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A series of cyclic sulfonium ylides **4a-h** reacted with titanium(IV) chloride in the presence of triethylamine to give the corresponding fused 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles **5a-h**, via a ring opening and recyclization. In contrast, treatment of compounds **4a**, **4b**, **4e** and **4f** with titanium(IV) chloride, triethylamine and dimethylamine hydrochloride gave the corresponding thiophenes **6a**, **6b**, **6e** and **6f**. Furthermore, compounds **6a** and **6b** easily underwent cyclization with sodium hydride to afford the corresponding **5a** and **5b**.

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Thienopyrroles, especially three different isomers **1**, **2** and **3** fused of *b* junction of pyrrole ring (Figure 1), are of interest because of their relationship to indoles. It is known that some of them have shown interesting biological properties [1,2]. Research in this field has mainly been centered on the preparation of analogues of naturally occurring indole derivatives [3-11]. However, the known methods for the synthesis of thienopyrroles have a number of limitations and very little study has thus far been devoted to 1*H*-thieno[3,4-*b*]pyrroles (type **3**). For these reasons, we have been interested in the development of new methods for the synthesis of thienopyrroles.

proceed through an initial ring opening between the oxygen and the 5-position of the furan ring. Thus, by analogy to our earlier work, we tried the ring opening reaction of cyclic sulfonium ylides **4** with titanium(IV) chloride. Although we examined the reaction of sulfonium ylides with titanium(IV) chloride according to our method [16], the reaction proceeded with violence and it was not clean. Hence, in order to overcome this limitation, we then envisaged that the Lewis acid-amine base complex could act as a milder ring opening promoter. Several investigators have reported an efficient transformation and cyclization by the

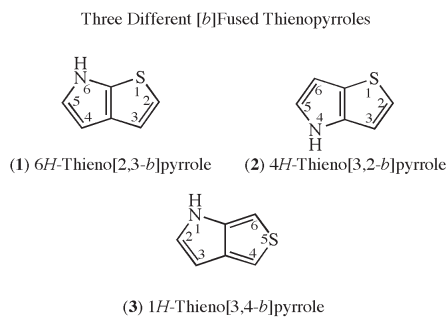
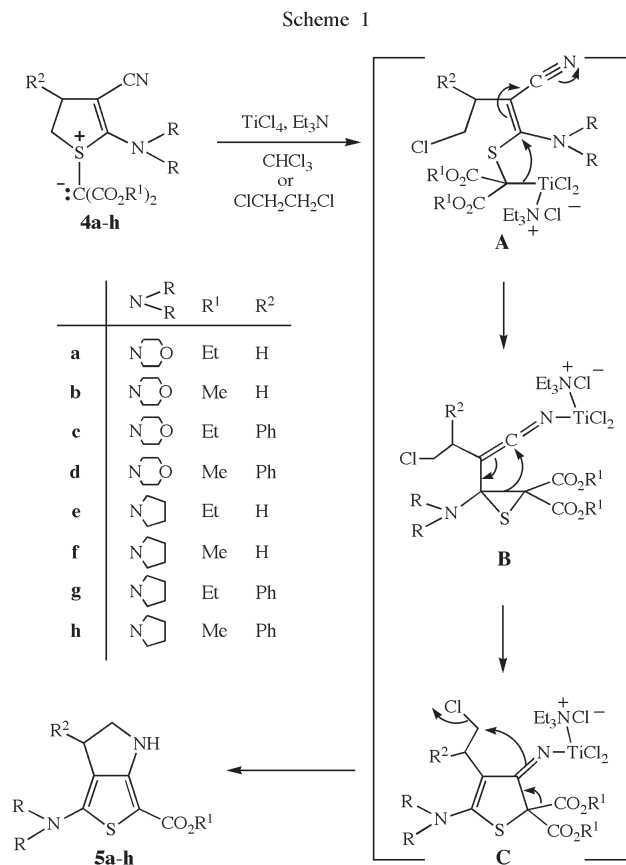


Figure 1

In the course of our studies on heterocyclic enamino-nitriles, we have shown that the sulfonium ylides **4** of 4,5-dihydro-3-thiophenecarbonitriles undergo ring cleavage at the S-C5 bond and subsequent recyclization in the presence of a base [12], sodium iodide and thionyl chloride [13]. Continuing with our interest in the chemical reactivity [14,15] of sulfonium ylides as starting materials, we report here a convenient method for preparing 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles using the S-C5 bond cleavage reaction of cyclic sulfonium ylides **4** by means of a Lewis acid-amine base system. In a preceding paper [16] we already reported that the reactions of 2-acylamino-4,5-dihydro-3-furancarbonitriles with titanium(IV) chloride



action of a titanium(IV) chloride-amine combination (e.g. amine: *tert*-butylamine, cyclohexylamine and benzylamine [17]; triethylamine [18]; tributylamine [19] and tetrabutylammonium iodide [20-24]). Based on these observations, we investigated the reactions of sulfonium ylides with titanium(IV) chloride-triethylamine.

When a mixture of **4a** [12] with titanium(IV) chloride in the presence of triethylamine in chloroform was refluxed for 5 hours, the expected 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrrole **5a** was obtained in 61% yield (Scheme 1). In this case, no ring opening product initially formed, such as the intermediate chlorine-containing compound **A**, was observed. The ir spectrum of **5a** displays a band at 3370 cm^{-1} due to a secondary amino group and at 1642 cm^{-1} due to a carbonyl group, whereas that of **4a** shows a band at 2195 cm^{-1} due to a conjugated cyano group and at 1630 and 1612 cm^{-1} due to carbonyl groups. The ^1H nmr spectrum of **5a** exhibits a D_2O exchangeable signal at $\delta = 6.19$ ppm attributable to the secondary amino proton and a three-proton triplet at $\delta = 1.20$ ppm for the methyl group of the ethyl ester function. On the other hand, the ^1H nmr spectrum of **4a** shows a six-proton triplet at $\delta = 1.28$ ppm for two methyl groups of the ester functionalities. In addition, on the basis of elemental analysis and mass spectrum, **5a** was identified as ethyl 2,3-dihydro-4-morpholino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate. Similarly, treatment of **4b-h** [12,13] by means of a titanium(IV) chloride-triethylamine combination gave the corresponding 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles **5b-h** (Table 1). Elemental analyses and spectral data of **5b-h** are consistent with the assigned structures (see experimental section). Though the detailed mechanism of the above reaction has not been clarified yet, the formation of 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles **5** could be explained by the possible mechanism presented in Scheme 1. Thus, treatment of **4** with a titanium(IV) chloride-triethylamine complex causes the cleavage of S-C5 bond to form the chloro derivative **A**, which is converted into the intermediate thiirane **B**. The ring expansion of **B** to the dihydrothiophene **C** easily occurs, which could then undergo restorative aromatization *via* dealkoxycarbonylation [12] and ring closure *via* dechlorination to afford the 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles **5**. In this reaction, we observed that 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles could not be obtained without triethylamine as a base. It makes us believe that this ring transformation can only be promoted by using a couple titanium(IV) chloride and triethylamine reagents.

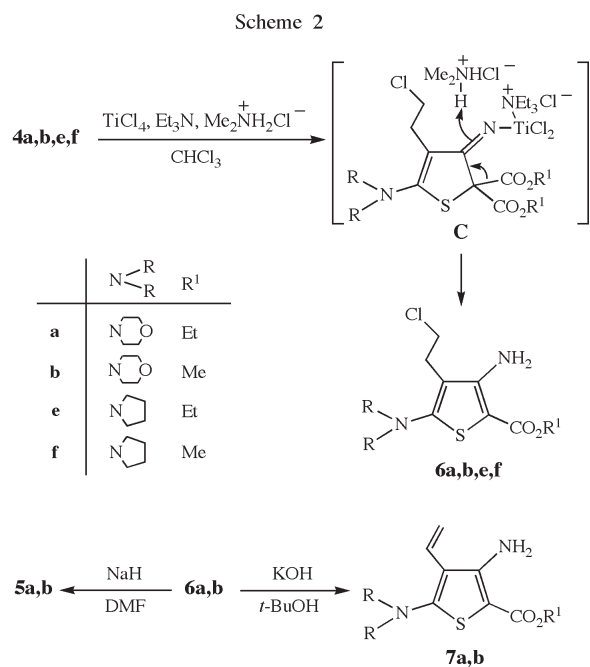
Fortunately, we found the reaction condition under which the chlorine-containing thiophenes **6a**, **6b**, **6e** and **6f** could be obtained (Scheme 2). Using dimethylamine hydrochloride as a proton source, the reaction of **4a**, **4b**, **4e** and **4f** with titanium(IV) chloride-triethylamine combination in refluxing chloroform for 3 hours produced the corresponding thiophenes **6a**, **6b**, **6e** and **6f** in 66, 59, 61 and

Table 1

Preparation of 1*H*-Thieno[3,4-*b*]pyrroles **5** According to Scheme 1

Entry	Substrate	Product	Yield (%)
1	4a	5a	61
2	4b	5b	56
3	4c	5c	47
4	4d	5d	37
5	4e	5e	54
6	4f	5f	61
7	4g	5g	52
8	4h	5h	28

44% yields, respectively. The ir spectra of **6a**, **6b**, **6e** and **6f** show an amino band in the 3330-3460 cm^{-1} region. The ^1H nmr spectra of the compounds exhibit a D_2O exchangeable signal at $\delta = 6.4$ -6.5 ppm attributable to the amino protons. Elemental analyses and spectral data of **6a**, **6b**, **6e** and **6f** are consistent with the proposed structures (see experimental section). In this case, it seemed possible that the intermediate **C** could trap a proton produced from dimethylamine hydrochloride. Hence, no ring closure of **C** proceeded.



Finally, we have examined the conversion of **6a** and **6b** into **5a**, **5b**, **7a** and **7b** in order to confirm their structures (Scheme 2). Compounds **6a** and **6b** were allowed to react with sodium hydride in *N,N*-dimethylformamide at 100° for 3 hours to give the corresponding 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles **5a** and **5b** in good yields (**5a**: 89%, **5b**: 86%). Subsequent treatment of **6a** and **6b** with potas-

sium hydroxide in refluxing *tert*-butyl alcohol for 3 hours caused an elimination of hydrogen chloride to form the thiophene derivatives **7a** and **7b** in 56 and 32% yields, respectively. The structure of **7a** was confirmed by direct comparison with an authentic sample described earlier [12].

In conclusion, we have developed a novel method for the construction of 2,3-dihydro-1*H*-thieno[3,4-*b*]pyrroles, proceeding by ring opening and recyclization reactions when cyclic sulfonium ylides are treated with a titanium(IV) chloride-triethylamine combination.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-302 spectrometer. The ¹H and ¹³C nmr spectra were recorded on a JEOL JNM-A 500 spectrometer at 500 and 126 MHz, respectively. The ¹H and ¹³C chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Positive FAB mass spectra were obtained on a JEOL JMS-HX 110 spectrometer. Elemental analyses were performed on a HERAUS CHNO-RAPID analyzer.

General Procedure for the Preparation of 2,3-Dihydro-1*H*-thieno[3,4-*b*]pyrroles **5a-h** from **4a-h** and Titanium(IV) Chloride-Triethylamine Complex.

To an ice-cooled and stirred solution of **4a-h** [12,13] (10 mmoles) and triethylamine (1.11 g, 11 mmoles) in chloroform (20 mL, in the case of the preparation of **5a**, **5b**, **5e** and **5f**) or in 1,2-dichloroethane (20 mL, in the case of the preparation of **5c**, **5d**, **5g** and **5h**) was added titanium(IV) chloride (2.09 g, 11 mmoles). After the mixture was refluxed for 5 hours, anhydrous sodium carbonate (10 g) and a saturated aqueous sodium carbonate solution (5 mL) were successively added to the reaction mixture with stirring and ice-cooling. The solid was removed by filtration and washed with hot chloroform. The combined filtrates were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel with chloroform as the eluent to give **5a-h**.

Ethyl 2,3-Dihydro-4-morpholino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5a**).

This compound was obtained as pale yellow columns (1.73 g, 61%), mp 207-209° (chloroform-petroleum ether); ir (potassium bromide): ν 3370 (NH), 1642 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.20 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃), 2.86 (t, J = 7.9 Hz, 2H, H₃), 3.13-3.15 (m, 4H, 2xNCH₂ (morpholine)), 3.66-3.68 (m, 4H, 2xOCH₂ (morpholine)), 3.79 (t, J = 7.9 Hz, 2H, H₂), 4.07 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 6.19 ppm (br s, 1H, NH); ¹³C nmr (DMSO-*d*₆): δ 14.6 (CO₂CH₂CH₃), 25.6 (C₃), 49.3 (2xNCH₂ (morpholine)), 52.1 (C₂), 58.5 (CO₂CH₂CH₃), 65.4 (2xOCH₂ (morpholine)), 112.5 (C_{3a}), 151.2 (C₄, C₆ and C_{6a}), 162.3 ppm (CO₂CH₂CH₃); ms: m/z 282 (M⁺).

Anal. Calcd. for C₁₃H₁₈N₂O₃S: C, 55.30; H, 6.43; N, 9.92. Found: C, 55.42; H, 6.38; N, 9.95.

Methyl 2,3-Dihydro-4-morpholino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5b**).

This compound was obtained as colorless prisms (1.51 g,

56%), mp 169-171° (acetone-petroleum ether); ir (potassium bromide): ν 3370 (NH), 1642 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 2.89 (t, J = 7.9 Hz, 2H, H₃), 3.13-3.15 (m, 4H, 2xNCH₂ (morpholine)), 3.59 (s, 3H, CO₂Me), 3.66-3.68 (m, 4H, 2xOCH₂ (morpholine)), 3.79 (t, J = 7.9 Hz, 2H, H₂), 6.28 ppm (br s, 1H, NH); ¹³C nmr (DMSO-*d*₆): δ 25.7 (C₃), 49.2 (2xNCH₂ (morpholine)), 50.2 (CO₂CH₃), 52.1 (C₂), 65.4 (2xOCH₂ (morpholine)), 112.4 (C_{3a}), 151.2 (C₄, C₆ and C_{6a}), 162.6 ppm (CO₂CH₃); ms: m/z 268 (M⁺).

Anal. Calcd. for C₁₂H₁₆N₂O₃S: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.78; H, 6.19; N, 10.44.

Ethyl 2,3-Dihydro-4-morpholino-3-phenyl-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5c**).

This compound was obtained as colorless columns (1.67 g, 47%), mp 160-162° (acetone-petroleum ether); ir (potassium bromide): ν 3380 (NH), 1643 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.22 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃), 2.94-3.29 (m, 4H, 2xNCH₂ (morpholine)), 3.31-3.36 (m, 2H, OCH₂ (morpholine)), 3.44-3.48 (m, 2H, OCH₂ (morpholine)), 3.54 (dd, J = 4.0, 9.5 Hz, 1H, H₃), 4.11 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 4.26 (t, J = 9.5 Hz, 1H, H₂), 4.43 (dd, J = 4.0, 9.5 Hz, 1H, H₂), 6.27 (br s, 1H, NH), 7.15-7.17 (m, 2H, aromatic H), 7.21-7.24 (m, 1H, aromatic H), 7.30-7.33 ppm (m, 2H, aromatic H); ¹³C nmr (DMSO-*d*₆): δ 14.6 (CO₂CH₂CH₃), 43.6 (C₃), 49.3 (2xNCH₂ (morpholine)), 58.6 (CO₂CH₂CH₃), 62.0 (C₂), 65.2 (2xOCH₂ (morpholine)), 114.8 (C_{3a}), 126.6, 126.9, 128.6, 143.8 (aromatic C), 152.3 (C₄, C₆ and C_{6a}), 162.3 ppm (CO₂CH₂CH₃); ms: m/z 358 (M⁺).

Anal. Calcd. for C₁₉H₂₂N₂O₃S: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.83; H, 6.18; N, 7.80.

Methyl 2,3-Dihydro-4-morpholino-3-phenyl-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5d**).

This compound was obtained as colorless needles (1.29 g, 37%), mp 203-205° (chloroform-petroleum ether); ir (potassium bromide): ν 3390 (NH), 1655 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 2.94-3.03 (m, 4H, 2xNCH₂ (morpholine)), 3.28-3.36 (m, 2H, OCH₂ (morpholine)), 3.44-3.48 (m, 2H, OCH₂ (morpholine)), 3.52-3.55 (m, 1H, H₃), 3.63 (s, 3H, CO₂Me), 4.23-4.28 (m, 1H, H₂), 4.43 (dd, J = 4.0, 9.2 Hz, 1H, H₂), 6.37 (br s, 1H, NH), 7.14-7.16 (m, 2H, aromatic H), 7.21-7.24 (m, 1H, aromatic H), 7.30-7.34 ppm (m, 2H, aromatic H); ¹³C nmr (DMSO-*d*₆): δ 43.6 (C₃), 49.2 (2xNCH₂ (morpholine)), 50.3 (CO₂CH₃), 62.0 (C₂), 65.2 (2xOCH₂ (morpholine)), 114.7 (C_{3a}), 126.6, 126.9, 128.6, 143.8 (aromatic C), 152.4 (C₄, C₆ and C_{6a}), 162.6 ppm (CO₂CH₃); ms: m/z 344 (M⁺).

Anal. Calcd. for C₁₈H₂₀N₂O₃S: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.68; H, 5.83; N, 8.19.

Ethyl 2,3-Dihydro-4-pyrrolidino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5e**).

This compound was obtained as colorless needles (1.44 g, 54%), mp 204-206° decomposition (chloroform-petroleum ether); ir (potassium bromide): ν 3370 (NH), 1635 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.19 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.88-1.92 (m, 4H, 2xCH₂ (pyrrolidine)), 2.92 (t, J = 8.0 Hz, 2H, H₃), 3.31-3.35 (m, 4H, 2xNCH₂ (pyrrolidine)), 3.77 (t, J = 8.0 Hz, 2H, H₂), 4.04 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 6.00 ppm (br, 1H, NH); ¹³C nmr (DMSO-*d*₆): δ 14.7 (CO₂CH₂CH₃), 24.9 (C₃), 25.2 (2xCH₂ (pyrrolidine)), 49.8 (2xNCH₂ (pyrrolidine)), 52.3 (C₂), 58.2 (CO₂CH₂CH₃), 107.8 (C_{3a}), 148.6 (C₄, C₆ and

C_{6a}), 162.3 ppm (CO₂CH₂CH₃); ms: m/z 266 (M⁺).

Anal. Calcd. for C₁₃H₁₈N₂O₂S: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.48; H, 6.59; N, 10.53.

Methyl 2,3-Dihydro-4-pyrrolidino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5f**).

This compound was obtained as colorless needles (1.55 g, 61%), mp 223-225° decomposition (chloroform-petroleum ether); ir (potassium bromide): ν 3380 (NH), 1640 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.88-1.94 (m, 4H, 2xCH₂ (pyrrolidine)), 2.92 (t, J = 8.2 Hz, 2H, H₃), 3.18-3.42 (m, 4H, 2xNCH₂ (pyrrolidine)), 3.57 (s, 3H, CO₂Me), 3.76 (t, J = 8.2 Hz, 2H, H₂), 6.10 ppm (br, 1H, NH); ¹³C nmr (DMSO-*d*₆): δ 24.9 (C₃), 25.2 (2xCH₂ (pyrrolidine)), 49.7 (2xNCH₂ (pyrrolidine)), 50.0 (CO₂CH₃), 52.2 (C₂), 107.7 (C_{3a}), 148.6 (C₄, C₆ and C_{6a}), 162.5 ppm (CO₂CH₃); ms: m/z 252 (M⁺).

Anal. Calcd. for C₁₂H₁₆N₂O₂S: C, 57.12; H, 6.39; N, 11.10. Found: C, 56.94; H, 6.47; N, 11.03.

Ethyl 2,3-Dihydro-3-phenyl-4-pyrrolidino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5g**).

This compound was obtained as colorless scales (1.77 g, 52%), mp 200-202° (chloroform-petroleum ether); ir (potassium bromide): ν 3400 (NH), 1640 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.21 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.72-1.77 (m, 4H, 2xCH₂ (pyrrolidine)), 2.91-2.96 (m, 2H, NCH₂ (pyrrolidine)), 3.25-3.32 (m, 2H, NCH₂ (pyrrolidine)), 3.48 (dd, J = 3.1, 9.2 Hz, 1H, H₃), 4.08 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 4.25 (t, J = 9.2 Hz, 1H, H₂), 4.47 (dd, J = 3.1, 9.2 Hz, 1H, H₂), 6.10 (br, 1H, NH), 7.14-7.15 (m, 2H, aromatic H), 7.18-7.22 (m, 1H, aromatic H), 7.29-7.32 ppm (m, 2H, aromatic H); ¹³C nmr (DMSO-*d*₆): δ 14.7 (CO₂CH₂CH₃), 25.1 (2xCH₂ (pyrrolidine)), 43.0 (C₃), 50.0 (2xNCH₂ (pyrrolidine)), 58.3 (CO₂CH₂CH₃), 62.2 (C₂), 110.5 (C_{3a}), 126.4, 126.7, 128.6, 146.2 (aromatic C), 150.0 (C₄, C₆ and C_{6a}), 162.3 ppm (CO₂CH₂CH₃); ms: m/z 342 (M⁺).

Anal. Calcd. for C₁₉H₂₂N₂O₂S: C, 66.64; H, 6.48; N, 8.18. Found: C, 66.62; H, 6.49; N, 8.17.

Methyl 2,3-Dihydro-3-phenyl-4-pyrrolidino-1*H*-thieno[3,4-*b*]pyrrole-6-carboxylate (**5h**).

This compound was obtained as colorless prisms (0.93 g, 28%), mp 193-195° (chloroform-petroleum ether); ir (potassium bromide): ν 3420 (NH), 1640 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.73-1.76 (m, 4H, 2xCH₂ (pyrrolidine)), 2.91-2.96 (m, 2H, NCH₂ (pyrrolidine)), 3.25-3.31 (m, 2H, NCH₂ (pyrrolidine)), 3.48 (dd, J = 3.1, 9.2 Hz, 1H, H₃), 3.61 (s, 3H, CO₂Me), 4.25 (t, J = 9.2 Hz, 1H, H₂), 4.47 (dd, J = 3.1, 9.2 Hz, 1H, H₂), 6.19 (br s, 1H, NH), 7.13-7.15 (m, 2H, aromatic H), 7.18-7.22 (m, 1H, aromatic H), 7.28-7.31 ppm (m, 2H, aromatic H); ¹³C nmr (DMSO-*d*₆): δ 25.1 (2xCH₂ (pyrrolidine)), 43.0 (C₃), 49.9 (2xNCH₂ (pyrrolidine)), 50.0 (CO₂CH₃), 62.2 (C₂), 110.5 (C_{3a}), 126.4, 126.7, 128.6, 146.2 (aromatic C), 150.1 (C₄, C₆ and C_{6a}), 162.5 ppm (CO₂CH₃); ms: m/z 328 (M⁺).

Anal. Calcd. for C₁₈H₂₀N₂O₂S: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.68; H, 6.16; N, 8.55.

General Procedure for the Preparation of Thiophenes **6a**, **6b**, **6e** and **6f** from **4a**, **4b**, **4e** or **4f** and Titanium(IV) Chloride-Triethylamine Complex in the Presence of Dimethylamine Hydrochloride.

To an ice-cooled and stirred solution of triethylamine (1.11 g,

11 mmole) in chloroform (20 mL) was added titanium(IV) chloride (1.90 g, 10 mmole). The mixture was stirred at room temperature for 30 minutes, and then **4a**, **4b**, **4e** or **4f** (10 mmole) and dimethylamine hydrochloride (1.63 g, 20 mmole) were successively added to the obtained solution with stirring and ice-cooling. The resulting mixture was refluxed for 3 hours. After the same work-up as described above for the preparation of **5a-h**, the residue was purified by column chromatography on silica gel with chloroform as the eluent to yield **6a**, **6b**, **6e** and **6f**. In the case of the preparation of **6a** and **6b**, further the elution provided **5a** (0.27 g, 9%) and **5b** (0.10 g, 4%), respectively.

Ethyl 3-Amino-4-(2-chloroethyl)-5-morpholino-2-thiophenecarboxylate (**6a**).

This compound was obtained as colorless scales (2.10 g, 66%), mp 127-129° (acetone-petroleum ether); ir (potassium bromide): ν 3420, 3330 (NH₂), 1662 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.22 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃), 2.87-2.88 (m, 4H, 2xNCH₂ (morpholine)), 2.92 (t, J = 7.8 Hz, 2H, H₁), 3.70-3.86 (m, 6H, 2xOCH₂ (morpholine) and H₂), 4.15 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 6.48 ppm (br s, 2H, NH₂); ¹³C nmr (DMSO-*d*₆): δ 14.4 (CO₂CH₂CH₃), 28.1 (C₁), 41.9 (C₂), 53.3 (2xNCH₂ (morpholine)), 59.0 (CO₂CH₂CH₃), 65.9 (2xOCH₂ (morpholine)), 116.4 (C₄), 132.0 (C₂), 154.0 (C₃), 159.5 (C₅), 163.7 ppm (CO₂CH₂CH₃); ms: m/z 318 (M⁺).

Anal. Calcd. for C₁₃H₁₉ClN₂O₃S: C, 48.98; H, 6.01; N, 8.79. Found: C, 49.14; H, 5.99; N, 8.92.

Methyl 3-Amino-4-(2-chloroethyl)-5-morpholino-2-thiophenecarboxylate (**6b**).

This compound was obtained as colorless scales (1.81 g, 59%), mp 165-167° (acetone-petroleum ether); ir (potassium bromide): ν 3420, 3330 (NH₂), 1670 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 2.87-2.89 (m, 4H, 2xNCH₂ (morpholine)), 2.92 (t, J = 7.8 Hz, 2H, H₁), 3.67 (s, 3H, CO₂Me), 3.69-3.73 (m, 6H, 2xOCH₂ (morpholine) and H₂), 6.50 ppm (s, 2H, NH₂); ¹³C nmr (DMSO-*d*₆): δ 28.1 (C₁), 41.9 (C₂), 50.6 (CO₂CH₃), 53.3 (2xNCH₂ (morpholine)), 65.9 (2xOCH₂ (morpholine)), 116.4 (C₄), 132.0 (C₂), 154.1 (C₃), 159.5 (C₅), 164.0 ppm (CO₂CH₃); ms: m/z 304 (M⁺).

Anal. Calcd. for C₁₂H₁₇ClN₂O₃S: C, 47.29; H, 5.62; N, 9.19. Found: C, 47.32; H, 5.62; N, 9.27.

Ethyl 3-Amino-4-(2-chloroethyl)-5-pyrrolidino-2-thiophenecarboxylate (**6e**).

This compound was obtained as colorless needles (1.83 g, 61%), mp 109-110° (acetone-petroleum ether); ir (potassium bromide): ν 3440, 3330 (NH₂), 1625 (C=O) cm⁻¹; ¹H nmr (DMSO-*d*₆): δ 1.19 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₃), 1.89-1.95 (m, 4H, 2xCH₂ (pyrrolidine)), 2.95 (t, J = 8.0 Hz, 2H, H₁), 3.37-3.39 (m, 4H, 2xNCH₂ (pyrrolidine)), 3.59 (t, J = 8.0 Hz, 2H, H₂), 4.09 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₃), 6.40 ppm (br, 2H, NH₂); ¹³C nmr (DMSO-*d*₆): δ 14.6 (CO₂CH₂CH₃), 25.2 (2xCH₂ (pyrrolidine)), 28.1 (C₁), 43.1 (C₂), 51.4 (2xNCH₂ (pyrrolidine)), 58.3 (CO₂CH₂CH₃), 102.0 (C₄), 132.3 (C₂), 147.2 (C₃), 156.6 (C₅), 163.3 ppm (CO₂CH₂CH₃); ms: m/z 302 (M⁺).

Anal. Calcd. for C₁₃H₁₉ClN₂O₂S: C, 51.56; H, 6.32; N, 9.25. Found: C, 51.78; H, 6.37; N, 9.21.

Methyl 3-Amino-4-(2-chloroethyl)-5-pyrrolidino-2-thiophenecarboxylate (**6f**).

This compound was obtained as colorless prisms (1.27 g,

44%), mp 140-142° (chloroform-petroleum ether); ir (potassium bromide): ν 3460, 3350 (NH₂), 1630 (C=O) cm⁻¹; ¹H nmr (DMSO-d₆): δ 1.89-1.96 (m, 4H, 2xCH₂ (pyrrolidine)), 2.95 (t, J = 8.0 Hz, 2H, H₁), 3.32-3.46 (m, 4H, 2xNCH₂ (pyrrolidine)), 3.59 (t, J = 8.0 Hz, 2H, H₂), 3.61 (s, 3H, CO₂Me), 6.40 ppm (br s, 2H, NH₂); ¹³C nmr (DMSO-d₆): δ 25.1 (2xCH₂ (pyrrolidine)), 28.1 (C₁), 43.0 (C₂), 50.0 (CO₂CH₃), 51.4 (2xNCH₂ (pyrrolidine)), 101.9 (C₄), 132.3 (C₂), 147.2 (C₃), 156.7 (C₅), 163.7 ppm (CO₂CH₃); ms: m/z 288 (M⁺).

Anal. Calcd. for C₁₂H₁₇ClN₂O₂S: C, 49.91; H, 5.93; N, 9.70. Found: C, 49.72; H, 5.87; N, 9.53.

The Preparation of **5a** and **5b** from **6a** or **6b** and Sodium Hydride.

To an ice-cooled and stirred solution of **6a** (1.59 g, 5 mmoles) or **6b** (0.61 g, 2 mmoles) in *N,N*-dimethylformamide [(10 mL, in the case of the preparation of **5a**) or (5 mL, in the case of the preparation of **5b**)] was added 60% sodium hydride powder [(0.22 g, 5.5 mmoles, in the case of the preparation of **5a**) or (88 mg, 2.2 mmoles, in the case of the preparation of **5b**)]. Stirring was continued at room temperature until the evolution of gas ceased. The solution was then stirred at 100° for 3 hours. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to furnish **5a** (1.25 g, 89%) and **5b** (0.46 g, 86%), which were identical with samples prepared from **4a** and **4b** and titanium(IV) chloride-triethylamine complex on the basis of a mixed melting point determination and a comparison of the ir spectra.

General Procedure for the Preparation of **7a** and **7b** from **6a** or **6b** and Potassium Hydroxide.

A mixture of **6a** (1.59 g, 5 mmols) or **6b** (1.52 g, 5 mmols) and potassium hydroxide (0.34 g, 6 mmoles) in *tert*-butyl alcohol (20 mL) was refluxed for 3 hours. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to provide **7a** (0.78 g, 56%) or **7b** (0.43 g, 32%). A second elution gave **5a** (50 mg, 3%) or **5b** (0.12 g, 9%). Compound **7a** was identical with an authentic sample [12] on the basis of a mixed melting point determination and a comparison of the ir spectrum.

Methyl 3-Amino-4-ethenyl-5-morpholino-2-thiophenecarboxylate (**7b**).

This compound was obtained as colorless plates, mp 126-128° (acetone-petroleum ether); ir (potassium bromide): ν 3410, 3320 (NH₂), 1670 (C=O) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.98-3.00 (m,

4H, 2xNCH₂ (morpholine)), 3.68 (s, 3H, CO₂Me), 3.70-3.72 (m, 4H, 2xOCH₂ (morpholine)), 5.39 (dd, J = 1.8, 11.9 Hz, 1H, olefinic H), 5.61 (dd, J = 1.8, 18.0 Hz, 1H, olefinic H), 6.44 (br s, 2H, NH₂), 6.53 ppm (dd, J = 11.9, 18.0 Hz, 1H, olefinic H); ¹³C nmr (DMSO-d₆): δ 50.6 (CO₂CH₃), 51.5 (2xNCH₂ (morpholine)), 65.5 (2xOCH₂ (morpholine)), 113.6 (C₄), 115.6 (CH₂=CH-), 127.4 (CH₂=CH-), 153.7 (C₂ and C₃), 160.0 (C₅), 164.0 ppm (CO₂CH₃); ms: m/z 268 (M⁺).

Anal. Calcd. for C₁₂H₁₆N₂O₃S: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.72; H, 6.05; N, 10.24.

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