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High chemoselectivity of C═S dipolarophile in 1,3-dipolar cycloaddition of nitrilimines and 1,2,4-triazepin-5-one derivatives: experimental, theoretical and X-ray study

Saida Azzouzi,[1] Malika El Messaoudi,[1]* M'hamed Esseffar,[1]* Rachid Jalal,[2] Félix H. Cano,[3] María del Carmen Apreda-Rojas[3] and Luis R. Domingo[4]

[1]Université Cadi Ayyad, Faculté des Sciences-Semlalia, Département de Chimie, BP 2390, Marrakech, Maroc
[2]Université Cadi Ayyad, Faculté des Sciences et Techniques, Département de Chimie, BP 549, Marrakech, Maroc
[3]Instituto de Química Física Rocasolano-CSIC Serrano, 119 E-28006 Madrid, Spain
[4]Instituto de Ciencia Molecular, Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, E-46100 Burjassot, Valencia, Spain

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ABSTRACT: Substituted 2,7-dimethyl-3-thioxo-3,4,5,6-tetrahydro-2*H*-[1,2,4]triazepin-5-one reacts as a dipolarophile with several *N*-aryl-*C*-ethoxycarbonylnitrilimines, in equimolar quantities, to give, in all cases, two types of products: diethyl 3-(*p*-aryl)-2-[*N*′-(*p*-aryl)-*N*″-(2′,7′-dimethyl-5′-oxo-5′,6′-dihydro-2*H*-[1,2,4]triazepin-3′-yl)-hydrazino]-2,3-dihydro[1,3,4]thiadiazole-2,5-dicarboxylate (**3a**–**3c** in 20–25% yield) and ethyl 4-(*p*-aryl)-5-imino-1,4-dihydro[1,3,4]thiadiazole carboxylate (**4a**–**4c** in 45–50% yield). When 1:2 stoichiometry was used, the formation of product **3** (50%) was favoured. The reaction is entirely chemo- and regioselective. The structures of the compounds obtained, where aryl stands for *p*-chloro-phenyl (**3b**) in the first type and for tolyl (**4a**) in the second type, were determined by X-ray crystallography and analysed by spectral methods (NMR and mass spectroscopy). The global and local electrophilicity/nucleophilicity have been analysed to rationalize the chemical reactivity of the reactants.

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KEYWORDS: 1,3-dipolar cycloadditions; chemoselectivity; nitrilimines; triazepines; electrophilicity/nucleophilicity

INTRODUCTION

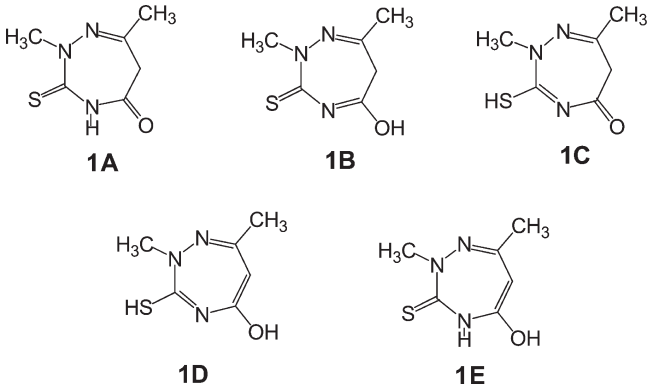
In view of their well-known anticonvulsant and anti-anxiety activity, many benzodiazepines and their oxo-derivatives have acquired both pharmaceutical and economical relevance.[1–4] Diazepines and triazepines have attracted particular attention as starting materials in the synthesis of fused heterocyclic systems susceptible to present pharmacological activities.[5–8] As in our previous studies using heterocyclic compounds as dipolarophiles in 1,3-dipolar cycloaddition reactions,[9–11] we consider in this work the condensation of several *N*-aryl-*C*-ethoxycarbonylnitrilimines on 1,2,4-triazepin-5-one **1** in order to access new triazepine derivatives of biological interest. This molecule holds great chemical interest because of the existence of different tautomeric forms that contain several dipolarophile sites (C═N, C═C, C═S and C═O) (Scheme 1). In another study,[7] we have shown that the condensation of a 1,2,4-triazepin-3,5-dithione on the same dipole occurred at the C═N dipolarophile site of tautomeric form **1B**. Curiously, in this study only the C═S dipolarophile site of tautomeric form **1A** was affected. It is worth noting that the reactivity of the C═S double bond is well documented by Huisgen *et al.*[13–17] where the thiones act as 'superdipolarophiles' in 1,3-dipolar cycloadditions, and by Sauer *et al.*[18] where the thiones act also as 'superdienophiles' in Diels–Alder reactions.

In what follows, we present the experimental results of the cycloaddition between 1,2,4-triazepin-5-one **1** and some substituted nitrilimines to elucidate the chemo- and regioselectivity of the reaction. Because 1,2,4-triazepine-5-one **1** presents several dipolarophile sites, a density functional theory-based reactivity index analysis has been used to explain why and how the C═S dipolarophile is the most reactive.

RESULTS AND DISCUSSION

The condensation of *N*-aryl-*C*-ethoxycarbonylnitrilimines, generated *in situ* from the appropriate precursors

**Correspondence to:* M. El Messaoudi and M. Esseffar, Université Cadi Ayyad, Faculté des Sciences-Semlalia, Département de Chimie, BP 2390, Marrakech, Maroc.
E-mail: elmessaoudi@ucam.ac.ma; essaffar@ucam.ac.ma



Scheme 1

ethylhydrazono-α-bromoglyoxalate and triethylamine,[19,20] with 1,2,4-triazepin-5-one **1** in dry benzene at room temperature, in equimolar quantities, leads, in all cases, to two types of products: diethyl 3-(*p*-aryl)-2-[*N*′-(*p*-aryl)-*N*′-(2′,7′-dimethyl-5′-oxo-5′,6′-dihydro-2*H*[1,2,4] triazepin-3′-yl)-hydrazino]-2,3-dihydro[1,3,4]thiadiazole-2,5-dicarboxylate **3a**–**3c** in 20–25% yield and ethyl 4-(*p*-aryl)-5-imino-1,4-dihydro [1,3,4]thiadiazole-2-carboxylate **4a**–**4c** in 45–50% yield (Scheme 2). When 1:2 stoichiometry was used in the case of **1** with *N*-*p*-chlorophenyl-*C*-ethoxycarbonylnitrilimine, the two products **3b** and **4b** are obtained in 49% and 37% yields, respectively. This shows that the 1:2 stoichiometry favours unambiguously the pathway leading to the main product **3b** resulting from the double condensation (Scheme 3).

It is worth mentioning that our numerous attempts to purify the other fragments **5a**–**5c** failed.

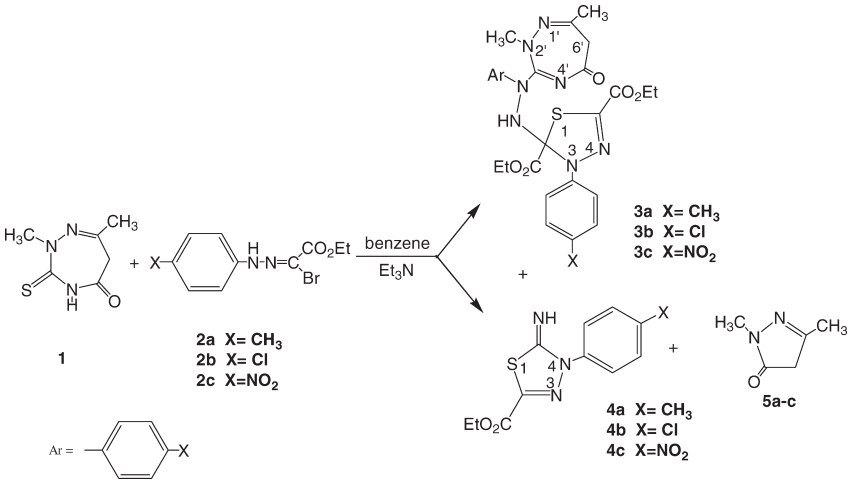
Spectral data (^{1}H NMR, ^{13}C NMR and mass spectroscopy) allowed the predominant orientation of the addition N_{dipole}—$C_{dipolarophile}$ (regioselectivity) and preferential C═S attack site of the triazepine **1** (chemoselectivity) to be determined. However, they do not permit precise characterization of the structures of compounds **3a**–**3c** and **4a**–**4c** of the cycloaddition reaction so we have determined these structures on the basis of X-ray crystallographic analysis of single crystals of **3b** and **4a** (Figs 1 and 2).

X-Ray crystallographic analysis

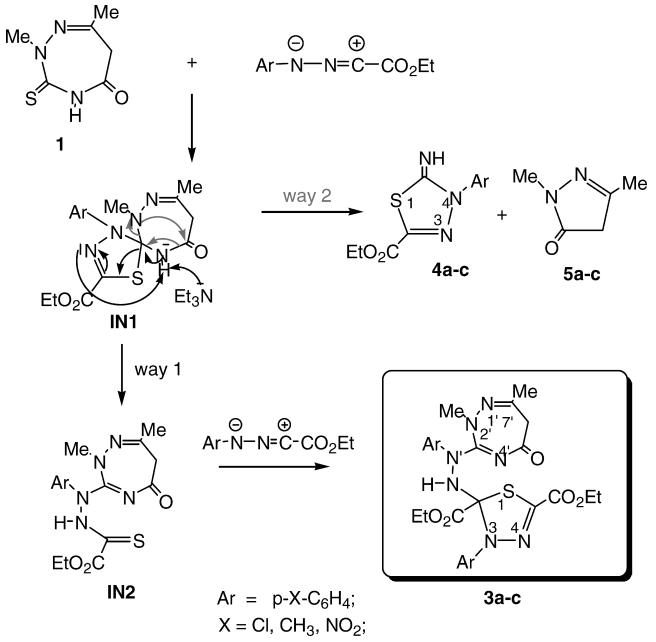
The molecular structures of **3b** ($C_{26}H_{27}Cl_2N_7O_5S$, triclinic; CCDC no. 206077) and **4a** ($C_{12}H_{13}ClN_3O_2S$, monoclinic; CCDC no. 206077) as determined in this work are shown in Figs 1 and 2. The most relevant parameters are given in Tables 1S and 2S in the supplementary material, available at the epoc website (http://www.wiley.com/epoc).

For **3b** there are two independent molecules in the unit cell. Owing to intermolecular N···H, O···H, S···H, CT···H (CT are the centroids of the six-membered rings) and π···H contacts, the molecules seem to arrange in columns through centres of symmetry and translations along the *a*-axis. Columns form sheets along the (011) direction through centres of symmetry and then pile up to form the crystal structured in a distorted hexagonal mode[21] of the mentioned columns. Intramolecular contacts contribute to the conformation of the molecule.

For **4a** the unit cell contains four molecules. Two molecules related by a centre of symmetry at (000), plus translations along the *a*-axis arranged in columns through intermolecular N···H and O···H contacts. These columns, which form sheets along the (011) direction, pile up to form hexagonal packing[21] supported mostly by hydrogen contacts through glide planes and screw axes. The intramolecular contacts S···H, N···H and O···H contribute to fix the planar conformation of the molecule. Bond distances and angles of the five-membered ring compare well with those in analogous compounds sought from the CSDS and are within the expected range (ref. codes: BIPTDZ, FOLHAP,



Scheme 2



Scheme 3

GOZLAI, SIPSOZ, SIPTEQ, SOJNEK, SUWCIW and VAHYAE).

NMR and mass spectrum analysis

The presence of a resonance signal at 3.50–3.65 ppm in ^{1}H NMR spectra of products **3a**–**3c**, attributed to the methylene group in position 6, rules out the addition of the dipole on C5═C6 of tautomeric forms **1D** and **1E**. The value of the chemical shift of the methyl group in position 7 ($\delta = 2.25$ ppm) discards also the condensation of the dipole on the dipolarophile site C7═N1 of triazepine **1**. On the other hand, the absence of the signal of the carbon of the thioxo group of **1** in ^{13}C NMR spectra justifies clearly the addition of the dipole to the dipolarophile site C3═S of triazepine **1**. The chemical shift of the carbon atom C2 at 99.6 ppm indicates the orientation of the addition N_{dipole}—$C_{dipolarophile}$ and rules out unambiguously the formation of the other possible regioisomer. In the opposite regioisomer, this carbon chemical shift should appear at a lower frequency of $\delta = 60.0$ ppm. It is noteworthy that the observed value (99.6 ppm) is in very good agreement with those described in the literature for a similar environment.[7,22] In the mass spectra (FAB), we noted essentially molecular peaks to $m/z = 580$ $[M+H]^+$, 620 $[M+H]^+$ and 642 $[M+H]^+$ for **3a**, **3b** and **3c**, respectively.

For compounds **4a**–**4c**, the chemical shifts in the case of ^{1}H and ^{13}C NMR are consistent with the proposed thiadiazolic structure. In the mass spectra all compounds gave the molecular ion.

From the X-ray structures and spectral data, the mechanism reported in Scheme 3 is proposed. The formation of the products can be explained by a monocondensation of the dipole with the C═S dipolarophile site of tautomeric form **1a** to give the cycloadduct intermediate **IN1**. This unstable cycloadduct evolves in two ways: by opening of the thiadiazole cycle leading to intermediate **IN2**, which by a second cycloaddition of the nitrilimine dipole on the C═S dipolarophile site of **IN2** gives triazepine

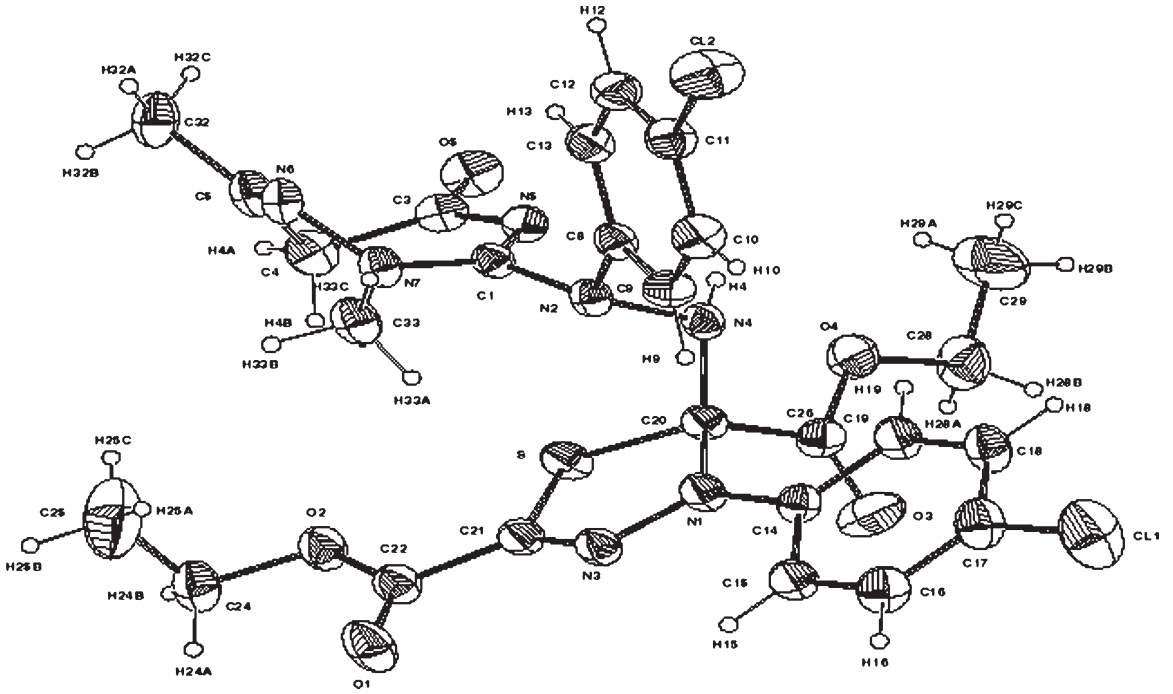


Figure 1. The molecular structure of compound **3b** (ORTEP: XTAL 3.6) with the numbering scheme. Displacement ellipsoids are drawn at 30% probability

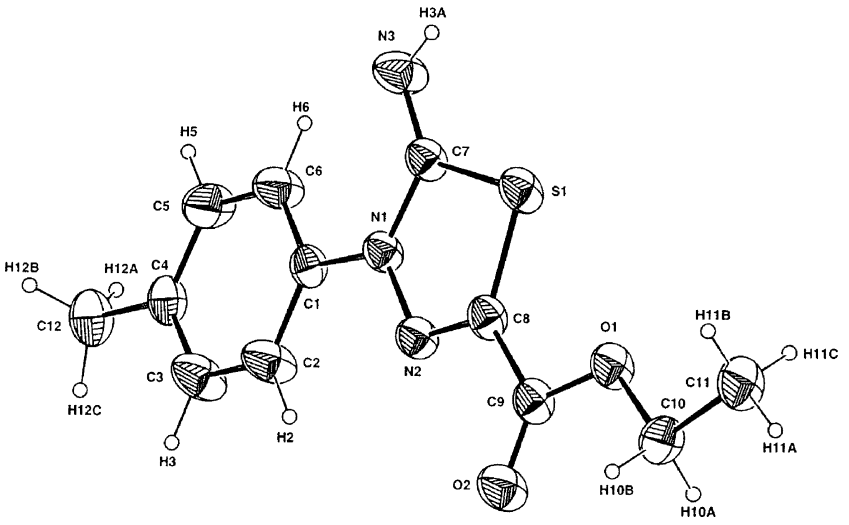


Figure 2. The molecular structure of compound **4a** (ORTEP: XTAL 3.6) with the numbering scheme. Displacement ellipsoids are drawn at 30% probability

3a–**3c** (see way 1 in Scheme 3); and by a nucleophilic attack of the nitrogen N2 lone pair on the carbon C3 of the triazepine, followed by opening of the triazepine cycle to form the thiazolic structure **4a**–**4c** (see way 2 in Scheme 3). It is noteworthy that the same chemoslectivity has been observed by one of us[23] in the case of the condensation of mesitonitrile oxide with triazepine **1**. Grubert *et al.*[24] also have found, from different kinds of potential reactive sites, that the C═S double bond is the most reactive of the pyrimidinethione using a nitrilimine as a dipole. This indicates the high reactivity of the C═S dipolarophile site.

Global and local electrophilicity analysis

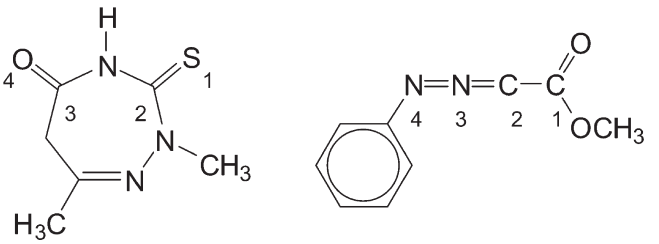
These 1,3-dipolar cycloadditions have been analysed using the global and local indexes defined in the context of density functional theory (DFT).[25] Recent studies devoted to 1,3-dipolar cycloadditions[26] have shown that these indexes[27] are powerful tools to acquire mechanism details of these reactions. In Table 1 the static global properties of 1,2,4-triazepin-5-one **1** and of phenyl substituted nitrilimines **2a**–**2d** are displayed. The electronic chemical potential[25] of 1,2,4-triazepin-5-one **1** ($\mu = -0.1319$ au) is higher than those of the phenyl-substituted nitrilimines **2a**–**2d** (in the range -0.1327 to -0.1657 au), therefore it is expected that in a polar process the charge transfer will take place from **1** to the nitrilimines **2a**–**2d**.

Table 1. Electronic chemical potential (μ, in au), chemical hardness (η, in au) and global electrophilicity (ω, in eV) of the 1,2,4-triazepin-5-one **1** and the phenyl nitrilimines **2a**, **2b**, **2c** and **2d**

	μ	η	ω
2c (NO_2)	−0.1657	0.1376	2.72
2b (Cl)	−0.1425	0.1436	1.92
2d (H)	−0.1369	0.1467	1.74
2a (CH_3)	−0.1327	0.1432	1.67
1	−0.1319	0.1746	1.36

1,2,4-Triazepin-5-one **1** has an electrophilicity[28] value of $\omega = 1.36$ eV. According to the absolute scale of electrophilicity based on ω indices, this compound may be classified as a moderate electrophile.[26a] The phenyl nitrilimines **2a**–**2d** have electrophilicity values in the range 1.67–2.72 eV. According to this scale they may be classified as strong electrophiles. The electrophilicity of these nitrilimines increases with the electron-withdrawing character of the substituent present at the phenyl ring. Thus, nitrilimine **2c** with the strong electron-withdrawing NO_2 group has the largest electrophilicity value of this series (see Table 1). The large $\Delta\omega$ value of 1.36 eV for the reaction with nitrilimine **2c**[26a,29] indicates that this cycloaddition will have a large polar character. Thus, in this cycloaddition, although nitrilinime **2c** will act as a good electrophile, 1,2,4-triazepin-5-one **1** will act as a nucleophile.

Analysis of the reactants with Fukui functions[30] allows the regioselectivity of the polar processes to be explained.[26c] The values of the Fukui functions for 1,2,4-triazepin-5-one **1** and phenylnitrilimine **2d** (Scheme 4) are summarized in Table 2. 1,2,4-Triazepin-5-one **1** has



Scheme 4

Table 2. Values of the nucleophilic (f_k^-) and electrophilic (f_k^+) Fukui functions for 1,2,4-triazepin-5-one **1** and nitrilimine **2d**

1,2,4-Triazepin-5-one **1**					
MO		S1	C2	C3	O4
45	f_k^-	0.85	0.06	0.00	0.00
Nitrilimine **2d**					
MO		C1	C2	N3	N4
51	f_k^+	0.21	0.10	0.17	0.12
52	f_k^+	0.07	0.48	0.27	0.07

the largest value of the nucleophilic Fukui function at the S1 sulphur atom, $f_k^- = 0.85$, and consequently this is the most nucleophilic site of **1**. Note that the O4 oxygen atom presents a negligible value of $f_k^- = 0.00$. The large resolution of the nucleophilic Fukui function at the sulphur atom also allows to explain the total experimentally observed chemoselectivity to be explaired.

The asymmetric phenyl nitrilimine **2d** has the largest nucleophilic activation at the carbonyl C1 carbon atom ($f_k^+ = 0.21$). Note that this carbon is not involved in the [3 + 2] cycloaddition. An analysis of the electrophilic Fukui function, f_k^+, at the molecular orbital LUMO + 1 of nitrilimine **2d** reveals that the C2 carbon atom presents the largest f_k^+ value of the dipole framework ($f_k^+ = 0.48$; see Table 2). Therefore, this carbon will be the preferred position of the N—N—C framework for nucleophilic attack in a polar cycloaddition. Analysis of the reactivity indexes indicates that these cycloadditions will take place with a large chemo- and regioselectivity via an asynchronous transition state where S—C bond formation will be more advanced than C—N bond formation. This analysis is in agreement with the chemo- and regioselectivity proposed for the 1,3-dipolar cycloaddition in Scheme 3.

CONCLUSION

In summary, in the present study we have studied the synthesis of novel triazepine derivatives to improve the library of therapeutic compounds. The selectivity of the 1,3-dipolar cycloaddition reaction of nitrilimines and 1,2,4-triazepine **1** has been analysed using NMR, mass spectroscopy, X-ray and DFT-based reactivity indexes. We have identified successfully the various products of the considered reaction and shown that the reaction is fully regio- and chemoselective. In all the cases studied here, the sulphur heteroatom of the dipolarophile interacts with the carbon atom of the dipole. Only the C=S dipolarophile site of triazepine **1** reacts with these nitrilimines. No dipole addition to the other double bonds (C=N, C=C or C=O) was observed. The results of global and local electrophilicity analysis are in good agreement with experimental predictions. It is of interest to note that evaluation of the biological activity of all the synthesized products on the central nervous system and on the HIV virus is intended.

COMPUTATIONAL METHODS

The global electrophilicity[28] ω is given by the expression $\omega = (\mu^2/2\eta)$ in terms of the electronic chemical potential μ and the chemical hardness η.[25] Both quantities may be approached in terms of the one-electron energies of the HOMO and LUMO molecular orbitals, ε_H and ε_L, as $\mu \sim (\varepsilon_H + \varepsilon_L)/2$ and $\eta \sim (\varepsilon_L + \varepsilon_H)$, respectively.[25] The HOMO and LUMO energies have been calculated at the ground state of the molecules al the B3LYP/6–31G* level.[31]

Electrophilic and nucleophilic Fukui functions[30] condensed to atoms have been evaluated from single-point calculations performed at the ground state of molecules at the same level of theory using a method described elsewhere.[32] This method evaluates Fukui functions using the coefficients of the frontier molecular orbitals involved in the reaction and the overlap matrix.

EXPERIMENTAL

Uncorrected melting points were taken on a Buchi 510 apparatus. The ^{1}H NMR spectra were recorded with a Bruker WP 400 CW, with Me_4Si as internal standard and $CDCl_3$ as solvent. The ^{13}C NMR spectra were measured on a Varian FT 80 (100 MHz). Mass spectra were recorded with a Jeol JMS DX 300. Column chromatography was carried out using E-Merck silica gel 60F 254. Reagents and solvents were purified in the usual way. The X-ray structures were solved by direct methods using the SHELX-97 and program refined by least-squares analysis using the SHELXL program.[33] Scattering factors, dispersion corrections and absorption coefficients were taken from International Tables for Crystallography.[34]

Crystal data for compound 3b

Triclinic, space group *P*-1, $T = 293(2)$ K, $a = 10.116(1)$, $b = 10.473(4)$ and $c = 14.676(3)$ Å, $\alpha = 105.04(3)°$, $\beta = 95.60(2)°$, $\gamma = 100.08(2)°$, $V = 1461.6(6)$ Å^3, $Z = 2$; observed reflections, 4525 with $I > 2\sigma(I)$, $R = 0.050$, $Rw = 0.141$.

Crystal Data for compound 4a

Monoclinic, space group $P2_1/c$, $T = 293(2)$ K, $a = 10.871(1)$, $b = 10.375(2)$ and $c = 11.218(2)$ Å, $\beta = 95.66(1)°$, $V = 1259.1(4)$ Å^3, $Z = 4$; observed reflections, 1900 with $I > 2\sigma(I)$, $R = 0.053$, $Rw = 0.143$.

General procedure of 1,3-dipolar cycloaddition reaction

Triethylamine (7.2 mmol) dissolved in dry benzene (10 ml) was added dropwise to a solution of 1,2,4-triazepin-5-one **1** (5 mmol) and ethylhydrazono-α-

bromoglyoxylate **2** (5.5 mmol) dissolved in dry benzene (20 ml). After stirring for 3 days at room temperature, the reaction mixture was washed several times with water (25 ml) and the organic layers were dried over anhydrous sodium sulphate, concentrated under reduced pressure and purified by chromatography on a silica gel column (hexane/ethyl acetate). The isolated product **3** was recrystallized in ethanol.

Diethyl 3-(*p*-tolyl)-2-[*N*′-(*p*-tolyl)-*N*′-(2′,7′-dimethyl-5′-oxo-5′,6′-dihydro-2*H*-[1,2,4] triazepin-3′-yl)-hydrazino]-2,3-dihydro[1,3,4]thiadiazole-2,5-dicarboxylate (3a). Yield: 580 mg (1 mmol, 20%), m.p. 146–147 °C (ethanol). ^{1}H NMR (400 MHz), δ(ppm): 0.95 (t, $J = 7.08$ Hz, 3H, OCH_2CH_3), 1.30 (t, $J = 7.10$, 3H, OCH_2CH_3), 2.10, 2.15 (2s, 6H, $2ArCH_3$), 2.25 (s, 3H, $=C7'—CH_3$), 2.80 (s, 3H, $N2'—CH_3$), 3.45 (m, 2H, $—C_6'H_2—$), 3.95–4.30 (2m, 4H, 2 OCH_2CH_3), 6.65–7.25 (m, 9H, 8HAr, NH). ^{13}C NMR (100 MHz), δ(ppm): 14.0, 14.7 (2 OCH_2CH_3), 21.2, 21.3 ($2ArCH_3$), 23.2 ($C7'—CH_3$), 42.3 ($N2'—CH_3$), 49.2 (C6′), 62.8, 64.0 (2 OCH_2CH_3), 100.4 (C2), 117.9, 124.6, 129.9, 130.6 (8CHAr), 131.2, 133.9, 136.9, 139.7, 143.0 (C7′, 4CAr), 157.4, 160.5 (C5, C3′), 163.1, 165.6, 166.5 (C5′, $2CO_2Et$). Mass spectrum (FAB) *m*/*z*: 580 ($[M+H]^+$, 2.5%), 321(100).

Diethyl 3-(*p*-chlorophenyl)-2-[*N*′-(*p*-chlorophenyl)-*N*′-(2′,7′-dimethyl-5′-oxo-5′,6′-dihydro-2*H*-[1,2,4] triazepin-3′-yl)-hydrazino]-2,3-dihydro[1,3,4]thiadiazole-2,5-dicarboxylate (3b). Yield: 770 mg (1.24 mmol, 25%); m.p. 151–152 °C (ethanol). ^{1}H NMR (400 MHz), δ(ppm): 1.00 (t, $J = 7.07$ Hz, 3H, OCH_2CH_3), 1.30 (t, $J = 7.10$ Hz, 3H, $OCH_2\ CH_3$), 2.15 (s, 3H, $=C7'—CH_3$), 2.90 (s, 3H, $N2'—CH_3$), 3.45–3.60 (AB, $J = 9.98$ Hz, 2H, $—CH_2—$), 4.05–4.30 (2m, 4H, $2O—CH_2—CH_3$), 6.65–7.30 (m, 9H, 8HAr, NH). ^{13}C NMR (100 MHz), δ(ppm): 14.0, 14.7 ($2O—CH_2CH_3$), 23.4 ($C7'—CH_3$), 42.2 ($N2'—CH_3$); 49.2 (C6′), 63.2, 64.4 (2 OCH_2CH3), 100.1 (C2); 118.7, 125.9, 129.5, 130.2 (8 *C*HAr), 131.3 132.8, 133.0, 140.6, 144.0 (C7′, 4CAr) 156.7, 160.1 (C5, C3′), 163.2, 165.2, 166.2 (C5′, $2CO_2Et$). Mass spectrum (FAB) *m*/*z*: 620 ($[M+H]^+$, 2.8%), 341(100).

In order to check the 1:2 stoichiometry we have used 5 mmol of 1,2,4-triazepin-5-one **1** with 11 mmol of the precursor *N*-*p*-chlorophenyl-*C*-ethoxycarbonylnitrilimine **2b**, under the experimental conditions described above; the reaction yields 1.53 g (2.47 mmol, 49%).

Diethyl 3-(*p*-nitrophenyl)-2-[*N*′-(*p*-nitrophenyl)-*N*′-(2′,7′-dimethyl-5′-oxo-5′,6′-dihydro −2*H*-[1,2,4] triazepin-3′-yl)-hydrazino]-2,3-dihydro[1, 3, 4]thiadiazole-2,5-dicarboxylate (3c). Yield: 639 mg (0.997 mmol, 20%), m.p. 142–143 °C (ethanol). ^{1}H NMR (400 MHz), δ(ppm): 1.05 (t, $J = 7.12$ Hz, 3H, OCH_2CH_3), 1.35 (t, $J = 7.40$ Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, $=C7'—CH_3$), 2.95 (s, 3H, $N2'—CH_3$), 3.50–3.65 (AB, $J = 10.13$ Hz, 2H, $—C6'H_2—$), 4.20–4.45 (2m, 4H, $2OCH_2CH_3$), 6.80–8.20 (m, 9H, 8HAr, N′H). ^{13}C NMR (100 MHz), δ(ppm): 14.1, 14.6 (2 $O—CH_2—CH_3$), 23.2 ($C7'—CH_3$), 42.2 ($N2'—CH_3$), 49.4 (C6′), 63.7, 65.1 (2 $O—CH_2—$), 99.6 (C2), 116.5, 123.3, 125.7, 125.8 (8 *C*HAr), 135.9 (C7″), 143.7, 145.8, 146.8, 151.1, 155.5, 159 (4CAr, C5, C3′), 163.5, 164.7, 165.7 (C5′, $2CO_2Et$). Mass spectrum (FAB) *m*/*z*: 642 ($[M+H]^+$, 1.5%), 352(100).

Ethyl 4-(*p*-tolyl)-5-imino-1,4-dihydro[1,3,4]thiadiazole carboxylate (4a). Yield: 657 mg (2.50 mmol, 50%), m.p. 132–133 °C (ethanol). ^{1}H NMR (400 MHz), δ(ppm): 1.25 (t, $J = 7.10$ Hz, 3H, OCH_2CH_3), 2.3 (s, 3H, $Ar—CH_3$), 4.25 (q, $J = 7.10$ Hz, 2H, $O—CH_2$), 7.05–7.40 (m, 5H, 4HAr, NH). ^{13}C NMR (100 MHz), δ(ppm): 14.6 (OCH_2CH_3), 21.5 ($Ar—CH_3$), 63.3 ($OCH_2—$), 124.6, 130.1 (4*C*HAr), 135.7, 138.2 (2CAr), 138.5, 158.6 (C2, C5), 162.6 (C═O). Mass spectrum (FAB) *m*/*z*: 264 ($[M+H]^+$, 100%).

Ethyl 4-(*p*-chlorophenyl)-5-imino-1,4-dihydro[1,3,4] thiadiazole carboxylate (4b). Yield: 710 mg (2.51 mmol, 50%), m.p. 140–141 °C (ethanol). ^{1}H NMR (400 MHz), δ(ppm): 1.30 (t, $J = 7.17$ Hz, 3H, OCH_2CH_3), 4.35 (q, $J = 7.17$ Hz, 2H, $O—CH_2—$), 7.25–7.70 (m, 5H, 4HAr, NH). ^{13}C NMR (100 MHz), δ(ppm): 14.6 ($O—CH_2—CH_3$), 63.5 ($O—CH_2—$), 125.0, 129.5 (4CHAr), 133.2, 137.1 (2CAr), 139.1, 158.6 (C2, C5), 161.8 (C═O). Mass spectrum (FAB) *m*/*z*: 284 ($[M+H]^+$, 100%); 154 (53).

As with product **3b**, the 1:2 stoichiometry yielded 526 mg (1.85 mmol, 37%).

Ethyl 4-(*p*-nitrophenyl)-5-imino-1,4-dihydro[1,3,4] thiadiazole carboxylate (4c). Yield: 660 mg (2.24 mmol, 45%), m.p. 155–156 °C (ethanol). ^{1}H NMR (400 MHz), δ(ppm): 1.33 (t, $J = 7.12$ Hz, 3H, $O—CH_2—CH_3$), 4.36 (q, $J = 7.08$ Hz, 2H, $O—CH_2—$), 7.63 (s, 1H, NH), 8.2–8.74 (m, 4H, 4HAr). ^{13}C NMR (100 MHz), δ(ppm): 14.5 (OCH_2CH_3), 63.8 ($O—CH_2—$), 122.4, 124.8 (4 *C*HAr), 125.6, 145.0 (2CAr), 145.6, 158.2 (C2, C5), 161.1 (C = O). Mass spectrum (FAB) *m*/*z*: 295 ($[M + H]^+$, 42%), 154 (90), 55 (100).

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