# Chelate synthesis of 2,2′-bipyridin-4-one

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A method for the synthesis of 2,2′-bipyridin-4-one from 4-amino-4-(2-pyridyl)-but-3-en-2-one *via* its diphenylboron chelates was proposed.

**Key words:** 4-amino-4-(2-pyridyl)-but-3-en-2-one, diphenylboron complexes, dimethylformamide dimethylacetal, 2,2′-bipyridin-4-one, chelate organic synthesis.

Previously[1—4] we have proposed original methods for the synthesis of a series of functionalized pyridines from aminovinyl ketones (AVK) based on condensation of diphenylboron chelates of AVK with amide acetals. In the present work we attempted to use a similar approach for the construction of bipyridine system from 4-amino-4-(2-pyridyl)-but-3-en-2-one (**1**), which was recently synthesized by us from acetylacetone and 2-cyanopyridine for the first time.[5]

The characteristic property of AVK **1** as a chelating ligand is its ability to participate in various types of coordination interaction. Thus, the reaction of this compound with butoxydiphenylborane results in the formation of a mixture of isomeric chelate complexes, five-membered (**2**) and six-membered (**3**) (Scheme 1).[5,6] This may apparently complicate the use of AVK **1** in the synthesis of bipyridine derivatives since the possibility of different behavior of chelates **2** and **3** with respect to amide acetals could not be ruled out. We have found, however, that both complex **2** and its isomer **3** give one and the same condensation product, six-membered chelate **4** with O,N-coordination, when boiled with DMF dimethylacetal (DMA DMF) in toluene. Thus, a mixture of isomers **2** and **3**, which is directly formed on borylation of AVK **1**, can be used in the reaction with DMA DMF. In this case the yield of the red crystalline complex **4** is as high as 82%. This chelate is readily soluble in ethanol and chloroform, less soluble in ether, and insoluble in hexane. Its $^1$H NMR spectrum contains only one set of signals. The $^{13}$C NMR spectroscopy data indicate that the aminovinylcarbonyl fragment is involved in the formation of the chelate ring, whereas the pyridine ring remains unbound. In fact, the chemical shifts of the C(3), C(4), C(5), and C(6) pyridine atoms in chelates **3** and **4** and also in AVK **1** are close.[5,6] On the contrary, when the N(Py) → B bond is formed, as for example, in complex **2**, the signal of the C(4) atom is usually shifted downfield, and the signal of the C(6) atom is shifted upfield. Finally, the position of the signal for the carbon atom of the COB fragment of compound **4** (δ 176.6) corresponds to the previously obtained $^{13}$C NMR spectral data for six-membered aminovinylcarbonylboron chelates.[2—4]

Complex **4** does not decompose in boiling butanol but refluxing in hexanol affords a mixture of 2,2′-bipyridin-4-one (**6**) and its diphenylboron chelate (**7**) in a ~1 : 2 ratio (according to the $^1$H NMR data). It seems likely that first the elimination of hexyloxydiphenylborane from compound **4** occurs to form free ligand **5** that transforms into bipyridone **6** as the result of intramolecular cyclization with the elimination of $Me_2NH$. Compound **6** is an effective chelating ligand capable of forming chelate **7**, which is stable in boiling hexanol, with hexyloxydiphenylborane. The incomplete transformation of compound **6** into complex **7** can probably be explained by the partial protolysis of hexyloxydiphenylborane by $C_6H_{13}OH$ under the experimental conditions. Therefore, for preparative purposes a mixture of ligand **6** and its complex **7** was treated with butoxydiphenylborane in boiling butanol. Chelate **7** (as a solvate with $CHCl_3$) was obtained by this way in 82.5% yield (with respect to complex **4**).

To synthesize bipyridone **6**, a mixture of compounds **6** and **7** was heated in a sealed tube with butanolic solution of HCl at 160—170 °C. Under these conditions, chelate **7** decomposes with the liberation of ligand **6**. The total yield of the latter was as high as 57% with respect to complex **4**.

Reference 7, which is devoted to the study of the structure of antibiotic caerulomycin (4-methoxy-2,2′-

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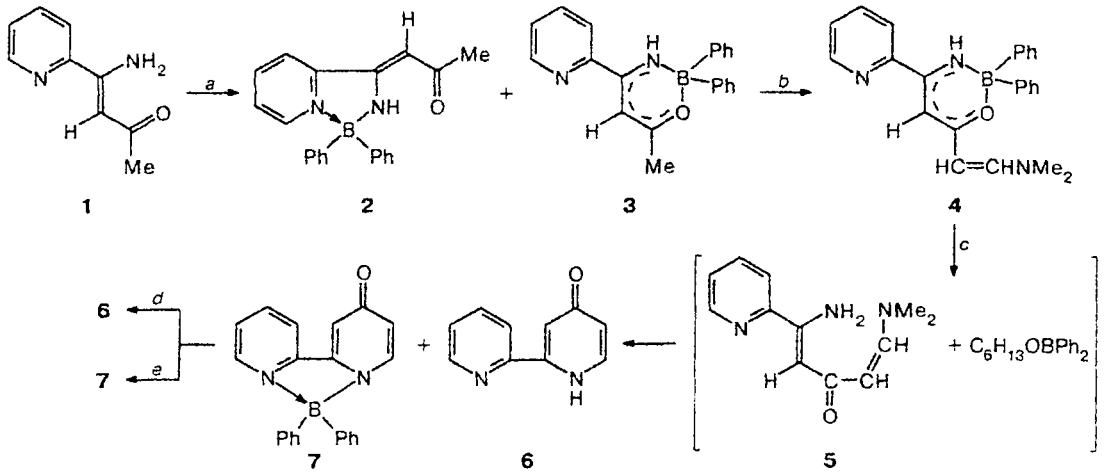
**Scheme 1**



**Reagents and conditions:** *a*. $Ph_2BOBu$ (see Ref. 5); *b*. DMA DMF, toluene, Δ; *c*. $C_6H_{13}OH$, Δ; *d*. 1) HCl, BuOH, 160—170 °C (in a sealed tube), 2) $NH_4OH$; *e*. $Ph_2BOBu$, BuOH, Δ.

bipyridin-6-aldoxime), describes the four-step synthesis of bipyridinone **6** from this antibiotic (m.p., IR and UV spectra only are given for the product **6** obtained).

Compound **6** is soluble in water and ethanol but insoluble in ether and hexane. In solutions it obviously exists mainly in the pyridone (rather than oxypyridine) form, which is, for example, indicated by the $^{13}C$ NMR spectral data in $CDCl_3$ (the characteristic signal of C=O with δ 178.8).

Bipyridone **6** is undoubtedly a promising chelating ligand and can be used for the preparation of complexes with various metals.

## Experimental

$^1H$ NMR and $^{13}C$ NMR spectra were recorded on Bruker WM-250 (250.13 MHz) and Bruker AM-300 (75.47 MHz) instruments. Chemical shifts are given 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. Elemental analysis of the synthesized compounds was carried out in the laboratory of microanalysis of the Institute of Organic Chemistry, Russian Academy of Sciences. A mixture of diphenylboron complexes **2** and **3** was obtained by the known procedure.[5] After the solvent was distilled off, the residue was washed with pentane and used without additional purification.

**Diphenylboron complex of 5-amino-1-dimethylamino-5-(2-pyridyl)-penta-1,4-dien-3-one (4).** A solution of a mixture of isomers **2** and **3** (6.0 g, 18.4 mmol) and DMA DMF (4.38 g, 36.7 mmol) in toluene (100 mL) was refluxed for 4 h under nitrogen. The red residue that formed was filtered off and washed with pentane to give 5.8 g (82.8%) of compound **4**, m.p. 249—250 °C (from benzene). Found (%): C, 74.98; H, 6.58; N, 10.46. $C_{24}H_{24}BN_3O$. Calculated (%): C, 75.59; H, 6.30; N, 11.02. MS, *m/z*: 304 $[M-Ph]^+$. $^1H$ NMR (DMSO-$d_6$), δ: 2.89 (br.s, 3 H, MeN) and 3.18 (br.s, 3 H, MeN); 5.08 (d, 1 H, CH=CHN, $J$ = 12.5 Hz); 5.91 (br.s, 1 H, CH=C—NH); 7.00—7.40 (m, 10 H, 2 Ph); 7.58 (m, 1 H, H-5); 7.82 (d, 1 H, CH=CHN, $J$ = 12.5 Hz); 7.97 (m, 1 H, H-4); 8.07 (m, 1 H, H-3); 8.11 (br.s, 1 H, NH); 8.74 (d, 1 H, H-6, $J$ = 5 Hz). $^{13}C$ NMR (DMSO-$d_6$), δ: 37.0 and 44.7 ($Me_2N$); 89.1 (d, CH=CHN, $J$ = 170 Hz); 92.1 (d, CH—C=O, $J$ = 158 Hz); 121.5 (d, C-3, $J$ = 166 Hz); 125.0; 126.0; 126.6; 153.0 (2 Ph); 125.6 (d, C-5, $J$ = 166 Hz); 137.7 (d, C-4, $J$ = 166 Hz); 149.4 (d, C-6, $J$ = 182 Hz); 149.5 (s, NHC=); 151.3 (d, CH—$NMe_2$, $J$ = 164 Hz); 157.9 (s, C-2); 176.6 (C=O).

**Diphenylboron complex of 2,2′-bipyridin-4-one (7).** *A*. Chelate **4** (2.2 g, 5.8 mmol) in hexanol (15 mL) was refluxed for 20 h under nitrogen. Hexanol was distilled off *in vacuo*, and the residue was purified on a $SiO_2$ column (the eluent was toluene and then and a 10 : 1 toluene—methanol mixture) to give 1.51 g (92.5%) of a mixture of chelate **7** and ligand **6** (**7** : **6** ≈ 2 : 1 according to the $^1H$ NMR data). Fractional crystallization from $CHCl_3$ afforded 0.45 g of complex **7**·$CHCl_3$, m.p. 297—298 °C. Found (%): C, 60.22; H, 3.93; B, 2.37; Cl, 23.05; N, 5.57. $C_{23}H_{18}BCl_3N_2O$. Calculated (%): C, 60,59; H, 3.95; B, 2.37; Cl, 23.38; N, 6.15. $^1H$ NMR (acetone-$d_6$), δ: 6.23 (d, 1 H, H-5, $J$ = 7.3 Hz); 7.05 (d, 1 H, H-3, $J$ = 1.8 Hz); 7.10—7.20 (m, 10 H, 2 Ph); 7.53 (d, 1 H, H-6, $J$ = 7.3 Hz); 7.82 (d, 1 H, H-5′); 7.93 (s, 1 H, $CHCl_3$); 8.55 (m, 2 H, H-3′ and H-4′); 8.74 (d, 1 H, H-6′, $J$ = 6.2 Hz). $^{13}C$ NMR (DMSO-$d_6$), δ: 112.7 (d, C-3, $J$ = 166 Hz); 119.6 (d, C-5, $J$ = 162 Hz); 121.3 (d, C-3′, $J$ = 175 Hz); 127.3 (C-5′); 127.3; 127.9; 132.4; 145.2 (2 Ph); 140.1 (dd, C-6, $^1J$ = 177, $^2J$ = 3 Hz); 143.3 (d, C-6′, $J$ = 180 Hz); 144.1 (d, C-4′, $J$ = 171 Hz); 144.6 (m, C-2); 148.4 (m, C-2′); 177.7 (d, C=O, $J$ = 6 Hz).

*B*. A mixture of chelate **7** (0.2 g) and ligand **6** (in a ~ 2 : 1 ratio) and $Ph_2BOBu$ (1.04 g) in butanol (2 mL) was refluxed for 30 min under nitrogen. Butanol was distilled off *in vacuo* and the residue was crystallized from $CHCl_3$ to afford 0.27 g (82.5%) of complex **7**·$CHCl_3$, m.p. 297—298 °C.

**2,2′-Bipyridine-4-one (6).** A mixture of chelate 7 and ligand **6** (~2 : 1, 0.21 g) was heated in a sealed glass tube for 9 h at 160—170 °C with a 6.9 *N* solution of HCl (4 mL) in butanol. Water (2 mL) was added to the reaction mixture. The aqueous layer was separated and water was distilled off *in vacuo* to give 0.17 g of **6** · HCl. The obtained salt was dissolved in water (1 mL) and a 25% aqueous ammonia (0.3 mL) was added to the solution. The solution was extracted many times with $CHCl_3$ to give 0.08 g (62%) of bipyridinone **6**, m.p. 146—147 °C (from acetone). Lit.:[7] m.p. 145 °C. MS, *m/z*: 172 $[M]^+$. $^1H$ NMR ($CDCl_3$), δ: 6.54 (dd, 1 H, H-5); 7.15(s, 1 H, H-3), 7.37 (dd, 1 H, H-6); 7.74 (d, 1 H, H-3′); 7.80—7.95 (m, 2 H, H-4′, and H-5′); 8.63 (d, 1 H, H-6′). $^{13}C$ NMR ($CDCl_3$), δ: 113.5 (C—3); 116.8 (C-5); 120.4 (C-3′); 124.8 (C-5′); 137.5 (C-4′); 139.2 (d, C-6, $J$ = 179 Hz); 146.6 (C-2); 149.2 (d, C-6′, $J$ = 179 Hz); 149.7 (C-2′); 178.8 (C=O).

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# Heterocyclization of acetylketene *N,S*-acetals with benzoyl cyanamide

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*N*-Unsubstituted mono- and diacetylketene *N,S*-acetals undergo cyclization with benzoyl cyanamide to form 2-amino-4-methylthiopyrimidine derivatives.

**Key words**: mono- and diacetylketene *N,S*-acetals, benzoyl cyanamide, 2-amino-4-methylthiopyrimidines.

Mono- and diacylketene *N,S*-acetals are used as convenient building blocks for the synthesis of heterocyclic systems.[1—3]

Previously we have shown that the scope of synthetic application for *N,S*-ketene acetals with unsubstituted $NH_2$ group can be significantly enlarged.[4—7] The most effective reagents of this type are 3-[amino(methylthio)methylene]pentane-2,4-dione (**1**) (readily obtained from acetylacetone and MeSCN)[8] and its deacetylation product, 1-amino-1-methylthiobut-1-en-3-one (**2**).

In the present work, functionally substituted pyrimidines have been synthesized by heterocyclization of compounds **1** and **2** with benzoyl cyanamide (**3**). Thus, refluxing of *N,S*-acetal **1** and cyanamide **3** in toluene afforded 5-acetyl-2-benzoylamino-6-methyl-4-methylthiopyrimidine (**4**). Debenzoylation of the latter with MeONa in MeOH gave *N*-unsubstituted aminopyrimidine **6** (Scheme 1).

In spite of the presence of the active C-nucleophilic center in molecule **2** (*e.g.*, cyclization of *N,S*-acetal **2** and benzoyl isothiocyanate into 5-acetyl-6-methylthio-2-phenyl-3*H*-pyrimidine-4-thione proceeds with the primary formation of the C—C-bond),[9] compound **2** behaves also as an *N*-nucleophile with respect to cyanamide **3**. The reaction of compounds **2** and **3** in boiling toluene resulted in the condensation product **5**, which was isolated as an oil, identified by $^1H$ NMR, and converted (without any purification) into crystalline aminopyrimidine **7** by debenzoylation. The structures of functionally substituted pyrimidines **6** and **7** are con-

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