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Synthesis and quantum calculations of 1,3-thiazoles and 1,3,4-thiadiazole derivatives via pyridinylthioureas

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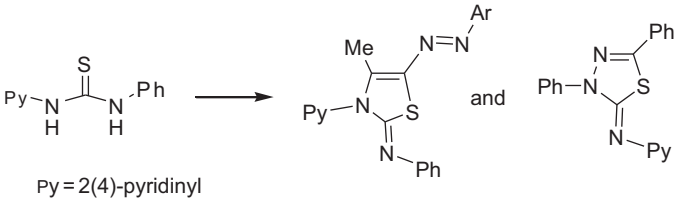
In this study, the reaction of 4- and 2-aminopyridines with phenyl isothiocyanate afforded the corresponding 1-phenyl-3-(pyridin-4-yl)thiourea **1** and its pyridin-2-yl analog **20**. The reaction of **1** with ethyl chloroacetate gave 3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one (**3B**), which upon a condensation reaction with aldehydes furnished 5-benzylidene derivatives **4a**–**c**. Compounds **1** and **20** underwent heterocyclization upon their reaction with hydrazonoyl chloride **5** and gave the corresponding 1,3,4-thiadiazoles **8** and **22**; however, the treatment of **1** and **20** with hydrazonoyl chloride **10** afforded the corresponding 1,3-thiazoles **14** and **25**. The quantum calculations were studied using the density functional theory of the starting materials and some products.



Keywords: pyridines; 1,3,4-thiadiazoles; 1,3-thiazoles; molecular orbital calculations; density functional theory

1. Introduction

1,3,4-Thiadiazoles have recently been reported by us and others as highly anti-inflammatory (*1*, *2*) and anticonvulsant (*1*, *3*) agents. In addition, 1,3-thiazoles have been found to have histamine H_3 antagonists that can be used for the treatment of neurological and psychiatric diseases (*4*) and to have antimicrobial (*5–7*), anti-HIV (*8*), anti-inflammatory (*9*), pesticidal (*10*) and anti-cancer (*11*) activities. Pyridine derivatives are one of the most used frameworks for medicines, food flavorings, dyes, agrochemicals, rubber chemicals and adhesives (*12*). The pyridine ring found

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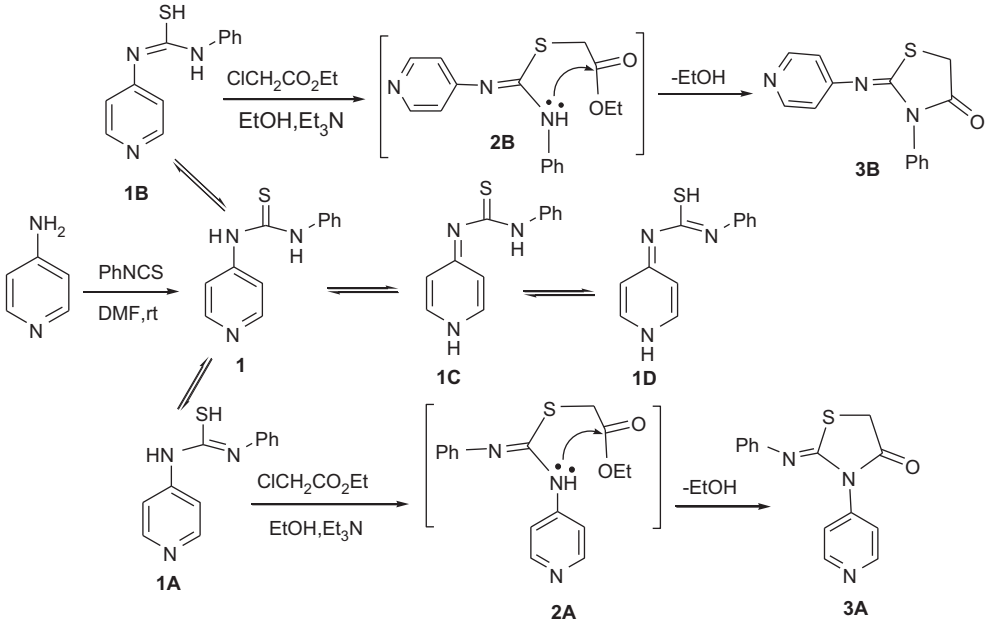
in acetylcholine is useful in the treatment of Alzheimer's disease (*13*) and has antitumor (*14*), antiamnesic (*15*), anticonvulsant and anti-inflammatory (*16*) and antiproliferative (*17*) activities. Moreover, pyridine derivatives have also been used as cardiotonic (*18*, *19*) agents. In addition, *N*, *N*′-disubstituted thiourea derivatives have been found to possess antiviral (*20*), antituberculous (*21*), antifungal (*22*) and herbicidal (*23*) activities. In continuation of our research work on 1,3,4-thiadiazole derivatives (*23–31*), this contribution is aimed at the synthesis of some new 1,3-thiazoles and 1,3,4-thiadiazole derivatives utilizing the reactive 1-phenyl-3-(pyridin-4-yl)thiourea **1** and its pyridin-2-yl analog **20** as the key starting materials. In addition, the quantum chemical calculations have been done to study the conformational behavior of the starting substrates **1** and **20**. Some of the proposed mechanisms have been studied theoretically for comparison with the experimental findings. The relative stabilities as well as the thermodynamic functions of some of the expected products have also been calculated.

2. Results and discussion

1-Phenyl-3-(pyridin-4-yl)thiourea **1** was prepared from the reaction of 4-aminopyridine with phenyl isothiocyanate in dimethylformamide (DMF), in the presence of potassium hydroxide, at room temperature according to the literature procedure (Scheme 1) (*32*). 1-Phenyl-3-(pyridin-4-yl)thiourea **1** has two labile hydrogen atoms at positions 1 and 3; therefore, it can be drawn in different tautomeric forms **1A–D** as illustrated in Scheme 1. However, the ^{1}H NMR spectrum in dimethyl sulfoxide (DMSO)-d_6 and quantum calculations using the density functional theory (DFT) proved that compound **1** is mainly present in the **1A** form.



Scheme 1. Synthesis of thiazolidin-4-one derivative **3B**.

The reaction of 1-phenyl-3-(pyridin-4-yl)thiourea **1** with ethyl chloroacetate in refluxing ethanol in the presence of triethylamine furnished a single product for which two structures can

Table 1. Total energy (E_t) in gas and solvents, relative total energy (ΔE_t), reaction enthalpy (ΔH_g), Gibbs free energy change in gas (ΔG_g) and in solvent (ΔG^o_{soln}), the solvation energy (G^o_s) and the free energy of solvation (ΔG^o_s) of the different isomers of 1-phenyl-3-(pyridin-4-yl)thiourea calculated using the B3LYP/6-31+G* level.

	1	**1A**	**1B**	**1C**	**1D**
E_t (g), au	−1026.4	−1026.3	−1026.4	−1026.4	−1026.3
E_t (w), au	−1026.4	−1026.4	−1026.4	−1026.4	−1026.4
E_t (ct), au	*−1026.4*	*−1026.4*	*−1026.4*	*−1026.4*	*−1026.3*
ZPE, au	0.21197	0.20757	0.20764	0.21215	0.20734
TC, au	0.22533	0.22138	0.22165	0.22549	0.22133
S, cal	120.15	121.83	123.36	119.12	122.22
ΔE_t, kcal/mol	0	14.89	10.29	8.73	27.85
ΔH_g, kcal/mol	0	9.65	5.26	8.56	20.74
ΔG_g, kcal/mol	0	9.15	4.3	9.87	20.12
G^o_s, kcal/mol	−10.68	−8.45	−8.09	−16.87	−15.84
	−4.41	*−3.41*	*−3.26*	*−6.9*	*−6.39*
ΔG^o_s, kcal/mol	0	2.23	2.49	−6.19	−5.16
	0	*1*	*1.15*	*−2.49*	*−1.98*
ΔG^o_{soln}, kcal/mol	*0*	11.38	6.79	3.68	14.96
	0	*10.15*	*5.45*	*14.38*	*18.14*

Note: E_t(g), total energy in gas; E_t(w), total energy in water; E_t(ct), total energy in carbon tetrachloride; and *S*, entropy.

be postulated: 2-(phenylimino)-3-(pyridin-4-yl)thiazolidin-4-one **3A** and 3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one **3B** (Scheme 1). The formation of thiazolidinone derivative **3A** or **3B** presumably proceeds via the elimination of HCl from the interaction of tautomer **1A** or **1B** with ethyl chloroacetate followed by intramolecular cyclization with the loss of an ethanol molecule under the hot basic reaction conditions. The spectral data were in complete accordance with structure **3A** or **3B**, but the quantum chemical calculations favored **3B**. The ^{1}H NMR spectrum of the reaction product revealed a singlet signal at δ 4.16 due to the methylene protons in addition to aromatic multiplets at δ 6.86–7.52. Its mass spectrum exhibited a peak at m/e 289 due to the molecular ion peak of the reaction product. The formation of **3B** is in contrast to the formation of 2-pyridylthiazolidinone that was reported in the literature (*33*). In addition, quantum calculations (Tables 1–3) proved that **1B** is the most stable isomer and the formation of **3B** is endothermically favored.

3-Phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one **3B** underwent a condensation reaction when treated with benzaldehyde in refluxing ethanol in the presence of a catalytic amount of piperidine to furnish a product identified as 5-benzylidene-3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one (**4a**) (Scheme 2). Furthermore, a similar condensation of thiazolidin-4-one derivative **3B** with other examples of aromatic aldehydes (4-chlorobenzaldehyde and 4-methoxybenzaldehyde) in refluxing ethanol in the presence of catalytic amounts of piperidine afforded the corresponding 5-arylidenethiazolidin-4-ones **42b** and **c** (Scheme 2). The structures of the reaction products were confirmed from their elemental analysis and spectral data. For example, the ^{1}H NMR spectrum of **4b** was free of the singlet due to CH_2 protons in the starting material and revealed instead a singlet at δ 7.81 due to the methine C=*CH* proton in addition to multiplets at δ 6.96–7.57 due to aromatic hydrogens. Its mass spectrum exhibited a peak at m/z 391 due to the molecular ion of the reaction product **4b**.

The reactivity of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) toward hydrazonoyl chlorides was also studied. Thus, the treatment of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) with hydrazonoyl chloride **5** in refluxing ethanol in the presence of triethylamine afforded only one isolable product. There are two possible reaction pathways, and consequently two expected structures for the reaction product can be suggested via intermediate **7**. The first pathway is the loss of an aniline molecule from intermediate **7** to give structure **8** and the second pathway is the loss of 4-aminopyridine

Table 2. Total energy (E_t) in gas and solvents, relative total energy (ΔE_t), reaction enthalpy (ΔH_g), Gibbs free energy change in gas (ΔG_g) and solvent (ΔG^o_{soln}), the solvation energy (G^o_s) and the free energy of solvation (ΔG^o_s) of the different isomers of 1-phenyl-3-(pyridin-2-yl)thiourea calculated using the B3LYP/6-31+G* level.

	20	**20A**	**20B**	**20C**	**20D**
E_t(g), au	−1026.4	−1026.4	−1026.4	−1026.4	−1026.3
E_t(w), au	−1026.4	−1026.4	−1026.4	−1026.4	−1026.4
E_t(ct), au	*−1026.4*	*−1026.4*	*−1026.4*	*−1026.4*	*−1026.3*
ZPE, au	0.2121	0.20783	0.20766	0.21224	0.20756
TC, au	0.22538	0.2215	0.22102	0.2255	0.22137
S, cal	119.46	120.87	119.55	119.24	122.07
ΔE_t, kcal/mol	0	16.13	8.78	8.53	25.5
ΔH_g, kcal/mol	0	11.02	3.18	8.69	20.14
ΔG_g, kcal/mol	0	10.06	3.15	8.76	19.36
G^o_s, kcal/mol	−8.51	−7.47	−6.2	−13.75	−11.53
	−3.6	*−3.07*	*−2.47*	*−5.67*	*−4.77*
ΔG^o_s, kcal/mol	0	1.04	2.31	−5.24	−3.02
	0	*0.53*	*1.13*	*−2.07*	*−1.17*
ΔG^o_{soln}, kcal/mol	*0*	11.1	5.46	3.52	16.34
	0	*10.59*	*4.28*	*6.69*	*18.19*

Note: Values in italic are calculated in carbon tetrachloride solvent.

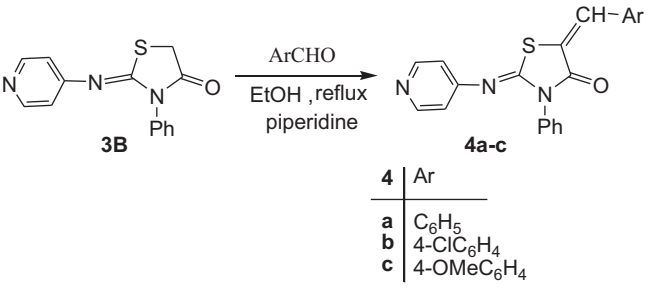
Table 3. Total energy (E_t) in gas and solvents, relative total energy (ΔE_t), activation energy in gas (E_a) and in solvent (ΔG^o_{soln}) and the solvation energy (G^o_s) of the TSs of the isomerization of 1-phenyl-3-(pyridin-2-yl)thiourea calculated using the B3LYP/6-31+G* level.

	$TS_{20\rightleftarrows 20D}$	**$TS_{20\rightleftarrows 20C}$**	**$TS_{20\rightleftarrows 20B}$**	**$TS_{20\rightleftarrows 20A}$**
E_t(g), au	−1026.3	−1026.3	−1026.4	−1026.3
E_t(w), au	−1026.3	−1026.32839	−1026.4	−1026.4
E_t(ct), au	*−1026.3*	*−1026.32116*	*−1026.4*	*−1026.4*
ZPE, au	0.20549	0.20581	0.20231	0.21687
TC, au	0.21863	0.2184	0.21993	0.21993
ΔE_t, kcal/mol	35.01	40.43	55.3	37.13
E_a, kcal/mol	27.22	36.84	51.26	30.27
G^o_s, kcal/mol	−6.82	−7.6	−7.56	−13.75
	−2.68	*−3.06*	*−3.19*	*−5.67*
ΔG^o_{soln}, kcal/mol	28.91	37.75	52.21	25.05
	28.14	*37.2*	*51.67*	*28.38*

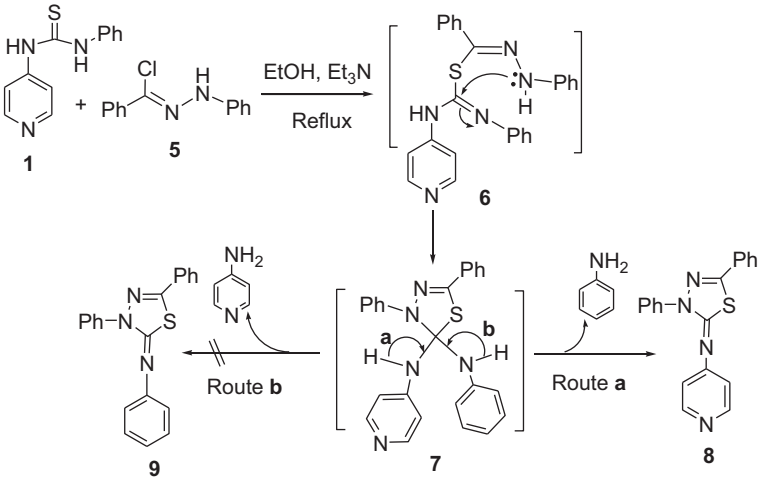
Note: Values in italic are calculated in carbon tetrachloride solvent.

molecule from intermediate **7** to give the other possible structure **9**. However, the spectral data (infrared (IR), MS, ^{1}H NMR and ^{13}C NMR) of the reaction product provided firm evidence that the reaction product is *N*-(3,5-diphenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)pyridin-4-amine **8** (Scheme 3). The ^{1}H NMR spectrum of the product revealed the presence of two doublets at δ 7.71 and 8.03 ($J = 7.8$ Hz) due to the 3-pyridine-*CH* and 2-pyridine-*CH* protons, respectively. The MS spectrum showed a peak at m/z 330 corresponding to the molecular ion (M^+) of the isolated product **8**. Quantum chemical calculations provided evidence that the two reaction pathways are energetically comparable but that the formation of **8** is slightly favored.

Similarly, when 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) was allowed to react with hydrazonoyl chloride **10b** in refluxing ethanol in the presence of triethylamine, it afforded a single isolable product. There are four possible structures **14**, **16**, **18** and **19** that can be suggested for the reaction product as displayed in Scheme 4. If the reaction proceeded following the above mechanism in Scheme 3, then the product will be either **18** or **19**; however, the mass spectrum was not compatible with either of these products. Therefore, it is suggested that the reaction had taken place by a different route as depicted in Scheme 4. In addition, the spectral data were in complete agreement with



Scheme 2. Reaction of thiazolidin-4-one derivative **3B** with aromatic aldehydes.



Scheme 3. Synthesis of 1,3,4-thiadiazole derivative **8**.

structure **14** and not with structure **16**. The mass spectrum of the reaction product showed a peak at *m*/*e* 371 due to the molecular ion of **14b**. Furthermore, the ^{1}H NMR and ^{13}C NMR spectra were also fully in accordance with the assigned structure: 4-methyl-5-(phenylazo)-2-(phenylimino)-3-(pyridin-4-yl)-(2*H*,3*H*)-1,3-thiazole (**14b**) (Scheme 4). The formation of structure **16** via the loss of an aniline molecule from intermediate **15** was ruled out based on spectral analyses of the reaction product. A similar behavior was observed when we conducted the reaction between thiourea **1** and hydrazonoyl chloride **10a** under the same reaction condition to give the corresponding 1,3-thiazole **14a** as outlined in Scheme 4.

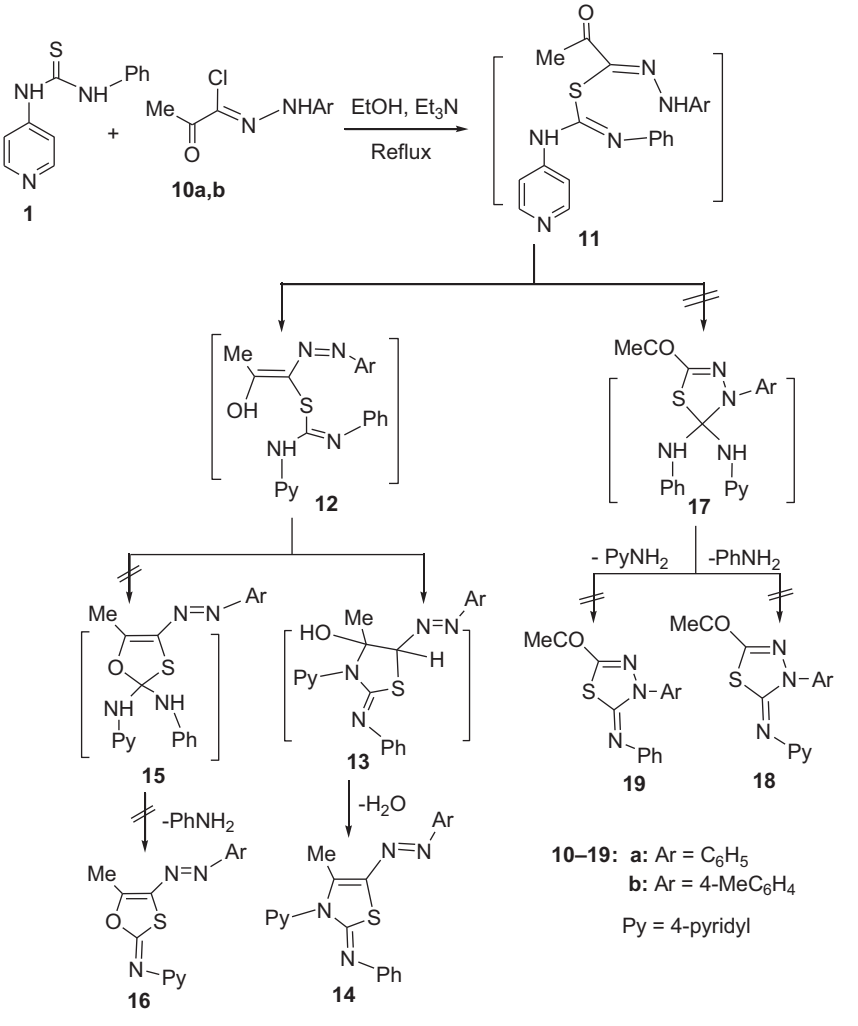
1-Phenyl-3-(pyridin-2-yl)thiourea **20** was prepared according to the literature procedure by the treatment of 2-aminopyridine with phenyl isothiocyanate and potassium hydroxide in *N*, *N*-DMF. Then, the reactivity of 1-phenyl-3-(pyridin-2-yl)thiourea (**20**) toward hydrazonoyl chlorides **5** and **10a** and **b** was examined under similar reaction conditions. Thus, heating of 1-phenyl-3-(pyridin-2-yl)thiourea (**20**) with hydrazonoyl chloride **5** in refluxing ethanol in the presence of triethylamine afforded only one isolable product. The spectral data (IR, MS, ^{1}H NMR and ^{13}C NMR) of the reaction product strongly supported *N*-(3,5-diphenyl-1,3,4-thiadiazol-2(3H)-ylidene)-pyridin-2-amine (**22**) (Scheme 5) as the product. The reaction took place via the loss of an aniline molecule from intermediate **21** to give structure **22** but not structure **23**.

When thiourea derivative **20** was similarly allowed to react with hydrazonoyl chloride **10a** in refluxing ethanol in the presence of triethylamine, it afforded a single isolable product. The

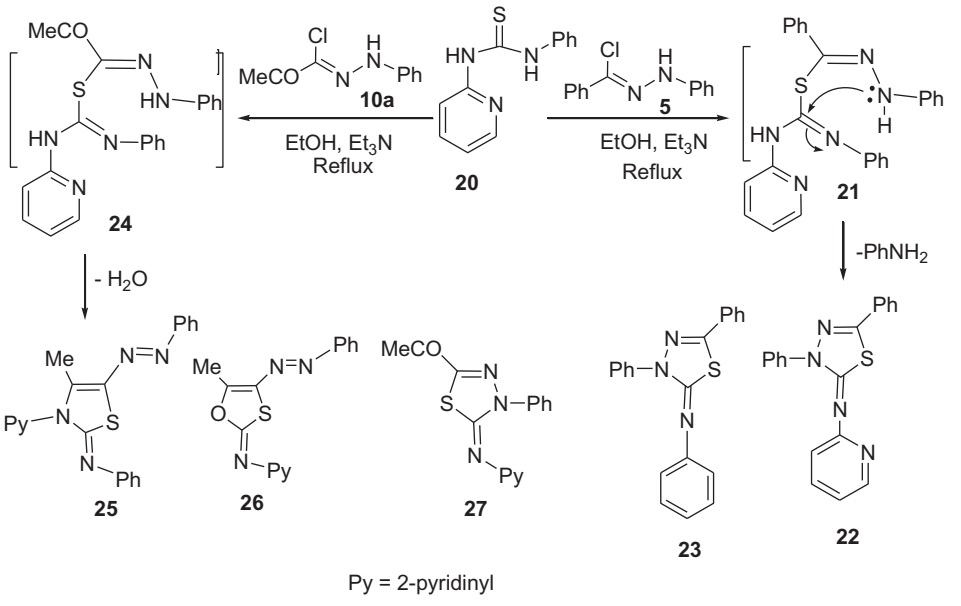
structure of the reaction product is expected to be one of the four possible structures **19** (Scheme 4) and **25**–**27** (Scheme 5). The spectral data (IR, MS, ^{1}H NMR and ^{13}C NMR) of the reaction product was in complete accordance with the assignment of its structure as **25** (Scheme 5) and ruled out alternative structures **19**, **26** and **27**. Mechanistically, the reaction took place in a manner similar to that suggested for the synthesis of compounds **14**–**19** as shown in Scheme 4. The mass spectrum of the reaction product showed a peak at m/e 371 due to the molecular ion (M^+) of **25**. Furthermore, the ^{1}H NMR and ^{13}C NMR spectra revealed 4-*Me*-thiazole protons and carbon at δ 2.60 and 24.87, respectively (see Section 4).

3. Molecular orbital calculations

The tautomeric behavior of **1** and its isomer **20** was theoretically studied using the B3LYP method and 6-31g** basis set, with the purpose of determining the most stable conformers



Scheme 4. Synthesis of 1,3-thiazole derivatives **14a,b**.



Scheme 5. Synthesis of 1,3,4-thiadiazole derivative **22** and 1,3-thiazole derivative **25**.

and their populations. In the first step, the three isomers 2-, 3- and 4-aminopyridines and their imino forms were optimized. The results show that the amino forms are more stable than the corresponding imino isomers. The differences in energies between the amino and imino forms were found to be 17.49, 24.17 and 17.31 kcal/mol for the three isomers 2-, 3- and 4-aminopyridines, respectively. The activation energy required for the amino–imino pyridine interconversion was also calculated. Its value in the case of 2-amino pyridine was 49.47 kcal/mol; accordingly, the amino form was the predominant isomer in this case, while the imino forms did not exist.

Second, the tautomerization processes **1** ⇄ **1A-D** and **20** ⇄ **20A-D** (Figure 1) were carefully considered in detail. In the gas phase, the most stable structure of each tautomer was determined, and its total energy, zero-point energy (ZPE) and the thermal corrections (TCs) are given in Tables 1 and 2. In the case of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**), the calculations showed that

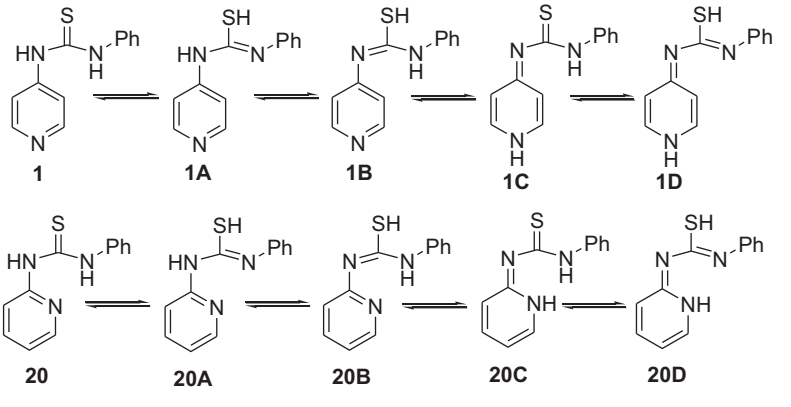


Figure 1. Tautomeric structures of the disubstituted thioureas **1** and **20**.

the thio form **1** had the lowest total energy; that is, it is the most stable conformer. Structure **1C** is higher in energy than **1** by 8.73 kcal/mol (Table 1), while the least stable structure, **1D**, is 27.85 kcal/mol higher in energy than **1**. The inclusion of ZPE and TCs did not alter their stability trend. The calculated ΔG_g values of the **1** $\rightleftarrows$ **1A-D** conversions support that **1** is the main conformer followed by **1B**, while **1D** cannot exist in the gas phase. Experimentally, the IR spectrum of compound **1** showed a band at 1340 cm^{-1} corresponding to the C9S bond and also the ^{1}H NMR spectrum in DMSO-d_6 proved that **1** is present as structure **1A**. As a result, we can conclude that in the gas phase, isomers **1**, **1A** and **1B** exist in equilibrium where the main one is **1**.

The calculated dipole moments of the five conformers were high, lying between 1.15 and 9.57 D. Therefore, a pronounced solvent effect on the above tautomerization was expected to be found. The polarities of **1D** and **1C** were the highest, while that of **1A** was the lowest. The tautomerizations were studied in water as a polar solvent and in carbon tetrachloride as a non-polar solvent. The total energy of each tautomer in solvents, the solvation energy and the free energy in solvents are given in Table 1. The results show that the five tautomers are more stabilized in polar solvents than in non-polar ones, which is attributed to their high dipole moments. The solvation energies of **1D** and **1C** in water were, respectively, −16.87 and −15.84 kcal/mol, while that of **1B** was the lowest, −8.09 kcal/mol. The same trends were found for carbon tetrachloride when it was used as a solvent. Finally, the free energy in solvents proves that **1** is still the main conformer in solution and the two isomers **1B** and **1A** exist in equilibrium with **1** but as minor contributors.

The transition states (TSs) for the two conversions **1** $\rightleftarrows$ **1A** and **1** $\rightleftarrows$ **1B** were located. The corresponding gaseous activation energies were calculated to be 25.61 and 27.07 kcal/mol, respectively, as outlined in Table 2. In spite of the stabilization of both TSs in both the solvents, the activation energies increased to 27.60 and 29.29 kcal/mol in water and to 26.96 and 28.95 kcal/mol in the non-polar solvent. Since both processes are endothermic and have positive ΔS values, it is expected that the amount of **1A** and **1B** increases at higher temperatures.

The tautomerization processes **20** $\rightleftarrows$ **20A-D** were also carefully studied using the same computational level. As was found for the pyridin-4-yl isomer, the thio form 1-phenyl-3-(pyridin-2-yl)thiourea (**20**) was the most stable conformer followed by **20C** and **20B**, which were 8.53 and 8.78 kcal/mol higher in energy. The free energy changes ΔG_g for the tautomerization processes **20** $\rightleftarrows$ **20A-D** were calculated. All the values were positive, revealing that in the gas phase the thio form **20** is the predominant species. The calculated ΔG_g for the **20** $\rightleftarrows$ **20B** conversion was 3.15, which indicates that in the gas phase the form **20B** can only exist as a minor contributor. The free energy changes in solution were also determined; these values suggest that the thio form **20** is the main one, while **20B** and **20C** exist as minor contributors in both the solvents. The four TSs for the conversions **20** $\rightleftarrows$ **20A-D** were also located in both the gas and solvent phases. The corresponding gaseous activation energies were calculated, and they are given in Table 3. The **20** $\rightleftarrows$ **20A** conversion had the lowest activation energy, 27.22 kcal/mol, while the **20** $\rightleftarrows$ **20C** conversion had the highest, 51.26 kcl/mol. The other two conversions **20** $\rightleftarrows$ **20B** and **20** $\rightleftarrows$ **20D** had the values of 36.84 and 30.27 kcal/mol, respectively. The four TSs were more stable in the solvent phase than in the gas phase, but the activation energies increased in water and in non-polar solvents, where compound **20** was found to be more solvated than the TSs. Since both processes are endothermic and have positive ΔS values, it is expected that the amount of **1A** and **1B** increases at higher temperatures.

Molecular orbital calculations could also be used to predict the most stable isomer among the two possible structures **3A** and **3B** that are postulated for the reaction product of 1-phenyl-3-(pyridin-4-yl)thiourea **1** with ethyl chloroacetate, as shown in Scheme 1. It was found that the total energies of the two isomers **3A** and **3B** were −1177.80266 and −1177.80507 au, respectively. Consequently, **3B** was relatively stable with lower stabilization energy (1.51 kcal/mol) than **3A**. The proposed mechanism of the above reaction was theoretically studied. Thus, the TSs

for the intramolecular cyclization of the two intermediates **2A** and **2B** were located and their energy barriers were determined. The results show that the energy barrier of the formation of **3A** is 42.66 kcal/mol, while that of **3B** is 37.98 kcal/mol. Therefore, the formation of **3B** is less endothermic and theoretically preferable.

As shown in Scheme 3, two products **8** and **9** from the reaction of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) with hydrazonoyl chloride **5** were expected through two possible routes **a** and **b** via intermediate **7**. The two routes were theoretically studied in order to evaluate the activation barrier in each. The total energy of the most stable form of intermediate **7** equals −1637.21148 au. The TSs corresponding to the two routes **a** and **b** were also calculated. The total energy of the TS of route **a** (TS1) was found to be −1637.14777 au, which is higher than that of **7** by 39.98 kcal/mol. However, the energy barrier of the TS of route **b** (TS2) was found to be 39.32 kcal/mol. Thus, route **a** (via the loss of aniline) is energetically preferable and consequently the formation of **8** is favored.

4. Experimental section

4.1. *General*

All melting points were measured on a Gallenkamp electrothermal melting point apparatus. The IR spectra were recorded for potassium bromide pellets on Pye Unicam SP 3-300 and FT IR 8101 PC Schimadzu IR spectrophotometers. The ^{1}H NMR spectra were recorded in deuterated chloroform or DMSO at 300 MHz on a Varian Mercury NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a GCMS-QP 1000 EX Shimadzu mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Hydrazonoyl chlorides **5** (*34*), **10a** (*35*) and **10b** (*36*), 1-phenyl-3-(pyridin-4-yl)thiourea (*32*) **1** and 1-phenyl-3-(pyridin-2-yl)thiourea (*37*) **20** were prepared according to procedures reported in the literature.

4.1.1. *3-Phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one* **(3B)**

To a solution of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) (0.23 g, 1 mmol) in ethanol (10 ml), ethyl chloroacetate (1.25 ml, 1.2 mmol) was added. Triethylamine (0.1 ml) was then added and the resulting mixture was heated at reflux for 6 h, during which the reactants were dissolved and the product was precipitated. The solid formed was filtered off, washed with ethanol/water (1:1), then dried and finally recrystallized from ethanol to afford pale yellow crystals of 1,3-thiazolidin-4-one derivative **3B** in 67% yield. mp. 179–181°C; IR (KBr) υ (cm^{-1}): 3044 (CH-arom.), 2949 (CH-aliph.), 1633 (C9O), 1587 (C9N); ^{1}H NMR (DMSO-d_6): δ 4.16 (s, 2H, CH_2), 6.85–7.52 (m, 9H, ArH); MS m/z (%): 268 (M^+-1, 8.2), 194 (8.6), 149 (9.0), 104 (22.0), 91 (15.9), 77 (61.2), 51 (100). For $C_{14}H_{11}N_3OS$ (269.32): Calcd. C, 62.43; H, 4.12; N, 15.60; S, 11.91. Found: C, 62.29; H, 4.06; N, 15.49; S, 11.85.

4.1.2. *Reaction of 1,3-thiazolidin-4-one* **(3B)** *with aromatic aldehydes: general procedure*

To a solution of 3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one **3B** (2 mmol) in ethanol (10 ml) was added the appropriate aromatic aldehyde (2 mmol), followed by the addition of few drops of piperidine, and the reaction mixture was then heated under reflux for 4–6 h. The reaction mixture was then left to cool to room temperature. The solid product that formed was collected by filtration, washed with ethanol and then recrystallized from DMF/water to give a pale yellow powder of the corresponding 5-arylidenethiazolidin-4-one derivatives **4a**–**c**.

5-Benzylidene-3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one (**4a**). Yield (65%); mp. 212–214°C; IR υ (cm^{-1}) 1640 (C9O), 1581 (C9C); ^{1}H NMR (DMSO-d_6) 6.98 (d, 2H, ArH, J = 8.1 Hz), 7.15–7.20 (m, 1H, ArH), 7.36–7.58 (m, 11H, ArH), 7.82 (s, 1H, C9C*H*–); MS m/z (%): 357 (M^+, 13.6), 356 (M^+-1, 53), 194 (74.8), 134 (100), 91 (19.3), 89 (13.9), 77 (52.7), 51 (36). For $C_{21}H_{15}N_3OS$ (357.42): Calcd. C, 70.57; H, 4.23; N, 11.76; S, 8.97. Found: C, 70.42; H, 4.19; N, 11.55; S, 8.92.

5-(4-Chlorobenzylidene)-3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one (**4b**). Yield (58%); mp. 192–194°C; IR (KBr) υ (cm^{-1}) 3027 (CH-arom.), 1646 (C9O), 1597 (C9C); ^{1}H NMR (DMSO-d_6) δ 6.97 (d, 2H, ArH, J = 7.5 Hz), 7.17 (m, 1H, ArH), 7.36–7.57 (m, 10H, ArH), 7.81 (s, 1H, C9C*H*–); MS m/z (%) 391 (M^+, 31.5), 261 (31.5), 194 (100), 168 (77.2), 132 (19.7), 106 (31.5), 91 (44.1), 77 (89.0), 51 (59.8). For $C_{21}H_{14}ClN_3OS$ (391.87): Calcd. C, 64.36; H, 3.60; N, 10.72; S, 8.18. Found: C, 64.27; H, 3.53; N, 10.61; S, 8.15.

5-(4-Methoxybenzylidene)-3-phenyl-2-(pyridin-4-ylimino)thiazolidin-4-one (**4c**). Yield (57%); mp. 202–204°C; IR (KBr) υ (cm^{-1}) 1641 (C9O), 1595 (C9C); ^{1}H NMR (DMSO-d_6): δ 3.78 (s, 3H, –OCH_3), 6.96–7.08 (m, 4H, ArH), 7.17–7.54 (m, 9H, ArH), 7.77 (s, 1H, C9C*H*–); MS m/z (%): 387 (M^+, 9.6), 386 (M^+-1, 28.1), 385 (23), 165 (11.3), 164 (100), 163 (98.1), 148 (28.8), 149 (30), 121 (12.3), 91 (8.1), 77 (29), 51 (17.2). For $C_{22}H_{17}N_3O_2S$ (387.45): Calcd. C, 68.20; H, 4.42; N, 10.85; S, 8.28. Found: C, 68.32; H, 4.88; N, 10.68; S, 8.21.

4.1.3. *Synthesis of 3,5-diphenyl-2-N-(pyridin-4-yl)imino-(2H,3H)-1,3,4-thiadiazole* **(8)**

To a stirred solution of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) (0.23 g, 1 mmol) in ethanol (10 ml), *N*−phenylbenzenecarbohydrazonoyl chloride **5** (1 mmol) was added followed by the addition of triethylamine (0.1 ml). The reaction mixture was heated at reflux for 6 h, during which the reactants were dissolved and a pale yellow-colored product was precipitated. The solid product was filtered off, washed with ethanol, dried and finally recrystallized from DMF/water to afford pale rose crystals of the 1,3,4-thiadiazole **8** derivative. Yield (80%). mp. 121–123°C; IR (KBr) υ (cm^{-1}) 1616 (C9N); ^{1}H NMR (DMSO-d_6) δ 7.04–7.12 (m, 3H, ArH), 7.31–7.52 (m, 7H, ArH), 7.71 (d, 2H, J = 7.8 Hz), 8.03 (d, 2H, J = 7.8 Hz); ^{13}C NMR (DMSO-d_6) δ 120.5, 122.3, 123.9, 125.9, 126.2, 128.7, 129.1, 129.7, 130.7, 139.2, 146.1, 151.8, 154.6; MS m/z (%) 330 (M^+, 4.0), 329 (M^+-1, 15.8), 227 (2.7), 194 (27.1), 135 (3.0), 104 (6.6), 91 (100), 77 (20.5). For $C_{19}H_{14}N_4S$ (330.40): Calcd. C, 69.07; H, 4.27; N, 16.96; S, 9.70. Found: C, 68.88; H, 4.19; N, 16.77; S, 9.62.

4.1.4. *2-(N-Phenylimino)-5-(arylazo)-4-methyl-3-(pyridin-4-yl)-(2H,3H)-1,3-thiazole (***14a** *and* **b***)*

To a stirred solution of 1-phenyl-3-(pyridin-4-yl)thiourea (**1**) (0.23 g, 1 mmol) in ethanol (10 ml) was added the appropriate hydrazonoyl chlorides **10a** and **b** (1 mmol) followed by the addition of triethylamine (0.1 ml). The reaction mixture was heated at reflux for 6 h, during which the reactants were dissolved and a pale yellow-colored product was precipitated. The solid product was filtered off, washed with ethanol, dried and finally recrystallized from DMF/water to afford an intense yellow powder of the 5-arylazo-1,3-thiazolidines **14a** and **b** derivatives, respectively.

2-(N-Phenylimino)-5-(phenylazo)-4-methyl-3-(pyridin-4-yl)-(2H,3H)-1,3-thiazole (**14a**). Yield (62%); mp. 166–168°C; IR (KBr) υ (cm^{-1}) 1618 (C9N); ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 6.91–7.68 (m, 14H, ArH); MS m/z (%) 372 (M^+, 5.4), 371 (M^+, 12.7), 118 (100), 77 (62.7), 51 (25.7). For $C_{21}H_{17}N_5S$ (371.46): Calcd. C, 67.90; H, 4.61; N, 18.85; S, 8.63. Found: C, 67.81; H, 4.41; N, 18.74; S, 8.48.

2-(N-Phenylimino)-5-(4-tolylazo)-4-methyl-3-(pyridin-4-yl)-(2H,3H)-1,3-thiazole (**14b**). Yield (69%); mp. 220–222°C; ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.42 (s, 3H, CH_3),

7.02–7.58 (m, 13H, ArH); ^{13}C NMR (DMSO-d_6) δ 13.4, 25.1, 114.8, 120.5, 121.6, 123.5, 128.7, 129.2, 129.5, 130.1, 135.7, 141.8, 146.6, 150.1, 151.9, 156.2; MS m/z (%) 382 (11.9), 261 (55.2), 208 (23.9), 132 (34.3), 106 (100), 91 (23.9), 77 (37.3). For $C_{22}H_{19}N_5S$ (385.48): Calcd. C, 68.55; H, 4.97; N, 18.17; S, 8.32. Found: C, 68.23; H, 4.78; N, 18.05; S, 8.37.

4.1.5. *Synthesis of 3,5-diphenyl-2-N-(pyridin-2-yl)imino-(2H,3H)-1,3,4-thiadiazole* **(22)**

To a stirred solution of 1-phenyl-3-(pyridin-2-yl)thiourea (**20**) (0.23 g, 1 mmol) in ethanol (10 ml), hydrazonoyl chloride **5** (1 mmol) was added followed by the addition of triethylamine (0.1 ml). The reaction mixture was heated at reflux for 6 h, during which the reactants were dissolved and a pale yellow-colored product was precipitated. The solid product was filtered off, washed with ethanol, dried and finally recrystallized from DMF/water to afford white crystals of 1,3,4-thiadiazole derivative **22** in 60% yield. mp. 183–185°C; IR (KBr) υ 1570 (C9N), 1535 (C9C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.07–8.52 (m, ArH); MS m/z (%): 330 (M$^+$, 5.4), 226 (4.9), 193 (11.4), 136 (11.9), 121 (13.5), 103 (30.3), 91 (74.1), 78 (100), 51 (96.2). For $C_{19}H_{14}N_4S$ (330.41) Calcd. C, 69.07; H, 4.27; N, 16.96; S, 9.70. Found: C, 68.85; H, 4.21; N, 16.83; S, 9.67.

4.1.6. *2-(N-Phenylimino)-5-(phenylazo)-4-methyl-3-(pyridin-2-yl)-(2H,3H)-1,3-thiazole* **(25)**

To a stirred solution of 1-phenyl-3-(pyridin-2-yl)thiourea (**20**) (0.23 g, 1 mmol) in ethanol (10 ml) was added hydrazonoyl chloride **10a** (1 mmol) followed by the addition of triethylamine (0.1 ml). The reaction mixture was heated at reflux for 6 h, during which the reactants were dissolved and a pale red-colored product was precipitated. The solid product was filtered off, washed with ethanol, dried and finally recrystallized from DMF/water to afford a pale red solid of 1,3-thiazolidine derivative **25** in 69% yield. mp. 176–178°C; IR (KBr) υ 1575 (C9N), 1536 (C9C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H, CH_3), 7.07–7.93 (m, 13H, ArH), 8.55 (m, 1H, pyridine-2-*H*); ^{13}C NMR (DMSO-d_6): δ 24.87, 114.76, 118.56, 120.27, 123.38, 124.55, 127.80, 128.74, 129.33, 138.16, 141.61, 145.83, 155.46; MS m/z (%): 371 (M$^+$, 3.1), 353 (12.1), 242 (29.2), 143 (11.4), 109 (39.2), 91 (100), 77 (71.1), 51 (80.0). For $C_{21}H_{17}N_5S$ (371.46) Calcd. C, 67.90; H, 4.61; N, 18.85; S, 8.63. Found: C, 67.69; H, 4.54; N, 18.78; S, 8.56.

4.2. *Computational details*

Theoretical calculations were performed using the DFT (*38*, *39*). All calculations were performed using the GAUSSIAN98 (*40*). All the structures were fully optimized without any constraints. The search for TSs was performed by employing the synchronous transit-guided quasi-Newton method (*41*, *42*) incorporated in the GAUSSIAN98 package. To characterize each stationary point as a minimum or a TS and to estimate the zero-point vibrational energies (ZPEs), the vibrational frequencies were computed for all the optimized species. The thermodynamic functions, the relative energy ΔE_t, the heat of formation ΔH and the free energy change ΔG were calculated using the appropriate equations as shown below:

The relative energy ΔE_t is given by $\Delta E_t = E_t$ (**20A**–**D**)–E_t (**20**).
Enthalpy change is given by $\Delta H_g = \Delta E_t + \Delta ZPE + \Delta TC$.
The Gibbs free energy change is given by $\Delta G_g = \Delta H_g - T\Delta S$, where ΔS is the entropy change.
The solvation energy G_s^o is calculated by $G_s^o = E_t$ (solution)–E_t(g).
The free energy of solvation (ΔG_s^o) is calculated by $\Delta G_s^o = G_s^o$ (**20A**–**D**)–G_s^o (**20**).
The Gibbs free energy change in solvent ΔG_{soln}^o is calculated by $\Delta G_{soln}^o = \Delta G_g \quad + \Delta G_s^o$.

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