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SYNTHESİS OF SUBSTİTUTED PYRİDINE DERİVATİVES BY THE THREE COMPONENT REACTİON BASED ON YLİDENE-CYANO-ACETAMİDES

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Received 16.01.2019

İt was established, that by one-pot three component interaction of substituted ylidene-cyanoacetamides (or ylidenemalononitriles)with malononitrile and (S)-(-)-1-phenyl-ethylamine in methanol solution, at room temperature and without catalyst new substituted iminopyridines were formed. The corresponding substituted terpyridine derivative was synthesized by one-pot three component reaction of pyridylidenecyanoacetamide, malononitrile and 2-amino-5-bromopyridine in methanol and heating for 5-7 minutes. Structures of all synthesized compounds confirmed by NMR spectroscopy.

Keywords: *ylidenecyanoacetamides, malononitrile, iminopyridines, terpyridine, NMR*
Doi.org/10.32737/2221-8688-2019-1-87-92

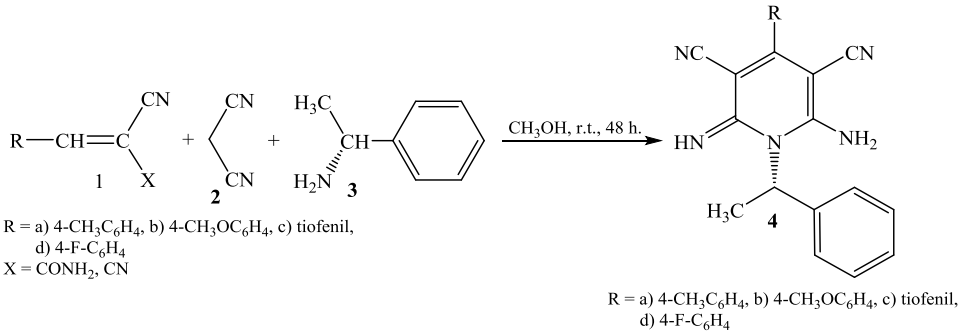
INTRODUCTION

Cyanopyridine fragment is the part of many natural physiologically active compounds. There are much information about antimicrobical and antiviral activity of cyanopyridines in world publications [1-2].

By the multicomponent interaction of carbonyl compounds, aldehydes and amine derivatives in the presence of various catalytic systems biologically active compounds containing quinazoline, pyridine, pyrimidine, indole, imidazole pyrane fragments had been synthesized [3-13].

RESULTS AND DISCUSSIONS

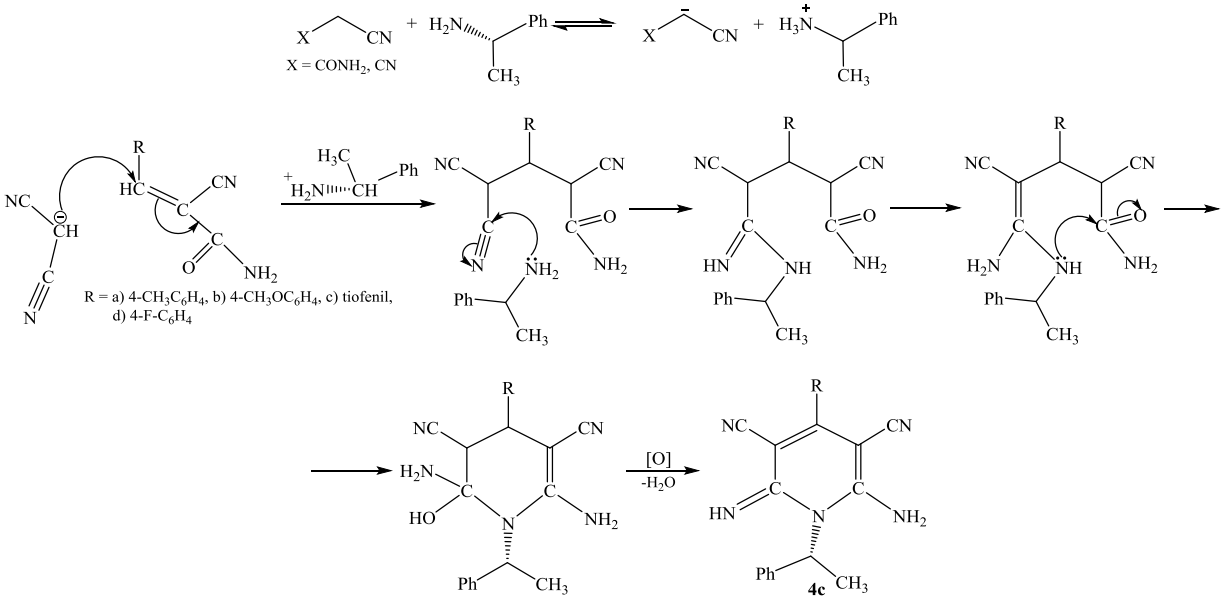
Corresponding substituted pyridine derivatives were synthesized by one-pot three component reaction of p-methyl-, p-metoxy substituted benzylidenecyanoacetamides (or thiopheneylidenecyanoacetamide) with malononitrile and (*S*)-(-)-1-phenylethylamine in methanol, at room temperature for 48 hours. It was established that, does not dependence using of benzylidenemalononitriles or benzylidenecyanoacetamides, the same reaction product was formed.



R = a) 4-$CH_3C_6H_4$, b) 4-$CH_3OC_6H_4$, c) tiofenil, d) 4-F-C_6H_4
X = $CONH_2$, CN

R = a) 4-$CH_3C_6H_4$, b) 4-$CH_3OC_6H_4$, c) tiofenil, d) 4-F-C_6H_4

The plausible mechanism of reaction and ^1H NMR spectra of synthesized compounds are given (Figure 1):



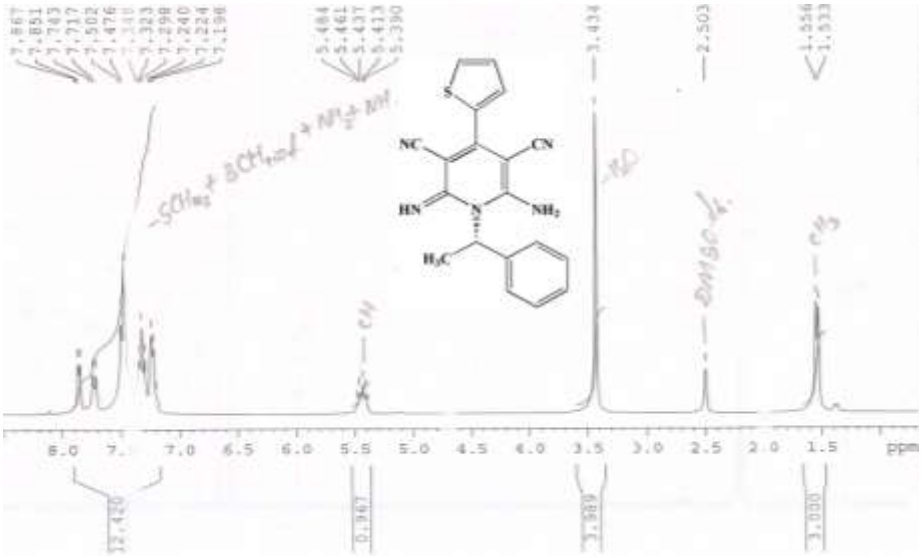
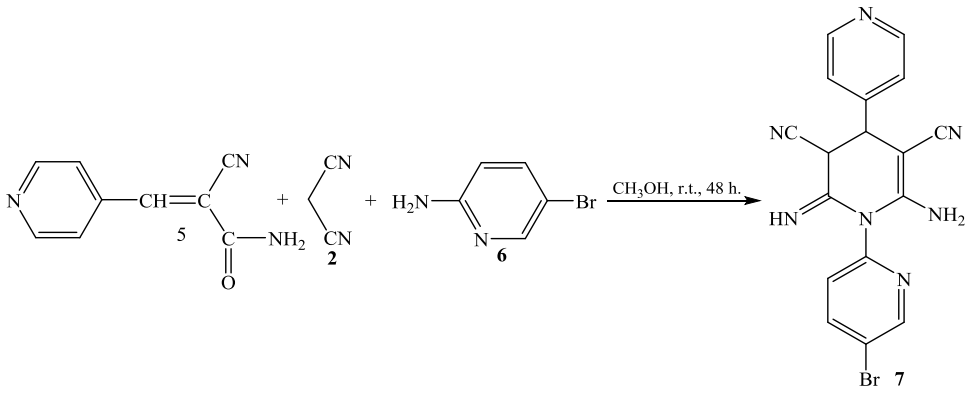


Fig. 1. ^{1}H NMR spectrum of 6-amino-2-imino-1-(1-phenylethyl)-4-(thiophen-2-yl)-1,2-dihydro-pyridine-3,5-dicarbonitrile (**4c**).

By the one-pot three-component reaction of pyridylylidenecyanoacetamide with malononitrile and 2-amino-5-bromopyridine in the same reaction conditions the corresponding substituted terpyridine derivatives (Figure 2) were synthesized (**7**).

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 on Stuart SMP30 apparatus without correction. ^{1}H, ^{13}C NMR spectra were recorded on Bruker Avance 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 progress of reactions.



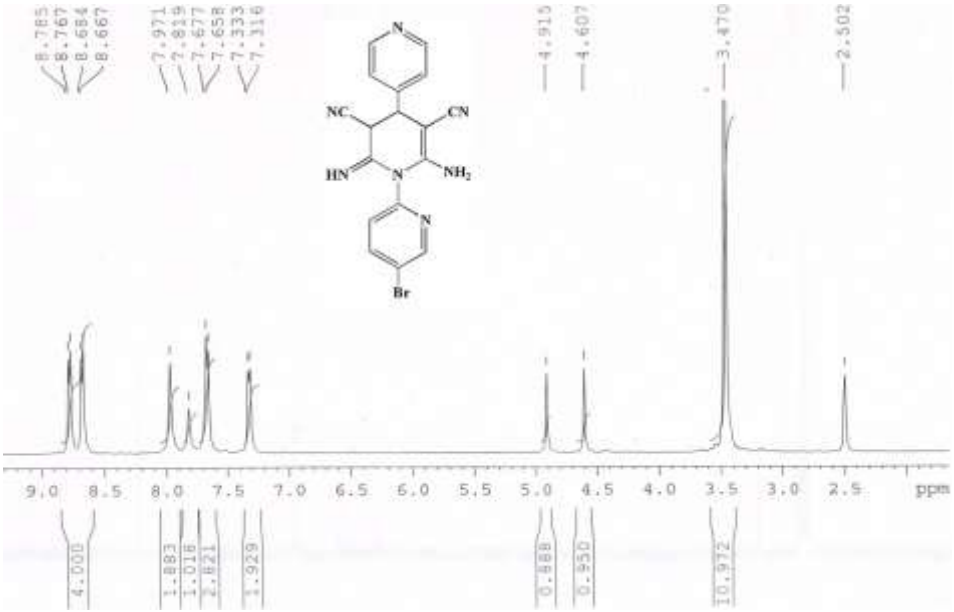


Fig. 2. ^{1}H NMR spectrum of 6'-amino-5-bromo-2'-imino-3',4'-dihydro-2'H-[2,1':4',4''-terpyridine]-3',5'-dicarbonitrile (**7**).

General experimental procedure

6-Amino-2-imino-1-(1-phenylethyl)-4-(p-tolyl)-1,2-dihydropyridine-3,5-dicarbonitrile (4*a*): 4-Methylbenzylidenecyanoacetamide, (3 mmol) malononitril (3.1 mmol) and (*S*)-(-)-1-phenylethylamine (3.1 mmol) stirrered in 35 ml of methyl alcohol. Then the reaction mixture is maintained at room temperature for 2 days. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:2). Crystals were precipitated after evaporation of solvent, filtered by paper, recrystallized from ethanol-water mixture and obtained in pure form (yield 0.94 g, 88.68%). $T_{mp.}$ = 180°C.

^{1}H NMR (300 MHz, DMSO-*d*6): 1.54 (d, 3H, CH_3, $^{3}J_{H\text{-}H}$ = 6,9); 2.38 (s, 3H, CH_3); 5.45 (m, 1H, CH); 7.20-7.69 (m, 12H, 9Ar-H+NH+NH_2). ^{13}C NMR (DMSO-*d*6), δ, m.h.: 21.38 (CH_3), 21.73 (Ar-$\underline{CH_3}$), 49.88 (Ar-$\underline{CH}$), 79.74 (=$C_{quat.}$), 80.83 (=$C_{quat.}$), 116.88 (CN), 117.03 (CN), 127.16 (3$CH_{arom.}$), 128.61 (2$CH_{arom.}$), 128.67 (2$CH_{arom.}$), 129.56 (2$CH_{arom.}$), 132.67 ($C_{arom.}$), 140.04 ($C_{arom.}$), 144.65 ($C_{arom.}$), 158.57 (=$C_{quat.}$), 160.34 (=$C_{quat.}$), 161.25 (=$C_{quat.}$).

Found, %: 74.74 C; 5.32 H, 19.77 N. $C_{22}H_{19}N_5$. Calculated, %: 74.79 C; 5.38 H, 19.83 N.

6-Amino-2-imino-4-(4-methoxyphenyl)-1-(1-phenylethyl)-1,2-dihydropyridine-3,5-dicarbonitrile (4b): Synthesized by the same way (yield 0.9 g, 82.57%). $T_{mp.}$ = 192°C.

^{1}H NMR (300 MHz, DMSO-*d*6), δ, m.h.: 1.54 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 6,6); 3.82 (s, 3H, OCH_3); 5.45 (m, 1H, CH); 7.10-7.81 (m, 12H, 9Ar-H+NH+NH_2). ^{13}C NMR (DMSO-*d*6), δ, m.h.: 21.74 (CH_3), 49.89 (Ar-CH), 55.71 (Ar-CH_3), 79.73 (=$C_{quat.}$), 80.82 (=$C_{quat.}$), 114.36 (2$CH_{arom.}$), 117.02 (CN), 117.17 (CN), 117.55 ($C_{arom.}$), 124.86 ($CH_{arom.}$), 127.13 (2$CH_{arom.}$), 127.19 ($C_{arom.}$), 127.52 (2$CH_{arom.}$), 130.43 (2$CH_{arom.}$), 144.65 ($C_{arom.}$), 158.64 (=$C_{quat.}$), 160.88 (=$C_{quat.}$), 161.31 (=$C_{quat.}$).

Found, %: 71.60 C; 5.21 H, 18.92 N. $C_{22}H_{19}N_5O$. Calculated, %: 71.54 C; 5.15 H, 18.97 N.

6-Amino-2-imino-1-(1-phenylethyl)-4-(thiophen-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (4c): Synthesized by the same way (yield 0.96 g, 93.20%). $T_{mp.}$ = 187°C.

^{1}H NMR (300 MHz, DMSO-*d*6): 1.54 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 6,9); 5.44 (m, 1H, CH-Ar); 7.20-7.87 (m, 11H, 5Ar-H+3$CH_{thiophen.}$+NH_2+NH=). ^{13}C NMR (75 MHz, DMSO-*d*6): 21.70 (CH_3), 50.00 (CH-Ar), 79.76 (=$C_{quat.}$), 80.91 (=$C_{quat.}$), 116.84 (CN), 116.96 (CN), 127.13 (2$CH_{arom.}$), 127.21 ($CH_{arom.}$), 128.10 ($CH_{thiophen.}$), 128.62 (2$CH_{arom.}$), 130.13 ($CH_{tiophen.}$), 130.76 ($CH_{tiophen.}$), 134.52 ($C_{arom.}$), 144.52 ($C_{tiophen.}$), 152.29 (=$C_{quat.}$), 158.69 (N=$C_{quat.}$), 161.37 (=$C_{quat.}$).

Found, %: 66.04 C; 4.29 H, 20.35 N. $C_{19}H_{15}N_5S$. Calculated, %: 66.09 C; 4.35 H, 20.29 N.

6-Amino-4-(4-fluorophenyl)-2-imino-1-(1-phenylethyl)-1,2-dihydropyridine-3,5-dicarbonitrile (4d): Synthesized by the same way (yield 0.83 g, 77.57%). $T_{mp.}$ = 241°C.

^{1}H NMR (300 MHz, DMSO-*d*6): 1.54 (d, 3H, CH_3, $^3J_{H\text{-}H}$ = 7,2); 5.44 (m, 1H, CH-Ar); 7.20-7.75 (m, 12H, 9Ar-H+NH+NH_2). ^{13}C NMR (DMSO-*d*6), δ, m.h.: 21.70 (CH_3), 49.89 (CH-Ar), 79.87 (=$C_{quat.}$), 80.97 (=$C_{quat.}$), 115.94-116.24 ($CH_{arom.}$), 116.72 (CN), 116.86 (CN), 127.17 (3$CH_{arom.}$), 127.20 ($CH_{arom.}$), 128.61 (3$CH_{arom.}$), 131.21-131.33 ($CH_{arom.}$), 131.96 ($C_{arom.}$), 144.60 ($C_{arom.}$), 158.44 (=$C_{quat.}$), 159.38 (=$C_{quat.}$), 161.14 (=$C_{quat.}$), 161.68-164.95 (F-$C_{arom.}$).

Found, %: 70.64 C; 4.54 H, 19.66 N. $C_{21}H_{16}N_5F$. Calculated, %: 70.59 C; 4.48 H, 19.61 N.

6'-Amino-5-bromo-2'-imino-3',4'-dihydro-2'H-[2,1':4',4''-terpyridine]-3',5'-dicarbonitrile (7):

4-Pyridylidenecyanoacetamide (3 mmol), malononitril (3.1 mmol) and 2-amino-5-bromopyridine (3.1 mmol) stirred in 35 ml of methyl alcohol. The reaction mixture is mixed with heating for 5-7 minutes. Then the reaction mixture is maintained at room temperature for 2 days. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:2). Crystals were precipitated after evaporation of solvent, filtered by paper, recrystallized from ethanol-water mixture and obtained in pure form (yield 0.85 g, 72.03%).$T_{mp.}$ = 236°C.

^{1}H NMR (300 MHz, DMSO-*d*6): 4.61 (s, 1H, CH); 4.91 (s, 1H, CH); 7.82 (s, 1H, =NH); 7.97 (s, 2H, NH_2); 7.32-8.78 (m, 7H, 7Ar-H). ^{13}C NMR (DMSO-*d*6), δ, m.h.: 40.95 (CH), 47.12 (CH), 47.35 (=$C_{quat.}$), 75.34 (=$C_{quat.}$), 110.96 ($C_{pyrd.}$), 112.38 (Br-$C_{pyrd.}$), 116.00 (CN), 117.30 (CN), 124.88 ($CH_{pyrd.}$), 124.98 ($CH_{pyrd.}$), 140.61 ($CH_{pyrd.}$), 143.93 ($CH_{pyrd.}$), 146.74 ($CH_{pyrd.}$), 150.40 ($CH_{pyrd.}$), 150.89 ($CH_{pyrd.}$), 163.56 (N=$C_{quat.}$), 163.56 (N-$C_{pyrd.}$).

Found, %: 51.72 C; 2.99 H, 24.83 N. $C_{17}H_{12}N_7Br$. Calculated, %: 51.78 C; 3.04 H, 24.87 N.

REFERENCES

1. Osama S. Moustafa & Ragaa A. Ahmad. Synthesis and Antimicrobial Activity of Some New Cyanopyridines, Isoxazoles, Pyrazoles, and Pyrimidines Bearing Sulfonamide Moiety. *Phosphorus, Sulfur, and Silicon and the Related Elements*. 2003, vol. 178, iss. 3, pp.475-484. DOI: 10.1080/10426500307933
2. Ibrahim T.S, El-Sayed H.A., Khayat M.T., Al-Mahmoudy A.M.M., Moustafa A.H.,. El-Deen A.K.S, Rostom S.A.F., Panda S.S. Synthesis of Nucleosides and Non-nucleosides Based 4,6-disubstituted-2-oxo-dihydropyridine-3-carbonitriles as Antiviral Agents. *Med Chem*. 2018, vol. 14(8), pp.791-808. DOI: 10.2174/1573406414666180522123524
3. Vijay Vilas Shinde, Yeon Tae Jeong. Organic-base-catalyzed diversity-oriented synthesis of novel pyrimido[1,2-*b*]indazole-3-carbonitrile. *Tetrahedron*. 2016, vol. 72, iss. 29, pp. 4377-4382. DOI:10.1016/j.tet.2016.06.002
4. Naghiyev F.N., Maharramov A.M., Asgarova A.R., Rahimova A.G., Akhundova M.A., Mamedov I.G. The investigation of reaction of various thiophene based knoevenagel adducts with acetoacetanilide. *Chemical Problems*. 2018, no. 3(16), pp.337-342. DOI:10.32737/2221-8688-2018-3-337-342
5. Vijay Vilas Shinde, Yeon Tae Jeong. Sonochemical FeF_3 catalyzed three-component synthesis of densely functionalized tetrahydroindazolo[3,2-b]quinazoline under solvent-free conditions. *Tetrahedron Letters*. 2016, vol. 57, iss.33, pp. 3795-3799. DOI: 10.1016/j.tetlet.2016.07.031
6. Amol B. Atar, Yong Seok Jeong, Yeon Tae Jeong. Iron fluoride: the most efficient catalyst for one-pot synthesis of 4H-pyrimido[2,1-*b*]benzothiazoles under solvent-free conditions. *Tetrahedron*. 2014, vol.70, iss. 34, pp. 5207-5213. DOI: 10.1016/j.tet.2014.05.094
7. Avuthu Vidya Sagar Reddy, Yeon Tae Jeong. Highly efficient and facile synthesis of densely functionalized thiazolo[3,2-a]chromeno[4,3-d]pyrimidin-6(7H)-ones using $[Bmim]BF_4$ as a reusable catalyst under solvent-free conditions. *Tetrahedron.* 2016, vol. 72, iss.1, pp. 116-122. DOI: 10.1016/j.tet.2015.11.010
8. Lei L., Hui X., Lei D., Junhua X. etc. An efficient metal-free cascade process for the synthesis of 4-arylpyrimido[1,2-*b*]indazole-3-carbonitrile derivatives. *Tetrahedron*. 2017, vol. 73, iss.36, pp. 5358-5365. DOI: 10.1016/j.tet.2017.07.035
9. Suman Pal, Lokman H. Choudhury, Tasneem Parvin. One-Pot Multicomponent Reactions for the Efficient Synthesis of Highly Functionalized Dihydropyridines. *Synthetic Communications*. 2013, vol. 43, iss.7, pp. 986-992. DOI: 10.1080/00397911.2011.618283
10. Suman Pal, Md. Nasim Khan, Lokman H. Choudhury. KF/Al_2O_3 Mediated Multicomponent Reactions for the Efficient Synthesis of Highly Substituted Dihydropyridines. *Journal of Heterocyclic Chemistry*. 2014, vol. 51, iss. S1, pp. E156-E162. DOI: 10.1002/jhet.1914
11. Ramadan Ahmed Mekheimer, Mariam Abdullah Al-Sheikh, Hanadi Yousef Medrasi and Najla Hosain Hassan Alsofyani. A Novel Synthesis of Highly Functionalized Pyridines by a One-Pot, Three-Component Tandem Reaction of Aldehydes, Malononitrile and N-Alkyl-2-cyanoacetamides under Microwave Irradiation. *Molecules*. 2018, vol. 23, pp. 619-630.DOI: 10.3390/molecules23030619
12. Prakasam Thirumurugan, Paramasivan T. Perumal. $InCl_3$ mediated one-pot synthesis of indol-3-yl pyridine and 2,2′-bipyridine derivatives through multi-component reaction. *Tetrahedron*. 2009, vol. 65, iss. 36, pp. 7620-7629. DOI: 10.1016/j.tet.2009.06.097
13. Chelliah Bharkavi, Pethaiah Gunasekaran, Sundaravel Vivek Kumar, Marimuthu Sakthi, Subbu Perumal. Facile four-component domino reactions for the synthesis of 2,6-diaryl-4-(1H-indol-3-yl)-3-cyanopyridines. *Tetrahedron Letters*. 2014, vol. 55, iss. 40, pp. 5486-5490. DOI: 10.1016/j.tetlet.2014.08.007

İLİDENSİANOASETAMİDLƏR ƏSASINDA ÜÇKOMPONENTLİ REAKSİYADAN ƏVƏZLƏNMİŞ PİRİDİN TÖRƏMƏLƏRİNİN SİNTEZİ

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Əvəzlənmiş ilidensianoasetamidlər (və ya ilidenmalononitrillər) ilə malononitril və (S)-(-)-1-fenil-etilaminin bir-mərhələli, üç-komponentli reaksiyası metanol mühitində, katalizatorsuz şəraitdə, ot-aq temperaturunda aparılmış və reaksiyadan yeni əvəzlənmiş iminopiridinlərin əmələ gəldiyi müəyyən edilmişdir. Metanol mühitində, katalizatorsuz şəraitdə, 5-7 dəqiqə isidilməklə piridili-densianoasetamidin malononitril və 2-amino-5-bromopyridin ilə birmərhələli, üçkomponentli reaksiyasından uyğun əvəzlənmiş terpiridin törəməsi sintez edilmişdir. Alınan birləşmələrin quruluşu NMR spektroskopiyasının köməyilə təsdiqlənmişdir.
Açar sözlər: *ilidensianoasetamidlər, malononitril, iminopiridinlər, terpiridin, NMR*

СИНТЕЗ ЗАМЕЩЕННЫХ ПИРИДИНПРОИЗВОДНЫХ ПУТЕМ ТРЕХКОМПОНЕНТНОЙ РЕАКЦИИ НА ОСНОВЕ ИЛИДЕНЦИАНОАЦЕТАМИДОВ

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Установлено, что путем одностадийной трехкомпонентной реакцией замещенных илиденцианоацетамидов (или илиденмалононитрилов) с малононитрилом и (S)-(-)-1-фенилэтиламином в среде метанола, при комнатной температуре без катализатора образуются новые замещенные иминопиридины. А соответствующие замещенные терпиридин производные синтезированы одностадийной, трехкомпонентной реакцией пиридилиденцианоацетамида, малононитрила и 2-амино-5-бромопиридина в метаноле при нагревании в течение 5-7 минут. Структуры всех синтезированных соединений подтверждены ЯМР-спектроскопией.
Ключевые слова: *илиденцианоацетамиды, малононитрил, иминопиридины, терпиридин, ЯМР*