Reactivity of Thienopyrroles. Synthesis of Isomeric Nitro and Bromothienopyrroles

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The preparation of ethyl 2-bromothieno[2,3-*b*]pyrrole-5-carboxylate, ethyl 2-bromothieno[3,2-*b*]pyrrole-5-carboxylate, ethyl 2-nitrothieno[2,3-*b*]pyrrole-5-carboxylate and ethyl 2-nitrothieno[3,2-*b*]pyrrole-5-carboxylate are described.

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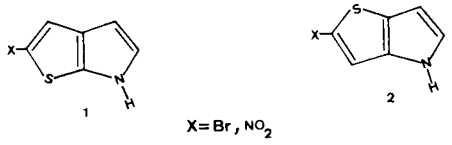
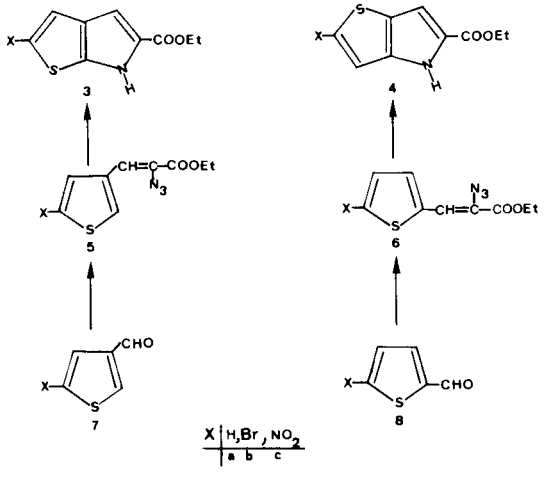
In connection with a more extensive program we are interested in the study of thienopyrrole systems [1] in order to determine their reactivity and to prepare intermediate compounds which can be modified to angular [2] and *o*-linear [3] polycyclic systems of biological interest.

Considerations concerning the effect of electron-withdrawing groups upon the orientation of electrophilic substitution in the thienopyrrole systems prompted us to attempt the preparation of the isomeric bromo and nitro compounds **1** and **2**.



Due to the instability of 6*H*-thieno[2,3-*b*]pyrrole and 4*H*-thieno[3,2-*b*]pyrrole, the few studies regarding the reactivity of such systems have been realized basically on their 5-carbethoxy derivatives.

In our work we have prepared **3** and **4** from ethyl azidothiopheneacrylates **5** and **6** according to Hemetsberger and Knittel [4] (see Scheme 1 below). Related to the preparation of the precursors isomeric thiophenecarbaldehyde derivatives, the bromination of **8a** with bromine in chloroform [5] allowed us to isolate a 54% yield of 5-bromo-2-thiophenecarbaldehyde (**8b**). In contrast, when the same conditions of bromination were applied to **7a**, 2,5-dibromo-3-thiophenecarbaldehyde [5] was obtained. The same reaction using anhydrous aluminum chloride gave compound **7b** in 48% yield [6]. Following the guidelines of Fournari [7] and Gronowitz [8] respectively, the thiophenecarbaldehydes **7c** and **8c** were obtained upon nitration. For the preparation of the azidoacrylate isomers **5** and **6**, we proceded *via* the reaction of **7b**, **7c**, **8b**, and **8c** with ethyl azidoacetate at low temperature (5-10°). The molar ratio of aldehdye to azide was 1:4.



The variable yields observed can be explained by the different stability of the azidothiopheneacrylates formed which were influenced by the presence of the thiophene ring and by the ease of formation of such azido derivatives. Thus we have observed the following: i) While the bromo compounds **5b** and **6b** can be obtained in similar yields (18% and 25% respectively), the last compound darkens in contact with air and must be immediately utilized for subsequent thermolysis. ii) The absence of substituents on the thiophene ring greatly increases the yields of condesations products **5a** and **6a** (50%, 55% respectively). iii) The presence of the nitro group on the thiophene ring does not permit the preparation of compound **6c** which was detected by ^{1}H-nmr. We have found that our results are in good agreement with the yields obtained by Fournari [10,11] in the preparation of azidothiopheneacrylates with an electron-withdrawing group such as the formyl group. This fact and the results obtained for **6c** led to discard the preparation of **5c**.

Thermolysis in refluxing xylene of the azidothiopheneacrylates **5a**, **5b**, **6a**, and **6b** allowed us to isolate the thienopyrroles **3a**, **3b**, **4a** and **4b**.

Compound **3b** also could be obtained by bromination of **3a** using aluminum chloride as the catalyst. With respect to compounds **3c** and **4c**, their preparation was accomplished by nitration of **3a** and **4a**, previously obtained. Concerning the nitration of thienopyrroles, none of the derivatives have been described in the literature.

Similarly to the nitration of thiophenes we tried the nitration using cupric nitrate in acetic anhydride according to Bacharach [12]. See the experimental for data of the five nitrated compounds obtained. Nitration with sulphonitric mixture gave uncharacterizable products.

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 Orgánica, Barcelona.

Azidothiophene Acrylates **5** and **6**. General Procedure.

A solution of 3.68 g (0.16 mole) of sodium in absolute ethanol (150 ml) was cooled in an ice-bath and a mixture of 0.04 mole of the corresponding thiophenecarbaldehyde **7** and **8** and 0.16 mole of ethyl azidoacetate was added dropwise during 30 minutes keeping the temperature between 5-10°. The reaction mixture was stirred for 30 minutes after which time a cold solution of ammoniun chloride was added. The resulting solution was extracted with ether. The ether extracts were washed, dried and evaporated to give a crude product. Chromatography of the crude product on a silica-gel column gave the corresponding azidothiopheneacrylate.

Ethyl 2-Azido-3-(3-thienyl)acrylate (**5a**) [4].

On elution with benzene-hexane (2:1), 1.5 g (50%) of white solid was obtained, mp 33°, lit 32° [4]; ir (potassium bromide): 2130 cm^{-1} ($-N_3$), 1720 cm^{-1} (-COO-); nmr (deuteriochloroform): δ 1.28 (t, CH_3, 3H), 4.22 (c, CH_2, 2H), 6.76 (s, ethenyl-H, 1H), 7.29 (m, H-5 of thiophene ring, 1H), 7.47 (dd, H-4 of thiophene ring, 1H, $J_{4,5}$ = 5.1 Hz, $J_{2,4}$ = 1.2 Hz), 7.86 (m, H-2 of thiophene ring, 1H).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.43; H, 4.06; N, 18.83; S, 14.34. Found: C, 48.22; H, 4.02; N, 18.85; S, 14.34.

Ethyl 2-Azido-3-(2-thienyl)acrylate (**6a**).

On elution with benzene-hexane (2:1), 4.73 g (55%) of white solid was obtained, mp 40-41°, lit 42° [4]; ir (potassium bromide): 2130 cm^{-1} ($-N_3$), 1715 cm^{-1} (-COO-); nmr (deuteriochloroform): δ 1.35 (t, CH_3, 3H), 4.25 (c, CH_2, 2H), 6.90 (s, ethenyl-H, 1H), 7.00 (dd, H-4 of thiophene ring, 1H, $J_{3,4}$ = 3.7 Hz, $J_{4,5}$ = 5.1 Hz), 7.27 (m, H-3 of thiophene ring, 1H), 7.44 (m, H-5 of thiophene ring, 1H, $J_{3,5}$ = 1.2 Hz).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.43; H, 4.06; N, 18.83; S, 14.34. Found: C, 48.30; H, 4.05; N, 18.79; S, 14.31.

Ethyl 2-Azido-3-(5-bromo-3-thienyl)acrylate (**5b**).

On elution with benzene-hexane (2:1), 1.97 g (18%) of an oil was obtained; ir (liquid film): 2110 cm^{-1} ($-N_3$), 1725 cm^{-1} (-COO-); nmr (deuteriochloroform): δ 1.30 (t, CH_3, 3H), 4.25 (c, CH_2, 2H), 6.60 (s, ethenyl-H, 1H), 7.28 (d, H-4 of thiophene ring, 1H), 7.40 (d, H-2 of thiophene ring, 1H, $J_{2,4}$ = 1.1 Hz).

Anal. Calcd. for $C_9H_8BrN_3O_2S$: C, 35.78; H, 2.67; Br, 26.45; N, 13.91; S, 10.61. Found: C, 35.81; H, 2.70; Br, 26.51; N, 13.90; S, 10.61.

Ethyl 2-Azido-3-(5-bromo-2-thienyl)acrylate (**6b**).

On elution with benzene-hexane (2:1), 2.74 g (25%) of an oil was obtained; ir (liquid film): 2130 cm^{-1} ($-N_3$), 1715 cm^{-1} (-COO-); nmr (carbon tetrachloride): δ 1.36 (t, CH_3, 3H), 4.24 (c, CH_2, 2H), 6.95 (d, ethenyl-H, 1H, H-3 of thiophene ring, 1H, $J_{3,4}$ = 4.0 Hz), 7.33 (d, H-4 of thiophene ring, 1H).

Anal. Calcd. for $C_9H_8BrN_3O_2S$: C, 35.78; H, 2.67; Br, 26.45; N, 13.91; S, 10.61. Found: C, 35.80; H, 2.70; Br, 26.50; N, 13.93; S, 10.64.

Ethyl Thienopyrrole-5-carboxylates **3** and **4**. General Procedure.

A solution of 0.018 mole of the corresponding azidothiopheneacrylate (**5** or **6**) in xylene was heated at reflux for 10 minutes. After evaporation of the solvent the solid obtained was recrystallized from methylene chloride.

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

From methylene chloride, 2.74 g (87%) of white solid was obtained, mp 120°, lit 117.5° [4]; ir (potassium bromide): 3300 cm^{-1} (NH), 1700 cm^{-1} (-COO-); nmr (deuteriochloroform): δ 1.38 (t, CH_3, 3H), 4.34 (c, CH_2, 2H), 6.88 (d, H-3, 1H, $J_{2,3}$ = 5.2 Hz), 6.92 (d, H-2, 1H), 7.08 (d, H-4, 1H, $J_{4,6}$ = 2 Hz), 10.47 (s, NH, 1H).

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.38; H,4.65; N, 7.18; S, 16.39. Found: C, 55.55; H, 4.60; N, 7.11; S, 16.40.

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

From methylene chloride, 3.19 g (91%) of white solid was obtained, mp 131-132°, lit 133° [4]; ir (potassium bromide): 3300 cm^{-1} (NH), 1675 cm^{-1} (-COO-); nmr (deuteriochloroform): δ 1.35 (t, CH_3, 3H), 4.31 (c, CH_2, 2H), 6.86 (dd, H-3, 1H, $J_{2,3}$ = 5.0 Hz, $J_{3,6}$ = 1.0 Hz), 7.10 (d, H-6, 1H, $J_{4,6}$ = 1.8), 7.25 (d, H-2, 1H), 9.70 (s, NH, 1H).

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.38; H, 4.65; N, 7.18; S, 16.39. found C, 55.30; H, 4.58; N, 7.15; S, 16.37.

Ethyl 2-Bromothieno[2,3-*b*]pyrrole-5-carboxylate (**3b**).

From methylene chloride, 1 g (73%) of white solid was obtained, mp 108-109°; ir (potassium bromide): 3280 cm^{-1} (NH), 1690 cm^{-1} (-COO-); nmr (deuteriochloroform): δ 1.45 (t, CH_3, 3H), 4.36 (c, CH_2, 2H), 7.00 (s, H-3, H-4, 2H), 10.00 (s, NH, 1H).

Anal. Calcd. for $C_9H_8BrNO_2S$: C, 39.43; H, 2.84; Br, 29.15; N, 5.11; S, 11.70. Found: C, 39.45; H, 2.80; Br, 29.20; N, 5.09; S, 11.68.

Ethyl 2-Bromothieno[3,2-*b*]pyrrole-5-carboxylate (**4b**).

From methylene chloride, 1.3 g (95%) of white solid was obtained, mp 169-170°; ir (potassium bromide): 3280 cm^{-1} (NH), 1690 cm^{-1} (COO-); nmr (deuteriochloroform): δ 1.35 (t, CH_3, 3H), 4.25 (c, CH_2, 2H), 6.90 (s, H-3, H-6, 2H), 9.50 (s, NH, 1H).

Anal. Calcd. for $C_9H_8BrNO_2S$; C, 39.43; H, 2.84; Br, 29.15; N, 5.11; S, 11.70. Found: C, 39.40; H, 2.78; Br, 29.20; N, 5.13; S, 11.72.

Bromination of Ethyl Thieno[3,2-*b*]pyrrole-5-carboxylate (**4a**).

To a solution of **4a** (0.195 g, 0.001 mole) in carbon disulphide (8 ml) 0.267 g (0.002 mole) of anhydrous aluminum chloride was added dropwise. The resulting solution was allowed to stir at room temperature for 1 hour. After this time cold water was slowly added. The organic layer was separated, washed with sodium carbonate solution, with water, dried over magnesium sulfate and the solvent removed. The residue was recrystallized from hexane-methylene chloride to give 0.230 g (84%) of a white solid characterized as compound **4b**.

Nitration of Ethyl Thienopyrrole-5-carboxylates **3a** and **4a**. General Procedure.

Cupric nitrate trihydrate (0.004 mole) was pulverized in a morter and introduced into 8 ml of acetic anhydride at 10-12°. Drop by drop, a solution of 0.005 mole of the thienopyrrole (**3** or **4**) in a minimum of acetic anhydride was added. The temperature was kept at 10-12° during 90 minutes and then 2 hours at room temperature. After this time the cupric salt was filtered and the solution was introduced into ice-cold water. The organic layer was washed with water until an insoluble solid was formed. The aqueous extracts were combined and extracted with ether. The insoluble solid was dissolved in ether and the ether solutions were combined and washed with sodium carbonate solution, with water and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue was purified by column chromatography (silica-gel, benzene).

Ethyl 2-Nitrothieno[2,3-*b*]pyrrole-5-carboxylate (**3c**).

On elution with benzene, 0.011 g (4%) of yellow solid was obtained, mp 163°; ir (potassium bromide): 3260 cm^{-1} (NH), 1735 cm^{-1} (COO), 1460 cm^{-1}, 1320 cm^{-1} (NO_2); nmr (deuterated dimethylsulfoxide): δ 1.35 (t,

CH_3, 3H), 4.30 (c, CH_2, 2H), 7.15 (d, H-4, 1H, $J_{4,6}$ = 1.5 Hz), 8.15 (s, H-3, 1H).

Anal. Calcd. for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36; N, 11.66; S, 13.35. Found: C, 45.07; H, 3.39; N, 11.65; S, 13.37.

Ethyl 2,4-Dinitrothieno[2,3-*b*]pyrrole-5-carboxylate (**3d**).

On elution with benzene 0.025 g (8%) of yellow solid was obtained, mp 138°; ir (potassium bromide): 3260 cm^{-1} (NH), 1720 cm^{-1} (COO), 1520 1335 cm^{-1} (NO_2); nmr (deuterated dimethylsulfoxide): δ 1.35 (t, CH_3, 3H), 4.30 (c, CH_2, 2H), 8.15 (s, H-3, 1H).

Anal. Calcd. for $C_9H_7N_3O_6S$: C, 37.90; H, 2.47; N, 14.37; S, 11.24. Found: C, 37.95; H, 2.42; N, 14.36; S, 11.21.

Ethyl 2-Nitrothieno[3,2-*b*]pyrrole-5-carboxylate (**4c**).

On elution with benzene, 0.414 g (34%) of yellow solid was obtained, mp 188-189°; ir (potassium bromide): 3270 cm^{-1} (NH), 1690 cm^{-1} (COO), 1470 cm^{-1}, 1300 cm^{-1} (NO_2); nmr (deuteriochloroform): δ 1.40 (t, CH_3, 3H), 4.35 (c, CH_2, 2H), 7.05 (dd, H-6, 1H, $J_{4,6}$ = 1.8 Hz, $J_{3,6}$ = 1 Hz), 7.85 (d, H-3, 1H), 9.80 (s, NH, 1H).

Anal. Calcd. for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36; N, 11.66; S, 13.15. Found: C, 45.05; H, 3.40; N, 11.65; S, 13.37.

Ethyl 2,6-Dinitrothieno[3,2-*b*]pyrrole-5-carboxylate (**4d**).

On elution with benzene, 0.607 g (42%) of yellow solid was obtained, mp 189°; ir (potassium bromide): 3260 cm^{-1} (NH), 1740 cm^{-1} (COO), 1490 cm^{-1}, 1325 cm^{-1} (NO_2); nmr (deuterated dimethylsulfoxide): δ 1.40 (t, CH_3, 3H), 4.35 (c, CH_2, 2H), 7.90 (s, H-3, 1H).

Anal. Calcd. for $C_9H_7N_3O_6S$: C, 37.90; H, 2.47; N, 14.37; S, 11.24. Found: C, 37.97; H, 2.40; N, 14.40; S, 11.25.

Ethyl 6-Nitrothieno[3,2-*b*]pyrrole-5-carboxylate (**4e**).

On elution with benzene, 0.04 g (3%) of yellow solid was obtained, mp 192°; ir (potassium bromide): 3250 cm^{-1} (NH), 1735 cm^{-1} (COO), 1472 cm^{-1}, 1320 cm^{-1} (NO_2); nmr (deuterated dimethylsulfoxide): δ 1.38 (t, CH_3, 3H), 4.40 (c, CH_2, 2H), 7.15 (d, H-3, 1H, $J_{2,3}$ = 5.8 Hz), 7.65 (d, H-2, 1H).

Anal. Calcd. for $C_9H_8N_2O_4S$: C, 45.00; H, 3,36; N, 11.66; S, 13.35. Found: C, 45.09; H, 3.35; N, 11.67; S, 13.35.

REFERENCES AND NOTES

[1] W. W. Gale, A. N. Scott and H. R. Snyder, *J. Org. Chem.*, **29**, 2160 (1964); S. Soth, M. Farnier and P. Fournari, *Bull. Soc. Chim. France*, 2511 (1975).

[2] E. Schitter and A. Furlenmeyer, *Helv. Chim. Acta.*, **35**, 2017 (1953).

[3] C. Paoletti, *Proc. Nat. Acad. Sci.*, **71**, 5078 (1974), Malcolm Sainsbury, *Chem. Brit.*, **15** (3), 127 (1979).

[4] H. Hemestberger and D. Knittel, *Monasth. Chem.*, **103**, 194 (1972).

[5] P. Fournari, R. Guilard and M. Person, *Bull. Soc. Chim. France*, 4115 (1967).

[6] J. L. Gol'dfard, Yu. B. Volkenstein, A. I. Belunkii, *Angew. Chem., Int. Ed. Engl.*, **7**, 519 (1968).

[7] P. Fournari and J. P. Chane, *Bull. Soc. Chim. France*, 479 (1962).

[8] S. Gronowitz, D. Moses, A. B. Hörnfeldt and P. Häkanson, *Ark. Kemi*, **17**, 165 (1960).

[9] O. Dann, *Chem. Ber.*, **76**, 419 (1943).

[10] M. Farnier, S. Soth and P. Fournari, *Can. J. Chem.*, **54**, 1074 (1976).

[11] P. Fournari, M. Farnier and S. Soth, *ibid.*, 1066 (1976).

[12] G. Bacharach, *J. Am. Chem. Soc.*, **49**, 1522 (1917).