Synthesis of 3-acetyl-2-amino-4-pyridone

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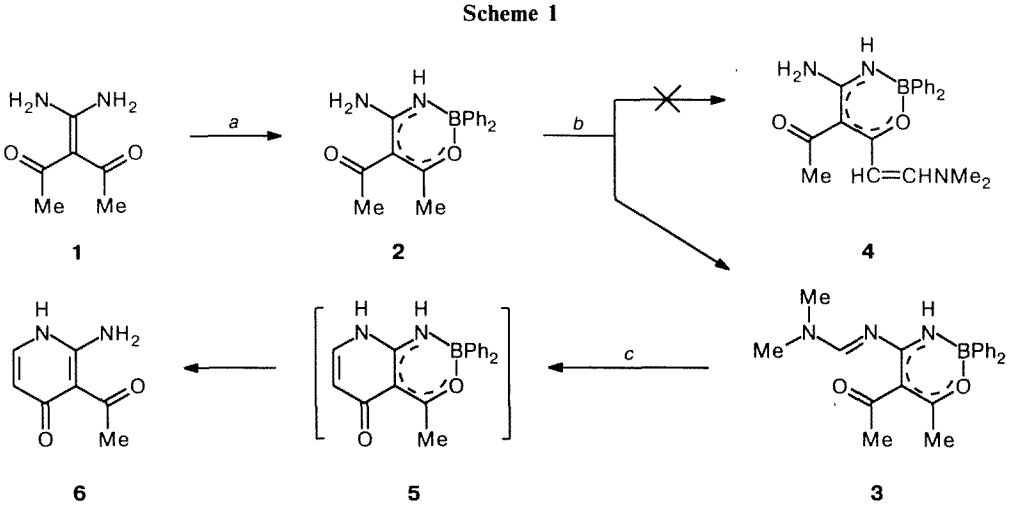
A method for synthesizing 3-acetyl-2-amino-4-pyridone has been suggested. The synthesis involves the condensation of dimethylformamide dimethylacetal at the NH_2 group of diphenylboron chelate diacetylketene aminal followed by its intramolecular cyclization under the action of NaOMe in MeOH.

Key words: diacetylketene aminal, diphenylboron chelates, dimethylformamide dimethylacetal, intramolecular cyclization; 3-acetyl-2-amino-4-pyridone.

Azines containing vicinal NH_2 and Ac groups are convenient blocks for constructing condensed nitrogen-containing heterocycles.[1,2] Previously two methods for preparing 3-acetyl-2-amino-4-pyridone derivatives have been suggested. One of them includes the addition of acetylketene *N*-benzoylaminal to aroylketenes (generated by thermolysis of 6-aryl-2,2-dimethyl-1,3-dioxyn-4-ones) to form 3-acetyl-6-aryl-2-benzoylamino-4-pyridones.[3,4] Another method based on the use of products of condensation of amide acetals at the methyl group of difluoro- or diphenylboron chelates of *N*-monosubstituted diacetylketene aminals results in the formation of 3-acetyl-2-R-amino-4-pyridones or their 6-Me-derivatives.[5]

In this work, the scheme of constructing the 4-pyridone system, using the "chelate assisted methodology," is presented (Scheme 1): earlier unknown 3-acetyl-2-amino-4-pyridone (**6**) was obtained from diacetylketene aminal (**1**). The corresponding diphenylboron chelate **2** was obtained by borylation of keteneaminal **1** with butoxydiphenylboron in boiling benzene. The ^{11}B NMR spectrum of this complex contains the signal corresponding to tetracoordinated boron, and the ^1H NMR spectrum of **2** in $CDCl_3$ contain two signals from methyl groups, which indicates the *N,O*-coordination of the B atom, because Me groups would be equivalent in the case of the alternative β-diketonate structure of chelate. This is also confirmed by the ^{13}C NMR spectra, in which the free CO group has a chemical shift of 198.2 ppm, and that of the COB group is 184.84 ppm (*cf.* spectra of chelates of dioxoketene aminals[6]). It turned out that dimethylformamide dimethylacetal in THF reacts at the NH_2 group of chelate **2**, but not at the methyl group (*cf.* condensation of amide acetals and diphenylboron complexes of the *N*-benzoyl derivative of ketene aminal **1**, in which NH_2 group is protected[5]).

Scheme 1



Reagents and conditions: *a*. Ph_2BOBu, C_6H_6, Δ; *b*. $(MeO)_2CHNMe_2$, THF, Δ; *c*. MeONa, MeOH, Δ, AcOH, ~20 °C.

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Thus, compound **3** with chelate structure is obtained in 94 % yield, while no formation of product **4** is observed. The structure of complex **3** is confirmed by the ^1H NMR spectrum (in $CDCl_3$), which contains the signals of the dimethylformamidine moiety and two acetyl groups. The action of MeONa upon chelate **3** in boiling MeOH results in its transformation into substituted 4-pyridone **6** isolated in 54 % yield. Similar type intramolecular cyclizations involving the dimethylaminoformamidine moiety and acetyl group bound to the pyrimidine ring have been used previously for the synthesis of derivatives of pyrido[2,3-*d*]pyrimidin-5-one.[1,2] It is likely that complex **3** results in intermediate chelate **5** that readily decomposes under the reaction conditions to yield target product **6**. The alternative route of transformation of **3** into **6** involving the decomposition of complex **3** followed by the cyclization of the free ligand likely should be excluded, because the attempts to synthesize compound **6** directly from ketene aminal **1** and dimethylformamide acetal were unsuccessful. (In addition, diacylketene aminals unprotected by chelate formation are readily deacylated in the presence of bases[7]). It is evident that, like the pyrimidine ring, the boron-containing chelate cycle activates the methyl group of the acetyl moiety of compound **3** toward electrophilic attack.

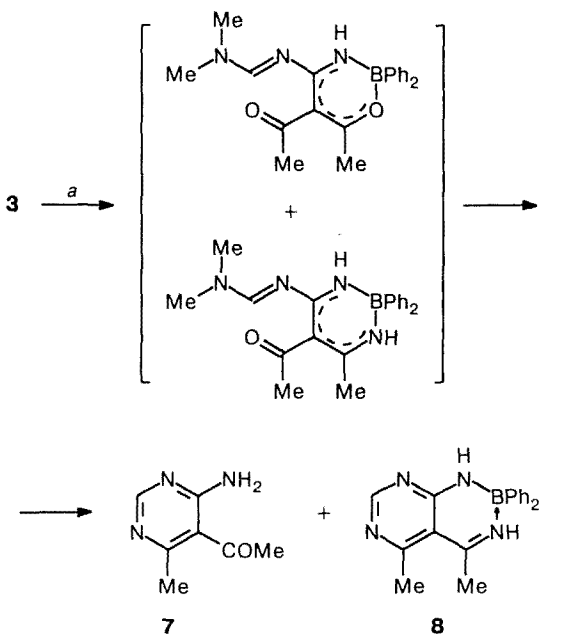
Pyridone **6** is the colorless crystalline substance that is highly soluble in water and alcohols and almost insoluble in the majority of other solvents except DMSO. These properties make it possible to easily purify this compound from organic admixtures. It is evident that compound **6** exists mainly as the pyridone form, not the hydroxypyridine form, which is supported by the data of ^1H and ^{13}C NMR spectroscopy (*cf.* the data[8] for 4-methoxypyridine and 1-methyl-4-pyridone).

We also tried to synthesize functionally substituted pyrimidines based on chelate **3**. It is found that the cyclization occurs, when a mixture of the latter and ammonium acetate is boiled in butanol (Scheme 2). However, the expected reaction product, 5-acetyl-4-amino-6-methylpyrimidine (**7**), is obtained in a low yield (14 %), while diphenylboron chelate of 5-acetimidoyl-4-amino-6-methylpyrimidine (**8**) is formed predominantly.

It can be supposed that the attack of ammonia to the carbonyl group coordinated to boron occurs along with the annelation of the pyrimidine cycle to chelate ring **3** (compare, *e.g.*, with transformations[9] of diphenylboron chelates of 4-amino-5,5,5-trihalopent-3-en-2-ones with primary amines). The resulting chelate **8** is considerably more stable than the complex formed by ligand **7** and does not decompose in boiling butanol. The structures of compounds **7** and **8** were confirmed by the spectral data.

Chelate **8** is a new representative of *N,N*-coordinated cyclic boron complexes and is probably of interest for special study.

Scheme 2



Reagents and conditions: *a*. NH_4OAc, BuOH, Δ.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker AM-300 and Bruker WM-250 spectrometers, respectively. IR spectra were recorded on a Perkin-Elmer 577 instrument. Mass spectra were obtained on a Varian MAT-311A spectrometer (EA, 70 eV). 3-(Diaminomethylene)pentane-2,4-dione (**1**) was synthesized by the known procedure.[10]

***N,O*-[3-(Diaminomethylene)pentane-2,4-dionato]diphenylboron (2).** A mixture of 2.44 g (17 mmol) of keteneaminal **1** and 4.90 g (20.6 mmol) of Ph_2BOBu in 20 mL of benzene was boiled for 30 min and cooled to ~20 °C, the precipitate formed was filtered off and washed with pentane. Colorless compound **2** (3.16 g, yield 60 %) was obtained, m.p. 227—228 °C (from benzene). IR (CH_2Cl_2), ν/cm^{-1}: 3475 (NH); 3395 (NH); 3340—3200 (NH); 1630 (CO); 1570. ^1H NMR ($CDCl_3$), δ: 2.34 (s, 3 H, Me); 2.52 (s, 3 H, Me); 4.90 (br.s, 1 H, NH); 5.35 (br.s, 1 H, NH); 7.18—7.42 (m, 10 H, 2 Ph); 9.25 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 26.12 (Me); 32.26 (Me); 105.71 (C(3)); 125.18, 126.66, 130.96, 151.44 (2 Ph); 159.20 (NCN); 184.84 (COB); 198.20 (CO). ^{11}B NMR, ($CDCl_3$), δ: 2.5.

***N,O*-{3-[(Dimethylaminomethylene)diamino]pentane-2,4-dionato}diphenylboron (3).** A mixture of 0.46 g (1.5 mmol) of chelate **2** and 0.30 mL (2.25 mmol) of dimethylformamide dimethylacetal in 15 mL of THF was boiled for 2 h, the solvent was evaporated to dryness, and 10 mL of hexane were added to the oil obtained. Hexane was evaporated, and a solid residue was recrystallized from a benzene—hexane mixture (3 : 1, 24 mL). Chelate **3** (0.29 g) was obtained. Compound **3** (0.22 g) was additionally precipitated from a filtrate with hexane (20 mL), the total yield was 94 %, m.p. 184—185 °C

(from a benzene—hexane mixture, 3 : 1). Found (%): C, 69.69; H, 6.82; B, 3.01; N, 11.93. $C_{18}H_{19}BN_2O_2$. Calculated (%): C, 69.82; H, 6.70; B, 2.99; N, 11.63. IR (KBr), ν/cm^{-1}: 3320 (NH); 1673 (CO); 1630, 1570, 1560, 1500. ^1H NMR ($CDCl_3$), δ: 2.18 (s, 3 H, Me); 2.42 (s, 3 H, Me); 3.06 and 3.10 (both s, 6 H, NMe_2); 6.13 (br.s, 1 H, NH); 7.15—7.48 (m, 10 H, Ph); 7.69 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 24.43 (q, MeCOB, ^1J = 129 Hz); 32.58 (q, MeCO, ^1J = 127 Hz); 35.04 and 40.90 (both q, NMe_2, ^1J = 139 Hz); 111.26 (C(3)); 126.09, 127.18, 131.80, 150.0 (2 Ph); 154.53 (d, CH, ^1J = 175 Hz); 167.34 (d, NCN, ^3J = 5 Hz); 184.46 (q, COB, ^2J = 6.0 Hz); 198.42 (q, CO, ^2J = 6.0 Hz).

3-Acetyl-2-amino-1*H*-pyridin-4-one (6). A mixture of chelate **3** (0.54 g, 1.5 mmol) and MeONa (1.5 mmol) in 10 mL of MeOH was boiled for 1.5 h, cooled to ~20 °C, and acidified with 0.3 mL of AcOH. The solvent was evaporated *in vacuo* to dryness, and benzene (10 mL) was added to the residue. A precipitate formed was filtered off and washed with benzene (20 mL) and chloroform (2×10 mL). A mixture of compound **6** and sodium acetate was obtained, from which 4-pyridone **6** was isolated by extraction with acetonitrile heated to boiling (3×20 mL). After evaporation of acetonitrile colorless compound **6** was obtained (0.12 g, yield 54 %), m.p. 291—294 °C (from acetonitrile). Found (%): C, 55.09; H, 5.26; N, 18.14. $C_7H_8N_2O_2$. Calculated (%): C, 55.25; H, 5.30; N, 18.41. IR (KBr), ν/cm^{-1}: 3310 (NH); 3240—2800 (NH, CH); 1635 (CO); 1555 (sh), 1510. ^1H NMR (DMSO-d_6), δ: 2.46 (s, 3 H, Me); 5.68 (d, 1 H, H(5), $J_{H,H}$ = 7.5 Hz); 7.19 (d, 1 H, H(6), $J_{H,H}$ = 7.5 Hz); 8.25 (br.s, 2 H, NH_2); 10.30 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 32.85 (q, Me, ^1J = 128 Hz); 104.85 (C(3)); 113.08 (d, C(5), ^1J = 168 Hz); 134.33 (dd, C(6), ^1J = 180 Hz, ^2J = 4.5 Hz); 156.54 (d, C(2), ^3J = 9.0 Hz); 178.70 (d, C(4), ^2J = 8.0 Hz); 199.21 (q, CO, ^2J = 5 Hz). MS, *m/z* (I_{rel} (%)): 152 $[M]^{+\cdot}$ (100), 137 $[M-Me]^+$ (97).

5-Acetyl-4-amino-6-methylpyrimidine (7) and diphenylboron chelate of 5-acetylimidoyl-4-amino-6-methylpyrimidine (8). A mixture of chelate **3** (0.36 g, 1 mmol) and $AcONH_4$ (1.5 g, 20 mmol) in 7 mL of butanol was boiled for 1 h, the solvent was evaporated *in vacuo* to dryness, and chloroform (10 mL) was added to the residue. The solution was chromatographed on a column filled with SiO_2 (a benzene—ethanol (50 : 2) mixture as the eluent). A mixture of compounds **7** and **8** was obtained to which benzene (25 mL) was added, and yellow crystals of chelate **8** (0.135 g, yield 43 %) were filtered off. The filtrate was evaporated, and the residue was sublimated (100—110 °C, 2 Torr) to obtain 0.021 g (14 %) of colorless pyrimidine **7**, m.p. 157—158 °C. Found (%): C, 55.68; H, 6.12; N, 28.05. $C_7H_9N_3O$. Calculated (%): C, 55.62; H, 6.00; N, 27.80. IR (KBr), ν/cm^{-1}: 3390 (NH); 3300—3000 (NH, CH); 1640 (CO); 1605, 1525. ^1H NMR ($CDCl_3$), δ: 2.61 (s, 3 H, Me); 2.66 (s, 3 H, Me); 6.70 (br.s, 2 H, NH_2); 8.43 (s, 1 H, H(2)). ^{13}C NMR ($CDCl_3$), δ: 26.21 (Me); 33.14 (COMe); 114.85 (C(5)); 157.98 (C(2)); 162.18 (C(4)); 166.38 (C(6)); 202.05 (CO). MS, *m/z* (I_{rel} (%)): 151 $[M]^{+\cdot}$ (100), 136 $[M-Me]^+$ (95).

Chelate **8**, m.p. 269—271 °C. Found (%): C, 72.48; H, 6.44; B, 3.67; N, 17.99. $C_{19}H_{19}BN_4$. Calculated (%): C, 72.63; H, 6.10; B, 3.44; N, 17.83. IR (KBr), ν/cm^{-1}: 3300—2800 (NH, CH); 1645, 1620, 1580, 1560, 1500. ^1H NMR (DMSO-d_6), δ: 2.48 (s, 3 H, Me); 2.67 (s, 3 H, Me); 7.05—7.36 (m, 10 H, Ph); 7.49 (br.s, 1 H, NH); 8.07 (s, 1 H, H (2)); 10.65 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 25.67 (qd, Me, ^1J = 130 Hz, ^3J = 5 Hz); 26.39 (q, Me, ^1J = 128 Hz); 106.01 (C(5)); 125.24, 126.75, 132.17, 152.80 (2 Ph); 160.46 (d, C(2), ^1J = 196 Hz); 161.35 (dd, C(4), ^2J = 5 Hz, ^3J = 11 Hz); 167.80 (C(6)); 171.16 (q, C=N, ^2J = 6 Hz). MS, *m/z*: 237 $[M-Ph]^+$.

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