Synthesis of Tetracyclic Systems: A Convenient Route to [1]Benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine and [1]Benzofuro[2,3-*e*]pyrrolo[1,2-*a*]pyrazine Derivatives

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In continuation of our work[1] on the synthesis of fused polycyclic systems (including investigation of their biological properties such as antineoplastic activity), we reported a novel synthesis of pyrrolothienopyrazines[2] in which the cyclization occurs via a Curtius rearrangement. We now report the application of this general cyclization principle to the synthesis of 4-oxo-4,5-dihydro[1]benzofuro[2,3-*e*]- **(9)** and 4-oxo-4,5-dihydro[1]benzofuro[3,2-*e*]pyrrolo[1,2-*a*]pyrazine **(10)**.

The starting materials, methyl 2-amino-1-benzothiophene-2-carboxylate **(1)** and ethyl 3-amino-1-benzofuran-2-carboxylate **(2)**, are prepared following the methods of Ref.[3] and Ref.[4], respectively. The aminoesters **1** and **2** are converted into the corresponding 1-pyrrolyl derivatives **3** and **4**, respectively, by reaction with 2,5-dimethoxytetrahydrofuran[5] in glacial acetic acid. Compounds **3** and **4** are hydrolyzed with potassium hydroxide in aqueous ethanol to yield the esters **5** and **6** which are converted into the azides **7** and **8**, respectively, using the procedure of Ref.[6]. Heating of the solid azides **7** and **8** at 250 °C or, better, refluxing their solution in *o*-dichlorobenzene leads to Curtius rearrangement with subsequent ring closure to afford the tetracyclic systems **9** or **10**. On the other hand, gentle heating of the azides **7** or **8** in dichloromethane effects their partial conversion into the isocyanate intermediates **11** or **12** (as shown by the N=C=O absorption at $\nu = 2040$ cm^{-1} in the I.R. spectra of the mixtures **7**+**11** and **8**+**12**). When the mixtures **7**+**11** or **8**+**12** are heated in *o*-dichlorobenzene, compounds **9** or **10**, respectively, are formed as the only products. This result confirms the pyrazine partial structure of **9** and **10** and excludes an isomeric pyrimidine partial structure. Further, we have clearly established the structure of homologous pyrrolothienopyrazines by N.M.R. measurements and unequivocal synthesis[7].

Methyl 3-(1-Pyrrolyl)-1-benzothiophene-2-carboxylate (3) or Ethyl 3-(1-Pyrrolyl)-1-benzofuran-2-carboxylate (4); General Procedure:

A mixture of methyl 3-amino-1-benzothiophene-2-carboxylate (**1**; 4.15 g, 0.02 mol) or ethyl 3-amino-1-benzofuran-2-carboxylate (**2**; 4.11 g, 0.02 mol), 2,5-dimethoxytetrahydrofuran (2.52 g, 0.02 mol), and glacial acetic acid (60 ml) is heated at reflux temperature for 1 h. The solvent is distilled under reduced pressure and the residual crude product is triturated with water.

Compound **3**: The solid residue is collected by suction, washed with water, and dried; yield: 4.4 g (85%); m.p. 114–115 °C (from methanol).

$C_{14}H_{11}NO_2S$	calc.	C 65.36	H 4.31	N 5.45	S 12.44
(257.3)	found	65.45	4.34	5.52	12.32

I.R. (KBr): $\nu = 1720$ (C=O); 1565, 1530, 1480, 1425, 1375, 1280, 1210, 765 cm^{-1}.

^{1}H-N.M.R. (90 MHz, DMSO-d_6/TMS): $\delta = 8.0$ (m, 1H, 7-H); 7.7–7.3 (m, 3H, 4-H, 5-H, 6-H); 7.0 (m, 2H, 2′-H, 5′-H); 6.3 (m, 2H, 3′-H, 4′-H); 3.73 ppm (s, 3H, CH_3).

Compound **4**: The oily residue is extracted with ether (3 × 50 ml). The extract is successively washed with saturated sodium carbonate solution (50 ml) and saturated sodium chloride solution (50 ml), dried with sodium sulfate, and evaporated to dryness in vacuo. The residual viscous product is distilled in vacuo; yield: 4.2 g (82%); b.p. 140 °C/5 torr.

$C_{15}H_{13}NO_3$	calc.	C 70.58	H 5.13	N 5.49
(255.3)	found	70.43	5.12	5.35

I.R. (KBr): $\nu = 1700$ (C=O); 1600, 1490, 1305, 1235, 1095, 900, 740 cm^{-1}.

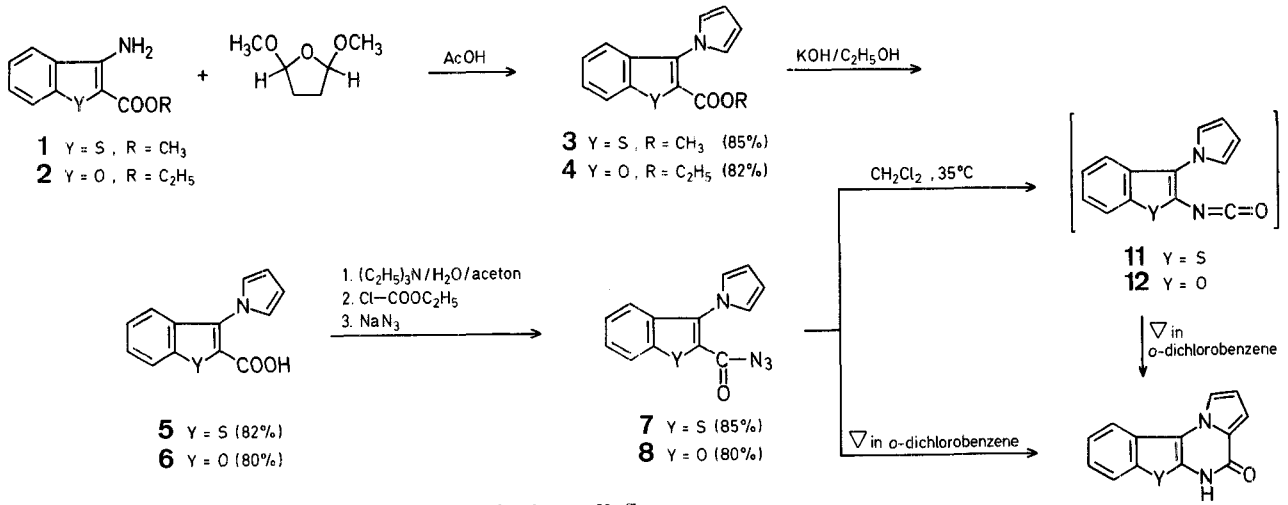
^{1}H-N.M.R. (DMSO-d_6/TMS): $\delta = 7.75$–7.2 (m, 4H, 4-H, 5-H, 6-H, 7-H); 7.15 (m, 2H, 2′-H, 5′-H); 6.3 (m, 2H, 3′-H, 4′-H); 4.28 (q, 2H, CH_2); 1.28 ppm (t, 3H, CH_3).

3-(1-Pyrrolyl)-1-benzothiophene-2-carboxylic Acid (5) or 3-(1-Pyrrolyl)-1-benzofuran-2-carboxylic Acid (6); General Procedure:

To a solution of compound **3** or **4** (4 g) in ethanol (40 ml) is added a solution of potassium hydroxide solution (4 g) in water (40 ml). The resultant mixture is heated at reflux temperature for 1.5 h. The hydrolysate is evaporated to 1/2 of its volume, cooled, and acidified with dilute hydrochloric acid. The precipitate is isolated by suction, washed with water, and taken up in saturated sodium hydrogen carbonate solution (80 ml). This solution is treated with charcoal and filtered. The filtrate is reacidified with dilute hydrochloric acid and the precipitate is isolated by suction, washed thoroughly with water, and dried.

Compound **5**; yield: 3.1 g (82%); m.p. 214 °C (from ethanol).

$C_{13}H_9NO_2S$	calc.	C 64.20	H 3.73	N 5.76	S 13.15
(243.3)	found	64.40	3.54	5.63	13.22



All melting points are uncorrected and were determined on a Kofler block apparatus. The I.R. spectra were recorded on a Perkin Elmer 157 G spectrometer, the ^{1}H-N.M.R. spectra on a Varian EM 390 spectrometer (except for compounds **7** and **8** which cannot be sufficiently purified because of their instability).

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I.R. (KBr): ν = 1680, 1655 (C=O); 1555, 1530, 1480, 1300, 1085, 765, 740 cm^{-1}.

^{1}H-N.M.R. (90 MHz, DMSO-d_6/TMS): δ = 7.9 (m, 1H, 7-H); 7.5–7.3 (m, 3H, 4-H, 5-H, 6-H); 6.9 (m, 2H, 2′-H, 5′-H); 6.2 (m, 2H, 3′-H, 4′-H); 5.0–4.0 ppm (broad, 1H, OH).

Compound **6**; yield: 2.8 g (80%); m.p. 255 °C (from ethanol).

$C_{13}H_9NO_3$	calc.	C 68.72	H 3.99	N 6.17
(227.2)	found	68.54	3.87	6.04

I.R. (KBr): ν = 1680 (C=O); 1590, 1575, 1495, 1445, 1370, 1310, 1180, 1100, 925, 735 cm^{-1}.

^{1}H-N.M.R. (90 MHz, DMSO-d_6/TMS): δ = 7.55–6.95 (m, 4H, 4-H, 5-H, 6-H, 7-H); 6.9 (m, 2H, 2′-H, 5′-H); 6.0 (m, 2H, 3′-H, 4′-H); 10–8.0 ppm (broad, 1H, OH).

2-Azidocarbonyl-3-(1-pyrrolyl)-1-benzothiophene (7) or 2-Azidocarbonyl-3-(1-pyrrolyl)-1-benzofuran (8); General Procedure:

To a stirred, cold (0 °C) solution of compound **5** or **6** (0.01 mol) in water (5 ml) and acetone (50 ml) is added a solution of triethylamine (1.2 g, 0.12 mol) in acetone (20 ml) followed after 30 min by a solution of ethyl carbonochloridate (1.3 g, 0.012 mol) in acetone (20 ml). Stirring is continued for 1 h, a solution of sodium azide (0.9 g, 0.014 mol) in water (10 ml) is added and the stirring again continued for 1.5 h, the temperature not being allowed to exceed 5 °C. The mixture is then poured onto cold water (300 ml), the precipitate is isolated by suction, washed with water, and dried at the pump.

Compound **7**; yield: 2.3 g (85%); m.p. 105 °C (dec).

I.R. (KBr): ν = 2150 (N_3); 1675 (C=O); 1555, 1530, 1475, 1280, 1235, 1205, 740 cm^{-1}.

Compound **8**; yield: 2.1 g (80%); m.p. 85 °C (dec).

I.R. (KBr): ν = 2140 (N_3); 1670 (C=O); 1540, 1520, 1490, 1415, 1350, 1220, 1070, 900, 735, 715 cm^{-1}.

4-Oxo-4,5-dihydro[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (9) or 4-Oxo-4,5-dihydro[1]benzofuro[2,3-*e*]pyrrolo[1,2-*a*]pyrazine (10); General Procedure:

A solution of compound **7** or **8** (2 g) in *o*-dichlorobenzene (30 ml) is heated at reflux temperature (185 °C) for 30 min and then allowed to cool. The precipitated product is isolated by suction, washed with water, and dried.

Compound **9**; yield: 1.8 g (90%); m.p. 300 °C (from acetonitrile).

$C_{13}H_8N_2OS$	calc.	C 65.00	H 3.36	N 11.66
(240.3)	found	64.81	3.34	11.85

I.R. (KBr): ν = 1660 (C=O); 1600, 1435, 1395, 1355, 1310, 760, 735 cm^{-1}.

^{1}H-N.M.R. (90 MHz, DMSO-d_6/TMS): δ = 8.3 (m, 2H, 1-H, 10-H); 7.96 (d, 1H, 7-H); 7.6–7.3 (m, 2H, 9-H, 8-H); 7.08 (dd, 1H, 3-H); 6.70 (dd, 1H, 2-H); 3.0–4.0 ppm (broad, 1H, NH).

Compound **10**; yield: 1.9 g (95%); m.p. 298 °C (from sublimation at 260 °C/5 torr).

$C_{13}H_8N_2O_2$	calc.	C 69.64	H 3.60	N 12.50
(224.2)	found	69.44	3.47	12.45

I.R. (KBr): ν = 1650 (C=O); 1445, 1400, 1330, 1315, 1185, 1135, 750, 740, 725 cm^{-1}.

^{1}H-N.M.R. (90 MHz, DMSO-d_6/TMS); δ = 8.0 (m, 2H, 1-H, 10-H); 7.60 (ddd, 1H, 7-H); 7.45–7.1 (m, 2H, 8-H, 9-H); 7.06 (dd, 1H, 3-H); 6.66 (dd, 1H, 2-H); 3.0–4.0 ppm (broad, 1H, NH).

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