Ring contraction and formation of spironolactone during reaction of dihydrolevoglucosenone with 2-pyridinecarboxaldehyde

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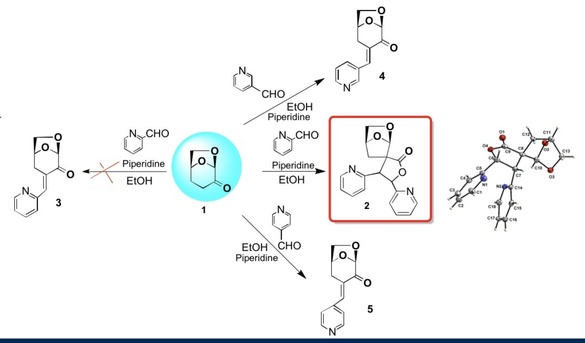
Abstract

The reaction of dihydrolevoglucosenone **1** (DHLG) Cyrene^R with aromatic aldehydes in the presence of a base produces *exo*-cyclic enones[1-2] as a main, and usually only, product. However, when 2-piridinealdehyde was used, we noticed a formation of an entirely different product **2** in a good 48 % yield. The NMR data and crystal structure differed significantly from those of a typical *exo*-cyclic enone **3**. The crystal structure unambiguously established the formation of a spironolactone structure. The product derived from the reaction of two aldehyde molecules with one molecule of DHLG. We are in the process of studying the mechanism leading to the formation of this unexpected product. Two plausible mechanisms are presented and discussed. Interestingly, the 3, and 4-piridinecarbaldehydes are reacting with DHLG *via* normal Knovenagel condensation with formation of typical exo-cyclic enones **4-5**.



Scheme 1. Summary of types of products obtained and crystal structure data for product **2**

Background

Many biologically active compounds are functionalized heterocycles. Antimicrobial, antiproliferative, and antibiotic properties have been determined for a number of spiro-heterocycles.[3] Synthesizing heterocycles that contain a spiro carbon moiety is a growing area of research. Synthetic strategies typically utilize nucleophilic addition, Diels-Alder reactions, cycloadditions and condensations, and domino reactions.[4] Research has identified domino oxa-Michael condensations to be a successful method of synthesizing spiro-heterocycles in high yields. Our methods utilize DHLG, a compound formed via catalytic reformation of products obtained from the pyrolysis of cellulose waste materials. DHLG reacts via Michael addition with aldehydes and ketones to form a number of potentially biologically active compounds. The reactivity of DHLG is being studied now for use in synthetic routes as opposed to its intended use as a dipolar, aprotic solvent.

Methods

Reactions were performed under one of three conditions:

1. Reagent alcohol as a solvent and piperidine as a catalyst
2. Acetonitrile as a solvent and TMG as a catalyst
3. Reagent alcohol as a solvent and pyrrolidine as a catalyst

Reaction mixtures were either heated to 45 - 50° C with stirring for 16.5 or 24 hours or refluxed for 24 hours.

Data

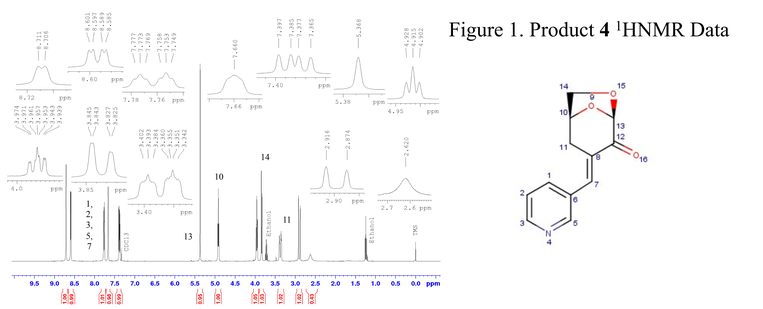


Figure 1. Product **4** ^{1}HNMR Data

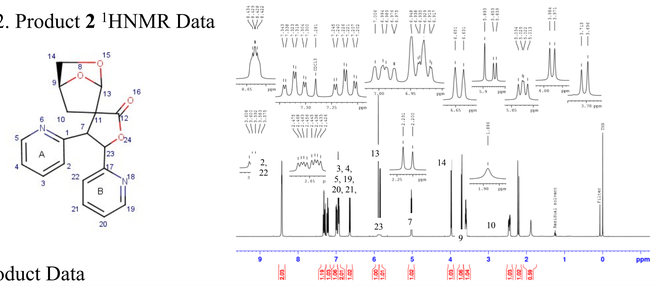
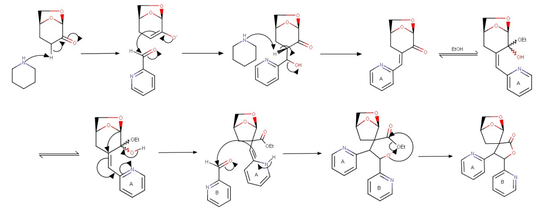


Figure 2. Product **2** ^{1}HNMR Data

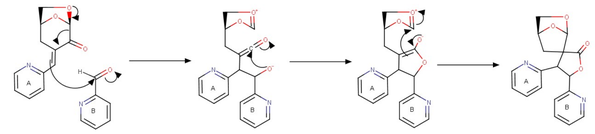
Table 1. Product Data

Reaction	Aldehyde	Method	Proposed Product	MW (g·mol^{-1})	MP (°C)	Yield (%)	$[\alpha]_D^{20}$ / °
1	2-pyridine carboxaldehyde	2	spironolactone	324.34	240-243	16.65	–
2	3-pyridine carboxaldehyde	2	enone	217.22	–	–	–
3	4-pyridine carboxaldehyde	2	enone	217.22	205-220	45.83	–
4	quinoline-2-carboxaldehyde	2	–	428.48	245-255	–	-495
5	2-pyridine carboxaldehyde	1	spironolactone	324.34	252-255	26.13	-195
6	3-pyridine carboxaldehyde	1	enone	217.22	151-162	64.58	-497
7	4-pyridine carboxaldehyde	1	enone	217.22	–	–	–
8	quinoline-2-carboxaldehyde	1	–	428.48	253-255	–	-498
9	quinoline-2-carboxaldehyde	3	–	428.48	253-255	–	–

Possible Spirolactonization Mechanisms



Scheme 2. Proposed mechanism for spironolactone formation via hemiketal equilibrium[2,5]



Scheme 3. Proposed mechanism for spironolactone formation via ketene intermediate formation[2,6]

Conclusions and Future Research

- 3- and 4-pyridine carboxaldehyde reacted to yield *exo*-cyclic enones.
- 2-pyridine carboxaldehyde reacted to yield spirolatone
- Quionoline-2-carboxaldehyde reaction data supports the formation of a mixture of enone isomers.
- Future work aims to determine the mechanisms by which these products are formed, as well as other potential synthetic techniques for spirocyclization using DHLG.

Acknowledgements

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