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

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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 $^1$H-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, antiasthematic, 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 (IIa-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. \(\text{IIa}\) and \(\text{IIb}\) were obtained from reaction of \(\text{Ia}\) and \(\text{Ib}\) with \(\text{CH}_3\text{I}\) in an alkaline medium. These synthetic reactions are summarized in Scheme 1.

Scheme 1

Results and Discussion

The characterization data of compounds \(\text{Ia}\) and \(\text{Ib}\) 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 \(^1\)H-NMR spectral data. The IR spectra of these compounds showed moderately strong bands around 3100-3360 cm\(^{-1}\), 1600-1650 cm\(^{-1}\) and 1250-1270 cm\(^{-1}\), characteristic of the NH, C=N and C=S groups, respectively. In the \(^1\)H-NMR spectra, a characteristic signal due to the –N-CH\(_2\)-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 \(\text{Ia}\) and \(\text{Ib}\). In the \(^1\)H-NMR the signal of the SH protons were recorded, although they were very weak and also the ready synthesis of the Mannich bases \(\text{IIa, IIIa-g, IIb and Ib}\) [16] from \(\text{Ia}\) and \(\text{Ib}\) confirmed the tautomerism. It has been reported that the crystal structures of \(\text{Ia}\)- and \(\text{Ib}\)-like compounds correspond to the thione form [17-19], but the reaction conditions for the synthesis of \(\text{IIa}\) prove that \(\text{Ia}\) can be in the thiol form too. Finally, the crystal structures of \(\text{Ia}\) and \(\text{Ib}\) [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. $^1$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); $^1$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); $^1$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, ºC | IR spectrum, \( \nu \), cm\(^{-1} \) | 'H NMR spectrum, \( \delta \), 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\(_3\)). |
| IIId      | 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). |
| IIIf      | 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\(_3\)). |
| IIIg      | 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, % |
|-----------|----------|---------|---------------|
| IIa       | 46.15    | C\(_7\)H\(_6\)N\(_2\)O\(_2\)S | 46.15 |
| IIb       | 46.38    | C\(_7\)H\(_7\)N\(_3\)OS | 46.40 |
| IIIa      | 49.41    | C\(_{11}\)H\(_{13}\)N\(_3\)O\(_3\)S | 49.43 |
| IIIb      | 58.49    | C\(_{14}\)H\(_{13}\)N\(_3\)O\(_2\)S | 58.52 |
| IIIc      | 55.45    | C\(_{14}\)H\(_{13}\)N\(_3\)O\(_2\)S | 55.43 |
| IIId      | 63.13    | C\(_{12}\)H\(_{15}\)N\(_3\)O\(_2\)S | 63.14 |
| IIIe      | 58.48    | C\(_{14}\)H\(_{13}\)N\(_3\)O\(_2\)S | 58.52 |
| IIIf      | 54.28    | C\(_{12}\)H\(_{15}\)N\(_3\)O\(_2\)S | 54.32 |
| IIIg      | 48.98    | C\(_{13}\)H\(_{10}\)N\(_4\)O\(_4\)S | 49.05 |
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