

ORIGINAL ARTICLE

Synthesis, characterization and *RHF/ab initio* simulations of 2-amino-1,3,4-thiadiazole and its annulated ring junction pyrimidine derivatives

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Abstract Michael addition reaction of the 2-amino-1,3,4-thiadiazole to chalcone as biselectrophile afforded 5,7-diphenyl-6-[1,3-diphenylpropan-1-on-3-yl][1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**3**) instead of 5,7-diphenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**5**) *via* further Michael addition at C₅ in pyrimidine moiety. The structure **3** was established through the aspect of *ab initio* calculations, elemental analysis and spectral data.

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Introduction

The diverse and interesting biological activity of thiadiazoles has been reported [1–4]. It is well known that these heterocycles are valuable building blocks. Many methods for preparation of these heterocyclic ring systems and their fused

analogues have been described in the literature [5,6]. 2-Amino-1,3,4-thiadiazoles as amidine moiety provided a useful method for the synthesis of thiadiazolopyrimidine [7]. Also, the *N*-alkylation could occur either on the endocyclic or on the exocyclic nitrogen atom [8].

The objective of this work is directed to annulate compound **1** *via* sequential cycloaddition followed by cyclocondensation reaction with enones as biselectrophile, in order to synthesize 5,7-diphenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**5**). Formation of compound **5** was unsuccessful and instead, we obtained 5,7-diphenyl-6-[1,3-diphenylpropan-1-on-3-yl][1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**3**), this result persuaded us to use *RHF/ab initio* calculations with the aim to explore the chemical reactivity of the interacted compounds including the investigation of different reaction processes on the basis of their expected quantum mechanical behavior and to envisage why compound **5** reacted with another equivalent mole of chalcone.

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Experimental

The melting point is in degree centigrade (uncorrected) and was determined on Gallenkamp electric melting point apparatus. The IR spectrum (cm^{-1}) was recorded using KBr discs on a Mattson 5000 FTIR Spectrophotometer at Microanalytical Center, Faculty of Science, Mansoura University. The ^1H NMR spectrum was carried out on a Varian Spectrophotometer at 300 MHz, using TMS as an internal reference and $\text{DMSO-}d_6$ as solvent at Chemistry Department, Faculty of Science, Cairo University. High Resolution Mass Spectra (HRMS) were recorded using both a Bruker HCT ultra and a high resolution (Bruker Daltonics micrOTOF) instruments from methanol or dichloromethane solutions using the positive Electrospray Ionization Mode (ESI). The *RHF/ab initio* quantum mechanical level of computation was employed in all calculations of molecular orbitals and quantum chemical parameters. The 6-31G** basis set was used for carbon, nitrogen, hydrogen atoms, whereas the 6-31++G** diffuse function basis set for Sulfur atom. All calculations were performed *in vacuo*, and no solvent effect was considered. The HyperChem ver 8.06 software package, accommodated on Core-Due 2 PC was employed.

5,7-Diphenyl-6-[1,3-diphenylpropan-1-on-3-yl][1,3,4]thiadiazolo[3,2-a]pyrimidine (**3**)

A mixture of 2-amino-1,3,4-thiadiazole (**1**) (0.5 g, 0.5 mmol) and benzalacetophenone (0.5 mmol) in ethanol/glacial acetic acid mixture (1:1, 10 mL) was refluxed for 15 h and then left to cool. The formed precipitate was filtered and recrystallized ethanol/DMF mixture (1:1) to afford the corresponding thiadiazolopyrimidine derivative **3** as yellow crystals; yield (43%);

Table 2 Calculated atomic charge densities and the HOMO atomic orbital coefficients for the amine **1a**.

Atom	Charge	Atomic orbital coefficients			
		2s	2p _z	2p _y	2p _x
S	+0.2163	0.0060	-0.1101	0.0018	0.0044
N ₃	-0.3633	-0.0661	-0.2289	0.0022	0.0199
N ₄	-0.2274	-0.0030	0.1776	0.0098	-0.0265
N ₆	-0.7227	-0.0499	0.3055	0.0239	0.0566

Table 3 Charge densities and LUMO^a atomic orbital coefficients of the chalcone **2**.

Atom	Charge	LUMO coefficients			
		2s	2p _z	2p _y	2p _x
O	-0.630	-0.0001	0.2462	-0.12781	-0.1249
C ₁	+0.852	-0.0014	-0.2428	0.1246	-0.2428
C ₂	-0.548	-0.0013	-0.3357	0.1729	0.1692
C ₃	+0.328	0.0104	0.5196	-0.2679	-0.2652

^a Orbital energy = +3.437 eV.

mp 285 °C; R_f = 0.6 [pet. ether (40–60): ethyl acetate (3:2.5)]; IR (KBr) (cm^{-1}), 3097 (CH, str.), 1666 (C=O), 1575 (C=C); ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ (ppm): at 4.57 (br, 1H), 4.91 (br, 1H), 5.91 (br, 1H), 6.61–7.84 (m, 21H, CH, Ar–H), 8.79 (s, 1H, C–H₇, pyrimidothiadiazole); (ESI, –98.7v) (+)-ESI mass spectrum showed three quasi-molecular ion peak at 500 (MH^+), 523 ($\text{MH}^+ + \text{Na}$) and 539 ($\text{MH}^+ + \text{K}$) pointing 399 as the molecular mass of **5**; HRMS(micrOTOF): m/z for $\text{C}_{32}\text{H}_{26}\text{N}_3\text{OS} + \text{Na}$, Calcd.:

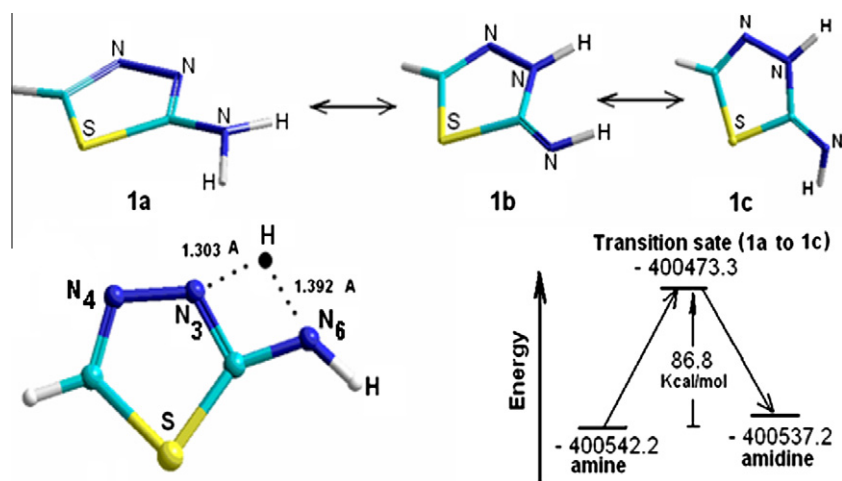


Fig. 1 Possible tautomeric forms of 2-amino-1,3,4-thiadiazole and the transition state for their conversion (**1a** → **1c**).

Table 1 Calculated energies of the tautomeric forms of 2-amino-1,3,4-thiadiazoles (**1a–c**, Fig. 1).

Character	Amine 1a	Amidine 1b	Amidine 1c	Transition State (1a → 1c)
Total energy (kcal/mol)	-400542.16	-400535.93	-400537.22	-400373.34
E (HOMO) (eV)	-9.595	-8.922	-8.891	-8.760
E (LUMO) (eV)	2.333	2.506	3.395	2.292
Dipole moment (debye)	3.737	2.436	1.979	2.596

523.6320. Found: 523.6479 ($MH^+ + Na$); Anal. Calcd for $C_{32}H_{25}N_3OS$ (499.632): C, 76.93; H, 5.04; N, 8.41%. Found: C, 76.96; H, 5.08; N, 8.39%.

Results and discussion

Initially, we have theoretically investigated the expected tautomeric behavior of compound **1**, to determine if it is acting

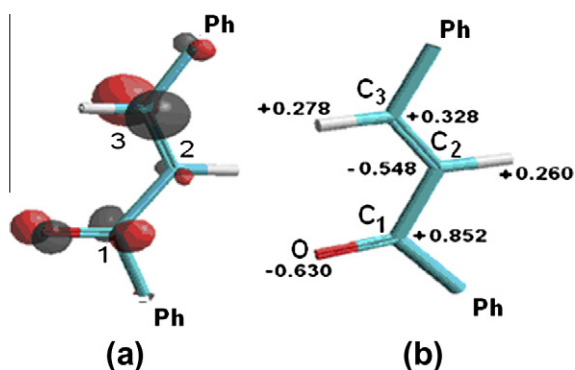


Fig. 2 (a) Orbital representation of LUMO of the chalcone (**2**) at a contour level of 0.12; (b) the calculated atomic charge densities.

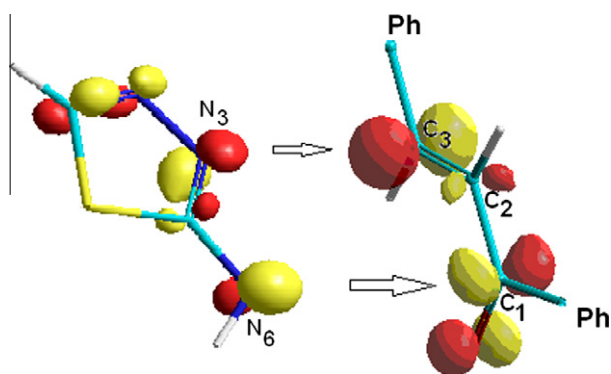
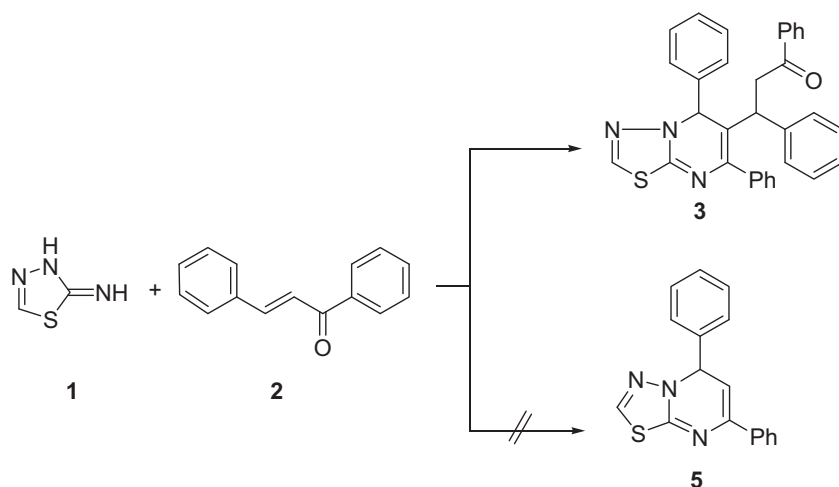


Fig. 3 The HOMO–LUMO interaction of **1b** with chalcone **2**.

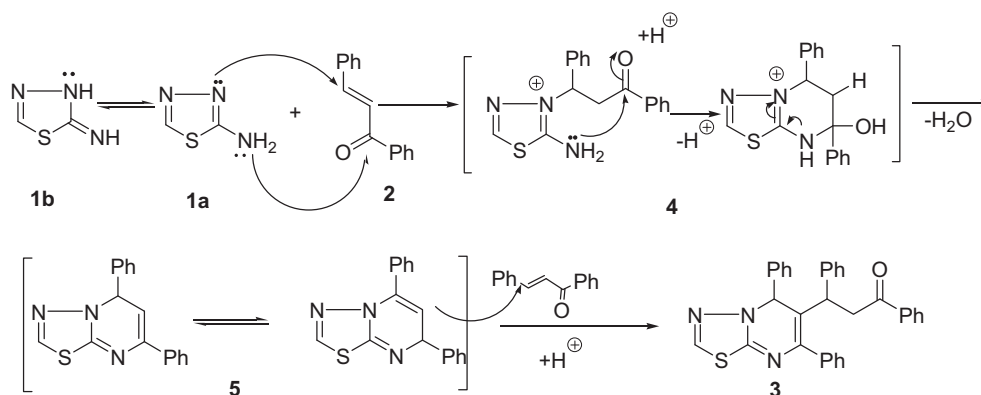
either as amine [2-amino-1,3,4-thiadiazole] (**1a**) or as semicyclic amidine [1,3,4-thiadiazol-2(3*H*)imine] (**1b**) (Fig. 1).

Results of geometry optimization for the different forms showed that, total energy value of the amine tautomer is that which has the lowest negative value (-400542.16 kcal/mol) when compared with the other two expected isomers of the semicyclic amidine tautomer **1b** and **1c** (-400535.93 and -400537.22 kcal/mol). Optimization job was confirmed in each case by calculating the normal vibrations and realizing the absence of the imaginary frequencies. These energy values mean that the amine tautomer is more stable than the semicyclic amidine (at least by about 4.94 kcal/mol). Moreover, we have also investigated the possible conversion process between the two tautomers, amine and amidine, by studying the expected transition state may formed as a result of the transfer of one of the amine-hydrogen atoms to the ring-imine-nitrogen (N_3 atom, see atomic numbering order in Fig. 1). The optimized geometrical parameters of the transition state were determined using the same method of computation. Results indicated that it has a total energy of (-400473.34 kcal/mol) higher than that of the amine form **1a** with (68.82 kcal/mol) (Table 1). This high energy barrier indicates that at the normal conditions the structure prevalence is for the amine form and not the amidine.

The amine molecule **1a** is expected to act as electron donor when interacted with an electrophile. Such interaction should take place between its highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the electrophile. Calculated atomic charge densities of **1a**, as obtained from *ab initio* calculations are depicted in Table 2. These values indicated that N_3 (the imine nitrogen) and N_6 (the amino nitrogen) atoms in **1a** possess the highest negative charge values (-0.363 and -0.7227 , respectively). Moreover, the calculated atomic orbital coefficients of HOMO of **1a**, as given in Table 2, indicated that, the 2s- and 2p_z-atomic orbitals have the highest contribution. 2s- and 2p_z-orbitals of the N_3 atom contribute the HOMO with the same phase (-0.0661 and -0.2289 , respectively) which indicate that they reinforce each other generating an active space for interaction. On the other hand, the highest atomic orbital coefficients of N_6 atom in the HOMO were found to be mainly from 2p_z-orbital ($+0.3055$) and have an opposite phase relative to that of the



Scheme 1 Synthesis of 5,7-diphenyl-6-[1,3-diphenylpropan-1-on-3-yl][1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**3**).



Scheme 2 The plausible reaction mechanism for the formation of 3 via intermediates 4 and 5.

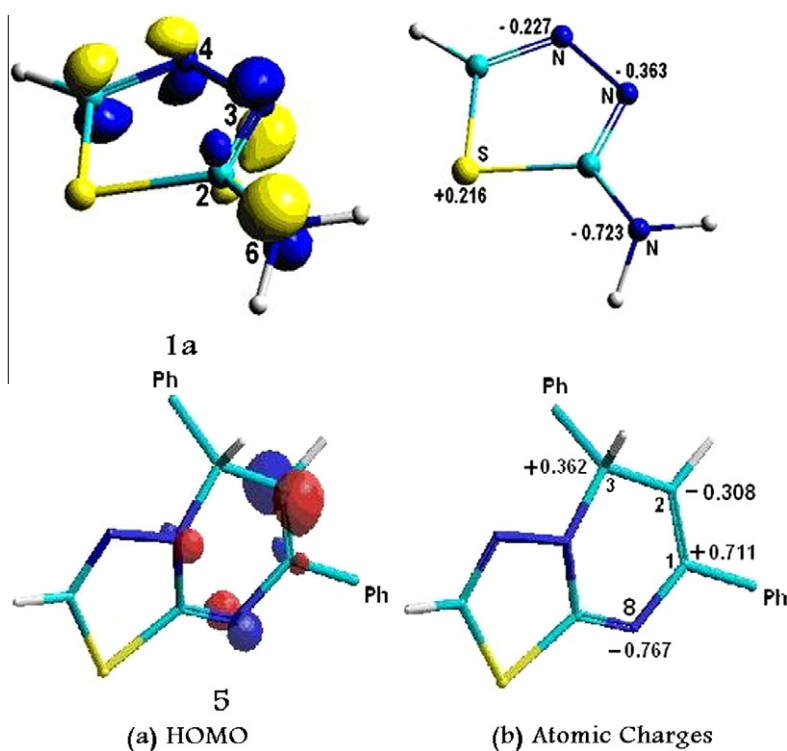


Fig. 4 (a) prospective representation of the HOMO of compounds 1a and 5; (b) atomic charges at the active positions.

N_3 atom. According to these values, it is obvious that 1a is available for interaction with an electrophile through its HOMO via N_3 and N_6 atoms (Table 2).

On the other hand, the chalcone 2 is expected to act as bis-electrophile, and interact with the amine 1a as electron acceptor. Its interaction should take place through its LUMO via the highest positive centers of the molecule. The Molecular geometry of chalcone 2 was optimized and the molecular orbitals were calculated employing the same level of computation used in case of the amine 1a. The calculated atomic charges and the atomic orbital coefficients of its LUMO for the expected reacting atoms are depicted in Table 3 and shown in Fig. 2. The ease of accepting electronic charge can be easily revealed from the low energy value of this LUMO (+3.347 eV). The Calculated charge densities on the different atoms showed

that the C_1 and C_3 atoms have the highest positive (+0.852 and +0.328, respectively). This indicates that these two atoms are the centers of interaction. Moreover, the calculated atomic orbital coefficients showed that it is mainly contributed from the p_z -atomic orbitals of C_3 and C_1 atoms with opposite phases (+0.519 and -0.242, respectively). This indicates that the electrophile molecule will interact with the amine 1a via its LUMO and through the C_3 and C_1 atoms (Table 3).

Interaction of HOMO of 1a with LUMO of chalcone 2 was investigated on the basis of their atomic orbital coefficients. Calculated data showed that the sp hybrid orbital of N_3 atom of 1a has the same orbital phase as the p_z -orbital of chalcone 2. Also the p_z -orbital coefficient of N_6 of 1a has the same orbital phase as p_z -orbital of C_1 of chalcone 2 (see Fig. 3). Therefore, the interaction of the two molecules will take place first

Table 4 Charge densities and HOMO atomic orbital coefficients of compound **5**.

Atom	Charge	HOMO coefficients			
		2s	2p _z	2p _y	2p _x
C ₁	+0.7108	-0.0052	-0.1546	-0.0061	0.0141
C ₂	-0.3076	0.0115	-0.3835	-0.0089	0.0298
C ₃	+0.3621	-0.0567	-0.0126	-0.0147	0.0014
N ₈	-0.7672	0.0032	0.2660	0.0233	-0.0477

through the interaction of N₃ of **1a** with C₃ of chalcone **2**, then the N₆ atom of **1a** with the carbonyl C₁ of chalcone **2** to form the intermediate compounds **4** and **5** (Scheme 2).

The intermediate **5** will be reacted with another molecule **2**. In this case **5** will behave as electron donor, (as enamine) attacking the electrophilic center of **2** (Scheme 1). Therefore, their interaction will take place through the HOMO of **5** and the LUMO of compound **2**. The calculated atomic charge densities for **5** (Fig. 4) indicated that the C₂ atom is that one carrying the highest -ve value (-0.308). On the other hand, the calculated atomic orbital coefficients of its HOMO showed that, it is highly contributed from the p_z-atomic orbital of the C₂-atom. These results strongly indicated that molecule **5** is adapted as a nucleophile to be attacked by another molecule of compound **2**. The chalcone **2** as discussed before will interact *via* its LUMO through its positively charged C₃-atom in a similar manner as before with the amine molecule (Table 4).

Regarding the reaction of **1** [9] with chalcone **2** in a mixture of ethanol/acetic acid, it give 5,7-diphenyl-6-[1,3-diphenylpropan-1-on-3-yl][1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**3**) instead of 5,7-diphenyl-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**5**), similar behavior has been reported [10].

The structure **3** was established on the basis of elemental analysis and spectral data. The plausible reaction mechanism for the formation of **3** *via* intermediates **4** and **5** is illustrated in the sequence of Scheme 2. The reaction mechanism is displayed *via* sequential cycloaddition followed by cyclocondensation reaction with enone as biselectrophile.

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