THIENOPYRROLIZINES II.[1] SYNTHESIS OF 4-IMINO (AND 4-AMINO)-4H-THIENO[2,3-b]-PYRROLIZINES

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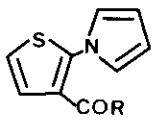
Abstract — Vilsmeier's thienopyrroliziniminium salts were treated with primary amines to give N-substitued thienopyrrolizinimines. Reduction of these imines gave the corresponding amino derivatives.

In continuation of our work on the synthesis of thiophenic analogs of pyrroloindoles (in relation with mitomycin antitumor activity [2], we wish to describe herein a convenient route for the synthesis of new 4-imino-and 4-amino-4H-thieno[2,3-b]pyrrolizines via an iminium salt.

We have recently published an original way of cyclisation of thienopyrrolizinone 1 using amides in Vilsmeier-Haack reactions [1] and applied this method to the synthesis of pyrroloindoles [3]. Further studies concerning this reaction prompted us to isolate the intermediary iminium salts of this reaction.

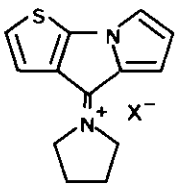
Thus when the pyrrolidinocarboxamide 3 was treated with boiling phosphoryl chloride, the reaction afforded after evaporation of the excess reagent the stable iminium 4. The structure of its cationic moiety was confirmed by IR and NMR spectroscopic data, but microelemental analyses showed that the anionic moiety was always a mixture of phosphorodichloridate and chloride. This compound is very soluble in aqueous medium and can be used in situ for further reactions. However the crude salt 4 could be purified by treatment first by sodium bicarbonate, then by perchloric acid to give the insoluble perchlorate 5.

These iminium salts 4 and 5 exhibited a high reactivity towards nucleophilic reagents. Thus treatment of an aqueous solution of 4 or 5 with sodium or potassium hydroxide gave the pyrrolizinone 1 as described before. The iminium 4 was treated with hydrazine hydrate at room temperature to give the hydrazone 6 which could not be obtained from pyrrolizinone 1 by reaction with hydrazine which instead lead to a desulfurisation of the thiophene ring. Similarly treatment of 4 with hydroxylamine hydrochloride in presence of sodium acetate gave the oxime 7 as a mixture of an equivalent



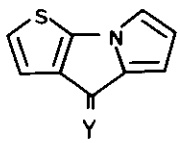
2 R = N_3

3 R =



4 X = PO_2Cl_2, Cl

5 X = ClO_4

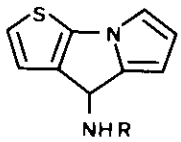


1 Y = O

6 Y = NNH_2

7 Y = NOH (E+Z)

8 — 14 Y = NR (Table I)



15 — 21 (Table II)

22 R = H

23 R = $COCH_3$

amount of E and Z forms. These latter could be obtained starting from 1.

Furthermore when an aqueous solution of the iminium salt 4 was treated at room temperature with an excess of water-soluble primary aliphatic amines, the instantaneous reaction afforded the imines 8 ⟶ 14 in quantitative yield (Table I). These imines could not be obtained by condensation of primary aliphatic amines with the pyrrolizinone 1. This reaction of the iminium salt 4 with primary aliphatic amine seems to be quite general with water soluble materials. Aromatic amines were unreactive under these conditions.

Reduction of these imines 8 ⟶ 14 in methanol with sodium borohydride gave the corresponding aminothienopyrrolizines 15 ⟶ 21 (Table II).

The amino compound 22 was obtained when ammonia was bubbled into a methanolic solution of the iminium salt 4 and the unstable pyrrolizinimine was reduced in situ with sodium borohydride. Acetylation of the unstable oil of 22 with acetic anhydride gave the stable acetamidothienopyrrolizine 23.

EXPERIMENTAL

General notes

Melting points are uncorrected. All new compounds gave satisfactory microanalyses (±0.3%).

Ir spectra were recorded on Perkin-Elmer 257 G spectrometer and only noteworthy absorptions (cm^{-1}) are listed. NMR spectra were recorded in DMSO-d_6 with TMS as international standard on a Varian EM 390 spectrometer.

2-(1-Pyrrolyl)-3-pyrrolidinocarbonylthiophene 3 — Pyrrolidine (50 ml) was added dropwise to a solution of 2-(1-pyrrolyl)-3-thenoyl azide 2 [1] (21.8g, 0,1 mole) in dichloromethane (500 ml) at room temperature with stirring. The reaction mixture was stirred for 12 h at this temperature and then washed with hydrochloric acid (1N, 3x150 ml). The organic layer was washed with water, dried ($CaCl_2$) and the solvent removed under vacuum. The residue was worked-up in ether to give a yellow oil (18g, 73%, bp°C 180/1mm).

ir νmax (KBr) 1610 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6) δ ppm 7.03 (d, 1H, H-4) ; 7.31 (d, 1H, H-5), 6.90 (m, 2H, H-2', H-5'), 6.20 (m, 2H, H-3', H-4'), 3.30 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 1.66 (m, 4H, CH_2).

Anal. Calcd for $C_{13}H_{14}N_2OS$: C,63.39; H, 5.73; N, 11.37; S, 13.01. Found: C, 63,25; H, 5.84; N, 11.35; S, 12.97.

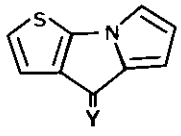
N-Cyclobutanothieno[2,3-b] pyrrolizin-4-iminium (mixture of chloride and phosphorodichloridate) 4

A solution of 2-(1-pyrrolyl)-3-pyrrolidinocarbonylthiophene 3 (20g) in phosphoryl chloride (200 ml) was refluxed for 1 h and then the excess of reagent was removed under vacuum. The red semi-solid residue (25g) was thoroughly washed with petroleum ether and dried. Recrystallization from 2-propanol gave red crystals (mp°C 260 dec.).

ir νmax (KBr) 1650 cm^{-1} ($\overset{+}{C}$=N); ^{1}H nmr (DMSO-d_6/D_2O) δ ppm 7.13 (s, 2H, H-2, H-3), 6.96 (dd, 1H, H-5), 6.25 (dd, 1H, H-6); 7.41 (dd, 1H, H-7), 4.10 (m, 2H, CH_2), 3.80 (m, 2H, CH_2), 2.21 (m, 4H, CH_2).

N-Cyclobutanothieno[2,3-b]pyrrolizin-4-iminium (perchlorate) 5 — Sodium hydrogenecarbonate (10g) was added portionwise with stirring at room temperature to a solution of iminium salt 4 (5g) in water (50 ml) ; the resulting alkaline solution (pH=13) was acidified by slow addition of concentrated perchloric acid. After 30 min, the red precipitate was filtered, washed with water and dried (5g, 93% from 3). Recrystallization from 2-propanol gave crystals (mp°C >250 expl.).

Table I



mp or bp, yields, IR and ^{1}H NMR spectral data of compound 6 ⟶ 14

Compound	Y	mp°C (solvent for recrystallization) or bp°C	Yield %	IR (KBr) ν max (cm^{-1})	^{1}H N M R					
					H2	H3	H5	H6	H7	Other signals
6	N-NH_2	238(Et_2O)	70	1630(C=N) 3400-3280 (NH_2)	7.00	7.00	6.73	6.21	7.23	7.05(NH_2)
7	a = NOH(E)* b = NOH(Z)*	E=250(EtOH) Z=190(EtOH)	90	1635(C=N) 3150-3000(OH)	7.03 7.05	7.03 7.21	6.60 6.37	6.16 6.12	7.27 7.26	11.76(OH) 11.63(OH)
8	N-CH_3	86 (Et_2O)	65	1610(C=N)	7.06	7.03	6.58	6.20	7.32	3.45(CH_3)
9	N-C_2H_5	100(Et_2O)	60	1625(C=N)	7.08	6.98	6.53	6.13	7.30	3.65(CH_2);1.33(CH_3)
10	N-nC_3H_7	130/5mm	68	1610(C=N)	7.05	7.05	6.50	6.18	7.30	3.56(CH_2);1.81(CH_2);1.00(CH_3)
11	N-nC_4H_9	124/5mm	65	1620(C=N)	7.03	7.03	6.50	6.18	7.30	3.61(CH_2);1.72(CH_2);1.40(CH_2); 0.93(CH_3)
12	N(CH_2)$_3$N(C_2H_5)$_2$	125/5mm	70	1615(C=N)	7.05	6.96	6.16	7.25	7.25	3.58(CH_2);2.45(CH_2);1.83(CH_2); 0.91(CH_3)
13	N-CH_2-C_6H_5	94 (petroleum ether: Et_2O 1:1)	60	1625(C=N)	7.03	7.03	6.70	6.16	7.30	4.76(CH_2);7.30(C_6H_5)
14	N-C_2H_4OH	152(Et_2O:me_2CO 1:1)	75	1620(C=N) 3150(OH)	7.03	7.03	6.40	6.18	7.30	3.75(CH_2);4.71(OH)

* Separated by fractional crystallization from ethanol.

Ir νmax (KBr) 1650 cm^{-1} ($\overset{+}{C}$=N) 1100 cm^{-1} (ClO_4^-); ^{1}H nmr (DMSO-d_6/D_2O) δ ppm 7.21 (s, 2H, H-2, H-3); 7.08 (dd, 1H, H-5); 6.25 (dd, 1H, H-6); 7.73 (dd, 1H, H-7); 4.16 (m, 2H, CH_2); 3.91 (m, 2H, CH_2); 2.13 (m, 4H, CH_2).

Anal. Calcd for $C_{13}H_{13}ClO_4N_2S$: C, 47.49; H, 3.99; N, 8.52; S, 9.75; Cl, 10.78. Found: C, 47.55; H, 4.08; N, 8.47; S, 9.70; Cl, 11.04.

General procedure for the preparation of hydrazone 6, oxime 7 and imines 8 ⟶ 14 — To a well stirred solution of iminium salt 4 (2g) in water (20 ml), the appropriate reagent was added at room temperature. After 5 min, the resulting precipitate was recovered either by filtration for the solid compound or by extraction with ether for the oily compounds. The solid compounds were washed with water, dried (Na_2SO_4), recrystallized from appropriate solvents. The organic extracts were washed with water and dried ($MgSO_4$). The solvent was removed and the residue distilled unter reduced pressure (see Table I).

General procedure for preparation of amines 15 ⟶ 21 — To a solution of one of the 4-alkylimino-4H-thienopyrrolizines 8 ⟶ 14 (1g) in methanol (50 ml), sodium borohydride (1g) was added. The mixture was refluxed for 30 min and the solvent removed. The residue was triturated with water (60 ml) and extracted with ether (3x50 ml). The organic layer was washed with water, dried (Na_2SO_4) and the solvent removed. The oily product was distilled under reduced pressure except for compound 21 which was recrystallized (see Table II).

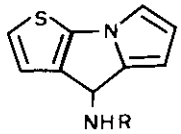
4-Acetamido-4H-thieno[2,3-b]pyrrolizine 23 — Ammonia was bubbled for 5 min into a solution of iminium salt 4 (1,5g) in methanol (60 ml). When the red starting solution became yellow, sodium borohydride (1g) was added in small portions. The mixture was stirred for 30 min at room temperature and the methanol was removed. The residue was triturated with water (60 ml) and then extracted with ether (3x50 ml).

The organic layer was washed with water and dried (Na_2SO_4). After evaporation of the solvent, the oily residue was distilled under reduced pressure to give the 4-aminothienopyrrolizine 22 as a colourless oil (0.5g, 45% from 3, bp 110°C/5mm.

Ir νmax (KBr) 3450-3360 cm^{-1} (NH_2); ^{1}H nmr (DMSO-d_6) δ ppm 7.00 (s, 2H, H-2, H-3), 6.10 (m, 2H, H-5, H-6), 7.00 (dd, 1H, H-7), 4.76 (s, 1H, H-4), 2.5. (s, 2H, NH_2).

The aminothienopyrrolizine 22 (0,25g) was dissolved in ether (10 ml) and then acetic anhydride (1 ml) was added. The reaction mixture was heated for 30 min at 40°C and then allowed to stand at room temperature for 12 h. The white crystalline precipitate was filtered and recrystallized from petroleum ether (0.25g, 73%, mp 210°C).

Table II



mp, or bp, yields, IR and ^{1}H NMR spectral data of compounds 15 ⟶ 21.

Compound	R	mp°C (solvent for recrystallization) or bp°C	Yield %	IR (KBr) ν max(cm^{-1})	^{1}H N M R						
					H2	H3	H5	H6	H7	H4	Other signals
15	CH_3	120/5mm	85	3300(NH)	7.00	7.00	6.16	6.16	7.05	4.76	2.30(CH_3);3.1(NH)
16	C_2H_5	100/5mm	80	3300(NH)	7.00	7.00	6.20	6.20	7.05	4.73	2.60(NH);2.60(CH_2);1.00(CH_3)
17	n-C_3H_7	115/5mm	90	3300(NH)	7.00	7.00	6.20	6.20	7.00	4.75	2.90(CH_2);1.30(CH_2);0.80(CH_3); 3.3(NH)
18	n-C_4H_9	120/5mm	85	3300(NH)	7.00	7.00	6.20	6.20	7.05	4.73	2.46(CH_2);1.33(CH_2);0.83(CH_3): 3.33(NH)
19	$(CH_2)_3N(C_2H_5)_2$	148/5mm	82	3295(NH)	7.00	7.00	6.20	6.20	7.05	4.73	3.30(CH_2);2.35(CH_2);1.03(CH_3); 3.30(NH)
20	$CH_2C_6H_5$	118/5mm	65	3300(NH)	7.00	7.00	6.13	6.13	7.05	4.76	3.80(CH_2);7.25(C_6H_5);3.30(NH)
21	C_2H_4OH	101($Et)_2O$: petroleum ether 1:1	88	3300(NH) 3100(OH)	7.00	7.00	6.11	6.11	7.05	4.73	3.38(CH_2);2.56(CH_2);3.38(NH); 4.40(OH)

ir νmax (KBr) 3260 cm^{-1} (NH); 1640 cm^{-1} (C=O); ^1H nmr (DMSO-d_6) δ ppm 7.03 (d, 1H, H-2), 6.86 (d, 1H, H-3), 6.10 (m, 2H, H-5, H-6), 7.10 (dd, 1H, H-7), 5.73 (s, 1H, H-4), 1.83 (s, 3H, CH_3), 8.41 (s, 1H, NH).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.54; H, 4.62; N, 12.84; S, 14.66. Found: C, 60.59; H, 4.62; N, 12.84; S, 14.58.

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