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LETTERS TO THE EDITOR

SYNTHESIS OF 4,6,6-TRIMETHYL-2-OXO-1,2,5,6-TETRAHYDROPYRIDINE-3-CARBONITRILE

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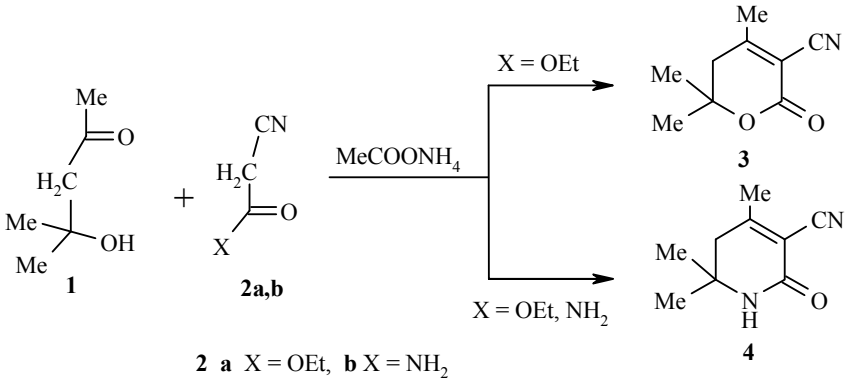
Six-membered lactams and their derivatives are of interest as potential cardiovascular, anticancer, and neurotropic drugs [1]. Methods have been described for obtaining 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile that include cyclocondensation of mesityl oxide [2] or acetone [3] with cyanoacetic ester in the presence of ammonium hydroxide or ammonium acetate.

We have established that 4,6,6-trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile can be obtained by condensation of 4-hydroxy-4-methyl-2-pentanone with cyanoacetic ester. In this case, depending on the amount of ammonium acetate reacted, either an oxygen-containing heterocycle or a nitrogen-containing heterocycle is formed.



2 a X = OEt, **b** X = NH_2

In the presence of catalytic amounts of ammonium acetate, for example, for a mole ratio of reagents **1**, **2a** and ammonium acetate equal to 1:1:0.5, the pyrone **3** is formed, as has been also shown by other authors [4]. If we increase the amount of ammonium acetate ten-fold, then we obtain product **4**. Thus under the studied conditions, ammonium acetate can have two functions, acting as both a catalyst and a reagent. By special experiments we showed that when treated with ammonium acetate, pyrone **3** is not converted to lactam **4** under the studied reaction conditions.

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We have shown that tetrahydropyridine **4** can also be obtained by condensation of pentanone **1** and cyanoacetamide **2b**. In this case, a catalytic amount of ammonium acetate is sufficient to form lactam **4**.

The ^{1}H NMR spectra were taken on a Varian Mercury-200 spectrometer (200 MHz) in $CDCl_3$, internal standard TMS.

4,6,6-Trimethyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonnitrile (4). A. A mixture of 4-hydroxy-4-methyl-2-pentanone (0.68 g, 5.88 mmol), cyanoacetic ester **2a** (0.93 g, 5.88 mmol), and ammonium acetate (2.27 g, 29.4 mmol) was boiled for 6 h with vigorous stirring. The white precipitate forming upon cooling the reaction mass was washed on a filter with a minimal amount of alcohol and recrystallized from alcohol. Obtained 0.1 g of compound **4**; mp 196-199°C. ^{1}H NMR spectrum, δ, ppm: 1.31 (6H, s, $(CH_3)_2$); 2.27 (3H, s, CH_3); 2.46 (2H, s, CH_2); 6.50 (1H, s, NH). Found, %: C 65.81; H 7.36; N 17.09. $C_9H_{12}N_2O$. Calculated, %: C 65.83; H 7.37; N 17.06.

B. A mixture of 4-hydroxy-4-methyl-2-pentanone (2.57 g, 22.1 mmol), cyanoacetamide **2b** (1.86 g, 22.1 mmol) and ammonium acetate (0.85 g, 11.06 mmol) was held for 3 months at room temperature. Then alcohol (2 ml) was added to the reaction mass and it was filtered. The product on the filter was washed with a minimal amount of alcohol and recrystallized from 15 ml of alcohol. Obtained 0.47 g of the white crystalline substance **4**; mp 196-198°C.

3-Cyano-4,6,6-trimethyl-5,6-dihydro-2-pyrone (3) was obtained by the method described in [4]; mp 109-110°C. The ^{1}H NMR spectrum is similar to the spectrum described in [4]. Found, %: C 65.08; H 6.81; N 8.42. $C_9H_{12}N_2O$. Calculated, %: C 65.44; H 6.71; N 8.48.

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