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Chemistry of Heterocyclic Compounds **2019**, *55*(6), 566–572

Synthesis and halocyclization of 3-cyano-4,6-dimethyl-2-pyridone allyl derivatives

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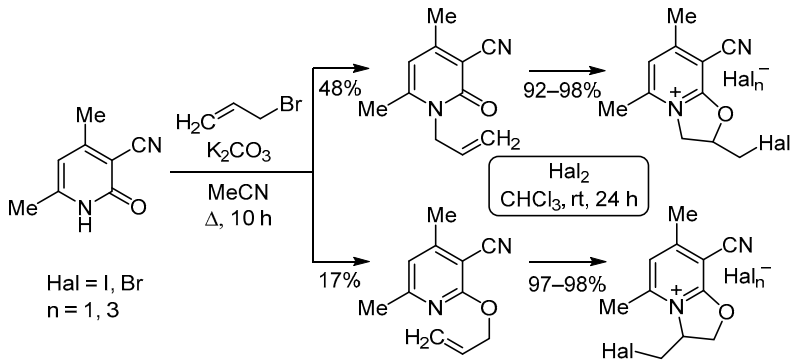


The sequence of condensation, alkylation, and halocyclization reactions during the synthesis of the target 2,3-dihydro[1,3]oxazolo[3,2-*a*]-pyridinium salts was investigated. The effect of basic catalysis on the chemoselectivity of the reaction of malononitrile with acetylacetone has been revealed. In neutral media, the selectivity of the formation of 3-cyano-4,6-dimethyl-2-pyridone increases. The presence of Et_3N, on the other hand, leads to the formation of side products. Allylation of 3-cyano-4,6-dimethyl-2-pyridone proceeds with the formation of regioisomeric 1-allyl-3-cyano-4,6-dimethyl-2-pyridone and 2-allyl-3-cyano-4,6-dimethyloxypyridine in a 3:1 ratio, while the high chemoselectivity of halocyclization of allyl derivatives with iodine or bromine results in practically quantitative yields of 2,3-dihydro[1,3]oxazolo[3,2-*a*]pyridinium salts.

Keywords: acetylacetone, allyl bromide, 1-allyl-3-cyano-4,6-dimethyl-2-pyridone, 2-allyloxy-3-cyano-4,6-dimethylpyridine, 8-cyano-5,7-dimethyl-2,3-dihydro[1,3]oxazolo[3,2-*a*]pyridinium halides, 3-cyano-4,6-dimethyl-2-pyridone, 3-cyano-2-(1,1-dicyano)but-3-enyl-4,6-dimethylpyridine, malononitrile, halocyclization.

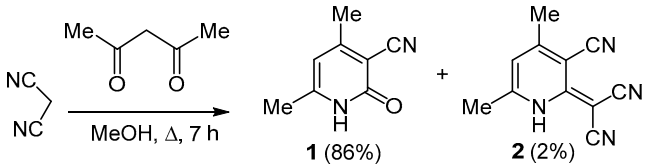
Pyridin-2(1*H*)-ones have pronounced biological activity owing to their structural closeness to natural pyrimidine bases. For example, functionalized 3-cyano-2-pyridones exhibit antitumor,[1] vasodilator,[2] anti-inflammatory,[3] and antimicrobial[4] activity, whereas [1,3]oxazolo[3,2-*a*]pyridines have anti-parasitic[5] and antihypertensive[6] properties. Pyridones, in addition, are important substrates in the synthesis of various heteroatom-containing polycyclic systems.[7] In particular, electrophilic heterocyclization reactions of *N*- and *O*-allyl derivatives of differently substituted pyridones[8] by the action of halogenating agents draw some interest. This approach allows access to organic dihydrooxazolo[3,2-*a*]pyridine salts. In medicinal chemistry, solubility in physiological, including intracellular, media is an important characteristic of biologically active compounds. Consequently, the possibility of selecting and applying annulated azinium salts in modern medicinal technologies involves the synthesis of a wide range of derivatives of this type of compounds and the study of the characteristics of their formation.

This work is devoted to the study of the allylation reaction of 3-cyano-4,6-dimethyl-2-pyridone (**1**) with allyl bromide followed by iodo- or bromocyclization to the target 2,3-dihydro[1,3]oxazolo[3,2-*a*]pyridinium salt.

It has previously been shown[9] that the reaction of acetylacetone with malononitrile in basic media leads to the formation of two products, 3-cyano-4,6-dimethyl-2-pyridone (**1**) ("Guareschi pyridine") and 2,6-dicyano-3,5-dimethylaniline.[10] According to other data,[11] however, pyridone **1** is the only condensation product of $CH_2(CN)_2$ with acetylacetone in the presence of an organic base.

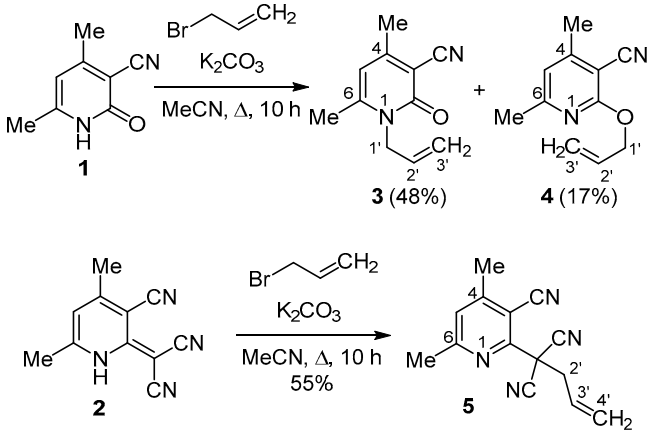
We found that pyridone **1** was formed in the reaction medium (yield 86%, Scheme 1), together with a small amount of 2-dicyanomethylidene-1,2-dihydropyridine 3-carbonitrile (**2**) (yield 2%, chromatographically isolated) as a result of seven-hour heating under reflux of equimolar amounts of malononitrile and acetylacetone in MeOH. Target product **1** gradually precipitated from a MeOH solution upon standing for 1 day and was easily purified by simple filtration and washing the precipitate on the filter with $CHCl_3$. The known 2-dicyanomethylidene-1,2-dihydropyridine-3-carbonitrile (**2**) is usually obtained by heating malononitrile dimer and acetylacetone in alcohol solutions in the presence of a secondary aliphatic amine.[12,13]

Scheme 1



Allylation of the isolated products **1** and **2** with allyl bromide was performed according to the previously developed method[14] in the K_2CO_3–MeCN system. The literature[15] contains data on the alkylation of pyridone **1** with ethyl bromide, benzyl chloride, or ethyl bromoacetate in MeCN in the presence of anhydrous K_2CO_3 and $(n\text{-Bu})_4N^+Br^-$, which proceeds with the formation of exclusively *N*-alkyl derivatives in 75–87% yields. In our study, the allylation reaction led to the formation of 1-allyl-3-cyano-4,6-dimethyl-2-pyridone (**3**) and 2-allyl-3-cyano-4,6-dimethyloxypyridine (**4**) (Scheme 2) in a 2.8:1 ratio according to the integrals of the proton signals of the respective products in the ^{1}H NMR spectrum of the reaction mixture. In previously carried out alkylation of 5-nitro-2-pyridone,[14] the ratio of *N*- and *O*-isomers was 20:1. Therefore, a noticeable increase in the yield of *O*-isomer **4** appears to be due to the influence of the methyl group in position 6 of pyridone **1**. This can be confirmed by the ratio of regioisomers (5:1) of previously synthesized 1-methallyl-4-methylquinolin-2(1*H*)-one and 2-methallyloxy-4-methylquinoline.[16] In the case of alkylation of 2-dicyanomethylidene-1,2-dihydropyridine-3-carbonitrile (**2**) with allyl bromide, the reaction ends with the formation of 3-cyano-2-(1,1-dicyano)but-3-enyl-4,6-dimethylpyridine (**5**) (Scheme 2).

Scheme 2



Isomers **3**, **4** were separated by preparative chromatography, eluent EtOAc–hexane, 1:3. The structure of the isomers was confirmed by ^{1}H and ^{13}C NMR spectroscopy data, including 2D ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC experiments. In the ^{1}H NMR spectra of compounds **3** and **4**, the signals of two methyl groups, a heterocyclic proton, and an allyl substituent are observed; however, in the spectrum of allyloxypyridine **4**, all proton signals are shifted downfield compared to the spectrum of pyridone **3**. In the ^{13}C NMR spectra of structures **3** and **4**, we observe signals characteristic to carbons of the NCH_2 (46.0 ppm) and OCH_2 groups (66.7 ppm) in allyl substituents. In addition, the signal of a heterocyclic C-5 atom of the aromatic ring in the ^{13}C NMR spectrum of compound **4** is shifted downfield ($\Delta\delta$ ~8 ppm) compared with the analogous signal in the spectrum of pyridone **3**.

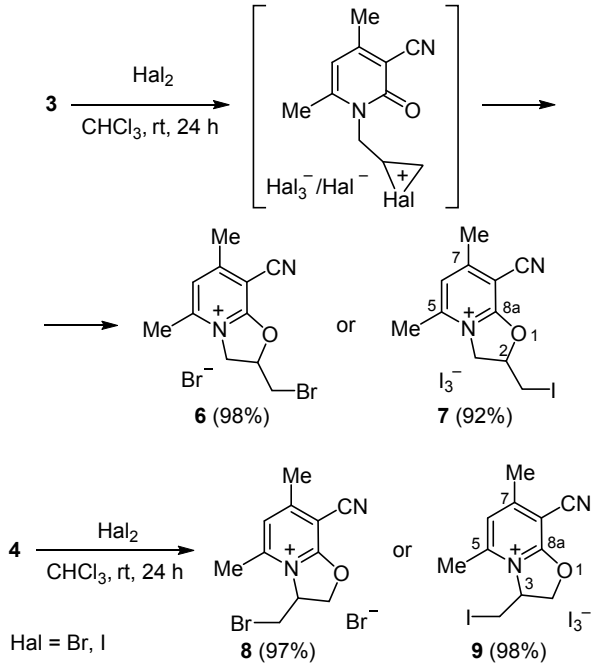
The structure of compound **5** was proposed on the basis of NMR spectroscopy and mass spectrometry data. In the ^{1}H NMR spectra of compound **5**, the signals of the protons of the methyl groups and the proton of the heterocycle are shifted downfield and correspond to chemical shifts of the aromatic pyridine ring, whereas the signals of the protons of the CH_2 group of the allyl moiety are noticeably shifted upfield compared to similar signals in the spectra of compounds **3** and **4**, which indicates the attack of allyl bromide to the carbon atom. This is confirmed by the data of a ^{1}H–^{13}C HMBC experiment, which showed correlations of methylene protons of the 2'-CH_2 allyl fragment with the unprotonated sp^3-hybridized C-1' atom (44.9 ppm), the pyridine C-2 atom (150.1 ppm), as well as with the carbon atom of the CN group (113.0 ppm), the signal of which has double intensity. In the high-resolution mass spectrum of compound **5**, an intense peak of the protonated molecular ion $[M+H]^+$ with *m*/*z* 237.1134 may be observed.

The structure of pyridone **3** was additionally confirmed by X-ray structural analysis. According to X-ray structural analysis, the compound crystallizes in the trigonal system (Fig. 1*a*). The pyridone ring is practically flat. The distribution of bond lengths in the heterocyclic ring is close to the expected one and reflects the transition from the aromatic to the conjugated polyene system when the carbonyl group is introduced into the pyridine ring. The allyl group is located orthogonal to the plane of the

heterocycle, its terminal carbon atoms exhibit significant mobility, causing large anisotropic thermal parameter values. Despite the coplanar arrangement of the aromatic fragments in the crystal (Fig. 1*b*), no π–π contacts between the heterocyclic rings are observed. Other significantly shortened contacts in the crystal are also absent, with the exception of the O(1)···H(7)–C(7) (*x*, *y*, *z* – 1) (2.40 Å, 0.32 Å less than the sum of the van der Vaals radii). This contact can be considered a hydrogen bond formed with the participation of a proton, polarized due to the effects of hyperconjugation of the methyl group. In this case, the CH acidity and proton mobility turns out to be similar to the proton mobility of methyl groups in 2- or 4-methyl-substituted *N*-alkylazinium salts.

Annulation of the five-membered oxazole ring in regioisomers **3** and **4** by the action of bromine or iodine was carried out in $CHCl_3$ according to a known procedure[14] (Scheme 3). It was established that in all cases, the reaction proceeded chemoselectively with practically quantitative yields of 2,3-dihydro[1,3]oxazolo[3,2-*a*]pyridinium halides **6**–**9**.

Scheme 3



The structure of halocyclization products **6**–**9** was confirmed by ^{1}H and ^{13}C NMR spectroscopy data, the full assignment of ^{1}H and ^{13}C signals was made on the basis of ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC experiment data. The presence of an asymmetric atom in molecules **6**–**9** leads to the non-equivalence of protons of the methylene groups; however, the values of the non-equivalence of chemical shifts differ significantly in regioisomers. The signals of sp^3-hybridized atoms C-2,3 and C-1' of the oxazole rings were assigned by the cross peaks in the ^{1}H–^{13}C HSQC spectra with methine protons and nonequivalent protons of methylene groups. Significant differences in chemical shifts of C-2,3 carbons allow identification of regioisomeric halocyclization products (Fig. 2).

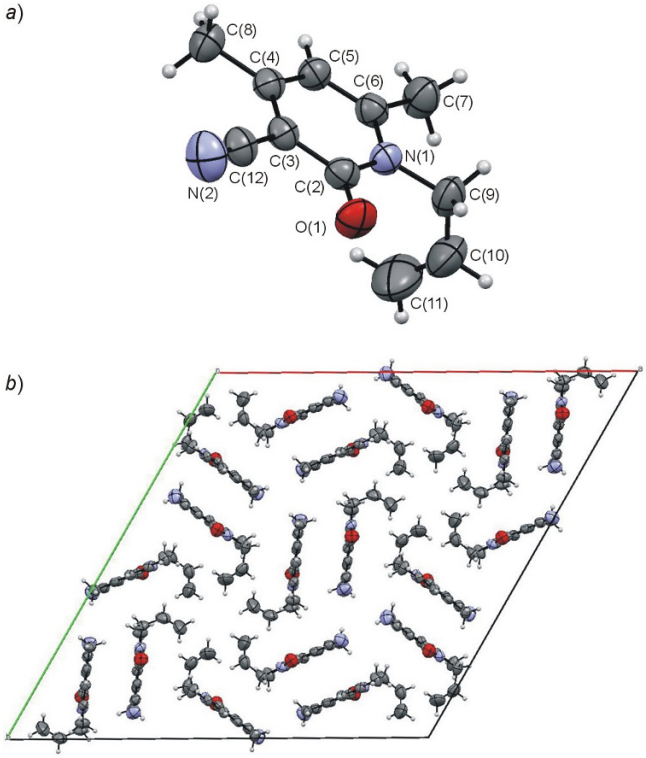


Figure 1. *a*) Molecular structure of compound **3** with atoms represented as thermal vibration ellipsoids of 50% probability. *b*) Fragment of the crystal packing of compound **3**.

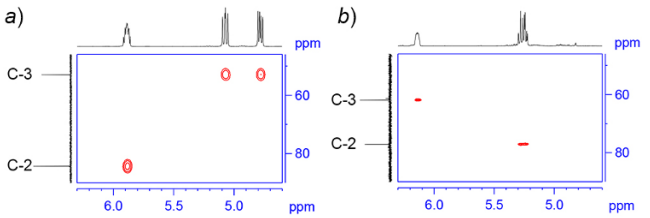
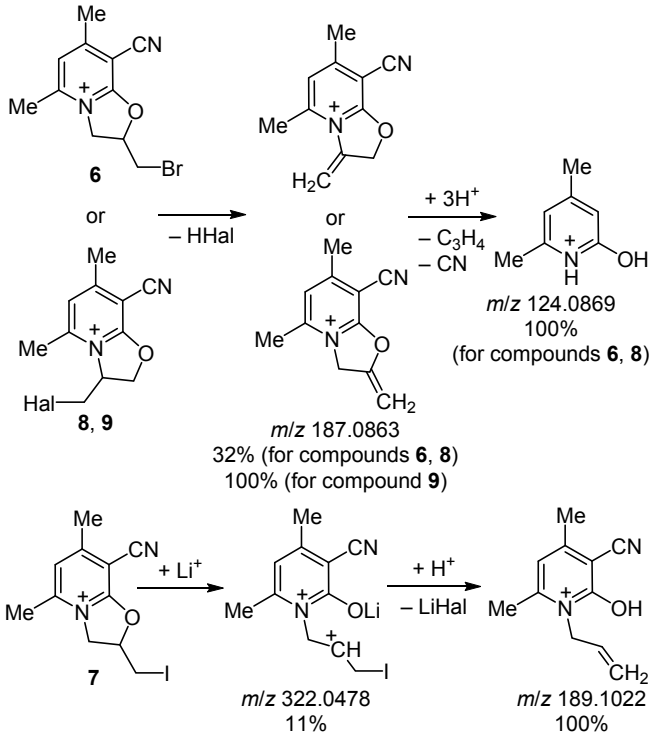


Figure 2. Fragments of ^{1}H–^{13}C HSQC (500 MHz, DMSO-d_6) spectra of regioisomeric products *a*) **6** and *b*) **8**.

A rather rare case of partial decyclization in DMSO-d_6 solution was recorded by us for triiodide **7**. Repeated registration of the ^{1}H NMR spectrum revealed the appearance and subsequent increase in the proton signal intensity of the original ketone **3** after several minutes. The high-resolution mass spectrum with an unusually low-intensity (0.4%) molecular ion peak $[M]^+$ with *m*/*z* 314.9985 shows a tendency for triiodide **7** to decyclize. Moreover, the composition of the characteristic peaks of fragment ions in the mass spectrum of compound **7** differs dramatically from that in the mass spectra of the three other halides **6**, **8**, and **9**. The most probable ion structures explaining this apparent difference are shown in Scheme 4. In addition, a noticeable increase in the C(2)–O(1) bond length, equal to 1.509 Å is observed in polyiodide **10** (Fig. 3) according to X-ray structural analysis, compared with 1.43 Å for the C–O bond in aliphatic compounds. On the contrary, the value 1.303 Å of the C(9)–O(1) bond length indicates its single-and-a-half character and the

conjugation of the oxygen atom with the double bond system of the heterocycle. The usual distance between the C and O atoms in the C=O groups is 1.21 Å.

Scheme 4



When allylpyridone **3** reacted with a twofold excess of I_2 in $CHCl_3$, triiodide **7** was formed, whereas with a threefold excess of I_2 in Me_2CO, 2-iodomethyl-2,3-dihydro-[1,3]oxazolo[3,2-*a*]pyridinium polyiodide **10** was produced with composition $2Cat^+[I_3^-\cdots I_2\cdots I_3^-]$ according to X-ray structural analysis data (Fig. 3). Compound **10** crystallizes in the centrosymmetric space group of the monoclinic system. When considering the iodine fragment in crystal **10**, one can distinguish centrosymmetric zigzags $[I(2)I(3)I(4)]^-\cdots I(5)I(5)\cdots[I(2)I(3)I(4)]^-$ (Fig. 3) in the form of a complex of two triiodide anions with molecular iodine. The atoms of each zigzag lay in the same plane, the zigzags are symmetric relating the center of the bond in the iodine molecule. The I(4)···I(5) distance is much larger (3.376 Å) than on the average is characteristic for isolated pentaiodide anions (3.147 Å).[17] Zigzag angle I(3)–I(4)–I(5) is 88.14°. Thus, the iodine molecule participates in the halogen bond, where the terminal atom of the triiodide anion acts as the donor of the electron density.

In the crystal lattice of compound **10** heterocyclic cations are combined into polymer chains through contacts between the nitrogen atom of the nitrile group of one molecule and the hydrogen atom of the methyl group at the C(5) atom of another molecule (2.519 Å) (Fig. 4).

To conclude, the allylation of 3-cyano-4,6-dimethyl-2-pyridone with allyl bromide occurs at the nitrogen and oxygen heteroatoms of the conjugated system. Competitive alkylation with a predominant addition at the nitrogen atom

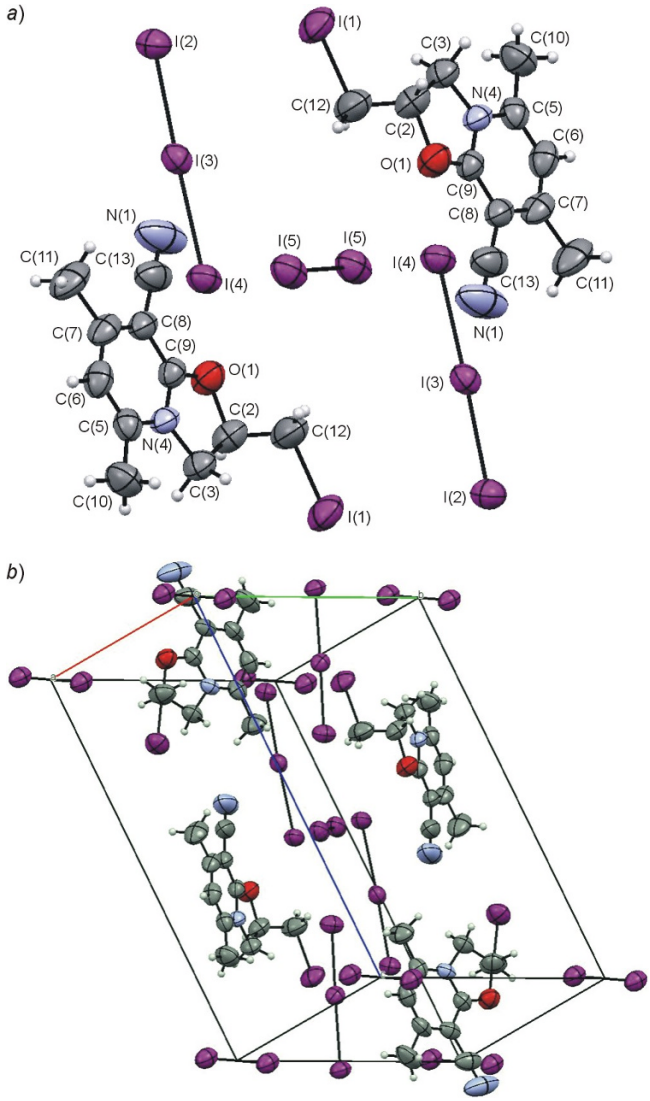


Figure 3. *a*) Molecular structure of compound **10** with atoms represented as thermal vibration ellipsoids with 50% probability. *b*) Fragment of the crystal packing of compound **10**.

leads to the formation of a mixture of regioisomeric 1-allyl-3-cyano-4,6-dimethyl-2-pyridone and 2-allyloxy-3-cyano-4,6-dimethylpyridine. In the case of 2-dicyanomethylidene-1,2-dihydropyridine-3-carbonitrile, the allylation reaction proceeds to form the C-isomer of 3-cyano-2-(1,1-dicyano)-but-3-enyl-4,6-dimethylpyridine. Subsequent bromo- or iodo-heterocyclization is chemoselective and is characterized by high yields of the target polycyclic compounds in the form of their salts.

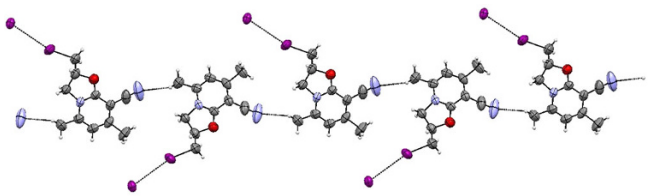


Figure 4. Formation of a pseudopolimer structure by cations of 2-iodomethyl-2,3-dihydro[1,3]oxazolo[3,2-*a*]pyridinium in a crystal of compound **10**.

Experimental

IR spectra were registered on a Spectrum One B PerkinElmer FT-IR spectrometer using a diffuse reflection attachment (compounds **3**, **4**, **6**–**9**) and an IRAffinity-1S Shimadzu spectrometer (compound **10**) in KBr pellets (4000–400 cm^{-1} range). ^1H and ^{13}C NMR spectra (500 and 126 MHz, respectively) were recorded on a Bruker Avance-500 spectrometer in DMSO-d_6. Internal standards were TMS (for ^1H nuclei) and solvent signal (39.5 ppm for ^{13}C nuclei). Complete assignment of ^1H and ^{13}C signals was done using the data of 2D ^1H–^{13}C HSQC and ^1H–^{13}C HMBC experiments. Mass spectrum for compound **1** was acquired on a QP-2010 Ultra Shimadzu GC-MS (EI ionization, 70 eV). HPLC MS/MS for compound **2** was recorded on an Agilent 1260 LC with a tandem mass spectrometer Agilent 6460 (dynamic MRM mode with electrospray ionization). High-resolution mass spectra were recorded with electrospray ionization for ions of positive polarity on a qTOF maXis Impact HD Bruker Daltonics super-high resolution mass spectrometer with standard ionization source in 50–2500 Da mass range, flow injection analysis mode. All data was collected and processed in the software package Compass for oTof series 1.7 (oTOF Control 3.4, Bruker Compass DataAnalysis 4.2). Elemental analysis was performed on a Carlo Erba EA-1108 Elemental Analyzer. Melting points were determined on a Boetius heating bench.

Synthesis of 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1) and (3-cyano-4,6-dimethylpyridin-2-(1*H*)-ylidene)propanedinitrile (2). A mixture of acetylacetone (2.00 g, 20 mmol) and malononitrile (1.30 g, 20 mmol) in MeOH (30 ml) was stirred magnetically and heated under reflux for 7 h. After the completion of the process, the reaction mixture was transferred to a cup, and the solvent was left to evaporate in air. The reaction mixture was separated by column chromatography on SiO_2, eluents $CHCl_3$–hexane, 3:2, at the final stage of chromatography pure $CHCl_3$. Three major fractions were collected. According to ^1H NMR data, the first fraction contained the starting materials, the second fraction contained product **2**, the third fraction contained product **1**. Physical characteristics of compounds **1**, **2** matched the literature data.

4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1).[11] Yield 2.53 g (86%), colorless crystals, mp 287–289°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.22 (3H, s, 4-CH_3); 2.29 (3H, s, 6-CH_3); 6.16 (1H, s, H-5); 12.31 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 148 $[M]^+$ (100), 121 (4), 120 (46), 119 (82), 105 (18), 93 (5), 92 (6), 80 (3), 79 (3), 78 (14), 77 (5), 76 (5), 67 (4), 66 (7), 65 (8), 64 (5), 63 (4), 53 (3), 52 (8), 51 (11), 50 (3), 42 (16), 41 (6), 40 (3), 39 (12), 38 (4).

(3-Cyano-4,6-dimethylpyridin-2(1*H*)-ylidene)propanedinitrile (2).[12] Yield 0.08 g (2%), colorless crystals, mp 253–255°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, 4-CH_3); 2.41 (3H, s, 6-CH_3); 6.72 (1H, s, H-5); 12.37 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 197 $[M+H]^+$ (100).

Allylation of 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1). A mixture of K_2CO_3 (2.07 g, 15 mmol) and cyanopyridone **1** (1.48 g, 10 mmol) in MeCN (8 ml) was heated under reflux for 15 min. Then a solution of 3-bromo-1-propene (1.3 ml, 15 mmol) in MeCN (3 ml) was added, and the mixture was heated under reflux for 10 h. After cooling, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The combined yield of *N*- and *O*-isomers **3**, **4** was 1.23 g (65%). The mixture of *N*- and *O*-isomers were separated by column chromatography on SiO_2, eluent EtOAc–hexane, 1:3.

4,6-Dimethyl-2-oxo-1-(prop-2-en-1-yl)-1,2-dihydropyridine-3-carbonitrile (3). Yield 0.91 g (48%), colorless crystals, mp 112–113°C (EtOAc). IR spectrum, ν, cm^{-1}: 780, 860 (Ar); 900, 986, 1006, 1039, 1075, 1190, 1204, 1290, 1347, 1420, 1544, 1582, 1642 (δ, C=C, C=N, C=O); 2220 (CN); 2956 (δ, C(Alk)–H); 3049, 3088 (δ, C(Ar)–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, 4-CH_3); 2.40 (3H, s, 6-CH_3); 4.65 (2H, dt, *J* = 4.9, *J* = 1.7, 1'-CH_2); 4.93–4.98 (1H, m, 3'-CH); 5.14–5.18 (1H, m, 3'-CH); 5.91 (1H, ddt, *J* = 17.3, *J* = 10.4, *J* = 4.9, 2'-CH); 6.34 (1H, s, H-5); ^{13}C NMR spectrum, δ, ppm: 19.9 (6-CH_3); 20.4 (4-CH_3); 46.0 (C-1'); 99.1 (C-3); 109.1 (C-5); 116.0 (CN); 116.4 (C-3'); 131.9 (C-2'); 152.5 (C-6); 158.5 (C-4); 160.0 (C-2). Found, *m*/*z*: 189.1021 $[M+H]^+$. $C_{11}H_{13}N_2O$. Calculated, *m*/*z*: 189.1028. Found, %: C 70.21; H 6.42; N 14.90. $C_{11}H_{12}N_2O$. Calculated, %: C 70.19; H 6.43; N 14.88.

4,6-Dimethyl-2-(prop-2-en-1-yloxy)pyridine-3-carbonitrile (4). Yield 0.32 g (17%), colorless crystals, mp 30–31°C (hexane). IR spectrum, ν, cm^{-1}: 766, 843 (Ar); 934, 988, 1016, 1111, 1155, 1284, 1339, 1416, 1436, 1455, 1567, 1596 (δ, C=C, C=N); 2224 (CN); 2926 (δ, C(Alk)–H); 3096 (δ, C(Ar)–H). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.41 (3H, s, 4-CH_3); 2.42 (3H, s, 6-CH_3); 4.91 (2H, dt, *J* = 5.3, *J* = 1.6, 1'-CH_2); 5.27 (1H, dq, *J* = 10.5, *J* = 1.6, 3'-CH); 5.42 (1H, dq, *J* = 17.3, *J* = 1.6, 3'-CH); 6.08 (1H, ddt, *J* = 17.3, *J* = 10.5, *J* = 5.3, 2'-CH); 6.97 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 19.5 (4-CH_3); 24.1 (6-CH_3); 66.7 (C-1'); 92.9 (C-3); 114.7 (CN); 117.8 (C-3'); 118.0 (C-5); 132.9 (C-2'); 154.8 (C-4); 160.5 (C-6); 162.7 (C-2). Found, *m*/*z*: 189.1021 $[M+H]^+$. $C_{11}H_{13}N_2O$. Calculated, *m*/*z*: 189.1028. Found, %: C 70.18; H 6.46; N 14.86. $C_{11}H_{12}N_2O$. Calculated, %: C 70.19; H 6.43; N 14.88.

(3-Cyano-4,6-dimethylpyridin-2-yl)(prop-2-en-1-yl)-propanedinitrile (5). A mixture of K_2CO_3 (0.02 g, 0.015 mmol) and cyanopyridine **2** (0.03 g; 0.015 mmol) in MeCN (8 ml) was heated under reflux for 15 min. Then, a solution of 3-bromo-1-propene (1.3 ml, 15 mmol) in MeCN (3 ml) was added, and the mixture was heated under reflux for 10 h. After cooling, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The product was purified by column chromatography on SiO_2, eluent hexane–$CHCl_3$, 4:1. Yield 0.02 g (55%), yellow oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.57 (3H, s, 4-CH_3); 2.58 (3H, s, 6-CH_3); 3.28–3.36 (2H, m, 2'-CH_2); 5.39–5.40 (1H, m, 4'-CH); 5.43–5.45 (1H, m, 4'-CH); 5.84 (1H, ddt, *J* = 17.0, *J* = 10.0, *J* = 7.2, 3'-CH); 7.64 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 20.1 (4-CH_3); 24.1 (6-CH_3); 41.1 (C-2'); 44.9 (C-1'); 105.0 (C-3); 113.0 (2CN); 113.8 (CN); 123.7 (C-4'); 125.8 (C-5); 128.8 (C-3'); 150.1 (C-2); 154.9 (C-4); 161.9 (C-6). Found, *m*/*z*: 237.1134 $[M+H]^+$.

$C_{14}H_{13}N_4$. Calculated, *m*/*z*: 237.1140. Found, %: C 71.20; H 5.11; N 23.73. $C_{14}H_{12}N_4$. Calculated, %: C 71.17; H 5.12; N 23.71.

Bromocyclization of ketone 3 and ether 4. A solution of Br_2 (0.027 ml, 0.54 mmol) in $CHCl_3$ (2 ml) was added dropwise with stirring and cooling to a solution of ketone **3** (0.050 g, 0.27 mmol) or ether **4** (0.075 g, 0.4 mmol) in $CHCl_3$ (2 ml). The formed mixture was stirred at room temperature for 1 day. The formed precipitate was filtered off. The product was recrystallized from MeCN or EtOAc.

2-Bromomethyl-8-cyano-5,7-dimethyl-2,3-dihydro-[1,3]oxazolo[3,2-*a*]pyridinium bromide (6). Yield 0.091 g (98%), colorless crystals, mp 226–228°C (MeCN). IR spectrum, ν, cm^{-1}: 739, 805 (Ar); 887, 909, 992, 1029, 1080, 1114, 1230, 1254, 1271, 1297, 1369, 1414, 1430, 1470, 1519, 1574, 1656 (δ, C=C, C=N); 2246 (CN); 2936 (δ, C(Alk)–H); 3000 (δ, C(Ar)–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.69 (3H, s, 7-CH_3); 2.73 (3H, s, 5-CH_3); 4.08 (1H, dd, *J* = 11.4, *J* = 5.9, 1'-CH_2); 4.11 (1H, dd, *J* = 11.4, *J* = 4.7, 1'-CH_2); 4.78 (1H, dd, *J* = 12.5, *J* = 7.1, 3-CH_2); 5.07 (1H, dd, *J* = 12.5, *J* = 9.6, 3-CH_2); 5.89 (1H, dddd, *J* = 9.6, *J* = 7.1, *J* = 5.9, *J* = 4.7, 2-CH); 7.65 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 19.2 (7-CH_3); 21.1 (5-CH_3); 32.2 (C-1'); 53.0 (C-3); 84.4 (C-2); 92.7 (C-8); 110.9 (CN); 121.2 (C-6); 153.7 (C-5); 160.9 (C-8a); 164.3 (C-7). Found, *m*/*z*: 267.0122 $[M–Br]^+$. $C_{11}H_{12}BrN_2O$. Calculated, *m*/*z*: 267.0133. Found, %: C 37.93; H 3.52; N 8.04. $C_{11}H_{12}Br_2N_2O$. Calculated, %: C 37.96; H 3.48; N 8.05.

3-Bromomethyl-8-cyano-5,7-dimethyl-2,3-dihydro-[1,3]oxazolo[3,2-*a*]pyridinium bromide (8). Yield 0.090 g (97%), colorless crystals, mp 196–198°C (EtOAc). IR spectrum, ν, cm^{-1}: 742, 765, 867 (Ar); 888, 912, 980, 1029, 1074, 1105, 1215, 1263, 1287, 1309, 1334, 1371, 1456, 1515, 1566, 1645 (δ, C=C, C=N); 2250 (CN); 2960 (δ, C(Alk)–H); 3020, 3056 (δ, C(Ar)–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.71 (3H, s, 7-CH_3); 2.87 (3H, s, 5-CH_3); 4.12 (1H, dd, *J* = 12.0, *J* = 2.2, 1'-CH_2); 4.21 (1H, dd, *J* = 12.0, *J* = 4.5, 1'-CH_2); 5.23 (1H, dd, *J* = 9.5, *J* = 4.0, 2-CH_2); 5.25 (1H, dd, *J* = 9.5, *J* = 8.4, 2-CH_2); 5.89 (1H, dtd, *J* = 8.4, *J* = 4.2, *J* = 2.2, 3-CH); 6.08 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 18.9 (5-CH_3); 21.3 (7-CH_3); 33.2 (C-1'); 61.9 (C-3); 77.1 (C-2); 93.4 (C-8); 110.8 (CN); 122.1 (C-6); 153.4 (C-5); 162.0 (C-8a); 165.5 (C-7). Found, *m*/*z*: 267.0124 $[M–Br]^+$. $C_{11}H_{12}BrN_2O$. Calculated, *m*/*z*: 267.0133. Found, %: C 37.99; H 3.45; N 8.07. $C_{11}H_{12}Br_2N_2O$. Calculated, %: C 37.96; H 3.48; N 8.05.

Iodocyclization of ketone 3 and ether 4. A solution of I_2 (0.135 g, 0.54 mmol) in $CHCl_3$ (2 ml) was added to a solution of ketone **3** (0.050 g, 0.27 mmol) or ether **4** (0.075 g, 0.4 mmol) in $CHCl_3$ (2 ml). The obtained mixture was stirred at room temperature for 1 day. The formed precipitate was filtered off. The product was recrystallized from EtOAc.

8-Cyano-2-iodomethyl-5,7-dimethyl-2,3-dihydro[1,3]-oxazolo[3,2-*a*]pyridinium triiodide (7). Yield 0.166 g (90%), pale purple-gray crystals, mp 123–125°C (EtOAc). IR spectrum, ν, cm^{-1}: 736, 810 (Ar); 859, 975, 1027, 1071, 1109, 1174, 1235, 1269, 1330, 1371, 1426, 1463, 1513, 1566, 1645 (δ, C=C, C=N); 2243 (CN); 2979 (δ, C(Alk)–H); 3060 (δ, C(Ar)–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.69 (3H, s, 7-CH_3); 2.72 (3H, s, 5-CH_3); 3.73 (1H, dd, *J* = 10.6, *J* = 6.2, 1'-CH_2); 3.76 (1H, dd, *J* = 10.5, *J* = 6.2, 1'-CH_2); 4.64 (1H, dd, *J* = 12.5, *J* = 7.2, 3-CH_2); 5.03 (1H, dd, *J* = 12.5, *J* = 9.4, 3-CH_2); 5.75 (1H, ddt, *J* = 9.4, *J* = 7.2, *J* = 6.2, 2-CH); 7.60 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 4.1 (C-1'); 19.1 (5-CH_3); 21.2 (7-CH_3); 54.2 (C-3); 85.0 (C-2); 92.8 (C-8); 110.9 (CN); 121.0 (C-6); 153.6 (C-5); 160.8 (C-8a); 164.3 (C-7). Found, *m*/*z*: 314.9985 $[M–I_3]^+$. $C_{11}H_{12}IN_2O$. Calculated, *m*/*z*: 314.9994. Found, %: C 18.95; H 1.76; N 4.02. $C_{11}H_{12}I_4N_2O$. Calculated, %: C 18.99; H 1.74; N 4.03.

8-Cyano-3-iodomethyl-5,7-dimethyl-2,3-dihydro[1,3]-oxazolo[3,2-*a*]pyridinium triiodide (9). Yield 0.176 g (98%), pale purple-gray crystals, mp 147–149°C (EtOAc). IR spectrum, ν, cm^{-1}: 753, 839 (Ar); 887, 979, 1024, 1064, 1102, 1184, 1223, 1255, 1282, 1321, 1332, 1367, 1425, 1453, 1510, 1557, 1641 (δ, C=C, C=N); 2242 (CN); 2948 (δ, C(Alk)–H); 3010, 3052 (δ, C(Ar)–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.70 (3H, s, 7-CH_3); 2.83 (3H, s, 5-CH_3); 3.81 (1H, dd, *J* = 11.8, *J* = 3.2, 1'-CH_2); 3.84 (1H, dd, *J* = 11.8, *J* = 5.2, 1'-CH_2); 5.09 (1H, dd, *J* = 9.6, *J* = 3.5, 2-CH_2); 5.22 (1H, т, *J* = 9.2, 2-CH_2); 5.78–5.82 (1H, m, 3-CH); 7.66 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 6.0 (C-1'); 18.7 (5-CH_3); 21.3 (7-CH_3); 61.8 (C-3); 78.5 (C-2); 93.5 (C-8); 110.8 (CN); 122.1 (C-6); 153.1 (C-5); 161.7 (C-8a); 165.3 (C-7). Found, *m*/*z*: 314.9988 $[M–I_3]^+$. $C_{11}H_{12}IN_2O$. Calculated, *m*/*z*: 314.9994. Found, %: C 19.02; H 1.73; N 4.07. $C_{11}H_{12}I_4N_2O$. Calculated, %: C 18.99; H 1.74; N 4.03.

8-Cyano-2-iodomethyl-5,7-dimethyl-2,3-dihydro[1,3]-oxazolo[3,2-*a*]pyridinium triiodide (10). A solution of I_2 (0.405 g, 1.60 mmol) in Me_2CO (3 ml) was added to a solution of ketone **3** (0.100 g, 0.53 mmol) in Me_2CO (3 ml); and the mixture was stirred at room temperature. After 24 h, Et_2O (10 ml) was added to the mixture. The formed precipitate was filtered off and dried. Yield 0.244 g (56%), purple-gray crystals, mp 99–101 °C. IR spectrum, ν, cm^{-1}: 737, 808 (Ar); 858, 974, 1024, 1070, 1107, 1170, 1234, 1269, 1327, 1368, 1427, 1462, 1512, 1564, 1643 (δ, C=C, C=N); 2241 (CN); 2978 (δ, C(Alk)–H); 3057 (δ, C(Ar)–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.69 (3H, s, 7-CH_3); 2.72 (3H, s, 5-CH_3); 3.73 (1H, dd, *J* = 10.6, *J* = 6.3, 1'-CH_2); 3.76 (1H, dd, *J* = 10.6, *J* = 6.0, 1'-CH_2); 4.64 (1H, dd, *J* = 12.4, *J* = 7.4, 3-CH_2); 5.04 (1H, dd, *J* = 12.4, *J* = 9.4, 3-CH_2); 5.75 (1H, ddt, *J* = 9.4, *J* = 7.2, *J* = 6.3, 2-CH); 7.60 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 4.2 (C-1'); 19.1 (5-CH_3); 21.2 (7-CH_3); 54.2 (C-3); 84.9 (C-2); 92.9 (C-8); 110.9 (CN); 121.1 (C-6); 153.6 (C-5); 160.8 (C-8a); 164.3 (C-7). Found, %: C 16.01; H 1.43; N 3.43. $C_{11}H_{12}I_5N_2O$. Calculated, %: C 16.06; H 1.47; N 3.40.

X-ray structural analysis of compounds 3 and 10. X-ray structural analysis of compound **3** was performed on an automatic 4-circle Xcalibur 3 diffractometer according to the standard routine (MoKα radiation (λ 0.71073 Å), graphite monochromator, ω-scanning with 1° step at 295(2) K). Empirical absorption correction was introduced. Solving and refinement of the structure was carried out using Olex2

program.[18] The structure was solved with the direct method by SHELXS program and refined against F^2 by the least-squares technique in the full-matrix anisotropic approximation for all non-hydrogen atoms by SHELXL program.[19] Hydrogen atom positions were calculated geometrically and refined according to the "rider" model. The main crystallographic parameters after the refinement of the structure: trigonal crystal, spatial symmetry group *R*3; *a* 27.1795(15), *c* 7.2973(4) Å; *V* 4668.5(5) Å^3; for a substance with empirical formula $C_{11}H_{12}N_2O$ *Z* 18; μ 0.079 mm^{-1}. Reflections (4620) were collected at the scattering angles $5.2 < 2\theta < 56.52°$, 2576 were independent (R_{int} 0.0247). R_1 0.0538, wR_2 0.1473 over reflections with $I > 2\sigma(I)$, R_1 0.1096, wR_2 0.1879 over all reflections, with the quality factor over F^2 1.000, $\Delta\rho_{max}/\Delta\rho_{min}$ 0.24/–0.15 e·Å^{-3}. The full set of X-ray structural data for compound **3** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1905628).

X-ray structural analysis of compound **10** was performed on an automatic 4-circle D8 QUEST Bruker diffractometer (MoKα radiation (λ 0.71073 Å), graphite monochromator at 296(2) K. The collection, editing of data, refinement of the parameters of the unit cell, as well as absorption correction were performed using SMART and SAINT-Plus programs.[20] All calculations of solving and refinement of the structure was carried out using SHELXL/PC[21] and OLEX2[18] programs. The structure was solved with the direct method and refined by the least-squares technique in anisotropic approximation for all non-hydrogen atoms. Complete tables of atomic coordinates, bond lengths, and bond angles for compound **10** were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1905739).

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