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Synthesis and DFT Calculation of a New Series of Enaminones based on 3-amino Coumarin

P. Nouraie[1], Sh. Moradi Dehaghi[1], A. Foroumadi[2,3*]

[1] *Department of Chemistry, Tehran North Branch, Islamic Azad University, Tehran, Islamic Republic of Iran*
[2] *Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran*
[3] *Drug Design and Development Research Center, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran*

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Abstract

In this paper, the synthesis of various enaminones from the reaction of 3-aminocoumarin and ethyl-2,4-dioxo-4-arylbutanoate in the presence of p-toluene sulfonic acid is reported. The reaction was examined under different solvents and catalytic systems, which clearly proved the importance of acidic catalyst in this organic transformation. This work was also accompanied by density functional theory (DFT) studies to justify the formation of final products.

Keywords: 3-aminocoumarin; Enaminones; DFT studies.

Introduction

Coumarin is an important structural unit that constitutes the core skeleton of many flavonoid compounds with various activities [1-4]. Additionally, coumarin-based molecules have been considered as a crucial starting material in organic synthesis. In particular, the synthesis and application of 3-aminocoumarins have received great interest from medicinal chemists [5-8], regarding their wide range of biological activities, such as central nervous system (CNS) inhibitory activity [9], anti-bacterial [10], anti-allergic [11], and anti-cancer properties [12,13]. The 3-aminocoumarin core is also known as the main part of natural antibiotics such as novobiocin, chlorobiocin, and coumermycin [14]. Considering this fact, many synthetic methods have been reported for the construction of this heterocyclic core. The most popular reaction for the synthesis of this core occurred between salicylaldehyde and acetic anhydride, known as perkin reaction [15-18].

Enaminones are useful and fascinating building block (N–C=C–C=O) for the synthesis of heterocyclic compounds. The conjugation of carbonyl group with enamine moiety offered both nucleophilic and electrophilic sites by which further reactions occurred to afford various valuable molecules. Accordingly, the enaminone-heterocyclic hybrid systems, particularly coumarin, gave organic chemists the opportunity to synthesize novel compounds.

Considering the importance of coumarin chemistry [15-19], herein, we investigated the reaction between 3-aminocoumarin and α,γ-diketoester derivatives by using *para*-toluene sulfonic acid (*p*-TSA) as the catalyst. Utilizing the organic-soluble solid acid catalyst is the useful feature of our protocol compared to previous

* Corresponding author: Tel: 00982166954708; Fax: 00982166461178; E-mail: aforoumadi@yahoo.com

reports. In previous reports, the inorganic acid, hydrochloric acid, was used by which corrosive effect on human tissue and irreversibly damage to respiratory organs, eyes, skin, and intestines are observed [20]. In this work, the starting material, 3-aminocoumarin, is synthesized from the reaction of *N*-acetylglycine and different salicylaldehyde derivatives, which hydrolyzed to 3-aminocoumarin under acidic condition. Then, according to our expertise [21-25], we investigated on the synthesis and computational studies of 4-oxo-2-((2-oxo-2*H*-chromen-3-yl) amino) but-2-enoates.

Materials and Methods

Chemistry

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications. Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker FT-500, using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Chemical shifts are expressed as δ (ppm). IR spectra were recorded on a Nicolet Magna FTIR 550 spectrophotometer using KBr disks in cm^{-1}.

General procedure for the synthesis of target compounds

3-Aminocoumarin (1 mmol), various α-γ-diketoesters (1 mmol), and *p*-TSA (15 mol %) were refluxed in ethanol (10 mL). The reaction progress was checked by TLC (mobile phase ethyl acetate: petroleum ether (3:7)) ff. After completion, the ice cold water was added to the reaction mixture to afford desired product. Further purification was accomplished by recrystallization from ethyl acetate/petroleum ether.

Ethyl (Z)-4-oxo-2-((2-oxo-2H-chromen-3-yl) amino)-4-phenylbut-2-enoate (5a)

Yellow solid; yield: 88 %; mp 212-214 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.92 (s, 1H, NH), 7.98 (d, 2H, J = 7.5 Hz), 7.56-7.41 (m, 5H), 7.33 (d, 1H, J = 8 Hz), 7.28 (t, 1H, J = 7.0 Hz), 7.21 (s, 1H, CH), 6.70 (s, 1H, CH), 4.34 (q, 2H, OCH_2 J = 6.7 Hz), 1.32 (t, 3H, CH_3, J = 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 191.79, 163.66, 158.95, 151.13, 147.28, 138.46, 132.56, 129.96, 128.60, 127.74, 127.01, 126.79, 125.11, 124.92, 119.39, 116.47, 99.02, 62.46, 13.99.

Ethyl (Z)-4-(4-fluorophenyl)-4-oxo-2-((2-oxo-2H-chromen-3-yl) amino) but-2-enoate (5b)

Yellow solid; yield: 80 %; mp 220-221 °C; IR (KBr, cm^{-1}) ν_{max}: 3413, 3342, 2363, 1733, 1613, 1478, 1459, 1303, 1229; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.93-7.81 (m, 1H), 7.26-7.06 (m, 8H), 6.62 (s, 1H, CH), 4.34 (q, 2H, OCH_2 J = 6.7 Hz), 1.32 (t, 2H, CH_3, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 189.13, 163.50, 158.80 (d, J = 240 Hz), 151.19, 147.30, 133.82, 133.75, 130.69, 130.05, 127.25 (d, J = 22 Hz), 126.62, 125.38, 124.93, 119.34, 116.49, 102.76, 96.12, 62.46, 13.96.

Ethyl (Z)-4-(4-chlorophenyl)-4-oxo-2-((2-oxo-2H-chromen-3-yl) amino) but-2-enoate (5c)

Yellow solid; yield: 78 %; mp 242-243 °C; IR (KBr, cm^{-1}) ν_{max}: 3336, 1712, 1163, 1589, 1501, 1459, 1309, 1286, 1242; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.92 (s, 1H, NH), 7.91 (d, 2H, J = 8.0 Hz), 7.45-7.39 (m, 5H), 7.33 (d, 1H, J = 8.0 Hz), 7.26 (t, 1H, J = 8.5 Hz), 6.62 (s, 1H, CH), 4.34 (q, 2H, OCH_2 J = 6.5 Hz), 1.32 (t, 3H, CH_3 J = 7.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 190.33, 163.47, 158.87, 151.21, 147.80, 138.95, 136.81, 130.10, 129.13 (2C), 128.90, 127.07, 126.69 (2C), 125.49, 124.96, 119.33, 98.35, 62.52, 14.00.

Ethyl (Z)-4-(4-bromophenyl)-4-oxo-2-((2-oxo-2H-chromen-3-yl) amino) but-2-enoate (5d)

Yellow solid; yield: 74 %; mp 232-234 °C; IR (KBr, cm^{-1}) ν_{max}: 3068, 2974, 1732, 1708, 1632, 1507, 1449, 1370, 1285, 1239; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm): 11.93 (s, 1H, NH), 8.11 (s, 1H), 7.90 (d, 2H, J=7.8 Hz), 7.67 (d, 2H, J = 8.1 Hz), 7.49-7.28 (m, 4H), 6.61 (s, 1H, CH), 4.35 (q, 2H, OCH_2, J = 7.2 Hz), 1.24 (t, 3H, CH_3, J = 7.1 Hz).

Ethyl (Z)-4-(3-bromophenyl)-4-oxo-2-((2-oxo-2H-chromen-3-yl) amino) but-2-enoate (5e)

Yellow solid; yield: 77 %; mp 221-223 °C; IR (KBr, cm^{-1}) ν_{max}: 3071, 2969, 1741, 1718, 1642, 1511, 1451, 1371, 1274, 1251; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.92 (s, 1H, NH), 7.98 (d, 2H, J = 7.5 Hz), 7.56-7.41 (m, 4H), 7.33 (d, 1H, J = 8.0 Hz), 7.28 (t, 1H, J = 7.1 Hz), 7.21 (s, 1H, CH), 6.70 (s, 1H, CH), 4.34 (q, 2H, OCH_2, J = 6.7 Hz), 1.32 (t, 3H, CH_3, J = 6.5 Hz).

Ethyl (Z)-4-(4-methoxyphenyl)-4-oxo-2-((2-oxo-2H-chromen-3-yl) amino) but-2-enoate (5f)

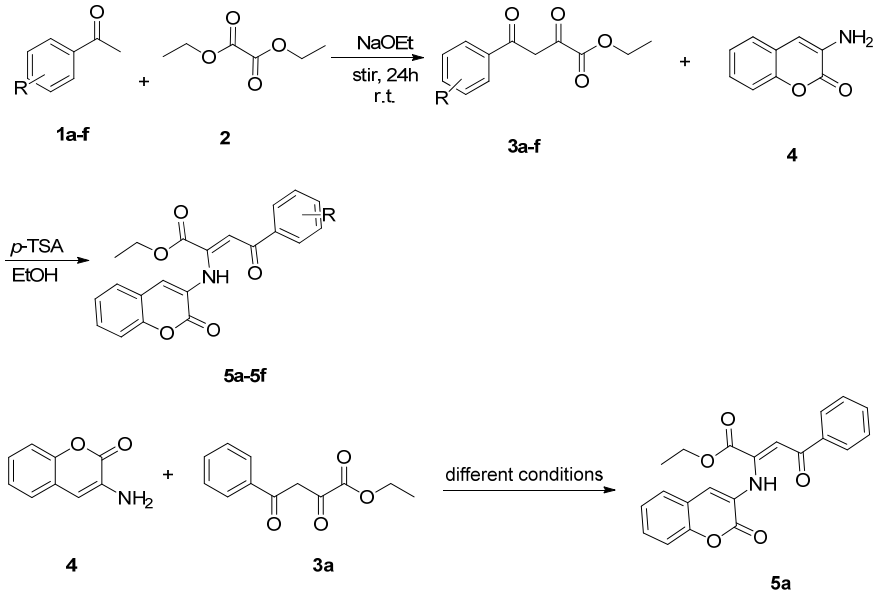
Yellow solid; yield: 79 %; mp 208-210 °C; IR (KBr, cm^{-1}) ν_{max}: 3074, 2967, 1735, 1710, 1641, 1511, 1452, 1372, 1287, 1240; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 11.88 (s, 1H, NH), 7.98-7.93 (m, 2H), 7.41-6.97 (m, 7H), 6.68 (s, 1H, CH), 4.33 (q, 2H, OCH_2, J = 6.5 Hz), 3.88 (s, 3H, OCH_3), 1.31 (t, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 190.40, 163.83, 158.97, 150.99, 146.50, 131.30, 129.99, 129.73, 126.89, 124.87, 124.38, 119.48, 116.42, 114.20, 113.83, 99.31,

97.71, 62.37, 55.55, 14.07.

Results and Discussion

Initially, various ethyl 2,4-dioxo-4-phenylbutanoates (**3a-f**) were synthesized by Claisen condensation reaction between diethyl malonoate (**2**) and different acetophenones (**1a-f**) in the presence of sodium ethoxide at room temperature. 3-Aminocoumarin was also prepared according to the previously reported procedure [26].

The reaction between 3-aminocoumarin and ethyl 2,4-dioxo-4-phenylbutanoate was chosen as the model reaction and optimized under different conditions. Among these conditions, the best result was obtained with 15 mol% *p*-TSA as the catalyst and ethanol as the solvent. Lower or higher amounts of catalyst gave the final compound in lower yields even after long reaction times (Table 1, entries 1-4). The replacement of ethanol with acetonitrile led to lower yields. By utilizing polyphosphoric acid and iodine as catalyst in different



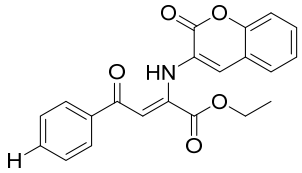
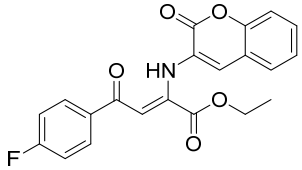
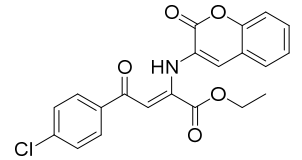
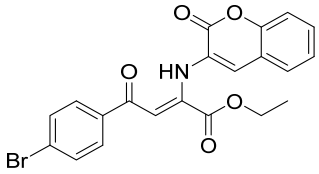
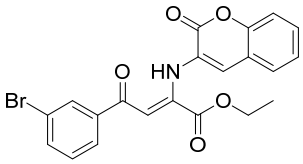
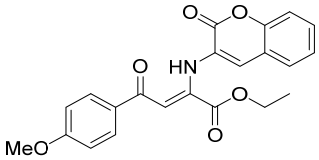
Scheme 1. Synthesis of target compounds.

[a] Isolated yields; [b] The reaction was conducted under reflux temperature; [c] The reaction was conducted at 80 °C; [d] Poly phosphoric acid and acetic acid were used as solvent and no catalyst was added. The reaction was also conducted at 80 °C.

Table 1. Optimization of reaction condition

Entry	Catalyst (mol%)	Solvent	Time/h	Yield (%)[a]
1	*p*-TSA (5)	Ethanol[b]	24	55
2	*p*-TSA (10)	Ethanol[b]	12	73
3	*p*-TSA (15)	Ethanol[b]	5	88
4	*p*-TSA (20)	Ethanol[b]	48	60
5	I_2 (20)	Acetonitrile[c]	10	45
6	I_2 (20)	Acetic acid	10	50
7	I_2 (20)	Ethanol[c]	10	63
8	Poly phosphoric acid (20)	Ethanol[b]	48	N.R.
9	---------	Acetic acid[d]	18	81
10	---------	Poly phosphoric acid[d]	48	20

Table 2. Synthesized products from the reaction of *α,γ*-diketoester and 3-aminocoumarin

Entry	Compounds	Time/h	Yield (%)	Melting point (^{o}C)
5a		2.5	88	212-214
5b		3.5	80	220-221
5c		3	78	242-243
5d		3.5	74	232-234
5e		4	77	221-223
5f		3.5	79	208-210

solvents, no improvement was achieved (Table 1, entries 5-8). We discovered that performing the reaction in acetic acid and polyphosphoric acid didn't result in higher yields. (Table 1, ent ries 9-10). In addition, the reaction could not be completed or gave good yields without using catalyst.

By this method, 6 enaminones were synthesized. The structure of target compounds was confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy (Table 2). The presence of the singlet signal at nearly 6.70 ppm confirmed the enamine structure of final product. The singlet signal related to CH_2 group was not detected in ^{1}HNMR. Relying on this fact, the possibility of imine formation become invalid. We also tried to convert final compounds to cyclized derivatives, but our attempts failed. The computational studies were selected to find out the reason.

Computational studies

DFT calculation was used to investigate the charge distribution and the type of highest occupied molecular orbital (HOMO), and lowest unoccupied molecular orbital (LUMO). In this study, DFT-based Becke's three-parameters; Lee–Yang–Parr exchange-correlation (B3LYP) functional employing 6–31G (d) basis set was selected to optimize the final compounds. All these calculations were performed using GAUSSIAN 09 suit of program.

It has been specified that the charge distribution amount on sp^2 carbon atom of coumarin ring was low to neutral (-0.151). As a result of this charge distribution pattern, no cyclized product was obtained. The presence

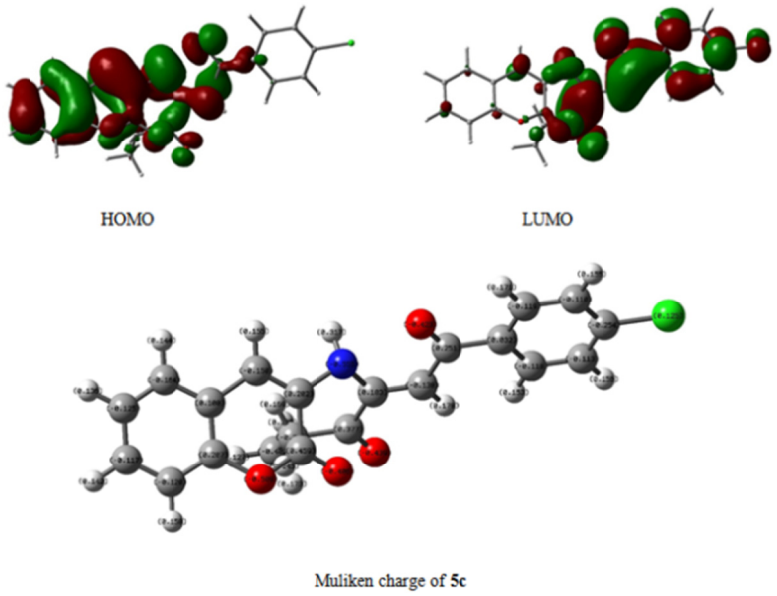


Figure 1. The molecular orbitals of compound **5c**

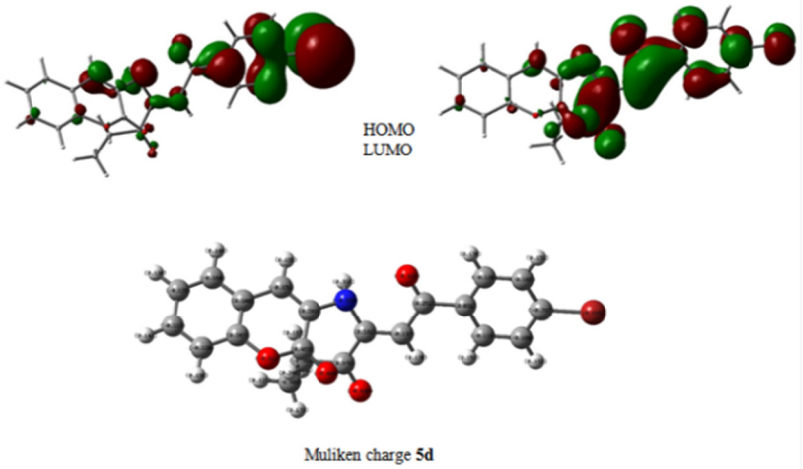


Figure 2. Molecular orbitals of compound **5d**

of different electron donating or electron withdrawing groups has made no difference in charge density of sp^2 carbon atom.

In HOMO of all compounds except bromine-containing derivative, the concentration of electron density is focused on coumarin. The phenyl ring did not participate in charge distribution. In compound **5c**, the charge distribution of coumarin ring in HOMO was higher than phenyl ring. While in LUMO, the electron density concentration was towards the phenyl ring. The highest electron density in unoccupied molecular orbital belonged to the carbonyl group. In compound **5f**, the electron density had the same pattern, while compounds **5d** and **5e** had completely different charge distribution pattern in both molecular orbitals. In compounds **5d** and **5e,** the electron density concentrated on phenyl ring and bromine atom in molecular orbital (HOMO) and coumarin ring was not participated in this contribution. In LUMO orbitals of **5d** and **5e,** the same pattern has been observed and the carbonyl groups have the highest charge density.

In all of these compounds, the charge density of sp^2 carbon atom of coumarin was low to neutral (-0.151), resulted in the reaction being stopped before the

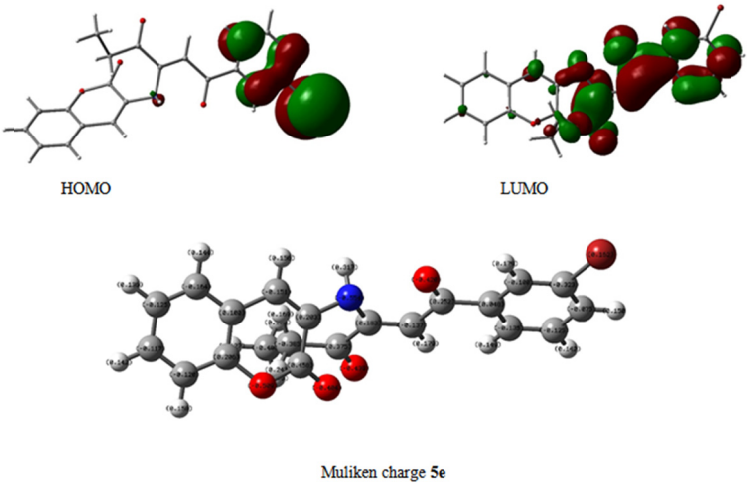


Figure 3. Molecular orbitals of compound **5e**

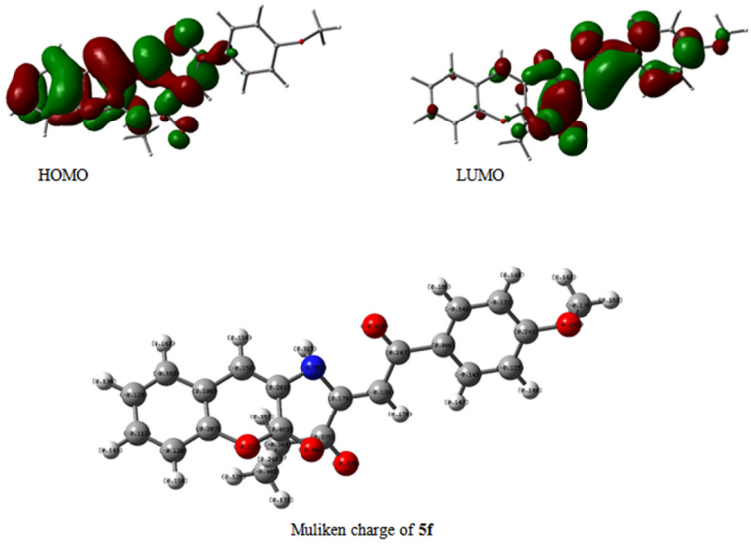


Figure 4. Molecular orbitals of compound **5f**

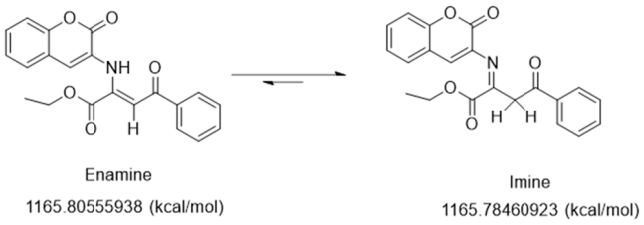


Figure 5. Enamine and imine structure SCF

formation of five-membered ring. The existence of the imine structure was surveyed by DFT calculation. In this part, we used the self-consistent field energy (SCF) for both imine and enamine structures. The graph

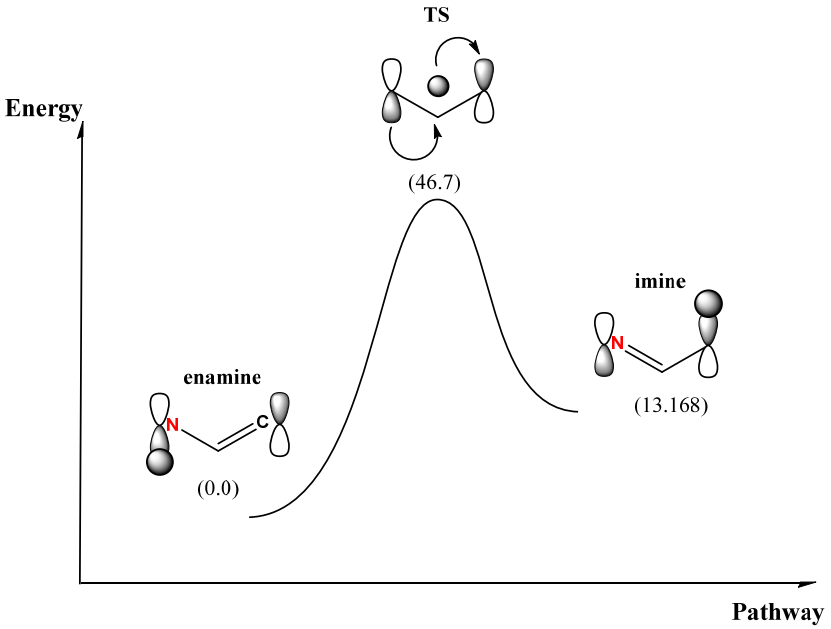


Figure 6. Graph of transition state of enamine and imine structure

showed the transition state (TS) energy of two structures. The high steric hindrance prevented 1,3-sigmatropic rearrangement, so, enamine structure was determined as the main product.

Conclusion

In summary, we described a mild approach to synthesize coumarin-enaminone containing compounds from the reaction of 3-aminocoumarin and *α,γ*-diketoesters. The DFT study confirmed the progression of the reaction and explained the difficulty associated with obtaining the cyclized product. Further studies on this compound are under investigation by our research team.

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