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Synthesis of 5-amino-3-(het)aryl-1*H*-1,2,4-triazoles *via* cyclization of (het)aroylaminoguanidines in aqueous medium

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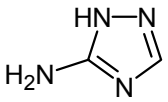
Abstract

The effective and clean procedure for the preparation of 5-amino-3-(het)aryl-1,2,4-triazoles (**3a-c**) *via* cyclization of (het)aroylaminoguanidines (**2a-c**) in water was reported. Two tautomeric forms, namely 5-amino-3-(het)aryl-1,2,4-triazoles (**A**) and 3-amino-5-(het)aryl-1,2,4-triazoles (**B**) were found to exist in tautomeric equilibrium. Form **A** was a predominant tautomer in DMSO solution (K_T = 9-33).

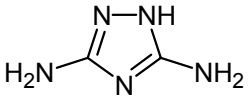
Key words: 1,2,4-triazoles, acylaminoguanidines, cyclization, aqueous medium, tautomerism.

Introduction

The 3(5)-amino-1,2,4-triazoles are known to be biologically active compounds. For example, the 5-amino-1,2,4-triazole itself has been used as the pesticide Amitrole and 3,5-diamino-1,2,4-triazole (Guanazole) is an antitumor drug that inhibits ribonucleotide reductase and DNA synthesis.



Amitrole



Guanazole

The 3(5)-amino-1,2,4-triazoles play a very important role as amidine type synthons in heterocyclic chemistry [1,2]. They are particularly useful for the syntheses of fused ring systems, such as imidazo[1,2-*b*][1,2,4]triazole, imidazo[2,1-*c*][1,2,4]triazole, 1,2,4-triazolo[1,5-a]pyrimidine and 1,2,4-traizolo[1,5-*a*][1,3,5]triazine possessing a variety of biological effects.

Heating several (het)aroylaminoguanidines, including **2a-c**, at 220-250 ºC has been reported to give 5-amino-3-(het)aryl-1,2,4-triazoles as cyclization products [3-5]. The intramolecular cyclization of **2a** with refluxing sodium ethoxide has been found to afford the formation of 5-amino-3-phenyl-1,2,4-triazole (**3a**) in low yield [3].

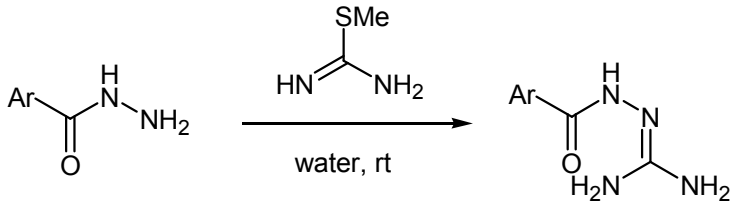
It has been shown that using water as a solvent may provide several advantages in many organic chemistry processes [6,7].

In this report we describe a new effective and clean method of preparation of 5-amino-3-(het)aryl-1,2,4-triazoles (**3a-c**) from **2a-c** in aqueous medium. The annular tautomerism in the obtained triazoles (**3a-c**) was investigated using NMR spectral data.

Results and discussion

The reaction of benzhydrazide (**1a**) with methyl isothiourea (Scheme 1) according to the reported method [3] was used for the preparation of benzamidoguanidine (**2a**). Nicotinamidoguanidine (**2b**) and isonicotinamidoguanidine (**2c**) were synthesized analogously from the appropriate hydrazides (**1b**,**c**).

Scheme 1

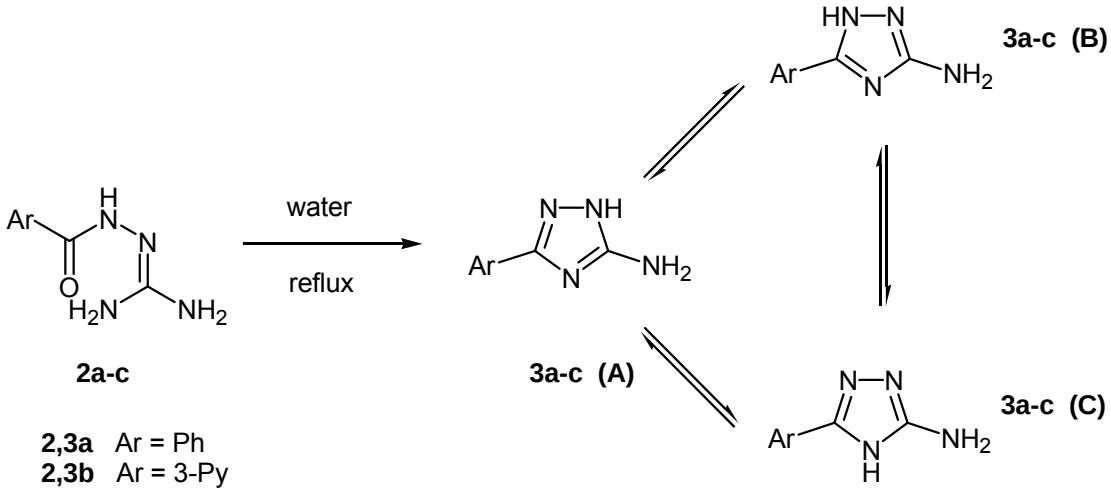


1a-c **2a-c**

1,2a Ar = Ph
1,2b Ar = 3-Py
1,2c Ar = 4-Py

When the (het)aroylaminoguanidines (**2a-c**) were heated in water (Scheme 2), 5-amino-3-(het)aryl-1,2,4-triazoles (**3a-c**) were obtained in almost quantitative yields (97-98%). The reaction was found to be clean and afforded products (**3a-c**) with satisfactory purity. Interestingly, heating **2a-c** at 140 ºC without solvent for 24 h did not result in the formation of triazoles **3a-c**.

Scheme 2



2a-c

2,3a Ar = Ph
2,3b Ar = 3-Py
2,3c Ar = 4-Py

Annular tautomerism is possible in the prepared triazoles (**3a-c**); they may exist in three tautomeric forms (**A**, **B** and **C**). A study of triazoles (**3a-c**) in DMSO solution using NMR spectroscopy concluded that the tautomer **A** dominated in the equilibrium. The tautomer **B** was found to be a minor, whereas the form **C** was not present to any measurable extent. The characteristic signals of ^{1}H NMR spectra of tautomers **A** and **B** as well as the tautomeric equilibrium constant (K_T) and the relative Gibbs free energies (ΔG_{298}) of individual tautomers.

Table

Tautomerism in 5(3)-amino-3(5)-(het)aryl-1,2,4-triazoles (**3a-c**)

Compound	^{1}H NMR signals of tautomeric forms **A** and **B** in DMSO-d_6, ppm				K_T	ΔG_{298}, kJ mol^{-1}
	3(5)-NH_2		H-N(1)			
	A	**B**	**A**	**B**		
2a	6.12	5.39	12.09	13.24	9	-5.4
2b	6.21	5.43	12.24	13.44	20	-7.4
2c	6.28	5.52	12.40	13.69	33	-8.7

In the conclusion, the cyclization of (het)aroylaminoguanidines (**2a-c**) in the aqueous medium seems to be an effective method for preparation of 5-amino-3-(het)aryl-1,2,4-triazoles (**3a-c**) which are predominant tautomers in the equilibrium with 3-amino-5-(het)aryl-1,2,4-triazoles.

Experimental

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-d_6 as a solvent and TMS as an internal reference.

(Het)aroylaminoguanidines (**2a-c**) were prepared from hydrazides of appropriate acide (**1a-c**), methyl isothiourea sulfate and sodium hydroxide in water according to the reported method [3].

*Benzamidoguanidine (**2a**)*

Yield 86%, mp 176 ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.97 (2H, br. s, NH_2), 7.16 (2H, br. s, NH_2), 7.29 (3H, m, $W_{1/2}$ = 9 Hz, H-3, H-4 and H-5), 7.95 (2H, m, $W_{1/2}$ = 12 Hz, H-2 and H-6), 11.01 (1H, br. s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 126.5 (C-3 and C-5), 127.3 (C-2 and C-6), 128.0 (C-4), 138.5 (C-1), 152.9 (N=*C*$(NH_2)_2$), 160.5 (C=O).

*Nicotinamidoguanidine (**2b**)*

Yield 72%, mp 211-212 ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.08 (2H, s, NH_2), 7.12 (2H, s, NH_2), 7.33 (1H, dd, *J* = 7.5, 4.9 Hz, H-5), 8.24 (1H, dt, *J* = 7.9, 1.9 Hz, H-4), 8.49 (1H, dd, *J* = 4.5, 1.5 Hz, H-6), 9.14 (1H, dd, *J* = 1.1 Hz, H-2), 10.86 (1H, br. s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 122.6 (C-5), 133.6 (C-3), 133.7 (C-4), 148.2 (C-6), 148.7 (C-2), 152.9 (N=*C*$(NH_2)_2$), 158.7 (C=O).

*Isonicotinamidoguanidine (**2c**)*

Yield 76%, mp 270-271 ºC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.97 (2H, s, NH_2), 7.08 (2H, s, NH_2), 7.84 (2H, dd, *J* = 4.5, 1.5 Hz, H-3 and H-5), 8.50 (2H, dd, *J* = 4.5, 1.5 Hz, H-2 and H-6), 10.66 (1H, br. s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 121.1 (C-3 and C-5), 146.0 (C-4), 149.0 (C-2 and C-6), 152.9 (N=*C*(NH_2)$_2$), 158.7 (C=O).

*5-Amino-3-(het)aryl-1,2,4-triazoles (**3a-c**)*

(Het)aroylaminoguanidines (**2a-c**) (0.02 mole) were heated under reflux in 15 ml of water for 3-5 h. After cooling, the precipitated triazoles (**3a-c**) were filtered, washed with ice-cold water and dried. The prepared compounds were sufficiently pure and could be used without further purification. After recrystallization from water mp of the compounds did not change.

*5-Amino-3-phenyl-1H-1,2,4-triazole (**3a**)*

Yield 97%, mp 186-187 ºC (lit. mp. 186-187 ºC [3]).

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.12 (2H, s, NH_2), 7.28-7.52 (3H, m, H-3', H-4' and H-5'), 7.92 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 12.09 (1H, s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 126.3 (C-3' and C-5'), 128.1 (C-4'), 128.3 (C-2' and C-6'), 132.3 (C-1'), 157.3 (C5), 158.3 (C3).

*5-Amino-3-pyridin-3-yl-1H-1,2,4-triazole (**3b**)*

Yield 98%, mp 224-225 ºC (lit. mp. 223 ºC [4]).

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.21 (2H, s, NH_2), 7.44 (1H, dd, *J* = 7.5, 4.9 Hz, H-5), 8.19 (1H, dt, *J* = 7.9, 1.9 Hz, H-4), 8.55 (1H, d, *J* = 4.1 Hz, H-6), 9.07 (1H, dd, *J* = 1.5 Hz, H-2), 12.24 (1H, s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 123.6 (C-5'), 127.8 (C-3'), 132.4 (C-4'), 146.5 (C-6'), 149.0 (C-2'), 156.1 (C-3), 157.5 (C-5).

*5-Amino-3-pyridin-4-yl-1H-1,2,4-triazole (**3c**)*

Yield 98%, mp 272-274 ºC (lit. mp. 273-274 ºC [4,5]).

^{1}H NMR (300 MHz, DMSO-d_6): δ 6.28 (2H, s, NH_2), 7.81 (2H, dd, *J* = 4.9, 1.5 Hz, H-3 and H-5), 8.62 (2H, dd, *J* = 4.9, 1.5 Hz, H-2 and H-6), 12.40 (1H, s, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ 119.5 (C-3 and C-5), 139.2 (C-4), 149.9 (C-2 and C-6), 156.4 (C-3), 157.6 (C-5).

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