Various approaches to the use of 3-acetyl-2-amino-4-hydroxy-1,3-pentadienecarbonitrile in heterocyclic synthesis

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Two approaches to the use of 3-acetyl-2-amino-4-hydroxy-1,3-pentadienecarbonitrile (**1**) in heterocyclic synthesis are considered. A method for preparing 3-acetyl-4-amino-5-cyano-2-methylpyridine directly from **1** and *N,N*-dimethylformamide dimethylacetal (DMF DMA) was proposed, together with a synthetic route to 2-(2-amino-3-cyano-6-hydroxyphenyl)-8-cyano-5-hydroxy-4-methylquinoline based on the transformation of hydroxyvinyl ketone **1** into its diphenylboron chelate and condensation of the latter with DMF DMA.

Key words: 3-acetyl-2-amino-4-hydroxy-1,3-pentadienecarbonitrile; *N,N*-dimethylformamide dimethylacetal; diphenylboron chelates; pyrydine and quinoline derivatives; intramolecular cyclization.

"Dimers" of malononitrile and of esters of cyanoacetic acid (ECA) as well as their "co-dimers", *i.e.*, products of the addition of methylene-active ECA at the C≡N bond of malononitrile, are known to be effective blocks for building functionally substituted heterocyclic compounds.[1—5] By analogy, 3-acetyl-2-amino-4-hydroxy-1,3-pentadienecarbonitrile (**1**), which is formed from acacH and malononitrile as a mixture of *E*- and *Z*-isomers,[6] can be regarded as a "co-dimer" of these reagents. Apparently, compound **1**, which contains a number of functional groups, NH_2, C≡N, C=O, and OH, is also of interest for heterocyclic synthesis.

A typical feature of hydroxyvinyl ketone **1** is its ability to form chelates. For example, diphenylboron chelate **2** (as an equilibrium mixture of *E*- and *Z*-isomers) can be readily obtained from compound **1** and butoxydiphenylborane.[6]

Previously we have found that the field of application of a number of β-dicarbonyl and aminovinylcarbonyl reagents to fine organic synthesis can be extended, due to the fact that the chemical properties of the boron complexes of these compounds differ from those of the free ligands.[7—12]

In this paper, we also show that two different approaches to the construction of heterocyclic systems from hydroxyvinyl ketone **1**, for example, using dimethylformamide dimethylacetal (DMF DMA), are possible; one of these approaches involves transformations of the free ligand **1** itself, while the other is based on the reactions of its chelate **2**. It was found that DMF DMA reacts readily with compound **1** at 20 °C to give a condensation product. Based on ^1H and ^{13}C NMR, IR, and mass spectra this product should be identified as 3-acetyl-2-amino-1-dimethylaminomethylene-4-oxo-2-pentenecarbonitrile (**4**) (Scheme 1). The alternative structure **5** of the amidine type should be rejected, since the spectroscopic data indicate unambiguously that the compound obtained contains an NH_2 group. Thus, in this case, reagent **1** behaves as a C-nucleophile, and its interaction with the acetal is apparently preceded by its isomerization to the methylene-active form **3** (judging from the ^1H NMR spectra in $CDCl_3$, a **1** ⇌ **3** equilibrium is established, although the proportion of the latter tautomer does not exceed 5—7%).

The ^1H and ^{13}C NMR spectra of compound **4** contain only one set of signals each. The absorption bands recorded in the region of N—H stretching vibrations in the IR spectrum of solutions of **4** indicate that an intramolecular hydrogen bond, N—H···O, is formed in the aminovinylcarbonyl moiety (one of the hydrogen atoms of the amino group remains free).

When compound **4** is treated with ammonium acetate in boiling butanol, it undergoes cyclization to give 3-acetyl-4-amino-5-cyano-2-methylpyridine (**6**) in a 40% yield. The structure of the product was confirmed by the data of IR spectroscopy, ^1H and ^{13}C spectroscopy, and mass spectrometry. Pyridine **6**, containing vicinal NH_2 and Ac groups, is a potential reagent to be used for the construction of bicyclic nitrogen-containing heterocyclic systems.

The reaction of DMF DMA with complex **2** also occurs under mild conditions, but in this case, the Me group bound directly to the boron-containing ring in **2** is also involved in condensation. Consequently, chelate **7**, which has, like complex **2**, a β-diketonate structure, is formed in this reaction in an 87% yield (Scheme 2). This is indicated by the data of ^1H NMR and IR spectroscopy, which confirm that molecule **7** contains a free NH_2 group. Similarly to chelate **2**, compound **7**

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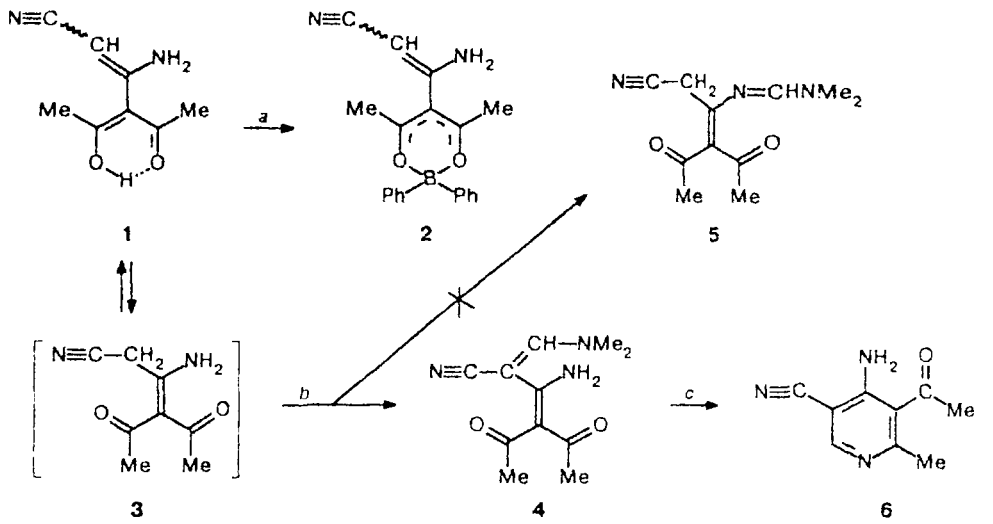
Scheme 1



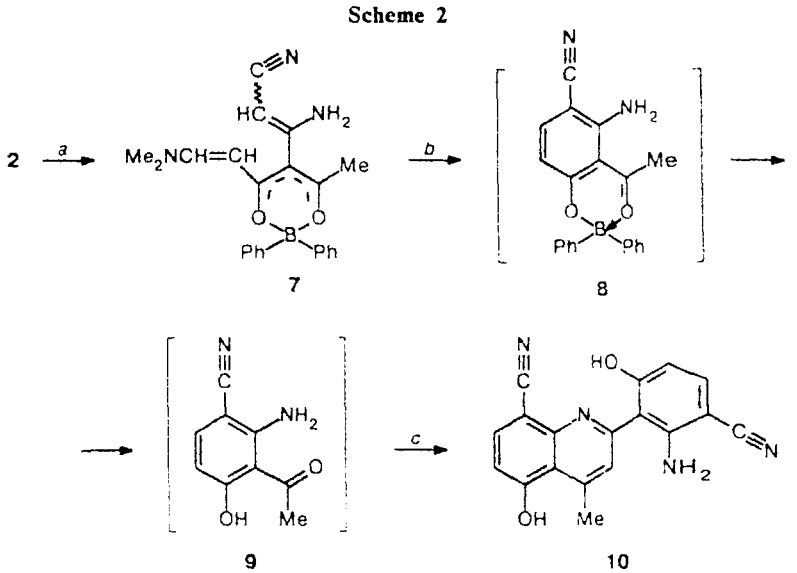
Reagents and conditions: *a*. Ph_2BOBu (see Ref. 6); *b*. DMF DMA, THF, –20 °C; *c*. NH_4OAc, BuOH, Δ or NH_3, EtOH, 90 °C.

exists in solutions as an equilibrium mixture of *E*- and *Z*-isomers (with respect to the C=C bond in the aminoacrylonitrile fragment).

It has been noted previously that the =CH-group protons in the *Z*-isomers of compound **1** and its complex **2** are shielded to a greater degree than the corresponding protons in the *E*-isomers. In conformity with this, the singlet at δ 3.90 in the spectrum of chelate **7** in $CDCl_3$ should be assigned to the *Z*-isomer, whereas the singlet at δ 4.42 should be assigned to the *E*-isomer. According to published data,[6,13] in compounds **1** and **2**, in enaminonitriles of the $N{\equiv}C{-}CH{=}C(R)NH_2$ type (R = Alk, Ar), and in chelate **7** in $CDCl_3$, the *Z*-form predominates (90%).

It was found that boiling complex **7** in BuOH yields 2-(2-amino-3-cyano-6-hydroxyphenyl)-8-cyano-5-hydroxy-4-methylquinoline (**10**) (see Scheme 2). The structure of this product was confirmed by spectroscopic data. For example, its mass spectrum contains peaks for ions with *m/z* 315 $[M-H]^+$ and 301 $[M-Me]^+$. The ^1H NMR spectrum of quinoline **10** has signals corresponding to the quinoline CH-groups [a singlet at δ 7.60 (C(3)H) and two doublets at δ 6.99 (C(6)H) and 8.07 (C(7)H)] as well as to the NH_2 (δ 6.43) and

Scheme 2



Reagents and conditions: *a*. DMF DMA, THF, –20 °C; *b*. BuOH, Δ, $-Me_2NH$, $-Ph_2BOBu$; *c*. BuOH, Δ, $-2\ H_2O$.

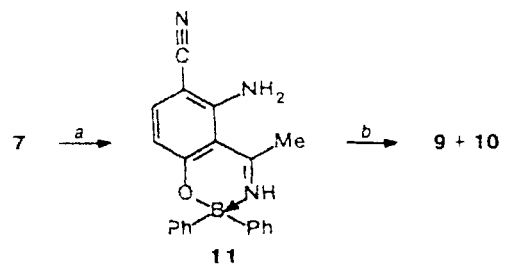
CH (δ 10.75 and 11.58) groups. The ^{13}C NMR spectrum of this compound, in addition to the signals due to the C atoms of the quinoline system and of the phenyl group, contains signals at δ 117.84 and 118.23 (2 C≡N) as well as at δ 23.56 (Me).

Probably, the transformation of complex **7** into quinoline **10** occurs (in conformity with Scheme 2) *via* intramolecular cyclization (in which the C atom of the aminoacrylonitrile fragment acts as the nucleophilic center), accompanied by elimination of Me_2NH and the formation of a benzene ring. The chelate ring is cleaved through the action of BuOH to give the free ligand, benzonitrile **9**, which contains vicinal NH_2 and MeCO groups. Self-condensation of compound **9** according to the Friedländer reaction pathway leads to quinoline **10**.

This scheme is supported by the data on the cyclization of chelate **7** in the presence of NH_3. In fact, when NH_3 was passed through a boiling solution of compound **7** in toluene, a product stable in air was isolated in a relatively low yield; according to the data of IR and ^1H NMR spectroscopy and mass spectrometry and the results of elemental analysis, this compound has the chelate structure **11** (Scheme 3). The structure of this complex is close to that of the intermediate chelate **8**, but, unlike the latter, it is stable toward boiling BuOH, since the N→B coordination bond is rather strong. This made it possible to develop a more efficient method for the synthesis of compound **11**. Boiling complex **7** with a butanolic solution of NH_3 affords chelate **11** in a 62% yield. Decomposition of compound **11** under mild conditions by HCl in EtOH, led, after neutralization of the reaction mixture, to a mixture consisting of polyfunctionally substituted benzene **9** and compound **10**, resulting from its self-condensation. (Compound **9** was identified by ^1H NMR spectroscopy.) These data are definite evidence for Scheme 2, illustrating the process of the transformation of chelate **7** into quinoline **10**.

Thus, preparation of compounds **10** and **11** from reagent **1** is a new example of using the "methodology of chelate organic synthesis" (see Refs. 14—17 and references therein).

Scheme 3



11

Reagents and conditions: *a*. NH_4OAc, BuOH, Δ, 1 h; *b*. HCl/EtOH, H_2O, 60—70 °C, 4 h.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250.13 MHz), and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument (75.47 MHz); chemical shifts are presented with respect to $SiMe_4$. IR spectra were recorded on a Perkin-Elmer 577 instrument. Mass spectra were obtained on a Varian MAT CH-6 spectrometer.

3-Acetyl-2-amino-1-dimethylaminomethylene-4-oxo-2-pentenecarbonitrile (4). DMF DMA (0.35 g) in 5 mL of THF was added to nitrile **1** (0.5 g), and the mixture was stirred for 1 h at 20 °C. Volatile products were evaporated *in vacuo*, and the residue was chromatographed on a column with SiO_2 (with chloroform and a 5 : 1 chloroform—acetone mixture as eluents) to give 0.3 g (45%) of compound **4**, m.p. 146—147 °C. MS, *m/z*: 221 $[M]^+$. IR ($CHCl_3$), ν/cm^{-1}: 3450, 3250 br (NH); 2204 (C≡N); 1620, 1578 (C=O, C=C). ^1H NMR (DMSO-d_6), δ: 2.14 (s, 6 H, 2 Me); 3.20 (s, 6 H, Me_2N); 7.28 (s, 1 H, CH); 7.9 (br.s, 1 H, NH); 10.3 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 30.79 (q, 2 MeCO, ^1J = 127 Hz); 46.6 (br.s, Me_2N); 72.37 (C=CH); 111.64 (AcC); 118.91 (d, C≡N, ^2J = 10.0 Hz); 155.49 (d, N=CH, ^1J = 171 Hz); 164.82 (C—NH_2); 198.42 (q, 2 CO, ^3J = 5.4 Hz).

3-Acetyl-4-amino-5-cyano-2-methylpyridine (6). ***A.*** A mixture of compound **4** (0.2 g, 0.9 mmol) and ammonium acetate (0.14 g) in 10 mL of butanol was refluxed for 1 h, the butanol was evaporated *in vacuo*, and the residue was chromatographed on a column with SiO_2 (using chloroform as the eluent) to give 0.063 g (40%) of pyridine **6**, m.p. 130—131 °C. Found (%): C, 61.70; H, 5.35; N, 23.01. $C_9H_9N_3O_2$. Calculated (%): C, 61.70; H, 5.18; N, 23.99. MS, *m/z*: 175 $[M]^{+\cdot}$. IR (KBr), ν/cm^{-1}: 3405, 3360 (NH_2); 2240 (CN); 1680, 1650 (C=O, C=C). ^1H NMR ($CDCl_3$), δ: 2.60, 2.70 (both s, 6 H, Me, MeCO); 6.35 (br.s, 2 H, NH_2); 8.40 (s, 1 H, CH). ^{13}C NMR (acetone-d_6), δ: 24.95 (q, Me, ^1J = 129 Hz); 32.20 (q, MeCO, ^1J = 129 Hz); 93.92 (t, C(5), ^3J = 6 Hz); 116.05 (d, C≡N, ^3J = 3.6 Hz); 120.69 (s, C(3)); 153.49 (t, C(4), ^3J = 5 Hz); 153.92 (d, C(6), ^1J = 183 Hz); 160.32 (d, C(2), ^2J = 12 Hz, ^3J = 6 Hz); 203.70 (q, C=O, ^3J = 6 Hz).

B. A mixture containing compound **4** (0.2 g, 0.9 mmol) in 4 mL of ethanol and a 1 *N* solution of ammonia in ethanol (6 mL) was kept in a sealed tube at 90 °C for 2.5 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a column with SiO_2 (using chloroform as the eluent) to give 0.066 g (42%) of pyridine **6**.

Diphenylboron chelate of 3-acetyl-2-amino-6-dimethylamino-1,3,5-hexatrienecarbonitrile (7). DMF DMA (0.18 g, 1.5 mmol) in 25 mL of THF was added to diphenylboron chelate **2** (0.5 g, 1.5 mmol), and the mixture was stirred for 1 h at 20 °C. The solvent was evaporated *in vacuo*, and the residue was purified on a column with SiO_2 (using chloroform as the eluent) to give 0.5 g (87%) of chelate **7** as a mixture of *Z*- and *E*-isomers, m.p. 183—184 °C (benzene—hexane). Found (%): C, 71.99; H, 6.38; B, 2.90. $C_{23}H_{24}BN_3O_2$. Calculated (%): C, 71.70; H, 6.28; B, 2.83. MS, *m/z*: 308 $[M-Ph]^+$. IR ($CHCl_3$), ν/cm^{-1}: 3350, 3410 (NH_2); 2215 (CN); 1620 (C=O, C=C). ^1H NMR ($CDCl_3$), δ (*Z*/*E* = 9 : 1, the signals for the *E*-isomer are given in brackets): 2.18 [2.24] (s, 3 H, Me); 3.00 [2.99] (s, 3 H, NMe); 3.29 [3.27] (s, 3 H, NMe); 3.90 [4.42] (s, 1 H, NC—CH); 4.70 [4.18] (s, 2 H, NH_2); 5.11 [5.13] (d, 1 H, CH, *J* = 12 Hz); 7.1—7.5 (m, 10 H, 2 Ph); 8.10 [8.12] (d, 1 H, Me_2NCH). ^{13}C NMR (DMSO-d_6), δ (*Z* [*E*]): 21.66 [21.46]

(q, Me, ^1J = 128 Hz); 37.72 [37.72] (q, NMe_2, ^1J = 140 Hz); 45.73 [45.73] (q, NMe_2, ^1J = 140 Hz); 62.76 [65.29] (d, NC—CH=, ^1J = 177 [165] Hz); 88.75 [88.50] (d, CH=, ^1J = 160 Hz); 109.14 [109.14] (s, MeCO—C); 119.54 [120.98] (s, CN); 125.27 [125.27], 126.61 [126.61], 131.09 [131.09], 150.85 [150.85] (2 Ph); 156.33 [156.33] (d, Me_2N—CH, ^1J = 173 Hz); 159.19 [160.04] (s, H_2N—C); 175.17 [174.98], 176.20 [175.68] (2 CO).

2-(2-Amino-3-cyano-6-hydroxyphenyl)-8-cyano-5-hydroxy-4-methylquinoline (10). A solution of chelate **7** (0.5 g, 1.3 mmol) in 5 mL of butanol was refluxed for 3 h. The solvent was evaporated *in vacuo*, and the residue was washed with ether to give 0.2 g of crude compound **10**, which was purified on a column with SiO_2 (using ether and a 5 : 1 ether—methanol mixture as eluents) to give 0.09 g (44%) of quinoline **10**, m.p. 325—326 °C. Found (%): C, 68.60; H, 3.76; N, 17.10. $C_{18}H_{12}N_4O_2$. Calculated (%): C, 68.35; H, 3.83; N, 17.71. MS, *m/z*: 315 $[M-H]^+$. IR (KBr), ν/cm^{-1}: 3500—2700 v.br (OH, NH); 2210 (CN); 1655, 1628, 1590, 1560. ^1H NMR (DMSO-d_6), δ: 2.89 (s, 3 H, Me); 6.38 (d, 1 H, C(5')H); 6.43 (s, 2 H, NH_2); 6.99 (d, 1 H, C(6)H, J = 8.2 Hz); 7.40 (d, 1 H, C(4')H, J = 8.8 Hz); 7.60 (s, 1 H, C(3)H); 8.07 (d, 1 H, C(7)H, J = 8.2 Hz); 10.75 (s, 1 H, OH); 11.58 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 23.56 (Me); 106.11, 109.92, 126.38, 134.51, 136.16 (5 CH); 117.84, 118.23 (2 CN); 160.51, 160.63 (2 CO); 87.42, 100.79, 109.71, 118.18, 146.35, 149.10, 151.03, 156.46.

Diphenylboron chelate of 3-amino-4-cyano-2-(1-iminoethyl)phenol (11). ***A.*** A mixture of chelate **7** (0.3 g, 0.78 mmol) and 0.2 g of ammonium acetate in 15 mL of butanol was refluxed for 1 h, the excess butanol was evaporated *in vacuo*, and the residue was purified on a column with SiO_2 (using chloroform as the eluent) to give 0.16 g (60%) of chelate **11**, m.p. 100—101 °C (decomp.) (benzene—hexane).

B. A mixture of chelate **7** (0.11 g, 2.9 mmol) and a 0.2 *N* solution of NH_3 in toluene (15 mL) was heated for 13 h in a sealed tube at 110 °C. The precipitate was filtered off, and the filtrate was evaporated *in vacuo* to give 0.035 g of crude product **11**, which was purified on a column with SiO_2 (using chloroform as the eluent) to give 0.028 g (28%) of chelate **11**.

C. A solution of chelate **7** (0.2 g, 0.52 mmol) in 10 mL of butanol was heated to boiling, and excess NH_3 (gas) was passed through this solution for 1.5 h. The solvent was evaporated *in vacuo*, the residue was triturated with hexane, and the precipitate was filtered off to give 0.11 g (62%) of chelate **11**. Found (%): C, 75.16; H, 5.60; B, 2.93; N, 12.09. $C_{21}H_{18}BN_3O$. Calculated (%): C, 74.36; H, 5.35; B, 3.19; N, 12.38. MS, *m/z*: 262 $[M-Ph]^+$. IR ($CHCl_3$), ν/cm^{-1}: 3500, 3400, 3350 (NH_2, NH); 2220 (C≡N); 1640, 1590 (C=O, C=C). ^1H NMR ($CDCl_3$), δ: 2.67 (s, 3 H, Me); 4.71 (s, 2 H, NH_2); 6.56 (d, 1 H, CH, J = 8.5 Hz); 7.1—7.5 (m, 11 H, CH, 2 Ph); 8.10 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 24.71 (q, Me, ^1J = 131 Hz); 87.29 (C—CN); 107.65 (br.s, MeC(=NH)—C); 111.31 (d, CHCO, ^1J = 168 Hz); 117.82 (d, C≡N, ^3J = 5.9 Hz); 126.56, 127.73, 128.36, 131.96 (2 Ph); 140.02 (d, NC—C—CH, ^1J = 164 Hz); 148.0 (s, B—C); 152.13 (d, NH_2C, ^3J = 8.9 Hz); 167.53 (d, CO, ^3J = 10 Hz); 169.71 (q, Me—C, ^2J = 6 Hz).

Reaction of chelate 11 with a solution of HCl in EtOH. A 3.2 *N* ethanolic solution of HCl (5 mL) and 0.1 mL of water were added to chelate **11** (0.25 g, 0.73 mmol), and the mixture was heated for 4 h at 60—70 °C. The volatile products were evaporated *in vacuo*, and water (5 mL) and a saturated aqueous solution of $NaHCO_3$ (3 mL) were added to the residue until the pH was 7. The precipitate was filtered off to give 0.078 g of a mixture of 3-amino-2-(1-aminoethyl)-4-cyanophenol (**9**) and quinoline (**10**) in a ratio of 2 : 1 (according to ^1H NMR spectrum). The ^1H NMR spectrum of compound **9** in DMSO-d_6, after elimination of the signals corresponding to quinoline **10**, δ: 2.52 (s, 3 H, Me); 6.25 (d, 1 H, CH, J = 8.5 Hz); 7.44 (d, 1 H, CH, J = 8.5 Hz); 7.24 (br.s, 2 H, NH_2); 11.37 (br.s, 1 H, OH).

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