J. Sci. I. R. Iran

Vol.10 No.
Summer 199

Research Note

A CONVENIENT AND GENERAL SYNTHESIS OF THIADIAZOLO [2,3-C] [1,2,4] TRIAZINES

M.M. Heravi* and Sh. E. Khadem

Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Islamic Republic of Iran

Abstract

Condensation and cyclization of 5-hydroxy-1,2,4-thiadiazol-2-yl hydrazine **1** with pyruvic acid, phenacyl bromide, propargyl bromide and allyl bromide afforded compounds **2,5,7 3,4,6** and **8** respectively. Reaction of **1** with epichlorohydrine afforded 4-hydroxy-N-[5-hydroxy-1,3,4-thiadiazolyl] pyrazolidine **9**.

Nitrogen heterocycles, analogues of purine are of considerable commercial importance as pharmaceuticals, veterenary anthelmintics and fungicides [1].

In continuation of our study on the chemistry of heterocyclic fused rings with bridgehead nitrogen atoms [2-7] and in view of possible biological activity, the synthesis of a series of 7-hydroxy 1,3,4-thiadiazolo [2,3,-c] [1,2,4] triazines was achieved.

Two routes were found for the synthesis of thiadiazolo [2,3-c] [1,2,4] triazine. The more straight forward route starts with 4-amino-3-thio-1,2,4-triazine derivatives [8-12]. An alternative two step synthesis, starting with thiadiazolyl hydrazine according to the method of Shafiee et al [13] seems also promising since different derivatives of thiadiazoles such as **1** are available. Here we wish to report the synthesis of new derivatives of thiadiazolo 1,2,4-triazines by use of this methodology, starting from **1**. By use of propargyl bromide an exo methylene was created for further manipulation, for functionalization and by use of allyl bromide a model study directed towards a practical diastereo selective synthesis of fused thiazole ring has been designed.

Keywords: Thiadiazolotriazine; Thiadiazole; Functionalization; General route

*Corresponding author: Chemistry and Chemical Engineering Research Center of Iran, P.O.Box, 14335-186, Tehran, Islamic Repbulic of Iran

5-Hydroxy-thiadiazolo-2-yl hydrazine **1** was synthesized from the reaction of thiohydrocarbazide and ethonylthio carbonyl thio acetic acid according to Kruzer procedure [14]. Compound **1** was condensed with pyruvic acid to afford pyruvic acid [2-hydroxy-1,3,4-[thiazolyl hydrazone] **2**. When **2** was heated in glacial acetic acid under reflux, 3-methyl-7-hydroxy-4H-1,3,4-thiadiazolo [2,3-c] [1,2,4] triazine -4-one **3** was obtained. One pot condensation and cyclization occurred when **1** was reacted

with phenacyl bromide. The product was identified as 4-phenyl-7-hydroxy, -2H-1,3,4-thiadiazolo [2,3-c] [1,2,4] triazine **4**.

Treatment of **1** with propargyl bromide in presence of catalytic amount of triethylamine gave 2-[2-propargylhydrazino]-5-hydroxy-1,3,4-thiadiazole **5**. We have recently described the use of Pd-salt for implementation of sequential carbometallation anion capture [15-18] and catalyzed intramolecular cyclization and functionalization of acetylenes [4,19,20,21]. Armed with these experiences, compound **5** was refluxed with a catalytic amount of bis (benzonitrile) palladium chloride [22] and triethylamine in a mixture of CH_3CN, CH_3OH, 2:1 for a long period of time to afford 2H, 3H-4-methylene-7-hydroxy-1,3,4-thiadiazolo [2,3-c] [1,2,4] triazine **6**.

Condensation of **1** with allyl bromide in refluxing acetonitrile gave -2-(2-allyl hydrazino)-5-hydroxy-1,3,4-thiadiazolo **7**. Acid catalyzed cyclization [23] of **7** gave 2H, 3H-4-methyl-7-hydroxy-thiadiazolo [2,3-c] [1,2,4] triazine **8**. This compound has a chiral center and can be considered as a model for possible asymmetric synthesis of thiadiazolo-1,2,4-triazines.

An interesting reaction took place when **1** was reacted with epichlorohydrine. **1** was refluxed with epichlorohydrine in a mixture of CH_3CN, MeOH, 1:1 for 4 h. After evaporation of solvent and crystallization white needles were obtained. From spectroscopic data structure **9** which is 4-hydroxy-N [5-hydroxy-1,3,4 thiadiazolyl] pyrazolidine, was assigned for the compound.

Experimental Section

The melting points are uncorrected and were obtained by a Koffer Richart type 7841 melting point apparatus. The IR spectra was obtained on a 4300 Shimadzu Spectrometer. The ^1H NMR spectra were recorded on a Varian 50A Spectrometer 60 MHZ using TMS as internal reference and mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

Pyruvic Acid [5-Hydroxy (1,3,4-thiadiazol-2-yl) hydrazone]

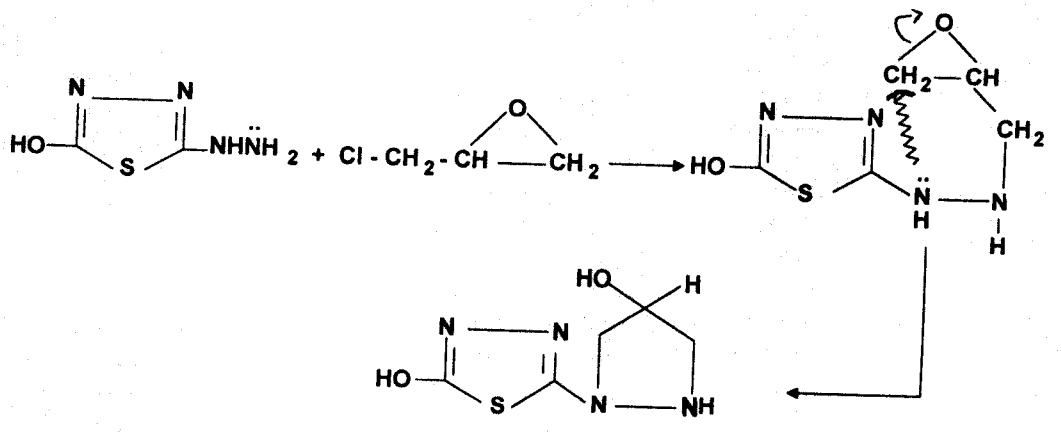
Compound **1** (0.3g; 2mmol) and pyruvic acid (0.18g, 2 mmol) were refluxed in ethanol (30 ml) for 2 h. The reaction mixture was cooled to room temperature. The yellow crystals were filtered off, washed with water and crystallizaed from pet-ether (60-80) Yield: 0.2g, 54%, mp 178-179°C, ^1H NMR, $\delta(CCl_4)$, 2(s, 3H, Me), 7.3 (s, 1H, NH), 10.5 (s, 1H, OH), 10.8 (s, 1H, COOH). IR (KBr disk) 3100 (OH), 1710 (C=O), 1540 (C-N), 1280 (NH) Cm^{-1}. M.S., M^+; m/z, 202.

4H-3-Methyl-7-hydroxythiadiazolo [2,3-c] [1,2,4] triazin-4-one 3

Compound **2** (0.2g, 1 mmol) was refluxed in glacial acetic acid for 7 h. The solvent was evaporated off in a vacuum. The crude was extracted with $CHCl_3$ to afford the title compound. Yield: 0.138, 75%, m.p. 183-185 C., ^1H NMR, δ (CCl_4), 2 (s, 3H, Me), 10.5 (s, 1H, OH), IR (KBr disk), 3100 (OH), 1710 (C=O) Cm^{-1}, M.S. M^+, m/z 184.

4-phenyl-7-hydroxythiadiazolo [2,3-c] [1,2,4] triazine 4

Compound 1 (0.3g, 2 mmol) and phenacyl bromide (0.4g, 2 mmol) were refluxed for 8 h in ethanol (30 ml). The reaction mixture was cooled to 4°C. The precipitate



Scheme 1

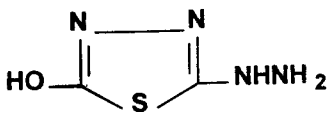
was filtered and crystallized from EtOH to afford the title compound Yield: 0.3g, 65%, mp 134-136°C, ^{1}H NMR, δ (CDCl3), 6.6 (s, 1H, NH), 7.3-77 (m, 5H, ph), 7.9 (s, 1H,= CH), 10.4 (s, 1H, OH), IR(KBr) disk), 3050, 3450, (NH, OH), 1650, 1450 Cm^{-1}, M.S.M$^+$, m/z, 232.

2(2-propargylhydrazino)-5-hydroxy-1,3,4-thiadiazolo 5

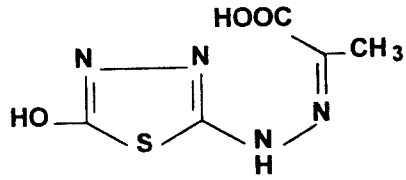
Compound 1 (1.5g, 0.01 mol), propargyl bromide (1.19g, 1.1 ml, 0.01 mol), triethylamine (2 drops) were refluxed in a mixture of CH_3CN-CH_3OH, 1:1 (50 mL) for 8 h. The solvents were evaporated off under reduce pressure and the residue was crystallized from EtOH t afford the title compound. Yield: 36g, 80%, mp 18 185°C, ^{1}H NMR, δ ($CDCl_3$), 2.6 (s, 1H, C ≡ CH), 4.1 (2H, CH_2), 6.5 (S, 1H, NH) 7.5 (S, 1H, NH), 10.5 (S, 1H OH), IR (KBr disk) 3450-3425 (NH, OH), 3250 (C CH) Cm^{-1}, M.S.M$^+$, m/z 170.

2H, 3H, 4-Methylene-7-hydroxy-1,3,4-thiadiazol [2,3-c] [1,2,4] triazine 6

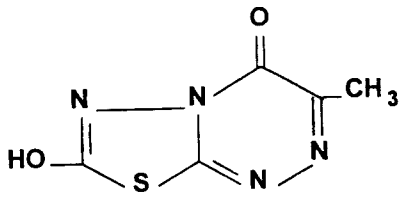
A mixture of **5** (0.51g, 3 mmol), bis (benzonitrile



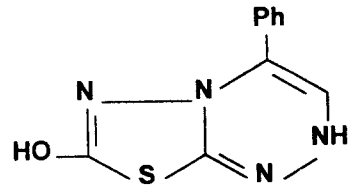
(1)



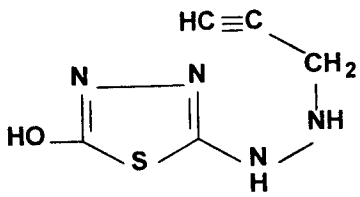
(2)



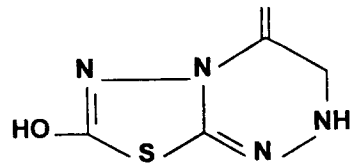
(3)



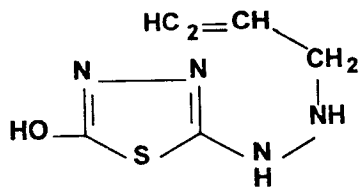
(4)



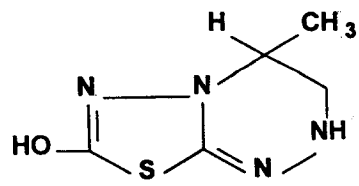
(5)



(6)



(7)



(8)

palladium chloride (0.06g, 0.03 mmol), triethylamine (2 drops) were refluxed in CH_3CN, MeOH, 2:1 (20 ml) for 18 h. The solvents were evaporated off under reduced pressure. The crude was directly subjected to column chromatography on silica gel using $CHCl_3$ as an eluent to afford the title compound. Yield: 0.33g, 65%, mp 233-235°C, ^1H NMR, δ ($CDCl_3$) 3.7 (S, 2H, CH_2), 5.6 (d, J= 1.8 Hz, 1H, exo methylene), 6.4 (d, 1H, J= 1.8Hz exo methylene) 7.8 (S, 1H, NH), 10.4 (S. 1H, OH) IR (KBr disk) 3000-3500 (NH, OH) Cm^{-1}.

2(2-Allylhydrazino)-5-hydroxy-1,3,4-thiadiazole 7

Compound **1** (3g, 0.02 mol) and allyl bromide (2.42g, 0.02 mol) were refluxed in acetonitrile for 6 hours. The reaction mixture was cooled to room temperature. The precipitate was filtered off and washed with pet ether to afford the title compound. Yield: 2.9, 84%, mp 180-181°C, ^1H NMR, δ ($CDCl_3$), 3.5 (d, 2H, CH_2), 5.5 (m, 2H, CH_2), 5.8 (s, 1H, NH), 6.2 (s, 1H, NH). IR(KBr disk) 3000-3500 (NH, OH), 1620 (CH_2 = CH-), 900-990 M.S, M^+, m/z 172.

2H, 3H-4-Methyl-7-hydroxythiadiazolo [2,3-c] [1,2,4-] triazine 8

Compound **7** (2.8g; 0.016 mol) was dissolved in Conc H_2SO_4 (20 ml). The reaction mixture was kept at 50°C for 1 h. To this mixture crushed ice was added and neutralized to pH **8** by addition of saturated solution of sodium hydroxide. The precipitate was filtered off, washed with water and crystallized from EtOH to afford the title compound. Yield: 1.82, 63%, mp 214-215°C, ^1H NMR δ ($CDCl_3$), 1.05 (d, 3H, Me), 2.75 (d, 2H, CH_2), 2.9 (m, 1H, CH), 7.8 (s, 1H, NH), 10.4 (S, 1H, OH). IR (KBr disk) 3000-3500 9NH, OH), 1320, 1100 Cm^{-1} M.S, M^+, m/z 172.

2 [5-Hydroxy-(1,3,4-thidiazol-2-yl)-4-Hydroxy-pyrazolidine] 9

Compound **1** (1.5 g, 0.01 mol) and epichlorohydrine (0.92g, 0.65cc) were refluxed in CH_3CN-CH_3OH, 1:1 (50 mL) for 4h. After cooling solid was filtered off, and crystallized from EtOH to afford the title compound. Yield: 0.92g, 48%, mp 195-196°C, ^1H NMR, δ ($CDCl_3$), 2 (s, 1 to, NH) 2.6 (d, 2H, CH_2), 2.8 (d, 2H, CH_2) 4.4 (d, 1H: OH), 10.5 (s, 1H, CHOH). IR (KBr disk), 3200-3300 (NH, OH) Cm^{-1}, M.S, M^+, m/z 188.

References

1. Preston, P. N. *Chem. Rev.*, **74**, 279, (1974).
2. Heravi, M. M., Beheshtiha, Y. S. and Bakavoli, M. *J. Sci I.R.Iran*, **5** (4), 168, (1994).
3. Heravi, M. M. and Firouznia, A., *Ibid.*, **6** (2), 93, (1995).
4. Heravi, M. M. and Bakavoli M. *J. Chem. Res.*, **110**, 480, (1995).
5. Heravi, M. M. and Khosrofar, P. *J. Sci. I.R. Iran* **7** (2), 86, (1996).
6. Heravi, M. M. and Shafaie, M. *Indian J. Heterocyclic Chem* **5**, (1), 83, (1995).
7. Heravi, M. M., Bakavoli, M. and Hashemi, Z. S. *Iran. J. Chem. and Chem. Eng.* **14**, (1), 41, (1995).
8. Darnow, A. and Marx, P. *Ber*, **9**, 2640, (1964).
9. Golgolab, H., Lalezari, I. and Hosseini-Gohari, L. *J. Heterocyclic Chem* **10**, (3), 387, (1973).
10. Mizutani, M., and Sanemitsu, Y. *J. Heterocyclic Chem.* **19**, 1571, (1982).
11. Molina, P., Alayarin, M. and Lapiz-Lazaro, A. *Tetrahedron*, **47** (33), 6747, (1991).
12. Heravi, M. M., Ibrahimian, R. A., Bakavoli, M. and Arbab Zavar, M.H. *Indian. J. Heterocyclic Chem.* **5**, 287, (1996).
13. Shafiee, A., Lalezari, I. and Mirshad., M., *J. Heterocyclic Chem.*, **13**, (1), 117 , (1976).
14. Kruzer, F. and Esmail, R. *J. Chem. Res.*, (8) **48**, (1989).
15. Nuss, J. M., Levine, B., Rennels, R. and Heravi, M. M *Tetrahedron Lett.* **32**, (39), 5243, (1991).
16. Heravi, M. M. and Nuss J. M. *J. Sci. I.R.I.* **4**, (3, 4), 194. (1993).
17. Heravi, M. M. and Bakavoli, M. *Chem. Soc. Pak.* **15**, (4), 257, (1993).
18. Nuss, J. M., Murphy, M. M., Rennis, R. and Heravi, M. M. *Tetrahedron Lett.* **34**, (19), 3079, (1993).
19. Heravi, M. M. and Bakavoli, M. J. *Chem. Soc. Pak.* **17**, (2), 118, (1995).
20. Heravi, M. M. Bakavoli, M., Tajbakhsh, M. and Beheshtiha Y. S. *Indian J. Heterocyclic Chem.* **5** (1), 77, (1995).
21. Heravi, M. M. Shafaie, M, Bakavoli, M., Sadeghi, M. M. and Khoshdast, A. R. *Indian J. Chem.* Section B. **35**, (13), 1260, (1996).
22. Kharasch, M. S., Seyler, R.C. and Mayo, F. R. *J. Am. Chem., Soc.* **60**, 882, (1938).
23. Wippich, P., Hendreich, C., Gutschow, M. and Leistner, S. *Synthesis*, **741**, (1996).
24. Heravi, M.M., Aghapoor, K. and Nooshabadi, M.A. *Synth. Commun.*, **28**(2), 233, (1998).