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Synthesis of Methyl-4-Oxo-2(E)-alkenoic Acid and Theoretical Investigation of Reaction Mechanism

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Abstract

The methyl derivative 4-Oxo-2(E)-alkenoic acid has been synthesized from maleic anhydride and methyl lithium. The potential reasons for the relatively low yield have been tried to explain by theoretical calculations. DFT computations showed that all the reaction taking part requires some energy to go over the activation barrier, however, the reactions are highly exothermic and the driving force for the reactions is the stability of the last products.

Keywords

4-Oxo-2(E)-alkenoic Acid, Maleic Anhydride, DFT, Energy Profile

1. Introduction

In current chemical and medicinal research, synthesis and biological evaluation of potentially new antibiotic agents is important. Due to multi-resistance being developed by several microbial strains against commonly used pharmaceutical drugs, there occurs a demand for designing and synthesizing more effective antibiotics with minimum side effects.

4-Oxo-2(E)-alkenoic acid type of compounds are biologically important and useful molecules in organic chemistry. They are versatile intermediates for organic synthesis in terms of bearing α,β-unsaturated-γ-diketones [1-10]. They have been synthesized and used since late 19th century, especially the aromatic derivatives. 4-Phenyl-4-oxo-2(E)-butenoic acid and its derivatives act as inhibitors of kynurenine-3-hydroxylase (KYN-3-OHase), an enzyme involved in the metabolism of kynurenine [11]. 4-Oxo-2(E)-nonenoic acid is a natural antibiotic (1 in Figure 1). It wasisolated from the mycelium of *Streptomyces olevaceus* Tu 4018 by Pfefferle *et al* [12]. It is reported to be important for its antibacterial activity against various Gram-positive and Gram-negative strains, especially against *staphylococcus aureus* ATCC 11632 [12].

Generally, 4-oxo-2-enoic acids and their derivatives (2-4 in Figure 1) display good biological activity. For example, (*E*)-4-phenyl-4-oxobut-2-enoic acid and its derivatives act as inhibitors of Kynurenine-3-hydroxylase (KYN-3-OHase), an enzyme involved in the metabolism of kynurenine and therefore, may be useful in the prevention and/or treatment of neurodegenerative diseases.

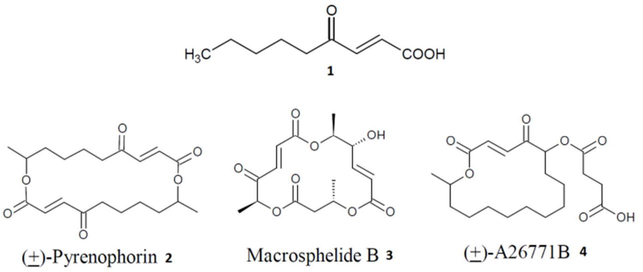

Figure 1. 4-oxo-2-enoic acid and its derivatives.

It is also found to be an inhibitor for human mitochondrial aldehyde dehydrogenase.[11] There are many other examples

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reported in the literature about the antifungal, antibacterial, and anti-inflammatory properties of the compounds having this functional array [12-17].

In the present article, the synthesis and theoretical investigation of the reaction mechanism for methyl derivatives of α, β-unsaturated-γ-diketones have been reported. The characterizations of the compounds have been done by NMR analysis. The products of the reactions are potential biological active compounds and useful precursors for other important compounds, as well.

2. Experimental

2.1. General

0.49 g (5 mmol) newly sublimed maleic anhydride [18] was dissolved in 40 mL dry THF in 100 mL flask. To this was added dropwise at -78°C under N_2 atmosphere 0.829 g (5 mmol) methylmagnesiumiodide dissolved in diethylether (1.69 mL from a 3M solution). After stirring for 1 hour, 10 mL saturated NH_4Cl was added at -78°C and allowed to warm to room temperature. The pH was adjusted to 2 by dropwise addition of HCl and the organic layer was extracted with ethylacetate (3x100 mL), dried over Na_2SO_4, and the solvent evaporated under vacuum. 0.87 g crude product was obtained in 66% yield. At -78°C, 1 [18], 2 [19] and 3 [20] was determined 35%, 62% and 3%, at room temperature 1, 2 and 3 was determined as 28%, 63% and 9%, respectively. The characterizations of the products have been performed by ^{1}H-NMR spectra with the following data.

(1) ^{1}H-NMR (400 MHz, $CDCl_3$): δ=7.08 (d, 1H, J=16 Hz, C-H), 6.65 (d, 1H, J=16 Hz, C-H), 2.38 (s, 3H, CH_3).

(2) ^{1}H-NMR (400 MHz, $CDCl_3$): δ=6.37 (d, 1H, J=13Hz, C-H), 5.73 (d, 1H, J=13 Hz, C-H), 1.71 (s, 6H, CH_3).

(3) ^{1}H-NMR (400 MHz, $CDCl_3$): δ=2.52-2.44 (m, 6H), 2.25 (s, 3H, CH_3).

2.2. Method of Computation

The geometry optimizations of all the structures leading to energy minima were achieved by using a molecular mechanics (MM2) method followed by semi-empirical PM3 self-consistent fields molecular orbital (SCF MO) method at the restricted level followed by STO type calculations. Then, geometry optimizations were achieved within the framework of density functional theory (DFT, B3LYP) at the level of 6-31G (d,p). The exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional and Lee, Yang, Parr (LYP) correlation correction functional.

Gaussian 09 and Spartan 14 package programs were used to perform all computational calculations [21, 22]. The frequency analysis for each compound did not yield any imaginary frequencies, indicating that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. However, the transition state geometries have been determined by only one negative frequency in the normal mode analysis. The normal mode analysis was performed for 3N-6 vibrational degrees of freedom, N being the number of atoms forming the molecule.

3. Results and Discussion

The reaction scheme to obtain the desired 4-Oxo-2(E)-alkenoic acid type derivatives is shown in Figure 2.

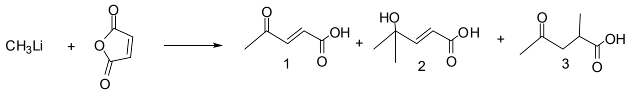

Figure 2. The reaction and the products.

The synthesis of methyl-4-Oxo-2(E)-alkenoic acid (1) can be achieved from the reaction of maleic anhydride and methyl lithium. However, the desired reaction product is obtained by only 35% and 28% yield at -78°C and room temperature, respectively. Although the products 2 and 3 may possess some important properties, they have different π-skeleton from the purpose of interest. Therefore, theoretical studies have been performed to draw the reaction energy profile in order to obtain information about the mechanism of the reaction. The energetics of the reaction may give clues for improving the yield of the desired compound. For the purpose, geometry optimizations have been performed for the reactants, the transition states and the products at the level of B3LYP/6-31G (d,p). The geometry optimized structures all the molecules and intermediates and the energy profile of the reaction are given in Figure 3 and Figure 4, respectively. The transition states are determined by high value imaginary frequencies together with distortion to become tetrahedral from planarity. The Intrinsic Reaction Coordinate (IRC) calculations used to confirm that transition states connects the reactants to products.

The first step of the reaction involves attacking of methyl lithium to the carbonyl of maleic anhydride which requires 29 kcal/mol energy. The first step of the reaction in total is highly exothermic. The intermediate structure (1) can react with a second methyl lithium to result 2 and 3 with two pathways. The attack of the second nucleophile requires higher energy but the stability of the products is the energy determinig point of the reaction. The activation barrier to obtain compound 3 is more than the compound 2, which explains the better yield of the latter over the former.

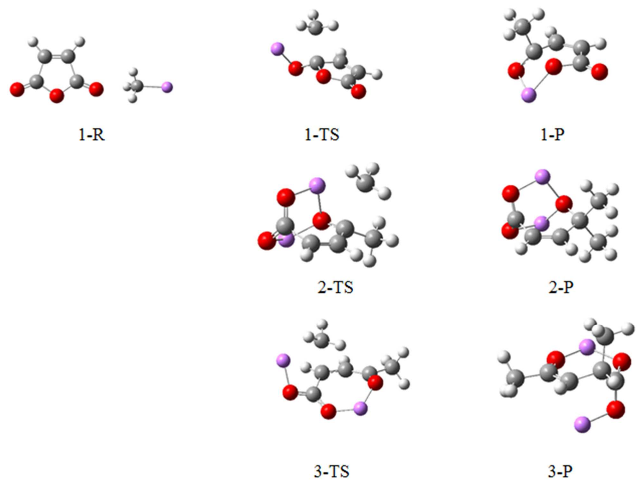

Figure 3. Optimized structures of reactants (R), transition states (TS) and products (P) of the reaction.

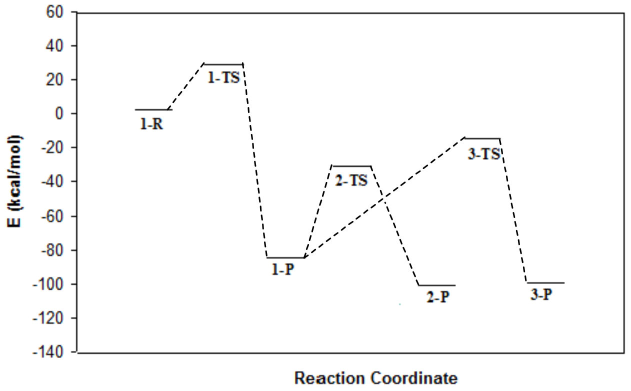

Figure 4. Energy profile of the reaction.

4. Conclusion

The synthesis of the methyl derivative 4-Oxo-2(E)-alkenoic acid has been achieved from maleic anhydride and methyl lithium. The potential reasons for the relatively low yield have been tried to explain by theoretical calculations. The computations showed that all the reaction taking part require some energy to go over the activation barrier, however, the reactions are highly exothermic and the driving force for the reactions is the stability of the last products. The reaction media may be further cooled and diluted to obtain the desired methyl 4-Oxo-2(E)-alkenoic acid derivative in high yield.

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