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Synthesis of *N*-(3(5)-Aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas and Their Tautomerism in DMSO Solution

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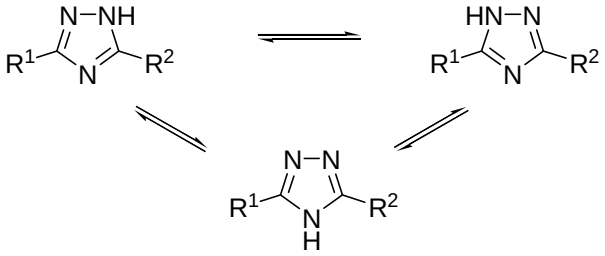
Abstract

N-(3(5)-Aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas were prepared from ethoxycarbonyl isothiocyanate and 3(5)-amino-5(3)-aryl-1,2,4-triazoles. The annular prototropic tautomerism in the compounds was investigated by ^{1}H NMR in DMSO solution. The tautomeric preferences depended on electronic properties of substituents on the phenyl ring and were well correlated with their Hammett constant values.

Introduction

Tautomerism is an intriguing phenomenon with a long history of investigation. Knowledge of the tautomeric preferences in organic molecules and the factors affecting the tautomeric equilibrium is essential for understanding the reactivity of compounds in chemical processes and their biological effects. The tautomerism in azoles has been a subject of discussion for many years.[1] Due to annular prototropic tautomerism, 1,2,4-triazoles without substituents on the ring nitrogen atoms, *a priori* can exist in three forms (Scheme 1). Analysis of the crystal data[2] showed that with rare exceptions,[3] unsymmetric 3,5-disubstituted 1,2,4-triazoles exist in the solid state as tautomer bearing an electron-acceptor substituent at position 3 and an electron-donor substituent at position 5. The precise experimental data on the annular tautomerism in 1,2,4-triazoles in solution are limited.[1] Tautomeric form with the hydrogen atom at N-1 adjacent to carbon atom bearing relatively less electronegative group was found to predominate in the solution. Recently, we identified the correlation between the Hammett constant of the substituents at *para*-position of the phenyl ring of 3(5)-amino-5(3)-aryl-1,2,4-triazoles and ΔG of the tautomeric equilibrium.[4]

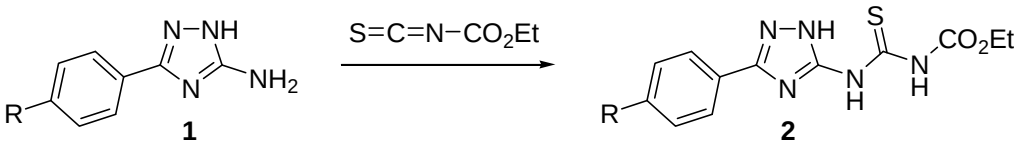
In this report, we established a similar relationship for structurally related *N*-(3(5)-aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**). Although this type of compounds is well known,[5] their structural properties, particularly tautomerism aspects remain unexplored.



Scheme 1

Results and Discussion

N-(3(5)-Aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**) were prepared *via* addition of ethoxycarbonyl isothiocyanate to 3(5)-amino-5(3)-aryl-1,2,4-triazoles (**1**) (Scheme 2). Despite several nucleophilic centres available in **1**, thermodynamically more stable products of the addition to exocyclic nitrogen *viz.* compounds **2** were isolated exclusively and with good yields (Table 1).



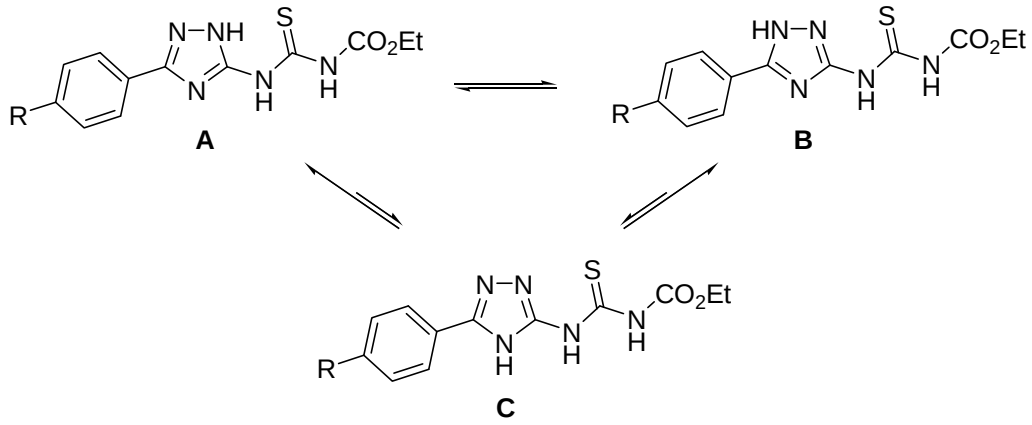
Scheme 2

Table 1. *N*-(3(5)-Aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**)

Compound	R	Yield, %	mp,[a] °C (solvent)
2a	H	85	180-181 (EtOH)[b]
2b	MeO	84	212 (EtOH)
2c	Me	80	215-216 (EtOH)
2d	F	86	209-210 (aq. EtOH)
2e	Cl	94	192-193 (EtOH)
2f	Br	88	220-221 (EtOH)
2g	CF_3	79	194-195 (aq. EtOH)
2h	NO_2	97	200-201 (EtOH)

[a] – with decomposition; [b] – lit.[5c] mp 178 °C

The tautomerism in triazoles **2** was studied using ^{1}H NMR spectroscopy (Table 2). To disfavor a potential intramolecular hydrogen bonding in the compounds due to the presence of C=S and CO_2Et hydrogen acceptors, DMSO-d_6 was used as a solvent. Similarly to our results[4] obtained previously for 3(5)-amino-5(3)-aryl-1,2,4-triazoles, forms **A** and **B** were found to be present in the solutions of triazoles **2**, while form **C** was not observed under the experimental conditions (Scheme 3). The equilibrium between the tautomers was established rapidly and the compositions did not change with time. The identical spectra of the tautomeric system **A-B** were observed instantaneously on dissolving the samples and after equilibration of the solution overnight.



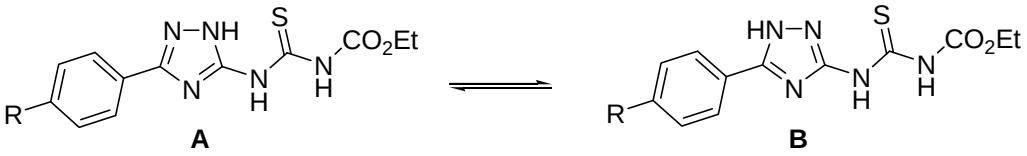
Scheme 3

The N(1)H signals of tautomers **A** and **B** in the ^{1}H NMR spectra in DMSO-d_6 were quite distinct allowing calculation of K_T values (Table 3). In comparison with parent 5-amino-1,2,4-triazoles **1**, compounds **2** had the mesomeric electronodonor effect of amino group compromised by the thiocarbonyl attached. That resulted in rather similar electronic properties of the aryl and carbethoxythiourea groups. Therefore, electronic properties of the substituents on the phenyl ring changed the predominant tautomeric form. Thus, form **B** was predominant for R = MeO, Me, H and F, while form **A** is major in case of more electronegative R (Cl, Br, CF_3 and NO_2). The K_T and ΔG_{298} values correlated well with the Hammett constant[6] of the substituents on the phenyl ring of **2** (Fig. 1). Therefore, the thermodynamic stability of form **A** in comparison with **B** increased proportionally the electron-withdrawing properties of the substituents R.

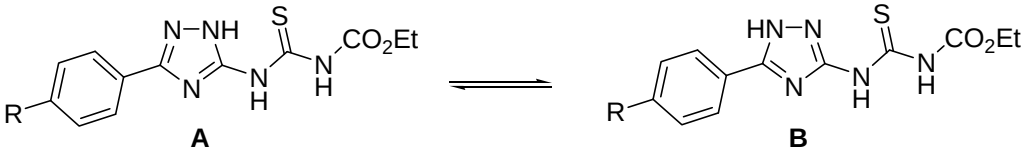
Table 2. ^{1}H NMR (300 MHz, DMSO-d_6) spectroscopic data of *N*-(3(5)-aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**)

Compd.	R	CO_2Et	Ar	tautomer **A**			tautomer **B**	
				NH	NH	N(1)H	2NH	N(1)H
2a	H	1.28, t, 3H, *J* = 7.1 Hz; 4.25, q, 2H, *J* = 7.1 Hz	7.37-7.66, m, 3H; 8.01, d, 2H, *J* = 7.2 Hz	11.87	12.16	13.93	11.56	14.47
2b	MeO	1.27, t, 3H, *J* = 7.0 Hz; 4.23, q, 2H, *J* = 7.0 Hz	6.98-7.20, m, 2H; 7.91, d, 2H, *J* = 8.7 Hz	11.82	12.05	13.77	11.54	14.24
2c	Me	1.27, t, 3H, *J* = 7.0 Hz; 4.24, q, 2H, *J* = 7.0 Hz	7.21-7.46, m, 2H; 7.87, d, 2H, *J* = 7.9 Hz	11.86	12.13	13.85	11.53	14.24
2d	F	1.27, t, 3H, *J* = 7.0 Hz; 4.24, q, 2H, *J* = 7.0 Hz	7.22-7.50, m, 2H; 8.01, dd, 2H, *J* = 8.7 Hz, $^{3}J_{HF}$ = 5.3 Hz	11.85	12.10	13.92	11.52	14.44
2e	Cl	1.29, t, 3H, *J* = 7.2 Hz; 4.26, q, 2H, *J* = 7.2 Hz	7.43-7.77, m, 2H; 8.01, d, 2H, *J* = 8.3 Hz	11.87	12.16	14.00	11.62	14.55
2f	Br	1.28, t, 3H, *J* = 7.0 Hz; 4.25, q, 2H, *J* = 7.0 Hz	7.61-7.85, m, 2H; 7.92, d, 2H, *J* = 8.3 Hz	11.86	12.13	14.00	11.59	14.55
2g	CF_3	1.28, t, 3H, *J* = 7.0 Hz; 4.25, q, 2H, *J* = 7.0 Hz	7.76-8.04, m, 2H; 8.19, d, 2H, *J* = 8.3 Hz	11.88	12.12	14.13	11.57	14.74
2h	NO_2	1.28, t, 3H, *J* = 7.0 Hz; 4.26 q, 2H, *J* = 7.0 Hz	8.23, d, 2H, *J* = 8.7 Hz; 8.29-8.48, m, 2H	11.89	12.13	14.25	11.58	14.86

Table 3. Tautomerism in *N*-(3(5)-aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**) in DMSO-d_6 solution



Compound	R	K_T	ΔG_{298}
2a	H	1.35	-0.74
2b	MeO	2.56	-2.33
2c	Me	1.89	-1.58
2d	F	1.08	-0.19
2e	Cl	0.81	0.52
2f	Br	0.79	0.58
2g	CF_3	0.47	1.87
2h	NO_2	0.32	2.82



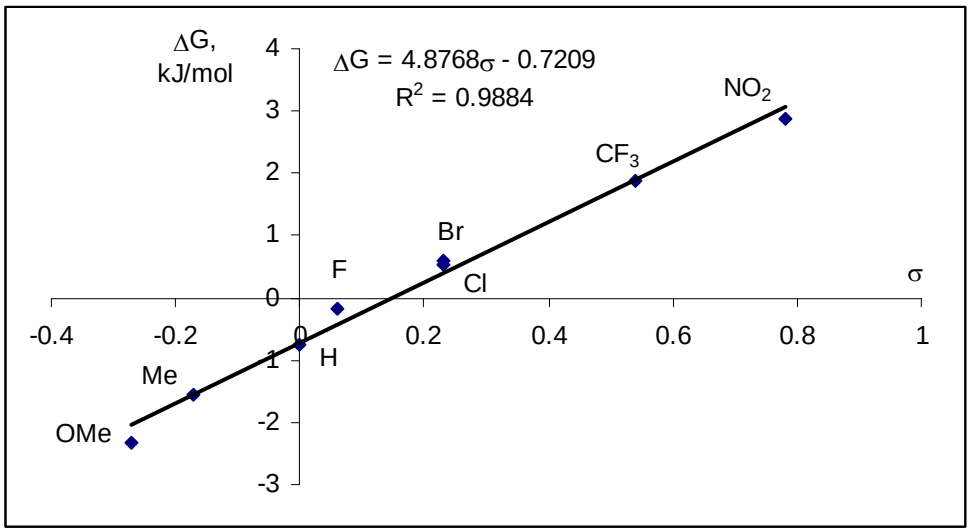


Figure 1. Correlation of ΔG for the tautomeric equilibrium of *N*-(3(5)-aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**) with the Hammett constant (σ) of the R group.

In conclusion, *N*-(3(5)-aryl-1,2,4-triazol-5(3)-yl)-*N'*-carbethoxythioureas (**2**) were successfully prepared and effect of the substituents on the tautomerism was studied.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker DPX-300 spectrometer in DMSO-d_6 and using TMS as an internal standard.

*General method for preparation of N-(3(5)-aryl-1,2,4-triazol-5(3)-yl)-N'-carbethoxythioureas (**2**).*

To the fine suspension of the corresponding 3(5)-amino-5(3)-aryl-1,2,4-triazole **1** (3.0 mmol) in anhydrous DMF (4 ml), ethoxycarbonyl isothiocyanate (3.3 mmol) was added. After stirring the mixture for 4.5-5.0 h at rt, cold water (50-60 ml) was added. The precipitated product was filtered, washed with cold water and recrystallized from EtOH or aqueous EtOH.

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