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Cathodically Promoted Highly Selective Michael Addition of Nitro Compounds to Levoglucosenone.

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Abstract: Regioselective Michael addition of nitro compounds to levoglucosenone (LG) is effectively catalyzed by cathodic electrolysis under mild conditions.

Levoglucosenone (1) is an interesting starting material because it is both chiral and contains an activated double bond. Moreover, this compound can be obtained from biomass by pyrolysis of wood wastes.[1] Levoglucosenone has been successfully used as a chiral starting material for syntheses of a variety of natural and unnatural compounds such as food toxins,[2] alkaloids,[3] antibiotics,[4] anhydrosugars,[5] prostaglandin analogues,[6] herbicides[7] etc.

One of the most attractive reactions for modification of the carbohydrate skeleton of LG is Michael addition.[4] By base-catalyzed reaction of LG with alcohols and thiols, the corresponding alkoxy- and alkylthio-derivatives have been obtained in good yields.[8] However, in the case of the addition of malonate and cyanoacetate, the yields were moderate (49-54%) and a yield of 70% could be achieved for malonate only by use of Ni(II) complexes as catalysts. It is probable that the suppressed yields were caused by oligomerization of LG under the basic conditions used in the reaction.[10] It should be noted that in all cases only exo-addition was observed to occur forming the 4-axial derivatives, *i.e. anti* to the 1,6-anhydro bridge.

The presence of a nitro group in a 4-substitutent of LG would be interesting owing to the possibility of further transformation of the nitro group as well as the formation of new C-C bonds at its activated α-carbon. In the literature, only the Michael addition of 2-nitropropane and nitromethane to LG have been reported.[9,11] It is interesting to consider the addition of ethyl nitroacetate and its derivatives to LG,[12] which allows the introduction of carbethoxy, nitro, alkyl and other functional groups to levoglucosenone. Subsequent transformation of these functionalities can be used for the synthesis of both unnatural amino acids and heterocycles.

It is known that the Michael addition reaction is effectively promoted by electrogenerated bases[13] or by direct cathodic electrolysis.[14] Recently it was shown that ethyl nitroacetate and its derivatives electrocatalytically react under mild conditions with Michael acceptors to form coupling products in high yield.[15] In the present work, this approach has been successfully applied for functionalization of LG.

Cathodic electrolysis of ethyl nitroacetate in the presence of an equimolar amount of levoglucosenone in a

solution of 0.01 M Bu_4NBr in MeCN produced **2** (Scheme 2) in 85% isolated yield. Only 0.10 F/mol of electricity was consumed and the reaction was completed in 1 h. Isolation of the product was very simple: a solution of the crude product was filtered through a layer of silica gel and, after evaporation of the solvent, the analytically pure product was obtained.

The key step of the reaction is the cathodic generation of the carbanion of ethyl nitroacetate by direct cleavage of the activated α-C-H bond (Scheme 1). The use of tetraalkylammonium salts as supporting electrolyte results in a very high reactivity of this carbanion.[16] Therefore, the cathodically generated anion reacts rapidly with LG with the result that the reaction medium remains essentially neutral, thus circumventing the base-catalyzed oligomerization of LG.

In an analogous fashion, the coupling products of LG with ethyl 2-nitropropionate (**3**), diethyl 2-nitroglutarate (**4**), 2-nitropropane (**5**), nitrocyclopentane (**6**), ethyl 2-nitro-4-pentenoate (**7**) and dinitromethane (**8**) were obtained (Scheme 2) in practically quantitative yields (82-96% isolated).

It should be noted that in all cases exclusively exo addition of the nitro-containing substituent was observed.

It has been shown[15] that under electrochemical conditions alkylation of ethyl nitroacetate and further Michael addition can be carried out in a one-pot procedure. This approach was used for synthesis of **7**. Electrochemical alkylation of ethyl nitroacetate with allyl bromide was first carried out to form ethyl 2-nitro-4-pentenoate. LG was then added and the cathodically promoted Michael reaction resulted in formation of **7** in 67% isolated yield.

In contrast to the present work, the reported chemical version[9] of the reaction of 2-nitropropane with LG required heating for 48 h and was accompanied by side reactions. The yield of **5** was only 15%. A higher yield (67%) was achieved by using 2-nitropropane as solvent, but the isolation of the product required column chromatography due to the presence of by-products.

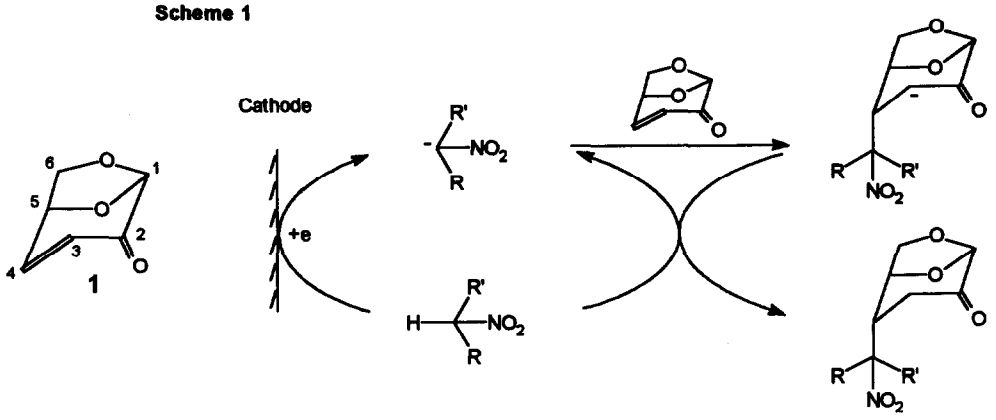
In general, the most effective bases for catalyzing Michael addition to LG have proven to be nitrogen-containing bases such as triethylamine or tetramethylguanidine. For purposes of comparison with the electrochemical method, we treated LG with ethyl nitroacetate at 20-25 °C in acetonitrile in the presence of a catalytic amount of triethylamine. The exo-derivative **2** was obtained with an isolated yield of only 38%. Under the same conditions, the products of condensation of LG with ethyl 2-nitropropionate (**3**) and diethyl 2-nitroglutarate (**4**) were obtained with isolated yields of 35 and 37% respectively. The use of Triton B, piperidine or tetramethylguanidine as well as increasing the temperature, did not improve the yield of the products.

Interesting results have been reported for the condensation of LG with nitromethane. Forsyth *et al.*[11] reported that the reaction of nitromethane and LG in the presence of tetramethylguanidine lead to excellent yields of either a coupling product with two molecules of LG and one of nitromethane (**9**) or one with one LG and two molecules of nitromethane, depending upon the ratio of reactants. When an equimolar mixture was used, a mixture of the two products was obtained with yields of 18% and 61% yields respectively. Results from the electrochemical method were slightly different. Electrolysis of an equimolar mixture of nitromethane and LG gave exclusively **9** (isolated yield of 92% based on LG).

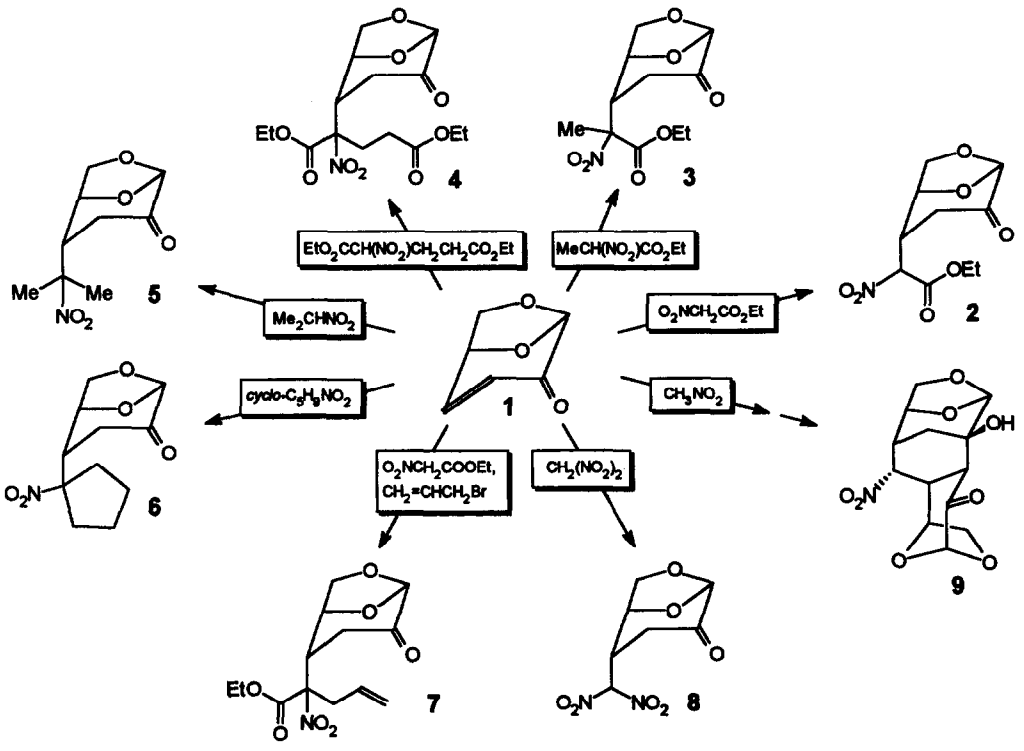
In summary, a wide variety of nitro derivatives of LG have been synthesized by electrochemically promoted Michael additions. The reaction proceeds under very mild conditions without using any base. These studies illustrate the suitability of the electrochemical method for functionalization of LG. We are presently investigating the addition to levoglucosenone of other organic substances containing activated element-hydrogen bonds.

Standard procedure. The electrolysis was carried out in a divided cell under galvanostatic conditions at a current density of 0.5-2 mA/cm^2 with vigorous stirring at room temperature. 10 mL of 0.05-0.1 M Bu_4NBr in abs. MeCN containing 0.25 g LG (0.002 M) and an equimolar amount of nitroalkane was used as catholyte. After passing 0.07-0.1 F/mol, the electrolysis was terminated. The solvent was evaporated and a solution of the residue in a mixture of ethyl acetate and hexane (1:3) was filtered through a 2-3 cm layer of silica gel. After evaporation of the solvent, the analytically pure substances were obtained. The assignment of the 4-axial-structure to the derivatives is based on comparison of ^{1}H-NMR[17] spectra (shifts and coupling constants for H^4 and H^5) with analogous compounds[9,8,11] as well as by comparison of physico-chemical data for **5** and **9** which have been previously reported.[9,11]

Scheme 1



Scheme 2



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17. ^{1}H-NMR (Compounds **2-4, 7** are mixtures of diastereomers), $CDCl_3$, ppm/TMS:
(2): 1.26t, 1.27t (CH_3; 3H, J=5.5); 2.25d, 2.30d (H^{3e}; 1H, J=17); 2.84dd, 2.91dd (H^{3a}; 1H, J=17,4); 3.13dd, 3.15dd (H^4; 1H, J=6,4); 4.03dd (H^{6exo}; 1H, J=8,5); 4.10d (H^{6endo}; 1H, J=8); 4.23q, 4.29q (CH_2; 2H, J=5.5); 4.54d, 4.88d (H^5; 1H, J=5); 5.07s, 5.08s (H^1; 1H); 5.27d, 5.31d (H^7; 1H, J=6).
(3): 1.23t, 1.25t (CH_3-ester; 3H, J=7); 1.84s, 1.88s (CH_3; 3H); 2.26d, 2.35d (H^{3e}; 1H, J=20); 2.68dd, 2.76dd (H^{3a}; 1H, J=20,9); 3.99dd (H^{6exo}; 1H, J=9,4); 4.01d (H^{6endo}; 1H, J=9); 4.26q (CH_2-ester; 2H, J=7); 4.61d, 4.86d (H^5; 1H, J=4); 5.06s (H^1; 1H).
(4): 1.24m ($2CH_3$-ester; 6H); 2.15-2.80m (6H); 2.96d, 3.00d (H^4; 1H, J=4);3.97d, 3.99d ($2H^6$; 2H, J=6);4.07q, 4.22q ($2CH_2$-ester; 4H, J=7,6); 4.82s, 4.96s (H^5; 1H); 4.99s (H^1; 1H).
(6): 1.54-1.78m (6H-cyclopentyl); 1.95dd (H^{3a}; 1H, J=16,7); 2.37d (H^{3e}; 1H, J=16; 2.58-2.77m (2H-cyclopentyl); 2.82d (H^4; 1H, J=7); 3.96s (H^{6endo}; 1H); 3.97d (H^{6exo}; 1H, J=4.5); 4.56d (H^5; 1H, J=4.5); 5.08s (H^1; 1H).
(7): 1.24t, 1.27t (CH_3-ester; 3H, J=7); 2.52-2.76m (H^{3e},H^{3a}; 2H); 2.93d, 2.98d (H^4; 1H, J=5); 3.03d, 3.08d ($C\underline{H}_2CH=$; 2H, J=7); 4.00m ($2H^6$; 2H); 4.26q, 4.27q (CH_2-ester; 2H, J=7); 4.80d, 4.97d (H^5; 1H, J=5); 5.04s (H^1; 1H); 5.16-5.25m ($=CH_2$; 2H); 5.41-5.66m (-CH=; 1H).
(8): 2.31d (H^{3e}; 1H, J=16); 3.02dd (H^{3a}; 1H, J=16,8); 3.38t (H^4; 1H, J=8); 4.13dd (H^{6exo}; 1H, J=8,6); 4.19d (H^{6endo};1H, J=8); 4.69d (H^5; 1H, J=6); 5.21s (H^1; 1H); 6.47d (H^7; 1H, J=8).

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