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Tautomerism and Reactions of 1*H*-1,2,4-Triazole-5-thiones with Hydrazonoyl Halides

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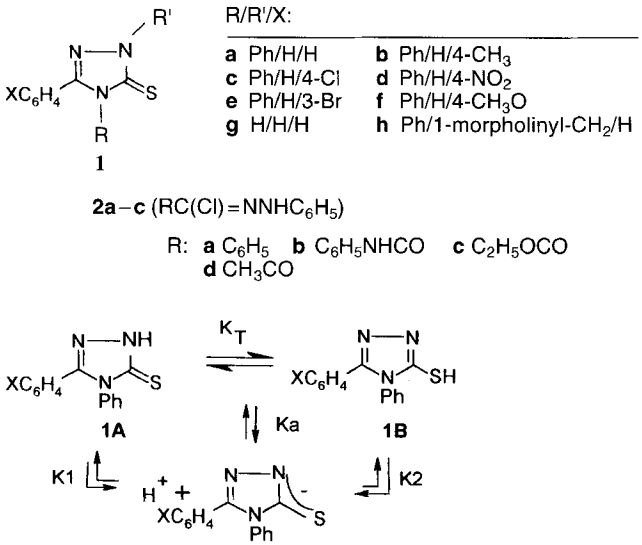
Abstract. The acid dissociation constants (K_a) of a series of 3,4-diaryl-1*H*-1,2,4-triazole-5-thiones (**1**) were determined and were found to correlated linearly with Hammett substituent constants; log K_a = 1.06 σ_x – 11.01. Such a result indicates that **1** exists essentially in one tautomeric form namely the thione form. Reactions of **1** with hydrazonoyl chlorides **2** gave the thiohydrazides **5**. Similar reaction of 3-phenyl-1*H*(4*H*)-1,2,4-triazole-5-thione **1g** with **2a** gave the thiohydrazide **5h** which was converted into 1,3,5-triphenyl-1,2,4-triazolo[3,4-*c*]-1,2,4-triazole (**9**). The latter was also prepared from 3-phenyl-5-methylthio-4*H*-1,2,4-triazole (**6**) and **2a**. The mechanism of the reaction of **1** with **2** is discussed.

Although many studies have been made on the physical and chemical properties of 1*H*-1,2,4-triazole-5-thione derivatives **1** [1], the reactions of the latter with hydrazonoyl halides 2 have not yet been studied [2]. Here we wish to report the results of our study of the reactions of **1a–h** with the hydrazonoyl halides **2a–d**. The objective of such a study was to elucidate the site selectivity in the reactions of **1** with **2**. To fulfill such an objective, it was felt necessary to shed first more light on the actual tautomeric form of the starting compounds **1**. This is because controversy over the actual tautomeric form of **1** exists in that some authors favoured the thione tautomer **1A** [3, 4] whereas other preferred the thiol tautomer **1B** [5] on the basis of appropriate IR and NMR spectral data. Furthermore, other authors indicated that **1** exists as equilibrium mixture of both forms **1A** and **1B** [6] (Scheme 1). Accordingly, the acid ionization constants of the series **1a–f** were determined by potentiometric method, and their correlation by the Hammett equation was tested. The application of this method to tautomerism studies of heterocyclic compounds has been frequently used and proved to be a tool as useful as other physical and theoretical methods [7].



Scheme 1

Results and Discussion

The pK_a values of the series **1a–f** determined in 80% (v/v) dimethylformamide–water mixture at 25 ± 0.1 °C

Tab. 1 pK_a Values of **1a–f** in 80% DMF–Water (v/v) at 25 °C and μ = 0.1

Compounds	$-\log K_a \pm s$ [a]	σ_x	$\sigma^*(XC_6H_4)$
1a	10.95	0.00	0.58
1b	11.22	–0.17	0.47
1c	10.76	0.23	0.75
1d	10.17	0.78	1.50
1e	10.63	0.39	0.86
1f	11.30	–0.27	0.36

[a]) standard deviation, s = ±0.01

and ionic strength of 0.1 are given in Tab. 1. The results show that the acidity of 1 is influenced by the substituent in the 3-phenyl group. Good linear plots were obtained when the log K_a data were plotted versus either the Hammett substituent constant σ_x or the inductive effect of the 3-aryl group $\sigma^*(XC_6H_4)$. The equations corresponding to these regression lines are:

$\log K_a = 1.06\ \sigma_x - 11.01$; (r = 0.996, s = 0.01)
$\log K_a = 0.995\ \sigma^*(XC_6H_4) - 11.59$; (r = 0.976, s = 0.01)

where r and s are the correlation coefficient and standard deviation, respectively. From the values of r and s, it is obvious that the log K_a values of **1a–f** are better correlated by Hammett substituent constant σ_x than by the inductive effect constant $\sigma^*(XC_6H_4)$ of the 3-aryl group.

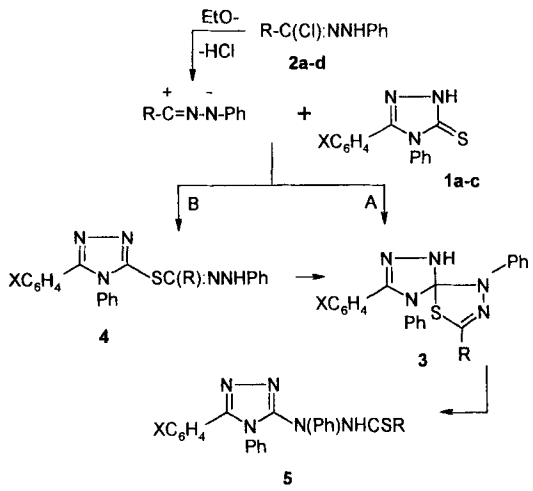
The observed linear correlation between log K_a and σ_x indicates that among the tautomeric thione **1A** and thiol **1B** forms predominantly form **1A** exists in solution with the triazole ring in a planar configuration. This is because if **1** exists as equilibrium mixture of say the thione **1A** and the thiol **1B** tautomers, the effective acid ionization constant K_a will be given by the equation:

$$K_a = [K_1/(1+K_T)] = [K_2K_T/(1+K_T)]$$

where K_1 and K_2 are the acid ionization constants of the thione and thiol tautomers **1A** and **1B**, respectively, and K_T is the tautomeric equilibrium constant (Scheme 1). According to this equation, a linear correlation between log K_a and σ_x would be observed only if $K_1 = K_2$, and this will never be the case as the acidity of the -NH- differs from that of the -SH group.

Furthermore, the value of the reaction constant ρ = 1.06 seems to be in favor of the thione form **1A** as it is close to that reported for 3-substituted phenyl-1,3,4-oxadiazole-5-thiones (ρ = 0.903) and which were shown to have the thione form [7a,d]. In addition, if **1B** were the predominant form for **1**, the value of ρ would have been less than 1.06 since the bridge between the substituent and the reaction site in **1B** is longer than in the thiono form **1A**.

Next, reactions of 3,4-diaryl-1*H*-1,2,4-triazole-5-thiones **1a–c** with hydrazonoyl chlorides **2a–d** were examined. Thus, treatment of each of **1** with the appropriate hydrazonoyl chloride **2** in ethanol in the presence of sodium ethoxide at room temperature, yielded in each case only one isolable product as evidenced by tlc analysis of the crude reaction product. On the basis of mass spectra and elemental analyses together with IR and ^1H NMR spectral data (see Experimental) to the products isolated from the studied reactions were assigned structure **5** (Scheme 2). For example, the IR spectra of such products taken in potassium bromide revealed in each case two characteristic absorptions in the regions 3282–3249 and 1458–1415 cm^{-1} assignable to the NH and thioamide-I bands, respectively. Their ^1H NMR spectra showed in each case a singlet near δ 10.2 ppm assignable to the thioamide NH proton resonance. The latter signal disappeared upon shaking the solution of the product in deuterated chloroform with deuterium oxide and a new signal appeared at δ 4.6 ppm assignable to DOH proton resonance.

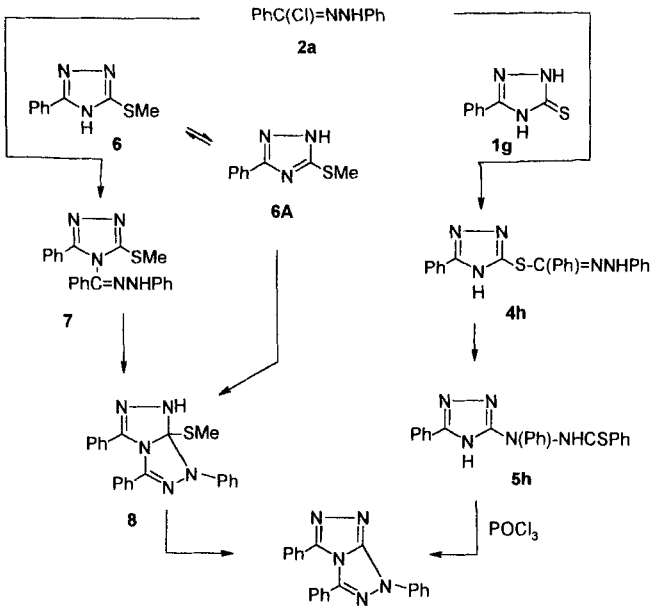


1	2	3–5	R/X
a	**a**	**a**	Ph/H
b	**b**	**b**	PhNHCO/4-CH_3
c	**b**	**c**	PhNHCO/4-Cl
b	**c**	**d**	EtOCO/4-CH_3
c	**c**	**e**	EtOCO/4-Cl
b	**d**	**f**	CH_3CO/4-CH_3
c	**d**	**g**	CH_3CO/4-Cl

Scheme 2

This structural assignment was substantiated by the results of the study of the reaction of **2a** with 3-phenyl-1*H*(4*H*)-1,2,4-triazole-5-thione **1g**. In our hands, treatment of **2a** with **1g** in ethanol in the presence of sodium ethoxide at room temperature afforded a product whose spectra (IR, ^1H NMR and mass) together with its elemental analytical data are consistent with structure **5h**

(Scheme 3). Refluxing the latter **5h** with phosphoryl chloride yielded a product free of sulfur and was identified as 1,3,5-triphenyl-1,2,4-triazolo[3,4-c]-1,2,4-triazole **9** [8] by its alternative synthesis from 3-phenyl-5-methylthio-4*H*-1,2,4-triazole **6** and **2a** (Scheme 3). Thus, when equimolar quantities of **2a** and **6** were refluxed in ethanol in the presence of sodium ethoxide, a product identical in all respects (*m.p.*, mixed *m.p.*, IR and mass spectra) with **9** was produced.



Scheme 3

To account for the formation of **5** from **1** and **2**, the two possible reaction pathways A and B, outlined in Scheme 2, are suggested. It is assumed that **1** reacts with **2** *via* a primary 1,3-dipolar cycloaddition of the nitrilium imide, generated in situ from **2** by the action of the ethoxide anion, to the C=S in **1** to give **3** (Route A, Scheme 2). Similar cycloadditions of nitrilium imides to 5-aroylamino-3*H*-1,3,4-thiadiazole-2-thione [9] and 1,3,4-triphenyl-1,2,4-triazole-5-thione to give spirocycloadducts were reported [10]. Alternatively, reaction of **1** with **2** starts with initial formation of the thiohydrazonate ester **4** (Route B, Scheme 2) by analogy to the formation of other thiohydrazonates from *N*-phenyl benzenecarbohydrazonoyl chloride **2a** with 1-phenyltetrazole-5-thione [11] and 2-mercapto-4,6-dimethylpyrimidine [12]. The formed thiohydrazonate ester **4** cyclizes intramolecularly to give the spiro intermediate **3**. This is similar to that behaviour of *S*-(4,6-dimethylpyrimidin-2-yl)*N*-phenyl benzenecarbothiohydrazonate [12]. The spirocycloadduct **3** formed from either route A or B, in turn, undergoes a ring–chain tautomerism to give the end product **5**.

In an attempt to isolate the proposed spirocycloadduct **3**, the reaction of **2a** with 1-(1-morpholinomethyl)-3,4-diphenyl-1*H*-1,2,4-triazole-5-thione **1h** was investigated. In our hands, such a reaction, when carried out in ethanol in the presence of sodium ethoxide at room temperature gave **5a** directly. This finding suggests that the 1-morpholinomethyl group is cleaved during the course of the reaction and that such a cleavage occurs prior to the formation of the spirocycloadduct **3h** or **3a**. This conclusion is substantiated by our finding that treatment of **1h** with sodium ethoxide in ethanol at room temperature afforded **1a**.

On the basis of the foregoing results, it is not unreasonable to assume that both intermediates **3** and **4** are consumed as soon as they are formed during the studied reactions of **1** with **2**. Furthermore, the results of the present study show that the 1*H*-1,2,4-triazole-5-thione ring system of **1**, unlike that of 3*H*-1,3,4-oxadiazole-2-thione and 3*H*-1,3,4-thiadiazole-2-thione, is stable during the course of the reactions with hydrazonoyl halides **2** [9, 13, 14].

Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using Fourier Transform Infrared and Pye Unicam SP300 Infrared spectrophotometers. 1H NMR spectra were recorded in deuterated chloroform using a Varian Gemini 200 NMR spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX varian MAT 711 and SSQ 7000 spectrometers. Elemental analyses were carried out at the Microanalytical laboratory of Cairo University, Giza, Egypt. The hydrazonoyl chlorides (**2a–d**) [15–18], and the other reagents namely 3-phenyl-1*H*(4*H*)-1,2,4-triazole-5-thione **1g** [19], 3-phenyl-5-methylthio-4*H*-1,2,4-triazole **6** [19], and 1-(1-morpholinomethyl)-3,4-diphenyl-1*H*-1,2,4-triazole-5-thione (**1h**) [20] were prepared as previously described.

3,4-Diaryl-1H-1,2,4-triazole-5-thiones (**1a–f**)

The desired triazolethiones **1a–f** were prepared by cyclization of the corresponding 1-aroyl-4-phenylthiosemicarbazides under alkaline conditions following the known procedure [5a, 21]. The previously unreported derivative **2e** had *m.p.* 230 °C (EtOH). – MS *m/e* (I, %) = 333 (82), 332 (100), 331 (80), 272 (15), 252 (11), 149 (28), 126 (12), 117 (16), 102 (32), 90 (38), 77 (78), 51 (83). – IR (KBr)/cm^{-1} = 3100, 1402 (-NHCS-). The physical constants of the other triazolethiones **1a–d** and **1f** were similar to those previously reported [21, 22].

$C_{14}H_{10}BrN_3S$ (332.2) calcd.: C 50.60 H 3.01 N 12.65 S 9.64
found: C 50.5 H 3.0 N 12.4 S 9.6.

Reaction of 2 with the 3,4-Diaryl-1*H*-1,2,4-triazole-5-thiones (1a–h): Synthesis of Thiohydrazides 5a–h (General Procedure)

To a stirred ethanolic sodium ethoxide solution, prepared from sodium metal (0.23 g) and absolute ethanol (20 ml), was added the appropriate thione **1** (10 mmol), and the mixture was stirred

for 10 min. To the resulting solution was added the appropriate hydrazonoyl chloride **2** (10 mmol), and the resulting mixture was stirred at room temperature for 12 h during which **2** dissolved and the crude reaction product precipitated. The latter was filtered, washed with water, dried and finally crystallized from the proper solvent to give products **5a–h**.

5a: Yield 70%, *m.p.* 177 °C (EtOH/AcOH) – ^{1}H NMR ($CDCl_3$): δ/ppm = 7.8 (m, 20H), 10.2 (s, 1H). – IR (KBr): ν/cm^{-1} = 3282, 1416 (-NHCS-).

$C_{27}H_{21}N_5S$	calcd.:	C 72.48	H 4.69	N 15.66
(447)	found:	C 72.3	H 4.5	N 15.8.

5b: Yield 80%, *m.p.* 220 °C (EtOH/dioxane). – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.3 (s, 3H), 7.0–7.5 (m, 19H), 8.4 (s, 1H), 10.2 (s, 1H). – IR (KBr): ν/cm^{-1} = 3280, 1441 (-NHCS-),1659 (CO).

$C_{29}H_{24}N_6OS$	calcd.:	C 69.05	H 4.76	N 16.67
(504.2)	found:	C 69.0	H 4.8	N 16.7.

5c: Yield 80%, *m.p.* 212 °C (EtOH/AcOH). – ^{1}H NMR ($CDCl_3$): δ/ppm = 7.0–7.5 (m, 19H), 8.4 (s, 1H), 9.9 (s, 1H). – IR (KBr): ν/cm^{-1} = 3249, 1441 (-NHCS-), 1663 (CO).

$C_{28}H_{21}ClN_6OS$	calcd.:	C 64.06	H 4.00	N 16.02
(524.3)	found:	C 64.1	H 4.1	N 16.0.

5d: Yield 75%, *m.p.* 186 °C (EtOH)). – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.3 (t, 3H), 2.3 (s, 3H), 4.1 (q, 2H), 7.0–7.5 (m, 14H), 10.2 (s, 1H). – IR (KBr): ν/cm^{-1} = 3250, 1418 (-NHCS-), 1700 (CO).

$C_{25}H_{23}N_5O_2S$	calcd.:	C 65.65	H, 5.03	N 15.32
(457.5)	found:	C 65.7	H 5.0	N 15.3.

5e: Yield 75%, *m.p.* 162 °C (MeOH). – ^{1}H NMR ($CDCl_3$): δ/ppm = 1.3 (t, 3H), 4.1 (q, 2H), 7.0–7.5 (m, 14H), 10.2 (s, 1H). – IR (KBr): ν/cm^{-1} = 3289, 1441(-NHCS), 1736 (CO).

$C_{24}H_{20}ClN_5OS$	calcd.:	C 60.31	H 4.19	N 14.66
(477.6)	found:	C 60.2	H 4.1	N 14.6.

5f: Yield 75%, *m.p.* 198 °C (EtOH). – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.3 (s, 3H), 2.4 (s, 3H), 7.0–7.7 (m, 14H), 10.2 (s, 1H). – IR (KBr): ν/cm^{-1} = 3250, 1458 (-NHCS), 1674 (CO).

$C_{24}H_{21}N_5OS$	calcd.:	C 67.45	H 4.92	N 16.39
(427.3)	found:	C 67.5	H 4.9	N 16.3.

5g: Yield 76%, *m.p.* 196 °C (MeOH). – ^{1}H NMR ($CDCl_3$): δ/ppm = 2.4 (s, 3H), 7.1–7.6 (m, 14H), 10.2 (s, 1H). – IR (KBr): ν/cm^{-1} = 3280, 1431 (-NHCS-), 1674 (CO).

$C_{23}H_{18}ClN_5OS$	calcd.:	C 61.68	H 4.02	N 15.64
(447.4)	found:	C 61.7	H 4.0	N 15.7.

5h: Yield 75%, *m.p.* 126 °C (MeOH).– ^{1}H NMR ($CDCl_3$): δ/ppm = 7.0–8.0 (m, 15H), 8.5 (s, 1H), 10.15 (s, 1H). – IR (KBr): ν/cm^{-1} = 3282, 1415 (-NHCS-).

$C_{21}H_{17}N_5S$	calcd.:	C 67.92	H 4.58	N 18.87
(371.2)	found:	C 67.9	H 4.5	N 18.8.

When the above procedure was repeated using equimolar quantities of **1h** and **2a** the product isolated was found identical in all respects as **5a** obtained from the reaction of **1a** with **2a**.

Cyclization of *N*-Phenyl-*N*-(3-phenyl-1,2,4-triazol-5-yl)-Thiobenzoic Hydrazide (5h)

1,3,5-Triphenyl-1,2,4-triazolo[3,4-c]-1,2,4-triazol

To phosphoryl chloride (20 ml) was added **5h** (1.86 g, 5 mmol), and the mixture was refluxed for 4 h, then cooled. The reaction mixture was poured on ice-cold water containing sodium acetate. The solid that precipitated was collected by filtration, washed with water and crystallized from glacial acetic acid to give pure 1,3,5-triphenyl-1,2,4-triazolo[3,4-*c*]-1,2,4-triazole **9**, *m.p.* 248 °C (Lit. *m.p.* 244–246 °C [8]).

1,3,5-Triphenyl-1,2,4-triazolo[3,4-c]-1,2,4-triazole (**9**)

To a solution of **6** in ethanol (15 ml) containing sodium ethoxide (5 mmol) was added the chloride **2a** (5 mmol), and the mixture was refluxed for 6 h and cooled. The solid that precipitated was filtered, washed with water, dried and finally crystallized from acetic acid to give pure **9** identical in all respects (*m.p.*, mixed *m.p*, IR) with that obtained above from the reaction of **5h** with phosphoryl chloride.

Determination of Acid Dissociation Constants of 1a–f

The acid dissociation constants, pK_a's, of the compounds **1a–f** were determined potentiometrically in 80% by volume dimethylformamide–water mixture at 25 ± 0.1°C and ionic strength ($NaNO_3$) of 0.1. A Radiometer pH meter, accurate to ± 0.01 pH unit was used for recording pH values. The experimental procedure and calculations of pK_a constants are the same as previously described [7]. The pK_a values obtained were reproducible to within ± 0.01 pK_a unit. The results are summarized in Tab. 1.

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