Addition of barbituric acids to benzoylcyanamide

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Derivatives of 5-diaminomethylenepyrimidine-2,4,6-trione were synthesized by adding barbituric and *N,N'*-dicyclohexylbarbituric acids to benzoylcyanamide in the presence of stoichiometric amounts of $Ni(OAc)_2$.

Key words: benzoylcyanamide, barbituric acids, nickel acetate; ketene aminals, derivatives of 5-diaminomethylenepyrimidine-2,4,6-trione.

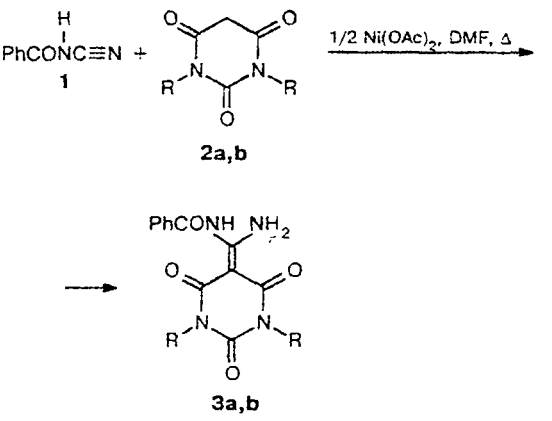
Previously,[1–4] we found that α,α-dioxoketene aminals, which are convenient reagents for heterocyclic synthesis[5–8] and effective chelating agents,[2,9] can be readily obtained from cyanamides and compounds with an active methylene group, β-diketones or alkyl β-ketocarboxylates, in the presence of catalytic amounts of $Ni(acac)_2$ or $Ni(OAc)_2$. It was demonstrated that the key stages of the catalytic cycle are the formation of reactive intermediates (chelate complexes of Ni with the initial β-dicarbonyl compounds) and their addition at the C≡N bond of cyanamide.[2]

Cyclic β-diketones that do not possess chelating ability also react with cyanamides, but only in the presence of stoichiometric amounts of $Ni(OAc)_2$ and under more drastic conditions.[10] These reactions lead to the formation of nickel chelates, which decompose in an acid medium to give free ligands, the corresponding ketene aminals.

In a continuation of the studies of the reactions of cyanamides with methylene-active compounds, the interaction of benzoylcyanamide (**1**) with barbituric acid (**2a**) and its *N,N'*-dicyclohexyl derivative (**2b**) was considered in the present work. It was found that when a mixture of compounds **1**, **2**, and $Ni(OAc)_2$ (in the molar ratio of 2 : 2 : 1) is refluxed in DMF, the corresponding derivatives of diaminomethylenepyrimidine-2,4,6-trione (**3a,b**), which represent a new type of heterocyclic ketene aminals, form (Scheme 1).

In the absence of a promotor (a Ni salt), cyanamide **1** does not react with acids **2a,b**. Catalytic amounts (5–10%) of neither $Ni(acac)_2$ nor $Ni(OAc)_2$ produce a positive effect. The role of $Ni(OAc)_2$ in the synthesis of ketene aminals **3a,b** can be illustrated by Scheme 2. Barbituric acids **2a,b** seem to initially react with $Ni(OAc)_2$ to give reactive Ni enolates, which further add at the C≡N bond of cyanamide **1** to form chelate compounds (**A**). Unlike complexes of a similar type that precipitate out of the reaction mixture when cyclic β-diketones

Scheme 1



R = H (**a**), *cyclo*-C_6H_{11} (**b**)

react with cyanamides and $Ni(OAc)_2$, less stable chelates **A** readily decompose to give free ligands **3a,b**, which can be thus obtained in one stage. (The instability of intermediates **A** can be easily explained by the fact that heterocyclic ketene aminals **3a,b** are apparently weak chelating agents.)

The structure of compounds **3a,b** was confirmed by spectral data. Ketene aminal **3a** is poorly soluble in organic solvents, which hampers its use in further transformations. In contrast, adduct **3b** is soluble in most solvents. Its debenzoylation under the action of MeONa in MeOH results in pyrimidinetrione **4** (unsubstituted at the diaminomethylene group), whose symmetric structure was confirmed by ^1H and ^{13}C NMR spectral data. Ketene aminal **4** is soluble in $CHCl_3$, C_6H_6, EtOH, and DMSO and can probably be used as a reagent in heterocyclic synthesis (*cf.*, for example, with the transforma-

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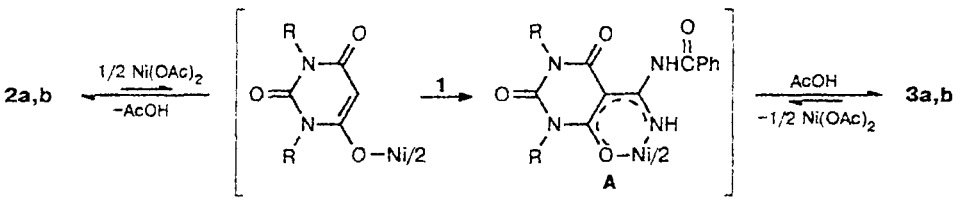
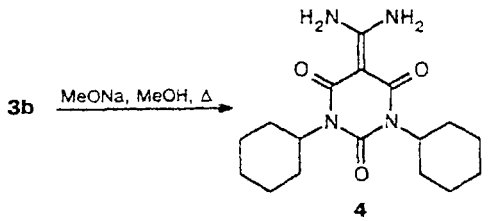
Scheme 2



tions of 7-diaminomethylene-4,5,6,7-tetrahydro-2*H*-indazol-6-one[11]).



Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument, and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. The IR spectra were recorded on a UR-20 spectrometer. The mass spectra were obtained on a Varian MAT-311A instrument (EI, 70 eV). Benzoylcyanamide[12] and 1,3-dicyclohexylbarbituric acid[13] were synthesized according to the procedures described earlier.

5-(*N*-Benzoyldiaminomethylene)pyrimidine-2,4,6-trione (3a). A mixture of acid **2a** (1.28 g, 10 mmol), cyanamide **1** (1.60 g, 11 mmol), and nickel(II) acetate (0.89 g, 5 mmol) in 20 mL of DMF was gradually (for 0.5 h) heated with stirring to boiling, refluxed for 2 h, and left overnight. The light brown precipitate was filtered off and treated with 20 mL of 2 *N* HCl solution in MeOH (Δ, 0.5 h), and the white powder was separated on a filter, dried and recrystallized from DMSO. Compound **3a** was obtained (1.37 g, 50%), m.p. >340 °C. Found (%): C, 52.47; H, 4.15; N, 20.00. $C_{12}H_{10}N_4O_4$. Calculated (%): C, 52.55; H, 3.68; N, 20.43. MS, *m/z*: 274 $[M]^+$. IR (KBr), ν/cm^{-1}: 3325, 3245—2600 (NH); 1785, 1734, 1690, 1665 (CO); 1600. ^{1}H NMR (DMSO-d_6), δ: 7.60—7.80 (m, 3 H, Ph); 7.98 (d, 2 H, Ph); 9.80 (br.s, 1 H, NH_2); 10.65 (br.s, 1 H, NH_2); 10.95 (br.s, 2 H, 2 NH); 14.47 (s, 1 H, NHCO).

5-(*N*-Benzoyldiaminomethylene)-1,3-dicyclohexylpyrimidine-2,4,6-trione (3b) was obtained analogously to compound **3a**; the reaction mixture was left overnight. The precipitate was filtered off and extracted on a filter with boiling chloroform. The extract was concentrated, and the pyrimidinetrione **3b** obtained was recrystallized from a benzene—hexane mixture (1 : 1). Yield 58%, m.p. 191—192 °C. Found (%): C, 66.12; H, 7.36; N, 12.80. $C_{24}H_{30}N_4O_4$. Calculated (%): C, 65.73; H, 6.90, N, 12.78. MS, *m/z*: 438 $[M]^+$. IR (KBr), ν/cm^{-1}: 3303, 3090, 2912, 2825 (NH, CH); 1700 sh, 1680, 1645, 1600, 1565, 1535. ^{1}H NMR ($CDCl_3$), δ: 1.40 (m, 6 H, 3 CH_2); 1.72 (m, 6 H, 3 CH_2); 1.91 (m, 4 H, 2 CH_2); 2.45 (m, 4 H, 2 CH_2); 4.81 (m, 2 H, 2 CHN); 7.66 (m, 3 H, Ph); 8.05 (m, 2 H, Ph); 10.10 (br, 1 H, NH_2); 11.25 (br.s, 1 H, NH_2); 14.89 (s, 1 H, NHCO).

5-Diaminomethylene-1,3-dicyclohexylpyrimidine-2,4,6-trione (4). Compound **3b** (0.79 g, 1.80 mmol) was added to a solution of sodium metal (40 mg, 1.80 mmol) in 5 mL of MeOH and refluxed for 0.5 h. After cooling, the mixture was acidified with AcOH, and the solvent was removed *in vacuo*. Pyrimidinetrione **4** was further isolated according to the above procedure. Yield 0.44 g (73%), m.p. 265—266 °C. Found (%): C, 61.19; H, 7.78; N, 17.34. $C_{17}H_{26}N_4O_3$. Calculated (%): C, 61.05; H, 7.84; N, 16.75. MS, *m/z*: 334 $[M]^+$. IR (KBr), ν/cm^{-1}: 3390, 3380 sh, 3160, 2930, 2850 (NH, CH); 1675, 1640, 1606, 1590, 1535. ^{1}H NMR (DMSO-d_6), δ: 1.25 (m, 6 H, 3 CH_2); 1.55 (m, 4 H, 2 CH_2); 1.65 (m, 2 H, CH_2); 1.76 (m, 4 H, 2 CH_2); 2.33 (m, 4 H, 2 CH_2); 4.89 (m, 2 H, CHN); 7.40 (br.s, 2 H, NH_2); 9.59 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 25.1, 26.0, 28.6 (10 $\underline{C}H_2$); 52.1 (d, 2 $\underline{C}H$, J = 134 Hz); 78.8 (C(5)); 149.8 (H_2N—$\underline{C}$—NH_2); 164.0, 164.1 (C(2), C(4), C(6)).

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Synthesis and structure of the Pd^{II} complex with 3,3-dinitropropylamine

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The reaction of 3,3-dinitropropylamine with $PdCl_2$ gave the previously unknown complex, bis(3,3-dinitropropylaminato-N,C^3)palladium(II). The structure of the complex was established by X-ray diffraction analysis.

Key words: 3,3-dinitropropylamine, reaction with palladium(II) chloride; bis(3,3-dinitropropylaminato-N,C^3)palladium(II), crystal structure; X-ray diffraction analysis.

It is known that complexes of palladium(II) with some organic diamines (diaminocyclohexane, diaminoethane, and diaminopropane), like *cis*-diamminedichloroplatinum(II),[1] exhibit antitumor activity.[2] The synthesis of unconventional complexes with new ligands that differ from known ligands both in composition and molecular design is of interest in the search for weakly toxic antitumor compounds. At this time there is no data on the use of terminal polynitro compounds as ligands in complexes of palladium and platinum. These complexes possess increased oxidation potentials and can serve as a source of nitric oxide, which is known[3—5] to be an endogenic bioregulator that affects vascular tone, the function of blood platelets, the nervous and immune systems, *etc.* It was found that 3,3-dinitropropylamine, which contains two reaction centers (anionic and amine) can act as such a ligand. Like amino acids,[6] this polynitroalkylamine acts as a bidentate ligand in the reaction with palladium(II) chloride to form the previously unknown complex, bis(3,3-dinitropropylaminato-N,C^3)palladium(II) (**1**).

According to the data of X-ray structural analysis, compound **1** is a chelate complex with a distorted planar square coordination about the Pd^{II} ion (Fig. 1). The Pd(1), N(1), N(2), C(6), and C(3) atoms deviate from

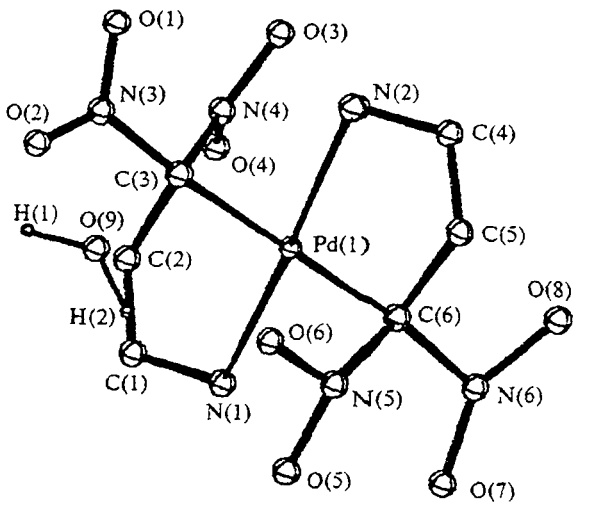

Fig. 1. Molecular and crystal structure of complex **1**.

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