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In Situ Hemi-Synthesis of New Unexpected Chiral Chromeno-Pyrimidine Derivative †

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Abstract: A hemi-synthesis reaction of barbituric Acid with an α,β-unsaturated aldehyde using Perillaldehyde from Essential oil of *Ammodaucus leucotrichus* subsp *leucotrichus*, affording to a chromeno-pyrimidine derivative. The reaction was carried out in Water/Ethanol medium without an added catalyst. The obtained pyrimidine was identified by their spectral ^{1}H, ^{13}C, HMBC and HSQC 2D NMR.

Keywords: hemi-synthesis; barbituric acid; chromeno-pyrimidine; chiral perillaldehyde

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1. Introduction

The derivatives of barbituric acid have a special place in pharmaceutical chemistry. Their biological activities range from classical applications in medical treatments as hypnotic, sedative, and anesthetic drugs [1] to the more recent reports indicating that they have applications in anti-tumor [2], anticancer [3], and anti-osteoporosis treatments [4]. In recent years, organic chemists have begun to place more emphasis on hemi-synthesis, using essential oils as a source of cheaper and more accessible starting materials in terms of yield and quantity. Among these molecules, the bis-imine of (s) -carvone [5] and imine of (S)-(-) -perillaldehyde [6], as well as the benzodiazepines and benzimidazole of perillaldehyde which are tested as antimicrobial [6]. In hemi-synthesis, carbonyls, especially aldehydes, constitute an essential element for access to new chiral heterocycles such as citronellal and perillaldehyde which have an asymmetric carbon [5–7].

2. Materials and Methods

2.1. Instrumentation and Reagents

All the reagents and solvents were purchased from Aldrich, Acros Organics and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 (400 and 100 MHz, respectively) spectrometer. DMSOd_6 was used as solvent; the chemical shifts are expressed in δ (ppm) and the coupling constants (*J*) in Hertz (Hz). Unequivocal ^{1}H assignments were made using 2D COSY ($^{1}H/^{1}H$), whereas ^{13}C assignments were made on the basis of 2D HSQC ($^{1}H/^{13}C$) and HMBC (delay for long-range *J*

C/H couplings were optimized for 7 Hz) experiments. Melting points were measured using BUCHI M-560/565 Melting apparatus.

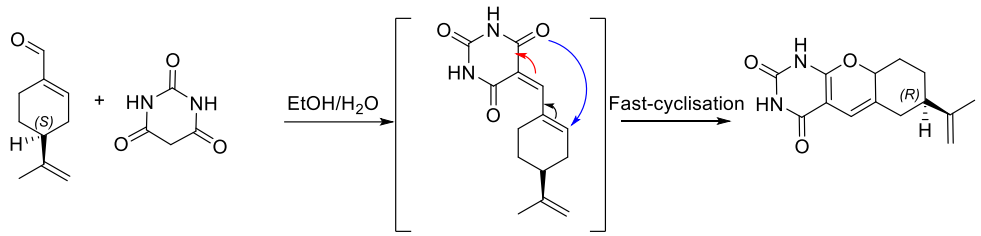
2.2. Chemistry

Barbituric acid 0.08 g (1eq) was dissolved in 5 mL of hot water (60 °C). The solution was stirred for about 10 min and then 1eq (113 mg) of essential oil (containing about 80% aldehyde) in 0.5 mL EtOH was added. The solution was stirred to the room temperature and kept for 72 h. The precipitate that formed was filtered and washed few times with hot water, then washed with ethyl acetate (3 × 5 mL) and dried at room temperature.

(7*R*)-7-(prop-1-en-2-yl)-1,6,7,8,9,9a-hexahydro-2*H*-chromeno[2,3-d]pyrimidine-2,4(3*H*)-dione. The product was obtained as white powder (0.07 g, 43%), mp.: 190–193°C.

3. Results and Discussion

In the common works literature, the action of aldehydes on the activated position of barbituric acid is known as a Knovenagel condensation using aromatic carbonyls or α,β-unsaturated aromatic aldehyde [8]. In our case, the use of peril aldehyde afforded to a chromeno pyrimidine by a simple auto-cyclisation in Water/EtOH medium Scheme 1.



Scheme 1. Mechanism of chromeno-pyrimidine derivative formation**.**

The NMR spectra of the product confirmed the structure of desired compound, the assignment of protons and carbon atoms being sustained by bidimensional spectroscopy (homonuclear COSY and heteronuclear HSQC and HMBC). ^{1}HNMR spectra of the obtained chromeno-pyrimidine reflect signals due to O-cyclisation proton and at δ 5.27 ppm. The signal at δ 5.94 ppm corresponding to 2*H*-chromene's proton and protons of NH pyrimidine derivative appear at δ 10.72, 11.54 ppm Figure 1.

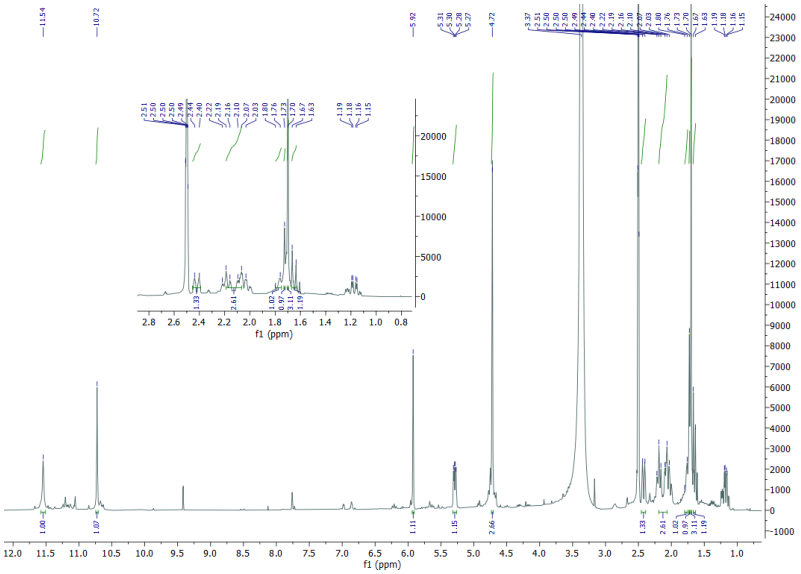


Figure 1. ^{1}H NMR spectra of chromeno-pyrimidine derivative. ^{13}C NMR spectra showed that, signals between δ 81 and 85 ppm could be unambiguously assigned to O-cyclisation carbon and pyrimidine's unsaturation respectively. The signals of carbonyls appear at 149 and 161 ppm Figure 2.

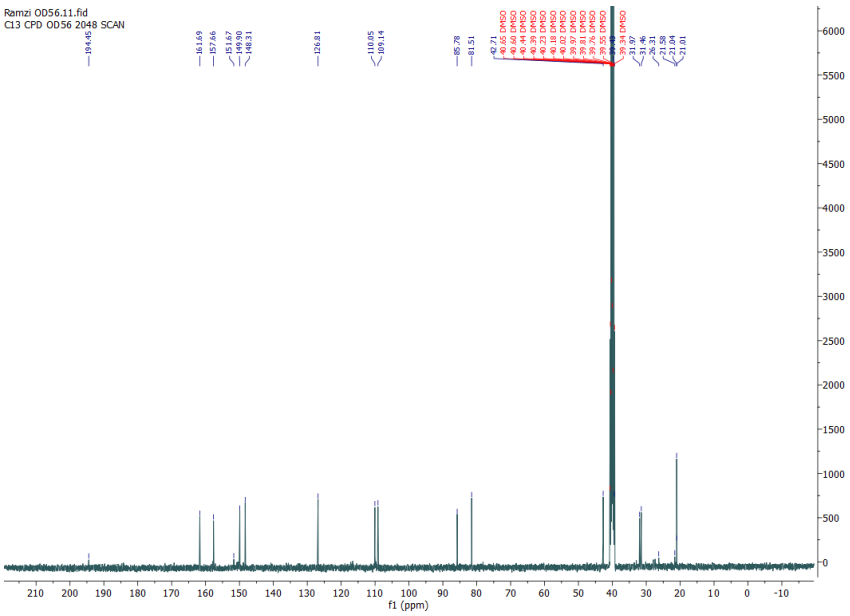


Figure 2. ^{13}C NMR spectra of chromeno-pyrimidine derivative.

4. Conclusions

In summary, we report the hemi-synthesis of new chiral chromeno-pyrimidine derivative using barituric acid and a natural aldehyde from essential oil under mild condition. The obtained product can be tested as antimicrobial and antibacterial agent.

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