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Chemistry

SYNTHESIS OF NEW 3-CYANOPYRIDINE-2(1H)-ONES WITH UNSATURATED SUBSTITUENTS AT C-4

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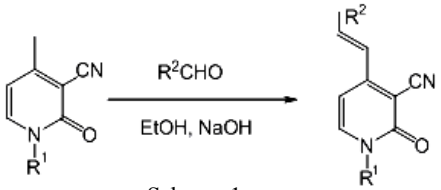
3-Cyanopyridine-2(1H)-ones containing unsaturated substituents at the position C-4 and various substituents at N-1 of the ring have been synthesized as new potential bioactive compounds by interaction of ethyl ylidene cyanoacetate with dimethylformamide dimethyl acetal, and simultaneous reamination-cyclization of obtained derivatives with amines to targeted 3-cyanopyridine-2(1H)-ones.

Keywords: 3-cyanopyridine-2(1H)-one, 2-oxo-1,2-dihydropyridine-3-carbonitrile unsaturated derivatives.

Introduction. The pyridine skeleton is found in a large variety of naturally occurring compounds and also in over 700 existing drugs having diverse biological activities [1, 2]. Recent investigations of biological activities presented that pyridinone derivatives with unsaturated substituents have valuable properties and display a variety of biological activities, in particular they can be used for inhibiting or treating a pathological condition or disorder linked to or mediated by a protein kinase in a mammal, or as positive allosteric modulators of MGLur-2 receptors [3–5]. 3-Cyano-2-pyridones reveals interesting anticancer activity due to their ability to interfere with different types of biological targets (e.g. PDE3, PIM1 Kinase and Survivin protein) [6].

In previous publications it was shown that some vinyl heterocycles are of a practical interest [7, 8]. In previous reports we described the synthesis of some substituted 3-cyanopyridine-2(1H)-ones with various substituents at the positions 1 and 4 of the pyridinone ring [9], including the syntheses of a number of 4-substituted vinyl-3-cyanopyridine-2(1H)-ones [10]. The last ones were obtained by condensation of synthesized 4-methyl--pyridine-2-ones with aromatic and heterocyclic aldehydes in dry ethyl alcohol media in the presence of sodium hydroxide. It should be noted, that the resulting compounds mainly comprised of cis- and trans-isomers mixture (see Scheme 1).



Scheme 1.

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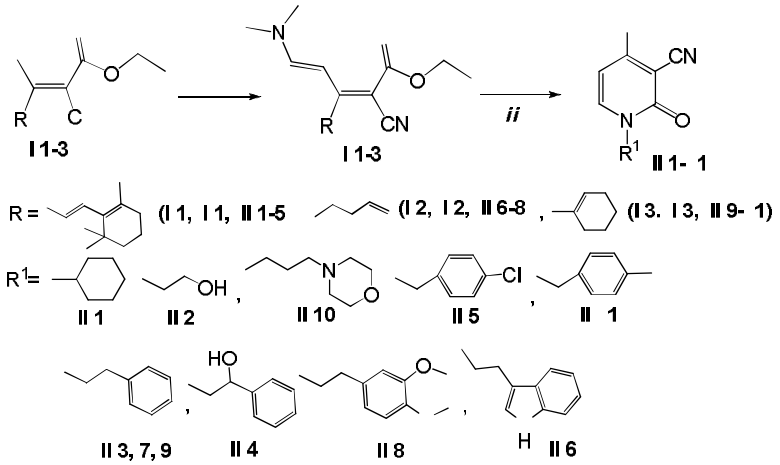
Described method does not allow to obtain 3-cyanopyridine-2(1H)-ones with unsaturated substituents other than vinyl. At the same time abovementioned method leads to the mixture of stereoisomers that can be undesirable from biological activity point of view.

Results and Discussion. Taking into account these facts, we decided to use a simple path for synthesizing compounds with various unsaturated substitutes. We started from ylidene cyanoacetic acid ethyl esters with unsaturated substituents **I 1–3** obtained from condensation of commercially available unsaturated methyl ketones with cyanoacetic acid ethyl ester. Synthesized ylidene cyanoacetic acid esters were condensed with N,N-dimethylformamide dimethyl acetal (DMFDMA) to obtain new dimethylaminovinyl derivatives **II 1–3** with good yields. The interaction was carried out in anhydrous xylene under reflux for 3 *h* (see Scheme 2).



Scheme 2. Reagents and conditions: (*i*) **I 1–3**, DMFDMA, xylene, reflux 3 *h*; (*ii*) **II 1–3**, NH_2R^1, xylene, reflux 15 *h*.

Obtained **II 1–3** when refluxed with primary amines (bp over 100°*C*) in anhydrous xylene form targeted 2-oxo-1,2-dihydropyridine-3-carbonitriles (**III 1–11**) in good yields (extra 2 after cessation of dimethylamine isolation). It could be mentioned, that 2-(2,6,6-trimethylcyclohex-1-enyl)vinyl substituent is a structural fragment of retinol (vitamin A).

NMR data of synthesized vinyl-derivatives (compounds **III 1–5**) show that they have only *trans*-configuration. In summary, a convenient synthesis of 3-cyanopyridine-2(1H)-ones with unsaturated substituents was developed.

Experimental Part. All melting points were determined on a SMP-10 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian Mercury 300 spectrometer operating at 300 *MHz* with TMS as internal standard in DMSO-d_6 : CCl_4 (1 : 3 and 3 : 1) solutions at 303.15 *K*. TLC analysis was performed on Silufol-254 UV plates, eluent acetone/benzene (1 : 3) detection was with UV light at 254 *nm* and iodine vapors. The elemental analyses matched the calculated composition.

General Procedure for Synthesis of 2-Cyano-3-substituted-but-2-enoic Acid Ethyl Esters (I 1–3). A stirred mixture of commercially available unsaturated methyl ketones (0.5 *mol*), ethyl cyanoacetate (0.5 *mol*), beta alanine (0.005 *mol*),

24 *mL* of glacial acetic acid and benzene (100 *mL*) was heated with Dean-Stark trap for 18 *h* (extra 2 *h* after cessation of water isolation). The mixture was allowed to cool to ambient temperature, benzene (30 *mL*) was added, and then the mixture was washed with water (3 × 30 *mL*). The combined aqueous washings were shaken with benzene (15 *mL*), then the combined benzene solutions were dried ($MgS0_4$), and the solvent was removed under reduced pressure. The residual oil was distilled under reduced pressure to give 2-cyano-3-substituted-but-2-enoic acid ethyl ester, which was used without further purification.

*(2Z,4E)-Ethyl 2-cyano-3-methyl-5-(2,6,6-trimethylcyclohex-1-enyl)penta-2,4--dienoate (**I 1**)*. Yield 53%, n_d^{25}=1.5660, bp 170–180 °C /2*mm*.

*(Z)-Ethyl 2-cyano-3-methylhepta-2,6-dienoate (**I 2**)*. Yield 52%, n_d^{25}=1.5630, bp 100–116 °*C* / 2 *mm*.

*(Z)-Ethyl 2-cyano-3-cyclohexenylbut-2-enoate (**I 3**)*. Yield 60%, n_d^{25}=1.5620, bp 150–160 °*C* / 2 *mm*.

General Procedure for Synthesis of Dimethylaminovinyl Derivative (II 1–3). A solution of each initial compound **I 1–3** (0.01 *mol*) in anhydrous xylene (20 *mL*) was treated with DMFDMA (0.011 *mol*). The reaction mixture was refluxed for 3 *h*, then was allowed to cool. Light petroleum (10 *mL*, bp 60–80°*C*) was added to the reaction mixture at room temperature. The formed solid products were collected by filtration and crystallized from light petroleum. Data of the compounds are shown below.

*(2E,4E)-Ethyl 2-cyano-5-(dimethylamino)-3-((E)-2-(2,6,6-trimethylcyclohex-1-enyl)vinyl)penta-2,4-dienoate (**II 1**)*. Yield 75%, mp 101–104°*C*. Mixture of two stereoisomers: **A** and **B** (1 : 2).

A (66%). ^{1}H NMR, *δ*, *ppm*: 7.31 d (*J* = 12.8 *Hz*, 1H), 6.91 d (*J* = 12.8 *Hz*, 1H), 6.41 d (*J* = 16.2 *Hz*, 1H), 6.27 d (*J* = 16.2 *Hz*, 1H), 4.15 q (*J* = 7.1 *Hz*, 2H), 3.11s (6H), 2.06 t (*J* = 6.0 *Hz*, 2H), 1.80 s (3H), 1.71–1.59 m (2H), 1.54–1.45 m (2H), 1.31 t (*J* = 7.1 *Hz*, 3H), 1.09 s (6H).

B (34%). ^{1}H NMR, *δ*, *ppm*: 7.31 d (*J* = 12.8 *Hz*, 1H), 6.83 d (*J* = 15.9 *Hz*, 1H), 6.25 d (*J* = 15.9 *Hz*, 1H), 5.58 d (*J* = 12.8 *Hz*, 1H), 4.11 q (*J* = 7.1 *Hz*, 2H), 3.11 s (6H), 2.06 t (*J* = 6.0 *Hz*, 2H), 1.80 s (3H), 1.71–1.59 m (2H), 1.54–1.45 m (2H), 1.31 t (*J* = 7.1 *Hz*, 3H), 1.09 s (6H).

*(E)-Ethyl 2-cyano-3-((E)-2-(dimethylamino)vinyl)hepta-2,6-dienoate (**II 2**)*. Yield 73 %, mp 66–69°*C*. Mixture of two stereoisomers: **A** and **B** (7: 3).

A (70%). ^{1}H NMR, *δ*, *ppm*: 7.55 d (*J* = 13.1 *Hz*, 1H), 6.94 d (*J* = 13.1 *Hz*, 1H), 5.96–5.81 m (1H), 5.13–4.94 m (2H), 4.12 k (*J* =7.1 *Hz*, 2H), 3.32–2.81 m (8H), 2.33–2.24 m (2H), 1.30 t (*J* =7.1 *Hz*, 3H).

B (30%). ^{1}H NMR, *δ*, *ppm*: 7.52 d (*J* = 12.8 *Hz*, 1H), 5.96–5.81 m (1H), 5.54 d (*J* = 12.8 *Hz*, 1H), 5.13–4.94 m (2H), 4.12 k (*J* =7.1 *Hz*, 2H), 2.65–3.01 m (8H), 2.23–2.14 m (2H), 1.30 t (*J* =7.1 *Hz*, 3H).

*(2Z,4E)-Ethyl 2-cyano-3-cyclohexenyl-5-(dimethylamino)penta-2,4-dienoate (**II 3**)*. Yield 76%, mp 156–157°*C*. Mixture of two stereoisomers: **A** and **B** (4 : 1).

A (80%). ^{1}H NMR, *δ*, *ppm*: 7.13 d (*J* = 12.7 *Hz*, 1H), 6.81 d (*J* = 12.7 *Hz*, 1H), 5.52 m (1H), 4.13 k (*J* =7.1 *Hz*, 2H), 3.20 br.s (3H), 3.01 br.s. (3H), 1.83–2.41 m (4H), 1.65–1.81m (4H), 1.30 t (*J* =7.1 *Hz*, 3H).

B (20%). ^{1}H NMR, *δ*, *ppm*: 7.14 d (*J* = 12.4 *Hz*, 1H), 5.51 d (*J* = 12.4 *Hz*, 1H), 5.27 m (1H), 4.08 k (*J* =7.1 *Hz*, 2H), 3.20 br.s. (3H), 3.01 br.s. (3H), 1.83–2.41 m (4H), 1.65–1.81 m (4H), 1.28 t (*J* =7.1 *Hz*, 3H).

General Procedure for Synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile (III 1–11). A mixture of each dimethylamino derivative **II 1–3** (0.005 *mol*) and corresponding amine (0.0055 *mol*) in anhydrous xylene (10 *mL*) was refluxed for 15–16 *h*. After the completion of the reaction, the mixture was cooled to room temperature. Light petroleum (10 *mL*, bp 60–80°*C*) was added to the reaction mixture. The solid products so formed were collected by filtration and crystallized from xylene.

(E)-1-Cyclohexyl-2-oxo-4-(2-(2,6,6-trimethylcyclohex-1-enyl)vinyl)-1,2--dihydropyridine-3-carbonitrile ***(III 1)***. Yield 52%, mp 150–152°*C*. ^{1}H NMR, *δ*, *ppm*: 7.75 d (*J* = 7.4 *Hz*, 1H), 7.12 d (*J* = 16.2 *Hz*, 1H), 6.59 d (*J* = 7.4 *Hz*, 1H), 6.56 d (*J* = 16.2 *Hz*, 1H), 4.7–4.59 m (1H), 2.11 t (*J* = 6.1 *Hz*, 2H), 1.96–1.88 m (2H), 1.82 s (3H), 1.87 –1.76 m (3H), 1.75–1.48 m (9H), 1.11s (6H).

(E)-1-(2-Hydroxyethyl)-2-oxo-4-(2-(2,6,6-trimethylcyclohex-1-enyl)vinyl)-1,2--dihydropyridine-3-carbonitrile ***(III 2)***. Yield 57%, mp 171–173°*C*. ^{1}H NMR, *δ*, *ppm*: 7.74 d (*J* = 7.2 *Hz*, 1H), 7.13 d (*J* = 16.2 *Hz*, 1H), 6.58 d (*J* = 7.2 *Hz*, 1H), 6.57 d (*J* = 16.2 *Hz*, 1H), 4.68 t (*J* = 5.3 *Hz*, 1H), 4.02–3.95 m (2H), 3.66 d (*J* = 9.9, 4.8 *Hz*, 2H), 2.11 t (*J* = 6.2 *Hz*, 2H), 1.83 s (3H), 1.69–1.61 m (2H), 1.54–1.48 m (2H), 1.11 s (6H).

(E)-2-Oxo-1-phenethyl-4-(2-(2,6,6-trimethylcyclohex-1-enyl)vinyl)-1,2--dihydropyridine-3-carbonitrile ***(III 3)***. Yield 48%, mp 147–149°C. ^{1}H NMR, *δ*, *ppm*: 7.60 d (*J* = 7.2 *Hz*, 1H), 7.27–7.20 m (5H), 7.10 d (*J* = 16.2 *Hz*, 1H), 6.57 d (*J* = 16.2 *Hz*, 1H), 6.48d (*J* = 7.2 *Hz*, 1H), 4.14 dd (*J* = 8.1, 6.8 *Hz*, 2H), 3.01–2.95 m (2H), 2.11t (*J* = 6.2 *Hz*, 2H), 1.83 s (3H), 1.69–1.61 m (2H), 1.53–1.48 m (2H), 1.11s (6H).

(E)-1-(2-Hydroxy-2-phenylethyl)-2-oxo-4-(2-(2,6,6-trimethylcyclohex-1-enyl) vinyl)-1,2-dihydropyridine-3-carbonitrile ***(III 4)***. Yield 62%, mp 171–173°*C*. ^{1}H NMR, *δ*, *ppm*: 7.71d (*J* = 7.2 *Hz*, 1H), 7.47–7.41m (2H), 7.37–7.29 m (2H), 7.28–7.20 m (1H), 7.15 d (*J* = 16.2 *Hz*, 1H), 6.60 d (*J* = 16.2 *Hz*, 1H), 6.57 d (*J* = 7.2 *Hz*, 1H), 5.49 d (*J* = 5.0 *Hz*, 1H), 4.91–4.82 m (1H), 4.34 dd (*J* = 13.0; 3.1 *Hz*, 1H), 3.63 dd (*J* = 13.0, 9.3 *Hz*, 1H), 2.12 t (*J* = 6.1 *Hz*, 2H), 1.84 s (3H), 1.74–1.60 m (2H), 1.56–1.44 m (2H), 1.12 s (6H).

(E)-1-(4-Chlorobenzyl)-2-oxo-4-(2-(2,6,6-trimethylcyclohex-1-enyl)vinyl)-1,2--dihydropyridine-3-carbonitrile ***(III 5)***. Yield 53%, mp 154–157°*C*. ^{1}H NMR, *δ*, *ppm*: 7.97d (*J* = 7.3 *Hz*, 1H), 7.42–7.38 m (2H), 7.32–7.28 m (2H), 7.13 d (*J* = 16.3 *Hz*, 1H), 6.61d (*J* = 7.3 *Hz*, 1H), 6.56 d (*J* = 16.3 *Hz*, 1H), 5.11s (2H), 2.11t (*J* = 6.1 *Hz*, 2H), 1.82 s (3H), 1.70–1.60 m (2H), 1.54–1.46 m (2H), 1.10 s (6H).

1-(2-(1H-indol-3-yl)ethyl)-4-(but-3-enyl)-2-oxo-1,2-dihydropyridine-3--carbonitrile ***(III 6)***. Yield 58%, mp 127–129°*C*. ^{1}H NMR, *δ*, *ppm*: 10.63 s (1H), 7.52 d (*J* = 7.8 *Hz*, 1H), 7.47 d (*J* = 6.9 *Hz*, 1H), 7.34–7.28 m (1H), 7.07–6.91m (3H), 6.04d (d, *J* = 6.9 *Hz*, 1H), 5.80 ddt (*J* = 16.9, 10.2, 6.6 *Hz*, 1H), 5.10–4.99 m (2H), 4.18 t (*J* = 7.2 *Hz*, 2H), 3.11 t (*J* = 7.1 *Hz*, 2H), 2.72 t (*J* = 7.6 *Hz*, 2H), 2.41–2.31m (2H).

4-(But-3-enyl)-2-oxo-1-phenethyl-1,2-dihydropyridine-3-carbonitrile ***(III 7)***. Yield 55%, mp 74–77°*C*. ^{1}H NMR, *δ*, *ppm*: 7.60 d (*J* = 6.9 *Hz*, 1H), 7.29–7.14 m (5H), 6.10 d (*J* = 6.9 *Hz*, 1H), 5.81ddt (*J* = 16.9; 10.2; 6.6 *Hz*, 1H), 5.11–4.98 m (2H), 4.14 t (*J* = 7.4 *Hz*, 2H), 2.98 t (*J* = 7.4 *Hz*, 2H), 2.75 t (*J* = 7.6 *Hz*, 2H), 2.39 m (2H).

4-(But-3-enyl)-1-(3,4-dimethoxyphenethyl)-2-oxo-1,2-dihydropyridine-3--carbonitrile ***(III 8)***. Yield 63%, mp 91–93°*C*. ^{1}H NMR, *δ*, *ppm*: 7.57d (*J* = 6.9 *Hz*, 1H), 6.78–6.62 m (3H), 6.11d (*J* = 6.9 *Hz*, 1H), 5.88–5.73 m (1H), 5.11–4.97 m (2H), 4.12 t (*J* = 7.1 *Hz*, 2H), 3.77s (3H), 3.76 s (3H), 2.90 t (*J* = 7.1 *Hz*, 2H), 2.74 t (*J* = 7.5 *Hz*, 2H), 2.44–2.33 m (2H).

4-Cyclohexenyl-2-oxo-1-phenethyl-1,2-dihydropyridine-3-carbonitrile ***(III 9)***. Yield 49%, mp 162–164°*C*. ^{1}H NMR, *δ*, *ppm*: 7.61d (*J* = 7.0 *Hz*, 1H), 7.32–7.13 m (5H), 6.21–6.15 m (1H), 6.04 d (*J* = 7.0 *Hz*, 1H), 4.18–4.10 m (2H), 3.03–2.96 m (2H), 2.35–2.23 m (4H), 1.83–1.67 m (4H).

4-Cyclohexenyl-1-(3-morpholinopropyl)-2-oxo-1,2-dihydropyridine-3-carbo-nitrile ***(III 10).*** Yield 66%, mp 114–115°*C*. ^{1}H NMR, *δ*, *ppm*: 7.82 d (*J* = 7.1 *Hz*, 1H), 6.20–6.15 m (1H), 6.12 d (*J* = 7.0 *Hz*, 1H), 3.97 t (*J* = 7.0 *Hz*, 2H), 3.62–3.52 m (4H), 2.40–2.30 m (8H), 2.29–2.23 m (2H), 1.93–1.83 m (2H), 1.83–1.66 m (4H).

4-Cyclohexenyl-1-(4-methylbenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile ***(III 11)***. Yield 62%, mp 154–156°*C*. ^{1}H NMR, *δ*, *ppm*: 7.89 d (*J* = 7.1 *Hz*, 1H), 7.29–7.22 m (2H), 7.14–7.09 m (2H), 6.20–6.16 m (1H), 6.14 d (*J* = 7.1 *Hz*, 1H), 5.06 s (2H), 2.33 s (3H), 2.33–2.22 m (4H), 1.82–1.66 m (4H).

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