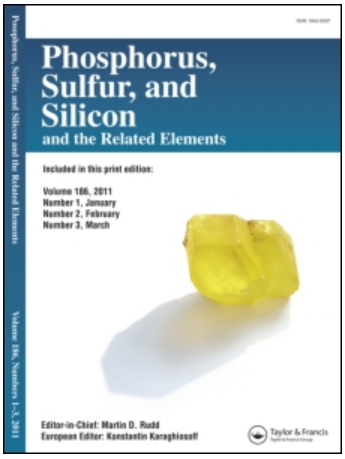


**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# 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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Online publication date: 27 October 2010

**To cite this Article** Heravi, M. M. , Bakherad, M. , Rahimzadeh, M. and Bakavoli, M.(2002) 'Solid Acid Induced Cyclocondensation: A Facile, One-Pot Synthesis of 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 10, 2403 — 2407
**To link to this Article: DOI:** 10.1080/10426500214303
**URL:** http://dx.doi.org/10.1080/10426500214303

*Phosphorus, Sulfur and Silicon*, 2002, Vol. 177:2403–2407

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290110432

# 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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(Received December 4, 2001; accepted January 29, 2002)



*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 sillica 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 satisfactorilly.*

*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 antimicrobial[1] 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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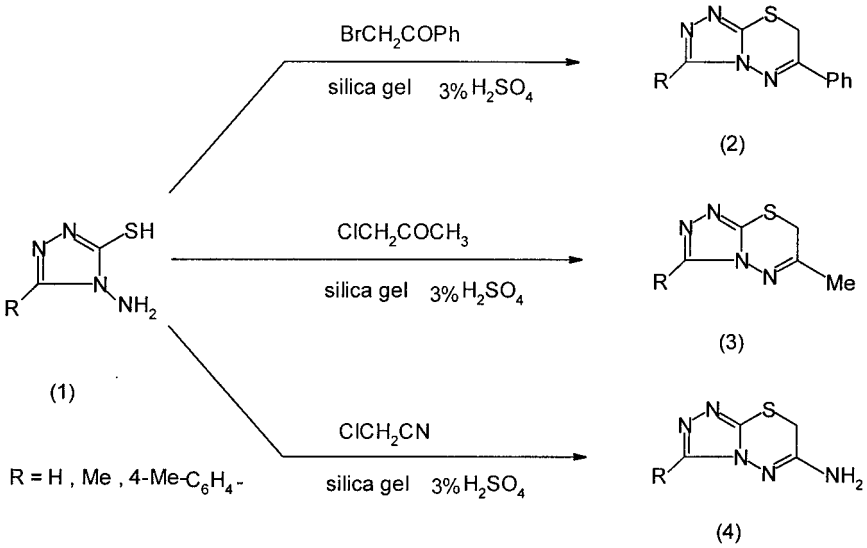
investigations towards the synthesis of heterocyclic systems via heterocyclization reactions,[5] we deemed it interesting to study the cyclocondensation of 4-amino-5-substituted-1,2,4-triazole-3-thiones **1** with $\alpha$-chloroacetonitrile and $\alpha$-haloketones in the presence of a solid acid. We 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]

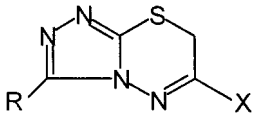
These compounds with $\alpha$-chloroacetonitrile and $\alpha$-haloketones underwent cyclocondensation when treated with finely ground sulfuric acid adsorbed on silica gel in boiling ethanol or isopropanol to yield 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **2–4** (Scheme 1).




**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 Calcd. (Found) | H Calcd. (Found) | N Calcd. (Found) | S Calcd. (Found) | δ (Dimethyl sulfoxide) (Multiplicity, assignment) |
|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | H | Ph | 226–227 (225)[8] | 75 | $C_{10}H_8N_4S$ | 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 | $C_{11}H_{10}N_4S$ | 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-$C_6H_4$ | Ph | 200–201 (198–99)[1] | 82 | $C_{17}H_{14}N_4S$ | 66.67 (66.64) | 4.57 (4.59) | 18.30 (18.28) | 10.46 (10.49) | 9.01–7.23 (m, 9H, aramatic), 4.00 (s, 2H, S—$CH_2$), 2.39 (s, 3H, $CH_3$—Ar) |
| **3a** | H | $NH_2$ | 270–271 | 67 | $C_4H_5N_5S$ | 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 | $C_5H_7N_5S$ | 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-$C_6H_4$ | $NH_2$ | 257–258 (255–56)[1] | 70 | $C_{11}H_{11}N_5S$ | 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 | $C_5H_6N_4S$ | 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 | $C_6H_8N_4S$ | 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-$C_6H_4$ | Me | 250–251 | 70 | $C_{12}H_{12}N_4S$ | 59.01 (59.03) | 4.92 (4.94) | 22.95 (22.93) | 13.12 (13.10) | 9.07–7.6 (m, 4H, aramatic), 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 Schimadzu Spectrometer as KBr disk. $^1$H 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), $\alpha$-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).

## REFERENCES


[1] N. F. Eweiss and A. A. Bahajaj, *J. Heterocycl. Chem*., **24,** 1173 (1987).

[2] G. Turan Zitouni, Z. A. Kaplacikli, K. Erol, and F. S. Kilias, *Farmaco*, **54,** 4, 218 (1999).

[3] (a) B. N. Goswami, J. C. S. Kataky, and J. N. Barwah, *J. Heterocycl. Chem*., **23,** 1439 (1986); (b) B. S. Holla, B. Kalluraya, and K. R. Stridhar, *Rev. Roum. Chim*., **33,** 277 (1988); *C. A*. **109,** 190372n; (c) Z. K. Abd El-Samie, M. J. AL-Ashmawi, B. Abd EL-Fattah, *Egypt J. Pharm, Sci*., **29,** 251 (1988); *C. A*. **110,** 231589e; (d) J. Mohan, *Chim. Acta. Turc*., **16,** 91 (1988); C. A. **111,** 232685r; (e) J. Mohan, G.S.R. Anjaneyulu, and K. V. S. Yamini, *Indian J. Chem*. Sect. B, **29B** 88 (1990); (f) H. M. Eisa, *Sulfur. Lett*., **10,** 239 (1990); (g) J. Mohan and P. Verma, *J. Indian Chem. Soc.*, **69,** 298 (1992); (h) B. S. Kalluraya, Holla. *Indian J. Heterocycl. Chem*., **2,** 245 (1993).

[4] M. M. Heravi, Montazeri, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *J. Chem. Res*., 464 & 584 (2000).

[5] (a) M. Bakavoli, A. Khodadady, M. Gassemzadeh, and M. M. Heravi, *Phosphorus, Sulfur, and Silicon*, **170,** 191 (2001); (b) M. M. Heravi, N. Montazeri, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *ibid*., **170,** 187 (2001); (c) M. Bakavoli, M. H. Ghorbani, M. Rahimizadeh, M. Gassemzadeh, and M. M. Heravi, *ibid*., **170,** 87 (2001); (d) *Indian J. Heterocycl. Chem*., **9,** 277 (2001); (e) M. Bakavoli, H. Germaninejad, M. Rahimizadeh, and M. M. Heravi, *Indian J. Heterocycl. Chem*., **10,** 317 (2001).

[6] F. Charez and R. Codinez, *Synth. Commun*., **22,** 159 (1992).

[7] (a) J. R. Reid and N. D. Heindel, *J. Heterocycl. Chem*., **13,** 925 (1976); (b) H. Beyer, C. F. Kroger, and G. Busse, *Ann. Chem*., **637,** 135 (1960).

[8] S. Bala, R. P. Gupta, M. L. Sachderva, A. Singh, and H. K. Pujari, *Indian J. Chem*., **16B,** 481 (1978).

[9] T. Saskai, E. Ito, and I. Shimizu, *J. Org. Chem*., **47,** 2757 (1982).

[10] K. S. Dhada, J. Mohan, V. K. Chadha, and H. K. Pujari, *Indian J. Chem*., **12,** 287 (1974); *C. A.*, **81,** 1366118z.