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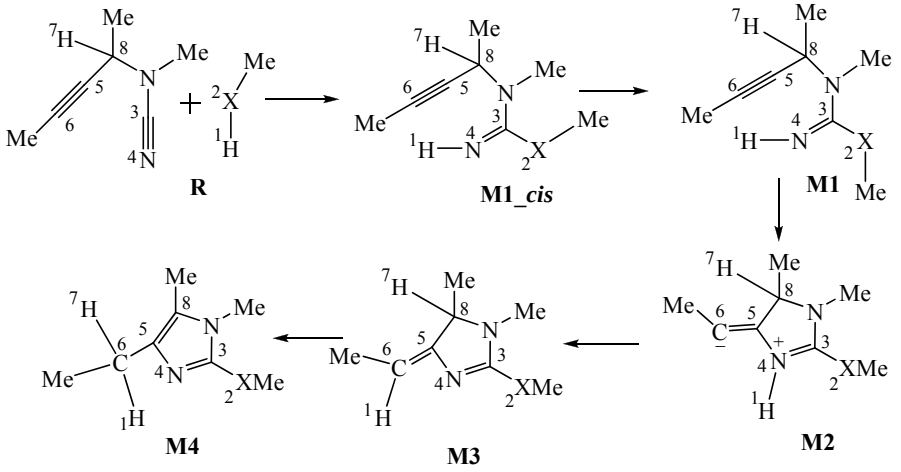
DFT STUDY OF THE ADDITION–CYCLIZATION–ISOMERIZATION REACTION BETWEEN PROPARGYL CYANAMIDES AND THIOL OR ALCOHOL: THE ROLE OF CATALYST

In this paper, we report theoretical studies of addition–cyclization–isomerization reaction of propargyl cyanamides with thiol and methanol by density functional theory (DFT) calculation. The results reveal that this reaction takes place *via* five steps: 1) nucleophilic attack of S or O atom to C atom in the cyanogen group of propargyl cyanamide to form a *cisoid*-intermediate; 2) the conversion of the latter to its *trans*-conformer; 3) nucleophilic attack by N atom at the alkyne group to produce a five-membered thermodynamically unstable zwitterionic 4-ethylidene-4,5-dihydroimidazole intermediate; 4) the proton transfer from N to C(4) atom to produce a more stable intermediate; 5) the proton transfer from C(5) to ethylidene group to form the final 4-ethyl-1,5-dimethyl-2-methylsulfanyl- or 4-ethyl-2-methoxy-1,5-dimethylimidazole. We find that the autocatalysis by thiol or methanol is able to largely decrease the energy barrier of intramolecular proton transfer in the isomerization step and the proton transfer in the addition step.

Keywords: propargyl cyanamides, DFT calculation, reaction mechanism.

Preparation of 2-thio-, 2-oxo- and 2-aminoimidazoles is usually accomplished by nucleophilic substitution of activated 2-sulfonyl-, 2-nitro-, or 2-haloimidazoles or by alkylation of imidazolethiones [1–2]. The substitution approach often requires multiple protecting group manipulations and oxidation. Recently, a methodology to generate 2-thio-, 2-amino-, and 2-oxoimidazoles through an addition–cyclization–isomerization reaction of propargyl cyanamides with thiol, amine and alcohol nucleophiles catalyzed by base is reported, which provide a rapid, effective method to form a S–C, N–C, or O–C (sp^2-hybridized carbon) bond [3–4]. However, the reaction mechanism of these reactions and the role of the base catalyst are still unclear. In this paper, we aim to study the mechanism of addition–cyclization–isomerization reaction of both alkyl thiols and methanol with propargyl cyanamides and to explain the role and function of the catalyst in this transformation. A series of DFT calculations was performed on the model systems (model system A for X = S and model system B for X = O) in order to examine the reaction pathways.

All theoretical calculations were performed by the Gaussian 03 [5] programs. All structures were optimized by employing the hybrid density functional B3LYP and standard 6-31G(d,p) basis set. A vibrational frequency calculation was then performed at the optimized geometry belonging to each reactant, product, transition state, and intermediate. We confirm that all reactants and intermediates have no imaginary frequencies, and each transition state has only one imaginary frequency. The zero-point energies (ZPE) have been calculated using the vibrational frequencies. The intrinsic reaction coordinate (IRC) calculations, at the same level of theory, have been performed to ensure that the transition states lead to the expected reactants and products (the supporting information can be received from the authors). The values of the relative energies (ΔE_0) have been calculated on the basis of the total energies of the stationary points. Relative enthalpies (ΔH) and free energies (ΔG) have been calculated with the standard statistical thermodynamics at 298.15 K.



In order to know the role of the catalyst, we initially studied the mechanism of the title reaction in absence of any catalysts (Scheme, here and further, only 8 atoms directly involved in the reaction are numbered). In this reaction, the initial, addition step, is nucleophilic attack of S or O atom to C atom of the cyanogen group of propargyl cyanamide to produce an intermediate **M1_*cis***. The rotation around C–X bond in the intermediate **M1_*cis*** gives the respective *trans*-conformation (**M1**). The cyclization process proceeds by the subsequent nucleophilic attack of the terminal N atom at the alkyne group that produces a highly energetically unfavorable five-membered cyclic intermediate **M2**. The proton H(1) shifts from N(4) to the ethylidene C(6) atom to give an intermediate **M3**. For the latter step, isomerization involves intramolecular proton transfer: the H(7) atom shifts from C(8) to C(6) to form the final product **M4**. The corresponding representation of the energy profile (ΔE_0) is illustrated in Figures 1 and 2. The ΔH and ΔG are shown in Tables 1 and 2.

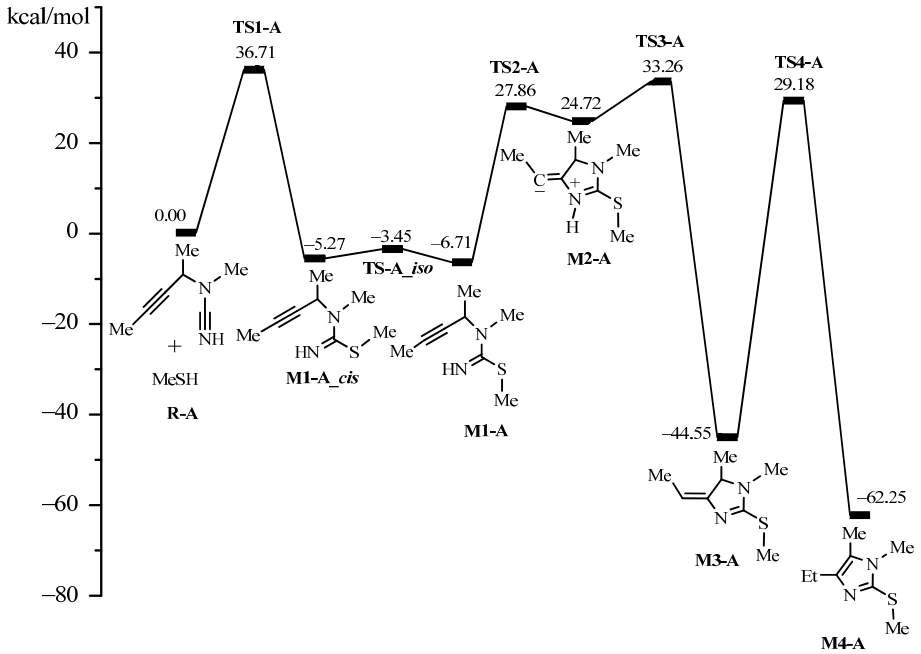


Fig. 1. Energy (kcal/mol) profile for the reaction pathways of addition–cyclization–isomerization reaction of propargyl cyanamides with thiol

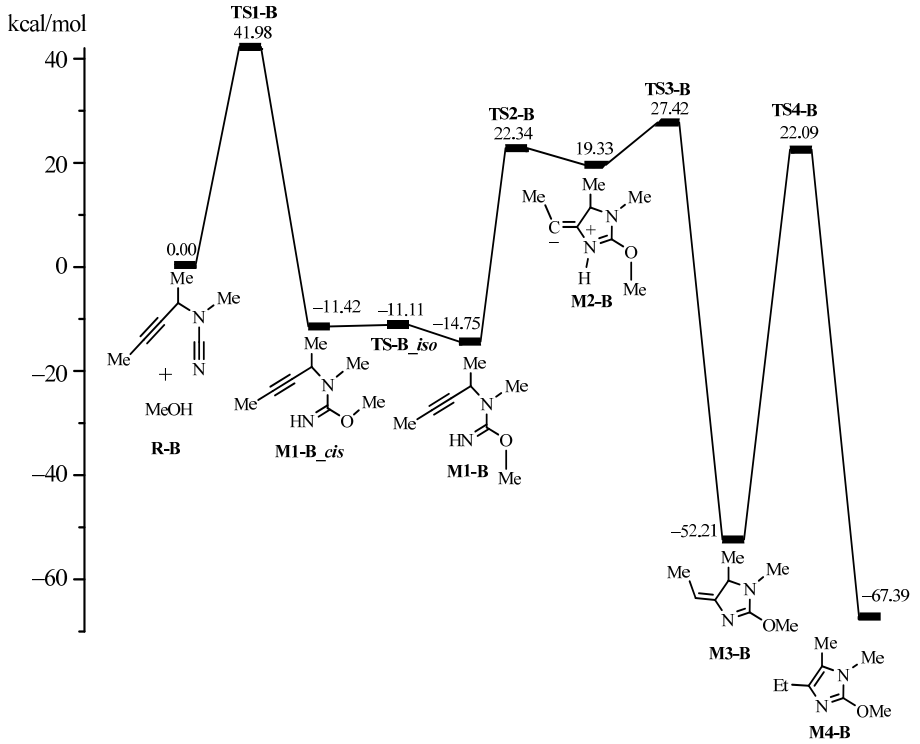


Fig. 2. Energy (kcal/mol) profile for the reaction pathways of addition–cyclization–isomerization reaction of propargyl cyanamides with methanol

Table 1

Essential thermodynamic parameters (kcal/mol) for critical structures of model system A

	R-A	TS1-A	M1-A	TS2-A	M2-A		TS3-A	M3-A	TS4-A	M4-A
ΔE	0.00	36.71	–6.71	27.86	24.72		33.26	–44.55	29.18	–62.25
ΔH	0.00	36.65	–7.34	26.61	23.53		31.81	–45.99	28.11	–63.57
ΔG	0.00	46.62	–5.08	41.16	38.21		47.00	–30.56	42.48	–49.20

Table 2

Essential thermodynamic parameters (kcal/mol) for critical structures of model system B

	R-B	TS1-B	M1-B	TS2-B	M2-B	TS3-B	M3-B	TS4-B	M4-B
ΔE	0.00	41.98	–14.75	22.34	19.33	27.42	–52.21	22.09	–67.39
ΔH	0.00	41.60	–15.69	20.90	17.88	25.73	–53.97	20.71	–69.03
ΔG	0.00	52.40	–3.45	35.14	32.63	41.10	–38.34	35.45	–54.03

In the addition–cyclization–isomerization reaction of propargyl cyanamides with thiol, for the first step, the Mulliken charges of S(2) and H(1) atoms of MeSH are –0.046 e and 0.061 e, which indicates that the cleavage of S–H bond is easy. The values of the Mulliken charges of C(3) and N(4) atoms in the cyanogen group of propargyl cyanamide 0.522 e and –0.482 e, respectively, (Table 3) indicate that nucleophilic attack of S(2) to the carbon of the cyano group (C(3)) is easier than electrophilic attack of H(1) to the nitrogen of the cyano group (N(4)). This process will leads to a transition state **TS1-A** with energy of 36.71 kcal/mol above that of

the reactants (Fig. 1). In transition state **TS1-A**, the S(2)–C(3) and N(4)–H(1) bonds are 2.778 and 1.106 Å, respectively. From the transition state **TS1-A**, an intermediate **M1-A_*cis*** is formed with the energy 5.27 kcal/mol lower than that of the reactants. Furthermore, the *cis*-intermediate **M1-A_*cis*** goes over to the respective *trans*-conformer **M1-A** *via* a low rotation (S–C(3)) barrier of 1.82 kcal/mol (**TS-A_*iso***). Because the conformer **M1-A** is slightly more stable (–1.44 kcal/mol) than its *cis*-isomer and they can be easily interconverted, we consider only the conformer **M1-A** in the subsequent studies.

The electrocyclic reaction proceeds through the transition state **TS2-A**. In transition state **TS2-A**, the C(3)–N(4) bond is 1.310 Å, while the distance between N(4) and C(5) where the new bond is to be formed is 1.707 Å (Fig. 3). The energy of transition state **TS2-A** is 34.57 kcal/mol higher than that of the intermediate **M1-A**. From transition state **TS2-A**, a five-membered zwitterionic cyclic structure **M2-A** with an exocyclic double bond is formed with the energy 31.43 kcal/mol higher than the intermediate **M1-A**. Owing to the thermodynamic instability of intermediate **M2-A**, the proton H(1) can be transferred from N(4) to C(6) easily to produce a thermodynamically favored neutral intermediate **M3-A** *via* a transition state **TS3-A**. In transition state **TS3-A**, the H(1)–N(4) bond length is 1.180 Å, while the H(1)–C(6) bond formed from this transitional state, is 1.705 Å (Fig. 3). Furthermore, the transition from **M2-A** to **M3-A** release energy of 69.27 kcal/mol and the reaction energy barrier is only 8.54 kcal/mol. The last step, isomerization of the double bond by the transfer of the proton H(7) from C(8) to C(6) produces imidazole **M4-A** through a transition state **TS4-A** . This isomerization though exothermic has a high activation energy of 73.73 kcal/mol. Finally, the energy of imidazole **M4-A** is 62.25 kcal/mol lower than that of the initial reactants (**R-A** + MeOH) and, therefore, the whole reaction is a highly exothermic.

Table 3

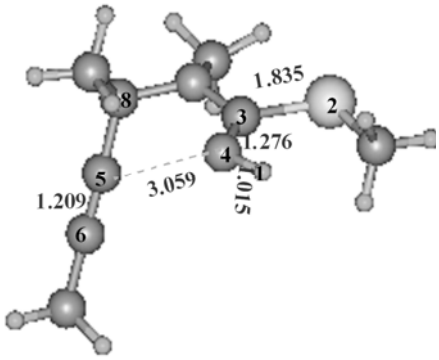
The Mulliken charge (e) values calculated by Gaussian 03 for the model system A

	MeSH	**R-A**	**TS1-A**	**M1-A**	**TS2-A**	**M2-A**	**TS3-A**	**M3-A**	**TS4-A**	**M4-A**
H(1)	0.061		0.289	0.230	0.250	0.260	0.199	0.083	0.440	0.086
S(2)	–0.046		–0.494	0.103	0.163	0.193	0.166	0.127	0.130	0.113
C(3)		0.522	0.676	0.309	0.353	0.369	0.337	0.318	0.290	0.262
N(4)		–0.482	–0.479	–0.566	–0.529	–0.489	–0.496	–0.526	–0.478	–0.514
C(5)				0.144	0.120	0.125	0.151	0.251	0.031	0.172
C(6)				–0.043	–0.234	–0.246	–0.211	–0.145	–0.170	–0.229
H(7)								0.110	0.210	0.124
C(8)								0.036	0.193	0.259

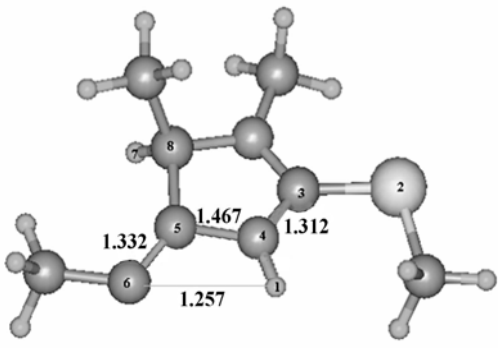
Table 4

The Mulliken charge (e) values calculated by Gaussian 03 for the model system B

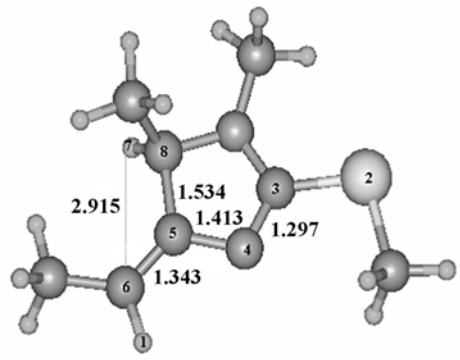
	MeOH	**R-B**	**TS1-B**	**M1-B**	**TS2-B**	**M2-B**	**TS3-B**	**M3-B**	**TS4-B**	**M4-B**
H(1)	0.306		0.344	0.219	0.245	0.256	0.195	0.080	0.043	0.085
O(2)	–0.532		–0.632	–0.494	–0.489	–0.492	–0.497	–0.518	–0.516	–0.526
C(3)		0.522	0.664	0.711	0.821	0.861	0.812	0.782	0.756	0.733
N(4)		–0.482	–0.544	–0.603	–0.574	–0.542	–0.547	–0.581	–0.520	–0.563
C(5)				0.140	0.115	0.120	0.135	0.268	0.031	0.172
C(6)				–0.047	–0.245	–0.259	–0.210	–0.162	–0.169	–0.233
H(7)								0.107	0.201	0.107
C(8)								0.039	0.195	0.256



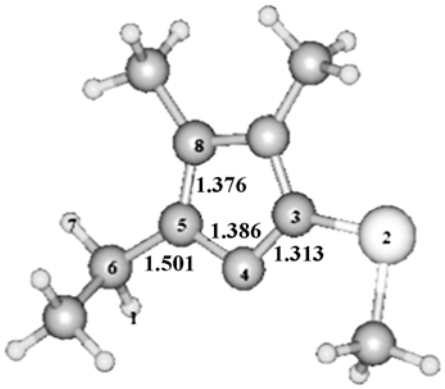
M1-A



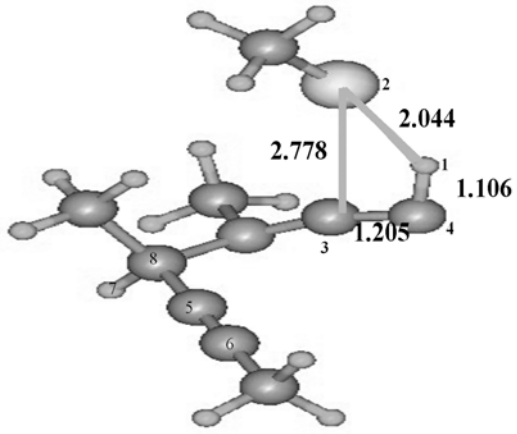
M2-A



M3-A

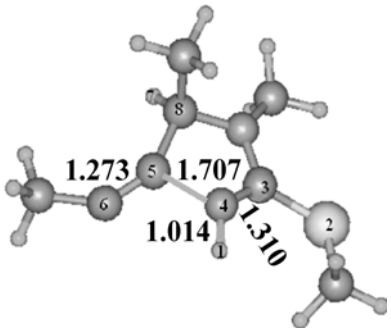


M4-A

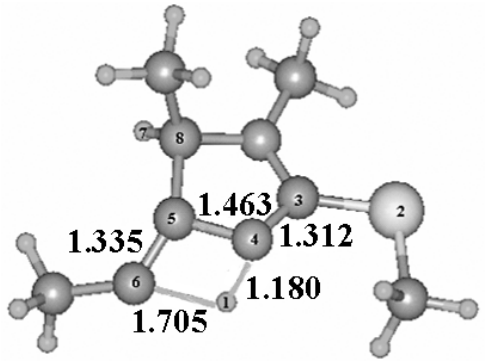


TS1-A

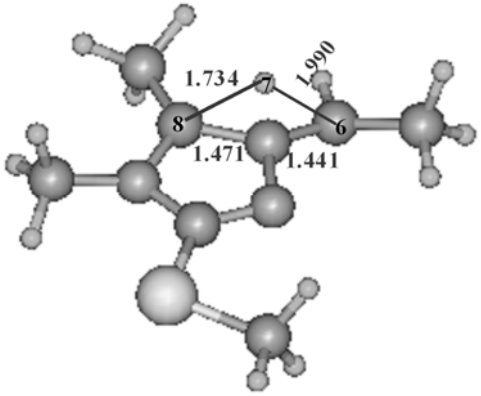
Fig. 3. Representation of the optimized structures of the intermediates and



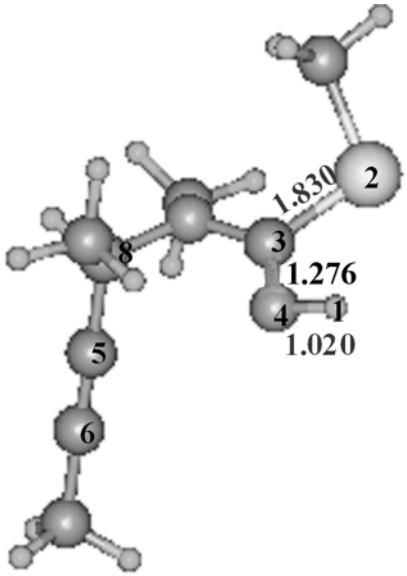
TS2-A



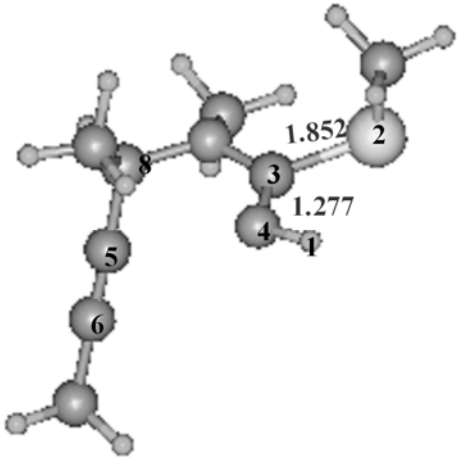
TS3-A



TS4-A



M1-A_*cis*



TS-A_*iso*

transition states for the model system A (bond lengths shown in Å)

Table 5

Essential thermodynamic parameters (kcal/mol) for transition states of model system A under catalysis

	TS4-A_NH_3	TS4-A_H_2O	TS4-A_MeSH	TS1-A_NH_3	TS1-A_H_2O	TS1-A_MeSH
ΔE_0	41.23	35.14	21.52	14.75	17.63	24.22
ΔH	40.16	33.82	21.15	13.62	16.38	23.85
ΔG	56.54	44.74	32.13	34.95	37.65	46.00

Table 6

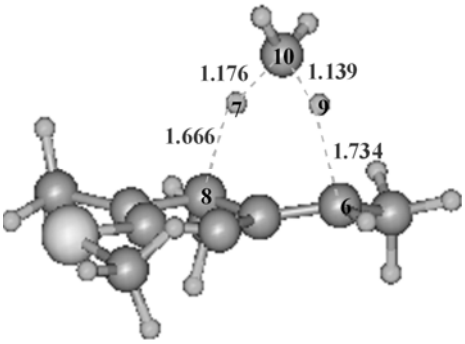
Essential thermodynamic parameters (kcal/mol) for transition states of model system B under catalysis

	TS4-B_NH_3	TS4-B_H_2O	TS4-B_MeOH	TS1-B_NH_3	TS1-B_H_2O	TS1-B_MeOH
ΔE_0	42.42	34.95	32.32	17.07	13.67	12.86
ΔH	41.35	33.70	31.88	15.31	11.67	11.61
ΔG	52.40	44.62	42.80	38.03	34.70	35.45

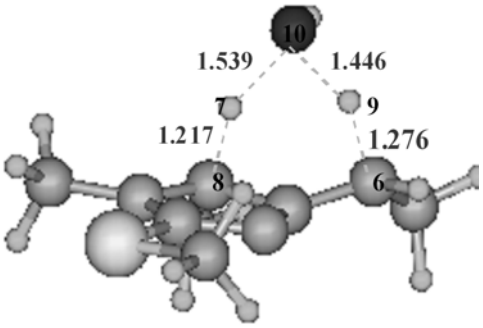
From Figure 1, it is easy to find out that the last step (**TS4-A**) holds the highest energy barrier of five reaction steps in the reaction process. The energy barrier is so high that it is difficult to carry out the intramolecular proton transfer isomerization process. We expect that the reason for the high barrier is a steric one. The distance between C(6) and H(7) is 2.915 Å in intermediate **M3-A** (Fig. 3), which is too far for the proton transfer. Furthermore, proton transfer between the carbon atoms in the alkyl group has a relatively high energy barrier. The above analysis indicates that the transfer of H(7) from C(8) to C(6) appears in reality to be catalyzed, which would result in a decrease of the energy barrier in this step. We suggest that a base catalyst is involved in the last step of this reaction. In order to confirm this hypothesis, we have investigated the proton transfer step catalyzed by the NH_3 as a base catalyst. In fact, a number of studies have reported that NH_3 and H_2O molecules acting as a base are able to facilitate proton transfer [6–8]. Furthermore, the proton transfer process can also involve the reactant (MeSH) acting as the catalyst that results in autocatalysis of the reaction.

As seen in Figure 4, in the transition state for the catalysed proton transfer in the last step under the catalysis (**TS4-A** + catalyst) the catalyst molecule (NH_3, H_2O, or MeSH) lies above the heterocyclic ring plane and simultaneously forms two hydrogen bonds. The distance between C(6) and the incoming H(7) has been shortened by taking the catalyst as the exchange carrier, which thus decreases the energy barrier. This result indicates that the catalyst plays the key role in making feasible the isomerization step. The activation energy barrier of the catalyzed proton transfer (Table 5) is considerably lower than that of transition state **TS4-A** (73.73 kcal/mol), the autocatalyst (MeSH) being the most effective. In another computational study it was reported that water in analogous way can catalyze proton transfer in the aminolysis of oxoesters and thioesters by similarly lowering the energy barrier both in gas phase and in solvent [9].

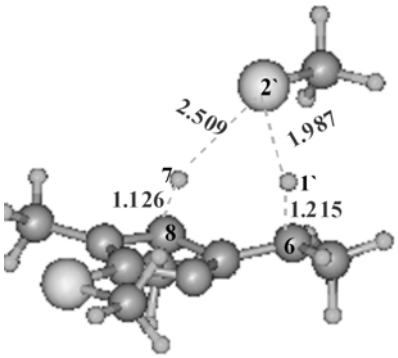
Furthermore, the first step (the addition of MeSH) also holds the marginally high energy in the reaction process involved in proton transfer. Therefore, we have investigated the first step catalyzed by the above-mentioned catalysis for the proton transfer (NH_3, H_2O, MeSH). From our calculation, the proton transfer takes place through proton exchange with the catalyst exchange carrier, lowering the energy barrier of the addition step. The activation energy barrier of the catalyzed proton transfer (Table 5) is considerably lower than that of transition state **TS1-A** (36.71 kcal/mol), NH_3 being the most effective as catalyst. Also the autocatalysis with MeSH has a good catalytic effect for proton transfer both in the isomerization step and in the addition step.



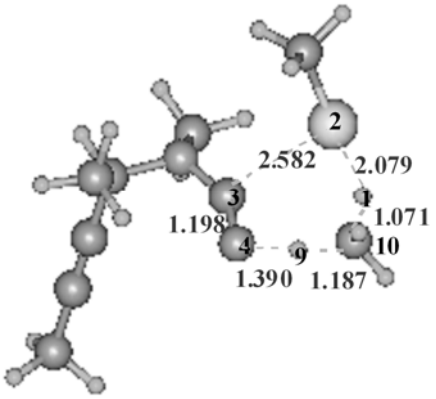
TS4-A_NH$_3$



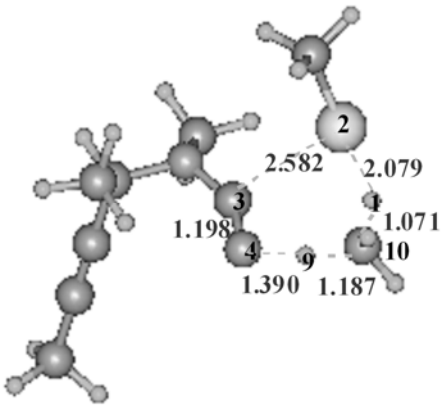
TS4-A_H$_2$O



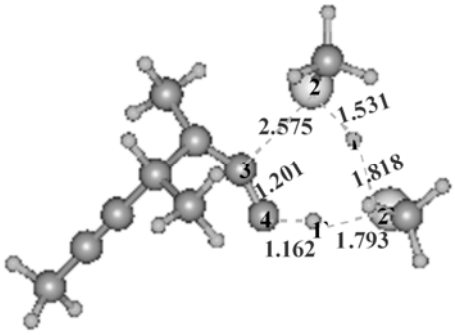
TS4-A_MeSH



TS1-A_H$_2$O

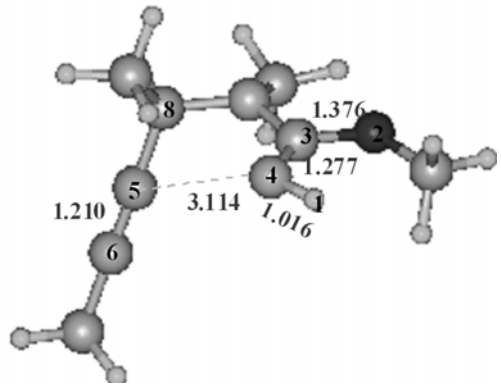


TS1-A_NH$_3$

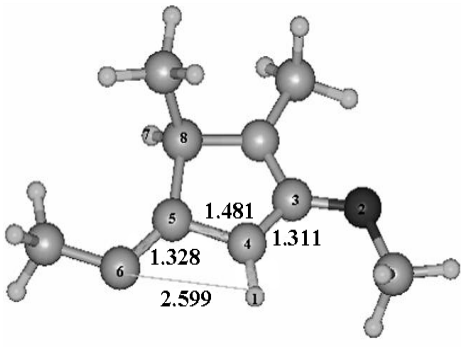


TS1-A_MeSH

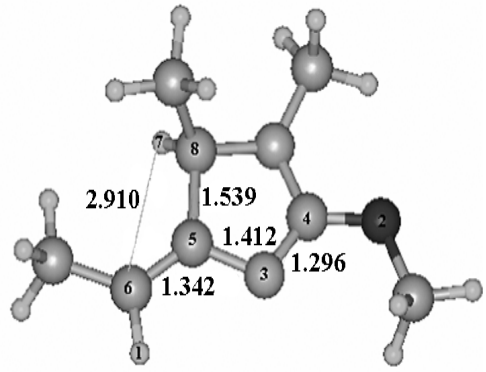
Fig. 4. Representation of the transition states under catalysis for the model system A (bond lengths shown in Å)



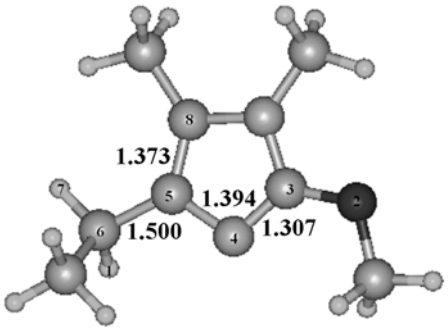
M1-B



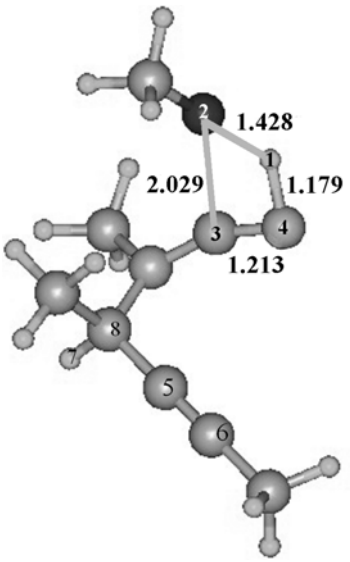
M2-B



M3-B

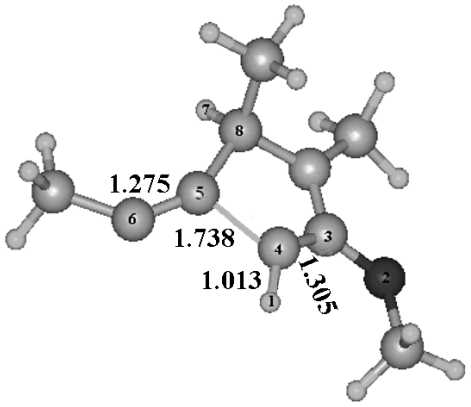


M4-B

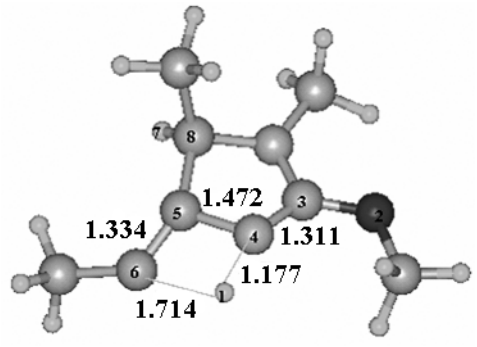


TS1-B

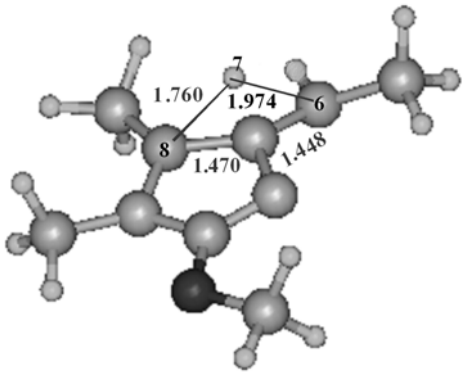
Fig. 5. Representation of the optimized structures of the intermediate



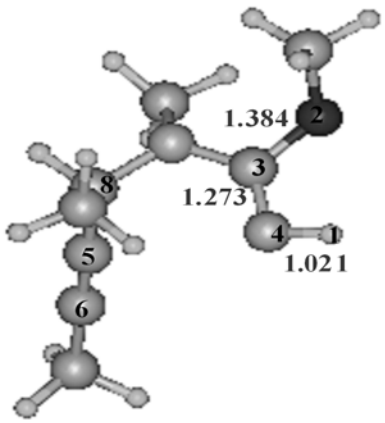
TS2-B



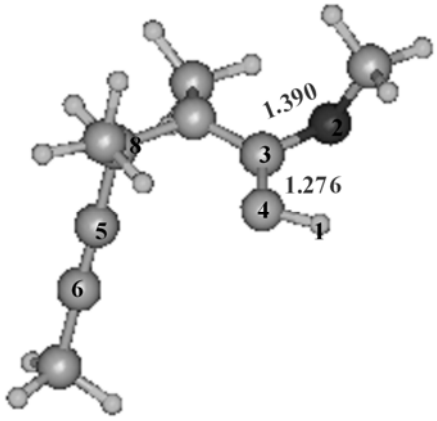
TS3-B



TS4-B

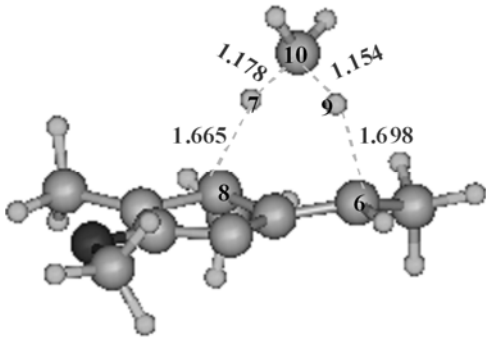


M1-B_*cis*

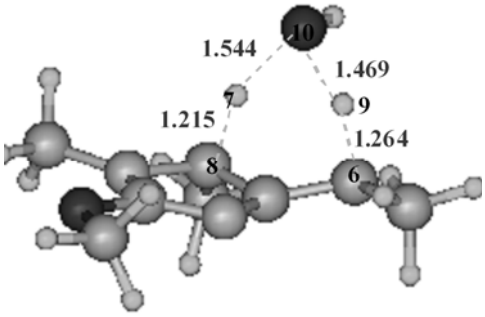


TS-B_*iso*

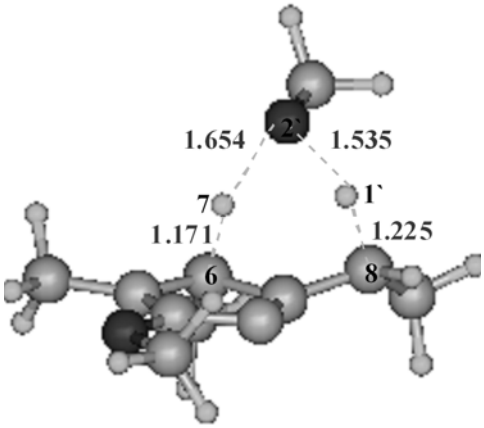
states for the model system B (bond lengths shown in Å)



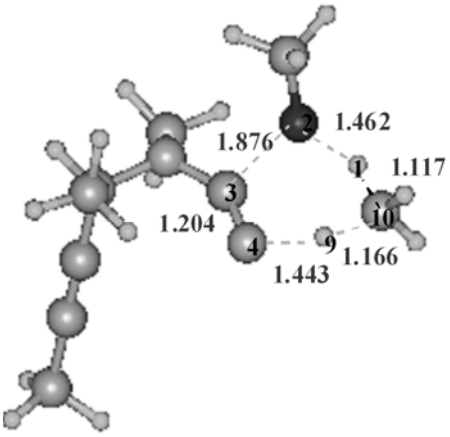
TS4-B_NH$_3$



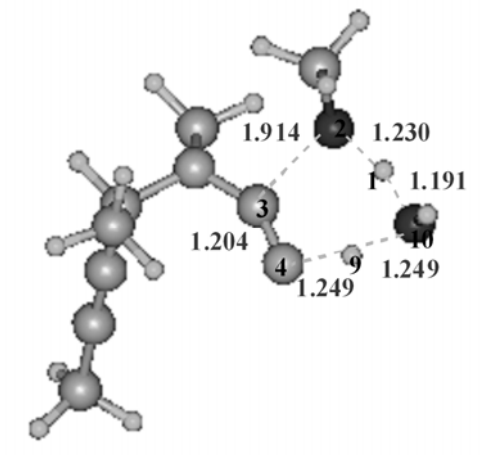
TS4-B_H$_2$O



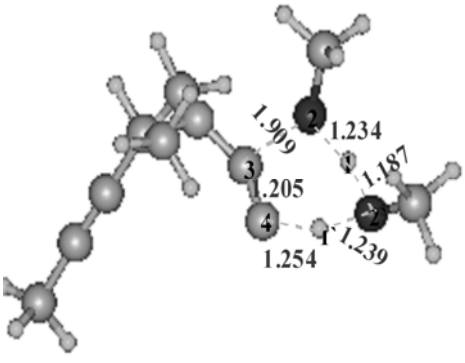
TS4-B_MeOH



TS1-B_NH$_3$



TS1-B_H$_2$O



TS1-B_MeOH

Fig. 6. Representation of the transition states under the catalysts for the model System B (bond lengths shown in Å)

In order to compare thiol with alcohol as reactants in the title reaction, we also studied the addition–cyclization–isomerization reaction of propargyl cyanamides with methanol (model system B). For the first step, from the Table 2, it is easier to carry out nucleophilic attack of S(2) to C(3) than nucleophilic attack of O(2) to C(3) in the model A. But the Mulliken charges on O(2) and H(1) in MeOH are –0.532e and 0.306e, respectively, which indicates that the cleavage of the O–H bond in MeOH is more difficult than that of the S–H bond in MeSH. This can explain that the transition state **TS1-B** (41.98 kcal/mol) has a higher energy than transition state **TS1-A**. Furthermore, the *cis*-intermediate **M1-B_*cis*** can be easily isomerized to reach the thermodynamically favored (–3.33 kcal/mol) *trans*-conformation **M1-B** by overcoming a small rotation (O(2)–C(3)) barrier of 0.31 kcal/mol (**TS-B_*iso***). For transition state **TS2-B**, the barrier is 37.09 kcal/mol. The thermodynamically unstable intermediate **M2-B** holds a higher energy of 34.08 kcal/mol than the intermediate **M1-B**, the transition state **TS3-B** holds only 8.09 kcal/mol, and the energy barrier of transition state **TS4-B** is 74.30 kcal/mol for the fourth step (Fig. 2 and Table 2).

From the Figure 2, the energy barrier of intramolecular proton transfer in the isomerization step and proton transfer in the first step are also quite higher, However, both energy barriers would be decreased in the presence of the catalyst (NH_3, H_2O, MeOH). With the catalyst, the value of transition state **TS4-B** (74.30 kcal/mol) will be decreased to 42.42 (**TS4-B_NH_3**), 34.95 (**TS4-B_H_2O**), and 32.32 kcal/mol (**TS4-B_MeOH**), and the value of transition state **TS1-B** will be decreased to 17.07 (**TS1-B_NH_3**), 16.31 (**TS1-B_H_2O**), and 12.86 kcal/mol (**TS1-B_MeOH**), respectively (Fig. 6 and Table 6). This result also indicates that the catalyst is important to decrease the energy barrier of intramolecular proton transfer in the isomerization step and proton transfer in the first step of this reaction. Furthermore, the autocatalysis (MeOH) also has the best catalytic effect for both the proton transfer in the isomerization step and the proton transfer in the addition step.

In this paper, a DFT investigation has been carried out to show an integrated mechanism for the addition–cyclization–isomerization reaction of propargyl cyanamides with thiol and methanol. The results reveal that this reaction takes place in five steps. But the energy barrier of the intramolecular proton transfer in the isomerization step (the last step) and the proton transfer in the addition step (the initial step) are too high to carry out the reaction. However, we find that the autocatalysis is able to largely decrease both energy barriers of the proton transfer, which indicates that the main function of catalyst is to catalyze the proton transfer.

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REFERENCES

1. M. A. Jarosinski, W. K. Anderson, *J. Org. Chem.*, **56**, 4058 (1991).
2. M.-E. Theoclitou, N. G. J. Delaet, L. A. Robinson, *J. Comb. Chem.*, **4**, 315 (2002).
3. R. L. Giles, R. A. Nkansah, R. E. Looper, *J. Org. Chem.*, **75**, 261 (2010).
4. R. L. Giles, J. D. Sullivan, A. M. Steiner, R. E. Looper, *Angew. Chem., Int. Ed.*, **48**, 3116 (2009).
5. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant,

J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. J. Gonzalez, A. Pople, *Gaussian 03*, *revision C.02*, Gaussian Inc., Wallingford CT, 2004.

6. A. Bottoni, V. Frenna, C. Z. Lanza, G. Macaluso, D. Spinelli, *J. Phys. Chem. A*, **108**, 1731 (2004).
7. A. Salvà, J. Donoso, J. Frau, F. Muñoz, *J. Phys. Chem. A*, **108**, 11709 (2004).
8. A. Salvà, J. Donoso, J. Frau, F. Muñoz, *J. Phys. Chem. A*, **107**, 9409 (2003).
9. W. Yang, D. G. Drueckhammer, *Org Lett.*, **2**, 4133 (2000).

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