

Theoretical Studies on Synthetic Mechanism of 7-Ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile

QI-SHAN HU^{1,*}, YUN-QING HE¹ and LAI-CAI LI²

¹College of Chemistry and Chemical Engineering, Sichuan University of Arts and Science, Dazhou 635711, P.R. China

²College of Chemistry and Material Science, Sichuan Normal University, Chengdu 610066, P.R. China

*Corresponding author: E-mail: huqs@163.com

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The mechanism of one-pot synthesis among acetone, propanal and malononitrile for the synthesis of 7-ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile was investigated by density functional theory (DFT). The geometries and the frequencies of reactants, intermediates, transition states and products were calculated at the B3LYP/6-311G(d) level. The vibration analysis and the IRC analysis verified the authenticity of transition states. The reaction processes were confirmed by the changes of charge density at the bond-forming critical point. The results indicated that (1) IM3D \rightarrow IM3E is rate-determining step; (2) The activation energy of the reaction is 224.7 kJ mol⁻¹.

Keywords: Density functional theory, Quinazolinones, Malononitrile.

INTRODUCTION

Quinazolinones and their derivatives constitute an important class of heterocyclic compounds. Many of them show insecticidal¹, analgesic², antifungal³, antibacterial⁴, anticancer, anti-inflammatory⁵ activities. Quinazolinone nucleus is found in many bioactive natural products. Quinazolinone derivatives are the important intermediate of a series of drugs. Therefore, the quinazolinone compounds attracted the interest of medicinal researchers. There are several reports on the synthesis of quinazolinones and their derivatives⁶⁻¹². One-pot synthesis method is used for the synthesis of quinazolinones and their derivatives^{13,14}. 7-ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile was synthesized from multi-component condensation of acetone, propanal and malononitrile with one-pot synthesis method¹⁵. There is no literature about the mechanism of synthesis of 7-ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile. The main purposes of this paper are (1) to investigate the microscopic mechanism of reaction among acetone, propanal and malononitrile for the synthesis of 7-ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile by density functional theory (DFT); and (2) confirm the rate-determining step of the reaction.

COMPUTATIONAL METHODS

The mechanism of reaction among acetone, propanal and malononitrile for the synthesis of 7-ethyl-2,2,5-trimethyl-4-

oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile was investigated by density functional theory (DFT). The geometries and the frequencies of reactants, intermediates, transition states and products were calculated at the B3LYP/6-311G(d) level. Stable structures were obtained. The parameters of geometry configuration are shown in Fig. 1(R1-P3). The vibration analysis and the IRC analysis proved the authenticity of intermediates and transition states. The reaction processes were confirmed by the changes of charge density at the bond-forming critical point (as shown by the numeric value in the parentheses in Fig. 1)^{16,17}. All calculations were carried out with the Gaussian 03 program¹⁸.

RESULTS AND DISCUSSION

The calculated energies (E) and relative energies (E_{rel}) of reactants, intermediates, transition states and products are listed in Table-1. All energies (E) include zero-point energy (ZPE) corrections. Vibration frequencies of reactants, intermediates and products are positive and vibration frequencies of all transition states have only one imaginary frequency. Fig. 2 is a schematic map of energy levels for the reaction.

Reaction mechanism and energies analysis of synthesis of IM1C: Firstly, R1 reacts with hydroxyl ion to form R1B directly. In basic solution, R1B attacks carbonyl group carbon atom of R3 to form IM1A. This is a nucleophilic reaction. IM1A forms IM1B through transition state TS1. In TS1, the

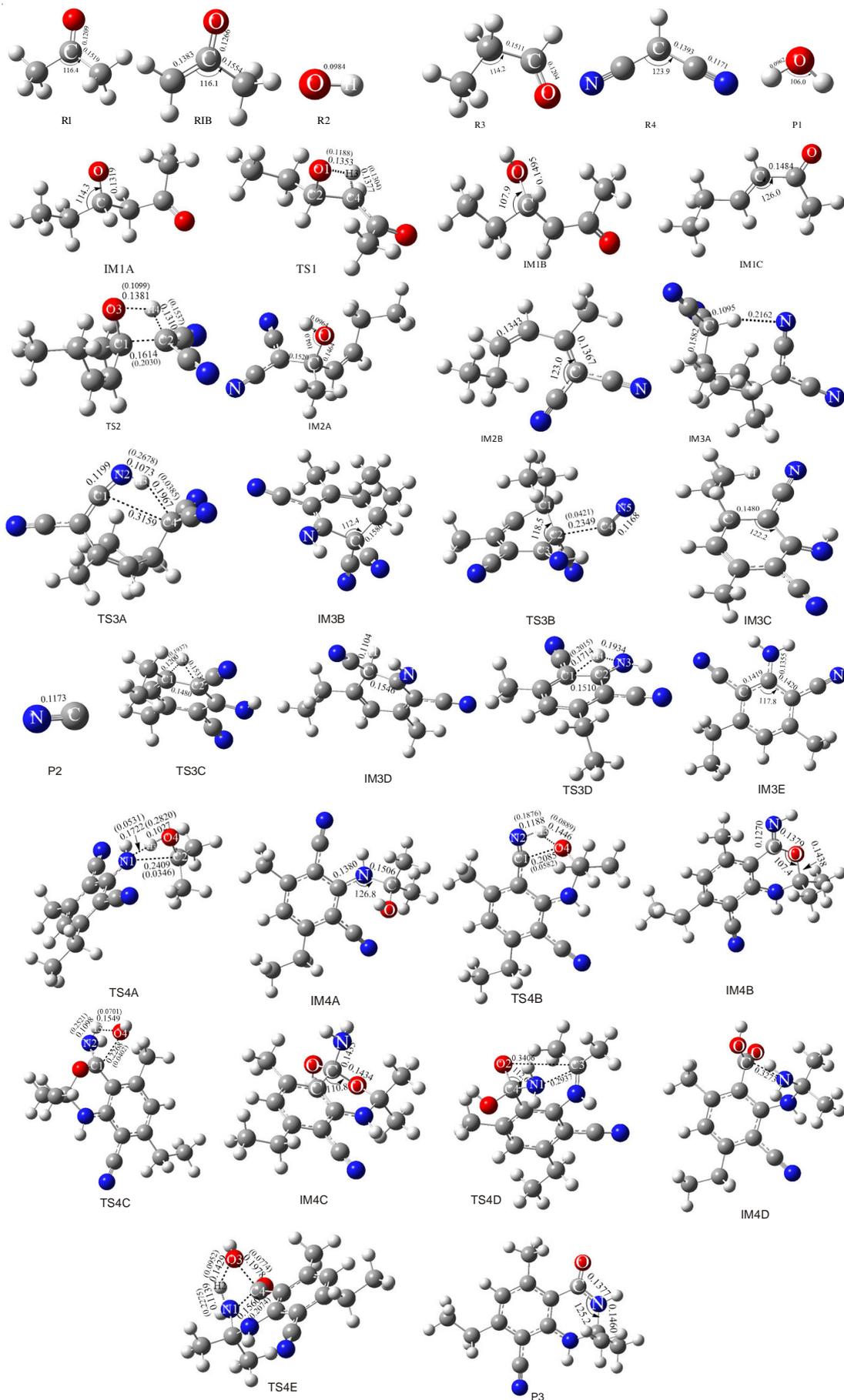


Fig. 1. Optimized geometric configurations of various compounds in the reaction: bond length in nanometers, bond angle in degree, charge density at bond-forming critical point in a.u.

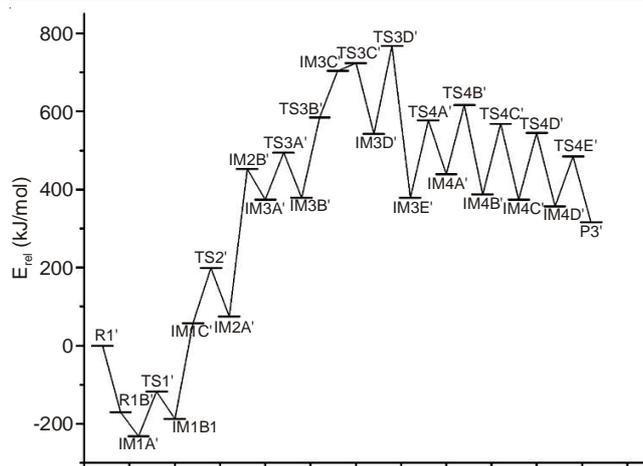


Fig. 2. Schematic map of energy levels in the reaction

bond length and the charge density at the bond-forming critical point of O1-H3 are 0.1353 nm and 0.1188 a.u., respectively and those of H3-C4 are 0.1377 nm and 0.1304 a.u., respectively and the activation energy is 114.8 kJ mol⁻¹. IM1B forms IM1C and hydroxyl ion. The mechanism of the reaction is: R1 + R2 → R1B + H₂O; R1B + R3 → IM1A → TS1 → IM1B → IM1C + OH⁻.

Reaction mechanism and energies analysis of synthesis of IM2B: In basic solution, the carbon atom of malononitrile with negative charge collides with the carbonyl carbon atom of IM1C forms intermediate IM2A through transition state TS2. In TS2, the bond length and the charge density at the bond-forming critical points of O3-H4, C2-H4 and C1-C2 are 0.1381 nm and 0.1099 a.u., 0.1310 nm and 0.1537 a.u. and

0.1614 nm and 0.2030 a.u., respectively. The activation energy is 141.9 kJ mol⁻¹. IM2A forms IM2B and hydroxyl ion directly. The mechanism of the reaction is: IM1C + R4 → TS2 → IM2A → IM2B + OH⁻.

Reaction mechanism and energies analysis of synthesis of IM3E: IM2A reacts with R4 to form IM3A and hydroxyl ion directly, this is a processes of no activation energy. IM3A forms IM3B through transition state TS3A. In TS3A, the bond length and the charge density at the bond-forming critical point of N2-H3 are 0.1073 nm and 0.2678 a.u., respectively and those of H3-C4 are 0.1967 nm and 0.0385 a.u., respectively and the activation energy is 120.1 kJ mol⁻¹. The charge densities of critical points of (3, +1) rings is 0.0068 a.u. This is a concerted reaction process with the closing of a ring and the transfer of a hydrogen atom. IM3B forms IM3C and cyanide ion through transition state TS3B. In TS3B, the bond length and the charge density at the bond-forming critical point of C2-C4 are 0.2349 nm and 0.0421 a.u., respectively and the activation energy is 205.7 kJ mol⁻¹. IM3C forms IM3D through transition state TS3C. In TS3C, the bond length and the charge density at the bond-forming critical point of C1-H3 are 0.1200 nm and 0.1937 a.u., respectively and the activation energy is 19.6 kJ mol⁻¹. IM3D forms IM3E through transition state TS3D. In TS3D, the bond length and the charge density at the bond-forming critical point of C1-H4 are 0.1714 nm and 0.2015 a.u., respectively and the activation energy is 224.7 kJ mol⁻¹. This is rate-determining step and this is a processes of transfer of a hydrogen atom. The mechanism of the reaction is: IM2b + R4 → TS2 → IM3A → TS3A → IM3B → TS3B → IM3C + CN⁻ → TS3C + CN⁻ → IM3D + CN⁻ → TS3D + CN⁻ → IM3E + CN⁻.

TABLE-1
ENERGIES(E) AND RELATIVE ENERGIES(E_{rel}) OF VARIOUS SPECIES AND IMAGINARY FREQUENCY OF TRANSITIONS

Species	E(a.u.)	E _{rel} (kJ mol ⁻¹)	v(cm ⁻¹)
R1'(2R1 + R2 + R3 + 2R4)	-1104.01715	0.0	-
R1B'(R1 + R1B + R3 + 2R4 + P1)	-1104.082082	-170.5	-
IM1A'(IM1A + R1 + 2R4 + P1)	-1104.095207	-232.3	-
TS1'(TS1 + R1 + 2R4 + P1)	-1104.06189	-117.5	-1650.7
IM1B'(IM1B + R1 + 2R4 + P1)	-1104.088741	-188.0	-
IM1C'(IM1C + R1 + R2 + 2R4 + P1)	-1103.995423	57.0	-
TS2'(TS2 + R1 + R2 + R4 + P1)	-1103.941361	199.0	-1603.3
IM2A'(IM2A + R1 + R2 + R4 + P1)	-1103.988586	75.0	-
IM2B'(IM2B + R1 + 2R2 + R4 + P1)	-1103.844874	452.3	-
IM3A'(IM3A + R1 + 2R2 + P1)	-1103.87459	374.3	-
TS3A'(TS3A + R1 + 2R2 + P1)	-1103.828828	494.4	-200.32
IM3B'(IM3B + R1 + 2R2 + P1)	-1103.872687	379.3	-
TS3B'(TS3B + R1 + 2R2 + P1)	-1103.794326	585.0	-432.85
IM3C'(IM3C + R1 + 2R2 + P1 + P2)	-1103.749109	703.7	--
TS3C'(TS3C + R1 + 2R2 + P1 + P2)	-1103.741654	723.3	-1017.38
IM3D'(IM3D + R1 + 2R2 + P1 + P2)	-1103.810309	543.1	-
TS3D'(TS3D + R1 + 2R2 + P1 + P2)	-1103.724735	767.7	-822.68
IM3E'(IM3E + R1 + 2R2 + P1 + P2)	-1103.872866	378.8	-
TS4A'(TS4A + 2R2 + P1 + P2)	-1103.797149	577.6	-370.81
IM4A'(IM4A + 2R2 + P1 + P2)	-1103.849873	439.2	-
TS4B'(TS4B + 2R2 + P1 + P2)	-1103.782528	616.0	-1633.57
IM4B'(IM4B + 2R2 + P1 + P2)	-1103.869692	387.2	-
TS4C'(TS4C + 2R2 + P2)	-1103.800794	568.0	-698.68
IM4C'(IM4C + 2R2 + P2)	-1103.874492	374.5	-
TS4D'(TS4D + 2R2 + P2)	-1103.809457	545.3	-52.73
IM4D'(TS4D + 2R2 + P2)	-1103.881268	356.8	-
TS4E'(TS4E + 2R2 + P2)	-1103.832646	484.4	-917.74
P3'(P3 + 2R2 + P1 + P2)	-1103.896717	316.2	-

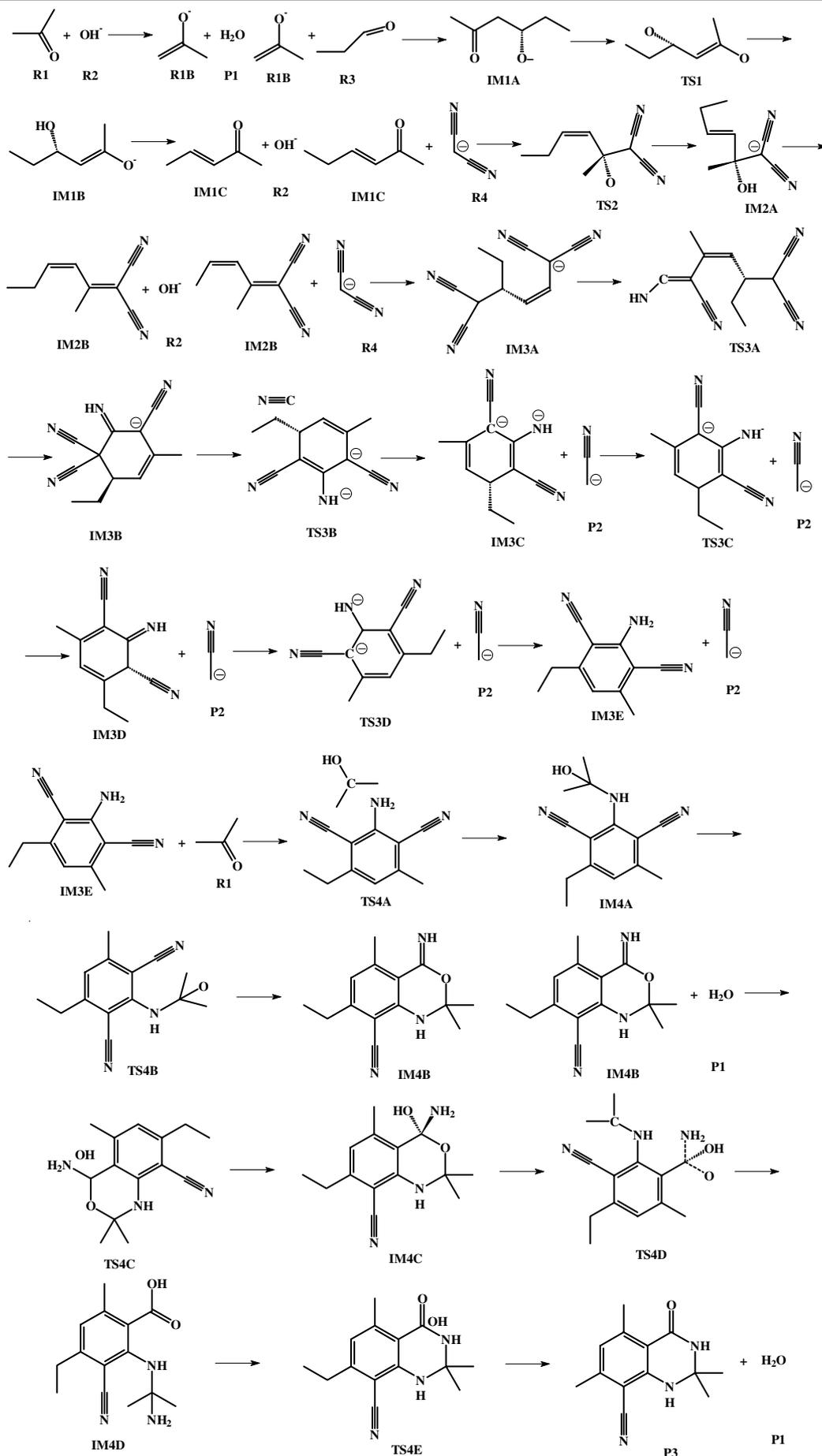
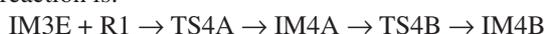


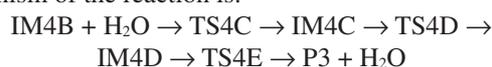
Fig. 3. Mechanism of Synthesis on 7-ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile

Reaction mechanism and energies analysis of synthesis

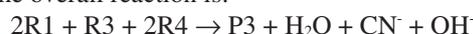
of IM4B: The amino nitrogen atom of IM3E attacks the carbonyl carbon atom of R1 to form IM4A through transition state TS4A. This is a nucleophilic reaction. This is also a processes of the transfer of a hydrogen atom of the amidogen. In TS4A, the bond length and the charge density at the bond-forming critical point of N1-H3, H3-O4 and N1-C2 are 0.1722 nm and 0.0531 a.u., 0.1027 nm and 0.2820 a.u. and 0.2409 nm and 0.0346 a.u., respectively and the activation energy is 198.8 kJ mol⁻¹. IM4A forms IM4B through transition state TS4B. This is a concerted reaction process with the closing of a ring and the transfer of a hydrogen atom. In TS4B, the bond length and the charge density at the bond-forming critical point of N2-H3, H3-O4 and C1-O4 are 0.1188 nm and 0.1876 a.u., 0.1446 nm and 0.0889 a.u. and 0.2085 nm and 0.0582 a.u., respectively and the activation energy is 176.8 kJ mol⁻¹. The mechanism of the reaction is:

**Reaction mechanism and energies analysis of synthesis**

of P3: IM4B \rightarrow P3 is a Dimroth arrangement reaction¹⁹. IM4B reacts with water to form IM4C through transition state TS4C. This is an electrophilic addition. In this processes, a C-N double bond is changed into a C-N single bond, it is a key step for the Dimroth arrangement reaction. In TS4C, the bond length and the charge density at the bond-forming critical point of C1-O4, H3-O4 and N2-H3 are 0.2268 nm and 0.0402 a.u., 0.1549 nm and 0.0701 a.u. and 0.1098 nm and 0.2521 a.u., respectively and the activation energy is 180.9 kJ mol⁻¹. IM4C forms IM4D through transition state TS4D and the activation energy is 170.7 kJ mol⁻¹. This is a concerted reaction process with the opening of a ring and transferring of the amidogen. I IM4D forms P3 through transition state TS4E. In TS4E, the bond length and the charge density at the bond-forming critical point of N1-C4, H2-O3, N1-H2, and O3-C4 are 0.1560 nm and 0.2074 a.u., 0.1429 nm and 0.0952 a.u. and 0.1978 nm and 0.0774 a.u., respectively and the activation energy is 127.7 kJ mol⁻¹. The mechanism of the reaction is:



The overall reaction is:



The details of the reaction mechanism of the reaction are shown in Fig. 3.

Conclusion

The mechanism of reaction among acetone, propanal and malononitrile for the synthesis of 7-ethyl-2,2,5-trimethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-8-carbonitrile was

investigated by density functional theory (DFT). IM3D \rightarrow IM3E is rate-determining step. The activation energy of the reaction is 224.7 kJ mol⁻¹. It is identical with Tang *et al.*¹⁵ conclusions.

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