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ELECTROCHEMICAL OXIDATION OF ALCOHOLS: PART II
PREPARATIVE ANODIC OXIDATION OF SECONDARY ALKANOLS EMPLOYING LITHIUM NITRATE[1]

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SUMMARY: The nitrate-mediated oxidation of simple alkanols to the corresponding ketones is described. Except for compounds containing several tertiary hydrogens the procedure is simple to perform and gives clean products in high current yield.

The oxidation of secondary alcohols to ketones is a standard procedure in organic synthesis. A large variety of synthetic procedures has been developed for carrying out this oxidation.[2] However, most of these depend upon the use of various chromium(VI) oxidants which then necessitate extractive workups and can leave potentially carcinogenic residues.[3]

In this laboratory we have been examining possible electrochemical alternatives for the anodic oxidation of alkanols.[4] In previous work we reported that the electrochemical oxidation of 1-butanol to butanal occurs with 77% current efficiency and no significant side products when oxidation occurs in the presence of lithium fluoroborate electrolyte at a platinum anode, either as neat alcohol or with the addition of 10% acetonitrile. This result compares very favorably to previously reported anodic oxidations of 1-butanol.[5] The only significant higher oxidation product obtained was butyl butanoate (6% of material yield).

Little previous work has been done on the oxidation of secondary alkanols to ketones.[6] Thus, we carried out a number of oxidations of 2-butanol as shown in Table 1. These oxidations were performed with 5 ml of alcohol in 45 ml of acetonitrile (or acetonitrile-water) with the electrolytes shown in the Table. Analysis of the products was by gas chromatography on Carbowax 20M (20') and by gravimetric determination of the 2,4-dinitrophenylhydrazone of the 2-butanone formed. The current passed was determined by a copper coulometer in series with the single compartment cell.

TABLE I: Anodic Oxidation of 2-butanol

Anode Material	Electrolyte	Solvent	Current Yield of 2-butanone
Pt	$LiBF_4$ (0.2M)	MeCN	51
Pt	Me_4NBF_4 (0.2M)	MeCN	38
Pt	$LiNO_3$ (0.2M)	MeCN	58
Pt	Me_4NBF_4 (0.05M)	MeCN:H_2O (9:1)	68
C	Me_4NBF_4 (0.05M)	MeCN	9

The low current yield of butanone in the case of the carbon anode oxidation was due to signnificant oxidative cleavage of either the 2-butanol or of the 2-butanone formed. There was a significant formation of acetaldehyde and of 2-butyl acetate in this reaction.

To determine whether the oxidation at platinum was synthetically useful, we carried out further oxidations of the alcohol both in the presence of solvent and on the neat alcohol. Earlier work had shown that the oxidation apparently can proceed either through direct oxidation of the alcohol at the electrode or through oxidation of the electrolyte (nitrate ion) followed by hydrogen abstraction from the alcohol. These two pathways for 3-pentanol are shown in Schemes I and II respectively.

Scheme I: Direct Electrochemical Oxidation of 3-pentanol (Oxygen-Based Radical Pathway)

$$\mathrm{Et_2CH\underset{\cdot\cdot}{\ddot{O}}H} \xrightarrow{-e^-} \mathrm{Et_2CH\underset{\cdot\cdot}{\dot{O}}H^+} \xrightarrow[-2H^+]{-e^-} \mathrm{Et_2C{=}\ddot{O}\colon}$$

Scheme II: Nitrate-Mediated Electrochemical Oxidation of 3-pentanol (Carbon-Based Radical Pathway)

$$(1)\qquad \mathrm{NO_3^-} \xrightarrow{-e^-} \mathrm{NO_3\cdot}$$

$$(2)\qquad \mathrm{Et_2CH\underset{\cdot\cdot}{\ddot{O}}H} \xrightarrow[(-H\cdot)]{NO_3\cdot} \mathrm{Et_2\dot{C}\underset{\cdot\cdot}{\ddot{O}}H} \xrightarrow[\substack{\text{or}\\ -e^-/-H^+}]{NO_3\cdot} \mathrm{Et_2C{=}\ddot{O}\colon}$$

To explore the usefulness of these two pathways, we employed both nitrate and fluoroborate electrolytes. The results of these experiments are shown in Table II.

Here as in the case of the 1-butanol oxidation, there appears to be a slight edge in favor of oxidation of the neat alcohol. Workup of the electrolysis mixture from neat alcohol oxidation would be easier, since efficient fractional distillation would separate the ketone from the residual alcohol and leave the electrolyte salt ready for further reaction. The difference between nitrate and fluoroborate electrolytes is strikingly illustrated by these results. While we did not explore the underlying mechanism for these differences, they are of considerable synthetic importance. Equally striking is the very large difference between 100% acetonitrile and 90% acetonitrile as solvent systems. This difference is apparently due to the action of the solvent (as opposed to solute water) as the proton donor at the cathode. In this single compartment electrolysis cell, the acetonitrile enolate ion is formed in the anhydrous solvent. This condenses with the 2-butanone (presumably at or near the cathode surface) to yield 26% of 2-hydroxy-2-methylpentanenitrile.

TABLE II: Preparative Electrolysis of 2-butanol at Platinum Electrodes

Electrolyte	Solvent	Yield
$LiNO_3$	——	93% [a]
$LiBF_4$	——	48% [a]
Me_4NBF_4	MeCN	7% [b]
Et_4NNO_3	MeCN	28% [b]
Et_4NNO_3	$MeCN:H_2O(9:1)$	83% [b]

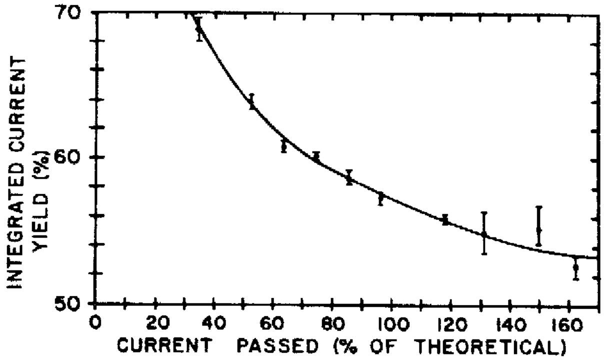
[a] Current yield after passing 20% of the theoretically required current.

[b] Material yield (based on 2-butanol used) after passing 40% excess current.

When attempting the neat alcohol oxidation with larger alcohols, the higher cell resistance and lower proton transfer efficiencies create additional problems. Hence, we explored the usefulness of 9:1 acetonitrile:water (v/v) as a preparative medium for this reaction. These oxidations were carried out with 0.14 M $LiNO_3$ electrolyte in a single compartment cell at platinum electrodes. The current was controlled at 100 mA and the cell was cooled with water to prevent thermal effects. The following alcohols were oxidized with current efficiencies exceeding 70% (at 27% of the theoretical current required for complete oxidation): 2-butanol, 2-pentanol, 3-pentanol, 2-hexanol, cyclohexanol, 4-methyl-2-pentanol and isoborneol. The low conversion was used to prevent further oxidation of the product. However, gc analysis showed very little side-product formation, so this precaution was probably unnecessary.

Significantly lower current efficiencies were found for only two alcohols: menthol and 2,6-dimethyl-4-heptanol. The reduced current efficiency in these cases appears to be due to the abstraction of hydrogens from tertiary positions in the molecules. These are the only cases in which we observed significant side product formation; these side products were not analyzed in detail. The effect of the number of tertiary positions can be seen by comparing the current yields for 2-hexanol (no tertiary hydrogens, 84% current yield), 4-methyl-2-pentanol (1 3°H, 74%), 2,6-dimethyl-4-heptanol (3 3°H, 57%), menthol (3 3°H, 29%). We have observed in previous work with steroid alcohols that the nmr spectra of the products gives evidence of attack on the tertiary hydrogens when nitrate-mediated oxidation is performed.[7]

We did observe that the current efficiency was time-dependent. For isoborneol we obtained the results shown in the Figure. There appears to be a limiting current efficiency of about 53%. The reason for this decline is not known, although it does not appear to be due to the buildup of other products. Determination of the ketone:alcohols ratio by the method of standard addition (after passage of 118% of the theoretical current) sets an upper limit of 2% for products not seen in the gas chromatograph. One possibility for this decline is that as the concentration of the alcohol declines, the reactions of the nitrate ion itself begin to predominate.[8]



Integrated current yield versus total current passed for the nitrate-mediated anodic oxidation of isoborneol in acetonitrile-water (9:1).

The favorable results in the nitrate ion electrolysis compared to other electrolytes is almost surely a result of its lower oxidation potential. In contrast to the +2.40 volts required for 2-butanol, the oxidation of nitrate ion occurs at +1.6 volts and that of fluoroborate at above 3.0 volts (all values measured in acetonitrile versus an Ag/(0.1 M $AgNO_3$) electrode).[9] This lower potential, combined with the known ease with which it attacks alkyl hydrogens, apparently leads almost exclusively to the type of oxidation shown in Scheme II.

The importance of the selectivity of the nitrate-mediated platinum anode oxidation is dramatically shown in the anodic oxidation of 2-hexanol. If the oxidation is carried out with fluoroborate at a carbon anode, there is only a 5% current yield of the expected 2-hexanone. However, there is three times as much 2,5-hexanedione formed. (Since the latter is a six-electron oxidation, its current yield is 45%.) There is also a trace amount of 2,5-dimethyltetrahydrofuran isolated. A logical pathway for the formation of these products would involve the abstraction of a hydrogen from the γ-carbon by the initially produced alkoxyl radical. Oxidation of this radical to the carbocation followed by intramolecular trapping by the alcohol functionality would yield the tetrahydrofuran. The diketone arises either from trapping of the carbocation by water and further oxidation or more likely from further oxidation of the tetrahydrofuran. When the reaction is carried out at a platinum electrode with tetraethylammonium nitrate electrolyte, a preparative yield of 80% ketone:6% dione is obtained.

In this work we have demonstrated the usefulness of the nitrate-ion mediated oxidation of secondary alkanols to the corresponding ketones. Good results can be expected both in the neat alcohol and in 9:1 acetonitrile:water solutions, except when the compounds has several tertiary hydrogens. The importance of the use of platinum anodes for the preparative reaction has been demonstrated. The simplicity of product isolation, the relatively low cost of the "oxidant", and the absence of transition metal contaminants make this procedure a potential alternative to standard methods of oxidation.

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