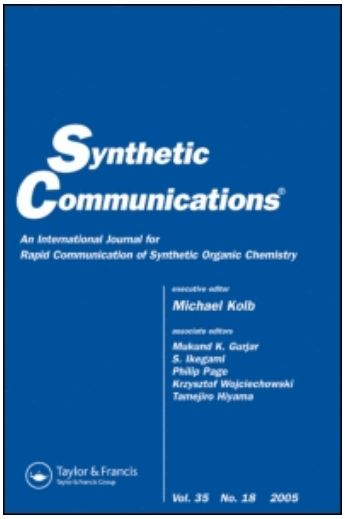


Synthetic Communications
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597304

Green Synthesis of a Novel Functionalized Tetrahydro-1,4-thiazepine and Computational Studies of Its Tautomeric Structures

M. Bakavoli [ab]; H. Beyzaei [a]; M. Rahimizadeh [a]; J. Tajabadi [b]
[a] Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran [b] Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad, Iran

To cite this Article Bakavoli, M., Beyzaei, H., Rahimizadeh, M. and Tajabadi, J.'Green Synthesis of a Novel Functionalized Tetrahydro-1,4-thiazepine and Computational Studies of Its Tautomeric Structures', Synthetic Communications, 39: 8, 1324 — 1331
To link to this Article: DOI: 10.1080/00397910802519943
URL: http://dx.doi.org/10.1080/00397910802519943

Synthetic Communications®, 39: 1324–1331, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802519943

Taylor & Francis
Taylor & Francis Group

Green Synthesis of a Novel Functionalized Tetrahydro-1,4-thiazepine and Computational Studies of Its Tautomeric Structures

M. Bakavoli,[1,2] H. Beyzaei,[1] M. Rahimizadeh,[1] and J. Tajabadi[2]
[1]Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran
[2]Department of Chemistry, School of Sciences, Islamic Azad University, Mashhad, Iran

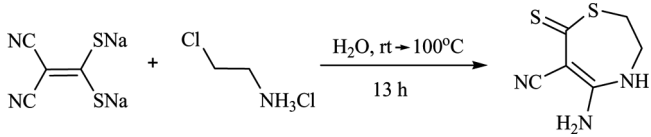
Abstract: Reaction of ethyl-2-cyano-3,3-dimercaptoacrylate dipotassium salt with 2-chloroethylamine hydrochloride in water afforded the novel (4E,6E)-ethyl 5-amino-2,3-dihydro-7-mercapto-1,4-thiazepine-6-carboxylate. The molecular geometry of the most stable tautomeric structure was investigated with DFT and AIM at the B3LYP level of theory using the 6-31G** and 6-311+G** basis sets.

Keywords: AIM, DFT, green synthesis, heterocyclization, 1,4-thiazepine

INTRODUCTION

In continuation of our interest in the green synthesis of novel polyfunctionalized 1,4-thiazepines as potential precursors for the synthesis of biologically important fused 1,4-thiazepines and the exploration of their tautomeric structures through both theoretical studies and analytical and spectral analyses, in a previous investigation[1] we studied the reaction of sodium 2,2-dicyanoethene-1,1-bis(thiolate) with 2-chloroethylamine hydrochloride in water to prepare the novel (Z)-5-amino-7-thioxo-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (Scheme 1).

Received September 4, 2008.
Address correspondence to M. Bakavoli, Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran. E-mail: mbakavoli@yahoo.com



Scheme 1.

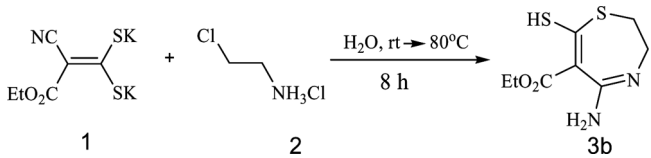
In this article, we report on the synthesis of the new (4E,6E)-ethyl 5-amino-2,3-dihydro-7-mercapto-1,4-thiazepine-6-carboxylate **3b** in water as the solvent, giving an account on its structural elucidation through both theoretical and spectral studies.

COMPUTATIONAL METHODOLOGY

Density functional theory (DFT) calculations were employed using the Gaussian 03 software package[2] with the 6-31G** and 6-311+G** basis sets, where the hybrid density functional,[3] in combination with the Lee–Yang–Parr correlation functional (B3LYP),[4] was used to optimize the geometrical structures. The same levels of theory were used for frequency analysis to characterize local energy minima (all real frequencies) and to provide the frequencies needed in the computation of the thermodynamic functions. The nature of the bonds in the tautomers was studied using the atoms in molecules (AIM) theory of Bader[5] by AIM2000 package[6] and the AIM method within the Gaussian program at the B3LYP/6-311+G** level.

RESULTS AND DISCUSSION

Stirring of a mixture of ethyl-2-cyano-3,3-dimercaptoacrylate dipotassium salt **1** and 2-chloroethylamine hydrochloride **2** in water first at room temperature for 2 h and then with heating at 80 °C for 6 h gave a solid compound (Scheme 2), which was expected to have tautomeric structures **3a–3g**. The structural assignment of the product was based on a theoretical investigation as well as analytical and spectral analyses.



Scheme 2.

The structure of all tautomers optimized at the B3LYP/6-311+G** level of theory are presented in Fig. 1 and Table 1.

As can be seen from the calculated Gibbs free energy values listed in Table 2, the B3LYP method suggests that the tautomer **3b** is the most stable tautomer in the gas phase.

The order of the stability of other tautomers is **3b** > **3d** > **3a** > **3c** > **3f** > **3e** > **3g** at the B3LYP/6-311+G** level of theory. Comparison for the two basis sets employed shows that splitting the basis set from double-ξ to triple-ξ and incorporation of diffuse functions on heavy atoms have no significant effect on the order of the stability of our tautomers. The most stable tautomer is **3b** by a margin of 3.5 kcal mol^{-1} with respect to **3d**, and **3a**, **3c**, **3d** and **3f** have a relative energy between them of less than 1.9 kcal mol^{-1}. Tautomers **3e** and **3g** have the larger values, of the relative energy. With respect to the structures of all the tautomers under investigation and because of their calculated relative energies, it can be assumed that in these structures, the C=N exocyclic bond can be taken as the main reason for the instability of these molecular systems. For

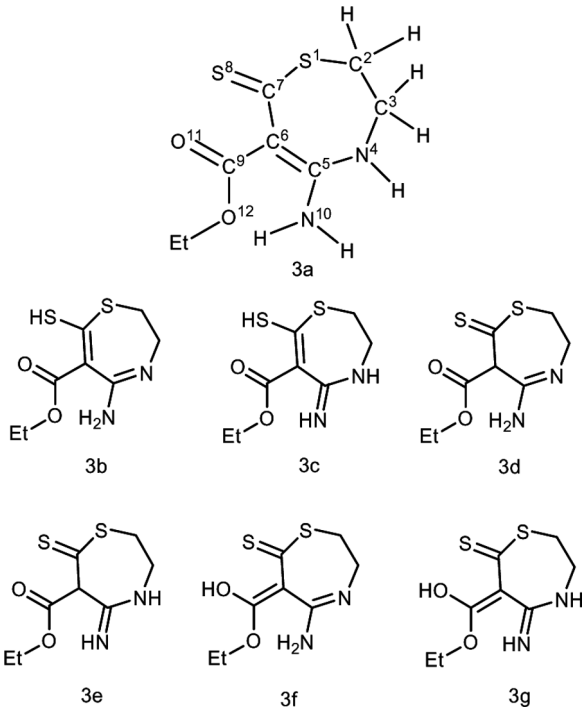


Figure 1. Various tautomeric structures of the functionalized 1,4-thiazepine **3a–3g** including the atom numbering scheme.

Table 1. Optimized geometry (bond length *r*, Å and bond angle, deg) for all tautomers **3a–3g**

Bond	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
r(S1C2)	1.836	1.857	1.851	1.856	1.836	1.861	1.840
r(C2C3)	1.531	1.526	1.533	1.521	1.519	1.523	1.515
r(C3N4)	1.457	1.447	1.451	1.453	1.473	1.446	1.468
r(N4C5)	1.364	1.280	1.386	1.273	1.400	1.279	1.405
r(C5C6)	1.414	1.510	1.508	1.542	1.538	1.508	1.513
r(C6C7)	1.458	1.370	1.361	1.528	1.527	1.423	1.411
r(C7S1)	1.854	1.789	1.795	1.740	1.743	1.782	1.785
r(C7S8)	1.639	1.754	1.757	1.650	1.644	1.701	1.698
r(C6C9)	1.482	1.475	1.481	1.539	1.538	1.406	1.412
r(C9O11)	1.206	1.222	1.221	1.202	1.206	1.298	1.299
r(C9O12)	1.384	1.352	1.341	1.344	1.338	1.328	1.317
r(C5N10)	1.364	1.381	1.277	1.379	1.276	1.382	1.279
∠(S1C2C3)	110.0	113.7	114.4	117.8	115.1	114.7	115.3
∠(C2C3N4)	114.1	111.7	114.9	111.8	115.2	110.8	114.8
∠(C3N4C5)	126.5	118.2	123.0	120.4	125.3	117.8	124.6
∠(N4C5C6)	123.1	125.4	116.2	127.6	119.1	125.8	120.5
∠(C5C6C7)	119.9	119.1	120.0	116.7	116.8	121.2	123.9
∠(C6C7S1)	114.7	122.5	121.2	125.1	122.3	121.2	118.1
∠(C7S1C2)	97.5	103.9	102.8	112.5	107.2	107.1	100.6
∠(S1C7S8)	118.2	109.2	110.3	116.1	117.4	113.2	114.9
∠(C6C7S8)	127.0	128.3	128.4	118.7	120.2	125.3	127.0
∠(C7C6C9)	117.1	122.6	122.9	112.3	113.2	121.1	120.6
∠(C5C6C9)	122.9	118.3	117.0	111.5	111.6	117.6	114.8
∠(C6C5N10)	124.1	115.5	117.3	113.0	115.4	115.3	114.9
∠(N4C5N10)	112.8	119.0	126.5	119.3	124.9	118.7	124.0
∠(C6C9O11)	126.0	126.8	125.9	126.6	126.3	125.9	125.1
∠(C6C9O12)	114.0	111.9	111.8	108.9	109.4	118.2	118.7
∠(O11C9O12)	119.9	121.3	122.3	124.5	124.2	115.9	116.1

example, consider the structures **3f** and **3g**. The AIM analyses shows that these two tautomers have an intramolecular hydrogen bonding O-H...S with the same strength (the values of the electron density, ρ, in H...S critical point for **3f** and **3g** are of the order of 0.06849^{au} and 0.06282^{au}) (Fig. 2).

Moreover, there is a repulsive interaction between N10...O12 in tautomer **3f**, whereas such an interaction in tautomer **3g** does not exist. On the other hand, the dihedral angle, S8C7C6C9 in these tautomers are in the order of -9.1° and 14.0° respectively, which indicates the presence of the same resonance in both tautomers (see bond lengths in Table 1 and values of ρ in Table 3).

Table 2. Relative energies (kcal mol^{-1}) before (ΔE_t) and after ($\Delta E_{(Et+ZPVE)}$) the zero-point vibrational energy correction as well as relative Gibbs free energies (kcal mol^{-1}) of various tautomers **3a–3g**

Parameter	Basis set	3a	3b[a]	3c	3d	3e	3f	3g
ΔE_t	6-31G**	1.95	0 (−1368.410340)	5.30	2.45	4.88	3.56	13.07
	6-311+G**	2.23	0 (−1368.612725)	4.89	2.46	5.21	4.41	13.42
$\Delta E_{(E_t+ZPVE)}$	6-31G**	4.14	0 (−1368.209737)	5.23	4.29	7.12	4.11	14.07
	6-311+G**	4.48	0 (−1368.413486)	4.90	4.36	7.57	5.12	14.68
ΔG	6-31G**	4.05	0 (−1368.252401)	5.09	3.40	6.56	4.33	14.13
	6-311+G**	4.39	0 (−1368.456374)	4.87	3.53	7.14	5.41	14.86

[a]The values in parentheses are E_{total} and G_{total} in Hartree.

In view of this argument, the considerable energy difference within these tautomers (9.5 kcal mol^{-1}) can be accounted for by the presence of the exocyclic C=N bond in **3g** tautomer, which brings about the relative

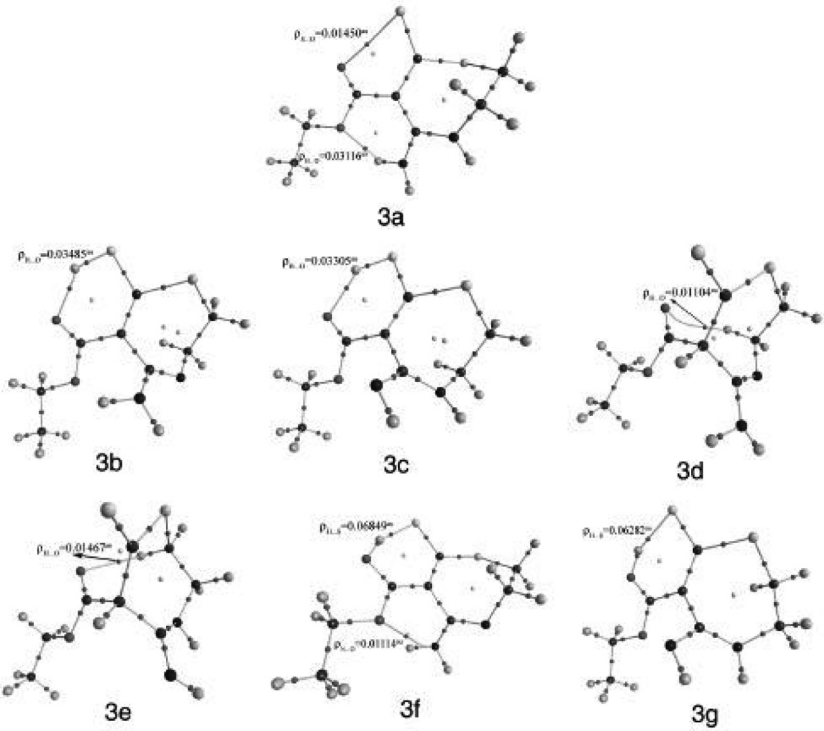


Figure 2. Position of the bond critical points in all tautomers **3a–3g**.

Table 3. Values of the electron density at some bond critical points for the **3a–3g** tautomers calculated at the $B3LYP/6\text{-}311{+}g^{**}$ level of theory

Bond	3a	3b	3c	3d	3e	3f	3g
S1–C2	0.17151	0.16464	0.16674	0.16620	0.17334	0.16389	0.17132
C2–C3	0.24407	0.24327	0.24199	0.24525	0.24813	0.24457	0.25114
C3–N4	0.25562	0.27349	0.26387	0.26874	0.25238	0.27414	0.25541
N4–C5	0.31902	0.38348	0.30322	0.38772	0.29812	0.38503	0.29550
C5–C6	0.29432	0.25246	0.25509	0.23776	0.23921	0.25238	0.25047
C6–C7	0.27245	0.31576	0.32117	0.24164	0.24150	0.28837	0.29492
C7–S1	0.16779	0.18776	0.18588	0.20416	0.20492	0.19039	0.19103
C7–S8	0.22968	0.19914	0.19786	0.22477	0.22662	0.21158	0.21185
C6–C9	0.26355	0.26912	0.26767	0.24196	0.24261	0.30021	0.29808
C9–O11	0.41941	0.40398	0.40445	0.42116	0.41726	0.33996	0.33793
C9–O12	0.27751	0.29879	0.30570	0.30352	0.30782	0.31411	0.32227
C5–N10	0.32302	0.31062	0.38802	0.31069	0.38829	0.30906	0.38653

instability for this tautomer compared to tautomer **3f**. Such a comparison can be conducted for other tautomers like **3b**, **3c, 3d**, and **3e**. Therefore, the stability of tautomer **3b** compared to other tautomers can be rationalized by the absence of the exocyclic C=N bond and also by the presence of the intramolecular hydrogen bonding S-H. . .O in the molecule (Fig. 2).

The ^{1}H NMR spectrum of the product in $CDCl_3$ exhibited three triplets at δ 1.30, 3.38, and 4.01 ppm attributed to the CH_3, S-CH_2, and N-CH_2 protons respectively and one quartet at δ 4.20 ppm assignable to the O-CH_2 protons. Two broad signals at δ 9.02 and 9.17 ppm resembling SH and NH_2 groups were removed on deuteration. IR spectrum of the product, which was taken on KBr disk, showed two different absorption bands at 3245 cm^{-1} and 2594 cm^{-1} assignable to NH_2 and SH groups and a band at 1663 cm^{-1} belonging to C=O group.

CONCLUSIONS

On the basis of theoretical investigation and spectral analysis, the reaction of **1** with **2** in water as the solvent gave exclusively the novel (4E,6E)-ethyl 5-amino-2,3-dihydro-7-mercapto-1,4-thiazepine-6-carboxylate **3b** as the most stable tautomer in the solid phase, which constitutes a potential precursor for the synthesis of various fused 1,4-thiazepines.

EXPERIMENTAL

Materials

All the reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from Merck and used as received. The melting point was recorded on an Electrothermal type 9100 melting-point apparatus. The ^{1}H NMR spectrum was recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. The infrared (IR) spectrum was obtained on a 4300 Shimadzu spectrometer, and only noteworthy absorptions are listed. The mass spectrum was observed on a Varian Mat CH-7 at 70 ev. Elemental analysis (C, H, N, S) was performed on a Thermo Finnigan Flash EA microanalyzer.

Ethyl-2-cyano-3,3-dimercaptoacrylate dipotassium salt **1** was prepared according to the literature method.[7]

IR (KBr) 1320, 1020, 930 cm^{-1}; (lit.[7] IR (KBr) 1314, 1027, 925 cm^{-1}). Anal. calcd. for $C_6H_5K_2NO_2S_2$ (265.44): C, 27.15; H, 1.90; N, 5.28; S, 24.16. Found: C, 27.34; H, 1.79; N, 5.12; S, 23.93.

(4E,6E)-Ethyl 5-Amino-2,3-dihydro-7-mercapto-1,4-thiazepine-6-carboxylate (3b)

A solution of **2** (100 mmol, 11.6 g) in water (100 ml) was added dropwise to a stirred solution of **1** (100 mmol, 26.5 g) in water (100 ml). Then, the mixture was stirred for 2 h at room temperature before it was heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature; the solid was filtered off, washed with water, and recrystallized from ethanol–water (1:1) as yellow needles to give 9.6 g (41%) of **3b**.

Mp 132 °C; IR (KBr) 3245, 2594, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$,100 MHz) δ: 1.30 (t, $J = 7.1$ Hz, 3H, CH_3), 3.38 (t, $J = 7.5$ Hz, 2H, S-CH_2), 4.01 (t, $J = 7.5$ Hz, 2H, N-CH_2), 4.20 (q, $J = 7.1$ Hz, 2H, O-CH_2), 9.02 (s, 1H, SH), 9.17 (s, 2H, NH_2); mass (70 eV) 232 m/z. Anal. calcd. for $C_8H_{12}N_2O_2S_2$ (232.32): C, 41.36; H, 5.21; N, 12.06; S, 27.60. Found: C, 41.48; H, 5.33; N, 11.84; S, 27.42.

REFERENCES

1. Bakavoli, M.; Rahimizadeh, M.; Raissi, H.; Beyzaei, H.; Tajabadi, J. Synthesis of a functionalized tetrahydro-1,4-thiazepine in water as the solvent and theoretical investigation of its tautomeric structures. *Monatsh. Chem.* **2008**, *139*, 1211–1215.
2. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T. Jr; Kudin, K. N.;

Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.03; Gaussian, Inc.; Pittsburgh, 2003.

3. Becke, A. D. Density-functional thermochemistry, III; The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
4. Lee, C.; Yang, W.; Parr, R. G. Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev.* **1988**, *37B*, 785–789.
5. Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: New York, 1990.
6. Biegler-Knig, F. AIM2000. University of Applied Science: Bielefeld, Germany.
7. Jensen, K. A.; Henriksen, L. Studies of thioacids and their derivatives, XIV: Reactions of carbon disulfide with active methylene compounds. *Acta Chem. Scand.* **1968**, *22*, 1107–1128.