Synthesis of spirocyclic 4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-*e*]indolizine derivatives

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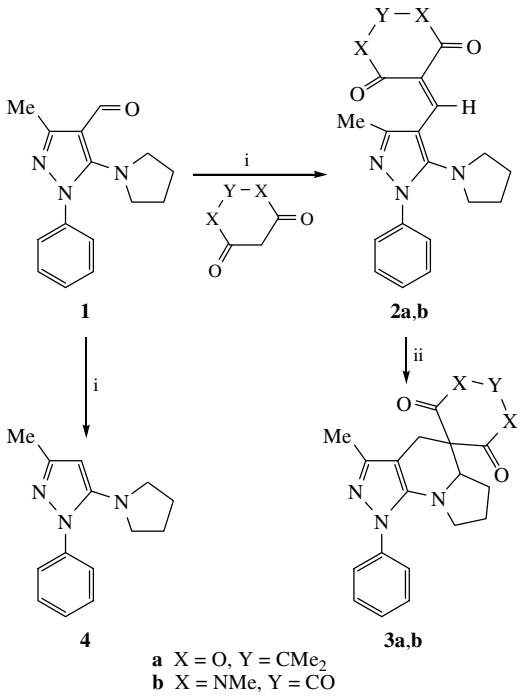
The condensation of 3-methyl-1-phenyl-5-pyrrolidinopyrazole-4-carboxaldehyde with *N*,*N*-dimethylbarbituric acid or Meldrum's acid followed by cyclization of the Knövenagel product by in a '*tert*-amino effect' reaction resulted in the heterocyclic spiro-derivatives of pyrazolo[3,4-*e*]indolizine.

Due primarily to their biological activities,[1–3] fused pyrazoles are of current interest. These ring systems are usually synthesised by multi-step pathways. The *tert*-amino effect[4] provides a powerful approach to ring systems containing a spiro moiety.[5,6] Here, we report an application of the *tert*-amino effect to the preparation of spirocyclic ring systems containing the 4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-*e*]indolizine nucleus.

Spirocyclic derivatives **3a**,**b** were obtained in two steps starting from pyrazolecarboxaldehyde **1**.† The reaction of aldehyde **1** with Meldrum's acid or 1,3-dimethylbarbituric acid in the presence of piperidine as a catalyst afforded Knövenagel products **2a**,**b**, which underwent rearrangement upon heating to afford spiro derivatives of indolizine **3a**,**b**‡ (Scheme 1). In contrast to the reaction of *ortho*-(*N*,*N*-dialkylamino)benzaldehydes with cyclic active methylene compounds,[7,8] vinyl derivatives **2a**,**b** were isolated in good yields.§ Note that aldehyde **1** is a thermally labile compound and is easily deformylated: on heating in solvents such as DMF, toluene, or ethanol pyrazole **4**¶ was formed. The structures of compounds were confirmed by N microanalysis, mass spectrometry, IR and ^{1}H NMR spectroscopy.

Thus, the *tert*-amino effect may offer a powerful approach to the synthesis of complex ring systems including spirocyclic derivatives, and we present the first examples of the application of pyrazolecarboxaldehyde to the synthesis of spiro derivatives of fused pyrazoles.



Scheme 1 *Reagents and conditions*: i, DMF, 25 °C, 24 h; ii, BuOH, 100 °C, 3 h.

† Pyrrolidine (0.83 ml, 0.70 mg, 9.88 mmol) and potassium carbonate (1.38 g, 9.88 mmol) were added to a solution of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (2.49 g, 9.49 mmol) in DMF (8.0 ml). The reaction mixture was refluxed at 150 °C for 20 h. The completion of the reaction was judged from TLC. Then the reaction mixture was cooled to ~20 °C, water (75 ml) was added, and the product was filtered off and dried.

*3-Methyl-1-phenyl-5-pyrrolidino-1*H*-pyrazole-4-carboxaldehyde* **1**. Yield 75%, mp 224 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 9.86 (s, 1H, CHO), 7.35–7.47 (m, 5H, H$_{Ar}$), 3.23–3.20 (m, 4H, CH$_2$), 2.29 (s, 3H, Me), 1.70–1.75 (m, 4H, 2CH$_2$). MS, *m*/*z*: 255 (M$^+$). Found (%): C, 70.66; H, 6.88; N, 17.15. Calc for $C_{15}H_{17}N_3O$ (%): C, 70.56; H, 6.71; N, 16.46.

‡ A solution of vinyl derivative **2a** or **2b** (0.72 mmol) in BuOH (10 ml) was heated at 100 °C for 3 h and then filtered through charcoal. The solvent was evaporated and the residue was recrystallised from ethyl acetate; compound **3** was filtered off and dried.

*2',2',3-Trimethyl-1-phenyl-4,5,5a,6,7,8-hexahydro-1*H*-spiro(pyrazolo-[3,4-e]indolizine-5,5'-[1,3]dioxane)-4',6'-dione* **3a**. Yield 86%, mp 188 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.50–7.47 (m, 2H, H$_{Ar}$), 7.44–7.40 (m, 2H, HAr), 7.28–7.24 (m, 1H, H$_{Ar}$), 4.03–4.00 (m, 1H, CH), 3.21–3.14 (m, 1H, CH), 3.04–3.01 (m, 1H, CH), 2.78–2.74 (dd, 1H, CH, *J'* 8.01 Hz, *J''* 2.56 Hz), 2.50–2.49 (m, 1H, CH), 2.12 (s, 3H, Me), 1.84–1.75 (m, 10H, 2Me, 2CH$_2$). ^{13}C NMR ([^{2}H$_6$]DMSO) δ: 170.15 (dd, CO, *J* 3.8 and 0.8 Hz), 166.00 (ddd, CO, *J* 7.6, 7.4 and 3.8 Hz), 145.56 [qdd, C(3), *J* 7.2, 2.3 and 2.9 Hz], 143.50 [br. s, C(9a)], 139.71 (tm, C$_i$, *J* 8.6 Hz), 128.89 (dd, C$_o$, *J* 162.3 and 7.2 Hz), 126.22 (dt, C$_p$, *J* 163.9 and 7.2 Hz), 123.12 (ddd, C$_m$, *J* 163.3, 7.2 and 7.2 Hz), 105.22 (qq, O–C–O, *J* 4.6 and 4.6 Hz), 96.30 [m, C(3a)], 67.91 [dm, C(5a), *J* 158.4 Hz], 49.72 [ddm, C(8), *J* 140.7 and 144.4 Hz], 46.38 [ddd, C(5), *J* 2.0, 5.3 and 4.4 Hz], 29.54 (qq, Me, *J* 128.4 and 2.8 Hz), 27.81 [dd, C(4), *J* 131.2 and 131.8 Hz], 27.27 (qq, Me, *J* 126.9 and 3.1 Hz), 27.03 [ddm, C(7), *J* 134.5 and 133.6 Hz], 22.95 [ddm, C(6), *J* 134.7 and 128.4 Hz], 12.09 (q, Me, *J* 127.0 Hz). MS, *m*/*z*: 381 (M$^+$, 100%). Found (%): C, 65.98; H, 6.17; N, 10.96. Calc. for $C_{21}H_{23}N_3O_4$ (%): C, 66.13; H, 6.08; N, 11.02.

*1',3',3-Trimethyl-1-phenyl-4,5,5a,6,7,8-hexahydro-1*H*-spiro(pyrazolo-[3,4-e]indolizine-5,5'-pyrimidine)-2',4',6'-trione* **3b**. Yield 78%, mp 224 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 7.49 (d, 2H, H$_{Ar}$, *J* 7.35 Hz), 7.43–7.39 (dd, 2H, H$_{Ar}$, *J'* 7.51 Hz, *J''* 8.26 Hz), 7.24 (m, 1H, H$_{Ar}$), 3.97–3.94 (dd, 1H, CH, *J'* 4.82 Hz, *J''* 3.20 Hz), 3.24 (s, 3H, NMe), 3.20–3.10 (dd, 1H, CH, *J'* 8.62 Hz, *J''* 6.22 Hz), 3.09 (s, 3H, NMe), 3.02–2.93 (dd, 2H, CH$_2$, *J'* 15.79 Hz, *J''* 4.6 Hz), 2.75–2.74 (m, 1H, CH), 2.20–2.11 (m, 1H, CH$_2$), 2.08 (s, 3H, Me), 1.82–1.58 (m, 3H, CH$_2$, CH). ^{13}C NMR ([^{2}H$_6$]DMSO) δ: 171.28 (br. s, CO), 168.66 (br. s, CO), 151.00 (hept, CO, *J* 2.6 Hz), 145.25 [qm, C(3), *J* 7.3 Hz], 143.66 [br. s, C(9a)], 139.85 (tm, C$_i$, *J* 7.2 Hz), 128.85 (dd, C$_o$, *J* 162.7 and 7.5 Hz), 125.97 (dt, C$_p$, 163.8 and 7.3 Hz), 122.85 (ddd, C$_o$, *J* 162.1, 7.0 and 7.8 Hz), 97.66 [m, C(3a)], 66.87 [dm, C(5a), *J* 157.0 Hz], 49.82 [ddm, C(8), *J* 142.2 and 140.2 Hz], 48.12 [br. s, C(5)], 29.03 [dd, C(4), *J* 132.5 and 135.7 Hz], 28.09 (q, NMe, *J* 142.3 Hz), 26.75 [dm, C(7), *J* 127.6 and 125.7 Hz], 26.65 (q, NMe, *J* 141.7 Hz), 23.27 [ddm, C(6), *J* 141.5 and 133.0 Hz], 12.08 (q, Me, *J* 126.9 Hz). MS, *m*/*z*: 393 (M$^+$, 100%). Found (%): C, 64.12; H, 6.02; N, 18.15. Calc. for $C_{21}H_{23}N_5O_3$ (%): C, 64.11; H, 5.89; N, 17.80.

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§ To a solution of aldehyde **1** (1.15 g, 4.53 mmol) in DMF (3 ml) methylene compounds (4.75 mmol) were added at room temperature. The reaction mixture was stirred for 24 h. After the addition of 20 ml of water, the precipitate was filtered off and the product was crystallised from ethanol.

*2,2-Dimethyl-5-(3-methyl-1-phenyl-5-pyrrolidino-1*H*-pyrazol-4-ylmethylene)[1,3]dioxane-4,6-dione* **2a**. Yield 70%, mp 204 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.39 (s, 1H, CH), 7.51–7.39 (m, 5H, H_{Ar}), 3.14–3.11 (dd, 4H, $2CH_2$, *J′* 7.3 Hz, *J″* 8.2 Hz), 2.29 (s, 3H, Me), 2.11 (t, 4H, $2CH_2$, *J* 6.4 Hz), 1.86 (s, 3H, Me), 1.74 (s, 3H, Me). ^{13}C NMR ([$^2H_6$]DMSO) δ: 163.35 (d, CO, *J* 6.3 Hz), 159.99 (d, CO, *J* 10.3 Hz), 151.91 [q, C(3), *J* 5.1 Hz], 150.50 [q, C(5), *J* 6.7 Hz], 147.90 (d, CH=, *J* 153.6 Hz), 139.70 (tm, C_i, *J* 9.2 Hz), 129.03 (dd, C_o, *J* 163.1 and 11.4 Hz), 128.20 (dt, C_p, *J* 163.1 and 6.1 Hz), 125.98 (ddd, C_m, *J* 163.3, 6.1 and 11.4 Hz), 107.17 (d, C=, *J* 2.8 Hz), 103.97 (hept, O–C–O, *J* 4.6 Hz), 103.37 [d, C(4), *J* 2.7 Hz], 51.85 (tm, $2NCH_2$, *J* 139.4 Hz), 26.84 (qq, 2Me, *J* 128.4 and 3.2 Hz), 25.09 (tm, $2CH_2$, *J* 131.7 Hz), 14.24 (q, Me, *J* 127.8 Hz). MS, *m*/*z*: 381 (M^+, 100%). Found (%): C, 66.25; H, 6.07; N, 11.25. Calc. for $C_{21}H_{23}N_3O_4$ (%): C, 66.13; H, 6.08; N, 11.02.

*1,3-Dimethyl-5-(3-methyl-1-phenyl-5-pyrrolidino-1*H*-pyrazol-4-ylmethylene)pyrimidine-2,4,6-trione* **2b**. Yield 68%, mp 254 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 8.29 (s, 1H, CH), 7.51–7.37 (m, 5H, H_{Ar}), 3.27 (s, 3H, NMe), 3.20 (s, 3H, NMe), 3.09–2.93 (m, 4H, $2CH_2$), 2.22 (s, 3H, Me), 1.82–1.78 (m, 4H, $2CH_2$). ^{13}C NMR ([$^2H_6$]DMSO) δ: 162.60 (CO), 159.42 (CO), 152.34 (CO), 151.47 [C(3)], 150.66 [C(5)], 146.28 (CH=), 139.99 (C_i), 129.04 (C_o), 127.97 (C_p), 125.71 (C_o), 108.61 [C(4)], 107.02 (C=), 52.02 (NCH_2), 28.10 (NMe), 27.74 (NMe), 25.15 (CH_2), 13.26 (Me). MS, *m*/*z*: 393 (M^+, 100%). Found (%): C, 64.25; H, 5.78; N, 18.02. Calc. for $C_{21}H_{23}N_5O_3$ (%): C, 64.11; H, 5.89; N, 17.80.

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¶ *3-Methyl-1-phenyl-5-pyrrolidino-1*H*-pyrazole* **4**: oil. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.53–7.51 (m, 2H, H_{Ar}), 7.46–4.42 (m, 2H, H_{Ar}), 7.30–7.27 (m, 1H, H_{Ar}), 5.58 (s, 1H, H_{pyr}), 2.98–2.87 (m, 4H, $2CH_2$), 2.11 (s, 1H, Me), 1.75–1.85 (m, 4H, $2CH_2$). MS, *m*/*z*: 227 (M^+, 100%). Found (%): C, 74.21; H, 7.88; N, 18.20. Calc. for $C_{14}H_{17}N_3$ (%): C, 73.98; H, 7.54; N, 18.49.