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New 1,3-Thiazoles and 1,3-Thiazines from 1-Thiocarbamoylpyrazoles

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Summary. New 1,3-thiazoles and 1,3-thiazines are prepared from 1-thiocarbamoyl-pyrazoles. The structures of the title compounds are established by a single crystal structure analysis. Furthermore, antiprotozoal activities of one compound have been determined.

Keywords. X-Ray structure determination; Cyclizations; Heterocycles; ω-Bromo-alkanoates.

Introduction

Pyrazolyl-1,3-thiazoles have been reported as antifungal [1, 2], antihypertensive [3], antiinflammatory [4–6], or diuretic agents [6]. Some derivatives are inhibitors of human platelet aggregation [7]. Usually they have been prepared from 2-hydrazino-1,3-thiazoles and 1,3-bifunctional carbonyl compounds [1, 2, 4] or from pyrazole-1-thioamides and α-bromoketones [3, 5–7] (Scheme 1). We now prepared pyrazolyl-1,3-thiazol-4-ones in a two-step procedure from α,β-unsaturated ketones.

Results and Discussions

The initial step of our method is the formation of 1-thiocarbamoyl-2-pyrazolines **6–9** in a one-pot reaction of α,β-unsaturated 3-arylketones **1–4** and hydrazinediium dithiocyanate (**5**) [8]. Compounds **6–9** were heated with ethyl bromoacetate in ethyl acetate giving pyrazolyl-1,3-thiazol-4-ones **10–13** in good yields. Since no ring formation has been observed for the reaction of **6** with ethyl 3-bromopropionate

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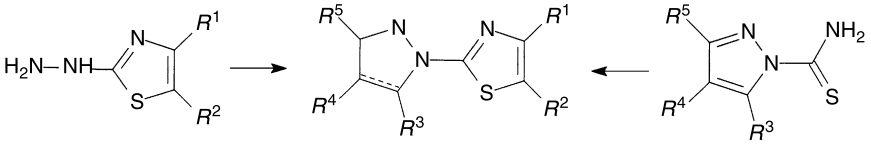
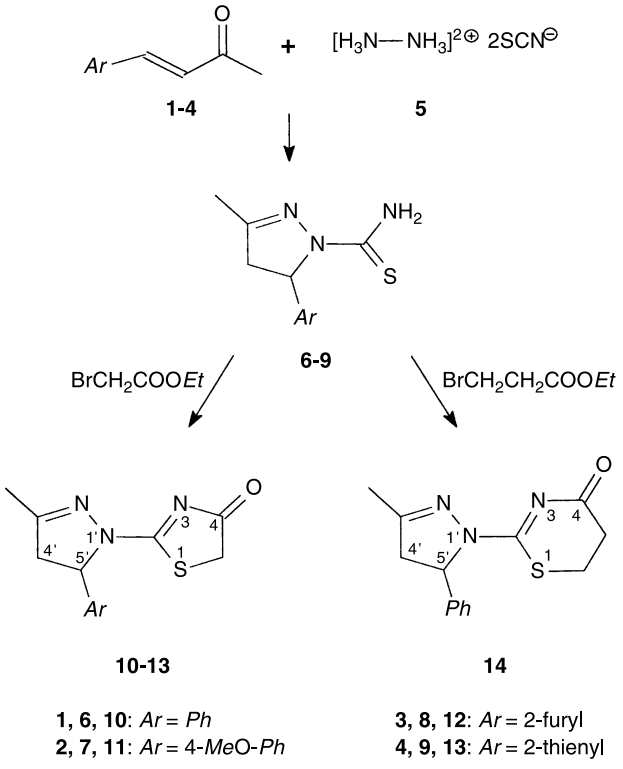


Scheme 1



Scheme 2

under these conditions, the reaction was performed in boiling chlorobenzene yielding pyrazolyl-1,3-thiazin-4-one **14** in good yields (Scheme 2).

The conversion of the thioamide carbons of compounds **6**–**9** to thiazole ring atoms of **10**–**13** caused a downfield shift of 1.5 ppm of their resonances in their ^{13}C NMR spectra. On the other hand, a 12 ppm upfield shift was observed for the corresponding signal of the 1,3-thiazine analogue **14**. Furthermore, the signals of the C-3 atoms of the pyrazole rings were shifted 2–4 ppm to higher frequencies due to the ring formations.

The configuration of the products was established by means of a single crystal structure analysis of **10** (Fig. 1).

*X-Ray Crystal Structure Analysis of **10***

The crystal structure analysis of **10** established the compound as a 2-(pyrazol-1-yl)-1,3-thiazol-4-one derivative. The pyrazole ring and the thiazole ring are almost

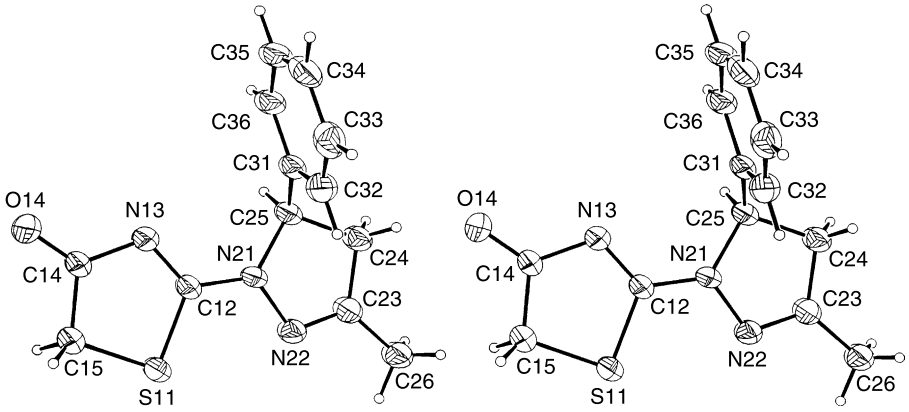


Fig. 1. Stereoscopic ORTEP [9] plot of **10** showing the atomic numbering scheme; the probability ellipsoids are drawn at the 50% probability level

Table 1. Activities of compound **10**, expressed as IC_{50} ($\mu g/cm^3$)[a]

Compound	*L. donovani*	*P. falciparum* K_1	*T. b. rhodesiense*	*T. cruci*	Cytotox. L6
10	>30	>5.0	12.0	>90	>90
standard	5.5	0.0018	0.00155	0.23	4.3

[a] Values represent the average of four determinations (two determinations of two independent experiments)

planar. Their least-squares planes enclose an angle of 6.1(2)°. The angle between the least-squares planes of the phenyl ring and the pyrazolyl ring is 86.5(2)°.

Biology

Substances with thiosemicarbazide partial structure have been reported to exhibit antimalarial [10] as well as antimycobacterial activities [11]. Therefore compound **10** was investigated for its activity against some causative organisms of tropical diseases including *Trypanosoma cruzi*, *Trypanosoma b. rhodesiense*, *Leishmania donovani*, and *Plasmodium falciparum.* Far beyond its cytotoxic concentrations compound **10** showed activity against *Trypanosoma b. rhodesiense*, a causative organism of sleeping illness (Table 1).

Experimental

Melting points: digital melting point apparatus Electrothermal IA 9200, uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). UV-VIS: Lambda 17 UV-VIS-spectrometer (Perkin Elmer). NMR spectra: Varian Inova 400 (300 K) 5 mm tubes, TMS resonance as internal standard. MS: Kratos profile spectrometer 70 eV electron impact. Microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; EA 1108 CHNS-O apparatus (Carlo Erba); their values were in satisfactory agreement with the calculated ones. Materials: Column-chromatography (CC): silica gel 60 (Merck 70–230 mesh), pore-diameter 60 Å; thin-layer chromatography

(TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm, 200×200 mm); the substances were detected in UV light at 254 nm.

*General Procedure for the Preparation of **10–13***

The pyrazol-1-ylthiocarboxamides **6–9** were suspended in ethyl acetate and ethyl bromoacetate was added. The mixture was refluxed for 4 h and the solvent was evaporated *in vacuo*. The residue was recrystallized or purified by means of CC.

2-(3-Methyl-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-1,3-thiazol-4(5H)-one
(**10**, $C_{13}H_{13}N_3OS$)

1.2 g (5.5 mmol) of **6** in 20 cm^3 of ethyl acetate reacted with 1.1 g (6.6 mmol) of ethyl bromoacetate. Recrystallization from ethanol/water afforded 1.35 g (95%) of **10** as a yellow powder. Mp 193°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.18$ (s, CH_3), 2.90 (dd, $J = 18.5$, 3.8 Hz, 4′-H), 3.58 (dd, $J = 18.8$, 11.2 Hz, 4′-H), 3.81 (s, 2 5-H), 5.65 (dd, $J = 11.3$, 3.8 Hz, 5′-H), 7.16–7.35 (m, 5 aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.08$ (CH_3), 38.89 (C-5), 47.48 (C-4′), 63.47 (C-5′), 125.56, 128.15, 128.97, 139.55 (aromatic C), 162.08 (C-3′), 177.54 (C-2), 187.41 (C-4) ppm; $R_f = 0.76$ (CH_2Cl_2:*Me*OH = 4:1); IR (KBr): $\bar{\nu} = 1703$, 1551, 1495, 1400, 1387, 1371, 1317, 1281, 1226, 1213, 1199, 703 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (log ε) = 259 (4.357) nm; MS (70 eV): m/z (%): = 259 ([M^+], 87.1), 218 (76.9), 203 (41.0), 184 (15.5), 176 (26.3), 168 (15.5), 144 (17.2), 104 (100.0), 103 (32.4), 77 (15.0); HRMS (EI+): calcd. ($C_{13}H_{13}N_3OS$): 259.077933; found: 259.07869.

*X-Ray Diffraction Data of **10***

All the measurements were performed using graphite-monochromatized MoK_α radiation at 95(2) K: $C_{13}H_{13}N_3OS$, $M_r = 259.32$, monoclinic, space group $P2_1/n$, $a = 9.455(3)$ Å, $b = 8.477(2)$ Å, $c = 15.867(5)$ Å, $\beta = 99.63(3)°$, $V = 1253.8(6)$ Å^3, $Z = 4$, $d_{calc} = 1.374$ g cm^{-3}, $\mu = 0.249$ mm^{-1}. A total of 2988 reflections was collected ($\Theta_{max} = 26°$), from which 2468 were unique ($R_{int} = 0.0432$), with 1351 having $I > 2\sigma(I)$. The structure was solved by direct methods (SHELXS-97) [12] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [13]. The non-hydrogen atoms were refined with anisotropic displacement parameters. The H-atoms were refined with common isotropic displacement parameters for the H-atoms bonded to the same C-atom or to the phenyl group and idealized geometries. For 168 parameters final R indices of $R = 0.0575$ and $wR^2 = 0.1846$ (GOF = 1.040) were obtained. The largest peak in a difference *Fourier* map was 0.302 e Å^{-3}. The final atomic parameters, as well as bond lengths and angles are deposited at the Cambridge Crystallographic Data Centre (CCDC 205638).

2-(5-(4-Methoxyphenyl)-3-methyl-4,5-dihydro-1H-pyrazol-1-yl)-1,3-thiazol-4(5H)-one
(**11**, $C_{14}H_{15}N_3O_2S$)

217 mg (0.87 mmol) of **7** in 12 cm^3 of ethyl acetate reacted with 483 mg (2.89 mmol) of ethyl bromoacetate. The residue was purified by means of CC using CH_2Cl_2:*Et*O*Et* = 4:1 giving 222 mg (88%) of **11** as a colourless resin. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.20$ (s, CH_3), 2.91 (dd, $J = 18.3$, 3.8 Hz, 4′-H), 3.54 (dd, $J = 18.5$, 11.2 Hz, 4′-H), 3.78 (s, OCH_3), 3.80 (s, 2 5-H), 5.58 (dd, $J = 11.2$, 3.8 Hz, 5′-H), 6.84 (d, $J = 8.8$ Hz, 2 m-aromatic H), 7.12 (d, $J = 8.8$ Hz, 2 o-aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.13$ (CH_3), 38.90 (C-5), 47.35 (C-4′), 55.24 (OCH_3), 63.08 (C-5′), 114.31, 127.14, 131.69, 159.42 (aromatic C), 162.01 (C-3′), 177.47 (C-2), 187.64 (C-4) ppm; $R_f = 0.11$ (CH_2Cl_2:*Et*O*Et* = 4:1); IR (KBr): $\bar{\nu} = 1696$, 1612, 1586, 1549, 1514, 1396, 1370, 1317, 1275, 1249, 1229, 1214, 1179 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (log ε) = 271 (4.470), 234 (4.079) nm.

2-(5-(2-Furyl)-3-methyl-4,5-dihydro-1H-pyrazol-1-yl)-1,3-thiazol-4(5H)-one
(**12**, $C_{11}H_{11}N_3O_2S$)

150 mg (0.72 mmol) of **8** in 10 cm^3 of ethyl acetate reacted with 400 mg (2.4 mmol) of ethyl bromoacetate. The residue was purified by means of CC using CH_2Cl_2:*Me*OH = 4:1 giving 170 mg (95%) of **12** as a yellowish resin. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.22$ (s, CH_3), 3.18 (dd, $J = 18.1$, 4.1 Hz, 4′-H), 3.41 (dd, $J = 18.1$, 11.0 Hz, 4′-H), 3.82 (s, 2 5-H), 5.71 (dd, $J = 11.2$, 4.1 Hz, 5′-H), 6.32 (dd, $J = 3.3$, 1.9 Hz, aromatic H), 6.49 (d, $J = 3.4$ Hz, aromatic H), 7.32 (d, $J = 1.7$ Hz, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.02$ (CH_3), 38.86 (C-5), 42.93 (C-4′), 56.83 (C-5′), 109.60, 110.66, 142.44, 149.45 (aromatic C), 162.04 (C-3′), 177.65 (C-2), 187.62 (C-4) ppm; $R_f = 0.84$ (CH_2Cl_2:*Me*OH = 4:1); IR (KBr): $\bar{\nu} = 1701$, 1551, 1504, 1402, 1385, 1368, 1319, 1274, 1238, 1215, 807 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (log ε) = 253 (4.270) nm.

2-(3-Methyl-5-(2-thienyl)-4,5-dihydro-1H-pyrazol-1-yl)-1,3-thiazol-4(5H)-one
(**13**, $C_{11}H_{11}N_3OS_2$)

160 mg (0.60 mmol) of **9** in 10 cm^3 of ethyl acetate reacted with 353 mg (2.1 mmol) of ethyl bromoacetate. The residue was purified by means of CC using CH_2Cl_2:*Me*OH = 4:1 giving 153 mg (96%) of **13** as a yellowish resin. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.22$ (s, CH_3), 3.08 (dd, $J = 18.3$, 3.2 Hz, 4′-H), 3.56 (dd, $J = 18.3$, 10.8 Hz, 4′-H), 3.83 (s, 2 5-H), 5.95 (dd, $J = 10.8$, 3.2 Hz, 5′-H), 6.93 (dd, $J = 4.8$, 3.8 Hz, aromatic H), 7.10 (d, $J = 3.4$ Hz, aromatic H), 7.22 (d, $J = 4.8$ Hz, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.12$ (CH_3), 38.94 (C-5), 47.02 (C-4′), 59.05 (C-5′), 125.27, 126.35, 126.93, 141.36 (aromatic C), 161.82 (C-3′), 177.80 (C-2), 187.54 (C-4) ppm; $R_f = 0.89$ (CH_2Cl_2:*Me*OH = 4:1); IR (KBr): $\bar{\nu} = 1698$, 1553, 1433, 1403, 1383, 1371, 1321, 1269, 1229, 1209, 1100, 708 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (log ε) = 266 (4.378) nm; MS (70 eV): m/z (%) = 265 ([M^+], 20.6), 224 (39.2), 209 (18.1), 150 (13.7), 136 (11.8), 110 (100.0), 97 (14.7), 86 (16.7), 69 (27.0), 58 (14.7), 46 (56.9).

2-(3-Methyl-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-5,6-dihydro-4H-1,3-thiazin-4-one
(**14**, $C_{14}H_{15}N_3OS$)

0.6 g (2.7 mmol) of **6** were suspended in 30 cm^3 of chlorobenzene. 2.4 g (13.2 mmol) of ethyl 3-bromopropionate were added. The mixture was refluxed over night and the solvent was evaporated *in vacuo*. The residue was purified by means of CC (CH_2Cl_2:*Me*OH = 4:1). Recrystallization from hexane/ethyl acetate afforded 0.61 g (82%) of **14** as a yellow powder. Mp 158°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.16$ (s, CH_3), 2.48 (ddd, $J = 15.2$, 10.0, 5.3 Hz, 5-H), 2.63 (ddd, $J = 15.2$, 6.7, 4.5 Hz, 5-H), 2.79 (dd, $J = 18.4$, 3.5 Hz, 4′-H), 3.09–3.18 (m, 2 6-H), 3.44 (dd, $J = 18.1$, 11.1 Hz, 4′-H), 5.76 (dd, $J = 11.1$, 3.5 Hz, 5′-H), 7.15–7.33 (m, 5 aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.34$ (CH_3), 24.64 (C-6), 30.73 (C-5), 46.35 (C-4′), 61.82 (C-5′), 125.46, 127.79, 128.86, 140.61 (aromatic C), 160.70 (C-3′), 163.84 (C-2), 177.06 (C-4) ppm; $R_f = 0.74$ (CH_2Cl_2:*Me*OH = 4:1); IR (KBr): $\bar{\nu} = 1663$, 1497, 1450, 1417, 1380, 1314, 1272, 1214, 1176, 1107, 701 cm^{-1}; UV-Vis (CH_2Cl_2): λ_{max} (log ε) = 283 (4.366) nm.

Biological Tests

The activities against *Trypanosoma cruzi*, *Trypanosoma b. rhodesiense*, *Leishmania donovani*, and *Plasmodium falciparum* were determined as reported [14].

The following compounds were used as standards: benznidazole (*Trypanosoma cruzi*), melarsoprol (*Trypanosoma b. rhodesiense*), pentamidine (*Leishmania donovani*), artemisinine (*Plasmodium falciparum*), and mefloquine for the determination of the cytotoxicity.

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