Synthesis of unexpected chromanone heterocycles from dihydrolevoglucosenone

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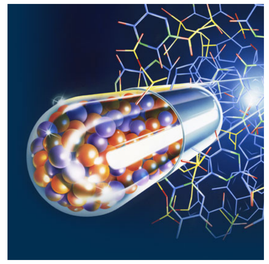
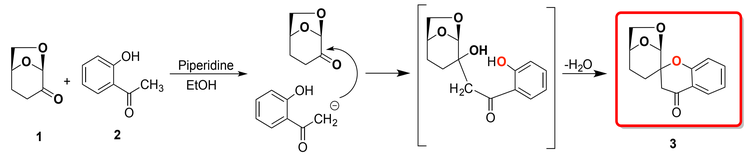


Abstract

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. We expanded the original protocol to include six-membered substituted aromatic o-hydroxyacetophenones. However, when DHGL **1** was reacted with o-hydroxyacetophenone, an entirely different product **3** was formed in a good 58 % yield. The ^{1}H and ^{13}C NMR data of **3** confirmed the unusual *spiro*-carbon structure. The product **3** seems to derive from the reaction of the acetophenone anion attacking C-2 carbonyl of DHLG **1**. Plausible mechanisms will be presented and discussed.



Scheme 1

In order to determine the potential effect of electron withdrawing and electron donating groups in aromatic acetophenones over the course of the reaction, we selected several ketones as depicted in Scheme 2 and Table 1. The preliminary results clearly show the formation of expected *spiro*-chromanones. All structures were determined by ^{1}H and ^{13}C NMR. Acetophenones, equipped with a -Cl, -Br, -F -NO_2 group in the C-5 position, form expected crystalline products.

Introduction

Enantioselective synthesis often utilizes carbohydrates as chiral starting materials because of their availability and affordability.[2] Dihydrolevoglucosenone, a chiral, bicyclic enone produced from the cellulose, has a significant potential for the synthesis of pharmacophore containing compounds.

So far, dihydrolevoglucosenone has been successfully reacted with numerous aromatic aldehydes *via* aldol condensation.[1,3,4] These reactions, for the most part, produce single, pure products in relatively high 65-92% yields. Beyond aldol condensation, reactivity of the *exo*-cyclic double bond and keto functionalization, are of significant interest. Our new approach to chromanone skeleton utilizing the reaction mechanism depicted in scheme 1 is the simplest strategy to introduce *spiro*-functionality at C-2 position.

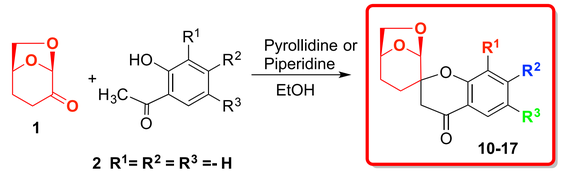
Many natural *spiro*-compounds exhibit some unusual conformational properties related to the biological activities[5] . We are in the process of investigation of additional chemical properties of this new class of C-2 *spiro*-sugar-containing heterecyclic molecules. It would be important to develop new functionalization reactions at carbonyl keto function and the opening of the 1,6-anhydro ring of sugar moiety of *spiro*-chromanones as well.

Methods

General Aldol Condensation Procedure: Equimolar amounts of o-hydroxyacetophenones aromatic and dihydrolevoglucosenone (0.1mmol) were dissolved in 30 mL ethanol. After the addition of a base catalyst, such as pyrrolidine, (0.5.mL) 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 dihydrolevoglucosenone **1** **(DHGL)** with 2'-hydroxyacetophenones (2-9) resulted in the formation of crystalline *spiro*-chromanones (10-17). Scheme 2 shows a suggested mechanism for this reaction.



Scheme 2

2 $R^1 = R^2 = R^3 =$ - H
3 $R^1 = R^2 =$ H, $R^3 =$ -Cl
4 $R^1 = R^2 =$ H, $R^3 =$ -Br
5 $R^1 = R^2 =$ H, $R^3 =$ -F
6 $R^1 = R^2 =$ H, $R^3 = -NO_2$
7 $R^1 = R^2 =$ H, $R^3 = -CH_3$,
8 $R^1 = R^2 =$ H, $R^3 = -OCH_3$
9 $R^1 =$ H, $R^2 = -CH_3$, $R^3 =$ -Cl

The aldol condensation reaction of an aromatic ketone containing a hydroxyl group in the *ortho* position is undergoing a domino reaction with a cyclization step resulting with formation of *spiro*-chromanone.

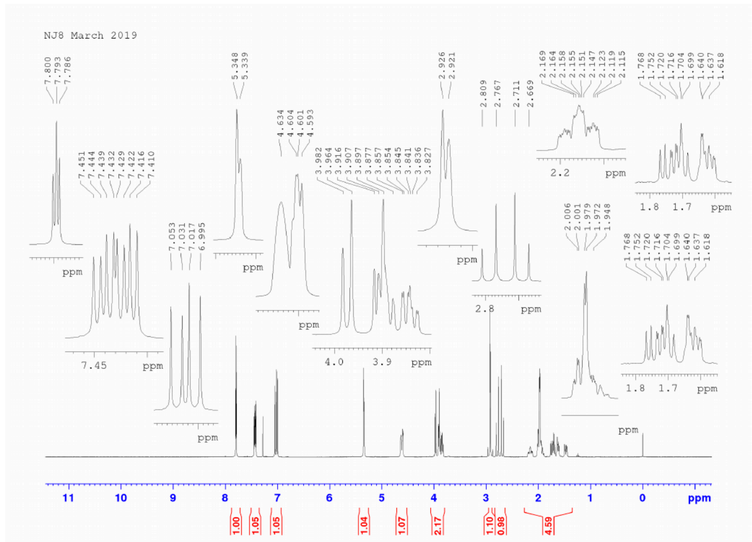
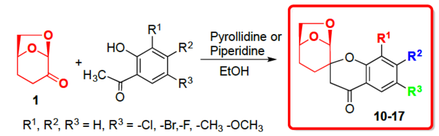


Fig. 1. ^{1}H NMR Spectra of *spiro*-chromanone 11

Table 1. Physical characteristic of *spiro*-chromanones **10-17**.



R^1, R^2, R^3 = H, R^3 = -Cl, -Br,-F, $-CH_3$ $-OCH_3$

Spirochromanone	R^1, R^2, R^3	m.p. °C	yield %	R_f[a]	$[\alpha]_D$ (CH_2Cl_2)
10	-H	123-126	64	0.17	-24.6
11	R^3 = -Cl	116-118	64	0.85	-36.6
12	R^3 = -Br	159-161	92	0.83	-29.6
13	R^3 = -F	184-186	43	0.81	-
14	R^3 = $-CH_3$	124-126	60	0.29	-25.1
15	R^3 = $-OCH_3$	202-204	62	0.84	-27.5
16	R^2 = $-CH_3$, R^3 = - Cl	118-120	82	0.81	-22.3
17	R^3 = $-NO_2$	159-160	48	0.77	-39.6

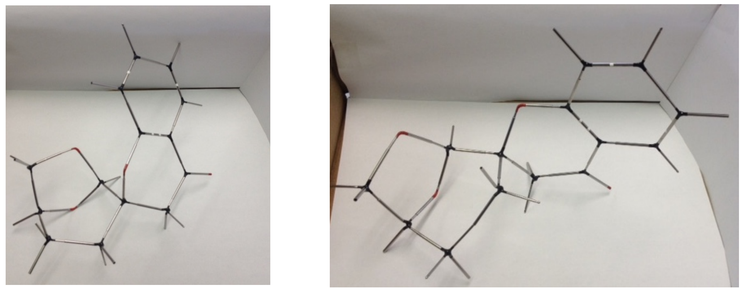


Fig. 1 Two possible conformers of spirochromanone 10

Conclusion

We synthesized several *spiro*-chromanones *via* stereoselective aldol condensation of o-hydroxy acetophenones with dihydrolevoglucosenone with concomitant domino cyclization:

1. **Spiro-chromanones cyclic were assigned -configuration.**
2. **The ^{13}C NMR signal for C-2 *spiro*-carbon is at δ = 159. 07, which is characteristic for dominant conformer.**
3. **Optical rotation (-24.6 to -39.6) is fully indicative of preferred stereochemistry.**

References

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