# Reactions of alkyl acetone-1,3-dicarboxylates with cyanamide and benzoylcyanamide*

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The reactions of cyanamide with dialkyl acetone-1,3-dicarboxylates in the presence of nickel acetylacetonate afforded alkyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates. The same compounds were obtained by intramolecular cyclization of adducts of acetone-1,3-dicarboxylates with benzoylcyanamide under the action of sodium alkoxides.

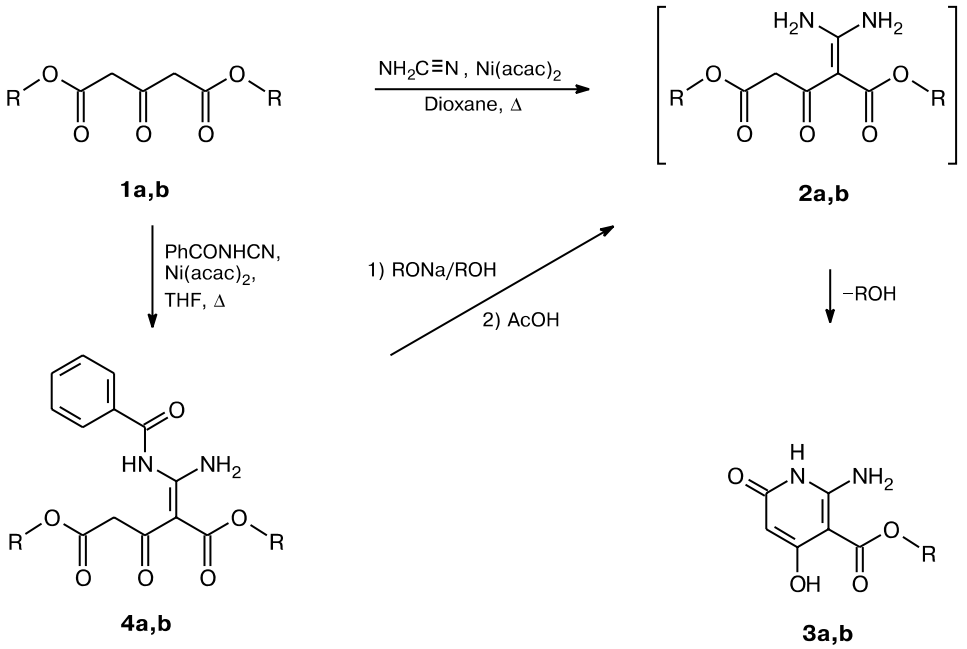
**Key words:** cyanamide, benzoylcyanamide, dialkyl acetone-1,3-dicarboxylates, nickel acetylacetonate, *N*-benzoylketene aminals, alkyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates, intramolecular cyclization.

Earlier,[1—3] we found that methylene-reactive alkyl β-oxocarboxylates can add at the C≡N bond of cyanamides in the presence of nickel acetylacetonate ($Ni(acac)_2$). These reactions allow one to synthesize the corresponding ketene aminals, which are convenient starting materials in various schemes for construction of nitrogen-containing heterocyclic systems.[4—8]

In the present work, we studied reactions of dimethyl and diethyl acetone-1,3-dicarboxylates (**1a,b**) with cyanamide and benzoylcyanamide. It turned out that when esters **1a,b** react with cyanamide in boiling dioxane in the presence of catalytic amounts of $Ni(acac)_2$, intermediate adducts **2a,b** undergo cyclization, with elimination of the corresponding alcohol, into alkyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylates **3a,b** (Scheme 1).

In contrast, the reactions of compounds **1a,b** with benzoylcyanamide led only to *N*-benzoylketene

**Scheme 1**




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

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aminals **4a,b**, which were isolated in 55 and 61% yields, respectively. Apparently, being affected by the benzoyl group, the N atoms of the diaminomethylene fragment in these compounds are less nucleophilic than those in N-unsubstituted ketene aminals **2a,b**. Indeed, no intramolecular cyclization of adducts **4a,b** occurred in boiling EtOH or dioxane; however, heating with RONa in ROH (R = Me and Et) gave debenzoylated compounds **2a,b**, which were immediately converted into pyridines **3a,b**.

Heterocycles **3a,b** are yellowish crystalline substances. They are poorly soluble in most organic solvents, yet being soluble in DMF and DMSO. Ketene aminals **4a,b** are crystalline substances that are soluble in dioxane, DMF, and DMSO. The structures of compounds **3a,b** and **4a,b** were confirmed by spectroscopic methods. Their mass spectra contain molecular ion peaks. The $^1$H NMR spectra of pyridines **3a,b** in DMSO-$d_6$ show a singlet at δ 4.90 for C(5)H and signals for the protons of the alkoxy groups. The $^1$H NMR spectra of ketene aminals **4a,b** in DMSO-$d_6$ contains only one set of signals. Earlier,[1] it was demonstrated that the spectra of unsymmetrical *N*-benzoylketene aminals obtained from ethyl acetoacetate and ethyl benzoylacetate also contain one set of signals for both the acyl and alkoxy groups, because the barrier to rotation about the C=C bond is very low due to a pronounced $p$—π conjugation in these compounds.

On the one hand, compounds **3a,b** are derivatives of 4-hydroxy-2-pyridone (3-deazauracil), which is a structural fragment of some natural biologically active compounds (*e.g.*, see Ref. 9 and references therein). On the other hand, they can be regarded as derivatives of 2-aminonicotinic acid, which is the effective substance of some antiinflammatory preparations (for a review see Ref. 10).

## Experimental

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker WM-250 instrument in DMSO-$d_6$. IR spectra were recorded on a Specord M-80 instrument (pellets with KBr). Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV, ionizing chamber temperature 250 °C, direct inlet probe).

Benzoylcyanamide was prepared according to a known procedure.[11]

**Methyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (3a).** A mixture of ester **1a** (1.91 g, 11 mmol), cyanamide (0.42 g, 10 mmol), and Ni(acac)$_2$ (0.13 g, 0.5 mmol) was refluxed in dioxane for 8 h and cooled to room temperature. The precipitate was filtered off, recrystallized from AcOH, washed with water, and dried *in vacuo* to give compound **3a** in 58% yield, m.p. >300 °C (AcOH). Found (%): C, 45.30; H, 4.47; N, 15.32. $C_7H_8N_2O_4$. Calculated (%): C, 45.65; H, 4.35; N, 15.20. MS, *m/z*: 184 $[M]^+$, 153 [M – OMe]. IR, ν/cm$^{-1}$: 3500, 3380 ($NH_2$); 3200—2700 (OH, NH); 1700—1590 (group of overlapping bands for C=O, C=N, and C=C). $^1$H NMR, δ: 3.80 (s, 3 H, MeO); 4.90 (s, 1 H, CH); 7.20 (s, 2 H, $NH_2$); 10.30 and 11.50 (both s, 1 H each, OH, NH). $^{13}$C NMR, δ: 51.81 (MeO); 79.47 and 87.59 (C(3), C(5)); 154.89 (C(4)); 161.93, 169.02 and 169.16 (C(2), C(6), CO).

**Ethyl 2-amino-4-hydroxy-6-oxo-1,6-dihydropyridine-3-carboxylate (3b)** was obtained analogously from ester **1b** and cyanamide. The yield of compound **3b** was 51%, m.p. >300 °C (AcOH). Found (%): C, 48.21; H, 5.20; N, 14.24. $C_8H_{10}N_2O_4$. Calculated (%): C, 48.48; H, 5.00; N, 14.14. MS, *m/z*: 198 $[M]^+$, 153 [M – OEt]. IR, ν/cm$^{-1}$: 3500, 3376 ($NH_2$); 3200—2700 (OH, NH); 1700—1560 (group of overlapping bands for C=O, C=N, and C=C). $^1$H NMR, δ: 1.30 (t, 3 H, Me, $J$ = 5.0 Hz); 4.30 (q, 2 H, $CH_2$, $J$ = 5.0 Hz); 4.90 (s, 1 H, CH); 7.20 (s, 2 H, $NH_2$); 10.35 and 11.52 (both s, 1 H each, OH, NH).

**Methyl 2-[(*N*-benzoyl)diaminomethylene]-3-oxoglutarate (4a).** A solution of ester **1a** (1.91 g, 11 mmol), benzoylcyanamide (1.45 g, 10 mmol), and Ni(acac)$_2$ (0.13 g, 0.50 mmol) in THF (6 mL) was refluxed for 8 h. The solvent was removed and the residue was recrystallized from EtOH, washed with water, and dried to give ester **4a** (1.76 g, 55%), m.p. 176—178 °C (ethanol). Found (%): C, 55.96; H, 5.02; N, 9.15. $C_{15}H_{16}N_2O_6$. Calculated (%): C, 56.25; H, 5.00; N, 8.75. MS, *m/z*: 320 $[M]^+$, 247 [M – 73]. IR, ν/cm$^{-1}$: 3352, 3236 (NH); 1732, 1692, 1636 (CO). $^1$H NMR, δ: 3.65, 3.72 (both s, 3 H each, MeO); 3.78 (s, 2 H, $CH_2$); 7.60—7.85 (m, 3 H, Ph); 8.00 (d, 2 H, Ph, $J$ = 7.0 Hz); 9.90, 10.35 and 14.60 (all s, 3 H, 3 NH).

**Ethyl 2-[(*N*-benzoyl)diaminomethylene]-3-oxoglutarate (4b)** was obtained analogously from ester **1b** and benzoylcyanamide. The yield of compound **4b** was 61%, m.p. 164—165 °C (ethanol). Found (%): C, 58.44; H, 5.72; N, 8.36. $C_{17}H_{20}N_2O_6$. Calculated (%): C, 58.62; H, 5.75; N, 8.00. MS, *m/z*: 348 $[M]^+$, 303 [M – 45]. IR, ν/cm$^{-1}$: 3328, 3208, 2936 (NH); 1732, 1680, 1646 (CO). $^1$H NMR, δ: 1.25 (m, 6 H, 2 Me, $J$ = 5.0 Hz); 3.80 (s, 2 H, $CH_2$); 4.15, 4.25 (both q, 4 H, 2 $CH_2O$, $J$ = 5.0 Hz); 7.60—7.85 (m, 3 H, Ph); 8.00 (d, 2 H, Ph, $J$ = 7.0 Hz); 9.90, 10.50, 14.65 (all s, 3 H, 3 NH).

**Cyclization of ketene aminals 4a,b into alkyl pyridine-3-carboxylates 3a,b.** Ketene aminal **4a** (10 mmol) was added to a solution of MeONa (10 mmol) prepared by dissolution of metallic sodium (0.23 g) in MeOH (10 mL). The reaction mixture was refluxed for 2 h and acidified with AcOH (0.60 g). The solvent was removed and the residue was treated with acetonitrile (5 mL), washed with water, and dried *in vacuo* to give pyridine **3a** in 50% yield.

Analogously, compound **3b** was obtained in 47% yield from ketene aminal **4b** and EtONa in EtOH.

The melting points and spectroscopic data for esters **3a,b** were identical with those synthesized from cyanamide and esters **1a,b**.

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