A Novel Practical Synthesis of Pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepines

Abdelali Daich, Jean Morel and Bernard Decroix*

Laboratoire de Chimie, UER des Sciences et des Techniques
de l'Université du Havre, 30 rue Gabriel Péri,
76600 Le Havre, France

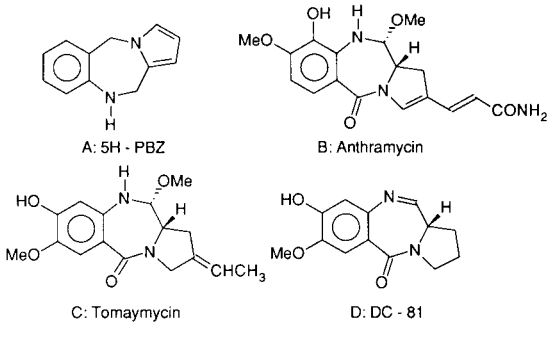
Received January 20, 1993

In an investigation of new heterocyclic systems, a novel way to obtain pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine **8** was effected by ring closure to the appropriate nitroaldehyde compound which was synthesized in five steps from 3-bromomethyl-2-nitrothiophene **1**.

J. Heterocyclic Chem., **30**, 675 (1993).

As it is known, several compounds with interesting biological properties possess in their molecules the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine skeleton **A**. Examples of these compounds like anthramycin **B** [1], tomaymycin **C** [2] or DC-81 **D** [3] are antitumor antibiotics (Scheme I). Within a search for synthetic tumor inhibitors, we have developed new convenient approaches to 6,7,5- [4] and 5,7,5-membered [5] tricyclic heteroaromatic ring systems. We have previously described pyrrolofurodiazepine [6] and pyrrolothienodiazepine derivatives [7-9] as analogs of the rings mentioned above.

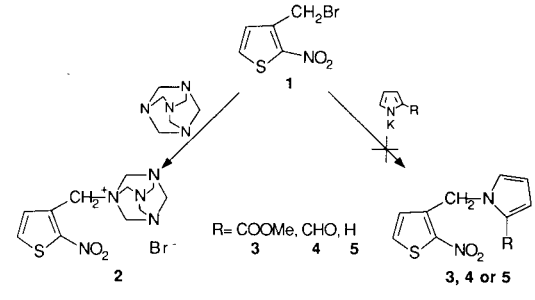
Scheme I



In fact, the pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine **10** had been prepared in two ways, both starting from methyl 3-bromomethylthiophene-2-carboxylate in a seven or six-step synthesis, with respectively an overall yield of 6.5% [7] and 11% [9]. The difficulty encountered, associated with poor yields of some intermediates in these initial synthesis, prompted us to investigate more efficient synthesis.

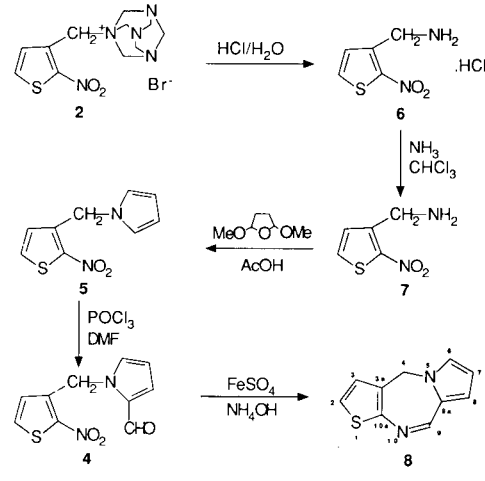
We wish to report herein an improved synthesis of compound **10**. The starting material 3-bromomethyl-2-nitrothiophene (**1**) was prepared according to a modification of the original sequence described by Snyder [10]. Thus, bromination of 3-methyl-2-nitrothiophene with a large excess of *N*-bromosuccinimide in boiling 1,2-dibromoethane for five hours yielded the bromide derivative **1** in 85% yield (lit [10] 60%). As shown in Scheme II, it was possible to convert the bromide **1** directly into the condensation products **3** (R = CO_2Me), **4** (R = CHO) and **5** (R = H) by a nucleophilic substitution with the potassium salt of 2-substituted pyrroles. In contrast to the results obtained under the same conditions with 2-nitrobenzyl bromide [11,12] or 2-nitrobenzyl chloride [13] we have not observed the substitution product.

Scheme II



Another approach was investigated. Treatment of **1** with hexamethylene tetramine in carbon tetrachloride [14] gave the quaternary ammonium salt **2** in good yield (98%). Aqueous acid hydrolysis of the preceding compound **2** gave the hydrochloride salt **6** in 82% yield from which the free base **7** could be readily liberated in the usual way by gaseous ammonia just prior to use (Scheme III). A modification of the procedure giving a pyrrole from a primary amino group [15] was developed in which the 2,5-dimeth-

Scheme III

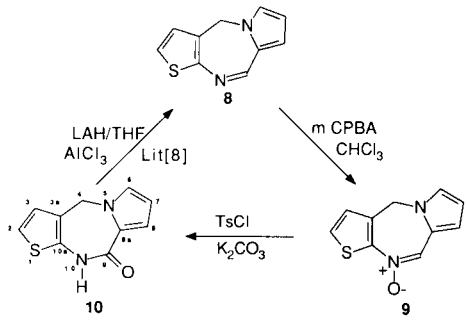


oxytetrahydrofuran and the acetic acid reagents were combined and preheated to 80° and a solution of the (2-nitrothien-3-yl)methylamine (**7**), in a small volume of acetic acid was added rapidly to the reaction mixture. The crude product was purified in a Soxhlet apparatus to give the 2-nitro-3-(1-pyrrolylmethyl)thiophene (**5**) in 71% yield.

Functionalization of the pyrrole ring was accomplished using the Vilsmeier-Haack reaction. Under these conditions the formylation occurs on the 2-position of the pyrrole ring to give the carboxaldehyde **4** in 71% yield according to the literature [7], no amount of the 3-carboxaldehyde was isolated while the reactivity of the 3-position has been shown elsewhere [16]. Reduction with ammoniacal ferrous sulfate [4] of **4** gave directly the title tricyclic ring by the intramolecular condensation of the supposed intermediate 1-(2-aminothien-3-ylmethyl)pyrrole-2-carboxaldehyde in 52% yield. The pyrrolo[1,2-*a*]thieno[2,3-*e*]-[1,4]diazepine (**8**) was obtained in an overall yield of 18% from the known 3-bromomethyl-2-nitrothiophene (**1**).

As shown in Scheme IV, another route to obtain the known cyclic lactam **10** [9] was explored. The diazepine **8** was oxidized with *m*-chloroperbenzoic acid in chloroform [17] to give the *N*-oxide derivative **9** in 85% yield. Treatment [18] of the pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine *N*-oxide (**9**) with tosyl chloride and aqueous potassium carbonate at room temperature in chloroform furnished the known 4*H*-pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepin-9(10*H*)-one (**10**) in 81% yield.

Scheme IV



All the compounds synthesized herein are characterized by elemental analysis, ir and ^1H and ^{13}C nmr spectra.

EXPERIMENTAL

Melting points were determined on a Leitz heat plate apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann IR-20 spectrometer. The nuclear magnetic resonance spectra were taken on a Bruker AC-200 (200 MHz) spectrometer in the solvents indicated. Chemical shifts are reported in ppm from tetramethylsilane as an internal reference and are given in δ units. Elemental analyses were performed by Laboratoire de Microanalyse de L'I.N.S.A de Rouen, place Emile Blondel, 76130 Mont-Saint-Aignan, France. The 3-methyl-2-nitrothiophene was prepared according to the literature [10].

3-Bromomethyl-2-nitrothiophene (**1**).

In a typical run, 33 g (230 mmoles) of 3-methyl-2-nitrothiophene dissolved in 70 ml of ethylene dibromide and 0.5 g of benzoyl peroxide were gently refluxed with stirring for 15 minutes. A mixture of 60 g (339 mmoles) of *N*-bromosuccinimide and 0.3 g of benzoyl peroxide was added in small portions over 30 minutes and the red-brown solution was allowed to reflux for an additional 5 hours. After cooling, 50 ml of carbon tetrachloride was added and the resulting succinimide on cooling was filtered off and washed with two 25 ml portions of carbon tetrachloride. The filtrate was washed with three 100 ml portions of water, dried and concentrated under reduced pressure. The crude oil was dissolved in 200 ml of hexane and the unreacted starting material, 3-methyl-2-nitrothiophene (8.5 g) was filtered off. After evaporation of the solvent, the oily substance was purified by distillation ($bp_{1.5}$ 117-130°) to give 32 g (85%) of the desired compound which solidified on standing, mp 59-61° (lit [10] mp 63-65°); ir (neat): ν 1535 and 1355 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.83 (s, 2H, CH_2), 6.91 (d, 1H, J = 5.2 Hz, H_4-thiophene), 7.42 (d, 1H, J = 5.2 Hz, H_5-thiophene).

Quaternary Ammonium Salt from Hexamethylenetetramine and 3-Bromomethyl-2-nitrothiophene **2**.

The bromomethylthiophene **1** (10 g, 45 mmoles) dissolved in 100 ml of dry carbon tetrachloride was slowly added to a boiling solution of 7.5 g (50 mmoles) of hexamethylenetetramine in 60 ml of dry carbon tetrachloride. After 3 hours of refluxing, the reaction mixture was filtered and kept at 5° overnight. The yellow salt was collected and washed twice with 50 ml of dry carbon tetrachloride. In this manner 11.5 g (98%) of quaternary ammonium bromide **2** was obtained. An analytical sample was obtained by recrystallization from ethanol, mp 185-188° dec; ^1H nmr (DMSO-d_6): δ 4.63 (m, 12H, 6 CH_2), 5.38 (s, 2H, CH_2–N), 7.55 (d, 1H, J = 5.2 Hz, H_4-thiophene), 8.25 (d, 1H, J = 5.2 Hz, H_5-thiophene).

Anal. Calcd. for $C_{11}H_{16}BrN_5O_2S$: C, 36.27; H, 4.43; N, 19.22. Found: C, 36.08; H, 4.22; N, 19.12.

(2-Nitrothien-3-yl)methylamine Hydrochloride (**6**).

A suspension of 3.62 g (10 mmoles) of the tetramine salt **2** in 100 ml of dry ethanol was treated slowly with 7.5 ml of concentrated hydrochloric acid with stirring. The resulting mixture was further heated at 50-55° for 4 hours. After filtration, the precipitate which formed on cooling at 5° in an ice-water bath was filtered, washed twice with 15 ml of cooled ethanol and air dried. The crude thienylmethylamine hydrochloride **6** was recrystallized from ethanol-diethyl ether 4:1 (v/v) as white crystals (1.8 g, 82%), mp 295-297° dec; ^1H nmr (DMSO-d_6): δ 4.45 (broad s, 3H, CH_2–N and HCl), 7.15 (d, 1H, J = 5.2 Hz, H_4-thiophene), 8.15 (d, 1H, J = 5.2 Hz, H_5-thiophene), 8.8 (broad s, 2H, NH_2, deuterium oxide-exchangeable).

Anal. Calcd. for $C_5H_7ClN_2O_2S$: C, 30.85; H, 3.62; N, 14.39. Found: C, 30.68; H, 3.51; N, 14.18.

(2-Nitrothien-3-yl)methylamine (**7**).

A stirred solution of 2 g (10.3 mmoles) of (2-nitrothien-3-yl)-methylamine hydrochloride (**6**) in 10 ml of water and 15 ml of chloroform was treated with an excess of gaseous ammonia over a period of 4 hours. After cooling, the mixture was filtered and the insoluble material washed with 10 ml of chloroform. The organic

phase was separated, washed with saturated sodium carbonate solution and dried over anhydrous sodium sulfate. Removal of the solvent gave 1.15 g (71% yield) of **7** as an unstable oil and was used for the next reaction without further purification; ir (neat): ν 3450-2980 (broad NH_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.9 (broad s, 2H, NH_2, deuterium oxide-exchangeable), 4.35 (s, 2H, CH_2-N), 7.25 (d, 1H, J = 5.35 Hz, H_4-thiophene), 7.60 (d, 1H, J = 5.35 Hz, H_5-thiophene).

2-Nitro-3-(1-pyrrolylmethyl)thiophene (**5**).

A stirred solution of 2,5-dimethoxytetrahydrofuran (7.55 g, 57 mmoles) in 50 ml of glacial acetic acid was heated to 80°. To this solution (2-nitrothien-3-yl)methylamine **7** (7.9 g, 50 mmoles) was added rapidly over a period of 5 minutes. The reaction mixture changed from colorless to black. After 30 minutes of reflux, the solvent was then evaporated under reduced pressure and the residue was dissolved in 100 ml of chloroform. The organic solution was washed with 10% sodium carbonate, then with brine and finally dried over anhydrous magnesium sulfate. The crude tar obtained after evaporation of solvent was purified in a Soxhlet extractor using hexane-dichloromethane (9:1, v/v) as the solvent. The solvent was evaporated to afford 7.38 g (71%) of compound **5** as a yellowish solid, mp 86-87° (diethyl ether-hexane); ir (potassium bromide): ν 1540 and 1355 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.5 (s, 2H, CH_2-N), 6.21 (d, 1H, J = 5.54 Hz, H_4-thiophene), 6.25 (t, 2H, H_3 and H_4 pyrrole), 6.74 (t, 2H, H_2 and H_5 pyrrole), 7.36 (d, 1H, J = 5.54 Hz, H_5-thiophene).

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.71; H, 3.78; N, 13.14.

1-(2-Nitrothien-3-ylmethyl)pyrrole-2-carboxaldehyde (**4**).

To 8 g (110 mmoles) of *N,N*-dimethylformamide cooled at 5-10°, phosphorus oxychloride (16.9 g, 110 mmoles) was added dropwise with stirring at a rate to maintain the temperature below 20°. After the addition was complete the mixture was stirred at room temperature for 15 minutes. 1,2-Dichloroethane (25 ml) was added and the solution was cooled again to 5°. A solution of 2-nitro-3-(1-pyrrolylmethyl)thiophene (**5**) (21 g, 101 mmoles) in 30 ml of 1,2-dichloroethane was added dropwise over a period of 20 minutes at the same temperature. After an additional 30 minutes at room temperature, the reaction mixture was refluxed for 4 hours under a low stream of nitrogen. The mixture was then cooled to room temperature and a solution of 75 g (550 mmoles) of sodium acetate trihydrate in 120 ml of water was added. The biphasic mixture was stirred vigorously at room temperature for 15 minutes, then refluxed for 1/2 hour. After cooling, the mixture was extracted with diethyl ether. The combined extracts were washed twice with saturated sodium bicarbonate, once with saturated sodium chloride, and dried over magnesium sulfate. Removal of the solvent afforded 20.7 g (87%) of a brown oil which solidified on cooling. Recrystallization from diethyl ether-hexane gave the aldehyde **4** as light yellow prisms, mp 102-104°; ir (potassium bromide): ν 1695 (C=O), 1545 and 1350 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.9 (s, 2H, CH_2-N), 6.25 (d, 1H, J = 5.51 Hz, H_4-thiophene), 6.36 (q, 1H, H_4-pyrrole), 7-7.13 (m, 2H, H_3 and H_5-pyrrole), 7.38 (d, 1H, J = 5.51 Hz, H_5-thiophene), 9.56 (s, 1H, CHO).

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.41; N, 11.86. Found: C, 50.71; H, 3.15; N, 11.54.

Pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine (**8**).

A solution of the nitroaldehyde **4** (2.1 g, 8.9 mmoles) in 160 ml of hot ethanol is added to a suspension of ferrous(II) sulfate heptahydrate (24.9 g, 89 mmoles) in 80 ml of water and 10 ml of concentrated aqueous ammonia. The mixture was heated at 100° for 2.5 hours with stirring while 25 ml of concentrated aqueous ammonia was added dropwise. The black solid was filtered off and washed with ethanol and discarded. The filtrate was extracted with chloroform and the organic layers were dried and concentrated to give a brown solid which was recrystallized from diethyl ether-hexane to give 0.87 g (52%) of the pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine (**8**), mp 121-123° (lit [7] mp 119-120° (ligroin)); ^{13}C nmr (deuteriochloroform): δ 154.7 C_9, 139.5 C_2, 130.5 C_3, 129.8 C_6, 128.6 C_{3a}, 127.5 C_{10a}, 121.5 C_{8a}, 119.6 C_8, 108.6 C_7, 47.8 C_4.

Pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepine *N*-Oxide (**9**).

To a stirred solution of 1.2 g (6.38 mmoles) of pyrrolo[1,2-*a*]-thieno[2,3-*c*][1,4]diazepine (**8**) in 25 ml of dry chloroform, 1.4 g (8 mmoles) of *m*-chloroperbenzoïc acid was added in small portions over a period of 1.5 hours. Stirring at room temperature was continued for two days. The solution was extracted twice with 10 ml of 10% aqueous sodium hydroxide. The organic layer was dried and concentrated. Recrystallization of the crude solid from ethanol-diethyl ether gave 1.1 g (85%) of the *N*-oxide **9** as a brown solid, mp 179-181°; ^1H nmr (deuteriochloroform): δ 5.05 (s, 2H, CH_2-N), 6.23 (dd, 1H, H_4-pyrrole), 6.58 (dd, 1H, H_3-pyrrole), 6.7 (d, 1H, J = 5.57 Hz, H_4-thiophene), 6.75 (t, 1H, H_5-pyrrole), 7.06 (d, 1H, J = 5.57 Hz, H_5-thiophene), 7.91 (s, 1H, N=CH).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.71. Found: C, 58.79; H, 3.91; N, 13.59.

4*H*-Pyrrolo[1,2-*a*]thieno[2,3-*e*][1,4]diazepin-9(10*H*)-one (**10**).

A heterogeneous reaction mixture consisting of 1.3 g (6.37 mmoles) of diazepine *N*-oxide **9**, 1.6 g (8 mmoles) of tosyl chloride in 40 ml of dry chloroform and 40 ml of 10% potassium carbonate solution was shaken at room temperature for 30 minutes until the starting *N*-oxide disappeared. The resulting precipitate was filtered off and washed twice with 10 ml of diethyl ether. The crude product was recrystallized from methanol-ligroin to give 1.05 g (81%) of the cyclic lactam as brown needles, mp 229° (lit [9] mp 231-232° (diethyl ether-ethyl acetate)); ^{13}C nmr (DMSO-d_6): δ 160 C_9, 138 C_2, 129.5 C_3, 128 C_{3a}, 126 C_{10a}, 124 C_6, 117.5 C_{8a}, 116 C_8, 108 C_7, 46 C_4.

REFERENCES AND NOTES

[1] W. Leimgruber, A. D. Batcho and F. Schenker, *J. Am. Chem. Soc.*, **87**, 5793 (1965).

[2] K. Kariyone, H. Yazawa and M. Kohsaka, *Chem. Pharm. Bull.*, **19**, 2289 (1971).

[3] D. E. Thurston, V. S. Murty, D. R. Langley and G. B. Jones, *Synthesis*, 81 (1990).

[4] G. Marchand, B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **21**, 877 (1984).

[5] G. Marchand, B. Decroix and J. Morel, *Chem. Scr.*, **23**, 80 (1984).

[6] F. Povazanec, B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **29**, 1507 (1992).

[7] B. Decroix and J. Morel, *J. Heterocyclic Chem.*, **28**, 81 (1991).

[8] A. Daïch, F. Povazanec and B. Decroix, *J. Heterocyclic Chem.*, **28**, 1911 (1991).

[9] A. Daïch and B. Decroix, *Bull. Soc. Chim. France*, **129**, 360 (1992).

[10] H. R. Snyder, L. A. Carpino, J. F. Zack, Jr. and J. F. Mills, *J. Am. Chem. Soc.*, **79**, 2556 (1957).

[11] L. Cecchi and G. Filacchioni, *J. Heterocyclic Chem.*, **20**, 871 (1983).

[12] F. Melani, L. Cecchi and G. Filacchioni, *J. Heterocyclic Chem.*, **21**, 813 (1984).

[13] J. S. Duceppe and J. Gauthier, *J. Heterocyclic Chem.*, **22**, 305 (1985).

[14] E. Compaigne and E. S. Neiss, *J. Heterocyclic Chem.*, **3**, 46 (1966).

[15] N. Clausen-kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1972).

[16] R. C. Effland, L. Davis, K. J. Kapples and G. E. Olsen, *J. Heterocyclic Chem.*, **27**, 1015 (1990).

[17] S. Gronowitz and G. Timari, *J. Heterocyclic Chem.*, **27**, 1127 (1990).

[18] S. Gronowitz and G. Timari, *J. Heterocyclic Chem.*, **27**, 1159 (1990).