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SYNTHESIS OF SOME FUNCTIONALIZED PYRIDONES DERIVATIVES

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It was established formation of new substituted pyridone derivativesin terms of addition reaction according to Michael with the participation of 2-cyano-3-(4-pyridul) acrylamide and benzoylacetone or ethyl alcohol in ether of acatecetic acid in the presence (MP) in methanol medium. The boiling of ethyl 5-cyano-2-hydroxy-2-methyl-6-oxo-4-phenylpiperidine-3-carboxylate in ethanole during 4 hours followed by dehydration and dehydrogenation (by air oxidation) generated 5-cyano-2-methyl -6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid. Under similar conditions there were synthesized appropriate products of substituted pyridone according to Michael' addition reaction through interacting of 4-bromobenzoylacetonitrile with 2-cyano-3-(2-fluorophenyl)acrylamide. Structures of all synthesized compounds were proven by NMR spectroscopy.

Keywords: *2-cyano-3-(4-pyridyl)acrylamide, fluorobenzylidenecyanoacetamide, 4-chloroacetoacetate, 4-bromobenzoylacetonitrile*

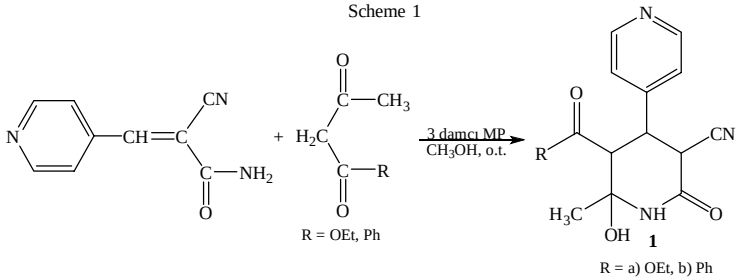
Introduction

2-Pyridone, tatomer of 2-hydroxypyridine, is one of the major heteroaromatic rings in natural products, bioactive molecules and pharmaceutical ingredients. Ciclopirox, milrinone, camptothecin, (-)-citisin, fredericamycin, perampanel, bioactive molecules and pharmaceutical ingredients contain valuable pyridone fragments in their composition. Also, synthesis methods of these compounds are different from in reaction conditions in literature [1-12]. Some articles [13-17] research into antimicrobial activity of pyridone derivatives.

Results and discussion

In the presence of methylpiperazine and methanol medium according to Michael addition reaction of benzoilacetone or ethyl acetoacetate, 2-cyano-3-(pyridine-4-yl) acrylamide at a room temperature was hydroxysubsituted pyridone derivatives.

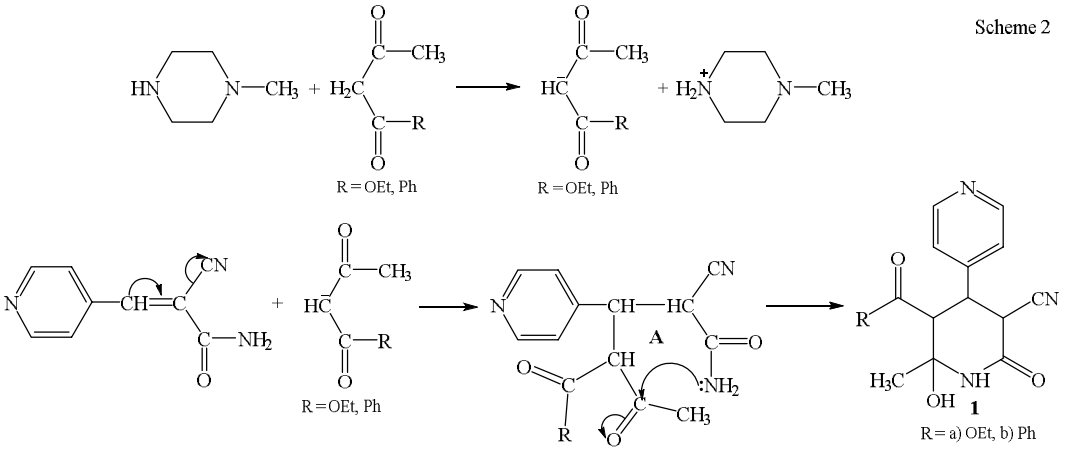
Scheme 1



Scheme 1. Reaction of 2-cyano-3-(4-pyridyl)acrylamide with benzoylacetone and ethyl acetoacetate.

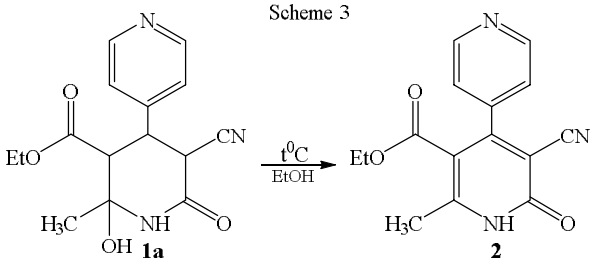
In our view, in the initial step of reaction the nucleophilic attack methylpiperazine to methylene-active compound results in the formation of corresponding anion (nucleophilic particle), which, in turn, drew to the CH-electrophilic center of the activated double bound to form intermediate **A** (according to Michael adduct). In the final step, in the intermediate **A**, the amide nitrogen attacked the carbonyl group to generate a desired ring closure product – pyridione (Scheme 2).

Scheme 2



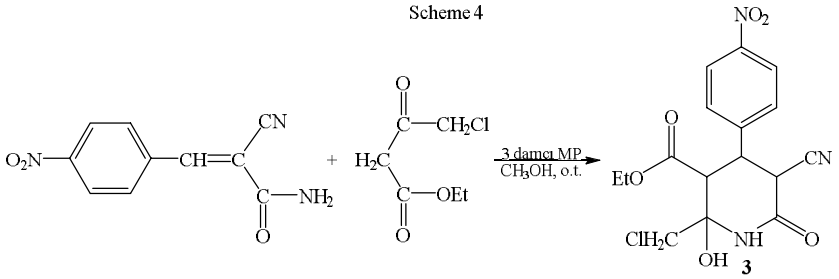
Boiling of ethyl 5-cyano-2-hydroxy-2-methyl-6-oxo-4-phenylpiperidine-3-carboxylate in ethanole for 4 hours was followed by dehydration and dehydrogenation (by air oxidation) to provide 5-cyano-2-methyl -6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid.

Scheme 3



Scheme 2. Synthesis of ethyl 5-cyano-2-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylat

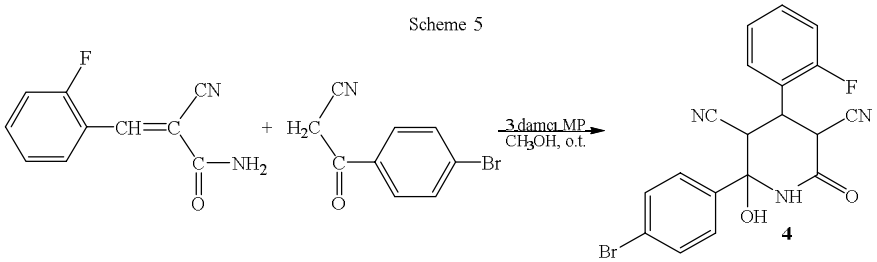
Scheme 4



Scheme 3. Reaction of 2-cyano-3-(4-nitrophenyl)acrylamide with ethyl 4-chloroacetoacetate.

Under the same reaction condition, the Michael addition of 4-bromobenzoylacetonitrile to 2-cyano-3-(2-fluorophenyl) acrylamide led to the formation of appropriate hydroxy substituted pyridone derivatives.

Scheme 5



Scheme 4. Reaction of 2-cyano-3-(2-fluorophenyl)acrylamide with 4-bromobenzoylacetonitrile.

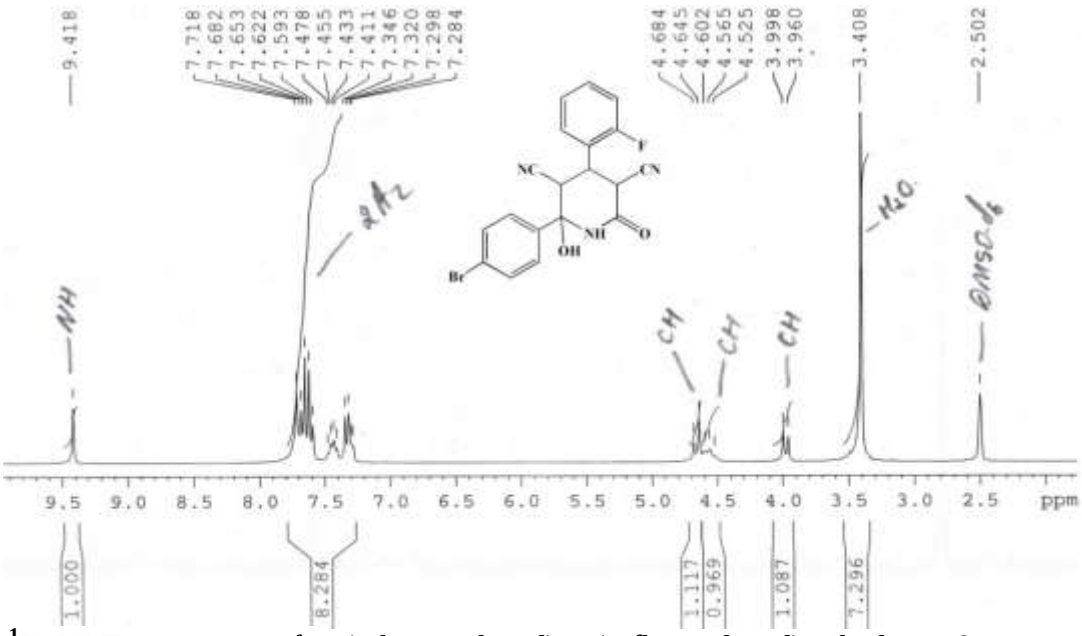


Fig.1. [1]H NMR spectrum of 2-(4-bromophenyl)-4-(2-fluorophenyl)-2-hydroxy-6-oxopiperidine-3,5-dicarbonitrile (**4**)

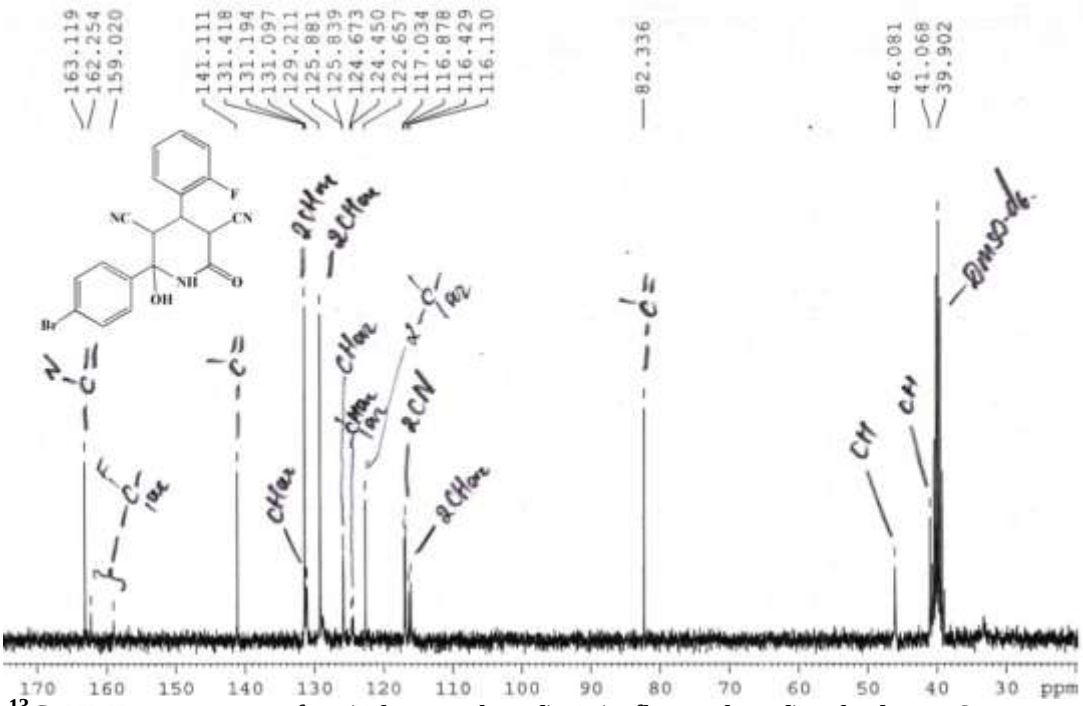


Fig.2. [13]C NMR spectrum of 2-(4-bromophenyl)-4-(2-fluorophenyl)-2-hydroxy-6-oxopiperidine-3,5-dicarbonitrile (**4**)

Experimental part. General remarks

All commercially available chemicals were obtained from Merck and Fluka (Sigma Aldrich) companies and used without further purification. Melting points were measured by Stuart SMP30 apparatus without correction. ^{1}H, ^{13}C NMR spectra (Fig.1) were recorded on BrukerAvance 300-MHz spectrometer at 300 and 75 MHz, respectively. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254) was used to monitor the reaction course.

Experimental procedures:

Ethyl 5-cyano-2-hydroxy-2-methyl-6-oxo-4-(pyridin-4-yl)piperidine-3-carboxylate (1a): 2-Cyano-3-(4-pyridyl)acrylamide (5.1 mmol) and ethyl acetoacetate (5.2 mmol) was stirred in 35 ml of methyl alcohol. Then 3-4 drops of 1-methylpiperazine were added to reaction mixture and stirred for 5 minutes. Then reaction mixture was held out at a room temperature for 48 h. Reaction course was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.27 g, 82.47%). $T_{mp.}$ = 173°C.

^{1}H NMR (300 MHz, DMSO-d_6): 0.84 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7); 1.47 (s, 3H, CH_3); 3.44 (d, 1H, CH, $^3J_{H\text{-}H}$ = 12.4); 3.82 (k, 2H, CH_2O, $^3J_{H\text{-}H}$ = 6.9); 3.92 (t, 1H, CH−Ar, $^3J_{H\text{-}H}$ = 12.3); 4.31 (d, 1H, CH, $^3J_{H\text{-}H}$ = 12.6); 6.27 (s, 1H, OH); 7.39 (d, 2H, $2CH_{pyrid.}$, $^3J_{H\text{-}H}$ = 5.1); 8.55 (d, 2H, $2CH_{pyrid.}$, $^3J_{H\text{-}H}$ = 5.1); 8.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 14.02 (CH_3CH_2), 28.34 (CH_3), 40.41 (CH−CN), 41.44 (CH−Ar), 54.24 (CH−CO_2), 60.64 (CH_2O), 80.72 (O−$C_{dördlü}$), 117.29 (CN), 123.85 ($2CH_{pyrid.}$), 148.63 ($C_{pyrid.}$), 150.33 ($2CH_{pyrid.}$), 162.56 (N−C=O), 168.58 (O−C=O).

Found, %: 59.35 C; 5.67 H; 13.81 N. $C_{15}H_{17}N_3O_4$. Calculated, %: 59.40 C; 5.61 H; 13.86 N.

5-Benzoyl-6-hydroxy-6-methyl-2-oxo-4-(pyridin-4-yl)piperidine-3-carbonitrile (1b): 2-Cyano-3-(4-pyridyl)acrylamide (5.1 mmol) and benzoylacetone (5.2 mmol) was stirred in 35 ml of methyl alcohol. After 3-4 drops of 1-methylpiperazine added to reaction mixture and stirred for 5 minutes. Then reaction mixture was held out at a room temperature for 48 h. Reaction course was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.32 g, 77.65%). $T_{mp.}$ = 192°C.

^{1}H NMR (300 MHz, DMSO-d_6): 1.35 (s, 3H, CH_3); 3.86 (t, 1H, CH−Ar, $^3J_{H\text{-}H}$ = 11.4); 4.60 (d, 1H, CH, $^3J_{H\text{-}H}$ = 12.3); 4.68 (d, 1H, CH, $^3J_{H\text{-}H}$ = 11.1); 6.46 (s, 1H, OH); 7.44-8.44 (m, 9H, 5Ar−H+$4CH_{pyrid.}$); 8.84 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 27.01 (CH_3), 40.78 (CH−CN), 42.98 (CH−Ar), 55.15 (CH−C=O), 82.86 (O−$C_{dördlü}$), 117.26 (CN), 123.83 ($2CH_{arom.}$), 129.04 ($2CH_{pirid.}$), 129.14 ($2CH_{arom.}$), 134.09 ($CH_{arom.}$), 138.17 ($C_{ar.}$), 148.52 ($C_{pyrid.}$), 150.25 ($2CH_{pyrid.}$), 162.43 (N−C=O), 199.23 (C=O).

Found, %: 68.00 C; 5.02 H; 12.60 N. $C_{19}H_{17}N_3O_3$. Calculated, %: 68.06 C; 5.07 H; 12.54 N.

Ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydro-[4,4'-bipyridine]-3-carboxylate (2): Ethyl 5-cyano-2-hydroxy-2-methyl-6-oxo-4-(pyridin-4-yl)piperidine-3-carboxylate (5.1 mmol) was dissolved in 35 ml of ethyl alcohol and 5 h refluxed. Then the resulting reaction mixture was placed in a glass. Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.07 g, 74.30%). $T_{mp.}$ = 147°C.

^{1}H NMR (300 MHz, DMSO-d_6): 0.70 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2); 2.45 (s, 3H, CH_3); 3.83 (k, 2H, CH_2O, $^3J_{H\text{-}H}$ = 7); 7.36 (d, 2H, $2CH_{pyrid.}$, $^3J_{H\text{-}H}$ = 5.1); 8.71 (d, 2H, $2CH_{pyrid.}$, $^3J_{H\text{-}H}$ = 5.1); 12.82 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 13.37 (CH_3CH_2), 19.13 (CH_3−C=), 61.43 (CH_2O), 101.07 (=$C_{dördlü}$), 111.09 (=$C_{dördlü}$), 115.42 (CN), 122.35 ($2CH_{pyrid.}$), 144.51 ($C_{pyrid.}$), 150.25 ($2CH_{pyrid.}$), 155.45 (=$C_{dördlü}$), 157.53 (=$C_{dördlü}$), 160.00 (N−C=O), 164.64 (O−C=O).

Found, %: 63.55 C; 4.65 H; 14.89 N. $C_{15}H_{13}N_3O_3$. Calculated, %: 63.60 C; 4.59 H; 14.84 N.

Ethyl 2-(chloromethyl)-5-cyano-2-hydroxy-4-(4-nitrophenyl)-6-oxopiperidine-3-carboxylate (3): 2-Cyano-3-(4-nitrophenyl)acrylamide (5.1 mmol) and ethyl 4-chloroacetoacetate (5.2 mmol) stirred in 35 ml of methyl alcohol. After 3-4 drops of 1-methylpiperazine added to reaction mixture and stirred for 5 minutes. Then reaction mixture hold out at room temperature

for 48 h. Reaction course was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.57 g, 80.51%). $T_{mp.}$ = 209°C.

^{1}H NMR (300 MHz, DMSO-d_6): 0.86 (t, 3H, CH_3, $^3J_{H-H}$ = 6.9); 3.68 (d, 1H, CH, $^3J_{H-H}$ = 12.3); 3.69 (s, 3H, $\underline{CH_2}Cl$); 3.85 (k, 2H, CH_2O, $^3J_{H-H}$ = 7); 4.10 (t, 1H, $\underline{CH}$−Ar, $^3J_{H-H}$ = 12.3); 4.63 (d, 1H, CH, $^3J_{H-H}$ = 12); 7.12 (s, 1H, OH); 7.70 (d, 2H, $2CH_{arom.}$, $^3J_{H-H}$ = 8.4); 8.24 (d, 2H, $2CH_{arom.}$, $^3J_{H-H}$ = 8.4); 9.10 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 13.97 ($\underline{CH_3}CH_2$), 40.13 ($\underline{CH}$−CN), 41.31 ($\underline{CH}$−Ar), 48.16 ($\underline{CH_2}Cl$), 49.80 ($\underline{CH}$−COO), 61.06 ($\underline{CH_2}O$), 83.03 (O−$\underline{C_{dördlü}}$), 117.01 (CN), 124.13 ($3CH_{arom.}$), 130.21 ($CH_{arom.}$), 147.10 ($C_{ar.}$), 147.47 ($C_{ar.}$), 163.30 (N−$\underline{C}$=O), 167.71 (O−$\underline{C}$=O).

Found, %: 50.39 C; 4.14 H; 11.07 N. $C_{16}H_{16}N_3O_6Cl$. Calculated, %: 50.33 C; 4.19 H; 11.02 N.

2-(4-Bromophenyl)-4-(2-fluorophenyl)-2-hydroxy-6-oxopiperidine-3,5-dicarbonitrile (4): 2-Cyano-3-(2-fluorophenyl)prop-2-enamide (5.1 mmol) and 4-bromobenzoylacetonitrile (5.2 mmol) stirrered in 35 ml of methyl alcohol. After 3-4 drops of 1-methylpiperazine were added to reaction mixture and stirrered for 5 minutes. Then reaction mixture were held out at a room temperature for 48 h. Reaction course was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of solvent, filtered, recrystallized from ethanol-water mixture and obtained in pure form (yield 1.77 g, 84.28%). $T_{mp.}$ = 121°C.

^{1}H NMR (300 MHz, DMSO-d_6): 3.98 (d, 1H, CH, $^3J_{H-H}$ = 11.4); 4.56 (t, 1H, CH, $^3J_{H-H}$ = 11.5); 4.66 (d, 1H, CH, $^3J_{H-H}$ = 11.7); 7.28-7.72 (m, 8H, 8Ar−H+OH); 9.42 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 39.90 ($\underline{CH}$−CN), 41.07 ($\underline{CH}$−Ar), 46.08 ($\underline{CH}$−CN), 82.34 (O−$\underline{C_{dördlü}}$), 116.13 (CH_{arom}), 116.43 (CH_{arom}), 116.88 (CN), 117.03 (CN), 122.66 (Br−$\underline{C_{ar.}}$), 124.45-124.67 ($C_{ar.}$), 125.88 (CH_{arom}), 129.21 ($2CH_{arom}$), 131.10-131.19 (CH_{arom}), 131.42 ($2CH_{arom}$), 141.11 ($C_{ar.}$), 159.02-162.25 (F−$\underline{C_{ar}}$), 163.12 (N−$\underline{C}$=O).

Found, %: 55.01 C; 3.20 H; 10.09 N. $C_{19}H_{13}N_3FBrO_2$. Calculated, %: 55.07 C; 3.14 H; 10.14 N.

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BƏZİ FUNKSİONALLAŞMIŞ PİRİDON TÖRƏMƏLƏRİNİN SİNTEZİ

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Metanol mühitində, metilpiperazinin (MP) iştirakında və otaq temperaturunda 2-siano-3-(4-piridil)akrilamid ilə benzoilasetonun və ya asetosirkə turşusunun etil efirinin Mixael birləşmə reaksiyasından müvafiq yeni əvəzlənmiş piridon törəmələrinin əmələ gəldiyi müəyyən edilmişdir. 5-Siano-2-hidroksi-2-metil-6-okso-4-fenilpiperidin-3-karboksil turşusunun etil efirinin 4 saat etil spirtində qaynadılmasından 5-siano-2-metil-6-okso-4-fenil-1,6-dihidropiridin-3-karboksil turşusunun etil efiri əmələ gəlmişdir. Eyni reaksiya şəraitində 4-brombenzoilasetonitrilin 2-siano-3-(2-flüorfenil)akrilamidə Mixael birləşmə reaksiyasından müvafiq piridon törəməsi alınmışdır. Həmçinin, eyni reaksiya şəraitində 2-siano-3-(4-nitrofenil)akrilamid ilə 4-xlorasetoasetat turşusunun etil efirinin qarşılıqlı təsir reaksiyasından uyğun piridon törəməsi sintez edilmişdir. Sintez edilmiş bütün birləşmələrin quruluşları NMR spektroskopiyasının köməyilə təsdiq edilmişdir.

Açar sözlər: *2-siano-3-(4-piridil)akrilamid, flüorbenzilidensianoasetamid, 4-xlorasetoasetat efiri, 4-brombenzoilasetonitril*

СИНТЕЗ ПРОИЗВОДНЫХ НЕКОТОРЫХ ФУНКЦИОНАЛИЗИРОВАННЫХ ПИРИДОНОВ

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Выявлено образование новых производных замещенных пиридонов в условиях реакции присоединения по Михаэлю при участии 2-циано-3-(4-пиридил)акриламида и бензоилацетона или этилового эфира ацетоуксусной кислоты в присутствии метилпиперазина (МР) в среде метанола. При кипячении в этиловом спирте этилового эфира 5-циано-2-гидрокси-2-метил-6-оксо-4-фенилпиперидин-3-карбоновой кислоты в течение 4 часов образуется этиловый эфир 5-циано-2-метил-6-оксо-4-фенил-1,6-дигидропирид-3-карбоновой кислоты. В аналогичных условиях были синтезированы соответствующие продукты замещенных пиридонов по реакции присоединения Михаэля взаимодействием 4-бромбензоилацетонитрила с 2-циано-3-(2-фторфенил)акриламидом и 2-циано-3-(4-нитрофенил)акриламида с этилового эфира 4-хлорацетоуксусной кислоты. Структуры всех синтезированных соединений доказаны методом ЯМР-спектроскопии.

Ключевые слова: *2-циано-3-(4-пиридил)акриламид, фторбензилиденцианоацетамид, 4-хлорацетоуксус- ный эфир, 4-бромбензоилацетонитрил*