Monatshefte für Chemie 127, 1027–1030 (1996)

Monatshefte für Chemie
Chemical Monthly

Synthesis of 3-Aminothiophene-2-thioamides

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Summary. 4-Dimethylamino-5,6-dihydro-2*H*-thiopyran-2-thiones (**1**) were alkylated to N,N-dimethyl-6-methylthio-2*H*-thiopyran-4(3*H*)-iminiumiodides (**2**). Aminolysis of the latter with ammonia led to 6-dimethylamino-2*H*-thiopyran-4(3*H*)-iminiumiodides (**3**) which were hydrolyzed to 3-amino-N,N-dimethyl-2,4-pentadienthioamides (**4**). Ring closure with sulfur gave 3-aminothiophene-2-thioamides (**5**). The configurations of the pentadienthioamides (**4**) have been investigated by NOE experiments. The structures of the thiophene-2-thioamides (**5**) were established by means of two-dimensional NMR techniques.

Keywords. [C–C–C–C] + [S]-addition; 3-Amino-2,4-pentadienthioamide; 3-Amino-2,4-heptadienthioamide; 3-Aminothiophene-2-thioamide; 2*H*-Thiopyran-4(3*H*)-iminiumiodides.

Synthese von 3-Aminothiophen-2-thiocarboxamiden

Zusammenfassung. 4-Dimethylamino-5,6-dihydro-2*H*-thiopyran-2-thione (**1**) wurden zu N,N-Dimethyl-6-methylthio-2*H*-thiopyran-4(3*H*)-iminiumiodiden (**2**) alkyliert. Die Umsetzung mit Ammoniak führte zur Bildung von 6-Dimethylamino-2*H*-thiopyran-4(3*H*)-iminiumiodiden (**3**). Diese wurden zu 3-Amino-N,N-dimethyl-2,4-pentadienthioamiden (**4**) hydrolysiert. Beim Erhitzen mit Schwefel erfolgte Cyclisierung zu 3-Aminothiophen-2-thiocarboxamiden (**5**). Die Konfiguration der Pentadienthioamide (**4**) wurde mit NOE-Messungen untersucht, die der Thiophen-2-thiocarboxamide (**5**) mit Hilfe zweidimensionaler NMR-Methoden aufgeklärt.

Introduction

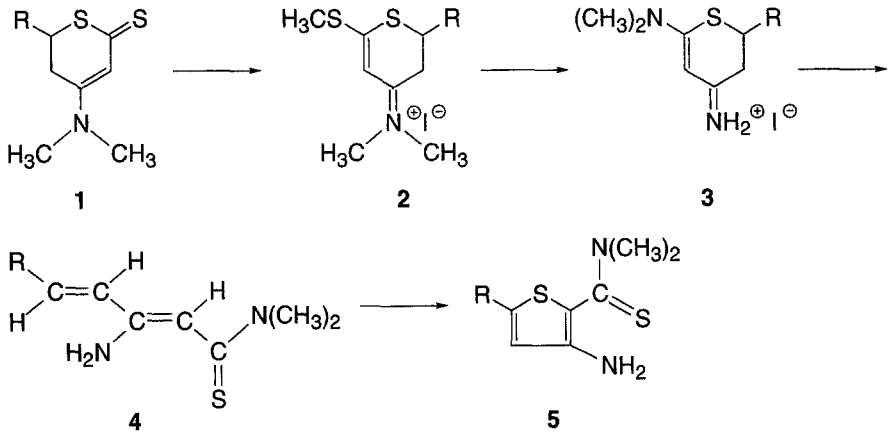
Thiophene-2-thioamides are usually prepared from the corresponding nitriles with hydrogensulfide [1, 2]. They have antibacterial activity, particularly against tubercle bacillus [3, 4]. Thiophene-2-thioamides with further substitution have not yet been reported, although derivatives of 5-substituted 3-aminothiophene-2-carboxylic acids are known to be valuable synthons for the preparation of various medicinal substances [5–7]. They are available by condensation of α- or β-chloroacrylonitriles with the corresponding mercaptoacetic acid analogues [8, 9]. This paper describes the synthesis of 5-substituted 3-aminothiophene-2- thioamides (**5**) from 3-amino-2,4-pentadienthioamides (**4**) by [C–C–C–C] + [S]-addition.

Results and Discussion

The 3-amino-2,4-pentadienthioamides **4a, b** were synthesized from 5,6-dihydro-2*H*-thiopyran-2-thiones **1a, b** [10] in three steps. Compounds **1a, b** were quantitatively

alkylated to the corresponding methylthioderivatives **2a, b** with iodomethane [11]. Upon treatment of **2a, b** with ammonia, dimethylamine was set free. The latter subsequently substituted the methylthio group giving the 4-amino-6-dimethylamino compounds **3a, b** as main products [12]. Those were hydrolized with alkali affording 3-amino-2,4-pentadienthioamides **4a, b** in good yields [13]. Only thioamides with (2*Z*, 4*E*)-configuration were formed. The *E*-configuration at the γ,δ-double bonds of **4a, b** was obvious from the coupling constants (16 Hz) of the two olefinic protons. NOE measurements established the *Z*-configuration at the α,β-double bond. Saturation of the α-protons of the thioamides **4a, b** led to definite NOEs (20% resp. 14%) at the γ-protons.

[C–C–C–C] + [S]-additions to 2-acylthiophenes are usually carried out at temperatures above 200 °C without solvent [14–16] or in high boiling solvents [17]. Melting together compounds **4a, b** with sulfur at 220 °C led to an evil-smelling reaction mixture from which, after troublesome workup, only small amounts of **5a, b** could be isolated in each case. To avoid decomposition of the $\alpha,\beta,\gamma,\delta$-unsaturated thioamides **4a, b** during the reaction, we refluxed them with excess sulfur in benzene. The thiophene-2-thioamides **5a, b** precipitated from the reaction mixture in acceptable yields.



a: R = Ph
b: R = iPr

The ring closure was obvious from the disappearance of two olefinic signals in the ^{1}H NMR spectra. The corresponding ^{13}C resonances for C-5 shifted 5 ppm upfield, whereas a downfield shift of 68 ppm for C-2 was observed. The ^{13}C signals of **3a, b** and **4a, b** were assigned by means of HMQC experiments. Differentiation between the ^{13}C resonances for the quaternary carbon atoms in **5a, b** was achieved by HMBC spectra which were optimized for 10 Hz couplings.

Experimental

All melting points are uncorrected (Büchi 510). IR: Perkin Elmer 2000 FT-IR; NMR: Varian Gemini (200 MHz), Bruker (360 MHz); solvent: *DMSO*-d_6, internal standard: *TMS*; Microanalyses: micro-

analytical laboratory at the Institute of Physical Chemistry, University of Vienna; interchangeable assignments are indicated by an asterisk.

6-Dimethylamino-2H-thiopyran-4(3H)-iminiumiodides (**3**)

Modified general procedure [13]: The respective N,N-dimethyl-6-methylthio-2*H*-thiopyran-4(3*H*)-iminiumiodides (0.1 mol) were dissolved in 250 ml ethanol. The reaction mixture was refluxed for 16 hours; during this time, a stream of ammonia was passed through. The formed mercaptane was captured in a gas washing bottle with dilute caustic soda. The solvent was removed *in vacuo*, and the residue was triturated with ethyl acetate. The crystallizate was filtered with suction, dried, and recrystallized.

(RS)-(±)-6-Dimethylamino-2-phenyl-2H-thiopyran-4(3H)-iminiumiodide (**3a**)

Yield: 21.1 g (58.6%); m.p.: 197 °C (chloroform/ethyl acetate); IR (KBr): $\tilde{\nu} = 3350$ (m), 1633 (m), 1594 (s), 1538 (s), 1368 (s) cm^{-1}; ^1H NMR: $\delta = 2.98$ (dd, $J = 16.9$, 3.4 Hz, 1H, 3-H), 3.27 (br, 6H, $(N(CH_3)_2)$), 3.35 (dd, $J = 16.9$, 12.3 Hz, 1H, 3-H), 4.92 (dd, $J = 12.3$, 3.4 Hz, 1H, 2-H), 5.81 (s, 1H, 5-H), 7.39–7.58 (m, 5H, aromatic H), 8.71, 8.89 (2s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 34.26$ (C-3), 41.70 ($N(CH_3)_2$), 44.14 (C-2), 87.79 (C-5), 127.94, 128.85, 128.99, 136.70 (aromatic C), 168.94 (C-6*), 169.22 (C-4*) ppm; $C_{13}H_{17}IN_2S$ (360.26); calcd.: C 43.34, H 4.76, I 35.22, N 7.78, S 8.90; found: C 43.49, H 4.81, I 35.04, N 7.75, S 9.10.

(RS)-(±)-6-Dimethylamino-2-(1-methylethyl)-2H-thiopyran-4(3H)-iminiumiodide (**3b**)

Yield: 24.1 g (73.9%); m.p.: 173 °C (water/ethanol); IR (KBr): $\tilde{\nu} = 3360$ (m), 3120 (m), 2920 (w), 1640 (s), 1550 (s), 1425 (m) cm^{-1}; ^1H NMR: $\delta = 1.00$, 1.02 (2d, $J = 6.5$ Hz, 6H, $CH(CH_3)_2$), 1.98 (m, 1H, $CH(CH_3)_2$), 2.71 (dd, $J = 16.7$, 11 Hz, 1H, 3-H), 2.87 (dd, $J = 16.7$, 3.7 Hz, 1H, 3-H), 3.21, 3.28 (2s, 6H, $N(CH_3)_2$), 3.41–3.51 (m, 1H, 2-H), 5.75 (s, 1H, 5-H), 8.61, 8.78 (2s, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 19.36$, 19.53 ($CH(CH_3)_2$), 30.44 ($CH(CH_3)_2$), 31.59 (C-3), 41.73 ($N(CH_3)_2$), 47.60 (C-2), 87.78 (C-5), 169.10 (C-6*), 169.30 (C-4*) ppm; $C_{10}H_{19}IN_2S$ (326.24); calcd.: C 36.82, H 5.87, I 38.90, N 8.58, S 9.83; found: C 36.90, H 5.79, I 38.49, N 8.46, S 10.05.

3-Amino-2,4-pentadienthioamides (**4**)

Modified general procedure [9]: Compounds **3** (0.05 mol) were stirred in a 2 *M* solution of caustic soda (0.2 mol) for 2 hours. The suspension was extracted with toluene (**4a**) or ether (**4b**) repeatedly until a clear aqueous solution remained. The combined extracts were washed three times with water and dried over sodium sulfate. The solvent was removed and the residue recrystallized.

(2Z,4E)-3-Amino-N,N-dimethyl-5-phenyl-2,4-pentadienthioamide (**4a**)

Yield: 9.2 g (79.2%); m.p.: 160 °C (ethanol); IR (KBr): $\tilde{\nu} = 3380$ (m), 1710 (w), 1640 (m), 1600 (s), 1540 (s) cm^{-1}; ^1H NMR: $\delta = 3.30$ (s, 6H, $N(CH_3)_2$), 5.50 (s, 1H, 2-H), 6.73 (d, $J = 16.2$ Hz, 1H, 4-H), 7.33 (d, $J = 16.2$ Hz, 1H, 5-H), 7.32–7.65 (m, 5H, aromatic H), 8.60–9.00 (br, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 41.40$ ($N(CH_3)_2$), 95.14 (C-2), 126.96, 128.60, 128.82, 135.88 (aromatic C), 128.05 (C-4), 132.16 (C-5), 154.69 (C-3), 188.19 (C-1) ppm; $C_{13}H_{16}N_2S$ (232.35); calcd.: C 67.20, H 6.94, N 12.06, S 13.80; found: C 67.11, H 7.04, N 12.14, S 13.88.

(2Z,4E)-3-Amino-6,N,N-trimethyl-2,4-heptadienthioamide (**4b**)

Yield: 7.7 g (77.6%); m.p.: 70 °C (heptane); IR (KBr): $\tilde{\nu} = 3370$ (m), 2950 (w), 1650 (m), 1595 (s), 1538 (s), 1372 (m) cm^{-1}; ^1H NMR: $\delta = 1.02$ (d, $J = 6.8$ Hz, 6H, $CH(CH_3)_2$), 2.33–2.52 (m, 1H, $CH(CH_3)_2$), 3.24 (s,

6H, $N(CH_3)_2$), 5.24 (s, 1H, 2-H), 5.83 (d, $J = 16$ Hz, 1H, 4-H), 6.43 (dd, $J = 16$, 6.7 Hz, 1H, 5-H), 8.70 (br, 2H, NH_2) ppm; ^{13}C NMR: $\delta = 21.84$ ($CH(CH_3)_2$), 30.72 (C-6), 41.30 ($N(CH_3)_2$), 93.16 (C-2), 126.66 (C-4), 142.06 (C-5), 155.19 (C-3), 188.16 (C-1) ppm; $C_{10}H_{18}N_2S$ (198.33); calcd.: C 60.56, H 9.15, N 14.12, S 16.17; found: C 60.81, H 9.22, N 14.14, S 16.11.

3-Aminothiophene-2-thioamides (**5**)

General procedure: The $\alpha,\beta,\gamma,\delta$-unsaturated thioamides **4** (0.01 mol) and sulfur (0.02 mol) were dissolved in 30 ml benzene. A stream of nitrogen was passed through the solution for 10 minutes. Then the reflux condenser was closed with a balloon. The reaction mixture was refluxed at 90 °C for at least 18 hours to form a suspension which was cooled and filtered with suction. The residue was washed with benzene, dried, and recrystallized.

3-Amino-N,N-dimethyl-5-phenylthiophen-2-thioamide (**5a**)

Reaction period: 24 h; yield: 1.75 g (66.7%); m.p.: 223 °C (chloroform/ethanol); IR (KBr): $\bar{\nu} = 3410$ (s), 3230 (m), 3050 (m), 1600 (s) cm^{-1}; ^1H NMR: $\delta = 3.14$ (s, 6H, $N(CH_3)_2$), 6.44 (s, 1H, 4-H), 7.36–7.72 (m, 5H, aromatic H), 8.76 (br, 1H, NH), 8.88 (br, 1H, NH) ppm; ^{13}C NMR: $\delta = 40.29$ ($N(CH_3)_2$), 89.23 (C-4), 126.93 (C-5), 127.78, 130.21, 139.59 (aromatic C), 143.01 (C-3), 159.46 (C=S), 162.63 (C-2) ppm; $C_{13}H_{14}N_2S_2$ (262.42); calcd.: C 59.51, H 5.38, N 10.68, S 24.44; found: C 59.32, H 5.30, N 10.59, S 24.72.

3-Amino-N,N-dimethyl-5-(1-methylethyl)thiophen-2-thioamide (**5b**)

Reaction period: 18 h; yield: 1.47 g (64.4%); m.p.: 202 °C (chloroform/benzene); IR (KBr): $\bar{\nu} = 3430$ (s), 3230 (m), 1590 (s), 1560 (s), 1475 (m), 1440 (m) cm^{-1}; ^1H NMR: $\delta = 1.20$ (d, $J = 7$ Hz, 6H, $CH(CH_3)_2$), 3.11 (s, 6H, $N(CH_3)_2$), 4.40 (sept, $J = 7$ Hz, 1H, $CH(CH_3)_2$), 6.30 (s, 1H, 4-H), 8.59 (br, 1H, NH), 8.66(br, 1H, NH) ppm; ^{13}C NMR: $\delta = 20.93$ ($CH(CH_3)_2$), 34.14 ($CH(CH_3)_2$), 40.26 ($N(CH_3)_2$), 89.12 (C-4), 138.33 (C-5), 140.16 (C-3), 158.23 (C=S), 161.70 (C-2) ppm; $C_{10}H_{16}N_2S_2$ (228.38); calcd.: C 52.59, H 7.06, N 12.27, S 28.08; found: C 52.49, H 6.90, N 12.32, S 27.82.

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Received February 12, 1996. Accepted March 26, 1996