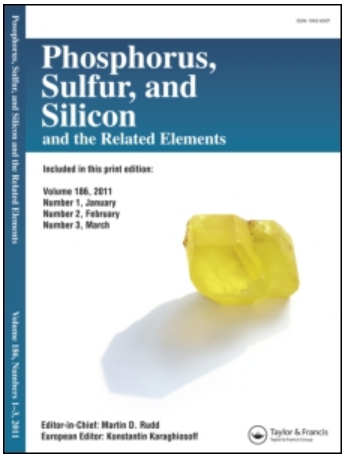

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Reactivity of N^1-Dithioester Substituted Pyridinand Pyrazincarboxamidrazones

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The N^1*-dithioester substituted pyridin- and pyrazincarboxamidrazones underwent cyclocondensation to 5-methylsulfanyl-1,3,4-thiadiazole or 1,2,4-triazole derivatives, depending on the reaction conditions. With an excess of secondary amines, pyrazincarboxamidrazone dithioester gave 5-amino-1,3,4-thiadiazoles and with an ethanoloamine a 1,2,4-triazole derivative. Prepared compounds were evaluated as potential tuberculostatic agents, but the minimum inhibitory concentrations values indicated no significant activity.*

Keywords 1,2,4-triazoles; 1,3,4-thiadiazoles; amidrazones; hydrazinecarbodithioic acid esters; tuberculostatics

INTRODUCTION

Many compounds having an amidrazone moiety have been described for their in vitro tuberculostatic activity, particularly 4-pyridin- and pyrazincarboxamidrazones[1] as well as their N^1-arylidene derivatives,[2,3] showed promising results. Recently, the antimycobacterial activity of N^1-hetarylmethylene-substituted pyridin- and pyrazincarboxamidrazones was investigated.[4,5] We found that a thioamide

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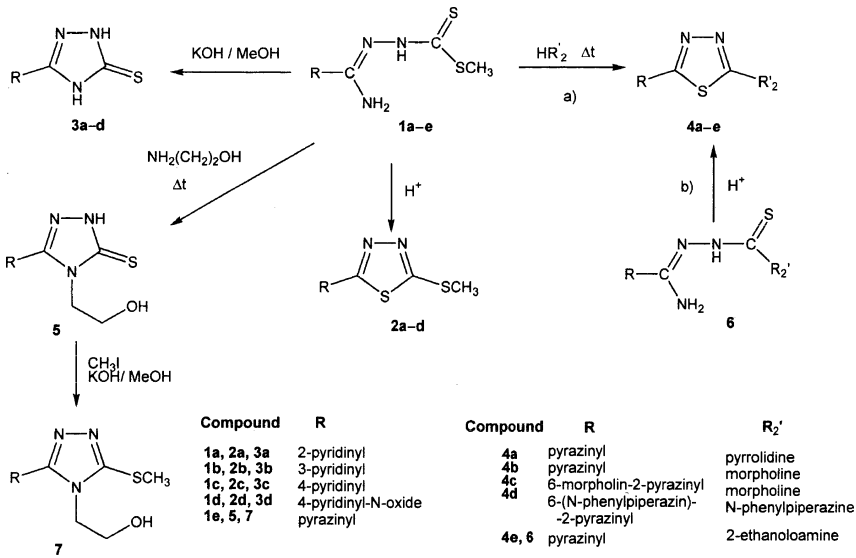
or dithioester group directly linked to the N^1 nitrogen atom also yielded compounds with considerable activity.[6,7] On the other hand, certain related 1,3,4-thiadiazole, 1,3,4-oxadiazole, and 1,2,4-triazole derivatives have already been tested and have shown activity as antimycobacterial,[8,9] antifungal,[10] and anticonlvusant[11] agents. These findings encouraged us to investigate more systematically products of cyclondensations of the amidrazone derivatives.

RESULTS AND DISCUSSION

Chemistry

The reactivity of dithioesters **1**[6] resembled that reported of N^1-thioacylamidrazones,[12] N^1-thioamidrazones,[13] and acylthiosemicarbazides.[14] They rapidly eliminated ammonia when treated with diluted hydrochloric acid to form 5-methysulphanyl-1,3,4-thiadiazoles (**2a–d**) (Scheme 1). The cyclocondensation of compounds **1** under basic conditions proceeded much more slowly, requiring that the reaction be carried out in refluxing alcoholic potassium hydroxide, and it led to 1,2,4-triazoles **3a–d**. By heating dithioesters **1** in excess of cyclic amines, the 1,3,4-thiadiazoles **4a–d** bearing an amine group on C-5 were produced. In order to get some information on the influence of the amine type on the reactivity of compounds **1**, we carried out a similar reaction of **1e** with ethanoloamine;



Compound	R
1a, 2a, 3a	2-pyridinyl
1b, 2b, 3b	3-pyridinyl
1c, 2c, 3c	4-pyridinyl
1d, 2d, 3d	4-pyridinyl-N-oxide
1e, 5, 7	pyrazinyl

Compound	R	R_2'
4a	pyrazinyl	pyrrolidine
4b	pyrazinyl	morpholine
4c	6-morpholin-2-pyrazinyl	morpholine
4d	6-(N-phenylpiperazin)--2-pyrazinyl	N-phenylpiperazine
4e, 6	pyrazinyl	2-ethanoloamine

SCHEME 1

in this case, the formation of triazole derivative **5** was observed. The latter product was clearly different from the isomeric thiadiazole **4e** obtained by acid promoted cyclocondensation reaction of thiosemicarbazide **6**[6] reaction, which generally gave amino-thiadiazoles.[15] The methylation of **5** under basic conditions yielded an *S*-alkylated product **7**.[16] The physical data of the obtained compounds are given in Table I.

For compound **5**, the ^{1}H NMR spectrum showed differences with that obtained for **4e**, confirming the unambigous assignment of the structure. The pattern of long-range proton-carbon correlations in ^{1}H-^{13}C HMBC spectrum of **5** showed a correlation between C-3 of the triazole ring and H-1 of the 2-ethanole fragment. In the case of **5**, the thione form was demonstrated by ^{1}H NMR (in DMSO-d_6) with $\delta_{\underline{NH}}$14.24 as a broad singlet, whereas for **4e**, the exocyclic NH signal (triplet) was present at δ 8.30.

In all cases, the cyclocondensation reactions of **1a–d** were regioselective and led to a thiadiazole or triazole system isolated after a simple work-up.

Microbiology

The tuberculostatic activity of the new compounds was tested *in vitro*. The following three bacterial strains were used: Mycobacterium tuberculosis H_{37}RV, the strain isolated from patients and resistant against isonicotinhydrazide, ethambutol and rifampicine, as well as the bacterial strain isolated from patients and susceptible to isonicotinhydrazide, ethambutol and rifampicine. The determination was performed in Youmans fluid medium containing 10% of bovine serum.[17] The minimal inhibitory concentration for the compounds studied was in a range of 50–500 μg/mL, thus indicating that cyclization led to compounds with much lowered tuberculostatic activity in comparison with the open-chain substrates studied previously.[6,7]

EXPERIMENTAL

Melting points were determined on a Reichert hot microscope and are uncorrected. IR spectra were measured with a Specord IR-75 spectrophotometer using potassium bromide and are given as cm^{-1}. ^{1}H NMR spectra were recorded on, either a Tesla Brno BS-478c (80 MHz), Tesla Brno BS-567A (100 MHz), or Varian Gemini 200 (200 MHz) at r.t. The ^{1}H^{-13}C HMBC NMR spectra were recorded with a Varian Unity 500 Plus (500 MHz). The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Coupling constants (J) values are given in Hz. EI mass spectra were obtained on

TABLE I Characteristics of the Synthesized Pyridinyl and Pyrazinyl Compounds

Compound no.	Formula	m.p. (°C) and solvent for crystallization	Yield (%)	IR (cm^{-1})	^1H NMR δ (ppm)
2a	$C_8H_7N_3S_2$	109–111 ($MeOH/H_2O$)	96	1600, 1576, 1483, 1424, 1360, 1003	($CDCl_3$, 80 MHz): 2.77 (s, 3H, CH_3); 7.30 (ddd, 1H pyridine, $J = 7.6; 4.6; 1.2$ Hz); 7.77 (td, 1H pyridine, $J = 7.8; 2.0$ Hz); 8.21 (br.d, 1H pyridine, $J = 7.6$ Hz); 8.57 (br.d, 1H pyridine, $J = 4.6$ Hz)
2b	$C_8H_7N_3S_2$	88–90 ($MeOH/H_2O$)	91	3020, 2920, 1424, 1360, 1072, 1240, 976	($CDCl_3$, 100 MHz): 2.90 (s, 3H, CH_3); 7.53 (dd, 1H pyridine, $J = 7.6$; 4.4 Hz); 8.32 (dt, 1H pyridine, $J = 7.6$, 0.8 Hz); 8.77 (m, 1H pyridine); 9.16 (br.s, pyridine)
2c	$C_8H_7N_3S_2$	118–120 (MeOH)	96	3030, 1584, 1440, 1408, 1360, 1328, 1216, 1088	($CDCl_3$, 80 MHz): 2.83 (s, 3H CH_3); 7.75 (d, 2H pyridine, $J = 5.0$); 8.71 (d, 2H pyridine, $J = 5.0$)
2d	$C_8H_7N_3OS_2$	230–234 (MeOH)	67	3020, 2920, 1616, 1584, 1563, 1508, 1456, 1360, 1312, 1264, 1072, 992	($CDCl_3$, 100 MHz): 2.74 (S, 3H, CH_3); 7.69 (d, 2H pyridine, $J = 5.2$ Hz); 8. 16 (d, 2H pyridine, $J = 5.2$ Hz)
3a	$C_7H_6N_4S$	272–274 (MeOH)	85	3232, 3020, 2840, 1563, 1540, 1472, 1444, 1424, 1360, 1224, 1152, 1083, 964	(DMSO-d_6, 200 MHz): 7.53 (dd, 1H pyridine, $J = 8.7$; 4.8); 7.97 (m, 2H pyridine); 8.67 (dt, 1H pyridine, $J = 4.8$; 1.3); 13.76; 13.93 (2br.s, 2H, NH)
3b	$C_7H_6N_4S$	268–270 (MeOH)	85	3390, 3050, 2900, 1616, 1600, 1572, 1500, 1456, 1232, 1136, 1040, 960	(DMSO-d_6, 100 MHz): 7.70 (m, 1H pyridine); 8.05 (dt, 1H pyridine, $J = 8.4$; 1.2 Hz); 8.82 (dd, 1H pyridine, $J = 4.4$; 1.6 Hz); 9.30 (d, 1H pyridine, $J = 1.2$ Hz)

3c	$C_7H_6N_4S$	293–294 (ethylene glycol/H_2O)	85	3440, 3280, 1616, 1584, 1552, 1528, 1456, 1232, 1008, 976	(DMSO-d_6, 200 MHz): 7.85 (dd, 2H pyridine, $J = 4.6$; 1.6 Hz); 8.74 (dd, 2H pyridine, $J = 4.6$; 1.6 Hz); 13.95 and 14.12 (2br.s, 2H, NH)
3d	$C_7H_6N_4OS$	266–268 (ethylene glycol/H_2O)	99	3400, 3040, 2960, 2592, 1615, 1520, 1476, 1296, 1243, 1200, 976	(DMSO-d_6, 80 MHz): 8.00 (d, 2H pyridine, $J = 5.8$ Hz); 8.50 (d, 2H pyridine, $J = 5.8$ Hz)
4a	$C_{10}H_{11}N_5S$	163–164 (EtOH)	34	2960, 2930, 2880, 2860, 1530, 1480, 1390, 1150, 1140	($CDCl_3$, 80 MHz): 2.00–2.20 (m, 4H, CH_2); 8.47–3.70 (m, 4H, CH_2); 8.47 (s, 2H pyrazine); 9–45 (s, 1H pyrazine)
4b	$C_{10}H_{11}N_5OS$	220–221 (EtOH)	25	2980, 2940, 2870, 1510, 1400, 1260, 1110	($CDCl_3$, 80 MHz): 3.60 and 3.80 (2t, 8H, CH_2, $J = 5.6$ Hz); 8.55 (br.s, 2H pyrazine); 9.45 (s, 1H pyrazine)
4c	$C_{14}H_{18}N_6O_2S$	276–275 (dioxane/MeOH)	36	2960, 2900, 2860, 1500, 1440, 1240, 1110	($CDCl_3$, 80 MHz): 3.60 (m, 8H, CH_2); 3.75 (m, 8H, CH_2); 8.07 and 8.72 (2s, 2H pyrazine)
4d	$C_{26}H_{28}N_8S$	239–240 (dioxane/MeOH)	25	3060, 2915, 2840, 2810, 1595, 1510, 1490, 1440, 1380, 1220, 1140	($CDCl_3$, 80 MHz): 3.20–3.42 (m, 8H, CH_2); 3.62–3.87 (m, 8H, CH_2); 6.82–7.05 (m, 6H Ph); 7.17–7.45 (m, 4H ph); 8.13 and 8.70 (2s, 2H pyrazine)
5	$C_8H_9N_5OS$	230–232 (MeOH/H_2O)	87	3150, 2904, 1504, 1463, 1392, 1344, 1295, 1243, 1043, 954, 852	(DMSO-d_6, 500 MHz): 3.62 (q, 2H, CH_2, $J = 5.8$ Hz); 4.56 (t, 2H, CH_2, $J = 5.9$ Hz); 4.76 (t, 1H, OH, $J = 5.8$ Hz); 8.81 (s, 2H pyrazine); 9.14 (s, 1H pyrazine); 14.28 (br s, 1H, NH)
7	$C_9H_{11}N_5OS$	178–179 (MeOH)	84	3213, 2935, 2870, 1520, 1472, 1403, 1156, 1072, 976	($CDCl_3$, 200 MHz): 2.81 (s, 3H, SCH_3); 4.07 and 4.56 (2t, 4H, CH_2, $J = 5.2$ Hz); 8.57 (dd, 1H pyrazine, $J = 2.6$; 1.4 Hz); 8.68 (d, 1H pyrazine, $J = 2.6$ Hz); 9.47 (d, 1H pyrazine, $J = 1.4$ Hz)

a LKB 2090 GCM instrument at 70 eV. Reaction courses and product purity were routinely monitored by TLC on silica gel precoated 60 F_{254} Merck plates. Elemental analyses (C, H, and N) were within ±0,4% of the theoretical value.

General Procedure for the Synthesis of 2-Substituted 5-Methylsulfanyl-1,3,4-thiadiazole (2a–d)

A mixture of S-ester **1** (2 mmol) in 10 mL of diluted (1:1) hydrochloric acid was refluxed for 5 min. and cooled, and the acid was neutralized with a solution of potassium carbonate. The precipitate was filtered and washed with water, and the crude product recrystallized to give **2**.

Compound **2b**; MS *m*/*z* (%): 211 (8, $M^+ + 2$), 210 (11, $M^+ + 1$), 209 (100, M^+) 122 (47), 105 (34), 104 (19).

General Procedure for the Synthesis of 3-Substituted 1,2,4-Triazolo-5-thiones (3a–d)

A mixture of *S*-ester **1** (2 mmol) and 0.25 g (4 mmol) potassium hydroxide in 10 mL of methanol was refluxed for 4 h. After cooling, the mixture was acidified with acetic acid, and the precipitate was filtered, washed with water, and recrystallized to give **3a–d**.

Compound **3b**; MS *m*/*z* (%): 180 (4, $M^+ + 2$), 179 (9, $M^+ + 1$), 178 (100, M^+), 119 (26), 105 (33).

General Procedure for the Synthesis of 2-Substituted 5-Amino-1,3,4-thiadiazoles (4a–d)

A mixture of *S*-ester **1** (5 mmol) and appropriate amine (pyrrolidine, morpholine, and N-fenylopiperazine) was refluxed for 3–6 h. After cooling, methanol was added to the mixture, and the precipitate was filtered and recystallized to give **4**.

5-(2-Ethanoloamino)-2-pyrazin-2-yl-[1,3,4]-thiadiazole (4e)

A mixture of thiosemicarbazone **6** (0.48 g, 2 mmol) and 10 mL of diluted (1:1) hydrochloric acid was refluxed for half an hour, cooled and neutralized with potassium carbonate solution. The precipitate was filtered and recrystallized from water to give 0.13 g (29%) of compound **4e**; m.p. 192–194°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 3.44 (q, 2H, CH_2, J = 5.4 Hz); 3.61 (q, 2H, CH_2, J = 5.4 Hz); 4.87 (t, 1H, OH, J = 5.4 Hz); 8.30 (br.t, 1H, NH, 5.4 Hz); 8.67 (m, 2H pyrazine); 9.27 (d, 1H pyrazine, J = 1.5 Hz).

4-(2-Ethanolo)-3-pyrazin-2-yl-2,4-dihydro-[1,2,4]-triazole-5-thione (5)

A mixture of *S*-ester **1e** (3 mmol) and 2-ethanoloamine (2 mL) was refluxed for 2 h. After cooling, the mixture was acidified with 2 mL of acetic acid, and the precipitate was filtered, washed with a small volume of cooled water, and recrystallized from methanol to give 0.60 g (87%) of thione **5**.

4-(2-Ethanolo)-5-methylsulfanyl-3-pyrazine-2-yl-[1,2,4]-triazole (7)

To a solution of potassium hydroxide (0.12 g, 2 mmol) in 10 mL of methanol thione **5** (0.45 g, 2 mmol) and methyl iodide (0.13 mL, 2 mmol) were added. This solution was stirred at r.t. for 1 h. After cooling, the precipitate was filtered and washed with water to afford compound **7** (0.40 g, 84%); m.p. 178–179°C (MeOH), lit. 159–160°C ($MeOH/H_2O$).[16]

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