Synthesis of derivatives of 3-acetyl-2-aminopyrrole and pyrrolo[2,3-*d*]pyrimidine from monoacetylketene aminals

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A new scheme for the synthesis of pyrrolo[2,3-*d*]pyrimidines from monoacetylketene aminals was proposed. Reactions of monoacetylketene *N*-benzoyl- and *N*-acetylaminals with α-bromoacetophenone afforded the corresponding 3-acetyl-2-acylamino-5-phenyl-1*H*-pyrroles, which underwent cyclization to 2,4,6-trisubstituted 7*H*-pyrrolo[2,3-*d*]pyrimidines under the action of ammonium acetate in boiling BuOH.

Key words: monoacetylketene aminals, α-bromoacetophenone, 3-acetyl-2-*RNH*-5-phenyl-1*H*-pyrroles, pyrrolo[2,3-*d*]pyrimidines.

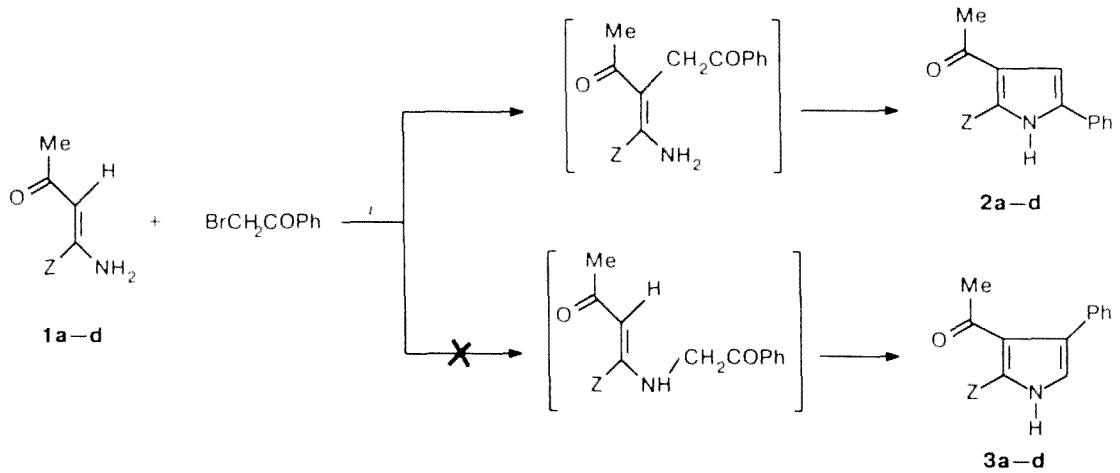
Earlier we developed an efficient strategy for the construction of fused nitrogen-containing heterocyclic systems involving the synthesis of α-oxoketene *N,N*- and *N,S*-acetals with unsubstuted NH_2 groups and their transformation to azoles and azines with vicinal NH_2 (NHBz) and COR substituents followed by annelation of the second ring (pyridine or pyrimidine). As a result, new convenient methods for the synthesis of functionally substituted pyrido[2,3-*d*]pyrimidines,[1–3] pyrimido[4,5-*d*]pyrimidines,[2] pyrazolo[3,4-*d*]pyrimidines,[4] and 1,2,3-triazolo[4,5-*d*]pyrimidines[5] have been proposed.

A similar approach was used in this work for the synthesis of pyrrolo[2,3-*d*]pyrimidines (7-deazapurines) from monoacetylketene aminals through the corresponding substituted pyrroles. This bicyclic system is of interest since the pyrrolo[2,3-*d*]pyrimidine moiety is a fragment of the structure of some antibiotics (for review, see Ref. 6).

It is known[7] that reactions of cyano- and ethoxycarbonylketene aminals with α-bromoketones afford the corresponding functionally-substituted pyrroles. Starting from monoacetylketene aminals (**1a—c**) and α-bromoacetophenone (BAP) (boiling in EtOH in the presence of $NaHCO_3$) we obtained the derivatives of 3-acetyl-2-aminopyrrole (**2a—c**) in 33—48 % yields (Scheme 1). Similarly, 3-acetyl-2-methylthio-5-phenylpyrrole (**2d**) (in 27 % yield) was synthesized from monoacetylketene *N,S*-acetal (**1d**).

The attack by BAP evidently proceeds at the C-nucleophilic center of acetals **1a—d** since the reaction at

Scheme 1



Z = PhCONH (**a**), MeCONH (**b**), $O(CH_2CH_2)_2N$ (**c**), MeS (**d**)

i. $NaHCO_3$, EtOH, Δ

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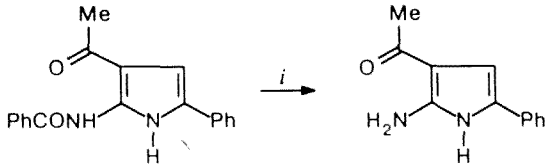
the N-center would afford pyrroles (**3a—d**) with phenyl group in position 4. The IR, ^{1}H NMR, and mass spectral data do not contradict either structure **2** or **3**, however, ^{13}C NMR spectroscopy unambiguously supports the first one. The spectra of the products involve a doublet at δ 103—108 (J = 172 Hz), which is attributed to the C-4 atom of the pyrrole cycle, and a singlet at δ 126—127 (C-5). These data correspond to those for unsubstituted pyrrole (107.6 (C-3 and C-4) and 117.3 (C-2 and C-5)), for 3-acetylpyrrole[8] (106.9 (C-4), 118.9 (C-5), 120.9 (C-3), and 126.0 (C-2)), and for 2-methyl-5-phenyl-1-vinylpyrrole[9] (109.2 (C-4) and 129.70 (C-5)).

Compounds **2a—d** are readily soluble in chloroform, acetone, and benzene and insoluble in petroleum ether. Unlike **2a**, pyrroles **2b—d** are also readily soluble in ethanol.

The attempts to obtain pyrroles with an unsubstituted NH_2 group from compounds **2a,b** appeared to be not very effective. For example, a twofold amount of MeONa is needed for debenzoylation of compound **2a**; the process proceeds very slowly and is accompanied by resinification. As a result, product **2e** was isolated in only 23 % yield (Scheme 2).

Scheme 2



2a **2e**

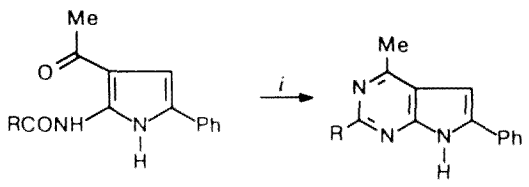
i. 2MeONa, MeOH, Δ.

In this connection, we chose directly compounds **2a,b**, which contain amide groups, as starting blocks for the construction of the pyrrolo[2,3-*d*]pyrimidine system. It was found that the reaction of ammonium acetate with pyrroles **2a,b** in boiling butanol results in the formation of the corresponding pyrrolo[2,3-*d*]pyrimidines **4a,b** in 98 and 56 % yields (Scheme 3). In this case, the possible side processes, debenzoylation or deacetylation of pyrroles **2a,b**, do not proceed (pyrrole **2e** was not found by TLC).

Pyrrolopyrimidines **4a,b** are readily soluble in chloroform, acetone, ethanol, and benzene and insoluble in petroleum ether. Their structures are confirmed by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy.

The synthesis of compound **4b** has been described previously.[10,11] It involves the palladium catalyzed reaction of 4-chloro-5-iodo-2,6-dimethylpyrimidine with styrene (or tributylstannane) followed by treatment of the cross-coupling products with NaN_3 and thermal or photochemical closure of the pyrrole ring.

Scheme 3



2a,b **4a,b**

R = Ph (**a**), Me (**b**)

i. $AcONH_4$, BuOH, Δ.

The melting point determined for compound **4b** differs from that given in Ref. 10 and 11, however, all its spectral characteristics correspond completely to the given structure. In particular, of the pyrrole structures **2b** and **3b** given above, the ^{13}C NMR data of compound **4b** coincide with the first one. The doublet at δ 96.45 in the spectrum of **4b** can only be attributed to the C-5 atom. If the initial pyrrole had structure **3b**, one would obtain pyrrolo[2,3-*d*]pyrimidine with the Ph-group at the C-5 atom and the doublet for the C-6 atom would be observed at a weaker field (*cf.* the ^{13}C NMR data for pyrrolo[2,3-*d*]pyrimidine: 99.4 (C-5) and 127.2 (C-6)).[12]

Thus, monoacetylketene aminals can be used for the construction of the pyrrolo[2,3-*d*]pyrimidine system.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer. IR spectra were recorded on a Perkin-Elmer 577 instrument and mass spectra were recorded on a Varian MAT-311A spectrometer (EI, 70 eV). Monoacetylketene aminals **1a—c** and monoacetylketene *N,S*-acetal **1d** were synthesized by the known procedures.[1,13,14]

3-Acetyl-2-benzoylamino-5-phenyl-1*H*-pyrrole (2a). A mixture of ketene aminal **1a** (0.41 g, 2 mmol), BAP (0.60 g, 3 mmol), and $NaHCO_3$ (0.34 g, 4 mmol) in EtOH (8 mL) was refluxed for 7 h. The boiling solution was filtered, and the filtrate was cooled to ~20 °C and allowed to stand for 12 h. The precipitate that formed was filtered off to afford 0.29 g (48 %) of pyrrole **2a** as yellowish crystals, m.p. 194—195 °C. Found (%): C, 75.22; H, 5.39; N, 8.95. $C_{19}H_{16}N_2O_2$. Calculated (%): C, 74.98; H, 5.30; N, 9.21. IR ($CHCl_3$), ν/cm^{-1}: 3390 (NH), 3280 (NH), 1655 (CO), 1630 (CO), 1605, 1585, 1545. ^{1}H NMR ($CDCl_3$), δ: 2.49 (s, 3 H, Me), 6.70 (d, 1 H, H(4), $J_{H,NH}$ = 3.0 Hz), 7.29 (m, 1 H, Ph), 7.42 (m, 2 H, Ph), 7.50—7.75 (m, 5 H, Ph), 8.03 (m, 2 H, Ph), 11.22 (br.s, 1 H, NH), 11.79 (br.s, 1 H, NHCO). ^{13}C NMR, ($CDCl_3$), δ: 27.25 (Me), 103.75 (dd, C(4), ^1J = 172, ^3J = 6 Hz), 109.47 (C-3), 126.70 (t, C-5, ^3J = 5 Hz), 123.75; 126.92; 127.50; 129.04; 131.34; 132.32; 132.82 (2 Ph), 137.82 (d, C(2), ^3J = 8 Hz), 165.90 (t, CON, ^3J = 5 Hz), 196.05 (q, CO, ^2J = 5 Hz). MS, m/z (I_{rel} (%)): 304 $[M]^{+\cdot}$ (73), 199 $[M-PhCO]^+$ (45), 105 $[PhCO]^+$ (100).

3-Acetyl-2-acetylamino-5-phenyl-1*H*-pyrrole (2b). A mixture of ketene aminal **1b** (0.5 g, 3.5 mmol), BAP (1.05 g, 5.3 mmol), and $NaHCO_3$ (0.59 g, 7.0 mmol) in EtOH (10 mL) was refluxed for 6 h. The solvent was evaporated *in vacuo*,

toluene (5 mL) was added to the residue, and the solution was chromatographed on a SiO_2 column (eluents toluene and toluene—ethanol, 200 : 1). From the suitable fractions, the solvent was evaporated, and the residue was crystallized from hexane to give 0.28 g (33 %) of pyrrole **2b**, m.p. 117—118 °C. Found (%): C, 69.58; H, 6.00; N, 11.82. $C_{14}H_{14}N_2O_2$. Calculated (%): C, 69.40; H, 5.82; N, 11.56. IR ($CHCl_3$), ν/cm^{-1}: 3390 (NH), 3300 (NH), 1675 (CO), 1630 (CO), 1605, 1585, 1545. ^1H NMR ($CDCl_3$), δ: 2.29 (s, 3 H, Me), 2.45 (s, 3 H, Me), 6.61 (d, 1 H, H(4), $J_{H,NH}$ = 3.0 Hz), 7.25 (m, 1 H, Ph), 7.40 (m, 2 H, Ph), 7.50 (m, 2 H, Ph), 10.70 (br.s, 1 H, NHCO), 11.05 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 242 $[M]^{+\cdot}$ (70), 200 $[M-COCH_2]^+$ (100).

3-Acetyl-2-morpholino-5-phenyl-1*H*-pyrrole (2c). A mixture of ketene aminal **1c** (0.85 g, 5 mmol), BAP (1.19 g, 6 mmol), and $NaHCO_3$ (0.63 g, 7.5 mmol) in EtOH (20 mL) was refluxed for 3 h. The solvent was evaporated *in vacuo*, and C_6H_6 (10 mL) was added to the residue. The solution was heated to boiling and filtered to remove the inorganic precipitate. The filtrate was cooled to ~20 °C, hexane (10 mL) was added, and the precipitate that formed was filtered off to afford 0.61 g (45 %) of pyrrole **2c**, m.p. 203—205 °C (from a 1 : 1 benzene—hexane mixture). Found (%): C, 70.92; H, 6.70; N, 10.14. $C_{16}H_{18}N_2O_2$. Calculated (%): C, 71.09; H, 6.71; N, 10.36. IR, (CH_2Cl_2), ν/cm^{-1}: 3455 (NH), 3285 (NO), 1642 (CO), 1605, 1590, 1570, 1530. ^1H NMR ($CDCl_3$), δ: 2.44 (s, 3 H, Me), 3.33 (t, 4 H, 2 CH_2), 3.88 (t, 4 H, 2 CH_2), 6.74 (d, 1 H, H(4), $J_{H,NH}$ = 2.6 Hz), 7.22 (m, 1 H, Ph), 7.36 (m, 2 H, Ph), 7.44 (m, 2 H, Ph), 8.40 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 28.46 (q, Me, ^1J = 127 Hz), 50.09 (t, 2 CH_2, ^1J = 137 Hz), 66.59 (t, 2 CH_2, ^1J = 144 Hz), 107.69 (dd, C(4), ^1J = 171, ^3J = 5 Hz), 111.73 (C-3), 125.94 (C-5), 123.71; 126.32; 128.76; 131.72 (Ph), 147.09 (d, C-2, ^3J = 7 Hz), 192.15 (q, CO, ^2J = 6 Hz).

3-Acetyl-2-methylthio-5-phenyl-1*H*-pyrrole (2d). A mixture of *N,S*-acetal **1d** (0.33 g, 2.5 mmol), BAP (0.75 g, 3.8 mmol), and $NaHCO_3$ (0.42 g, 5 mmol) in EtOH (8 mL) was refluxed for 7 h. The solvent was evaporated *in vacuo*, C_6H_6 (5 mL) was added to the residue, and the solution was chromatographed on a SiO_2 column (eluents benzene and $CHCl_3$). From the suitable fractions, the solvent was evaporated, and C_6H_6 (5 mL) and then hexane (15 mL) were added to the residue. The precipitate formed was filtered off to afford 0.155 g (27 %) of pyrrole **2d**, m.p. 152—153 °C. Found (%): C, 67.45; H, 5.65; N, 6.01; S, 13.48. $C_{13}H_{13}NOS$. Calculated (%): C, 67.50; H, 5.66; N, 6.06; S, 13.86. IR (CH_2Cl_2), ν/cm^{-1}: 3435 (NH), 3280 (NH), 1645 (CO), 1605, 1590, 1570, 1500. ^1H NMR ($CDCl_3$), δ: 2.55 (s, 6 H, SMe and COMe), 6.89 (s, 1H, H-4), 7.28 (m, 1 H, Ph), 7.41 (m, 2 H, Ph), 7.51 (m, 2 H, Ph), 8.96 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 231 $[M]^{+\cdot}$ (100), 216 $[M-Me]^+$ (77), 198 $[M-HS]^+$ (56).

3-Acetyl-2-amino-5-phenyl-1*H*-pyrrole (2e). A mixture of pyrrole **2a** (0.304 g, 1 mmol) and MeONa (2 mmol) in MeOH (10 mL) was refluxed for 4 h. The reaction mixture was acidified with AcOH, and the solvent was evaporated *in vacuo*. The dark precipitate was washed with H_2O (20 mL), dried, and extracted with boiling C_6H_6 (6 mL). The extract was cooled to 20 °C, and the precipitate that formed was filtered off to afford 0.046 g (23 %) of pyrrole **2e**, m.p. 212—215 °C (dec.). Found (%): C, 71.90; H, 6.09; N, 13.87. $C_{12}H_{12}N_2O$. Calculated (%): C, 71.98; H, 6.04; N, 13.99. IR (CH_2Cl_2), ν/cm^{-1}: 3455 (NH), 3340 (NH), 1630 (CO), 1600, 1585, 1565, 1510, 1500. ^1H NMR (DMSO-d_6), δ: 2.19 (s, 3 H, Me), 6.33 (br.s, 2 H, NH_2), 6.65 (s, 1 H, H(4)), 7.09 (m, 1 H, Ph), 7.31 (m, 2 H, Ph), 7.50 (m, 2 H, Ph), 10.80 (br.s, 1 H, NH). MS, *m/z* (I_{rel} (%)): 200 $[M]^{+\cdot}$ (100), 185 $[M-Me]^+$ (62).

4-Methyl-2,6-diphenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (4a). A mixture of pyrrole **2a** (0.304 g, 1 mmol) and $AcONH_4$ (3.08 g, 40 mmol) in Bu^nOH (10 mL) was refluxed for 2 h. Then another portion of $AcONH_4$ (3.08 g) was added, and the mixture was refluxed for 4 h. The solvent was evaporated at ~100 °C *in vacuo*, and the residue was washed with H_2O (2×20 mL) and dried to afford 0.28 g (98 %) of colorless pyrrolopyrimidine **4a**, m.p. 206—209 °C. Found (%): C, 79.57; H, 5.43; N, 14.82. $C_{19}H_{15}N_3$. Calculated (%): C, 79.97; H, 5.30; N, 14.73. IR ($CHCl_3$), ν/cm^{-1}: 3450 (NH), 1590, 1575. ^1H NMR ($CDCl_3$), δ: 2.90 (s, 3 H, Me), 6.82 (s, 1 H, H-5), 7.10—7.70 (m, 8 H, Ph), 8.44 (m, 2 H, Ph), 11.12 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 21.97 (q, Me, ^1J = 128 Hz), 96.46 (dd, C-5, ^1J = 174, ^3J = 5 Hz), 117.83 (C 4a), 125.40; 128.21; 128.26; 128.45; 128.72; 129.63; 130.74; 138.81 (2 Ph), 139.12 (C-6), 153.58 (d, C-7a, ^3J = 7.4 Hz), 158.24 (t, C-2, ^3J = 3.5 Hz), 159.46 (q, C-4, ^2J = 6.4). MS, *m/z*: 285 $[M]^{+\cdot}$.

2,4-Dimethyl-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (4b) was obtained similarly to **2a** starting from pyrrole **2b** (0.24 g, 1 mmol) (boiling time 8 h). The product was separated from unreacted pyrrole **2b** by column chromatography on SiO_2 (eluents C_6H_6, and then 100 : 1 and 50 : 1 C_6H_6—EtOH mixtures). From the suitable fractions, the solvent was evaporated. A 8 : 1 hexane—benzene mixture (18 mL) was added to the residual oil, and the crystals that precipitated were filtered off to afford 0.12 g (56 %) of pyrrolopyrimidine **4b**, m.p. 198—199 °C (*cf.* with the data in Ref. 10 and 11). Found (%): C, 75.54; H, 6.03; N, 19.16. $C_{14}H_{13}N_3$. Calculated (%): C, 75.31; H, 5.87; N, 18.82. IR ($CHCl_3$), ν/cm^{-1}): 3450 (NH), 1595, 1585. ^1H NMR ($CDCl_3$), δ: 2.61 (s, 3 H, Me), 2.77 (s, 3 H, Me), 6.78 (s, 1 H, H-5), 7.30—7.50 (m, 3 H, Ph), 7.70 (m, 2 H, Ph), 11.75 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 21.65 (q, Me, ^1J = 128 Hz), 25.84 (q, Me, ^1J = 127 Hz), 96.45 (d, C-5, ^1J = 175 Hz), 116.92 (C-4a), 125.78; 128.62; 129.12; 131.44 (Ph), 138.30 (C-6), 153.23 (d, C-7a, ^3J = 7 Hz), 159.24 and 160.30 (both q, C-2 and C-4, ^2J = 6 Hz). MS, *m/z*: 223 $[M]^{+\cdot}$.

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