Synthesis of Isomeric β-Haloethylthienopyrroles

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The preparation of ethyl 4-(2-bromoethyl)thieno[2,3-*b*]pyrrole-5-carboxylate and ethyl 6-(2-bromoethyl)thieno[3,2-*b*]pyrrole-5-carboxylate by reaction of *t*-butyl 2-(2-thienyl)carbazate and *t*-butyl 2-(3-thienyl)carbazate with ethyl-5-bromo-2-oxopentanoate are described.

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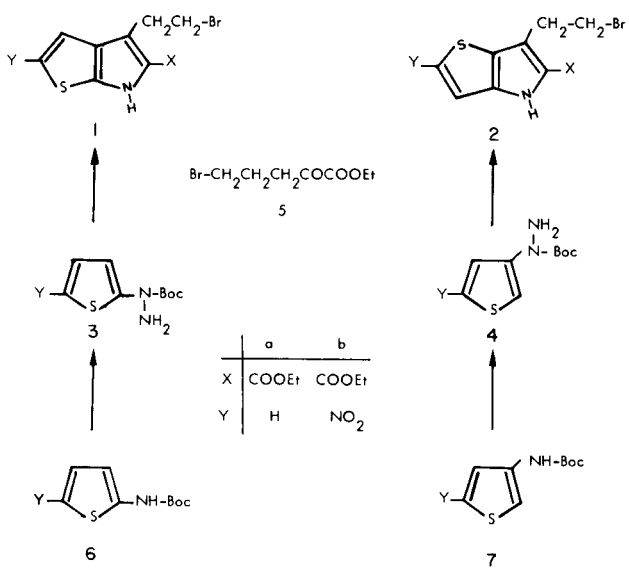
Due to our interest in the preparation of polycyclic systems from thienopyrroles we have attempted the synthesis of the key intermediates **1** and **2**. Concerning the stability that the 5-carbethoxy group confers on thieno[2,3-*b*]pyrrole and thieno[3,2-*b*]pyrrole [1] and the possibility to use these compounds in the synthesis of tetracyclic systems according to the recent work of G. Kalaus [2] we proceeded with the preparation of the 5-carbethoxythienopyrroles.

Among the different synthetic alternatives for such compounds we have selected the cyclisation of thiophene precursors adequately substituted obtained from *N*-protected thienylhydrazines [3,4] (see Scheme 1). Thus, whereas the condensation reaction of *N*-protected thienylhydrazine **3b** with 1,3-dicarbonyl compounds allowed us to isolate thienylpyrazoles [5], the condensation of **3a** and 4a with ethyl 5-bromo-2-oxopentanoate (**5**) was satisfactory giving the expected products **1a** and **2a**.

Scheme 1



For the preparation of thienylhydrazines **3** and **4**, we have followed the guidelines of Binder [3] developed for 2-thienylhydrazines. This procedure is based upon the formation of the sodium salt of the requisite *t*-butyl thiophenecarbamate, compound **6** [3,6] and compound **7** [7] in our work, and subsequent reaction of the salt obtained with an aminating agent *O*-(4-nitrobenzoyl)hydroxylamine (**8**) [8] or *O*-(2,4-dinitrophenoxy)hydroxylamine (**9**) [9]. In our hands, as can be seen in Table I whereas **6a**, gave the hydrazine derivative in good yield (experiment 1), the isomeric carbamate **7a** under the same conditions (experiment 3) did not permit the isolation of **4a**. The starting carbamate was recovered unchanged. The change of the solvent, dimethylformamide by dioxane (experiment 4), and with an increase in the reaction temperature a mixture of products was obtained. The ^{1}H-nmr spectra of the mixture showed the absence of the *t*-butoxycarbonyl protecting group. Regarding the instability of thienylhydrazines and the stabilizing character of the nitro group in the aminothiophene derivatives [6], we tested the amination reaction with the nitrated carbamate **7b** (experiment 7) without satisfactory results. In contrast, the isomeric nitrocarbamate **6b** (experiment 2) gave the hydrazino derivative **3b** in good yield

Since this fact could be interpreted as due to the nonformation of the sodium salt we proceeded to isolate the salt of compounds **6a** and **7a**. Thus, whereas **6a** gave the sodium salt by heating the carbamate with sodium hydride in toluene, by contrast **7a** under the same conditions permitted us to isolate a white solid identified as *N,N'*-di-(3-thienyl)urea (**12**). The formation of this compound can be explained as is indicated in figure 1. Due to the thermal instability of **7a** and its sodium salt, more moderate conditions were used. Thus the heating of **7a** in dimethylformamide at 50-60° during 30 minutes using sodium hydride as the base and **9** as the aminating agent, we were able to isolate **4a** (experiment 6). Finally we proceeded

Figure 1

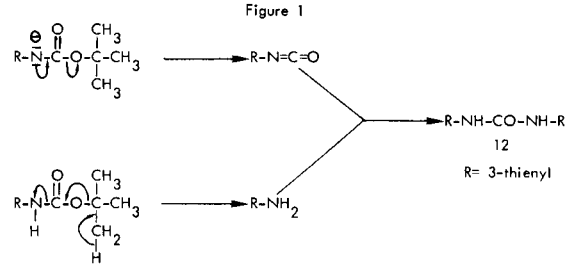


Table I

Experiment	Amino derivative	Conditions of anion formation	Aminating agents	% Hydrazino	Other products
1	**6a**	NaH/Dioxane reflux 3 hours	**8**	**3a** (79%)	—
2	**6b**	NaH/Dioxane reflux 3 hours	**8**	**3b** (68%)	—
3	**7a**	NaH/Dioxane reflux 3 hours	**8**	—	12% of **7a**
4	**7a**	NaH/DMF 120° 1 hour	**8**	—	lost Boc group
5	**7a**	NaH/Dioxane DMF [a]	**8**	—	8% of **7a**
6	**7a**	NaH/DMF 50-60° 30 minutes	**9**	**4a** (66%)	—
7	**7b**	NaH/Dioxane reflux 3 hours	**8**	—	5% of **7b**

[a] DMF was added to dissolve the solid formed after heating at reflux 3 hours in dioxane.

with the synthesis of compounds **1** and **2** by reaction of thienylhydrazines **3** and **4**, with the carbonyl compound **5**. The heating of the compounds **3a** and **4a** with **5a** in ethanol at reflux as is indicated in the esperimental part, allowed us to obtain the ethyl-4-(2-bromoethyl)thieno[2,3-*b*]pyrrole-5-carboxylate (**1a**) and the ethyl 6-(2-bromoethyl)thieno[3,2-*b*]pyrrole-5-carboxylate (**2a**) with yields of 50% and 43% respectively.

By contrast, the condensation between **3b** and **5** in methanol as solvent did not lead to the thienopyrrole **1b**, isolating instead the corresponding hydrazone, methyl 5-bromo-2-[2-(5-nitro-2-thienyl)hydrazono]pentanoate (**13**). Several experiments directed to the cyclisation of compound **13** (concentrated hydrochloric acid or polyphosphoric acid) were fruitless.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12B spectrometer using TMS as an internal standard. Chemical shifts are reported as δ values in parts per million (ppm). Infrared spectra were measured on a Pye-Unicam SP 1100 spectrophotometer. Elemental analysis were performed by Instituto de Química Oránica, Barcelona.

t-Butyl 2-(2-Thienyl)carbazate (**3a**).

This compound was prepared according to Binder's method [3].

t-Butyl 2-(5-Nitro-2-thienyl)carbazate (**3b**).

This compound was prepared by us previously [5].

t-Butyl 2-(3-Thienyl)carbazate (**4a**).

To a suspension of 0.040 g (0.0013 mole) of sodium hydride (80% in paraffin) in 2 ml of dimethylformamide under an atmosphere of nitrogen, 0.245 g (0.0012 mole) of **7a** was added. The resulting mixture was heated 30 minutes at 50-60°. After this time the solution was cooled to 10°. Then 0.265 g (0.0013) mole of compound **9** in 1 ml of dimethylformamide was added dropwise. The mixture was stirred overnight at room temperature and then ice was added. The resulting mixture was extracted with methylene chloride and the organic layer was dried over magnesium sulfate and the solvent was removed. Then residue was purified by silica-gel chromatography. On elution with hexane-methylene chloride (7:3) 0.180 g (70%) of white solid was obtained, mp 38-39°; ir (potassium bromide): 1710 cm^{-1} (COO); nmr (carbon tetrachloride): δ 1.52 (s, *t*-butyl-H, 9H), 4.22 (s, NH_2, 2H), 7.30-6.90 (m, H-2, H-3, H-4 of thiophene ring, 3H).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07; S, 14.96. Found: C, 50.48; H, 6.61; N, 13.10; S, 14.95.

t-Butyl 5-Nitro-3-thiophenecarbamate (**7b**).

To a solution of the acylazide **10** (0.70 g, 0.0035 mole) in dry dioxane (10 ml) was added 0.33 g (0.0045 mole) of *t*-butyl alcohol. The reaction mixture was slowly heated under reflux for 1 hour. After this time the mixture was distilled giving a residue which was recrystallized from hexane-methylene chloride to give 0.568 g (67%) of a yellow solid, mp 125°; ir (potassium bromide): 3370 cm^{-1} (NH), 1725 (COO); nmr (deuteriochloroform): δ 1.50 (s, *t*-butyl-H, 9H), 7.15 (s, NH, 1H), 7.35 (d, H-4, 1H, $J_{2,4}$ = 1 Hz), 7.80 (d, H-2, 1H).

Anal. Calcd. for $C_9H_{12}N_2O_4S$: C, 44.26; H, 4.92; N, 11.48; S, 13.11. Found: C, 44.28; H, 4.90; N, 11.45; S, 13.11.

5-Nitro-3-thenoylazide (**10**).

To a solution of 1.35 g (0.007 mole) of 5-nitro-3-thenoyl chloride (**11**) in 7 ml of chloroform at 0°, 0.50 g (0.0077 mole) of sodium azide in a minimum of water was added dropwise with vigorous stirring. The reaction mixture was allowed to stir at 0° for 30 minutes and 90 minutes more at room temperature. The organic layer was separated, dried over magnesium sulfate and the solvent was evaporated *in vacuo* giving a residue which was recrystallized from benzene-hexane to give 1 g (72%) of yellow solid, mp 72°; ir (potassium bromide): 2080 cm^{-1} (N_3), 1700 cm^{-1} (CO); nmr (carbon tetrachloride): δ 8.27 (s, H-2, H-4, 2H).

Anal. Calcd. for $C_5H_2N_4O_3S$: C, 30.31; H, 1.02; N, 28.27; S, 16.18. Found: C, 30.29; H, 1.00; N, 28.27; S, 16.19.

5-Nitro-3-thenoyl Chloride (**11**).

A solution of 1.356 g (0.0078 mole) of 5-nitro-3-thiophenecarboxylic acid [10] in 10 ml of thionyl chloride was heated at reflux for 3 hours. After this time, the excess thionyl chloride was evaporated *in vacuo*. The residue was purified on a silica-gel column using benzene as the eluent giving 1.45 g (96%) of yellow solid, mp 125-126°; ir (potassium bromide): 1800 cm^{-1} (CO) nmr (deuteriochloroform): δ 8.37 (d, H-4, 1H), 8.46 (d, H-2, 1H, $J_{2,4}$ = 1 Hz).

Anal. Calcd. for $C_5H_2ClNO_3S$; C, 31.35; H, 1.05; Cl, 18.50; N, 7.31; S, 16.74. Found: C, 31.38; H, 1.08; Cl, 18.52; N, 7.33; S, 16.77.

Procedure for the Preparation of the Sodium Salt of **6a** and **7a**.

A mixture of 0.199 g (0.001 mole) of **6a** and 0.029 g (0.00097 mole) of sodium hydride (80% in paraffin) in 30 ml of dry toluene was heated at reflux for 6 hours. The hot solution was filtered and 0.11 g (51%) of dark solid was obtained; nmr (deuterated dimethylsulfoxide): δ 1.45 (s, *t*-butyl-H, 9H), 6.00-6.90 (m, thiophene ring, 3H).

A mixture of 0.199 g (0.001 mole) of **7a** and 0.029 g (0.00097 mole) of sodium hydride (80% in paraffin) in 30 ml of dry toluene was heated at reflux for 6 hours. The dark solid obtained was recrystallized from chloroform giving 0.078 g (70%) of white solid, mp 250°; ir (potassium bromide): 3295 cm^{-1} (NH), 1640 cm^{-1} (CO); nmr (deuterated dimethylsulfoxide): δ 7.00-7.30 (m, thiophene ring, 3H), 8.90 (s, NH, 1H).

Ethyl 4-(2-Bromoethyl)thieno[2,3-*b*]pyrrole-5-carboxylate (**1a**).

A solution of 1.07 g (0.005 mole) of **3a**, 1.114 g (0.005 mole) of compound **5** [11] and 0.5 ml of concentrated chlorhydric acid in 50 ml of ethanol, under an atmosphere of nitrogen was heated at reflux for 2 hours. After this time, the solution was concentrated and water was added. The resulting mixture was extracted with methylene chloride and the organic layer was dried with magnesium sulfate. The solvent was removed and the residue recrystallized from hexane to give 2.75 g (50%) of white solid, mp 117°; ir (potassium bromide): 3300 cm^{-1} (NH), 1680 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.42 (t, CH_3, 3H), 3.60 (m, CH_2, 4H), 4.40 (c, CH_2, 2H), 6.91 (d, H-3, 1H), 7.02 (d, H-2, $J_{2,3}$ = 5.4 Hz), 9.50 (s, NH, 1H).

Anal. Calcd. for $C_{11}H_{12}BrNO_2S$: C, 43.47; H, 4.00; Br, 26.44; N, 4.64; S, 10.61. Found: C, 43.48; H, 4.03; Br, 26.45; N, 4.60; S, 10.65.

Ethyl 6-(2-Bromoethyl)thieno[3,2-*b*]pyrrole-5-carboxylate (**2a**).

A solution of 1.017 g (0.0005 mole) of **4a**, 0.112 g (0.0005 mole) of compound **5** and 0.05 ml of concentrated chlorhydric acid in 5 ml of ethanol was treated as is indicated more above for **1a**. From hexane 0.065 g (43%) of white solid was obtained, mp 141°; ir (potassium bromide): 3300 cm^{-1} (NH), 1680 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.41 (t, CH_3, 3H), 3.62 (m, CH_2, 4H), 4.39 (c, CH_2, 2H), 6.94 (d, H-3, 1H), 7.34 (d, H-2, 1H, $J_{2,3}$ = 5.2 Hz), 9.00 (s, NH, 1H).

Anal. Calcd. for $C_{11}H_{12}BrNO_2S$: C, 43.47; H, 4.00; Br, 26.44; N, 4.64; S, 10.61. Found: C, 43.50; H, 4.02; Br, 26.44; N, 4.62; S, 10.63.

Preparation of Ethyl 6-(2-Bromoethyl)-2-nitrothieno[2,3-*b*]pyrrole-5-carboxylate (**2b**).

A solution of 0.520 g (0.002 mole) of **4b**, 0.445 g (0.002 mole) of compound **5** and 0.2 ml of concentrated hydrochloric acid in 20 ml of methanol under an atmosphere of nitrogen, was heated at reflux for 4 hours. After this time, the solution was concentrated and water was added. The resulting mixture was extracted with methylene chloride and the organic layer was dried with magnesium sulfate. The solution was concentrated and purified by silica-gel chromatography. On elution with methylene chloride a yellow solid was obtained which was recrystallized from hexane-methylene chloride to give 0.250 g (36%) of methyl 5-bromo-2-(5-nitro-2-thienyl)hydrazonopentanoate (**13**), mp 126-127°; ir (potassium bromide): 1690 cm^{-1} (COO); nmr (deuteriochloroform): δ 2.20 (c, CH_2, 2H), 2.71 (t, CH_2, 2H), 3.50 (t, CH_2Br, 2H), 3.82 (s, CH_3, 3H), 6.16 (d, H-4, 1H, $J_{3,4}$ = 5.6 Hz), 7.68 (d, H-3, 1H).

Anal. Calcd. for $C_{10}H_{12}BrN_3O_4S$: C, 34.30; H, 3.45; Br, 22.82; N, 12.00; S, 9.16. Found: C, 34.35; H, 3.48; Br, 22.82; N, 12.06; S, 9.17.

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