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ELECTROCHEMICAL TRANSACYLATIONS: A MILD SYNTHESIS OF ESTERS

Richard W. Johnson*, M. D. Bednarski, B. F. O'Leary and E. R. Grover

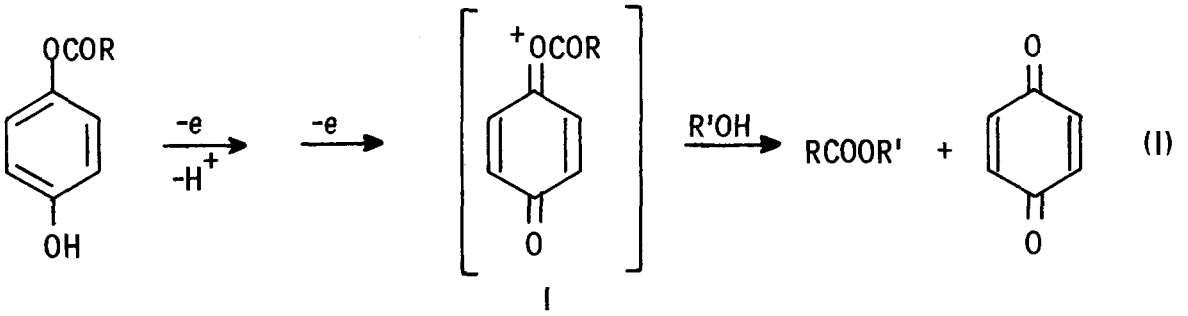
Department of Chemistry, Harvard University, Cambridge, MA 02138

Abstract: Esters can be synthesized by electrochemically oxidizing hydroquinone carboxylates in the presence of alcohols. High yields are obtained in acidic or basic solutions and at low temperatures.

Studies on macrocyclic antibiotics have demonstrated the need to develop mild and efficient methods for effecting transacylations.[1] Recently published procedures[2] have employed better nucleophilic catalysts, metal complexation, double activation, and redox-coupled dehydration. We felt that electrochemical reactions might also provide a viable solution to this problem, because they can supply significant amounts of energy (1 volt = 23 Kcal) under very mild conditions. We have been investigating electrophores which perform electrochemical transacylations, and we report here our results regarding ester synthesis using hydroquinone carboxylates.

In order to utilize the available electrochemical energy, the electron transfer chemistry must be coupled to the chemical activation required for bond forming reactions. One scheme for accomplishing this uses the oxidation of hydroquinone to quinone to generate an excellent leaving group *in situ*. Its potential was initially recognized by Todd in his work on oxidative phosphorylation.[3] Concerning acyl transfers, Cohen[4] demonstrated that chemical oxidation of hydroquinone acetates in acetic acid produces acetic anhydride (98%), and Clark[5] found that chemical oxidation of hydroquinone benzoates in alcohol solvent affords the corresponding alkyl benzoate, but in variable yield (0 - 100%). Electrochemically, anodic oxidation of durohydroquinone diacetate effects a deacylation to produce duroquinone (acyl product unidentified).[6] Utley modified this reaction, using 2,3,5,6-tetramethoxyquinol diacetate, to perform electrochemical Friedel-Crafts

acetylations of, e.g. benzene (34%) and toluene (90%). This reaction illustrates the strength of the acylating agent involved.



(I)

I

In performing direct electrochemical transacylations to alcohols, we have focused primarily on hydroquinone monoesters, eq. 1, and our results are summarized in Table I. The monoesters were obtained by acylation of p-benzyloxyphenol followed by hydrogenolysis, and all exhibited an irreversible oxidation around +1.6 V vs. s.c.e. as measured by cyclic voltammetry. Preparative oxidation in the presence of alcohol produced the corresponding ester in good yield, Table I, the synthetic potential being best illustrated by the formation of the hindered ester t-butyl pivalate in 80% yield at -30°C. These transacylations can be performed under a variety of conditions, since the electron transfer processes can operate independently of the medium. In general a beaker-type cell purged with N_2 was used with a carbon felt anode (Union Carbide X3100), a platinum wire cathode isolated in a fritted tube, and acetonitrile or methylene chloride as solvent. Oxidation under controlled potential conditions, using a Ag/AgCl reference electrode cleanly passed two equivalents of charge, and the reaction then stopped. We also found that controlled current oxidations could be performed easily using a regulated DC power supply with a current density of 5 - 10 ma/cm^2 and 2.1 equivalents of charge, and the yield was unchanged.[8] The reactions can be run at low temperature or even in the presence of a suspension of Na_2CO_3 to neutralize the acid produced, Table I.

We have also examined the hydroquinone derivatives listed in Table II, all of which are reasonable electrophores for transacylation. These systems allow for reaction at lower potentials, B and C, or alternative strategies during the synthesis, i.e. D can be made by direct monoacylation of the corresponding hydroquinone.

As regards mechanism, we believe these reactions occur by direct acyl transfer via an intermediate acyl quinone cation, I, for several reasons. Analogous intermediates are involved in electrochemical phosphoryl transfers.[9] Transfer of hexanoyl to cyclohexanol-O-D introduces no deuterium in the alpha position, i.e. ketene are not formed. Pivaloyl transfers with little decarboxylation. Lastly, addition of ethanol to the reaction mixtures immediately after electrolysis produces no ethyl ester.

Some problems still need to be solved. Stoichiometric transfers proceed in lower yield, as does transfer of benzoyl, and acylation of amines is not possible due to competitive oxidation of the amine at the electrode. We hope to solve these using substantially different electrophores, as well as extend our work to the formation of macrolactones and transacylations with amino acids. However, even at this early stage, some of the unique advantages offered by the electrochemical reaction, especially those regarding reaction conditions, can be seen.

Table I

Yields for ester formation[a]

R'OH O R-C-	hexanol	cyclo-hexanol	t-butanol
hexanoyl	95	85	
		85[c]	70
		80[d]	
cyclohexanoyl	94	50[b]	80[b]
pivaloyl	92	50	80[b]

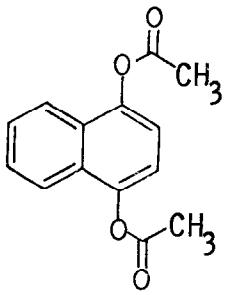
[a] Yields determined by gas chromatography, conditions not optimized. Reactions performed with a 5 - 10 fold excess of alcohol.

[b] Reaction run at -30°C.

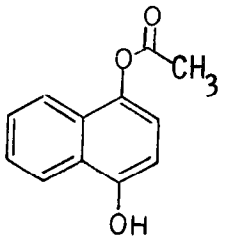
[c] Reaction run in the presence of Na_2CO_3.

[d] Controlled current conditions with DC power supply.

Table I



A



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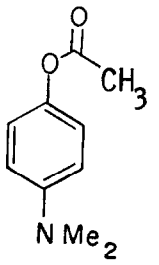
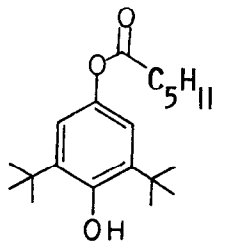


C



D

	A	B	C	D
Ep (vs s.c.e.)	+1.60	+1.10	+.90	+1.45
Yield (Hexyl Ester)	60%	70%	88%	50%

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8) Regulated D.C. power supplies are readily available, most biochemists have one for electrophoresis. They can be used to control current, and anode and cathode connections can be determined by a short electrolysis of a dilute HI solution, I_2 appearing at the anode. More information is available upon request.

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