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A combined experimental and theoretical study of the alkylation of 3,5-dithioxo-[1,2,4]triazepines

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The chemo- and regioselective alkylation reactions of 3,5-dithioxo[1,2,4]triazepine 1 in a basic medium with α,ω-dibromoalkanes 2a–c, Br$(CH_2)_n$Br ($n = 1$–3), are studied experimentally and theoretically. These alkylations, which occur at the thioxo sulfur atom in position 5, afford mainly 5-bromomethylthio-2,7-dimethyl- 2,3-dihydro-4H[1,2,4]triazepin-3-one 3 for $n = 1$, 6,8-dimethyl-5-thioxo-2,3,4,5-tetrahydro-6H[1,3]thiazolo[4,5-d][1,2,4]triazepine 4 for $n = 2$ and 7,9-dimethyl-6-thioxo-2,3,4,5,6,7-hexahydro[1,3]thiazino [4,5-d][1,2,4]triazepine 5 for $n = 3$. Theoretical calculations have been carried out at the B3LYP/6-31G* and B3LYP(benzene)/6-311+G*//B3LYP/6-31G* levels, in order to rationalize the experimental observations. Both chemo- and regio-selectivities of the alkylation reactions are analyzed. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: triazepines; alkylation; S_N2 mechanism; transition structures; DFT calculations

INTRODUCTION

Triazepines and their derivatives are found to be associated with various biological activities such as cancer,[1] viral infections (HIV),[2] and cardiovascular disorders.[3,4] The fusion of heterocyclic rings to different faces of the heptatomic nucleus was shown to enhance the activity profiles.[5–7] The synthesis and characterization of a family of triazepine derivatives are of particular interest to the chemical and biological communities.[8–10] The chemistry and biochemistry of triazepine derivatives have been intensively investigated.[11–20] However, chemoselective alkylation of these compounds, which depends highly on the size of the haloalkane and the nature of the triazepine heteroatom, has not been yet satisfactorily studied. From an industry point of view, understanding the alkylation mechanism could help in optimizing the reaction conditions and designing a new haloalkane and/or a new catalyst for a more efficient process. To the best of our knowledge, there is only one experimental study on the alkylation of these triazepines.[21] No theoretical or combined experimental and theoretical analysis of the alkylation of these compounds were found. For this reason, and because of our interest in synthesis of novel heterocyclic compounds in the case of triazepine derivatives,[11–13] we have prompted us to face this problem of alkylation process both experimentally and theoretically. For this purpose, we have studied the alkylation reactions of 3,5-dithioxo[1,2,4]triazepine **1** with α,ω-dibromoalkanes **2a**–**c** (Scheme 1). Because the sulfur atoms of the thioxo groups, the N4 nitrogen atom and the C6 carbon atom of triazepine **1** could be reactive toward alkylation reaction, the formation of all corresponding regioisomers was theoretically analyzed.

Our aim is to present a combination of experimental and theoretical study of the alkylation reactions of triazepine **1** in a basic medium with α,ω-dibromoalkanes **2a**–**c** in order to better understand the mechanistic features of these processes and to rationalize the experimental results. Since experimental efforts toward the preparation and isolation of the obtained products have been described in another work,[21] we content here to explore briefly the NMR spectrum of the obtained regioisomers as a first step. In a second part, we examine all the probably reactive channels associated to these alkylation reactions using DFT method at the B3LYP/6-31G* and B3LYP(benzene)/6-311+G*//B3LYP/6-31G* levels.

RESULTS AND DISCUSSION

Alkylation reactions of 3,5-dithioxo[1,2,4]triazepine 1

We have followed, in these alkylation reactions, the well-established standard method[22–26] using the liquid–liquid phase transfer technique. Thus, the alkylation reactions of triazepine **1**

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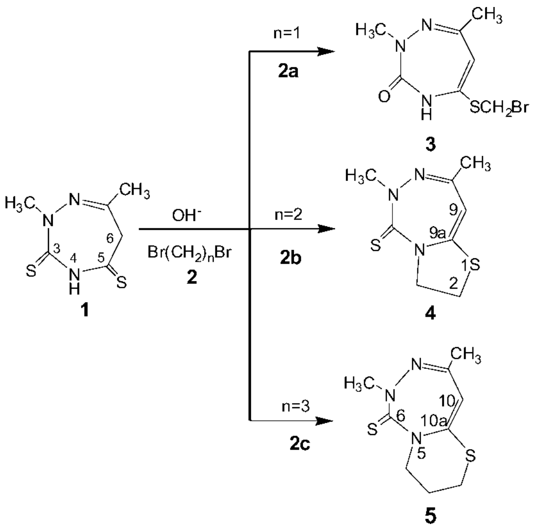


Scheme 1.

with the α,ω-dibromoalkanes **2a**–**c** in a basic medium, using triethylammonium chloride as catalyst and benzene as solvent, at room temperature, lead to compounds **3** ($n = 1$), **4** ($n = 2$), and **5** ($n = 3$) in 40, 80, and 85% yields, respectively (as shown in Scheme 1). The obtained structures were established from NMR, IR, and mass spectrometry data.

In ^1H NMR, the obtained product **3** is particularly justified by the presence of a methylene group (SCH_2Br), highly deshielded, at 5.23 ppm, and an ethylenic proton at 5.0 ppm. We noted also two methyl groups at 3.31 and 1.93 ppm assigned to $N—CH_3$ and $C_7—CH_3$, respectively. In the ^{13}C NMR spectrum of product **3,** the chemical shifts at 52.2 and 102.2 ppm permit to confirm again the presence of a methylene group and a trisubstituted double bond (C=C), respectively. This spectrum is characterized mainly by the presence of two signals at 167.8 and 188.0 ppm assigned to the carbon atoms of a carbonyl group, in position 3, and C_5, respectively. The presence of a carbonyl group is also confirmed in the IR spectrum by a band at 1690 cm^{-1}. Compound **3** results from a double alkylation of **1** with two 1,2-dibromomethane molecules on the two sulfur atoms in positions 3 and 5, followed by a hydrolysis on position 3 of the corresponding di-alkylated intermediate **7** (Scheme 2). It is to note that C_6 has not been alkylated.

In the case of product **4**, the ^1H NMR spectrum presents principally the signals of an ethylenic proton at 5.52 ppm, and two methylene groups of a thiazole cycle at 3.10 ppm assigned to ($S—CH_2$) and 4.56 ppm attributed to ($N_4—CH_2$). In the ^{13}C NMR spectrum, the presence of a double bond C=CH and two methylene groups is confirmed by the carbon chemical shifts at 105.4, 29.1, and 55.7 ppm corresponding to carbon C_9, $S—CH_2$, and $N_4—CH_2$, respectively. This structure is confirmed in this spectrum by the chemical shift of the thiocarbonyl carbon atom at 188.7 ppm and the chemical shift of carbon atom C_{9a} at 168.3 ppm. The mass spectrum fragmentations are in good agreement with the proposed structure.

The ^1H NMR spectrum of compound **5** is found to be similar to those of structure **4**. We note in particular the signals of three methylene groups at 2.23, 2.85, and 3.92 ppm attributed to ($C—CH_2—C$), ($S—CH_2$), and ($N_5—CH_2$), respectively. We observe also the presence of ethylenic proton in position 10 at 5.55 ppm. In the case of ^{13}C NMR spectrum, the proposed structure is confirmed by the presence of three methylene groups ($C—CH_2—C$) at 23.8 ppm, ($S—CH_2$) at 26.5 ppm, and ($N_5—CH_2$) at 48.1 ppm. The carbon of thioxo group is clearly identified in this spectrum at 194.2 ppm. C_{10} and C_{10a} carbon atoms appear at 114.5 and 166.4 ppm. In the mass spectra the molecular peaks at $m/z = 213$ (100%) for compound **4** and $m/z = 227$ (100%) for compound **5**, were in good agreement with monoalkylation reaction on one C=S group.

In all cases, these results show that the active center is the sulfur atom of the thioxo group present in position 5 of triazepine **1**. In the case of $n = 2$ and $n = 3$, cyclization occurs with the nitrogen atom in position 4. No cyclization was observed with the carbon atom at position 6.

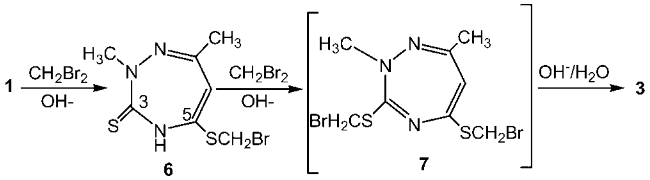
Theoretical study of the alkylation reactions of 3,5-dithioxo[1,2,4]triazepine 1

In order to investigate the reactivity of triazepine **1** in the alkylation reactions, the nucleophilic substitution reactions of anions **8** and **9,** obtained by deprotonation of triazepine **1** in a basic medium, with dibromomethane **2a** and 1,2-dibromoethane **2b**, were studied.

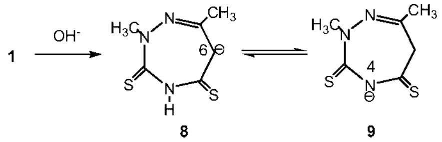
*Alkylation of 3,5-dithioxo[1,2,4]triazepine **1** with dibromomethane **2a***

The relatively acidic triazepine **1** is converted in its corresponding anion by treatment with a base. Due to the fact that triazepine **1** possesses three acidic hydrogens, one on N_4 and two on C_6, the deprotonation can yield two anions, **8** and **9**, which can be in equilibrium (as shown in Scheme 3). In these anions the negative charge is delocalized on the conjugated π system of triazepine **1**. As a consequence, there are several nucleophilic centers able to attack to dibromomethane **2a**. Both chemo and regioselectivities of the nucleophilic substitution reactions of anions **8** and **9** toward **2a** were studied (as shown in Scheme 4).

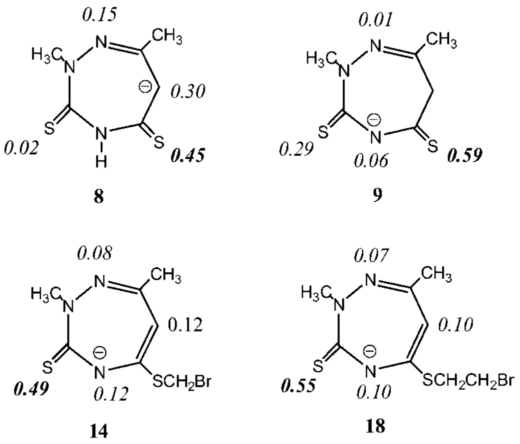
Firstly, we performed an analysis of the Fukui function for an electrophilic attack,[27] f_k^-, at anions **8** and **9** in order to characterize the more nucleophilic centers of these species. The values of the Fukui functions for an electrophilic attack of **8** and **9** are shown in Chart 1. For anion **8**, large Fukui functions are found at C_6 and $S_{5'}$ atoms. The value found at $S_{5'}$ atom larger than that at C_6 one indicates that the former will be the more



Scheme 2.

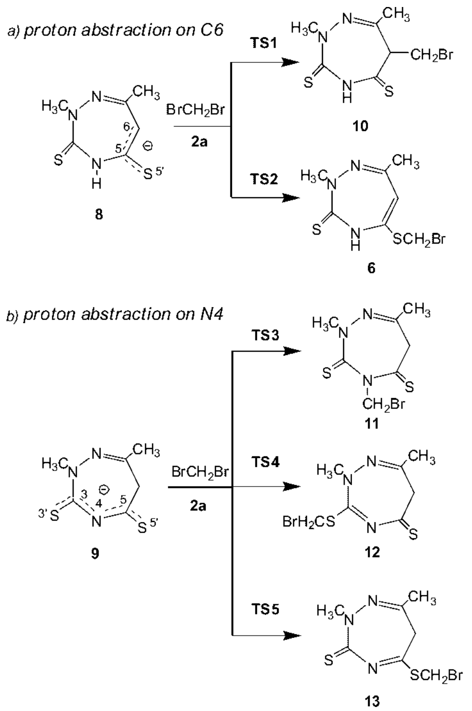


Scheme 3.



Fukui functions for electrophilic attack, f_k^-.
In bold the more nucleophilic center of the anions.

Chart 1.



Scheme 4.

nucleophilic center of **8**. From this analysis, we selected to study the reactive channel associated to the electrophilic attack of **2a** on C_6 and $S_{5'}$ centers of **8** (as shown in Scheme 4). For anion **9**, the analysis of the Fukui functions reveals that the $S_{3'}$ and $S_{5'}$ sulfur atoms are the more nucleophilic centers of this anion. As for anion **8**, the $S_{5'}$ sulfur atom corresponds to the more nucleophilic site of this species. Note that the $S_{5'}$ sulfur atom corresponds also to the more basic center of the neutral triazepine **1**.[28]

In benzene, anion **9** is 2.9 kcal/mol more energetic than anion **8** (energy values correspond to B3LYP(benzene)/6-311+G*//B3LYP/6-31G* results; as shown in Table 1). These species will be in equilibrium in solution. So, we decided to study the reactive channels associated to the nucleophilic attacks of the C_6 and $S_{5'}$ centers of anion **8** and those associated to the nucleophilic attacks of the $S_{3'}$, N_4, and $S_{5'}$ centers of anion **9** to the carbon atom of **2a** (as shown in Scheme 4).

Analysis of the stationary points associated to these alkylations indicates that these reactions occur via bimolecular nucleophilic substitution (S_N2) mechanisms. The activation energies associated with the nucleophilic attack of the C_6 and $S_{5'}$ centers of anion **8** to the carbon atom of **2a** are 15.5 (**TS1**) and 12.3 (**TS2**) kcal/mol, respectively (as shown in Table 1). The reactive channel associated to the nucleophilic attack of the $S_{5'}$ center of **8** to **2a** via **TS2** is clearly favored over the attack of the C_6 center via **TS1**, $\Delta\Delta E = 3.2$ kcal/mol, in clear agreement with the chemoselectivity experimentally observed and with the analysis of the Fukui functions at anion **8**. However, the formation of the alkylated product **10** (−21.8 kcal/mol) is thermodynamically more favorable than the formation of the product **6** (−9.6 kcal/mol) (The relative energies of the products given in Table 1 are $\Delta E = (\Sigma E_{prod} - \Sigma E_{react})$ where ΣE_{prod} correspond to the energies of the molecular complexes obtained from the IRC calculations toward the products). The more exothermic character for the formation of **10** than that for **6** can be related with the increase in bond energy associated to the σ bond formed in these S_N2 reactions: C—C > S—C. Therefore, there is a clear kinetic control at these alkylation reactions.

The activation energies associated with the nucleophilic attack of the $S_{3'}$, N_4, and $S_{5'}$ centers of anion **9** to **2a** are 12.9 (**TS3**), 12.4 (**TS4**), and 10.3 (**TS5**) kcal/mol, respectively. The reactive channel associated to the nucleophilic attack of $S_{5'}$ of anion **9** to the carbon atom of **2a**, via **TS5**, is already more favored than the attack of the two other positions, in good agreement with the analysis of the Fukui functions at anion **9**. The formation of compounds **11**, **12**, and **13** is also exothermic (as shown in Table 1). If we consider that anions **8** and **9** are in equilibrium, the more favorable reactive channel for the alkylation of **1** in a basic medium corresponds to the formation of product **6** via **TS2**. Note that **TS5** is located 1.0 kcal/mol above **TS2**.

The geometries of the TSs involved in the S_N2 reactions of anions **8** and **9** with **2a** are given in Figs 1 and 2, respectively. The lengths of the forming bonds at the TSs are 2.251 Å (C—C) at **TS1**, 2.480 Å (S—C) at **TS2**, 2.003 Å (N—C) at **TS3**, 2.391 Å (S—C) at **TS4**, and 2.415 Å (S—C) at **TS5**, while the lengths of the C—Br breaking bonds at these TSs are in a short range: between 2.534 and 2.597 Å. At these TSs, the X—C—Br (X=C, N, S) bond angles are in the range of 160.0–164.0°. The three atoms involved in the forming and breaking bonds are in a nearly linear arrangement, deformed only by the presence of a second bromine atom on **2a**. These geometrical parameters indicate that at these TSs the carbon atom of dibromomethane is sp^2-hybridized, and are, therefore, in agreement with TSs expected for a S_N2 mechanism.

The extent of bond forming and breaking along the reaction pathway is provided by the concept of bond order (BO).[29] The BO values of the forming bonds at the TSs are 0.36 (C—C) at **TS1**, 0.44 (S—C) at **TS2**, 0.40 (N—C) at **TS3**, 0.49 (S—C) at **TS4**, and 0.48 (S—C) at **TS5**, while the BO values of the breaking bonds are in a short range: between 0.44 and 0.49. These values indicate that these TSs correspond to synchronous bond forming and breaking processes.

Table 1. Total (*E*, in au) and relative energies (Δ*E*, in kcal/mol) in the gas phase and in benzene for the stationary points involved in the alkylation reactions of 3,5-dithioxo[1,2,4]triazepine **1**

	B3LYP/6-31G*		B3LYP(benzene)/6-311+G*//B3LYP/6-31G*	
	E	Δ*E*	*E*	Δ*E*
8	−1194.122375		−1194.324628	
9	−1194.117884	2.8	−1194.319951	2.9
2a	−5182.713025		−5187.609626	
TS1	−6376.818859	10.4	−6381.909630	15.5
TS2	−6376.824207	7.0	−6381.914659	12.3
10 + **Br**	−6376.859359	−15.0	−6381.969072	−21.8
6 + **Br**	−6376.839725	−2.7	−6381.949573	−9.6
TS3	−6376.815225	9.8	−6381.909046	12.9
TS4	−6376.814688	10.2	−6381.909895	12.4
TS5	−6376.818103	8.0	−6381.913116	10.3
11 + **Br**	−6376.838344	−4.7	−6381.951467	−13.7
12 + **Br**	−6376.827957	1.9	−6381.940877	−7.1
13 + **Br**	−6376.839127	−5.2	−6381.945656	−10.1
14	−3804.510112		−3807.159634	
TS6	−8987.207850	9.6	−8994.751541	11.1
TS7	−8987.203311	12.4	−8994.742521	16.8
TS8	−8987.201556	13.5	−8994.740715	17.9
7 + **Br**	−8987.225051	−1.2	−8994.787306	−11.3
15 + **Br**	−8987.231109	−5.0	−8994.789871	−12.9
16 + **Br**	−8987.247623	−15.4	−8994.806965	−23.7
2b	−5222.037715		−5226.942587	
TS9	−6416.146140	8.8	−6421.247548	12.3
17 + **Br**	−6416.151552	5.4	−6421.277668	−6.6
18	−3843.821895		−3846.481749	
TS10	−3843.812407	6.0	−3846.471299	6.6
TS11	−3843.792216	18.6	−3846.451426	19.0
4 + **Br**	−3843.851383	−18.5	−3846.526168	−27.9
19 + **Br**	−3843.858693	−23.1	−3846.533106	−32.2

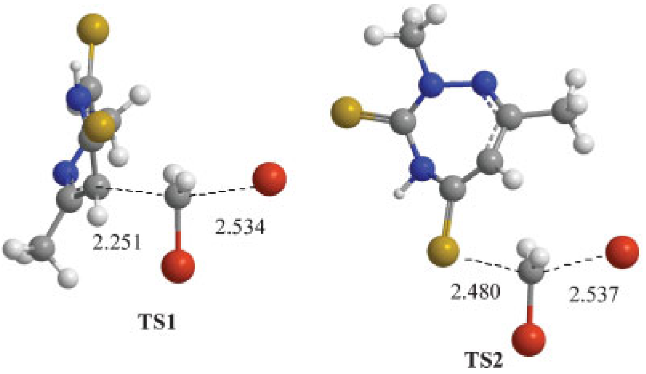


Figure 1. B3LYP/6-31G* transition structures involved in the S_N2 reactions of anion **8** with dibromomethane **2a**. The distances are given in Å?

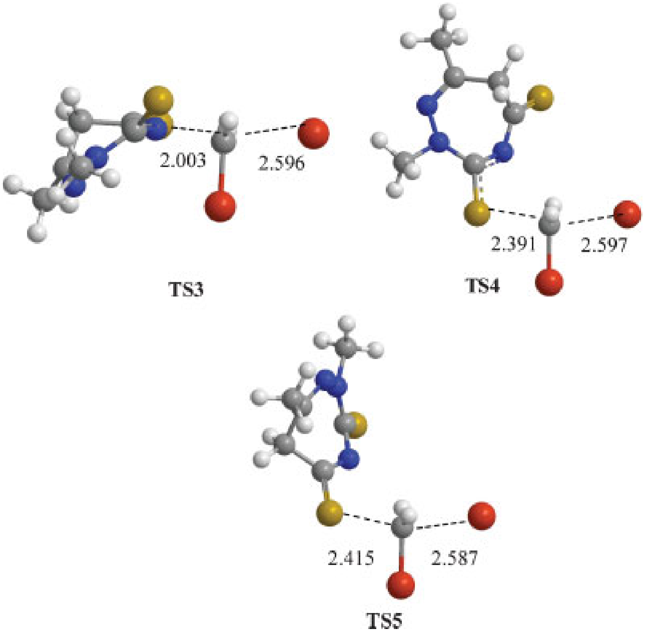
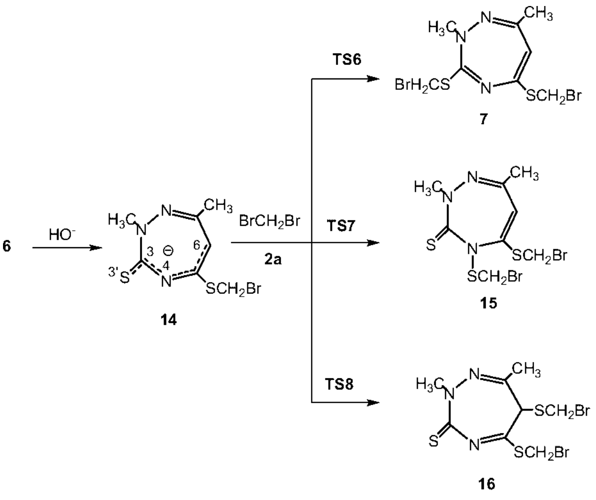


Figure 2. B3LYP/6-31G* transition structures involved in alkylation reactions of anion **9** with dibromomethane **2a**. The distances are given in Å

*Alkylation of compound **6** with dibromomethane **2a***

In the presence of 2 moles of base and 2 moles of **2a**, triazepine **1** yields the dialkylderivative **7**, via an alkylation reaction of the anion intermediate **14** (as shown in Schemes 2 and 5). Deprotonation at N_4 of the monoalkylderivative **6** gives the anionic intermediate **14**, which acts as a nucleophile toward **2a**. Due to the delocalization of the negative charge of anion **14** on the triazepinic system, this intermediate presents also several nucleophilic sites. Analysis of the Fukui functions for an electrophilic attack at anion **14** (as shown in Chart 1), indicates that $S_{3'}$ atom will be the more nucleophilic center of **14**. In consequence, the electrophilic attack to the second molecule of **2a** should take place in this sulfur atom.

For the alkylation reaction of the anion intermediate **14**, three reactive channels were considered (as shown in Scheme 5). They are related to the nucleophilic attack of the $S_{3'}$, N_4, and C_6 centers of anion **14** at the carbon atom of **2a**. As for the alkylation



Scheme 5.

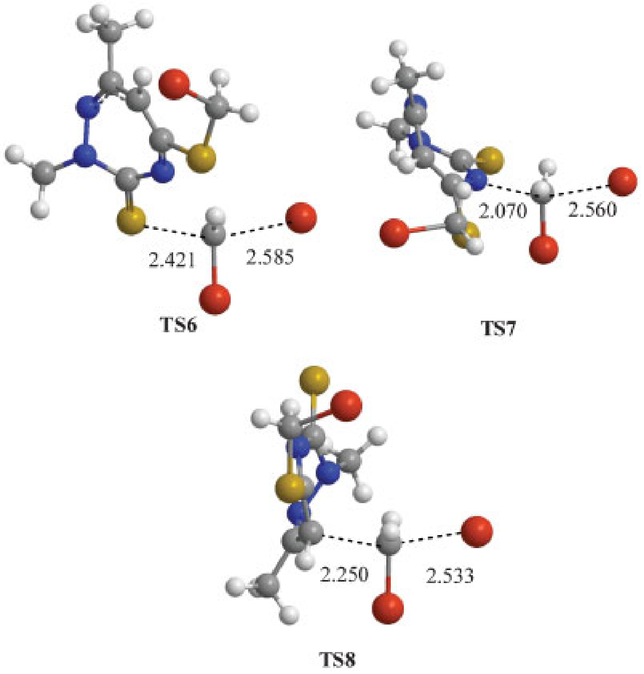


Figure 3. B3LYP/6-31G* transition structures involved in alkylation reactions of anion intermediate **14** with dibromomethane **2a**. The distances are given in Å.

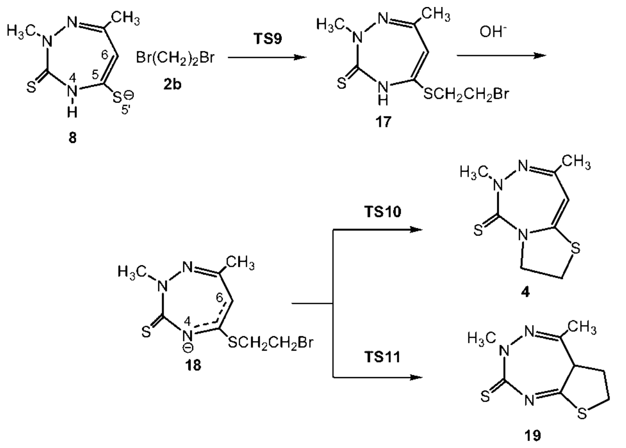
reactions of anions **8** and **9** with **2a**, these reactions have a S_N2 mechanism. The activation energies associated to the three reactive channels are 11.1 (**TS6**), 16.8 (**TS7**), and 17.9 (**TS8**) kcal/mol. The more favorable reactive channel corresponds to the attack of $S_{3'}$ sulfur atom on the carbon atom of **2a**, via **TS6**. These energy results are in clear agreement with the total chemoselectivity experimentally observed. These reactions are exothermic in the range −11.3–−23.7 kcal/mol.

The geometries of the TSs involved in these S_N2 reactions are given in Fig. 3. The lengths of the forming bonds at the TSs are 2.421 Å (S—C) at **TS6**, 2.070 Å (N—C) at **TS7**, and 2.250 Å (C—C) at **TS8**, while the lengths of the breaking bonds are in a short range: between 2.533 and 2.585 Å. At these TSs, the X—C—Br (X=C, N, S) bond angles are in the range of 159.9–164.6°. The geometries of these TSs are closer to those found on the alkylation of anions **8** and **9**.

The BO values of the forming bonds are 0.48 (S—C) at **TS6**, 0.38 (N—C) at **TS7**, and 0.36 (C—C) at **TS8**, while the BO values of the C—Br breaking bond are 0.40 at **TS6**, 0.48 at **TS7**, and 0.49 at **TS8**.

*Alkylation of 3,5-dithioxo[1,2,4]triazepine **1** with 1,2-dibromoethane **2b***

Formation of the bicyclic compound **4** is a domino reaction that involves an intermolecular nucleophilic attack of anion **8** to 1,2-dibromoethane **2b**, in a S_N2 reaction, followed by an intramolecular nucleophilic attack (S_Ni) on anion **18** (as shown in Scheme 6). Taking into account the results obtained for the alkylation reaction of **1** with **2a** in a basic medium (Section 'Alkylation of 3,5-dithioxo[1,2,4]triazepine **1** with dibromomethane **2a**'), we have considered the first alkylation reaction studying only the attack of the $S_{5'}$ center of anion **8** to one of the two symmetrically substituted carbons of **2b**. The activation energy associated to the S_N2 reaction via **TS9** is 12.3 kcal/mol. This energy is the same as that for the reaction of anion **8** with **2a**, via **TS2**. Formation of intermediate **17** is slightly exothermic, −6.6 kcal/mol.



Scheme 6.

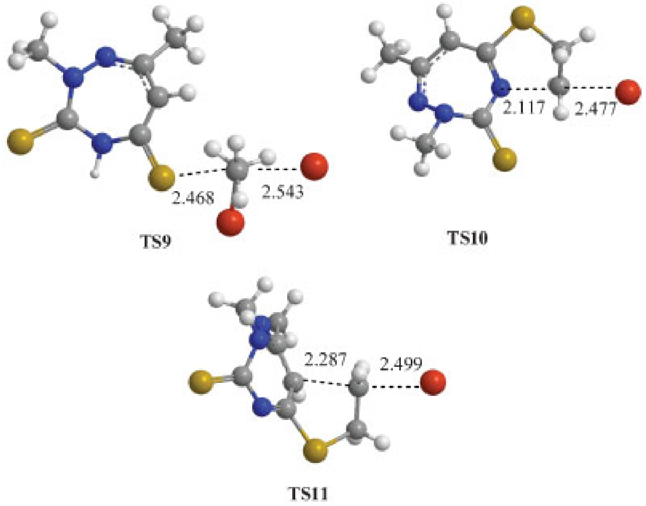


Figure 4. Structures of the transition states involved in domino reactions of triazepine **1** with dibromoethane **2b** in a basic medium. The distances are given in Å.

The second step of this domino reaction is a S_Ni process promoted by the nucleophilic attack of the anion generated by deprotonation of **17**, intermediate **18**, to the bromo substituted methylene in **17**. After deprotonation of compound **17** at N_4 nitrogen atom, the negative charge is delocalized into the conjugated system of **18**. Therefore, the subsequent S_Ni reaction can take place at N_4 or C_6 positions of the anion intermediate **18**. The two reactive channels have been studied (as shown in Scheme 6). The activation energies associated to these S_Ni processes are 6.6 (**TS10**) and 19.0 (**TS11**) kcal/mol. These energies indicate that the cyclization at N_4 is clearly favored over cyclization at C_6, in good agreement with the experimental results. Formation of both bicyclic compounds **4** and **19** are exothermic in −27.9 and −32.2 kcal/mol, respectively. As for the S_N2 reactions, there is a clear kinetic control in these S_Ni processes.

The geometries of the TSs involved in the domino reaction between anion **8** and **2b** are given in Fig. 4. The lengths of the S—C forming and C—Br breaking bonds at **TS9** are 2.468 and 2.543 Å, respectively. These lengths are similar to those found at **TS1**. At **TS9**, the S—C—Br bond angle is 162.7°. At the TSs involved in the intramolecular alkylations, the lengths of the forming and breaking bonds are 2.117 Å (N—C) and 2.477 Å (C—Br) at **TS10** and 2.287 Å (C—C) and 2.499 Å (C—Br) at **TS11**. At these TSs, the X—C—Br (X═N, C) bond-angle values are 172.6° at **TS10** and 170.1° at **TS11**.

Finally, the BO values of the S—C forming and C—Br breaking bonds at **TS9** are 0.45 and 0.46, respectively. At the TSs associated with the intramolecular alkylations, the BO values of the forming and breaking bonds are 0.34 and 0.52 at **TS10** and 0.32 and 0.49 at **TS11**, respectively. The S_Ni processes via **TS10** and **TS11** are more asynchronous than the S_N2 one via **TS9**.

CONCLUSIONS

The chemo- and regioselective alkylation reactions of 3,5-dithioxo-[1,2,4]triazepine **1** in a basic medium with α,ω-dibromoalkanes **2a**–**c** $Br(CH_2)_nBr$ ($n = 1$–3) have been investigated experimentally and theoretically. These reactions afford several products depending on the length of the α,ω- dibromoalkane. Thus, dibromomethane **2a**, $n = 1$, leads to alkylation on the sulfur atom at position 5 with 40% yield. In the presence of a large excess of **2a**, triazepine **1** is subsequently alkylated at position 3. In contrast, the use of 1,2-dibromoethane **2b**, $n = 2$, and 1,3-dibromopropane **2c**, $n = 3$, leads to the formation of a new five- and six-membered fused heterocycles via an intermolecular alkylation on the thioxo sulfur atom at position 5, followed by an intramolecular alkylation at the nitrogen atom of triazepine **1** with 80% yield. All these products were characterized using NMR and mass spectroscopy.

Theoretical calculations have been carried out at the B3LYP/6-31G* level for geometries and the B3LYP(benzene)/6-311+G*//B3LYP/6-31G* level for energies in order to rationalize the experimental observations. Analysis of the potential energy surfaces for these alkylation reactions indicates that the more favorable reactive channels correspond to the alkylation on the thioxo sulfur atom at position 5 of triazepine **1** via a S_N2 mechanism. Formation of the fused bicyclic compound **4**, using 1,2-dibromoethane **2b**, is a domino reaction that is, initialized by the intermolecular alkylation on $S_{5'}$ atom, followed by deprotonation and an intramolecular alkylation on $N_{4'}$ atom. Analysis of the Fukui functions for an electrophilic attack at the anions involved in these alkylation reactions indicates that the thioxo sulfur atom at position 5 is the more nucleophilic site of the deprotonated triazepine.

EXPERIMENTAL

Melting points were taken on a Buchi 510 apparatus and were uncorrected. The ^1H NMR spectra were recorded with the following instruments: Bruker WP 400 CW and AC 250. TMS was used as an internal reference. The ^{13}C NMR spectra were measured on a Varian FT 80 (300.0 MHz). The IR spectrum was obtained using Perkin-Elmer 683 apparatus. Mass spectrum was recorded with a Jeol JMX DX 300. Column chromatography was carried out using E-Merck silica gel 60F 254. Reagents and solvents were purified in the usual way.

General procedure for the alkylation reactions of 3,5-dithio[1,2,4]triazepine 1 with α,ω-dibromoalkanes 2a,b

The alkylation reactions were carried out by means of the phase transfer technique from a solution of 2,7-dimethyl-3,5-dithioxo[1,2,4]triazepine **1** (0.0046 mol) in benzene (10 ml). Triethylammoniumbenzylchloride (0.013 mol) was used as a catalyst. When the mixture was stirring for 15 min, a solution of 3 g of NaOH in 3 ml of H_2O and the α,ω-dibromoalkanes **2a**,**b** were added. After stirring for 6 h at room temperature, the mixture was diluted with water and extracted with benzene. The organic layers were dried over anhydrous sodium sulfate, concentrated under reduced pressure. The crude was chromatographied on a silica gel column (eluent: hexane/ether) to give compounds **3**, **4**, and **5**.

*5-Bromomethylthio-2,7-dimethyl-2,3-dihydro-4H[1,2,4]triazepin-3-one **3***

Yield = 40%. m.p: 87–88 °C (EtOH). ^1H NMR (CCl_4): δppm: 1.93 (s, 3H, C_7—CH_3); 3.31 (s, 3H, N_2—CH_3); 5.0 (s, 1H, ═C_6—H); 5.23 (s, 2H, S—CH_2—Br), 6.5 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δppm: 22.7 (C_7—CH_3); 43.8 (N_2—CH_3); 52.2 (S—CH_2—Br), 102.2 (C_6), 157.7 (C_7), 167.8 (C═O), 188.0 (C_5). IR, νcm^{-1}: 1690 (C═O).

Mass spectrum m/z: 263 (M^+).

*6,8-Dimethyl-5-thioxo-2,3,4,5-tetrahydro-6H[1,3]thiazolo[4,5-d][1,2,4]triazepine **4***

Yield 80% (oil). ^1H NMR ($CDCl_3$): δppm: 1.98 (s, 3H, C_8—CH_3); 3.42 (s, 3H, N_6—CH_3); 4.56 (t, 2H, $J = 7.6$Hz, N_4—CH_2—), 3.10 (t, 2H, $J = 7.6$Hz, S—CH_2—); 5.52 (s, 1H, = C_9H). ^{13}C NMR ($CDCl_3$): δppm: 22.4 (C_8—CH_3), 29.1 (S—CH_2), 44.8 (N_6—CH_3), 55.7 (N_4—CH_2), 105.4 (C_9), 155.3 (C_8), 168.3 (C_{9a}), 188.7 (C_5 = S).

Mass spectrum: m/z: 213 (M^+, 100%), 198, 185, 180, 172.

*7,9-Dimethyl-6-thioxo-2,3,4,5,6,7-hexahydro[1,3]thiazino[5,6-d][1,2,4]triazepine **5***

Yield 85%; m.p.: 92–93 °C (EtOH). ^1H NMR (CCl4): δppm: 1.92 (s, 3H, C_9—CH_3), 2.23 (m, 2H, C_2—CH_2—C_4), 2.85 (m, 2H, SCH_2), 3.23 (N_7—CH_3), 3.92 (m, 2H, N_5—CH_2), 5.55 (═C_{10}H), 6.1 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δppm: 21.2 (C_8—CH_3), 23.8 (C_2—CH_2—C_4), 26.5 (S—CH_2), 43.5 (N_7—CH_3), 48.1 (N_5—CH_2), 114.5 (C_{10}), 156.6 (C_9), 166.4 (C_{10a}), 194.2 (C_6═S).

Mass spectrum: m/z: 227 (M^+, 100%), 212, 199, 194, 186, 185.

Computational techniques

Quantum chemical calculations were performed with the use of the Gaussian 03 set of programs.[30] All structures were fully optimized with the density functional theory (DFT) using Becke's three parameter hybrid method[31] and correlation functional of Lee–Yang–Parr (B3LYP)[32] in conjunction with the 6-31G* basis set.[33] The stationary points were characterized by harmonic vibrational frequency analysis in order to verify that minima and transition structures have zero and one imaginary frequency, respectively. The intrinsic reaction coordinate (IRC)[34] path was constructed in order to verify further its identity and also map out a minimum energy reaction pathway. The optimization was carried out using the Berny analytical gradient optimization method.[35,36] The Wiberg bond indices[29] have been computed by using the NBO analysis.[37,38] Solvent effects on the energies were considered by B3LYP/6-311+G* single-point calculations on the B3LYP/6-31G* gas-phase structures using a self-consistent reaction field (SCRF)[39–41] based on the polarizable continuum model (PCM) of the Tomasi's group.[42–44] Since these reactions are carried out in benzene, we have selected its dielectric constant at 298.0 K, $\varepsilon = 2.25$. This methodology is refereed as B3LYP(benzene)/6-311+G*//B3LYP/6-31G*.

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