Reactions of 4,5-Dihydro-1,4-Benzothiazepin-3(2*H*)-one 1,1-Dioxide and 1,5-Dihydro-4,1-Benzothiazepin-2(3*H*)-one 4,4-Dioxide Derivatives with Vilsmeier Reagent and DMFDMA

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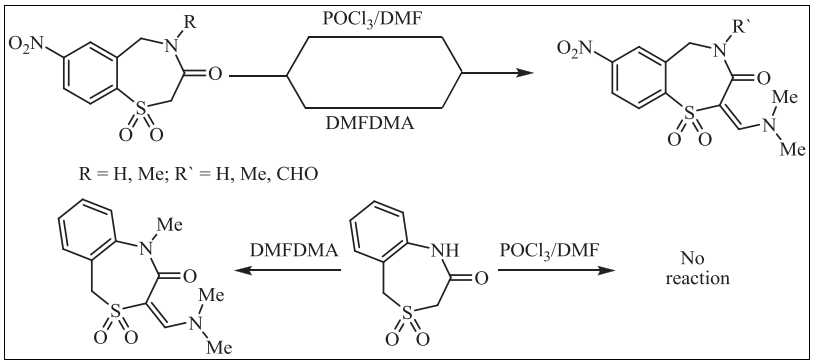

The regioselectivity of the interaction between isomeric 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one 1,1-dioxide and 1,5-dihydro-4,1-benzothiazepin-2(3*H*)-one 4,4-dioxide derivatives with the Vilsmeier reagent and DMFDMA (N,N-dimethylformamide dimethylacetal) has been investigated. The structures of synthesized compounds are confirmed by ^{1}H, ^{13}C NMR, elemental analysis, and X-ray data.

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INTRODUCTION

In recent years, a number of compounds that show high levels of biological activity were found among benzothiazepine derivatives. Both 1,5- and 1,4-benzothiazepines have generated great interest [1–3]. For example, diltiazem [4] (*cis*-(+)-[2-(2-dimethylaminoethyl)-5-(4-methoxyphenyl)-3-oxo-6-thia-2-azabicyclo[5.4.0]undeca-7,9,11-trien-4-yl] ethanoate) – a well-known drug (calcium channel blocker) used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. This compound has a 1,5-benzothiazepine scaffold **I** (Fig. 1). Some 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one **I** derivatives are used in the treatment of cardiovascular diseases [5], including bradykinin agonists [6], growth hormone secretagogues (GHSs) [7], and Ca antagonists [8]. N-alkyl-3,4-dihydro-1,4-benzothiazepin-5(2*H*)-one **II** derivatives are known to show properties of Ca antagonists [9] and antitumoral agents [10]. Substituted 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones **III** can be used in the treatment of seizures, neurological disorders such as epilepsy [11,12]and as neuroprotective agents to protect against conditions such as stroke [12]. Among 1,5-dihydro-4,1-benzothiazepin-2(3*H*)-ones **IV**, there are squalene synthase inhibitors [13], antidepressants [14,15], and anticonvulsants [16,17].

A review of the literature shows that 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **I** and 3,4-dihydro-1,4-benzothiazepin-5(2*H*)-ones **II** are well studied, while isomeric 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones **III** and 1,5-dihydro-4,1-benzothiazepin-2(3*H*)-ones **IV** have been less well studied.

We proposed earlier two alternative methods for the synthesis of 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one derivatives [18,19]. The synthesis of 1,5-dihydro-4,1-benzothiazepin-2(3*H*)-one has been described in 1965 [20]. Substituted benzothiazepinones have attracted the attention of chemists because of their reactivity. The carboxamide group is one of the functional groups possessing synthetic potential, and widely-used. Electron withdrawing groups are known to cause high activity of adjacent methylene groups in reactions with electrophilic agents. Introduction of a carbonyl group or its analogues opens new possibilities for the synthesis and modifications of different heterocyclic systems.

The Vilsmeier reagent is the most commonly used formylating agent. Several reviews have been written [21–23] during decades of existence of the Vilsmeier reaction. The interest to usage of DMFDMA has increased in the last years [24]. Comparison of Vilsmeier reagent and DMFDMA has not been reported. The aim of this work was to compare interaction of the above mentioned formylating agents with some sulfones.

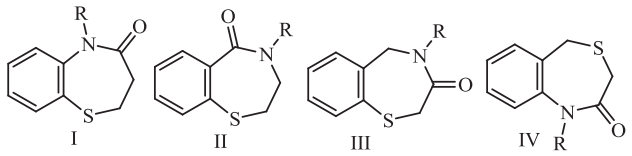


Figure 1. Some of possible isomers of benzothiazepinones.

RESULTS AND DISCUSSION

There are two activated methylene group, which can be attacked by electrophiles, in both isomeric 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one 1,1-dioxides **V** and 1, 5-dihydro-4,1-benzothiazepin-2(3*H*)-one 4,4-dioxides **VI** (Fig. 2). We predicted that different chemical environment of these groups causes the CH_2 between SO_2 and CO to be more reactive to electrophilic agents. In addition to that, each individual case has some specific peculiarities, caused by chemical nature of substrates and electrophiles.

We have developed two methods for the synthesis 4-methyl-7-nitro-4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one. Oxidation of this compound leads to corresponding sulfone **1** [19]. We expected to obtain dimethylaminomethylene derivative using DMFDMA and chloroaldehyde as the Vilsmeier reagent. But treatment of sulfone **1** with Vilsmeier reagent and DMFDMA was found to afford compound **2** (Scheme 1).

The structure of compound **2** is confirmed by X-ray diffraction data (Fig. 3). Moreover, there are characteristic signals in ^{1}H NMR spectrum of compound **2**: singlet = CH- at 7.36 ppm and two singlets of methyl groups at 2.93 and 3.24 ppm, that confirm the presence of the dimethylaminomethylene group. Compound **2** exists in crystal phase as *E*-isomer (the S1-C10-C11-N3 torsion angle is −179.5(3)°). The exocyclic C=C double bond also is significantly twisted (the C9-C10-C11-N3 torsion angle is −15.1(5)°). Probably,

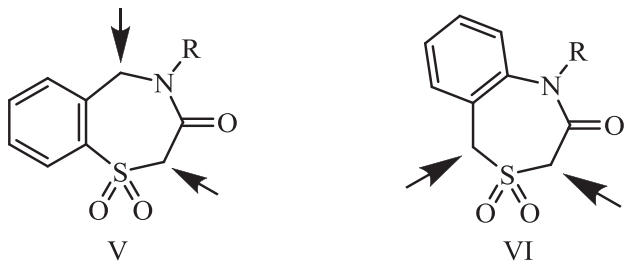
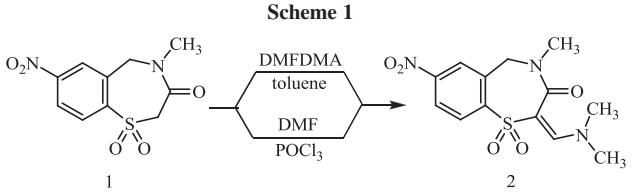


Figure 2. Possible directions to formylating agent attack.

Scheme 1



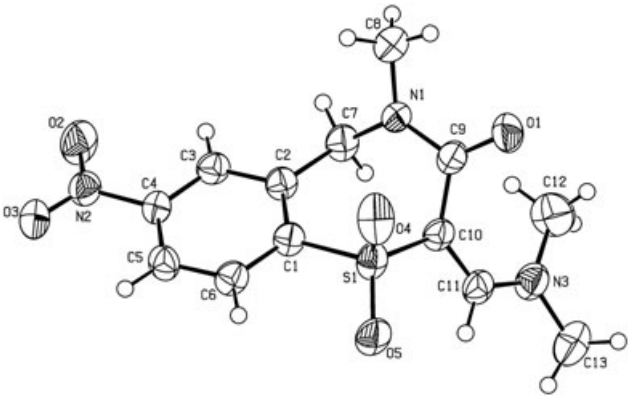


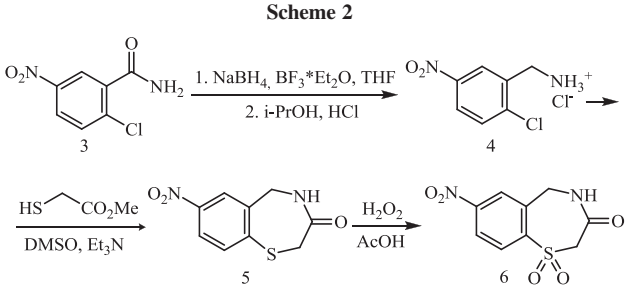
Figure 3. Molecular structure of compound **2** according to results of X-ray diffraction study.

this is caused by significant steric repulsion between dimethylamino group and atoms of ring (shortened intramolecular contact C12-H12A. . .C9 2.56 Å, van der Waals radii sum [25] is 2.87 Å). The seven-membered ring adopts a distorted half-chair conformation with deviation of the N1, C9 and C10 atoms from mean plane of remaining atoms of ring by 0.840(5) Å, 0.453(6) Å and −0.586(5) Å, respectively.

It was interesting to investigate the reaction of 7-nitro-4, 5-dihydro-1,4-benzothiazepin-3(2*H*)-one 1,1-dioxide **6** with formylating agents. The long time we could not obtain the desired compounds **5**, **6**, according to described methods [18,19] due to difficulties in synthesis of (2-chloro-5-nitrobenzyl)amine **4**. In spite of the apparent simplicity of structure of amine **4**, the synthesis of this compound has not been described. After many attempts, the synthesis of compound **4** has been carried out: commercially available 2-chloro-5-nitrobenzamide **3** has been reduced by *in situ* generated borane from $BF_3{\cdot}OEt_2$ and $NaBH_4$ (Scheme 2). Compound **5** has been obtained by described method [18] in 82 % yield. Treatment of 7-nitro-4,5-dihydro-1, 4-benzothiazepin-3(2*H*)-one **5** with peracetic acid led to corresponding sulfone **6** in 85 % yield.

Characteristic signals in ^{1}H NMR spectra of compounds **5** and **6** are singlets at 3.93 and 4.85 ppm (2-CH_2), doublets at 4.50 and 4.80 ppm (5-CH_2) and triplets at 8.18 and 8.67 ppm (NH) correspondingly.

Scheme 2



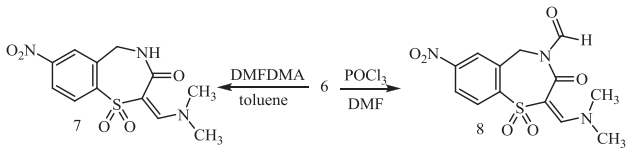
Reaction of sulfone **6** and DMFDMA afforded the expected product **7** similarly to dimethylaminomethylene derivative **2** (Scheme 3). The ^{1}H NMR spectrum of compound **7** is characterized by the signals of the aromatic protons and also the regular chemical shift of the protons on C-5 at 4.64 as doublet (J = 4.8 Hz), the signal on NH is found at 8.22 ppm as triplets (J = 4.8 Hz). There are also singlets of methyl groups at 2.94 and 3.23 ppm and singlet of =CH- at 8.22. The triplet of NH is exchangeable in ^{1}H NMR spectrum recorded with addition D_2O, and doublet of 5-CH_2 becomes singlet.

Treatment of sulfone **6** with the Vilsmeier reagent led to introduction of dimethylaminomethylene group and formylation of nitrogen in position 4 (Scheme 3).

There is a characteristic singlet for the formyl group at 8.91 ppm, which is present in the ^{1}H NMR spectrum in addition of D_2O. Signals of other groups of compound **8** are shifted to low field in comparison with compounds **7**: singlet = CH- at 7.76 ppm, singlets of methyl groups at 2.97 and 3.38 ppm and singlet of 5-CH_2. Finally, the structure of compound **8** was established by X-ray diffraction study (Fig. 4).

Compound **8** exists in crystal phase as the *E*-isomer (the S1-C10-C11-N3 torsion angle is 172.4(1)°). Exocyclic C=C double bond is significantly twisted (the C9-C10-C11-N3 torsion angle is −19.2(2)°). Again, this is probably caused by steric repulsion between dimethylamino group and atoms of ring (shortened intramolecular contact C12-H12A. . .C9 2.74 Å, van der Waals radii sum [25] is 2.87 Å).

Scheme 3



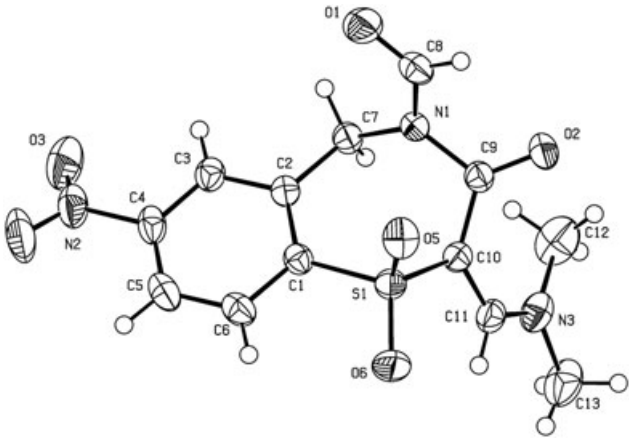


Figure 4. Molecular structure of compound **8** according to results of X-ray diffraction study.

The seven-membered ring adopts a distorted half-chair conformation with deviation of the N1, C9 and C10 atoms from mean plane of remaining atoms of ring by −0.628(2) Å, 0.102(2) Å and 0.879(2) Å, respectively.

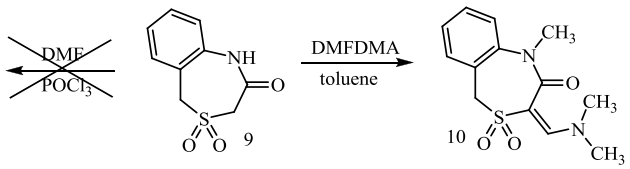
The next step of this work was the investigation of interaction of isomeric sulfone **9** [20] with formylating agents. An interesting fact has been observed, that treatment of compounds **9** with Vilsmeier reagent did not led to dimethylaminomethylene derivative (Scheme 4). Instead of that we obtained mixture of undesirable side products. Possibly, ring opening took place.

Performing the reaction of sulfone **9** with 2 equivalents of DMFDMA in toluene allowed us to obtain compound **10** in 63 % yield. DMFDMA is known to have the properties of formylating and alkylating agents [24]. In our case we observed both of mentioned properties.

The structure of compound **10** is confirmed by X-ray diffraction study (Fig. 5) and NMR spectra. There are characteristic signals in ^{1}H NMR: wide singlet (6H) of $N(CH_3)_2$ at 2.82 ppm, singlets of methyl, methylene and =CH- groups at 3.35, 4.34 and 6.64 ppm correspondingly.

Compound **10** exists in crystal phase as the *E*-isomer (the S1-C8-C10-N2 torsion angle is 176.5(2)°). Twisting of exocyclic C=C double bond is considerably smaller than in molecules **2**, **8** (the C9-C8-C10-N2 torsion angle is −9.6(3)°) despite of stronger steric repulsion between dimethylamino group and atoms of ring (shortened intramolecular contact

Scheme 4



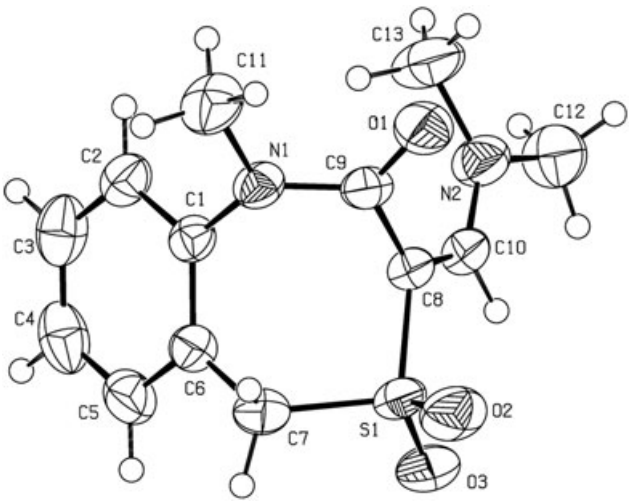


Figure 5. Molecular structure of compound **10** according to results of X-ray diffraction study.

C13-H13A. . .C9 2.49 Å, van der Waals radii sum [25] is 2.87 Å). The seven-membered ring adopts a boat conformation with deviation of the S1, C8 and C9 atoms from mean plane of remaining atoms of ring by 1.532(3) Å, 2.070(2) Å and 1.071(3) Å, respectively.

In summary, we have compared reactivity of 4,5-dihydro-1, 4-benzothiazepin-3(2H)-one 1,1-dioxides **V** and 1,5-dihydro-4,1-benzothiazepin-2(3H)-one 4,4-dioxides **VI** in reactions with formylating agents. We observed the introduction of dimethylaminomethylene groups in positions between SO_2 and CO, as was predicted. But each case has own specificity. It has been shown that the nature of the aromatic ring influences on reactions of the NH groups. When the molecule contains an anilide NH, we observed alkylation by DMFDMA. When the NH is the part of aliphatic amide we saw that DMFDMA did not alkylate the NH, but the Vilsmeier reagent leads to N-formylation. We have shown that DMFDMA and the Vilsmeier reagent are useful for introduction of a carbonyl group and its analogues. It should be noted that DMFDMA are more convenient in some syntheses.

EXPERIMENTAL

X-ray diffraction study of compound 2, 8 and 10. Crystallographic data and parameters of experiments are listed in Table 1. Intensities of reflections were measured on an automatic «Xcalibur 3» diffractometer (graphite monochromated $Mo_{K\alpha}$ radiation, CCD-detector ω scaning). All structures were solved by direct method using SHELX97 package [26]. Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with Uiso = nUeq of carrier non-hydrogen atom (n = 1.5 for methyl group and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 was performed for non-hydrogen atoms using anisotropic approximation. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.

All commercially available chemicals were purchased from Aldrich (St. Louis, MO, USA) and Merck (Darmstadt, Germany). NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Varian Mercury 400 spectrometer. Elemental analyses were determined on a vario MICRO cube elemental analyzer. Melting points were measured with a small Boetius apparatus equipped with a VEB Analytic RNMK apparatus. Purity of the compounds synthesized was monitored by TLC on Silufol UV-254 plates with 9:1 chloroform–methanol as eluent.

General procedure for the reaction of sulfones with Vilsmeier reagent. To magnetically stirred dry DMF (14 mL) at 0 °C was added dropwise phosphorus oxychloride (8.3 mL, 40 mmol). After 30 minutes at 0 °C the solution of corresponding sulfone (10 mmol) in dry DMF (6 mL) was added. The mixture obtained was stirred for 6 hours at 60–70 °C. The solution was poured onto crushed ice (150 g) and the resulting solid was filtered, washed with water and dried.

Table 1

Crystallographic data, parameters of experiments and structure refinement of structures of compounds **2**, **8**, **10**.

	2	**8**	**10**
Crystal data:			
Empirical formula	$C_{13}H_{15}N_3O_5S$	$C_{13}H_{13}N_3O_6S$	$C_{13}H_{16}N_2O_3S$
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
a, Å	15.1599(17)	8.4101(2)	7.7711(4)
b, Å	6.7385(8)	8.5343(2)	12.5922(7)
c, Å	14.8507(16)	20.1471(5)	13.9856(6)
β, °	105.238(12)	95.756(2)	96.167(5)
V, Å^3	1463.7(3)	1438.75(6)	1360.64(12)
Z	4	4	4
D_c, g/sm^{-3}	1.476	1.567	1.369
μ(MoKα), mm^{-1}	0.249	0.262	0.243
T, K	293	293	293
F(000)	680	704	592
Data collection:			
Independent Reflelections	3538	4595	4395
R_{int}	0.0769	0.0169	0.0381
$2\theta_{max}$	57.7	64.1	64.1
Refinement:			
Parameters	202	210	175
Reflections with $F > 4\sigma(F)$	2029	3805	2690
R_1 [$F^2 > 2\sigma(F^2)$]	0.0673	0.0372	0.0468
wR_2 (all data)	0.1795	0.1085	0.1324
S (goodness-of-fit)	1.02	1.06	1.01
CCDC dep. Numbers	885596	885594	885595

General procedure for the reaction of sulfones with DMFDMA. A mixture of DMFDMA (0.27 mL, 20 mmol) and corresponding sulfone (10 mmol) in dry toluene (50 mL) was heated at reflux for 3 hours. The resulting solution was concentrated in vacuo. To the residue *i*-PrOH (10 ml) was added. The precipitate was filtered, washed and dried.

(2E)-2-[(Dimethylamino)methylene]-4-methyl-7-nitro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one 1,1-dioxide (2). This compound was obtained as pale yellow solid (dioxane); mp 243–245 °C; ^{1}H nmr (DMSO-d_6): δ 2.93 (s, 3H, CH_3), 2.99 (s, 3H, NCH_3), 3.24 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 7.36 (s, 1H, CH), 8.10 (d, 1H, H9, J = 8.4 Hz), 8.34 (d, 1H, H8, J = 8.4 Hz), 8.41 (s, 1H, H6); ^{13}C nmr (DMSO-d_6): δ 35.10, 47.14, 53.05, 67.03, 96.69, 124.83, 125.24, 126.70, 136.93, 148.79, 150.24, 151.19, 165.25. *Anal.* calcd. for $C_{13}H_{15}N_3O_5S$: C, 47.99; H, 4.65; N, 12.92. Found: C, 48.01; H, 4.66; N, 12.90.

2-Chloro-5-nitrobenzylamine hydrochloride (4). To a magnetically stirred suspension of amide 2-chloro-5-nitrobenzoic acid **1** (20.0 g, 0.1 mol) and sodium borohydride (15.2 g, 0.4 mol) in dry THF (300 mL) at 20 °C was added dropwise boron trifluoride etherate (50.8 mL, 0.4 mol). The resultant mixture was stirred at 50 °C for 24 hours, concentrated in vacuo. Then water (250 ml) was added. Aqueous solution was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. To residue was added *i*-PrOH (15 mL) and calculated amount of hydrochloric acid. The precipitate was collected by filtration, washed Et_2O, and dried to give 2-chloro-5-nitrobenzylamine hydrochloride **2** (13.8 g, 62 %). White solid; mp >300 °C; ^{1}H nmr (DMSO-d_6): δ 4.21 (s, 2H, CH_2), 7.75

(d, 1H, H3, J = 8.8 Hz), 8.22 (dd, 1H, H4, J = 2.4, 8.8 Hz), 8.59 (d, 1H, H6, J = 2.4 Hz), 8.7-9.0 (br s, 3H, N^+H_3); ^{13}C nmr (DMSO-d_6): δ 39.66, 125.15, 125.74, 131.21, 134.53, 140.28, 146.52. *Anal*. calcd. for $C_7H_8Cl_2N_2O_2$: C, 37.69; H, 3.62; N, 12.56. Found: C, 37.70; H, 3.62; N, 12.53.

7-Nitro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (5). To a stirred solution of 2-chloro-5-nitrobenzylamine hydrochloride **2** (11.15 g, 0.05 mol) and triethylamine (20.9 mL, 0.15 mol) in 25 mL DMSO was added methyl thioglycolate (4.5 mL, 0.05 mol). After being stirred at 60 °C for 5 h, the reaction mixture was cooled to room temperature, quenched with water (250 mL), and then stirring was continued 30 min. The precipitate was filtered off, washed by acetone and dried to give 8.51 g (76%) of 7-nitro-4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one **5**. Pale yellow solid; mp 263–265 °C; ^1H nmr (DMSO-d_6): δ 3.93 (s, 2H, 2-CH_2), 4.50 (d, 2H, 5-CH_2, J = 6.4 Hz), 7.33 (d, 1H, H9, J = 8.8 Hz), 7.96 (dd, 1H, H8, J = 2.0, 8.8 Hz), 8.59 (d, 1H, H6, J = 2.0 Hz), 8.18 (t, 1H, NH, J = 6.4 Hz); ^{13}C nmr (DMSO-d_6): δ 32.04, 44.76, 123.24, 125.26, 128.56, 135.38, 144.55, 146.06, 169.71. *Anal.* calcd. for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.20; H, 3.62; N, 12.50.

7-Nitro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one 1,1-dioxide (6). A mixture of **3** (6.72 g, 0.03 mol) and 30% H_2O_2 (18 mL) in 200 ml acetic acid was stirred at 40 °C for 3 days. The resultant reaction mixture was concentrated in vacuo. MeOH 25 mL was added to residue, precipitate was collected by filtration, washed MeOH, dried. The pure product was obtained by crystallization from AcOH. White solid; mp 296–298 °C; ^1H nmr (DMSO-d_6): δ 4.80 (d, 2H, 5-CH_2, J = 5.6 Hz), 4.85 (s, 2H, 2-CH_2), 8.16 (d, 1H, H9, J = 8.4 Hz), 8.35-8.38 (m, 2H, H6, H8), 8.67 (t, 1H, NH, J = 5.6 Hz); ^{13}C nmr (DMSO-d_6): δ 44.09, 59.51, 124.05, 124.76, 127.68, 138.15, 148.26, 149.23, 163.31. *Anal*. calcd. for $C_9H_8N_2O_5S$: C, 42.19; H, 3.15; N, 10.93. Found: C, 42.21; H, 3.13; N, 10.95.

(2E)-2-[(Dimethylamino)methylene]-7-nitro-4,5-dihydro-1, 4-benzothiazepin-3(2H)-one 1,1-dioxide (7). This compound was obtained as pale yellow solid (dioxane); mp 277–278 °C; ^1H nmr (DMSO-d_6): δ 2.94 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 4.64 (d, 2H, CH_2, J = 4.8 Hz), 7.39 (s, 1H, CH), 8.09 (d, 1H, H9, J = 8 Hz), 8.22 (t, 1H, NH, J = 4.8 Hz), 8.28-8.30 (m, 2H, H6, H8); ^{13}C nmr (DMSO-d_6): δ 41.15, 45.20, 47.20, 96.93, 124.33, 124.71, 126.74, 138.35, 148.95, 150.36, 151.75, 167.18. *Anal.* calcd. for $C_{12}H_{13}N_3O_5S$: C, 46.30; H, 4.21; N, 13.50. Found: C, 46.33; H, 4.20; N, 13.49.

(2E)-2-[(Dimethylamino)methylene]-7-nitro-3-oxo-2,3-dihydro-1,4-benzothiazepine-4(5H)-carbaldehyde 1,1-dioxide (8). This compound was obtained as pale yellow solid (dioxane); mp 257–258 °C; ^1H nmr (DMSO-d_6): δ 2.97 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 7.76 (s, 1H, CH), 8.14 (d, 1H, H9, J = 7.6 Hz), 8.34 (d, 1H, H8, J = 7.6 Hz), 8.50 (s, 1H, H6), 8.91 (s, 1H, CHO); ^{13}C nmr (DMSO-d_6): δ 41.95, 44.44, 47.82, 96.84, 124.40, 125.06, 125.93, 135.18, 148.34, 149.14, 154.98, 161.90, 165.83. *Anal*. calcd. for $C_{13}H_{13}N_3O_6S$: C, 46.01; H, 3.86; N, 12.38. Found: C, 46.00; H, 3.88; N, 12.40.

(3E)-3-[(Dimethylamino)methylene]-1-methyl-1,5-dihydro-4,1-benzothiazepin-2(3H)-one 4,4-dioxide (10). This compound was obtained as pale yellow solid (toluene, 63%); mp 196 °C; ^1H nmr (DMSO-d_6): δ 2.81 (s, 6H, $2CH_3$), 3.34 (s, 3H, NCH_3), 4.39 (s, 2H, CH_2), 6.64 (s, 1H, CH), 7.25-7.44 (m, 4H, C_6H_4); ^{13}C nmr (DMSO-d_6): δ 36.05, 36.06, 39.59, 57.90, 99.24, 124.54, 127.26, 128.47, 130.13, 130.89, 144.46, 146.04, 162.96. *Anal*. calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found: C, 55.70; H, 5.77; N, 10.01.

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