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SOLID ACID INDUCED CYCLOCONDENSATION: A FACILE, ONE-POT SYNTHESIS OF 7H-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINES

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7H-[1,2,4]Triazolo[3,4-b][1,3,4]thiadiazines are synthesized in good yields by the catalytic action of sulfuric acid adsorbed on silica gel. Starting from 4-amino-5-substituted-1,2,4-triazole-3-thiones and employing cyclocondensation reaction with α -chloroacetonitrile and α -haloketones, the desired triazolothiadiazines have been synthesized satisfactorily.

Keywords: α -Haloketones; cyclocondensation; solid acid; triazolothiadiazine

INTRODUCTION

7H-[1,2,4]Triazolo[3,4-b][1,3,4]thiadiazines are a class of heterocycles with known antimicrobial¹ and analgesic activities.² The routes to these fused heterocyclic compounds ideally involve cyclocondensation of 4-amino-5-substituted-1,2,4-triazole-3-thiones with α -chloroacetonitrile or α -haloketones in neutral or basic media.³ An examination of the literature disclosed that acid catalyzed cyclocondensation of these compounds to their corresponding 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines have received relatively little attention and only one article was found that showed the use of an acid catalyst for this conversion.¹

In connection with our work on the use of solid acids as promoters for fine chemical preparations,⁴ and in the course of our

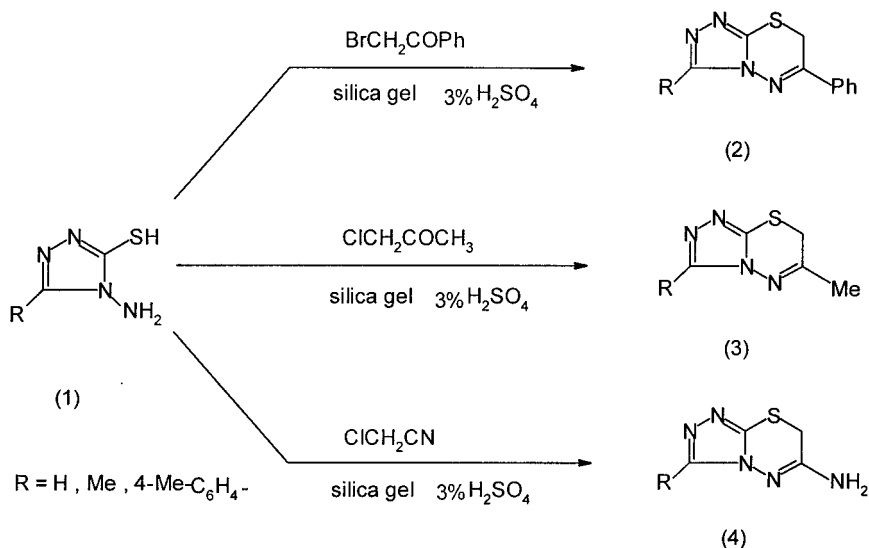
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investigations towards the synthesis of heterocyclic systems via heterocyclization reactions,⁵ we deemed it interesting to study the cyclocondensation of 4-amino-5-substituted-1,2,4-triazole-3-thiones **1** with α -chloroacetonitrile and α -haloketones in the presence of a solid acid. We have found that the one-pot cyclocondensation of the triazole **1** with either reagents can be carried out in good yield over sulfuric acid adsorbed on silica gel to give the desired 7H-[1,2,4,]triazolo[3,4-b][1,3,4]thiadiazines **2-4**.

The catalyst is easily prepared by mixing chromatographic grade silica (Merck, kieselgel 60, 70–230 mesh) with 3% of its weight with sulfuric acid dissolved in acetone following a reported procedure.⁶ This catalyst, a yellow-brown powder, can be stored in a dessicator for a long period of time without appreciable loss of activity.

The required 4-amino-5-substituted-1,2,4-triazole-3-thiones **1** were prepared as previously reported.⁷

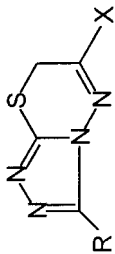
These compounds with α -chloroacetonitrile and α -haloketones underwent cyclocondensation when treated with finely ground sulfuric acid adsorbed on silica gel in boiling ethanol or isopropanol to yield 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **2-4** (Scheme 1).



SCHEME 1

The structure assigned to compounds **2-4** was on the basis of their analytical and spectral data (Table I) and in the case of known compounds by comparison with authentic samples.

TABLE I Analytical and Spectral Data of Triazolothiadiazines 2-4



Compound		R	X	m.p. °C (lit. mp)	Yield %	Molecular formula	C		H		N		S	δ (Dimethyl sulfoxide) (Multiplicity, assignment)
							Calcd. (Found)		Calcd. (Found)		Calcd. (Found)		Calcd. (Found)	
2a	H		Ph	226–227 (225)[8]	75	C ₁₀ H ₈ N ₄ S	55.56 (55.54)	3.70 (3.74)	25.92 (25.91)	14.82 (14.81)	8.42 (s, 1H, triazole), 8.40–7.57 (m, 5H, ph), 4.52 (s, 2H, S–CH ₂)			
2b	Me		Ph	162–163 (161–163)[9]	80	C ₁₁ H ₁₀ N ₄ S	57.40 (57.44)	4.34 (4.31)	24.34 (24.3)	13.92 (13.93)	7.94–7.5 (m, 5H, ph), 4.00 (s, 2H, S–CH ₂), 2.59 (s, 3H, CH ₃ , Triazole)			
2c	4-Me-C ₆ H ₄		Ph	200–201 (198–99)[1]	82	C ₁₇ H ₁₄ N ₄ S	66.67 (66.64)	4.57 (4.59)	18.30 (18.28)	10.46 (10.49)	9.01–7.23 (m, 9H, aromatic), 4.00 (s, 2H, S–CH ₂), 2.39 (s, 3H, CH ₃ –Ar)			
3a	H		NH ₂	270–271	67	C ₄ H ₅ N ₅ S	30.96 (30.90)	3.23 (3.27)	45.17 (45.2)	20.65 (20.63)	9.87 (s, 1H, triazole), 7.1 (s, 2H, NH ₂), 3.17 (s, 2H, S–CH ₂)			
3b	Me		NH ₂	255–256	65	C ₅ H ₇ N ₅ S	35.50 (35.51)	4.14 (4.18)	41.42 (41.38)	18.94 (18.92)	7.03 (s, 2H, NH ₂), 3.65 (s, 2H, S–CH ₂), 2.27 (s, 3H, CH ₃ , triazole)			
3c	4-Me-C ₆ H ₄		NH ₂	257–258 (255–56)[1]	70	C ₁₁ H ₁₁ N ₅ S	53.87 (53.86)	4.49 (4.45)	28.58 (28.62)	13.06 (13.07)	7.94–7.33 (d,d, 4H, aromatic), 6.29 (s, 2H, NH ₂), 4.34 (s, 2H, S–CH ₂), 2.4 (s, 3H, CH ₃ –Ar)			
4a	H		Me	85–86 (85–87)[10]	60	C ₅ H ₆ N ₄ S	38.96 (38.9)	3.89 (3.82)	36.37 (36.45)	20.78 (20.83)	9.55 (s, 1H, triazole), 4.23 (s, 2H, S–CH ₂), 2.5 (s, 3H, CH ₃)			
4b	Me		Me	103–104	75	C ₆ H ₈ N ₄ S	42.86 (42.78)	4.79 (4.74)	33.34 (33.4)	19.04 (19.08)	3.81 (s, 2H, S–CH ₂), 2.39 (s, 3H, CH ₃ , triazole), 2.29 (s, 3H, CH ₃)			
4c	4-Me-C ₆ H ₄		Me	250–251	70	C ₁₂ H ₁₂ N ₄ S	59.01 (59.03)	4.92 (4.94)	22.95 (22.93)	13.12 (13.10)	9.07–7.6 (m, 4H, aromatic), 4.2 (s, 2H, S–CH ₂), 2.57 (s, 3H, CH ₃ –Ar), 2.38 (s, 3H, CH ₃)			

In summary, the 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines have been synthesized by a convenient method using sulfuric acid adsorbed on silica gel as the catalyst.

EXPERIMENTAL SECTION

M.P.s were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Shimadzu Spectrometer as KBr disk. ¹H NMR spectra were recorded on a Bruker (100 MHz) instrument. Mass spectra were obtained from Varian CH-7 at 70 eV. Microanalysis were performed by Tarbiat Modarres University, Tehran, Iran.

General Procedure for the Preparation of 7H-3-Substituted-6-phenyl-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazines 2a–c

A mixture of **1** (1 mmol), phenacyl bromide (1 mmol), and finely ground sulfuric acid adsorbed on silica gel (0.2 g) in isopropanol (5 ml) was refluxed for 4 h and filtered. The filtrate was concentrated and the precipitate recrystallized from ethanol to give white to pale yellow crystals (data in Table I).

General Procedure for the Preparation of 7H-3-Substituted-6-methyl-[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazines 3a–b

A mixture of **1** (1 mmol), chloroacetone (1 mmol), and finely ground sulfuric acid adsorbed on silica gel (0.2 g) in ethanol (5 ml) was refluxed for 5 h. The catalyst was filtered off and the filtrate was concentrated. The precipitate was recrystallized from ethanol to give white to pale yellow crystals (data in Table I).

General Procedure for the Preparation of 7H-3-Substituted-6-amino[1,2,4]triazolo-[3,4-b][1,3,4]thiadiazines 4a–b

A mixture of **1** (1 mmol), α -chloroacetonitrile (2 mmol), and finely ground sulfuric acid adsorbed on silica gel (0.2 g) was refluxed for 6 h. After removing the catalyst and concentrating the filtrate, the residue was recrystallized from ethanol to give white to pale yellow crystals (data in Table I).

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