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ELECTROSYNTHESIS OF NEW STEREOISOMERS OF ALKYL- AND ARYLTHIO DERIVATIVES OF LEVOGLUCOSENONE

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Abstract: Cathodically initiated Michael addition of thiols to levoglucosenone using small currents produces the previously unknown *threo* addition product in several instances. The normal *erythro* isomer, identified as the kinetic product, tends to be formed when large currents are used. The slow, low current electrolyses promote equilibration of the two forms so that *erythro* can be converted to *threo* by the retro reaction and readdition. Additions to R-(+)-apoverbenone and R-(-)-carvone are also reported.

Levoglucosenone,[1] **1**, is a biomass-derived material that is readily obtained by pyrolysis of cellulose.[2] Because it is both chiral and contains an activated double bond, **1** is a very useful starting material for synthesis of chiral natural products.[3]

In previous work[4] it was shown that a variety of derivatives of levoglucosenone could be obtained in high yield by the cathodic generation (*via* electrogenerated base) of anions of nitro compounds that subsequently underwent Michael addition to **1**. The nitro derivatives that were obtained arose from attack of the nitronate anion at the less hindered *exo* face to produce the *erythro* isomers (*i.e.*, the added group occupied an axial position in the ketone-containing six-membered ring. cf Scheme 1). In fact, this is the only isomer that has been reported for the chemical version of the Michael addition of different CH-acids,[5a,b] alcohols[5c] and thiols[5d] to levoglucosenone.

There is apparently no energetic reason that the *threo* isomers should not be obtained. This notion was supported by AM1 calculations which showed, for a variety of addends, that the two isomers have very similar energies with calculated heats of formation differing by <3 kcal/mol. We now report that both *erythro* and *threo* isomers can be selectively prepared by addition of thiols to levoglucosenone under cathodic electrolysis conditions.

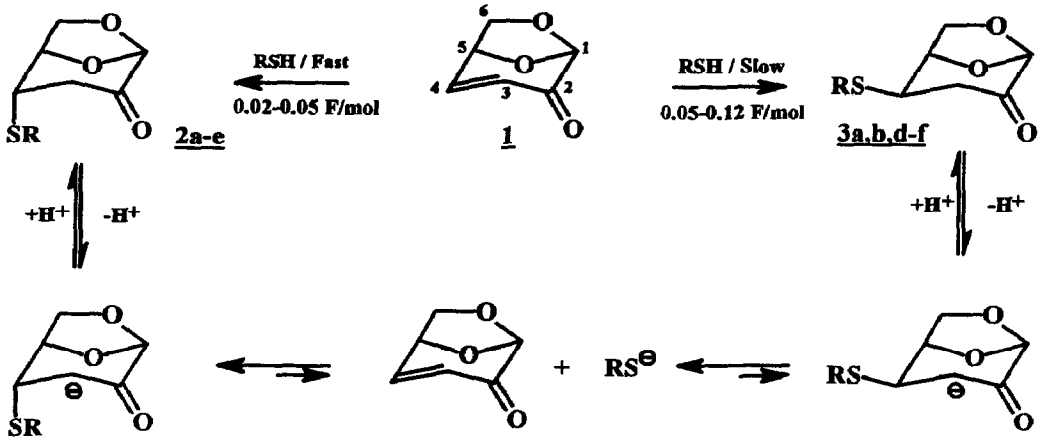
Electrolysis[6] of thiols at a platinum cathode in the presence of an equimolar amount of levoglucosenone was conducted in a divided cell in a solution of 0.002 M Bu_4NBr in MeCN. Only a catalytic amount of electricity (0.02-0.12 F/mol) was required to give the addition products in almost quantitative yields (Table). The cathode compartment was purged with nitrogen to avoid air oxidation of thiolate anions. After removal of MeCN, the electrolysis products were isolated by column chromatography (silica gel, eluent: hexane/ethyl acetate).

The key step of the reaction is the cathodic generation of thiolate anions by direct cleavage of the S-H bond with the assumed formation of dihydrogen. Because thiolate anions with tetraalkylammomium cations as counter ions are such strong nucleophiles,[7] the addition proceeds rapidly and in high yield.

When n-octanethiol or n-decanethiol was reduced in the presence of **1** at normal current densities (*ca.* 0.2-0.3 mA/cm^2; 0.5-1 hour), the *erythro* isomer **2a,b** was obtained in high yield. However, when the electrolysis was

performed at 0.01-0.02 mA/cm^2 for a longer period of time (4-6 hr), 90% (isolated yield) of the product found in the catholyte was the *threo* isomer **3a,b**. Slow electrolysis at low current density appears to be the key to obtaining the *threo* isomer. In fact, it was found that the isolated and purified *erythro* isomers **2a,b** could be converted to **3a,b** in excellent yield simply by subjecting a solution of **2a,b** to these same low current electrolysis conditions.

We propose that in this case the *threo* isomer is the thermodynamically favored product that is formed when the solution is maintained for a sufficient time under basic conditions where the retro addition reaction[8] can occur. Multiple separation and readdition of the thiolate will eventually allow thermodynamics to prevail.



R = C_8H_{17} **(a)**, $C_{10}H_{21}$ **(b)**, 2-naphthyl **(c)**, *p*-Cl-C_6H_4 **(d)**, *p*-MeO-C_6H_4 **(e)**, *p*-O_2N-C_6H_4 **(f)**

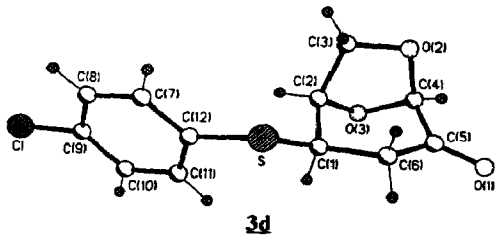
Scheme 1

Obviously the stereochemistry of the addition is affected by the size of incoming group. For example, addition of the more voluminous 2-naphthalenethiol produced the *erythro* isomer **2c** in >90% yield. Some *threo* isomer was detected in the crude product but attempted isomerization of **2c** to **3c** was not successful.

Fast, high current electrolysis of the *p*-chloro- and *p*-methoxybenzenethiols produces mainly the expected *erythro* isomers **2d,e**, but under slow electrolysis conditions **3d** and **3e** are formed in larger amounts, *threo*/*erythro* being about 1.5 for the former and 3 for the latter. Electrolytic equilibration was achieved by electrolysis of pure isolated *threo* (**3d**) or *erythro* (**2d**) isomers of the *p*-chlorobenzenethiol derivative. The resulting *threo*/*erythro* (about 1.5; the same ratio was found starting with either isomer) was identical to that obtained above by addition at low current.

It should be noted that when electrolysis of *p*-methoxybenzenethiol was carried out in an undivided cell with a sacrificial Mg-anode, exclusive formation of the *erythro*-isomer was observed. Perhaps this change in stereochemistry is related to the effect of Mg^{2+} cation on the reactivity of the thiolate anion.[7]

The structure of the new *threo* isomer of the *p*-chlorobenzenethiol derivative was confirmed by X-ray crystallography.[9]



3d

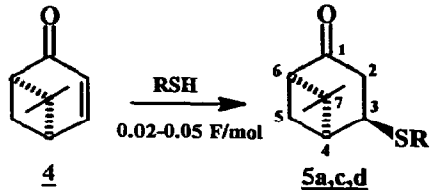
Electrochemical Michael Addition of Thiols to Cyclic Enones (Pt-cathode; Bu_4NBr-MeCN)[10]

Thiol	Enone	Charge, F/mol	Time, h	Product	Yield, % (isol.)
n-$C_8H_{17}SH$	1	0.05	1	2a	86
n-$C_8H_{17}SH$	1	0.10	4	3a	86
n-$C_{10}H_{21}SH$	1	0.02	0.5	2b	93
n-$C_{10}H_{21}SH$	1	0.10	6	3b	82
2-Naphthalenethiol	1	0.04	0.5	2c	95
2-Naphthalenethiol	1	0.12	5	2c	93
p-Cl-C_6H_4-SH	1	0.05	1	2d; 3d	63; 29
p-Cl-C_6H_4-SH	1	0.11	5	2d; 3d	36; 54
p-MeO-C_6H_4-SH	1	0.05	1	2e; 3e	70; 21
p-MeO-C_6H_4-SH	1	0.10	6	2e; 3e	23; 68
p-MeO-C_6H_4-SH	1	0.03	1	2e	93[a]
p-O_2N-C_6H_4-SH	1	0.05	14 days	3f	60
n-$C_{10}H_{21}SH$	4	0.02	0.5	5a	95
p-Cl-C_6H_4-SH	4	0.05	1	5b	90
2-Naphthalenethiol	4	0.04	1	5c	95
n-$C_8H_{17}SH$	6	0.10	1	7	70

[a] Undivided electrolysis: Pt-cathode and Mg-anode.

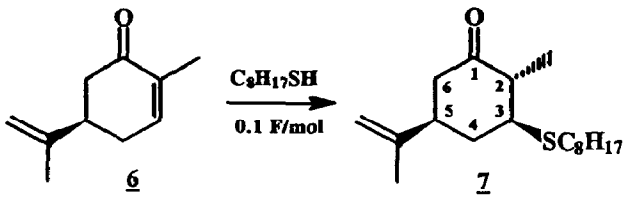
Addition of *p*-nitrobenzenethiol proceeded very slowly and only after two weeks in carefully purged solution was a moderate yield of *threo* isomer **3f** obtained. The slower reaction is consistent with the fact that this thiol is a weaker nucleophile. The *erythro* isomer has not yet been detected.

For comparison, thiols were also added under cathodic electrolysis conditions to R-(+)-apoverbenone (**4**) for which conjugative 1,4-addition *trans* to the geminal-dimethyl-bearing bridge has been reported.[11] In each case, only one isomer **5a,c,d** was isolated (Scheme 2) and isomerization was not observed apparently because the retro Michael reaction does not occur under the electrolysis conditions or because **5a,c,d** are the thermodynamically more stable forms. The structure of **5c** was also confirmed by X-ray crystallography.[9]



4 5a,c,d

Scheme 2



6 7

Scheme 3

We also added n-octanethiol to R-(-)-carvone (**6**) under slow electrolysis conditions and were able to detect and isolate only one isomer[10] (**7**) while the addition of thiophenol to carvone was found[12] to produce two isomers with the predominant form dependent upon the reaction conditions.

Acknowledgements. This research was supported by the National Science Foundation and the CAST Program, National Research Council.

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3. See for example: (a) Ebata, T.; Matsumoto, K.; Yoshikoshi, H.; Koseki, K.; Kawakami, H.; Okano, K.; Matsushita, H. *Heterocycles* **1993**, *36*, 1017-1026. (b) Matsumoto, K.; Ebata, T.; Takashi, K.; Koshi, K.; Kawaki, H.; Matsushita, H. *Heterocycles* **1991**, *32*, 225-2240. (c) Isobe, M.; Fukuda, Y.; Nishikawa, T.; Chabert, P. *Tetrahedron Lett.* **1990**, *31*, 3327-3330.
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6. The experimental procedures have been described: Niyazymbetov, M. E.; Evans, D. H. *J. Org. Chem.* **1993**, *58*, 779-783.
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9. We thank Prof. A. R. Rheingold for the structure determination, details of which will be presented in the full paper.
10. ^{1}H-NMR for selected compounds, $CDCl_3$, 250 MHz except as noted, ppm/TMS:

    2d: 2.45d (H^{3e}; 1H, J=16.9 Hz); 2.96dd (H^{3a}; 1H, J=16.9, 7.2 Hz); 3.65d (H^4; 1H, J= 7.2 Hz); 3.98s (H^{6exo}; 1H); 3.99s (H^{6endo}; 1H); 4.65bs (H^5; 1H); 5.14s (H^1; 1H); 7.28d and 7.38d (4H-arom., J=8.5 Hz).

    3d: 2.46dd (H^{3e}; 1H, J=16.1, 12.1 Hz); 2.72dd (H^{3a}; 1H, J=16.1, 6.6 Hz); 3.79m (H^4; 1H); 3.89dd (H^{6exo}; 1H, J=8.2, 5.2 Hz); 4.40d (H^{6endo}; 1H, J=8.2); 5.10s (H^1; 1H); 7.29d and 7.35d (4H-arom., J=8.9 Hz).

    5d: 0.83s (CH_3; 3H); 1.30s (CH_3; 3H); 1.82d (H^4; 1H, J=11.0 Hz); 2.23bt (H^{5a}; 1H, J=4.6 Hz); 2.40dd (H^{2a}; 1H, J=19.0, 8.2 Hz); 2.44dt (H^{5e}; 1H, J=11.0, 5.0 Hz); 2.53t (H^6; 1H, J=5.0 Hz); 2.76dd (H^{2a}; 1H, J=19.0, 8.3 Hz); 3.71t (H^3; 1H, J=8.2 Hz).

    7 (500 MHz): 0.90t (CH_3; 3H, J=6.3 Hz); 1.22m (10H); 1.39d (CH_3; 3H, J=6.0 Hz); 1.42s (CH_3, 3H); 1.45m (CH_2CH_2S; 2H); 1.56m (H^5; 1H); 1.86m ($H^{4e,a}$; 2H); 1.92dq (H^2; 1H, J=12.0, 6.0 Hz); 2.08-2.20m ($H^{6e,a}$; 2H); 2.27t (CH_2S; 2H, J=6.3 Hz); 2.33dt (H^3; 1H, J=12, 3 Hz); 4.61s and 4.68s (CH_2=; 2H).
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