

NITROIMIDAZOLES VII [1]. SYNTHESSES, ANTI-BACTERIAL AND ANTIFUNGAL ACTIVITIES OF 4-SUBSTITUTED-2-THIAZOLYLHYDRAZONES

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Abstract

Reaction of readily available 2-formyl-1-methyl-5-nitroimidazole (**1**) with 4-substituted-2-hydrazinotiazoles (**2**) afforded 2-formyl-1-methyl-5-nitroimidazole 4-substituted-2-thiazolyhydrazones (**3**). Reaction of thiochroman-4-one (**4**) with thiosemicarbazide gave thiochroman-4-one thiosemicarbazone (**5**). Reaction of compound **5** with α -haloaldehyde or ketones yielded thiochroman-4-one 4-substituted-2-thiazolyhydrazones (**6**). The antibacterial and antifungal activities of compounds **3** and **6** against a number of microorganisms were determined.

Introduction

The antituberculous activity of 4-substituted-2-thiazolyhydrazine or corresponding hydrazones have been reported [2-4]. It was also shown that thiochroman-4-one thiosemicarbazone has antiviral activity [5]. The syntheses of 1-methyl-2-(2-pyridyl)-nitroimidazoles as a possible effective drug against tropical diseases has recently been reported [6]. We have decided to combine 4-substituted-2-thiazolyhydrazine with nitroimidazole and thiochroman-4-one in order to study their antibacterial and antifungal activities.

Results and Discussion

Reaction of 2-formyl-1-methyl-5-nitroimidazole (**1**) [6] with 4-substituted-2-hydrazinotiazoles (**2**) [7] afforded the desired compound 2-formyl-1-methyl-5-nitroimidazole 4-substituted-2-thiazolyhydrazones (**3**) in high yield. Reaction of thiochroman-4-one (**4**) with thiosemicarbazide in boiling acetic acid gave the

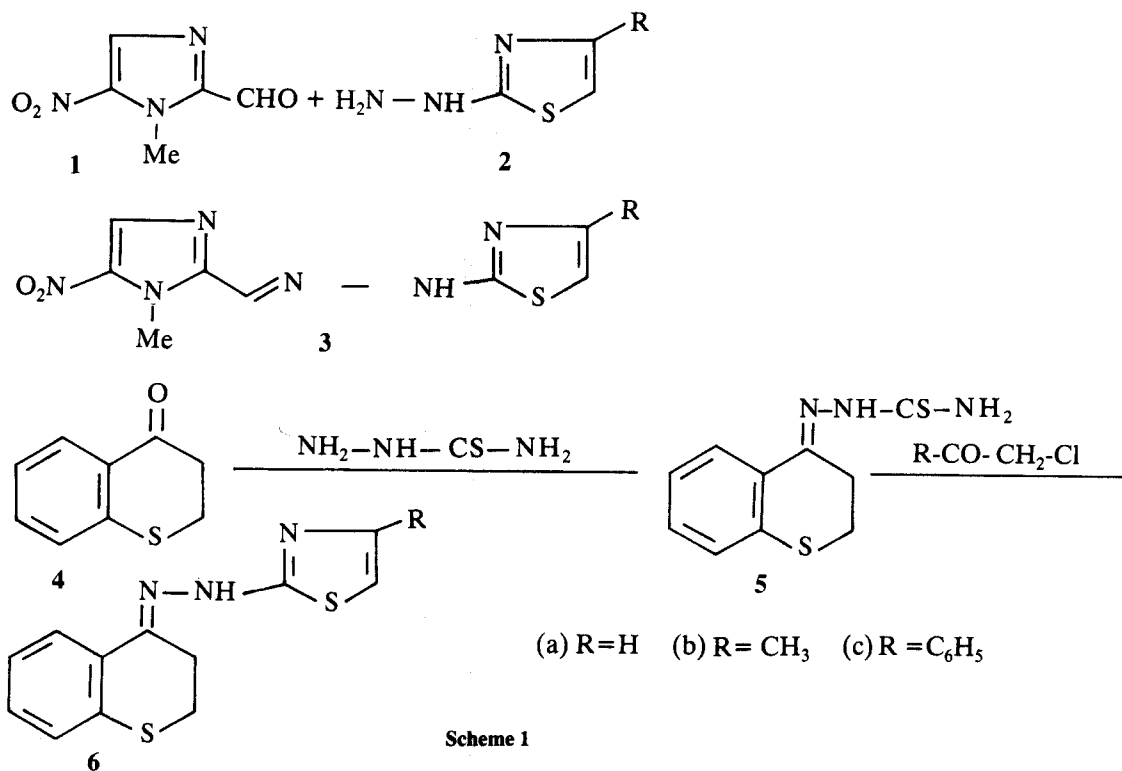
corresponding thiosemicarbazone (**5**) [5]. Reaction of compound **5** with 1,2-dichlorodietyl ether or α -haloketones yielded thiochroman-4-one 4-substituted-2-thiazolyhydrazones (**6**) (see Scheme 1)

The antibacterial and antifungal activities of compounds **3** and **6** were determined. Compound **3b** was active against *S. Aureus* and *B. Subtilis*. Compound **3a** was active against *B. Subtilis*. Compound **6b** was active against *S. Aureus* and *C. Albicans* (see Table 1).

Table 1-Antibacterial and antifungal activities of compounds **3** and **6**. The amount of each compound in a disk in μ g; average zone size, mm.

Compound No.	Concentration	10	30	Furazolidone(10 μ g)
3b	<i>S. Aureus</i>	7	9	25
6b	<i>S. Aureus</i>	7	10	25
3a	<i>B. Subtilis</i>	12	14	21
3b	<i>B. Subtilis</i>	10	12	21
6b	<i>C. Albicans</i>	10	15	

The antibacterial activity against other microorganisms was not significant (see Experimental Section).



The antibacterial and antifungal activities of other compounds were not significant.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Perkin Elmer Model 267 spectrograph (Potassium bromide disks). The NMR spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 eV.

2-Formyl-1-methyl-5-nitroimidazole 2-Thiazolyhydrazone (3a).

To a stirring solution of 2-formyl-1-methyl-5-nitroimidazole (155 mg, 1 mmol) in ethanol (3 ml) was added a solution of 2-thiazolyhydrazine hydrochloride (151.5 mg, 1 mmol) [7] in water (2 ml). The mixture was heated in a water bath gently. After 10 min, the precipitate was filtered to give 184 mg (73%) of 3a; m.p. 222-223°C; uv (ethanol): λ_{\max} 397 (log ϵ = 4.32), 300 (log ϵ = 4.20) and 230 nm (log ϵ = 4.15); IR: 3130, 3090 (H-C aromatic), 1620 (C=N) 1530 and 1470 cm^{-1} (NO_2); NMR (CF_3COOH): 8.73 (s, 1H, HC=N), 8.53 (s,

1H, H-C₄ imidazole), 7.63 (d, 1H, H-C₄ thiazole $J_{4,5}$ = 4 Hz), 7.23 (d, 1H, H-C₅ thiazole, $J_{4,5}$ = 4 Hz) and 4.42 (s, 3H, N-CH₃); ms: m/e (%) 252 (M^+ , 45), 100 (45), 55 (31) and 36 (100)

Anal. Calcd: for $\text{C}_8\text{H}_8\text{N}_6\text{O}_2\text{S}$: C, 38.10; H, 3.17; N, 33.33. Found: C, 38.02; H, 3.04; N, 33.21.

2-Formyl-1-methyl-5-nitroimidazole 4-Methyl-2-thiazolyhydrazone (3b)

Starting from 1 and 2a this compound was prepared similar to 3a in 83% yield; m.p. 242-243°C; uv (ethanol): λ_{\max} 400 (log ϵ = 4.20); 302 (log ϵ = 4.17) and 235 nm (log ϵ = 4.15); NMR ($\text{CDCl}_3\text{-CF}_3\text{COOH}$): 8.56 (s, 1H, HC=N); 8.43 (s, 1H, H-C₄ imidazole), 6.75 (s, 1H, H₅ thiazole) and 4.38 (s, 3H, CH₃); ms: m/e (%) 266 (M^+ , 100), 153 (15), 140 (10), 127 (16), 114 (63), 100 (15), 69 (17) and 42 (21).

Anal. Calcd for $\text{C}_9\text{H}_{10}\text{N}_6\text{O}_2\text{S}$: C, 40.60; H, 3.76; N, 31.58. Found: C, 40.46; H, 3.62; N, 31.41.

2-Formyl-1-methyl-5-nitroimidazole 4-phenyl-2-thiazolyhydrazone (3c)

Starting from 1 and 2c this compound was prepared similar to 3a in 85% yield; m.p. 269-270°C; uv (ethanol): λ_{\max} 405 (log ϵ = 4.15), 287 (log ϵ = 4.29), and 234 nm (log ϵ = 4.26); NMR ($\text{CDCl}_3\text{-CF}_3\text{COOH}$): 8.56 (s, 1H, HC=N), 8.38 (s, 1H, H-C₄ imidazole),

7.65(m, 5H, Phenyl), 7.06 (s, 1H, HC₃ thiazole) and 4.33 (s, 3H, CH₃); ms: m/e (%) 328 (M⁺, 77), 176 (100), 134 (85), 104 (15), 77(15), and 42(27)

Anal. Calcd. for C₁₄H₁₂N₆O₂S: C, 51.22; H, 3.66; N, 25.61. Found: C, 51.05; H, 3.74; N, 25.79.

Thiochroman-4-one 2-Thiozolyhydrazone Hydrochloride (6a)

A solution of thiochroman-4-one thiosemicarbazone (237 mg, 1 mmol) and 1,2-dichlorodiethylether (286 mg, 2 mmol) in ethanol (15 ml) was refluxed for 1 hr. After cooling ether was added until the crystals began to appear. It was allowed to stand at 0-5 °C for 1 hr and the precipitate was filtered to give 137 mg (46 %) of 6a; m.p. 191-192 °C; uv (ethanol): λ_{max} 346 (log ε = 4.23), 327 (log ε = 4.21), 265 (log ε = 3.92) and 235 (log ε = 4.28); NMR (CF₃COOH), 8.0 (m, 1H, aromatic), 7.37 (d, 1H, H₄ thiazole, J_{4,5} = 4 Hz), 7.23 (m, 3H, aromatic), 6.85 (d, 1H, H₅ thiazole, J_{4,5} = 4 Hz) and 3.10 (s, 4H-CH₂-CH₂-); ms: m/e (%) 261 (M⁺, 32), 233 (12), 162 (50), 134 (67), 109 (45), 100 (100), 90 (29), 77 (21), 69 (30), 55 (75), 45 (80) and 36 (59).

Anal. Calcd. for C₁₂H₁₂ClN₃S₂: C, 48.40; H, 4.03; N, 14.12. Found: C, 48.52; H, 4.13; N, 14.21.

Thiochroman-4-one 4-Methyl-2-thiazolyhydrazone (6b)

A solution of 5 (2.39 g, 0.01 mol), α-chloroacetone (9.25 g, 0.1 mol) and sodium acetate (0.82 g, 0.1 mol) in ethanol (20 ml) was refluxed for 30 min. The mixture was filtered. After cooling the solution the crystals were harvested to give 2.40 g (73 %) of 6b acetate; m.p. 106-107 °C; uv (ethanol): λ_{max} 347 (log ε = 4.28), 266 (log ε = 4.02) and 235 (log ε = 4.35); IR: 3200 (NH), 3060, 3030 (aromatic), 1680 (C=O); NMR (CDCl₃): 8.0 (m, 1H, aromatic), 7.17 (m, 3H, aromatic), 6.13 (s, 1H, H₅ thiazole), 3.10 (s, 4H, -CH₂-CH₂-), 2.23 (s, 3H, CH₃) and 2.08 (s, 3H, CH₃COO); ms: m/e (%): 275 (M⁺, 100), 162 (45), 135 (15), 114 (35), 59 (40, CH₃COO) and 45 (48).

Anal: Calcd for C₁₅H₁₇N₃O₂S₂: C, 53.73; H, 5.07; N, 12.54. Found: C, 53.59; H, 5.18; N, 12.39.

Compound 6b acetate was dissolved in chloroform. The chloroform was washed with sodium bicarbonate solution, dried (Na₂SO₄) and evaporated. The residue was crystallized from ether to give 6b m.p. 106-107 °C. IR: 3180, 3160 (aromatic), 1570 and 1550 (aromatic); NMR (CDCl₃): 8.16 (m, 1H, aromatic), 7.16 (m, 3H, aromatic), 6.15 (s, 1H, H₅ thiazole),

2.96 (s, 4H, -CH₂-CH₂-) and 2.30 (s, 3H, CH₃).

Anal. Calcd for C₁₃H₁₃N₃S₂: C, 53.73; H, 5.07; N, 12.54. Found: C, 52.64; H, 5.17; N, 12.65.

Thiochroman-4-one 4-Phenyl-2-thiazolyhydrazone (6c)

A solution of 5 (2.37 g, 0.01 mol), α-chloroacetophenone (3.09 g, 0.02 mol) and sodium acetate (0.82 g, 0.01 mol) in ethanol (50 ml) was refluxed for 30 minutes. After filtering and cooling the precipitate was filtered to give 2.86 g (85 %) of 6c; m.p. 159-160 °C; uv (ethanol): λ_{max} 348 (log ε 4.32) and 258 (log ε = 4.49); NMR (CDCl₃): 7.93 (m, 3H, aromatic), 7.23 (m, 6H, aromatic), 6.93 (s, 1H, H₅ thiazole) and 2.80 (s, 3H, CH₃); ms: m/e (%) 337 (M⁺ 48), 176 (100), 162 (47), 134 (87), 109 (25) and 77 (25) 45 (20)

Anal. Calcd for C₁₈H₁₅N₃S₂: C, 64.09; H, 4.45; N, 12.46. Found: C, 64.25; H, 4.33; N, 12.31.

Antibacterial and Antifungal Assay-all compounds were tested against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538 p), *Escherichia coli*, *Klebsiella pneumoniae*, *proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella Paratyphi B*, *Candida albicans*, *Aspergillus niger*, *Penicillium sp*, *Microsporium canis* and *Microsporium gypseum*.

For antibacterial assay Compounds 3a-3c were dissolved in chloroform-acetic acid (80:20) and compounds 6a-6c were dissolved in ethanol. They were diluted to 1 mg/1 ml concentration. To standard paper disk of 6 mm. diameter the latter solution was added until the desired amount of compound was absorbed by the disk (see table 1). The disks were placed on inoculated assay medium surface. Furazolidone was used for comparison.

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