Monatsh Chem 139, 1211–1215 (2008)
DOI 10.1007/s00706-008-0905-5
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Synthesis of a functionalized tetrahydro-1,4-thiazepine in water as the solvent and theoretical investigation of its tautomeric structures

Mehdi Bakavoli[1,2], Mohammad Rahimizadeh[1], Heidar Raissi[3], Hamid Beyzaei[1], Javad Tajabadi[2]

[1] Department of Chemistry, School of Science, Ferdowsi University, Mashhad, Iran
[2] Department of Chemistry, School of Science, Islamic Azad University, Mashhad, Iran
[3] Department of Chemistry, School of Science, Birjand University, Birjand, Iran

Received 14 January 2008; Accepted 25 January 2008; Published online 8 April 2008

Abstract Reaction of sodium 2,2-dicyanoethene-1,1-bis(thiolate) with 2-chloroethylamine hydrochloride in water afforded the novel (*Z*)-5-amino-7-thioxo-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile. The molecular geometry of the most stable tautomeric structure was investigated with DFT and AIM at the *B3LYP* level of theory using the standard 6-31G** basis set.

Keywords Green synthesis; 1,4-Thiazepine; Heterocyclization; DFT; AIM.

Introduction

1,4-Thiazepine is a privileged structure because of its presence in a number of pharmacologically important compounds. Several derivatives of 1,4-thiazepin-5-one [1, 2] and -2,4-dione [3] are being developed for the treatment of cancer and heart and inflammatory diseases. These derivatives aid in treating diseases by acting as inhibitors to angiotensin converting enzyme (*ACE*), neutral endopeptidase (*NEP*) [4], leukocyte adherence [5], and the inhibition of calcium release in heart mitochondria [6]. Synthesis approaches to these compounds are varied and involve addition [7], condensation [8], coupling [9], rearrangement [10], and thermolysis [11] methodologies in multistep synthesis.

As part of our ongoing studies on the synthesis of bioactive heterocycles [12] and due to the emergence of water as a versatile solvent for organic chemistry [13], we became interested to pursue the green synthesis of the novel functionalized tetrahydro-1,4-thiazepine (**3a**) as a potential precursor for the synthesis of various fused 1,4-thiazepines.

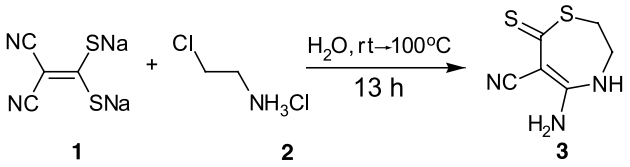
In this paper we wish to report on the synthesis and structural elucidation of (*Z*)-5-amino-7-thioxo-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (**3a**) through both theoretical investigation and analytical and spectral analyses.

Results and discussion

Stirring of a mixture of sodium 2,2-dicyanoethene-1,1-bis(thiolate) (**1**) and 2-chloroethylamine hydrochloride (**2**) in water first at room temperature for 1 h, then by heating at reflux for 12 h gave a solid compound (Scheme 1), which was expected to have either tautomeric structures **3a**–**3g**. The structural assignment of the product was based on a theoretical investigation as well as analytical and spectral analyses.

The structures of all tautomers optimized at the *B3LYP*/6-31G** level of theory are presented in Fig. 1 and Table 1. As a result of these calculations,

Correspondence: Mehdi Bakavoli, Department of Chemistry, School of Science, Ferdowsi University, 91775-1436 Mashhad, Iran. E-mail: mbakavoli@yahoo.com



Scheme 1

the stability order of these tautomers is according to Table 1 given by **3a** > **3b** > **3d** > **3e** > **3c** > **3f** > **3g**. Our results explicitly also show that the ZPVE has no significant effect on this stability order (see Table 2).

The position of the bond critical points (CPs) found in the most stable tautomer (**3a**) is shown in Fig. 2. CPs (red points in Fig. 2) are points in the electron density where the first derivatives of the electron density vanishes. The value of electron density (ρ), the eigenvalues of the second derivatives, their sums (the *Laplacian* $\nabla^2\rho$) and the ellipticities calculated at the bond CPs were evaluated for all tautomers of *B3LYP*/6-31G** level. However, they were omitted (except **3a**) for space saving, but are

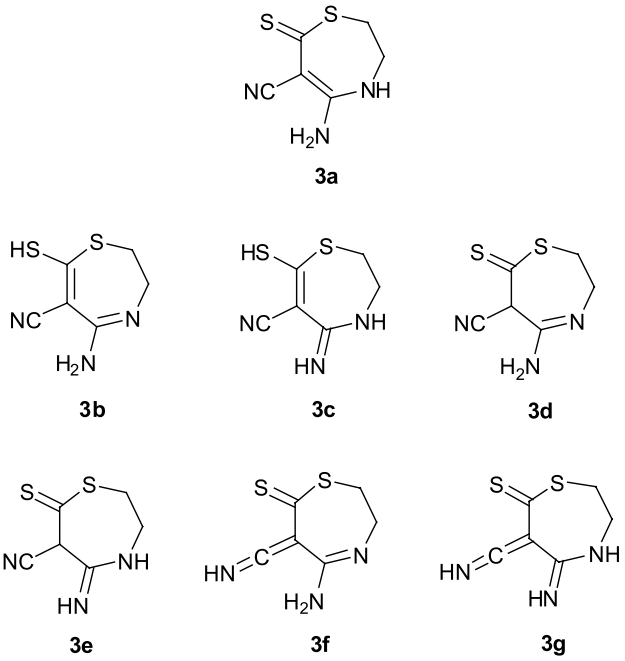


Fig. 1 Various tautomeric structures of the functionalized 1,4-thiazepine **3a**

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

	3a	3b	3c	3d	3e	3f	3g
r(C1C2)	1.449	1.372	1.367	1.537	1.542	1.464	1.456
r(C1S3)	1.775	1.775	1.785	1.758	1.749	1.766	1.770
r(C1S4)	1.670	1.768	1.779	1.640	1.640	1.667	1.671
r(C2C5)	1.412	1.499	1.503	1.554	1.544	1.506	1.504
r(C2C7)	1.436	1.426	1.430	1.466	1.470	1.346	1.353
r(C5N8)	1.357	1.284	1.382	1.279	1.390	1.278	1.383
r(C5N10)	1.371	1.377	1.281	1.365	1.279	1.386	1.286
r(C6S3)	1.838	1.860	1.851	1.866	1.840	1.860	1.847
r(C6C9)	1.526	1.523	1.531	1.528	1.524	1.524	1.530
r(C7N11)	1.166	1.166	1.164	1.161	1.161	1.208	1.202
r(N8C9)	1.452	1.448	1.449	1.448	1.469	1.449	1.451
∠(S3C1C2)	128.1	126.1	124.6	119.3	120.1	123.2	124.8
∠(S4C1C2)	121.1	124.8	119.6	123.2	120.9	121.8	122.4
∠(S4C1S3)	110.7	108.9	115.5	117.4	119.0	114.7	112.7
∠(C5C2C1)	132.6	122.9	125.6	111.6	115.7	126.8	131.6
∠(C6S3C1)	111.0	106.0	104.2	112.7	106.2	111.2	110.6
∠(C7C2C1)	114.9	119.8	118.9	113.0	112.2	117.3	115.6
∠(N8C5C2)	127.4	126.2	116.3	123.7	119.2	127.2	118.6
∠(C9C6S3)	113.2	113.8	113.7	119.2	114.5	115.2	114.2
∠(N10C5C2)	119.9	114.2	116.7	115.1	114.2	113.3	116.2
∠(N11C7C2)	171.3	178.5	177.4	174.3	178.9	174.3	175.3
∠(C9N8C5)	127.2	118.6	124.8	119.5	127.9	118.6	125.4
∠(C6C9N8)	112.5	112.5	113.6	112.0	115.5	110.9	113.1
∠(H12C6H13)	108.1	109.3	108.6	108.7	107.8	108.9	108.2
∠(H15C9H16)	107.4	106.8	106.7	105.8	107.2	107.0	106.8

[a] Other structural parameters are available upon request

Table 2 Total optimized energies E_t/a.u., Zero Point Vibrational Energies $ZPVE$/a.u., $(E_t + ZPVE)$/a.u., and relative energies/kJ · mol^{-1} of various tautomers **3a**–**3g**

	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
E_t	−1193.46323	−1193.44984	−1193.43739	−1193.44458	−1193.43966	−1193.43080	−1193.42108
ΔE_t	0.0	35.1	67.8	49.0	61.9	85.1	110.7
$ZPVE$	0.13152	0.12769	0.12742	0.13028	0.13129	0.12960	0.12932
$E_t + ZPVE$	−1193.33171	−1193.32215	−1193.30997	−1193.31430	−1193.30837	−1193.30120	−1193.29176
$\Delta E_{(E_t+ZPVE)}$	0.0	25.1	57.1	45.7	61.3	80.1	104.9

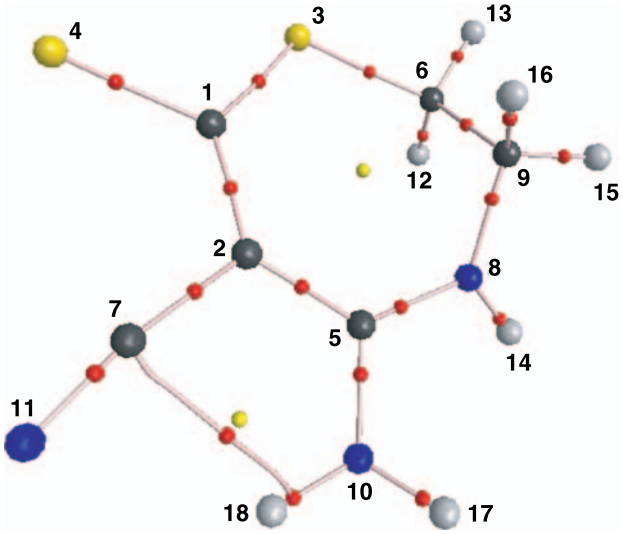


Fig. 2 The position of the bond critical points in the most stable tautomer **3a** including its atom numbering scheme

available upon request. These values for **3a** are listed in Table 3. As expected, a ring critical point (yellow point in Fig. 2) is found close to the center of the ring, as shown in Fig. 2. The existence of a bond critical point between N–H and C shows that a weak N–H. . .C hydrogen bond is formed in **3a** (see Fig. 2). This hydrogen bond can cause more stability in **3a**. The values of ρ and $\nabla^2\rho$ for the C–H bonds are similar to those of the C–H bonds of benzene [14]. In Table 3, the small ellipticities of the bonds confirm the expected picture of a single bond dominated by σ contributions.

The spectral data are also supporting the most stable tautomer **3a**. The ^{13}C NMR spectrum of **3a** exhibited signals of the methylene and vinyl carbons at $\delta = 30.28$ (S–CH_2), 52.86 (N–CH_2), 75.45 (N≡C–*C*), 175.53 (H_2N–C), and that of the C=S at 189.56 ppm. The ^{1}H NMR spectrum in *DMSO*-d_6 as

Table 3 Properties of the electron density at bond critical points for the **3a** tautomer at the *B3LYP*/6-31G** level of theory

Bond	ρ	$\nabla^2\rho$	λ_1	λ_2	λ_3	ε
S3–C6	0.17487	0.06887	−0.26256	−0.24147	0.22855	0.08733
C6–H12	0.28122	0.24646	−0.73370	−0.72973	0.47786	0.00544
C6–H13	0.27983	0.24462	−0.72812	−0.72599	0.47561	0.00294
C6–C9	0.25034	0.14585	−0.47827	−0.46340	0.35827	0.03208
C9–H16	0.28546	0.25810	−0.77247	−0.75133	0.49138	0.02813
C9–H15	0.28389	0.25276	−0.76088	−0.73818	0.48800	0.03075
C9–N8	0.26295	0.18605	−0.49935	−0.48750	0.24265	0.02432
N8–H14	0.34527	0.45636	−1.32258	−1.25023	0.74735	0.05787
N8–C5	0.32850	0.26340	−0.73891	−0.63569	0.32100	0.16238
C5–N10	0.32438	0.27984	−0.72590	−0.63559	0.24212	0.14210
N10–H18	0.34138	0.45999	−1.35765	−1.29844	0.81613	0.04560
N10–H17	0.34228	0.45123	−1.30283	−1.23901	0.73692	0.05151
C2–C5	0.29994	0.19692	−0.63409	−0.47295	0.31934	0.34072
C2–C7	0.27935	0.18303	−0.55439	−0.48047	0.30274	0.15384
C7–N11	0.46111	−0.05890	−0.93558	−0.91153	2.08272	0.02638
C1–C2	0.27802	0.16822	−0.55857	−0.47024	0.35593	0.18784
C1–S4	0.21581	0.02059	−0.20388	−0.19795	0.31945	0.02995
C1–S3	0.19369	0.08520	−0.30324	−0.25206	0.21449	0.20304
C7–H18	0.01850	−0.01986	−0.01816	−0.00624	0.10383	0.08733

the solvent exhibited two triplets at $\delta = 3.61$ and 4.32 ppm attributed to the S–CH_2 and N–CH_2 protons. Two broad signals at $\delta = 7.50$ and 12.17 ppm resembling NH_2 and NH groups were removed on deuteration. The FT-IR spectrum of **3a** in KBr showed two different absorption bands at $\bar{\nu} = 3435$ and 3320 cm^{-1} assignable to NH_2 and NH groups, 1570 and 2182 cm^{-1} attributed to C=S and C≡N groups.

In conclusion, on the basis of theoretical investigations and spectroscopic analysis, the reaction of **1** with **2** in water as the solvent gave exclusively the novel (*Z*)-5-amino-7-thioxo-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (**3a**) as the most stable tautomer, which constitutes a potential precursor for the synthesis of various fused 1,4-thiazepines.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectrum was obtained on a 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. The ^{1}H NMR (100 MHz) spectra was recorded on a Bruker AC 100 spectrometer. The ^{13}C NMR (125 MHz) spectrum was recorded on a Bruker Avance DRX-500 Fourier transformer spectrometer. Chemical shifts are reported in ppm downfield from *TMS* as internal standard. Elemental analysis (C, H, N, S) was performed on a Thermo Finnigan Flash EA microanalyzer; its result agreed favorably with the calculated values.

Computational methodology

All the computations in the present study were performed by using the *Gaussian* 98 series of programs [15]. The geometry optimizations were carried out by means of the *B3LYP* method with 6-31G** basis set. Harmonic vibrational frequencies were evaluated at the same level of theory in order to account for the Zero Point Vibrational Energy (*ZPVE*) correction. The nature of the bands in the tautomers was studied by using the Atoms In Molecules (AIM) theory of *Bader* [16] by means of AIM2000 software [17], calculated at the *B3LYP*/6-31G** level of theory.

Sodium 2,2-dicyanoethene-1,1-bis(thiolate) (**1**) was prepared according to Ref. [18] as a yellow, water-soluble compound which did not melt below 250°C. Compound **2** was purchased from Aldrich and used without further purification.

(Z)-5-Amino-7-thioxo-2,3,4,7-tetrahydro-1,4-thiazepine-6-carbonitrile (**3a**, $C_6H_7N_3S_2$)

A solution of 11.6 g **2** (0.1 mol) in 100 cm^3 H_2O was added dropwise to a stirred solution of 18.6 g **1** (0.1 mol) in 100 cm^3 H_2O. Then, the mixture was stirred for an hour at room temperature before it was heated under reflux for 12 h. The reaction mixture was cooled to room temperature and the solid was filtered off and washed with water and ethanol. The solid obtained was recrystallized from methanol: water 2:1 as yellow needles to give 11.4 g (61%) **3a**. Mp 216°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 12.17$ (s, 1H), 7.50 (s, 2H), 4.32 (t, $J = 7.1$ Hz, N–CH_2), 3.61 (t, $J = 7.2$ Hz, S–CH_2) ppm; ^{13}C NMR (125 MHz, *DMSO*): $\delta = 30.28$ (S–CH_2), 52.86 (N–CH_2), 75.45 (*C*–C≡N), 119.42 (C≡N), 175.53 (C–NH_2), 189.56 (C=S) ppm; IR (KBr): $\bar{\nu} = 3435$, 3320, 2182, and 1570 cm^{-1}; MS (70 eV): $m/z = 185$ (M^+).

References

1. Van den Hoven BG, Alper H (2001) J Am Chem Soc 14:1017
2. Marcaccini S, Miguel D, Torroba T, Garcia-Valverde M (2003) J Org Chem 68:3315
3. Skiles JW, Suh JT, Williams BE, Menard PR, Barton JN, Love B, Jones H, Neiss ES, Schwab A, Mann WS, Khandwala A, Wolf PS, Weinryb I (1996) J Med Chem 29:784
4. a) Amblard M, Daffix I, Bedos P, Berge G, Pruneau D, Paquet JL, Luccarini JM, Belichard P, Dodey P, Martinez J (1999) J Med Chem 42:4185; b) Amblard M, Daffix I, Berge G, Calmes M, Dodey P, Pruneau D, Paquet JL, Luccarini JM, Belichard P, Martinez J (1999) J Med Chem 42:4193; c) Robl JA, Sun CQ, Stevenson J, Ryono DE, Simpkins LM, Cimarusti MP, Dejenka T, Slusarchyk WA, Chao S, Stratton L, Misra RN, Bednarz MS, Asaad MM, Cheung HS, Abboa-Offei BE, Smith PL, Mathers PD, Fox M, Schaeffer TR, Seymour AA, Trippodo NC (1997) J Med Chem 40:1570
5. Boschelli DH, Connor DT, Kramer JB, Unangst PC (1996) U.S. Patent 5,489,586
6. a) Medh JD, Rex KA, Benedict CR, Sordahl LA (1991) J Cardiovasc Pharmacol 18:473; b) Kawai A, Inoue H, Narita H, Nagao T (1991) European Patent 416,479
7. a) Crescenza A, Botta M, Corelli F, Santini A, Tafi A (1999) J Org Chem 64:3019; b) Bohrisch J, Faltz H, Patzel M, Liebscher J (1994) Tetrahedron 50:10701
8. Mohacsi E, O'Brein JP (1991) J Heterocycl Chem 28:2051
9. a) Karikomi M, Yamazaki T, Abematsu Y, Masuzawa K, Toda T (1998) Heterocycles 48:1523; b) Mohseine A, Christiaens L (1996) Heterocycles 46:2567
10. Crescenza A, Botta M, Corelli F, Tafi A (1999) Heterocycles 51:1639
11. Jourdain F, Pommelet JC (1997) Synth Commun 27:483
12. a) Bakavoli M, Nikpour M, Rahimizadeh M, Saberi MR, Sadeghian H (2007) Bioorg Med Chem 15:2120; b) Rahimizadeh M, Nikpour M, Bakavoli M (2007) J Heterocycl Chem 44(2):463; c) Bakavoli M, Davoodnia A, Shahnaee R (2008) Chin Chem Lett 19:12
13. Li CJ, Chen L (2006) Chem Soc Rev 35:68
14. Madsen GKH, Iversen BB, Larsen FK, Kapon M, Reisner GM, Herbstein FH (1998) J Am Chem Soc 120:10040

15. Gaussian 98, Revision A.6, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Gonzalez C, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, Pople JA (1998) Gaussian, Inc., Pittsburgh PA
16. Bader RFW, Atoms in molecules (1990) A Quantum Theory. Oxford University Press, New York
17. AIM2000 designed by Friedrich Biegler-Knig, University of Applied Science, Bielefeld, Germany
18. Hummel HU, Wolf C (1986) Z Naturforsch B: Anorg Chem Org Chem 41:1206