

5-Furan-2-yl[1,3,4]oxadiazole-2-thiol, 5-Furan-2-yl-4H [1,2,4] triazole-3-thiol and Their Thiol-Thione Tautomerism

M. Koparır *, A. Çetin and A. Cansız

Department of Chemistry, Faculty of Science, Fırat University, 23119, Elazığ, Turkey.

*Author to whom correspondence should be addressed; e-mail: mkoparir@hotmail.com

Received: 30 June 2004; in revised form: 15 July 2004 / Accepted: 1 August 2004 / Published: 28 February 2005

Abstract: 5-Furan-2-yl[1,3,4]oxadiazole-2-thiol (**Ia**) and 5-furan-2-yl-4H-[1,2,4]-triazole-3-thiol (**Ib**) were synthesized from furan-2-carboxylic acid hydrazide. Mannich bases and methyl derivatives were then prepared. The structures of the synthesized compounds were confirmed by elemental analyses, IR and ¹H-NMR spectra. Their thiol-thione tautomeric equilibrium is described.

Keywords: 1,3,4-Oxadiazoles; 1,2,4-triazoles; Mannich bases; thiol-thione tautomerism.

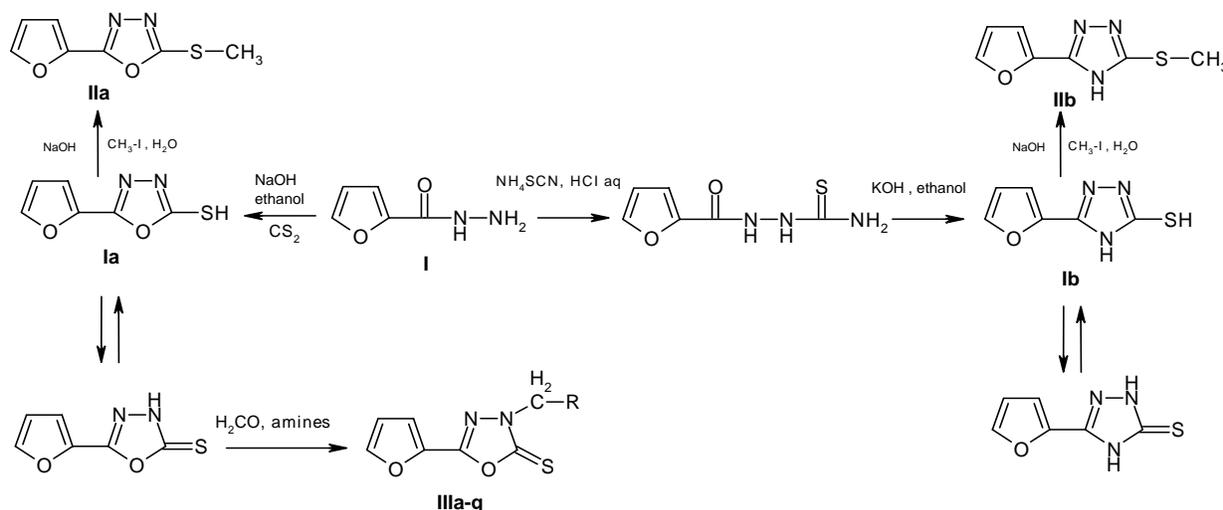
Introduction

Triazoles and their derivatives have been proven to be effective bactericides, pesticides and fungicides [1-3]. Further, some findings that the 1,2,3-triazole nucleus is associated with diverse pharmacological activities such as analgesic, antiasthmatic, diuretic, antihypertensive and antiinflammatory properties have made them important chemotherapeutic agents [4-7]. Derivatives of 1,3,4-oxadiazole are also known to have a broad spectrum of biological activities [8-10]. Acyl hydrazides have been in general use as the starting materials in some 1,2,4-triazole and 1,3,4-oxadiazole syntheses [11, 12]. In addition there are some studies on electronic structures and thiol-thione tautomeric equilibrium of heterocyclic thione derivatives [13-15].

In the present study 5-furan-2-yl[1,3,4]oxadiazole-2-thiol (**Ia**) and 5-furan-2-yl-4H[1,2,4]-triazole-3-thiol (**Ib**) and some of their derivatives were synthesized. Compound **Ia** was synthesized by the ring closure reaction of furan-2-carboxylic acid hydrazide with carbon disulfide. A series of Mannich bases of 5-furan-2-yl[1,3,4]oxadiazole-2-thiol (**IIIa-g**) were then synthesized by the reaction of **Ia** with suitably substituted amines and formaldehyde in ethanol. 5-Furan-2-yl-4H[1,2,4]triazole-3-thiol (**Ib**) was prepared by the reaction of the appropriate 2-furoyl thiosemicarbazide and potassium hydroxide in

ethanol for 3 h under reflux, followed by acidification with acetic acid. The 2-furoyl thiosemicarbazide employed in these reactions was obtained by refluxing the corresponding furan-2-carboxylic acid hydrazide with ammonium thiocyanate in presence of aq. hydrochloric acid for 3 h. **IIa** and **IIb** were obtained from reaction of **Ia** and **Ib** with CH_3I in an alkaline medium. These synthetic reactions are summarized in Scheme 1.

Scheme 1



Results and Discussion

The characterization data of compounds **Ia** and **Ib** are given in the Experimental section and that of the other compounds synthesized is summarized in Table 1. All the newly synthesized compounds gave satisfactory analyses for the proposed structures, which were confirmed on the basis of their IR and $^1\text{H-NMR}$ spectral data. The IR spectra of these compounds showed moderately strong bands around $3100\text{--}3360\text{ cm}^{-1}$, $1600\text{--}1650\text{ cm}^{-1}$ and $1250\text{--}1270\text{ cm}^{-1}$, characteristic of the NH, C=N and C=S groups, respectively. In the $^1\text{H-NMR}$ spectra, a characteristic signal due to the $-\text{N-CH}_2\text{-N-}$ protons appeared at 5.00–6.05. The signal due to the NH protons appeared at 5.50–5.52. The signals due to the aromatic protons appeared as multiplets at 6.50–8.40.

We have observed that extensive thiol-thione tautomerism exists in compounds **Ia** and **Ib**. In the $^1\text{H-NMR}$ the signal of the SH protons were recorded, although they were very weak and also the ready synthesis of the Mannich bases **IIa**, **IIIa-g**, **IIb** and **Ib** [16] from **Ia** and **Ib** confirmed the tautomerism. It has been reported that the crystal structures of **Ia**- and **Ib**-like compounds correspond to the thione form [17–19], but the reaction conditions for the synthesis of **IIa** prove that **Ia** can be in the thiol form too. Finally, the crystal structures of **Ia** and **Ib** [17, 18] corresponded to the thione form, but they showed thiol-thione tautomerism in solution.

Experimental

General

Melting points were determined in open capillary tubes on a digital Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded in KBr with a Mattson 1000 FT-IR spectrometer. $^1\text{H-NMR}$ spectra were recorded on a FX 90 JEOL 90MHz NMR and Varian Gemini 200MHz, spectrometers in CDCl_3 + DMSO-d_6 with TMS as an internal standard. Elemental analyses were done on a LECO-CHNS-938. Starting chemicals were obtained from Merck or Aldrich.

5-Furan-2-yl[1,3,4]oxadiazole-2-thiol (Ia). A mixture of furan-2-carboxylic acid hydrazide (0.01 mole, 1.26 g), sodium hydroxide (0.01 mole, 0.4 g), carbon disulfide (0.02 mole, 1.2 mL) and absolute ethanol (100 mL) was heated under reflux for 12 h. The excess solvent was removed by vacuum evaporation, and the residue was dissolved in water and acidified with acetic acid. The product was recrystallised from water-ethanol (60-40). Yield 55 %; mp: 135-137 °C; IR, cm^{-1} : 3356 (NH), 1642 (C=N), 1255(C=S); $^1\text{H-NMR}$, ppm: 6.56-7.65 (m, 3H, furyl), 13.70 (s, 1H, SH).

5-Furan-2-yl-4H[1,2,4]triazole-3-thiol (Ib). An equimolar quantity of furan-2-carboxylic acid hydrazide (0.01 mole, 1.26 g), ammonium thiocyanate (0.01 mole, 1.52 g) and hydrochloric acid (5 mL) in absolute ethanol (50 mL) was refluxed for 4 h. The white solid that appeared on cooling was filtered and the excess solvent was removed by vacuum evaporation. The residue was recrystallised from DMF-ethanol (30-70 v/v) to give *1-(2-furoyl)-3-thiosemicarbazide* (Yield 90 %; mp: 233-235 °C). This intermediate (0.01 mole 1.85 g) was refluxed in 10 % sodium hydroxide solution (5 mL) for 3 h. The resulting solution was cooled and filtered. The filtrate was acidified with hydrochloric acid to pH 5-6. The solid which appeared was filtered, dried and recrystallised from dilute ethanol. Yield 75 %; mp: 295 °C; IR, cm^{-1} : 3356-3155 (NH), 1642 (C=N), 1255(C=S); $^1\text{H-NMR}$, ppm: 13.80 (s, 1H, SH), 6.56-7.65 (m, 3H, furyl), 5.10 (s, 1H, NH).

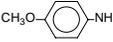
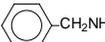
General Procedure for the Preparation of **IIa,b**.

A mixture of thione **Ia-b** (0.005 mole), sodium hydroxide (0.005 mole, 0.2 g), and methyl iodide (0.006 mole, 0.840 g) was stirred in water for 14 h. The resulting thioether solution was removed by vacuum evaporation, and the products collected by filtration, washed with water, dried and recrystallised from a suitable solvent. Spectroscopic and physical data are summarized in Table 1.

General Procedure for the Preparation of **IIIa-g**.

A mixture of **Ia** (0.01 mole, 1.56 g) and an alkyl or aryl amine (0.01 mole) was refluxed in ethanol (50 mL) with 36 % formaldehyde (0.02 mole, 1.7 mL) for 3 h. The resulting solid was crystallised from a suitable solvent. Spectroscopic and physical data are summarized in Table 1.

Table 1. Analytical and spectroscopic data for compounds **IIa,b** and **IIIa-g**.

Comp. No.	R	X	Yield, %	mp, °C	IR spectrum, ν , cm^{-1}	^1H NMR spectrum, δ , ppm (J , Hz)			
IIa		O	45	161	2982 (CH), 1636(C=N), 1260(C=S).	6.60-7.60 (m, 3H, furyl), 2.10 (s, 3H, SCH ₃)			
IIb		NH	50	132	3130(NH), 2982(CH), 1636(C=N), 1260(C=S).	6.60-7.50 (m, 3H, furyl), 5.70 (1H, NH), 2.10 (s, 3H, SCH ₃)			
IIIa		O	82	133	2990(CH), 1632(C=N), 1270(C=S).	6.56-7.60 (m, 3H, furyl), 5.0 (s, 2H, N-CH ₂ -N), 3.70-3.50 (m, 4H, CH ₂ -O-CH ₂), 2.70-2.60 (m, CH ₂ -N-CH ₂).			
IIIb		O	60	145	3320(NH), 2970(CH), 1630 (C=N), 1268(C=S).	8.24-7.60 (m, 4H, Ar.CH), 6.50-7.60 (m, 3H, furyl), 5.50 (br, 1H, N-CH ₂ -NH), 5.90 (d, J=7 2H, N-CH ₂ -NH), 2.15 (s, 3H, CH ₃).			
IIIc		O	62	148	3315(NH), 2970(CH), 1630 (C=N), 1268(C=S).	8.40-7.80 (m, 4H, Ar.CH), 6.50-7.60 (m, 3H, furyl), 5.50 (br, 1H, N-CH ₂ -NH), 5.90 (d, J=7 2H, N-CH ₂ -NH), 3.70 (s, 3H, OCH ₃).			
III d		O	50	193	3330(NH), 2982(CH), 1636(C=N), 1280(C=S).	8.20-7.80 (m, 7H, Ar.CH), 6.50-7.60 (m, 3H, furyl), 5.52 (br, 1H, N-CH ₂ -NH), 5.85 (d, J=7 2H, N-CH ₂ -NH).			
IIIe		O	40	128	3323(NH), 2982(CH), 1636(C=N), 1260(C=S).	8.25-7.90 (m, 5H, Ar.CH), 6.50-7.60 (m, 3H, furyl), 5.52 (br, 2H, -NH), 5.92 (d, J=7 2H, N-CH ₂ -NH), 3.80 (d, J=9 Ar-CH ₂ -NH).			
III f		O	70	133	2982(CH), 1636(C=N), 1265(C=S).	6.50-7.60 (m, 3H, furyl), 5.80 (s, 2H, N-CH ₂), 2.10-2.80 (m, 10H, CH ₂).			
III g		O	35	174	3315(NH), 2982(CH), 1636(C=N), 1270(C=S).	8.40-7.80 (m, 4H, Ar.CH), 6.50-7.60 (m, 3H, furyl), 5.50 (br, 1H, N-CH ₂ -NH), 6.05 (d, J=7 2H, N-CH ₂ -NH).			
Comp No.	Found, %				Formula	Calculated, %			
	C	H	N	S		C	H	N	S
IIa	46.15	3.29	15.33	17.58	C ₇ H ₆ N ₂ O ₂ S	46.15	3.32	15.37	17.60
IIb	46.38	3.87	23.11	17.65	C ₇ H ₇ N ₃ OS	46.40	3.89	23.19	17.69
IIIa	49.41	4.89	15.72	11.98	C ₁₁ H ₁₃ N ₃ O ₃ S	49.43	4.90	15.72	12.00
IIIb	58.49	4.54	14.60	11.13	C ₁₄ H ₁₃ N ₃ O ₂ S	58.52	4.56	14.62	11.16
IIIc	55.45	4.32	13.83	10.55	C ₁₄ H ₁₃ N ₃ O ₃ S	55.43	4.32	13.85	10.57
III d	63.13	3.99	13.00	10.00	C ₁₇ H ₁₃ N ₃ O ₂ S	63.14	4.05	12.99	9.92
IIIe	58.48	4.55	14.60	11.13	C ₁₄ H ₁₃ N ₃ O ₂ S	58.52	4.56	14.62	11.16
III f	54.28	5.68	15.78	12.01	C ₁₂ H ₁₅ N ₃ O ₂ S	54.32	5.70	15.84	12.08
III g	48.98	3.15	17.59	10.10	C ₁₃ H ₁₀ N ₄ O ₄ S	49.05	3.17	17.60	10.07

References

1. Sengupta, A.K.; Bajaj, O.P.; Chandura, U.J. Synthesis and antibacterial activity of some phenoxyacetyl thiosemicarbazides, substituted 1,3,4-oxadiazoles, 1,2,4-triazoles and alkyl-phenyl carbamates of substituted 1,3,4-oxadiazole-2-thiones. *J. Ind. Chem. Soc.* **1978**, *55*, 962.
2. Singh, H.; Yadav, L.D.S.; Battacharya, B.K.J. Synthesis of some new bis(1,2,4-triazol-3-yl) disulfides, sulfides and sulfones as potential pesticides. *J. Ind. Chem. Soc.* **1979**, *56*, 1013.
3. Giri, S.; Singh, H.; Yadav, L.D.S.; Kahre, R.K. Synthesis of some new 1, 3, 4-oxa(thia)diazoles and 1,2,4-triazoles as potential fungicides. *J. Ind. Chem. Soc.* **1978**, *55*, 168.
4. Yale, H.L.; Piale, J.J. Substituted S-Triazoles and Related Compounds. *J. Med. Chem.* **1966**, *9*, 42.
5. Hirota, T.; Sasaki, K.; Yamamoto, H.; Nakayama, T. Polycyclic n-hetero compounds 36 Syntheses and antidepressive evaluation of 11,13,15,17-tetraazasteroids and their 17-oxides. *J. Heterocycl. Chem.* **1991**, *28*, 257.
6. Goswami, B.N.; Katakya, J.C.S.; Baruah, J.N. Synthesis and antibacterial activity of 1-(2,4-dichlorobenzoyl)-4-substituted thiosemicarbazides, 1,2,4-triazoles and their methyl-derivatives. *J. Heterocycl. Chem.* **1984**, *21*, 1225.
7. Sengupta, A.K.; Misra, H.K. Studies on potential pesticides 13 Synthesis and evaluation of s-(3-substituted phenoxyethyl-4-aryl/cyclohexyl-4h-1,2,4-triazol-5-yl)-2-mercaptomethyl benzimidazoles for anti-bacterial and insecticidal activities. *J. Ind. Chem. Soc.* **1981**, *58*, 508.
8. Ram, V.J.; Vlietinck, A.J. Chemotherapeutical agents .7. Synthesis and pesticidal activities of sulfides and sulfones derived from bis[4-aryl-1,2,4-triazoline-5-thione-3-yl]alkane and 5-phenyl-1,3,4-oxadiazole-2-thione. *J. Heterocycl. Chem.* **1988**, *25*, 253.
9. Boschelli D.H.; Connor, D.T.; Bornemeier, D.A.; Dyer, R.D.; Kennedy, J.A.; Kuipers, P.J.; Okonkwo, G.C.; Svhrer, D.J.; Wright, C.D. 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole analogs of the fenamates - in-vitro inhibition of cyclooxygenase and 5-lipoxygenase activities. *J. Med. Chem.* **1993**, *36*, 1802.
10. Bahadur, S.; Pandey, K.K. Synthesis of para-alkyl-(2-benzimidazolyl)-methyl-minobenzoates and corresponding hydrazides as possible anti-malarial agents. *J. Ind. Chem. Soc.* **1980**, *57*, 447.
11. Cansız, A.; Koparr, M.; Demirdag, A. Synthesis of some new 4,5-substituted-4H-1,2,4-triazole-3-thiol derivatives. *Molecules* **2004**, *9*, 204.
12. Rostom, S.A.F.; Shalaby, M.A.; EL-Demellawy, M.A. Polysubstituted pyrazoles, part 5. Synthesis of new 1-(4-chlorophenyl)-4-hydroxy-1h-pyrazole-3-carboxylic acid hydrazide analogs and some derived ring systems. A novel class of potential antitumor and anti-HCV agents *Eur. J. Med. Chem.* **2003**, *38*, 959.
13. Aydogan, F.; Turgut, Z.; Olcay, N.; Erdem, S.S. Synthesis and electronic structure of new aryl- and alkyl-substituted 1,3,4-oxadiazole-2-thione derivatives. *Turk. J. Chem.* **2002**, *26*, 159.
14. Charistos, D.A.; Vagenes, G.V.; Tzavellas, L.C.; Tsoleridis, C.A.; Rodios, N.A. Synthesis and a UV and IR spectral study of some 2-aryl-delta(2)-1,3,4-oxadiazoline-5-thiones. *J. Heterocycl. Chem.* **1994**, *31*, 1593.
15. Tsoleridi, C.A.; Charistos, D.A.; Vagenes, G.V. UV and MO study on the deprotonation of some 2-aryl-delta(2)-1,3,4-oxadiazoline-5-thiones. *J. Heterocycl. Chem.* **1997**, *34*, 1715.
16. Cansiz, A.; Servi, S.; Koparr, M.; Altintas, M.; Digrak, M. Synthesis and biological activities of some Mannich bases of 5-(2-furyl)-1,2,4-triazole-3-thiones. *J. Chem. Soc. Pakistan* **2001**, *23*, 237.

17. Ozturk, S.; Akkurt, M.; Cansiz, A.; Cetin, A.; Sekerci, M.; Heinemann, F.W. 5-(furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione. *Acta Cryst. E.* **2004**, *E60*, O322.
18. Ozturk, S.; Akkurt, M.; Cansiz, A.; Koparir, M.; Sekerci, M.; Heinemann, F.W. 4-(4-Chlorophenyl)-3-(furan-2-yl)-1H-1,2,4-triazole-5(4H)-thione. *Acta Cryst* **2004**, *E60*, O425.
19. Ozturk, S., Akkurt, M.; Cansiz, A.; Koparir, M.; Sekerci, M.; Heinemann, F.W. 3-Benzyl-4-(4-chlorophenyl)-1H-1,2,4-triazole-5(4H)-thione. *Acta Cryst* **2004**, *E60*, O642.

Sample availability: Available from the authors.

© 2005 by MDPI (<http://www.mdpi.org>). Reproduction is permitted for noncommercial purposes.