

## Formation of *Exo*-Cyclic Enones from Formyl Benzoic Acids and Dihydrolevoglucosenone

Cassie Oldt, Zbigniew J. Witezak\*, and Donald E. Mencer

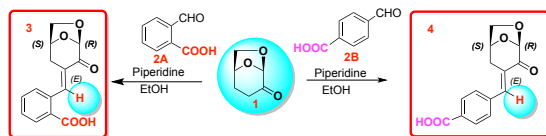
Department of Pharmaceutical Sciences, & Department of Chemistry and Biochemistry,  
Wilkes University, Nesbitt School of Pharmacy, Wilkes-Barre, 84 W. South Street, PA 18766.

E-mail: zbigniew.witezak@wilkes.edu



### Abstract

The reaction of dihydrolevoglucosenone **1** (DHLG) Cyrene<sup>R</sup> with aromatic aldehydes in the presence of a base (piperidine or pyrrolidine) produces *exo*-cyclic enones as a main (and usually only) product. We extended this approach to use 2-formyl and 4-formyl benzoic acids in order to verify the importance of a carboxylic functional group for the overall course to the condensation reaction. In both cases, we were able to isolate crystalline product **4** in good 69% **3** (oil) in 75% yield. The <sup>1</sup>H and <sup>13</sup>C NMR data of **3** and **4** confirmed the normal *exo*-cyclic enone structure and free -COOH group. Also, the “free” -COOH functional group of **3** and **4** was attempted to convert into new products *via* standard esterification and amidation. Plausible mechanism will be presented and discussed.



Scheme 1

We expanded the original protocol<sup>1</sup> to include substituted six-membered aromatic aldehydes. In order to determine the potential effect of electron withdrawing and electron donating groups in aromatic aldehydes over the course of the reaction, we selected two formyl benzoic acids **2A** and **2B** as depicted in Scheme 1 and Table 1. The preliminary results clearly show the formation of expected *exo*-cyclic enones.

### Introduction

Enantioselective synthesis often utilizes carbohydrates as chiral starting materials because of their availability and affordability.<sup>2</sup> Dihydrolevoglucosenone, a chiral, bicyclic enone produced from the pyrolysis of cellulose, has significant potential for the synthesis of pharmacore containing compounds.

So far, dihydrolevoglucosenone has been successfully reacted with numerous aromatic aldehydes *via* aldol condensation.<sup>1,3</sup> These reactions, for the most part, produce a single, pure product in relatively high yields. However, some of these reactions have produced more complex products than expected.

Beyond aldol condensation, reactivity of the *exo*-cyclic double bond and keto functionalization at C-2 are of significant interest and potential application in the synthesis of other heterocyclic derivatives with potential biological activity.

Additionally, the exploration of possibility of isomerization of *E* to *Z* enone is an important factor to establish the differences in enones stability and reactivity as well.

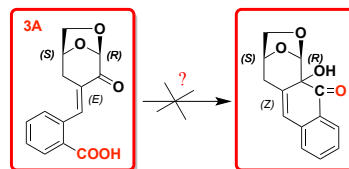
### Methods

**General Aldol Condensation Procedure:** Equimolar amounts of aromatic aldehydes **2A** or **2B** and dihydrolevoglucosenone **1**, were dissolved in 30 mL ethanol. After the addition of a base catalyst, such as piperidine, (0.5mL) the reaction mixture was refluxed for 24-72 hours. Reaction progress was monitored by TLC. After concentration, products were either obtained as oils or isolated as crystalline precipitates, filtered, and washed with ice-cold ethanol.

### Results

The reaction of 4-formyl benzoic acid (**2B**) with dihydrolevoglucosenone (DHGL) resulted in the expected *exo*-cyclic enone (**4**) in pure crystalline form. When 2-formyl benzoic acid (**2A**) reacted with dihydrolevoglucosenone, (DHGL) we detected by TLC, formation of two products with  $R_f = 0.67$  and  $R_f = 0.87$  respectively. (Table 1).

Our attempts to interpret the results of the reaction and identify the second product with  $R_f = 0.67$  are underway. One of the possible explanations is that during the prolonged heating the thermodynamically stable *E*-enone is forming first, and then slowly isomerizes to *Z* enone with the formation of a cyclic minor co-product. However, the NMR analysis of mixture of both products (**3**) is not conclusive and will require additional separation techniques such as preparative TLC or HPLC for complete separation of both components. Scheme 2 shows a suggested mechanism for this reaction.



Scheme 2



Crystalline enone 4.

Table 1. Physical characteristic of *Exo*-cyclic enones **3** & **4**.

Enone	m.p. °C	yield %	$R_f^a$	$[\alpha]_D^{25}$ (CH <sub>2</sub> Cl <sub>2</sub> )
<b>3</b>	--	--	0.64, 0.87	--
<b>4</b>	208-212	62	0.76	-226.1246

### Conclusion

We synthesized first carboxylic *exo*-cyclic enone *via* stereoselective aldol condensation:

1. *Exo*-cyclic enone was assigned *E*-configuration.
2. In the case of *o*-formylbenzoic acid, **2A** additional cyclic minor product was obtained. (Not characterized). The isolation and purification of this product is underway.

### References

1. Witezak Z. J., Bielski R, Mencer DE, *Tetrahedron Lett.* 58 (2017) 4069-4072
2. Hohol, R., Acure, H., Witezak Z. J. Bielski R., Kirschbaum, K., Andreana P., Mencer, D. *Tetrahedron*, (2018), 74, 7303-7309.
3. Ledingham, E. T., Stockton, K. P., and Greatrex, B. W. (2017). *Australian Journal of Chem.*, 70, 1146-1150.