1, the corresponding amino alcohols 3 were formed, and could be converted to the aldehydes of interest. The same amino alcohols were reported for the reduction of 1 with diborane in THF[3] or with sodium in isoamylalcohol[4]. It was suggested

that the initial products of 1 are the corresponding oxazolidines 2 which consequently undergo reductive cleavage to 3 (scheme 2) at a rate faster than the reduction of 1.



1 R = Ar
4 R = Ph
7 R = CH_3
8 R = $C(CH_3)_3$

2 R = Ar
5 R = Ph

3 R = Ar
6 R = Ph

Scheme 2

We found it curious that the oxazolidines 2, which have only an aromatic ring as electrophore, would reduce more rapidly than the oxazolines 1, which have an extended π system. This paper presents results of the electrochemical investigation of 2-oxazolines. The goal was to find conditions for the electroreduction of such compounds and to use electrochemistry to probe the mechanism of the reductive cleavage.

Three substrates were investigated 4, 7 and 8. Cyclic voltammetry in DMF(0.25M$(C_4H_9)_4NBF_4$) at a Hg drop cathode showed a cathodic peak for 4 at -2.49V(SCE) the other two gave no peaks.

Preparative reductions of 4 were carried out at a Hg pool cathode using a constant current. The solvent was THF-4% H_2O (0.25M$(C_4H_9)_4NBF_4$). These conditions have been reported[1c] useful for similar reductions. Experiments were performed using both a divided and an undivided cell. The potentials during the reactions were measured versus a Ag wire placed close (~ 1mm) to the mercury pool and were found to be -1.8 to -2.0V in the divided cell and fairly constant, at -1.8V, in the undivided cell.

In the first experiments 2 $Fmol^{-1}$ of charge was passed in a divided cell. After workup the mass yield was 75% and from nmr analysis, using an internal standard, the mixture was found to consist of 39% amino alcohol 6 and 61% reactant 4. The oxazolidine 5, was not detected. Positive identification of the product was made by comparison to a sample of 6 synthesized by alkali metal reduction of 4. Although the current efficiency was lower in the undivided cell (56% vs. 78% based on a $4e^-$ reduction), it was more convenient since no divider was required and the resistance in the cell was kept to a minimum. Also the pH, which was monitored during the reaction, remained neutral throughout the reaction whereas in the divided cell the solution became very basic.

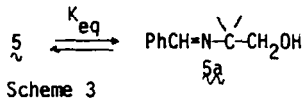
To rule out the possibility that the oxazolidine 5 is formed during the reaction but hydrolyzed, blank experiments were made on independently prepared 5 in electrolyte solutions. To one was added $(C_4H_9)_4NOH$ to bring the pH up to 11 and to the other was added HBF_4 to bring the pH down to 3. The solutions were allowed to stir for periods corresponding to the times required for electrolysis. No change in 5 was observed.

Having established 6 to be the only product, a reduction of 4 was performed passing enough charge to consume all starting material. The reduction was done in an undivided cell with a constant current of 16 $mAcm^{-2}$ and passing 5.2 $Fmol^{-1}$. The potential dropped from -1.8 to -1.6 V during the reaction while the pH remained neutral. Workup provided 86% mass yield with 91% of that being 6.

Attempts to preparatively reduce the two 2-alkyl-2-oxazolines 7 and 8 were performed under the same conditions described for 4. During the reactions the potentials

were very negative (3.0 to -3.5 vs. Ag wire) and a characteristic black solid formed on the electrode and produced a suspension in the reaction mixture. This solid has been attributed to the reduction of $(C_4H_9)_4N^+$ from the electrolyte and formation of a tetrabutylammonium-mercury composite[1d]. The progress of the reactions was monitored by gc with an internal standard. Buildup of tributylamine, from decomposition of the electrolyte was observed but no other products were detected. After transfer of $2Fmol^{-1}$ the reaction mixtures were worked up and analyzed by gc and nmr. The amounts of 7 and 8 decreased by 10% and 35% respectively but no amino alcohols, oxazolidines, or other products in a significant amount (> 5%) were observed. It is worthwhile to note that no other method for reducing simple 2-alkyl-2-oxazolines to the corresponding oxazolidines exists.

To understand why 6 rather than 5 was obtained by electroreduction of 4, the CV of 5 in DMF was recorded. It showed a peak at -2.32 V (SCE) while, as stated previously, the peak for 4 was at -2.49V(SCE). The fact that the reduction potential of 5 is more positive than that of 4 was intriguing, since 5 has no obvious reducible functionality. Reduction of isolated aromatic rings has been found to occur at very negative potentials[1] (- 3V) and it was reasonable to assume that a non-activated aromatic ring such as that in 5 would not react at -2.32 V. However, 5 is known to exist in an equilibrium with the ring opened tautomer 5a (scheme 3)[5] and this isomer is expected to have a reduction potential near that of 4. During preparative electrolysis of 4 the cathode potential would be negative enough to reduce 5a and lead to 6.



Scheme 3

In an attempt to find conditions favoring the cyclic product 5, the equilibrium constant K_{eq}, was determined in several solvents. The amounts of 5a and 5 were measured using nmr, by integration of the vinylic proton of 5a at 8.3 ppm and the proton alpha to oxygen and nitrogen of 5 at 5.5 ppm. Their ratio (5a/5) yielded K_{eq}. The results, shown in the Table, compare well with values reported elsewhere and the trend here is consistent

Table. Equilibrium constants (Keq) for the ring opening of 5 to 5a (scheme 3) determined by nmr.

Solvent	Keq[a]	reported[5c] Keq[b]
CCl_4		0.5
$CHCl_3$	0.7	0.6
Dimethylcarbonate		1.3
Benzene	1.2	
Acetonitrile		1.6
Diglyme	2.0	
THF	2.4	2.0
Acetone		2.4
DMF	7.0	
Acetamide		8.3
DMSO	c	9.6

[a]22°C, concentration = 1M; [b]38°C, concentration = 1 mol/20 mol solvent; [c]No 5 detected.

with the hypothesis[5] that the equilibrium is related to the ability of the solvent to hydrogen bond to 5a and therefore aid in the ring opening process. It is apparent that the ring opening of 5 to give the imine 5a, which is easier to reduce, could not be avoided by simply changing solvent.

In summary, these results demonstrate a convenient high yield method for producing amino alcohol 6. This method may be of particular importance for conversion of 2-oxazolines like 4 to amino alcohols, when either the reactant or the product are pH sensitive. The use of cyclic voltammetry clarifies the mechanism for ring cleavage under the electrochemical and the Meyers conditions.

EXPERIMENTAL

The cell, electrodes and instruments for cyclic voltammetry have been described[1d]. Gc analysis was performed on a Varian Model 3700 Gas Chromatograph with a 10' stainless steel 1/8" column packed with 10% OV-210 on Chromosorb W-AW-DMCS (80/100 mesh). Anisole was used as the internal standard. Nmr analysis was performed on a 60 MHz Hitachi R-24B instrument using CH_2Cl_2 as an internal standard. The oxazolines 4, 7 and 8 were prepared according to known procedures[6] as was 2-phenyl-4,4-dimethyloxazolidine (5)[7]. Lithium in liquid ammonia reduction of 4 provided N-benzyl-2-amino-2-methylpropanol (6)[2b].

Preparative Electrolyses were all performed at a constant current (14-16 $mAcm^{-2}$) with a Hewlett Packard 712C DC power supply. The cathode was a mercury pool (12 cm dia), the counter electrode was a Pt foil (2 cm^2) and the cell was described elsewhere[1c]. The amount of reactant was 350-400 mg for 4 and 130-200 mg for the others. The reactant was dissolved in 20-25 mL THF-4% H_2O with 0.25M$(C_4H_9)_4NBF_4$ as the supporting electrolyte. Reaction progress was monitored by gc with anisole as the internal standard. Upon completion, the products were isolated by extraction with ether[1c] and identified by comparison (^1H nmr) with authentic samples.

Acknowledgment: The authors are grateful to the National Science Foundation and to the 3M Corporation for support of this work.

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