Research Article

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Formation of pyrazol-1,3,4-thiadiazoles through 1,3-dipolar cycloadditions of 3-thioxo-[1,2,4]-triazepin-5-one with nitrilimines: an experimental and computational study†

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In this work the experimental results and the computational study of the title compounds and some ancillary compounds are reported. Two bicyclic pyrazol-1,3,4-thiadiazole derivatives were synthesized by reaction between 6-dimethylaminomethylene-3-thioxo-[1,2,4]-triazepin-5-one 1 and several nitrilimines 2a–f to give corresponding spirocycloadducts 3a–f, which undergo a rapid rearrangement leading to the new bicyclic compounds, 4a–f and 5a–f. These obtained bicyclic products were characterized by ^{1}H and ^{13}C NMR spectroscopy and finally by X-ray crystallography. Theoretical calculations have been carried out using DFT methods to rationalize the formation of the two new bicyclic compounds. Two reaction types are involved in the formation of the compounds 4a–f and 5a–f. The first one is a 1,3-dipolar cycloaddition (13DC) reaction between 1 acting as dipolarophile and 2a–f as dipoles. The results indicate that the cycloaddition between 1 and 2g, as model of 2a–c, takes place via a high asynchronous bond-formation process. The regioselectivity obtained from the calculations is in complete agreement with the formation of the unique spirocycloadducts 3a–f. The second reaction leading to the formation of the final products is a domino process that is initiated by the quick and irreversible cleavage in a catalytic acid environment of triazepenic ring. Copyright © 2008 John Wiley & Sons, Ltd.

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INTRODUCTION

Triazepine derivatives have attracted a great deal of attention because of their ability to act as anti-convulsant and anti-anxiety. Their oxo and thioxo derivatives have acquired both pharmaceutical and economical relevance.[1] Triazepines and diazepines have attracted a great attention as starting materiel in the synthesis of fused heterocyclic systems of potential pharmacological activities.[2–9] Different triazepine derivatives have exhibited significant biological activities.[10–13] The area of biological interest of this family of compounds have been extended to various diseases such as cancer,[7] viral infections (HIV)[8] and cardiovascular disorders.[9,10] It is known that the pharmacological activity appears to be enhanced when a further heterocyclic ring is linked to the heptatomic nucleus.[14,15] They are reported as excellent ligands with transition metals inducing a large application in organometallic chemistry.[16–18]

In the context of our current interest in the synthesis of novel heterocyclic compounds,[19–23] susceptible to have biological activity, we have now studied the 1,3-dipolar cycloaddition (13DC) reaction between 6-dimethylaminomethylene-3-thioxo-[1,2,4]-triazepin-5-one **1** and C,N-disubstituted nitrilimines **2a–f** (Scheme 1), which were generated *in situ* from the appropriate precursors and triethylamine. However, we have found that along the purification of reaction mixture by column chromatography, the corresponding spirocycloadducts **3a–f** were transformed into the bicyclic compounds **4a–f** and **5a–f**. Herein, we present the experimental results of the title reaction together with a

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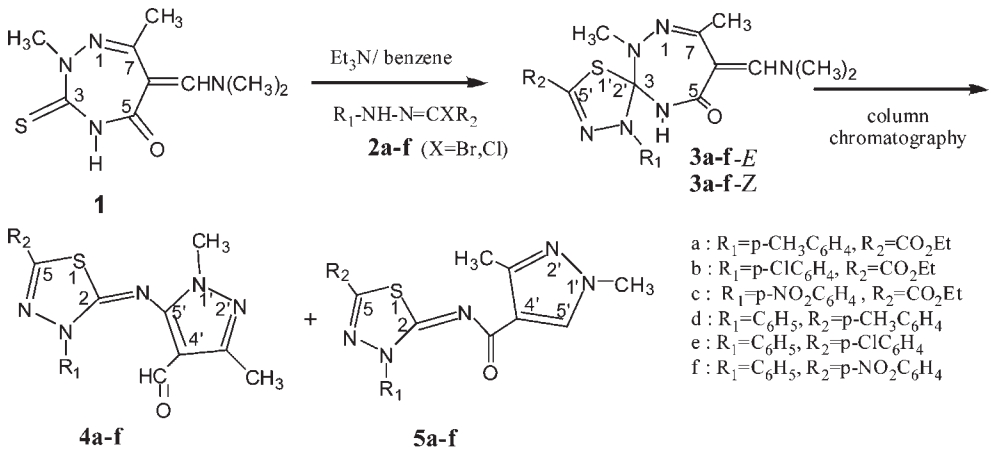
† *Dedicated to the memory of Tourya El Messaoudi 1975–2003.*



Scheme 1.

theoretical study providing an explanation for the formation of the two new bicyclic compounds. Firstly, we describe the synthesis of the novel triazepine **1** and the 13DC reaction with the nitrilimines **2a–f**. Then, a theoretical study of the molecular mechanism of the chemical reactions experimentally observed is performed.

RESULTS AND DISCUSSION

Experimental results

*Synthesis of 3-thioxo-[1,2,4]-triazepin-5-one **1***

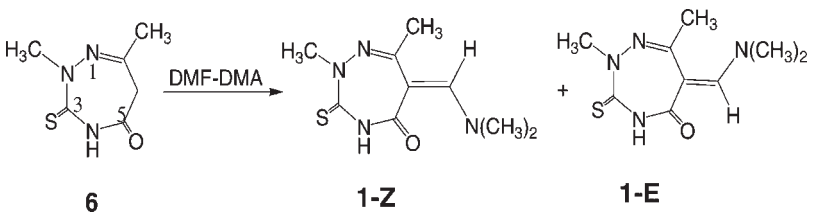
The 3-thioxo-[1,2,4]-triazepin-5-one **1** was obtained in good yield (70%) by stirring a mixture of [1,2,4]-triazepine **6** and dimethylformamide-dimethylacetal (DMF-DMA) during 1 h at 5 °C (as shown in Scheme 2).

NMR spectra of the obtained product showed the presence of a mixture of two stereoisomers **1**-Z and **1**-E. The percentage of these stereoisomers was deduced by ^{1}H NMR spectrum: 34 and 66% respectively. The structures of the two stereoisomers were assigned easily by NMR spectra and mass spectrum. In ^{1}H NMR spectrum, the presence of the exocyclic double bond C═C is pointed out by two singlets at 7.05 and 7.55 ppm attributables respectively to ethylenic proton —C═CH of structures **1**-Z and **1**-E. This attribution of these values is supported by a simulation of ^{1}H RMN chemical shifts related to ethylenic protons. The higher chemical shift of the ethylenic proton of **1**-E is due to the proton proximity to the carbonyl group. The ^{13}C NMR spectrum of these stereoisomers is characterized mainly by the absence of resonance signal of methylene group in position 6 and by the presence of signal of carbon C_6 at 96.5 ppm for **1**-Z and 96.1 ppm for **1**-E. The chemical shifts at 154.5 ppm for **1**-E and 154.1 ppm for **1**-Z attributed to the carbon of exocyclic double bond (—C═CH), permitted to confirm again the presence of this exocyclic double bond. The carbons of thioxo and oxo groups are also clearly identified in this spectrum (177.5 and 168.2 ppm for **1**-E and 177.2 and 164.9 ppm for **1**-Z, respectively).

*1,3-Dipolar cycloaddition of 3-thioxo-[1,2,4]-triazepin-5-one **1** with N-aryl-C-ethoxycarbonyl-nitrilimines and diarylnitrilimines **2a–f**.*

Nitrilimines **2a–f** were generated *in situ* by treating appropriate ethylhydrazono-α-bromoglyoxylate for **2a–c** and α-chloroarylidene phenylhydrazones for **2d–f** with triethylamine. After treatment of the 3-thioxo-[1,2,4]triazepin-5-one **1** with nitrilimines **2a–c** at room temperature over 72 h, the spirocycloadducts **3a–c** were isolated as a mixture of two stereoisomers **3**E and **3**Z in a ratio 7:3 (as shown in Scheme 1 and Table 2). In the case of the addition of nitrilimines **2d–f**, the cycloadducts **3d–f** were not obtained when the dichloromethane was used as solvent of extraction. However, when this solvent was replaced by benzene, the thin-layer chromatography and the NMR spectra of the reaction crude showed the presence of three compounds: **3d–f**, **4d–f** and **5d–f**. Note that, during the separation of the reaction mixture on column chromatography, the cycloaducts **3a–f** were transformed to the bicyclo compounds **4a–f** and **5a–f**. It is to note that this type of spirocycloaducts are described as unstable products (Table 1).[23,24]

Formation of the spirocycloadducts **3a–c** was detected by NMR and mass spectra of their crude reaction. The orientation in the structures **3a–c** and the active site of **1** were unequivocally determined on the basis of diagnostic ^{1}H and ^{13}C NMR data. This result was confirmed also by X-ray diffraction analysis of **4e** and **5d** compounds (Fig. 1). In the proton NMR spectrum of



Scheme 2.

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Table 1. Reaction of 3-thioxo-[1,2,4]-triazepin-5-one **1** with nitrilimines **2a–f**

2	R1	R2	3	(E/Z) percentage[a]	Yield (%)	Ratio (**4:5**)
2a	*p*-$CH_3C_6H_4$	CO_2Et	**3a**	68–32	67	55:45
2b	p-ClC_6H_4	CO_2Et	**3b**	67–33	70	54:46
2c	*p*-$NO_2C_6H_4$	CO_2Et	**3c**	72–28	66	53:47
2d	C_6H_5	*p*-$CH_3C_6H_4$	**3d**[b]	—	48	54:46
2e	C_6H_5	p-ClC_6H_4	**3e**[b]	—	48	56:44
2f	C_6H_5	*p*-$NO_2C_6H_4$	**3f**[b]	—	42	56:44

[a] Estimated from NMR spectra of the reaction mixture.
[b] **3d–f** were obtained as a mixture with **4d–f** and **5d–f** and the percentage were not estimated.

3-E and **3**-Z cycloadducts, the presence of the exocyclic double bond was justified clearly by two singlets at (7.72–7.75) ppm for **3**-E and (7.01–7.07) ppm for **3**-Z characteristics of olefinic protons. The observed shielding of methyl group linked to N_2 at (2.58–2.60) ppm for **3**-E and (2.50–2.58) ppm for **3**-Z (instead of 3.50 ppm initially) permits to confirm the preferential attack site (C═S) of the addition of **1**. On the other hand, in ^{13}C NMR spectrum of the two stereoisomers, the chemical shifts of the carbon atoms at (144.2–145.8) ppm and (118.2–118.9) ppm for **3**E and (144.5–146.0) ppm and (117.6–118.4) ppm for **3**Z assigned respectively to ═CH and C_6 exclude categorically the addition on the exocyclic double bond dipolarophile site. The reactive C═S site of the addition was confirmed again in this spectrum by the absence of thioxo group signal. The carbon chemical shifts at (97.2–98.5) ppm and (98.2–98.6) ppm assigned respectively to spiranic carbons of **3**-E and **3**-Z are consistent with these structures. The proposed regiochemistry of the addition is in good agreement with that observed for other related systems.[25] The nitrogen atom of the dipole is linked to the carbon atom of dipolarophile site C═S. No condensation products of the dipole on the other dipolarophile sites (C═C, C═N and C═O) has been observed. It is to note that while the extraction was made using a more polar solvent, as dichloromethane, the cycloadduct **3** was not isolated evolving directly the conversion to the compounds **4** and **5**.

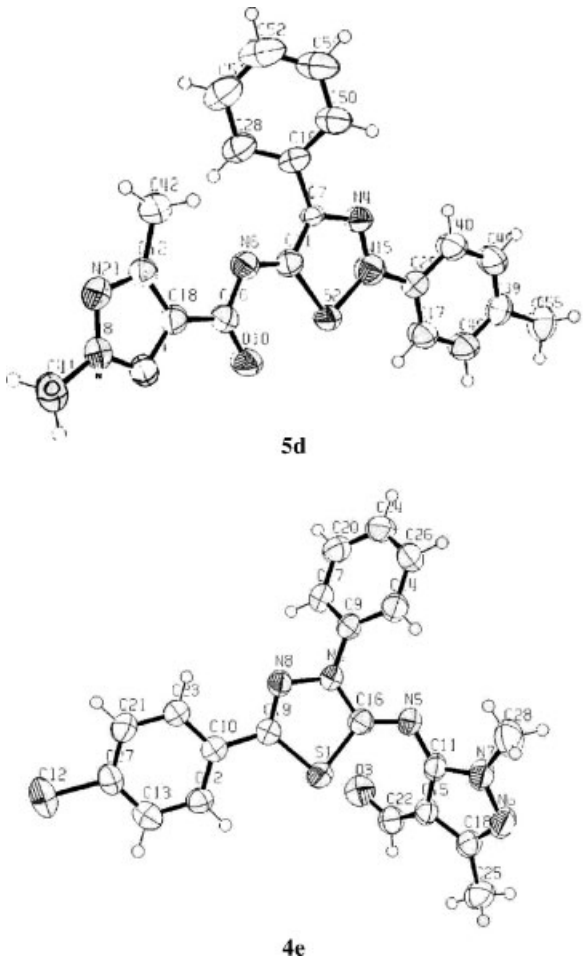


Figure 1. The molecular structure of compound **4e** and **5d** (ORTEP: XTAL 3.6) with the numbering scheme. Displacement ellipsoids are drawn at 30% probability

For the isolated 1,2-pyrazol-1,3,4-thiadiazole **4e** and **5d**, the X-ray diffraction and spectral data are in accordance with the proposed structures (Scheme 1). Thus, the examination of NMR spectra and mass spectrum shows that these products are formed by monocycloaddition of nitrilimine on the C═S double bond. Then the corresponding cycloadducts are transformed into **4a–f** and **5a–f** compounds. In ^1H NMR spectra of **4a–f** compounds, we noted in particular the chemical shift of aldehyde proton at about (9.74–9.83) ppm. The ═C—CH_3 and N—CH_3 protons resonate as singlet at (2.38–2.56) ppm and (3.50–3.84) ppm, respectively. Methyl and methylene of CO_2Et group show triplet and quartet at about (1.32–1.43) ppm and (4.37–4.49) ppm, respectively. In ^{13}C NMR spectra of **4a–f** the aldehyde carbonyl is confirmed again by the presence of the pick at (182.4–183.3) ppm. The signals of the carbon atoms C_5 (151.4–153.0) ppm, $C_{4'}$ (108.4–109.1) ppm, $C_{5'}$ (149.8–151.3) ppm and C_2 (160.5–162.0) ppm confirm also the proposed structures. For compounds **5a–f**, the presence of the olefinic protons is pointed out by a singlet at about (7.82–7.89) ppm. On the other hand, the ^{13}C NMR spectra reveal mainly the signal of carbon of carbonyl group at about (171.3–171.8) ppm and the signals at (118.3–119.1), (135.1–136.7), (147.9–151.8), (151.9–156.3) and (163.4–164.9) ppm, attributed respectively to carbons $C_{4'}$, $C_{5'}$, $C_{3'}$, C_5, C_2.

To sum up, the 13DC reactions of 3-thioxo-[1,2,4]-triazepin-5-one **1** with the nitrilimines **2a–f** are completely chemo and regioselective. In all cases the carbon atom of dipoles is linked to the sulfur atom of dipolarophile C═S site of **1**. No addition of dipoles were observed on the C═N and C═O double bonds,

and the exocyclic C═C double bond. However, along the purification of reaction mixture, the corresponding spirocycloadducts **3a–f** were quickly transformed into the bicycle compounds **4a–f** and **5a–f**.

X-ray crystallography analysis

The molecular structures of **4e** and **5d** ($C_{21}H_{18}N_5OS$, triclinic and $C_{21}H_{16}ClN_5OS$, monoclinic) determined X-ray crystallography in this work are shown in Fig. 1. The structures of **4d** and **5e** were obtained by slowly evaporating a benzene solution. Analysis of these X-ray structures allows to obtain some interesting features for the conversion of the spirocycloadducts **3a–f** in the compounds **4a–f** and **5a–f**: (i) the [1,2,4]triazepine ring is not present in these compounds, (ii) the five-membered ring formed along the 13DC reaction remains in these structures, (iii) the enamine substituent present in triazepine **1** is hydrolysed along these processes, (iv) two new five-membered heterocycle compounds are formed along the reaction and (v) these heterocycle compounds contain an α,β-unsaturated carbonyl group: one aldehyde on **4e** and one ketone on **5d**.

Theoretical study

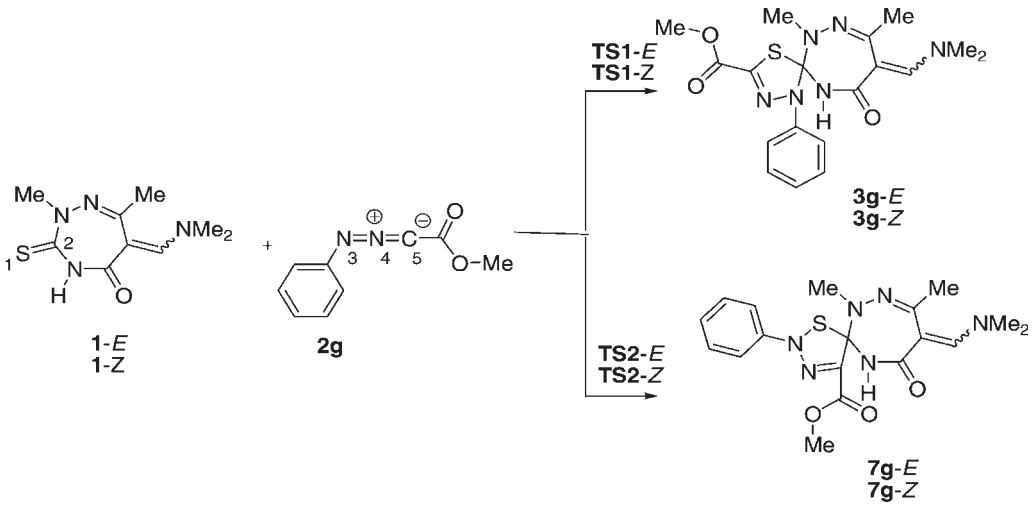
*Study of the 1,3-dipolar cycloaddition reaction between 3-thioxo-[1,2,4]-triazepin-5-one **1** and C-methoxycarbonyl-nitrilimine **2g***

Firstly, the 13DC reaction between 3-thioxo-[1,2,4]-triazepin-5-one **1** and the C-methoxycarbonyl-nitrilimine **2g**, as a model of the nitrilimines **2a–c**, was studied (as shown in Scheme 3). As it has been indicated in the experimental part, in spite of the presence of four dipolarophile sites in **1**, these reactions take place with a total chemoselectivity; only the C═S double bond participates as dipolarophile in these 13DC reactions.[23] According to the experimental result, we decided to perform the computational study of the addition of the nitrilimine **2g** to the C═S double bond of **1**. For this 13DC reaction, the two regioisomeric channels associated to the addition of **2g** to the unsymmetric C═S double bond of **1** were studied. In addition, the E/Z configurational dispositions of the exocyclic C═C double bond present on **1** were also considered. An analysis of the stationary points found along the four reaction paths points out that these 13DC reactions have one-step mechanism. Thus, four TSs, **TS1**-E, **TS1**-Z, **TS2**-E, **TS2**-Z, and four [3 + 2] spirocycloadducts **3g**-E, **3g**-Z, **7g**-E and **7g**-Z were located and characterized (as shown in Scheme 3). The B3LYP/6-31G* total and relative energies are collected in Table 2.

The activation energies associated to the formation of the spirocycloadducts **3g**-E and **3g**-Z, via **TS1**-E and **TS1**-*Z*, present very low values: 3.5 and 3.7 kcal/mol, respectively. The E/Z configuration of the exocyclic C═C double bond has not any appreciable incidence on the activation energies. These cycloadditions are strongly exothermic: −23.6 (**3g**-E) and −23.2 (**3g**-Z) kcal/mol. On the other hand, formation of the regiosiomeric cycloadducts **7g**-E and **7g**-Z present very large activation energies: 21.0 (**TS2**-E) and 21.7 **(TS2**-Z) kcal/mol. These energy results are in agreement with the complete regioselectivity experimentally observed. Formation of the regioisomeric cycloadducts are also less exothermic: −12.9 (**7g**-E) and −15.1(**7g**-Z) kcal/mol.

The geometries of the TSs involved in these 13DC reactions are depicted in Fig. 2. At the more favourable regioisomeric TSs, **TS1**-E and **TS1**-Z, the length of the S1—C5 forming bond is 2.408 and 2.407 Å, while the distance between the C2 and the N3 atoms is 3.288 and 3.321 Å, respectively. These values point out to very asynchronous bond-formation processes in which the S1—C5 bond-formation is anticipated to the C2—N3 one. At the more unfavourable regioisomeric TSs, **TS2**-E and **TS2**-Z, the length of the C2—C5 forming bond is 2.096 and 2.092 Å, while the length of the S1—N3 bond is 2.482 Å. These TSs are more advanced and more synchronous.

Analysis of the bond orders (BO) and the charge transfer (CT) at the TSs allows to establish the electronic nature of these 13DC reactions. At the more favourable regioisomeric TSs, **TS1**-E and **TS1**-Z, the BO values of the S1—C5 forming bond are 0.33 and 0.34, while the BO values between the C2 and the N3 atoms are 0.03. These BO values indicate that only the S1—C5 bond is being formed at these asynchronous TSs. On the other hand, at the more unfavourable regioisomeric TSs, **TS2**-E and **TS2**-Z, the BO values of the C2—C5 and S1—N3 forming bonds are 0.43 and



Scheme 3.

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Table 2. Total (E, au) and relative (ΔE, kcal/mol) energies, in gas-phase and benzene, and total (G, au) and relative (ΔG, kcal/mol) free energies in benzene for stationary points involved in the 13DC reactions of **1**-E and **1**-Z with **2g**

	Gas-phase		Benzene			
	E	ΔE	E	ΔE	G	ΔG
1-E	−1043.772302		−1043.781561		−1043.598519	
1-Z	−1043.772618		−1043.781063		−1043.597913	
2g	−607.634412		−607.638885		−607.528673	
TS1-E	−1651.401206	3.5	−1651.413185	4.6	−1651.100245	16.9
TS1-Z	−1651.401206	3.7	−1651.412283	4.8	−1651.100349	16.8
3g-E	−1651.444258	−23.6	−1651.454657	−21.5	−1651.134958	−4.9
3g-Z	−1651.443973	−23.2	−1651.453334	−20.9	−1651.130806	−2.3
TS2-E	−1651.373260	1.0	−1651.383731	23.0	−1651.068242	37.0
TS2-Z	−1651.372481	21.7	−1651.382129	23.7	−1651.066401	37.8
7g-E	−1651.427249	−12.9	−1651.435868	−9.7	−1651.118121	5.3
7g-Z	−1651.431159	−15.1	−1651.438630	−11.7	−1651.119144	4.7

0.30, respectively. These values point to concerted bond formation process where the C2—C5 bond formation is more advanced than the S1—N3 one.

The CT at these cycloadditions was analysed sharing the natural charges between the dipole and the dipolarophile fragments. At the more favourable regioisomeric TSs, the CT that fluxes from the 3-thioxo-[1,2,4]-triazepin-5-one **1** to the nitrilimine **2g** is 0.26 e at both E/Z TSs. This large value indicates that these TSs have some zwitterionic character. On the other hand, at the more unfavourable regioisomeric TSs the CT is negligible, 0.05 e, and it takes place in the opposite direction. This analysis indicates that the two regioisomeric cycloadditions are associated to unlike chemical processes. While the TSs associated to the most favourable regioisomeric channels can be associated to two-centre interactions between the most nucleophilic site of the 3-thioxo-[1,2,4]-triazepin-5-one **1,** the sulfur S1 atom, and the most electrophilic site of nitrilimine **2g**, the carbon C5 atom, the TSs associated to the more unfavourable regioisomeric channels can be related to four-centre interactions characteristic of concerted cycloaddition processes. The flux of the CT found at the more favourable TSs is in agreement with the large electrophilic character of the nitrilimine **2g**, $\omega = 1.75$ eV, than that of 3-thioxo-[1,2,4]-triazepin-5-one **1**-E, $\omega = 1.30$ eV.[26]

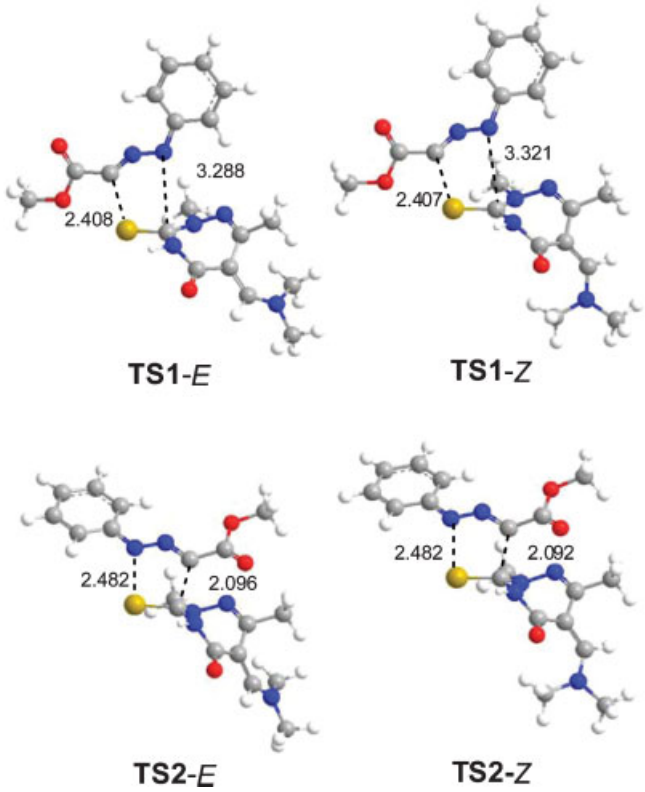


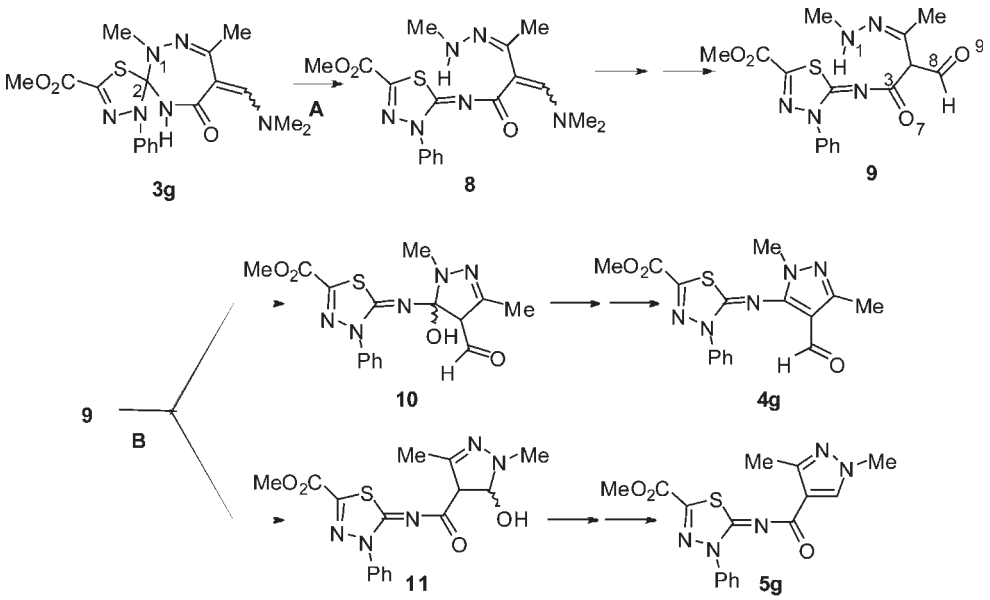
Figure 2. Transition structures for the 13DC reactions of 3-thioxo-[1,2,4]-triazepin-5-one **1**-E and **1**-Z with **2g**. The values of the bond lengths are given in Å

As these cycloadditions have some polar character, and solvent can modify the energies, effect of benzene was considered. In benzene, all species are stabilized between 3 and 8 kcal/mol. The more stabilized species are **TS1**-E and **TS1**-Z due to their polar character, 7.5 and 7.0 kcal/mol, respectively. However, the separated reagents become slightly more solvated. As a consequence, the activation energies increase to 1.1 kcal/mol. Solvent effects have not any incidence on the regioselectivity of the studied reaction.

Finally, the inclusion of the thermal corrections and entropies to the total energies in benzene raises the free energies between 12 and 19 kcal/mol due to the bimolecular nature of these cycloadditions (as shown in Table 2). The free activation energies associated to **TS1**-E and **TS1**-Z are 16.9 and 16.8 kcal/mol. The regioisomeric TSs remains *ca.* 20 kcal/mol above the more favourable TSs. Finally, formation of the spirocycloadducts **3g**-E and **3g**-Z are slightly exergonic, −4.9 and −2.3 kcal/mol, respectively.

*Study of conversion of spirocycloadducts **3a–f** into bicycloderivatives **4a–f** and **5a–f***

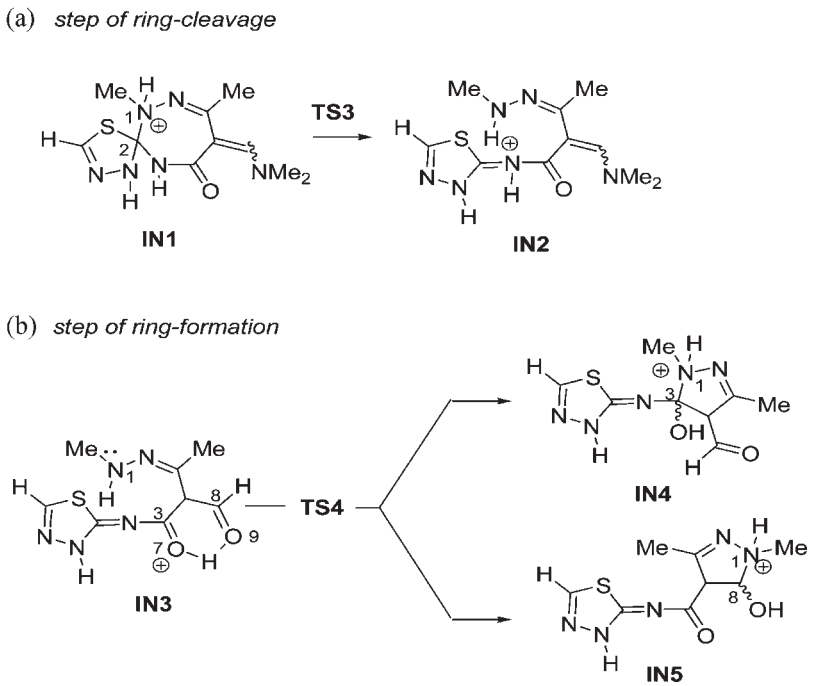
The spirocycloadducts **3a–f** are very unstable, and they are converted quickly into the two bicyclo compounds **4a–f** and **5a–f** (as shown in Scheme 1). Therefore, we have considered to study these conversions. Based on these observations obtained from the X-ray crystallography analysis of the compounds of **4e** and **5d**



Scheme 4.

(refer to Section 1.3) we have proposed a mechanism for the conversions that considers all structural changes (as shown in Scheme 4). In a first step, the triazepine ring is opened by a N1—C2 breaking bond process to give the intermediate **8**. Then, the enamine substituent present in **8** is hydrolysed to the corresponding aldehyde, yielding the dicarbonylic intermediate **9**. Note that the ring cleavage and the enamine hydrolysis are independent. However, due to the large instability of these spirocompounds in an acid medium (mentioned later) we assume that the ring cleavage takes place firstly. After the enamine hydrolysis, the two carbonyl groups on **9** can experiment an intramolecular condensation reaction with the terminal amine N1 atom. Formation of the new N—C bond via the intramolecular nucleophilic attack of the amine to each carbonyl group present on **9** allows the formation of the two new five-membered heterocycles. Finally, a water elimination process on the bicyclic intermediates **10** and **11** allows the formation of **4g** and **5g**.

Due to the complexity of this mechanism, we decided to study the two more significant elementary steps (as shown in A and B in Scheme 4). They include the ring cleavage of the triazepine ring, step A, and the ring closure of the dicarbonylic intermediate **9** with formation of the new bicyclic intermediates **10** and **11**, step B. Note that hydrolysis of enamines and condensation reactions



Scheme 5.

Table 3. Total (E, au) and relative (ΔE, kcal/mol) energies, in gas-phase and dichloromethane and total (G, au) and relative (ΔG, kcal/mol) free energies in dichloromethane, for the more relevant stationary points corresponding to the reaction model for transformation of spirocycloadduct **3g–4g** and **5g** products

	B3LYP/6-31G*		B3LYP/6-31 + G*		B3LYP/6-31G*			
	Gas-phase				Dichloromethane			
	E	ΔE	E	ΔE	E	ΔE	G	ΔG
IN1	−1192.905939		−1192.928240		−1192.977586		−1192.75108	
TS3	−1192.901739	2.6	−1192.924370	2.4	−1192.974637	1.9	−1192.74961	0.9
IN2	−1192.944099	−23.9	−1192.965038	−23.1	−1193.011543	−21.3	−1192.78486	−21.2
IN3	−1134.158984		−1134.180397		−1134.236299		−1134.07706	
TS4	−1134.157262	1.1	−1134.163718	10.5	−1134.234001	1.4	−1134.07179	3.3
IN4	−1134.161908	−1.8	−1134.183691	-2.1	−1134.238627	−1.5	−1134.07442	1.7
IN5	−1134.198415	−24.7	−1134.220647	−25.3	−1134.274285	−23.8	−1134.10736	−19.0

of carbonyl compounds with amines are common reactions in the chemistry of the carbonyl group. In addition, due to that the thiazole ring does not participate in the domino reaction, the methoxycarbonyl and phenyl groups present in the thiazole ring have been replaced by two hydrogen atoms in order to work with a more reduced model.

All steps of the proposed mechanism need an acid catalysis in order to facilitate the breaking- and forming-bond processes associated to each elementary process (as shown in Scheme 5). After the protonation of the N1 nitrogen atom of the triazepinone ring of the spirocycloadduct **3**, the activation energy associated to the N1—C2 breaking-bond of the intermediate **IN1** via **TS3**, is only of 2.6 kcal/mol. This ring cleavage process is very exothermic, −23.9 kcal/mol. These energy results indicate that in acid environment the spirocycloadducts **3a–f** are kinetically and thermodynamically very unstable, yielding irreversibly the open intermediates as **8** (as shown in Scheme 4). Note that the N1 nitrogen atom of these spirocycloadducts corresponds to the most basic centre of these molecules.

For the ring-closure step with formation of the five-membered heterocycles present in **4g** and **5g**, we found a unique **TS4** followed by a downhill intrinsic reaction coordinate (IRC) until the path bifurcates into two equivalent downhill pathways allowing the formation of the intermediate **IN4**, result of the nucleophilic attack of the amine N1 nitrogen atom to the ketone C3 carbon atom, and the intermediate **IN5**, result of the attack of this nitrogen atom to the aldehyde C7 carbon atom. **TS4** is located only 1.1 kcal/mol above the intermediate **IN3**. Formation of the intermediates **IN4** and **IN5** is exothermic in −1.8 and −24.7 kcal/mol, respectively. The low exothermic character of **IN4** can be related to the loss of the conjugation associated to the nucleophilic attack to the ketone group. Spite of the low exothermic character of formation of the intermediate **IN4**, the quick exchange of the N1 proton by an acid/base process can turn irreversible this step after water elimination. Full optimization of the stationary points associated to the paths A and B at the B3LYP/6-31 + G* does not produce appreciable changes (as shown in Table 3). Only the relative energy of **TS4** increases to 10.5 kcal/mol.

The geometries of **TS3** and **TS4** are given in Fig. 3. At **TS3**, the length of the N1—C2 breaking bond is 2.138 Å, while the BO value is 0.31. At **TS4**, the distance between the amine N1 nitrogen atom and the aldehyde carbonyl C7 carbon atom and the ketone carbonyl C3 carbon atom is 2.909 and 2.787 Å, respectively. These large distances point out the early character of this TS.

At the intermediate **IN3** the protonation takes place at the most basic ketone O7 oxygen atom, but the proton forms also a strong hydrogen bond with the aldehyde O9 oxygen atom, with a bond length of 1.615 Å. This behaviour remains also at **TS4**. The IRC from **TS4** to **IN4** shows that along the nucleophilic attack of the amine N1 nitrogen atom to the aldehyde C7 carbon atom, the proton moves from the ketone O7 oxygen atom to the aldehyde O9 oxygen atom, thus stabilizing the negative charge that develops at the aldehyde O9 oxygen atom along the nucleophilic attack to the C8 carbon atom. The same mechanism, related to the synthesis of pyrazoles reaction of hydrazines with β-dicarbonyl compounds, has been studied by Elguero and coworkers.[27–29]

Dichloromethane stabilizes all structures between 42 and 49 kcal/mol, as a consequence of the cationic character of these species. However, the inclusion of solvent effect does not modify

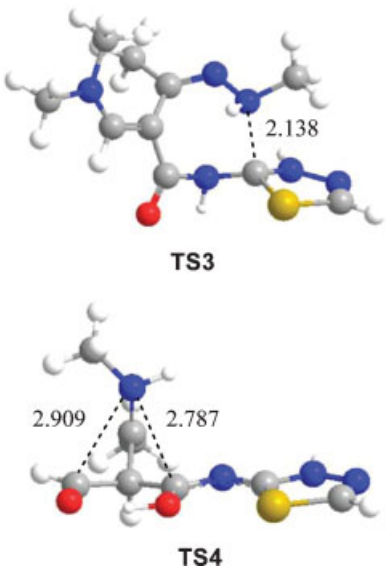


Figure 3. Transition structures involved in the reaction model for the transformation of spirocycloadduct **3g–4g** and **5g** products

the gas-phase relative energies. Finally, the inclusion of the thermal corrections and entropies to the total energies in dichloromethane causes minor changes on the relative free energies associated to this domino process due to the intramolecular nature of the two elementary steps. The activation free energies for the two elementary steps present very low values, 0.9 kcal/mol (**TS3**) and 3.3 kcal/mol (**TS4**) (as shown in Table 3). These values support the feasibility of these steps. On the other hand, formation of the intermediate **IN2** is a strongly exergonic process, −21.2 kcal/mol. Therefore, in an acid medium, the spirocycloadducts as **3g** are kinetically and thermodynamically very unstable in clear agreement with the experimental outcome.

In conclusion, both energy results and geometries associated to the A and B elementary steps studied in Scheme 5 support the mechanism proposed in Scheme 4 for the transformation of the spirocycloadduct **3g** into the bicyclo compounds **4g** and **5g**. Note that for the other non-studied elementary steps of Scheme 4, it is assumed that they take place easily.

CONCLUSION

New bicyclic pyrazol-1,3,4-thiadiazole derivatives **4a–f** and **5a–f** have been synthesized by reaction between the 3-thioxo-[1,2,4]-triazepin-5-one **1** and several nitrilimines **2a–f**. The studied reactions take place through two reaction types: a 13DC reaction between **1** and **2a–f**, and a domino reaction allowing the conversion of the corresponding spirocycloadducts **3a–f** into the final bicyclic compounds **4a–f** and **5a–f**, which were characterized by NMR and X-ray analyses. The mechanism of the two reaction types have been theoretically studied using DFT calculations at the B3LYP/6-31G* level. The spirocycloaduct **3g** is obtained through a 13DC reaction via a high asynchronous mechanism with a very low activation energy. The computational results support the total regioselectivity experimentally observed. For the conversion of the spirocycloadducts **3a–f** into the two biciclyc compounds **4a–f** and **5a–f**, a domino reaction that comprises the cleavage of the triazepin ring, hydrolysis of the enamine substituent, and two intramolecular condensation reactions to form the two new five-membered heterocycles has been proposed. The elementary steps responsible for the N2—C3 cleavage of the triazepin ring and the intramolecular nucleophilic addition reaction to the carbonyl groups to yield the thiazolo and diazolo rings have been studied. The energy results obtained for these elementary steps support the suitability of the proposed mechanism, allowing to explain formation of the two bicyclic pyrazol-1,3,4-thiadiazole derivatives.

COMPUTATIONAL METHODS

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)[32–35] in conjunction with the 6-31G* and 6-31 + G*[36] basis sets. 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. Starting from a transition structures, the IRC[37] pathway has also been constructed in order to verify further its identity and also map out a minimum energy reaction pathway. Net atomic charges of the stationary points were obtained by using the natural bond orbital (NBO) approach.[38,39] The solvent effects have been considered by B3LYP/6-31G* single point calculations over the gas phase optimized structures using a self-consistent reaction field[40] (SCRF) based on the PCM method of the Tomasi's group.[41–43] Since these reactions are carried out in benzene and dichloromethane, we have selected its dielectric constants at 298.0 K. The values of the free energies in benzene and dichloromethane were calculated with the standard statistical thermodynamics at 298.15 K and 1 atm.[36] Thermodynamic calculations were scaled by a factor of 0.96.

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 13C NMR spectra were measured on a Varian FT 80 (20.0 MHz). Mass spectra were recorded with a JEOL JMS DX 300. Column chromatography was carried out using E-Merck silica gel 60F254. Reagents and solvents were purified in the usual way. The data collections of X-ray structures were performed at 293 K on a Nonius κ-CCD single crystal diffractometer, using Mo Kαradiation ($\lambda = 0.7173$ Å). Crystal-detector distance was fixed at 35 mm, and a total of 220/325 images were collected using the oscillation method, with scan angle per frame 2° oscillation and 20 s. exposure time per image. Data collection strategy was calculated with the program Collect.[44] Data reduction and cell refinements were performed with the programs HKL Denzo and Scalepack.[45,46] The crystal structure was solved by direct methods, using the program SIR-97.[47] Anisotropic least-squares refinement was carried out with SHELXL-97.[48] All non hydrogen atoms were anisotropically refined. Some Hydrogen atoms were located in a difference Fourier maps and the remaining ones located geometrically. Geometrical calculations were made with PARST.[49,50] The crystallographic plots were made with mercury.[51]

Synthesis of [1,2,4]triazepine 1

A solution of 3-thioxo[1,2,4]triazepin-5-one **6** (5.8 mmol.) and DMF-DMA (20 ml) was stirred for 1 h at 5 °C. The precipitated solid was filtered off under reduced pressure and the crude solid subjected to silica-gel using 80/20% ethyl acetate/hexane mixture as eluent gave a 66:34 mixture of two isomers **1**-E and **1**-Z in good yield 65%.

(E)-6-(dimethylaminomethylene)-2,7-dimethyl-3-thioxo-3,4,5,6-tetrahydro-2H-[1,2,4] triazepin-5-one 1-E

Percentage: 66, 1H NMR ($CDCl_3$): δ ppm: 2.08 (s, 3H, C_7—CH_3), 3.07 (s, 6H, $N(CH_3)_2$), 3.57 (s, 3H, N_2—CH_3), 7.55 (s, 1H, H—C═), 7.84 (s, 1H, NH). 13C NMR ($CDCl_3$): δ ppm: (C_7—CH_3), 44.95 (N—$(CH_3)_2$), 45.3 (N_2—CH_3), 154.5 (H—C═), 96.1 (C_6), 164.2 (C_7), 168.2 (C_5), 177.4 (C_3), Mass spectrum (FAB) m/z: 475 $[M + H]^+$.

(Z)-6-(dimethylaminomethylene)-2,7-dimethyl-3-thioxo-3,4,5,6-tetrahydro-2H-[1,2,4] triazepin-5-one 1-Z

Percentage: 34, 1H NMR ($CDCl_3$): δ ppm: 2.18 (s, 3H, C_7—CH_3), 3.07 (s, 6H, $N(CH_3)_2$), 3.50(s, 3H, N_2—CH3), 7.05 (s, 1H, H—C═), 7.90 (s,

1H, NH). 13C NMR ($CDCl_3$): δ ppm: 22.0 (C_7—CH_3), 44.9 (N—$(CH_3)_2$), 44.7 (N_2—CH_3), 154.1 (H—C═), 96.5 (C_6), 163.6 (C_7), 164.9 (C_5), 177.2 (C_3), Mass spectrum (FAB) m/z: 475 $[M+H]^+$.

General procedure for preparation of products 3a–*c*, 4a–c and 5a–c

To a solution of 1,2,4-triazepine **1** (5 mmol) and ethylhydrazono-α-bromoglyoxylate (5.5 mmol) in dry benzene (30 ml), triethylamine (7.2 mmol) dissolved in dry benzene (10 ml) was added dropwise. After stirring for 72 h at room temperature, the solvent was then removed under vacuum and the mixture was diluted with water (25 ml) and extracted with dichloromethane (3 × 50 ml). The organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure and the yellow crystalline product thus obtained **3a–c** was further transformed to pure **4a–c** and **5a–c** compounds by chromatography on a silica gel column (eluent: hexane/ethylacetate, 75/25).

Ethyl (6E)-(2,7-dimethyl-5-oxo-6-((dimethylamino)methylene)-3,4,5,6-tetrahydro-2H-[1,2,4]triazepine-3-spiro-2′-(3′-(p-tolyl)-2′,3′-dihydro[1,3,4]thiadiazole-5′-carboxylate ***3a***

1H NMR ($CDCl_3$): δ ppm: 1.26–1.30 (m, 3H, $COOCH_2CH_3$), 2.04 (s, 3H, C_7—CH_3), 2.60 (s, 3H, N_2—CH_3), 3.10 (s, 6H, $N(CH_3)_2$), 4.22–4.33 (m, 2H, —CH_2—O), 7.75 (s, 1H, C_6═CH), 6.40 (s, 1H, NH), 6.92 (d, 2H, J = 9.31 Hz, H—Ar), 7.36 (d, 2H, J = 9.31 Hz, H—Ar). 13C NMR ($CDCl_3$): δ ppm: 14.4 ($COOCH_2\underline{CH_3}$), 14.7 (C_7—CH_3), 24.7 (N_2—CH_3), 40.7 ($N(CH_3)_2$), 62.8 (—CH_2—O), 98.5 ($C_{2'}$), 118.2 (C_6), 117.4, 129.7 (CHAr), 134.4, 135.6 (CAr), 144.9 (C_6═CH), 154.5 (C_7), 160.4 ($C_{5'}$), 165.6 (C═OC_2H_5), 169.2 (C_5).

Ethyl (6Z)-(2,7-dimethyl-5-oxo-6-((dimethylamino)methylene)-3,4,5,6-tetrahydro-2H [1,2,4]triazepine-3-spiro-2′-(3′-(p-tolyl)-2′,3′-dihydro[1,3,4]thiadiazole-5′-carboxylate ***3a***

1H NMR ($CDCl_3$): δ ppm: 1.26–1.30 (m, 3H, $COOCH_2\underline{CH_3}$), 1.99 (s, 3H, C_7—CH_3), 2.50 (s, 3H, N_2—CH_3), 3.10 (s, 6H, $N(CH_3)_2$), 4.22–4.33 (m, 2H, —CH_2—O), 7.02 (s, 1H, C_6═CH), 6.87 (s,1H, NH), 6.87 (d, 2H, J = 9.31 Hz, H—Ar), 7.30 (d, 2H, J = 9.31 Hz, H—Ar). 13C NMR ($CDCl_3$): δ ppm: 14.3 ($COOCH_2\underline{CH_3}$), 14.4 (C_7—CH_3), 21.4 (N_2—CH_3), 41.1 ($N(CH_3)_2$), 63.5 (—CH_2—O), 98.2 ($C_{2'}$), 117.6 (C_6); 117.2, 129.3 (CHAr); 134.5, 135.1 (CAr), 145.1 (C_6═CH), 155.3 (C_7), 162.0 ($C_{5'}$), 165.7 (C═OC_2H_5), 169.3 (C_5).

Ethyl (6E)-(2,7-dimethyl-5-oxo-6-((dimethylamino)methylene)-3,4,5,6-tetrahydro-2H [1,2,4]triazepine-3-spiro-2′-(3′-(p-chlorophenyl)-2′,3′- dihydro[1,3,4]thiadiazole-5′-carboxylate ***3b***

1H NMR ($CDCl_3$): δ ppm: 1.35–1.37 (m, 3H, $COOCH_2CH_3$), 2.07 (s, 3H, C_7—CH_3), 2.58 (s, 3H, N_2—CH_3), 3.14 (s, 6H, $N(CH_3)_2$), 4.28–4.37 (m, 2H, —CH_2—O), 7.72 (s, 1H, C_6═CH), 6.40 (s, 1H, NH), 7.10 (d, 2H, J = 9.31 Hz, H—Ar), 7.93 (d, 2H, J = 9.31Hz, H—Ar). 13C NMR ($CDCl_3$): δ ppm: 14.4 ($COOCH_2CH_3$), 14.6 (C_7—CH_3), 24.6, (N_2—CH_3), 40.3 ($N(CH_3)_2$), 62.8 (—CH_2—O), 97.2 ($C_{2'}$), 118.9 (C_6), 121.3, 125.5 (CHAr), 130.4, 136.6 (CAr), 144.2 (C_6═$\underline{C}$H), 152.8 (C_7), 159.3 ($C_{5'}$), 165.8 (C═OC_2H_5), 169.8 (C_5).

Ethyl (6Z)-(2,7-dimethyl-5-oxo-6-((dimethylamino)methylene)-3,4,5,6-tetrahydro-2H [1,2,4]triazepine-3-spiro-2′-(3′-(p-chlorophenyl)-2′,3′-dihydro[1,3,4]thiadiazole-5′-carboxylate ***3b***

1H NMR ($CDCl_3$): δ ppm: 1.35–1.37 (m, 3H, $COOCH_2CH_3$), 2.00 (s, 3H, C_7—CH_3), 2.56 (s, 3H, N_2—CH_3), 3.14 (s, 6H, $N(CH_3)_2$), 4.28–4.37 (m, 2H, —CH_2—O), 7.01 (s, 1H, C_6═CH), 6.73 (s, 1H, NH), 7.13 (d, 2H, J = 9.31 Hz, H—Ar), 7.87 (d, 2H, J = 9.31 Hz, H—Ar). 13C NMR ($CDCl_3$): δ ppm: 14.2 ($COOCH_2CH_3$), 14.3 (C_7—CH_3); 21.8, (N_2—CH_3), 40.8 ($N(CH_3)_2$), 63.6 (—CH_2—O), 98.3 ($C_{2'}$); 118.4 (C_6), 121.1, 125.0 (CHAr), 130.5, 137.2 (CAr), 144.5 (C_6═CH), 153.7 (C_7); 160.0 ($C_{5'}$), 165.6 (C═OC_2H_5), 169.9 (C_5).

Ethyl (6E)-(2,7-dimethyl-5-oxo-6-((dimethylamino)methylene)-3,4,5,6-tetrahydro-2H [1,2,4]triazepine-3-spiro-2′-(3′-(p-nitrophenyl)-2′,3′-dihydro[1,3,4]thiadiazole-5′-carboxylate ***3c***

1H NMR ($CDCl_3$): δ ppm: 1.36–1.39 (m, 3H, $COOCH_2CH_3$), 2.08 (s, 3H, C_7—CH_3), 2.60 (s, 3H, N_2—CH_3), 3.15 (s, 6H, $N(CH_3)_2$), 4.31–4.41 (m, 2H, —CH_2—O), 7.75 (s, 1H, C_6═CH), 6.45 (s, 1H, NH), 7.79 (d, 2H, J = 9.35 Hz, H—Ar), 8.11 (d, 2H, J = 9.35 Hz, H—Ar). 13C NMR ($CDCl_3$): δ ppm: 14.5 ($COOCH_2CH_3$), 14.6 (C_7—CH_3), 24.6, ($N_{2'}$—CH_3), 40.4 ($N(CH_3)_2$), 63.0 (—CH_2—O), 97.9 ($C_{2'}$), 118.6 (C_6), 118.3, 125.3 (CHAr), 138.4, 143.4 (CAr), 145.8 (C_6═CH), 153.9 (C_7), 160.1 ($C_{5'}$), 165.7 (C═OC_2H_5), 169.7 (C_5).

Ethyl (6Z)-(2,7-dimethyl-5-oxo-6-((dimethylamino)methylene)-3,4,5,6-tetrahydro-2H [1,2,4]triazepine-3-spiro-2′-(3′-(p-nitrophenyl)-2′,3′-dihydro[1,3,4]thiadiazole-5′-carboxylate ***3c***

1H NMR ($CDCl_3$): δ ppm: 1.36–1.39 (m, 3H, $COOCH_2CH_3$), 2.00 (s, 3H, C_7—CH_3), 2.58 (s, 3H, N_2—CH_3), 3.15 (s, 6H, $N(CH_3)_2$), 4.31–4.41 (m, 2H, —CH_2—O), 7.07 (s, 1H, C_6═CH), 6.76 (s,1H, NH), 7.81 (d, 2H, J = 9.33 Hz, H—Ar), 8.05 (d, 2H, J = 9.331 Hz, H—Ar). 13C NMR ($CDCl_3$): δ ppm: 14.3 ($COOCH_2CH_3$) 14.4 (C_7—CH_3), 21.3 (N_2—CH_3), 40.9 ($N(CH_3)_2$), 63.9 (—CH_2—O), 98.6 ($C_{2'}$), 118.1 (C_6), 118.2, 124.8 (CHAr), 138.5, 144.0 (CAr), 146.0 (C_6═CH), 154.7 (C_7), 161.8 ($C_{5'}$), 165.8 (C═OC_2H_5), 169.8 (C_5).

Ethyl (E)-2-(4′-formyl-1′,3′-dimethyl-1H-[1,2]pyrazol-5′-ylimino)-3-p-tolyl-2,3-dihydro [1,3,4]thiadiazole-5-carboxylate ***4a***

mp: 151–152 °C (EtOH). 1H NMR ($CDCl_3$): δ ppm: 1.32 (t, 3H, J = 7.19 Hz, —CH_2—$\underline{CH_3}$), 2.33 (s, 3H, Ar—CH_3), 2.38 (s, 3H, $C_{3'}$—CH_3), 3.50 (s, 3H, $N_{1'}$—CH_3), 4.37 (q, 2H, J = 7.19 Hz, —O—CH_2—), 7.21, 7.67 (2d, J = 9.25 Hz, 4H, HAr), 9.74 (s, 1H, CHO). 13C NMR ($CDCl_3$): δ ppm: 13.4 ($COOCH_2CH_3$), 14.5 ($C_{3'}$—CH_3), 21.5 (Ar—CH_3), 34.8 ($N_{1'}$—CH_3), 63.6 (O—CH_2), 108.8 ($C_{4'}$), 124.5, 129.9, 135.8, 138.9 (CAr), 141.5 ($C_{3'}$), 151.3, 151.4 ($C_{5'}$, C_5), 158.1 (CO_2Et), 162.0 (C_2), 183.0 (CHO). Mass spectrum (FAB): m/z 386 $[M+H]^+$ 100%.

Ethyl (E)-2-(1′,3′-dimethyl-1H-[1,2]pyrazol-4′-ylcarbonylimino)-3-p-tolyl-2,3-dihydro [1,3,4]thiadiazole-5-carboxylate ***5a***

mp: 183–184 °C (EtOH). 1H NMR ($CDCl_3$): δ ppm: 1.44 (t, 3H, J = 7.14 Hz, —CH_2—$\underline{CH_3}$), 2.45, 2.50 (2s, 6H, Ar—CH_3, $C_{3'}$—CH_3), 3.83 (s, 3H, $N_{1'}$—CH_3), 4.49 (q, 2H, J = 7.14 Hz, —O—CH_2—), 7.33, 7.75 (2d, J = 9.19 Hz, 4H, HAr), 7.84 (s, 1H, $C_{5'}$—$\underline{H}$). 13C NMR ($CDCl_3$): δ ppm: 14.3, 14.5 ($COOCH_2CH_3$ and $C_{3'}$—CH_3), 21.6 (Ar—CH_3), 39.3 ($N_{1'}$—CH_3), 63.5 (O—CH_2—), 118.9 ($C_{4'}$), 125.4, 129.8, 135.7, 139.2 (CAr), 136.7 ($C_{5'}$), 147.9, 151.9 ($C_{3'}$, C_5), 159.0, 164.9 (CO_2Et, C_2), 171.8 (CO). Mass spectrum (FAB): m/z 386 $[M+H]^+$ 100%.

Ethyl (E)-2-(4′-formyl-1′,3′-dimethyl-1H-[1,2]pyrazol-5′-ylimino)-3-p-chlorophenyl-2,3-dihydro[1,3,4]thiadiazole-5-carboxylate ***4b***

mp: 158–159 °C (EtOH). 1H NMR ($CDCl_3$): δ ppm: 1.42 (t, 3H, J = 7.18 Hz, —CH_2—CH_3), 2.48 (s, 3H, $C_{3'}$—CH_3), 3.60 (s, 3H, $N_{1'}$—CH_3), 4.45 (q, 2H, J = 7.18 Hz, —O—CH_2—), 7.49–7.87

(2d, $J = 9.24$ Hz, 4H, HAr), 9.80 (s, 1H, CHO). 13C NMR ($CDCl_3$): δ ppm: 13.3 ($COOC_2H_5$), 14.5 ($C_{3'}$—CH_3), 34.9 ($N_{1'}$—CH_3), 63.9 (O—CH_2), 109.1 ($C_{4'}$), 125.6, 126.5, 134.3, 136.8 (CAr), 142.3 ($C_{3'}$), 150.7, 151.4 ($C_{5'}$, C_5), 158.0 (CO_2Et), 161.7 (C_2), 183.2 (CHO). Mass spectrum (FAB): m/z 406 $[M + H]^+$ 100%.

Ethyl (E)-2-(1′,3′-dimethyl-1H-[1,2]pyrazol-4′-ylcarbonylimino)-4-p-chlorophenyl-2,3-dihydro[1,3,4]thiadiazole-5-carboxylate ***5b***

mp: 199–200 °C (EtOH). 1H NMR ($CDCl_3$): δ ppm: 1.47 (t, 3H, $J = 7.13$ Hz, —CH_2—CH_3), 2.54 (s, 3H, $C_{3'}$—CH_3), 3.88 (s, 3H, $N_{1'}$—CH_3), 4.52 (q, 2H, $J = 7.13$ Hz, —O—CH_2—), 7.55–7.90 (2d, $J = 9.18$ Hz, 4H, HAr), 7.86 (s, 1H, $C_{5'}$—H). 13C NMR ($CDCl_3$): δ ppm: 14.3, 14.6 ($COOCH_2CH_3$ and $C_{3'}$—CH_3), 39.4 ($N_{1'}$—CH_3), 63.7 (O—CH_2—), 118.7 ($C_{4'}$), 126.5, 129.4, 134.8, 137.6 (CAr), 135.7 ($C_{5'}$), 148.4, 151.9 ($C_{3'}$, C_5), 158.8, 164.8 (CO_2Et, C_2), 171.7 (CO). Mass spectrum (FAB): m/z 406 $[M + H]^+$ 100%.

Ethyl (E)-2-(4′-formyl-1′,3′-dimethyl-1H-[1,2]pyrazol-5′-ylimino)-3-p-nitrophenyl-2,3-dihydro[1,3,4]thiadiazole-5-carboxylate ***4c***

mp: 167–169 °C (EtOH). 1H NMR ($CDCl_3$): δ ppm: 1.43 (t, 3H, $J = 7.21$ Hz, —CH_2—CH_3), 2.48 (s, 3H, $C_{3'}$—CH_3), 3.61 (s, 3H, $N_{1'}$—CH_3), 4.49 (q, 2H, $J = 7.21$ Hz, —O—CH_2—), 8.28–8.36 (2m, 4H, HAr), 9.83 (s, 1H, CHO). 13C NMR ($CDCl_3$): δ ppm: 13.2 ($COOCH_2CH_3$), 14.5 ($C_{3'}$—CH_3), 35.0 ($N_{1'}$—CH_3), 64.1 (—O—CH_2), 109.3 ($C_{4'}$), 123.8, 124.9, 143.4, 146.6 (CAr), 143.6 ($C_{3'}$), 149.8, 151.9 ($C_{5'}$, C_5), 157.7 (CO_2Et), 161.3 (C_2), 183.3 (CHO). Mass spectrum (FAB): m/z 417 $[M + H]^+$ 100%.

Ethyl (E)-2-(1′,3′-dimethyl-1H-[1,2]pyrazole-4′-carbonylimino)-3-p-nitro-phenyl-2,3-dihydro[1,3,4]thiadiazole-5-carboxylate ***5c***

mp: 213–214 °C (EtOH). 1H NMR ($CDCl_3$): δ ppm: 1.47 (t, 3H, $J = 7.17$ Hz, —CH_2—CH_3), 2.54 (s, 3H, $C_{3'}$—CH_3), 3.88 (s, 3H, $N_{1'}$—CH_3), 4.53 (q, 2H, $J = 7.17$ Hz, —O—CH_2—), 8.36–8.44 (2m, 4H, HAr), 7.89 (s, 1H, $C_{5'}$—H). 13C NMR ($CDCl_3$): δ ppm: 14.3, 14.5 ($COOCH_2CH_3$) and $C_{3'}$—CH_3), 39.4 ($N_{1'}$—CH_3), 63.9 (O—CH_2—), 118.3 ($C_{4'}$), 124.8, 125.2, 143.9, 147.0 (CAr), 135.7 ($C_{5'}$), 149.3, 152.2 ($C_{3'}$, C_5), 158.6, 164.7 (CO_2Et, C_2), 171.5 (CO). Mass spectrum (FAB): m/z 417 $[M + H]^+$ 100%.

General procedure for preparation of products 3d–f, 4d–f and 5d–f

To a solution of 5 mmol of dimethylaminomethylene-3-thioxo-1,2,4-triazepin-5-one **1** and 5 mmol of α- chloroarylidenephenylhydrazone in 20 ml of dry benzene was added 1.6 ml of dry triethylamine dissolved in dry benzene. After stirring for 72 h at room temperature, the reaction mixture was extracted with benzene (3×50ml) and the organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure. The yellow crude solid thus obtained **3d–f** were further transformed to pure **4d–f** and **5d–f** compounds by chromatography on a silica gel column using ethyl acetate/hexane as eluent.

(E)-2-(4′-formyl-1′,3′-dimethyl-1H-[1,2]pyrazol-5′-ylimino)-5-p-tolyl-3-phenyl-2,3-dihydro[1,3,4]thiadiazole ***4d***

mp: 141–142 °C (EtOH). 1H NMR ($CDCl_3$): δ (ppm): 2.39 (1s, 3H, Ar—CH_3), 2.46 (s, 3H, $C_{3'}$—CH_3), 3.60 (s, 3H, $N_{1'}$—CH_3), 7.23–8.01 (m, 9H, HAr), 9.80 (s, 1H, CHO). 13C NMR ($CDCl_3$): δ (ppm): 13.5 ($C_{3'}$—CH_3), 21.5 (Ar—CH_3), 34.4 ($N_{1'}$—CH_3), 108.4 ($C_{4'}$), 123.4, 126.2, 127.4, 128.9, 129.8 (5 CH—Ar), 126.8, 138.8, 141.7 (3 CAr), 149.6, 150.7, 153.0 ($C_{3'}$, $C_{5'}$, C_5), 161.2 (C_2), 183.0 (CHO).

Mass spectrum, (m/z): 389 $[M]^+$ (100%), 208, 91.

(E)-2-(1′,3′-dimethyl-1H-[1,2]pyrazol-4′-ylcarbonylimino)-3-p-tolyl-5-phenyl-2,3-dihydro-[1,3,4]thiadiazole ***5d***

mp: 175–176 °C (EtOH). 1H NMR ($CDCl_3$): δ (ppm): 2.16 (1s, 3H, Ar—CH_3), 2.41 (s, 3H, $C_{3'}$—CH_3), 3.83 (s, 3H, $N_{1'}$—CH_3), 7.86 (s, 1H, $C_{5'}$—H), 7.26–8.00 (m, 9H, HAr). 13C NMR ($CDCl_3$): δ (ppm): 13.9 ($C_{3'}$—CH_3), 21.5 (Ar—CH_3), 38.9 ($N_{1'}$—CH_3), 118.9 ($C_{4'}$), 124.7, 126.5, 127.9, 128.7, 129.9 (5 CH—Ar), 127.2, 139.3, 141.6 (3 CAr), 135.1 ($C_{5'}$), 151.3, 156.3 ($C_{3'}$, C_5), 163.5 (C_2), 171.3 (CO).

Mass spectrum, (m/z): 389 $[M]^+$ 123(100%), 280, 208, 91.

(E)-2-(4′-formyl-1′,3′-dimethyl-1H-[1,2]pyrazol-5′-ylimino)-3-p-chlorophenyl-5-phenyl-2,3-dihydro[1,3,4]thiadiazole ***4e***

mp: 165–166 °C (EtOH). 1H NMR ($CDCl_3$): δ (ppm): 2.55 (1s, 3H, $C_{3'}$—CH_3), 3.60 (1s, 3H, $N_{1'}$—CH_3), 7.35–8.00 (m, 9H, HAr), 9.82 (s, 1H, CHO). RMN 13C NMR ($CDCl_3$): 13.8 ($C_{3'}$—CH_3), 34.8 ($N_{1'}$—CH_3), 108.9 ($C_{4'}$), 123.9, 127.9, 128.0, 129.4, 129.8 (5CH—Ar), 128.5, 137.7, 139.0 (3 CAr), 148.7, 151.3, 152.8, 161.2 ($C_{3'}$, $C_{5'}$, C_5, C_2), 183.3 (CHO).

Mass spectrum, (m/z): 409 $[M]^+$, 389, 91(100%).

(E)-2-(1′,3′-dimethyl-1H-[1,2]pyrazol-4′-ylcarbonylimino)-5-p-chlorophenyl-3-phenyl-2,3-dihydro[1,3,4]thiadiazole ***5e***

mp: 195–196 °C (ETOH). 1H NMR ($CDCl_3$): δ (ppm): 2.52 (s, 3H, $C_{3'}$—CH_3), 3.84 (s, 3H, $N_{1'}$—CH_3), 7.82 (s, 1H, $C_{5'}$—H), 7.26–7.99 (m, 9H, HAr). 13C NMR ($CDCl_3$): δ (ppm): 14.3 ($C_{3'}$—CH_3), 39.3 ($N_{1'}$—CH_3), 119.1 ($C_{4'}$), 125.0, 128.2, 128.5, 129.2, 129.9 (5 CH—Ar), 128.9, 137.7, 139.6 (3 CAr), 135.6 ($C_{5'}$), 151.8, 155.1 ($C_{3'}$, C_5), 163.7 (C_2), 171.7 (CO).

Mass spectrum, (m/z): 409 $[M]^+$, 300, 123(100%), 91.

(E)-2-(4′-formyl-1′,3′-dimethyl-1H-[1,2]pyrazol-5′-ylimino)-2,3-dihydro-5-p-nitro-phenyl-3-phenyl[1,3,4]thiadiazole ***4f***

mp: 144–146 °C (EtOH). 1H NMR ($CDCl_3$): δ (ppm): 2.48 (s, 3H, $C_{3'}$—CH_3), 3.61 (s, 3H, $N_{1'}$—CH_3), 7.26–8.33 (m, 9H, HAr), 9.83 (s, 1H, CHO). 13C NMR ($CDCl_3$): δ (ppm): 13.2 ($C_{3'}$—CH_3), 34.5 ($N_{1'}$—CH_3), 108.6 ($C_{4'}$) 123.7, 124.4, 127.0, 128.0, 129.1 (5 CH—Ar), 135.2, 138.3, 147.0 (3 CAr); 149.0 ($C_{3'}$), 151.1, 151.4 ($C_{5'}$, C_5), 160.5 (C_2), 182.4 (CHO).

Mass spectrum, (m/z): 420 $[M]^+$, 123(100%), 91.

(E)-2-(1′,3′-dimethyl-1H-[1,2]pyrazol-4′-ylcarbonylimino)-3-p-nitrophenyl-5-phenyl-2,3-dihydro[1,3,4]thiadiazole ***5f***

mp: 210–211 °C (EtOH). 1H NMR ($CDCl_3$): δ (ppm): 2.53 (s, 3H, $C_{3'}$—CH_3), 3.85 (s, 3H, $N_{1'}$—CH_3), 7.88 (s, 1H, $C_{5'}$—H), 7.26–8.38 (m, 9H, HAr). 13C NMR ($CDCl_3$): δ (ppm): 13.9 ($C_{3'}$—CH_3), 39.0 ($N_{1'}$—CH_3), 118.5 ($C_{4'}$), 124.5, 124.7, 127.3, 128.4, 128.9 (5 CH—Ar), 135.8, 139.0, 149.0 (3 CAr), 135.3 ($C_{5'}$), 151.5, 153.4 ($C_{3'}$, C_5), 163.4 (C_2), 171.4 (C═O).

Mass spectrum, (m/z): 420 $[M]^+$ (100%), 91.

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