DOI 10.1007/s10593-018-2381-0

Chemistry of Heterocyclic Compounds **2018**, *54*(10), 964–970

Synthesis, structure, and biological activity of 2,6-diazido-4-methylnicotinonitrile derivatives

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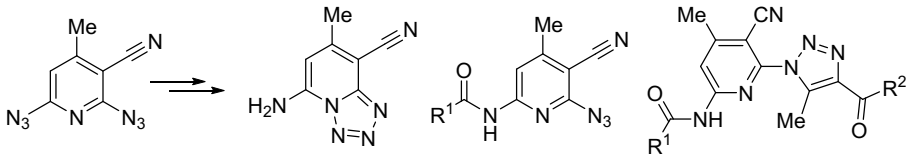
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2018, *54*(10), 964–970

Submitted July 16, 2018
Accepted after revision October 22, 2018



R^1 = 2,6-$F_2C_6H_3$, Cy, cyclopropyl; R^2 = Me, OEt

A number of 2,6-diazido-4-methylnicotinonitrile derivatives has been synthesized as prospective novel plant growth regulators. The 2-[(triphenylphosphoranylidene)amino]tetrazolo[1,5-*a*]pyridine derivative is selectively formed from 2,6-diazido-4-methylnicotinonitrile under the conditions of the Staudinger reaction, from which *N*-(6-azido-5-cyano-4-methylpyridin-2-yl)acylamides can be obtained by sequential reduction and acylation. The obtained azidopyridines are converted into the corresponding 1,2,3-triazoles when treated with 1,3-dicarbonyl compounds in the presence of Et_3N. Field studies showed that some of the synthesized compounds were effective growth regulators of wheat.

Keywords: azidopyridines, iminophosphoranes, nicotinonitriles, 1,2,3-triazoles, Dimroth reaction, Staudinger reaction, growth regulating activity.

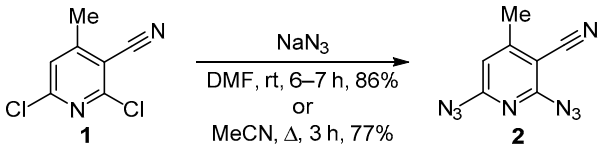
Organic azides are highly reactive compounds and are often used as intermediates in fine organic synthesis. The use of the classical Huisgen cycloaddition reaction in combination with organo– and metallocatalysis made it possible to synthesize a variety of 1,2,3-triazole derivatives.[1–5] In addition, compounds with the azido group are able to participate in cycloaddition reactions with nitroolefins,[6] enamines,[7] active methylene compounds.[8] All of this allowed to obtain products with a wide range of useful properties that can be used in medicine and technology.[9–12] The accumulated significant experimental material in the chemistry of organic azides indicates relevance of research in this field. At the same time, the number of studies devoted to the properties of azidopyridines is limited.[13-15]

Continuing our research on the synthesis of biologically active derivatives of nicotinic acid,[16–25] we attempted to obtain azide derivatives of nicotinonitrile in order to synthesize new agrochemicals, in particular, crop growth regulators, based on them.

Various methods are known for introducing the azido group into a molecule.[26–28] We used the nucleophilic substitution reaction of the chlorine atom by the azido group in dichloronicotinonitrile **1**. Thus, 2,6-dichloro-4-methylnicotinonitrile (**1**) reacts smoothly with sodium azide to form 2,6-diazido-4-methylnicotinonitrile (**2**) (Scheme 1). With DMF as a solvent, the reaction completed in 6–7 h at room temperature, the target product was isolated in 86% yield. In MeCN solution, the reaction requires heating at the boiling point of the solvent for 3 h, affording the product in 77% yield (Scheme 1).

The use of an equimolar ratio of reagents, lowering the temperature of the reaction, as well as employing other solvents (EtOH, Me_2CO, etc.) does not lead to the

Scheme 1



monoazido derivative, but results in an incomplete reaction. 2,6-Diazido-4-methylnicotinonitrile (**2**) is obtained as colorless shiny crystals which quickly darken in the light. When stored in the dark, the color does not change, and it decomposes with an explosion upon melting. In the mass spectrum (EI ionization) of compound,[2] the molecular ion peak is recorded as the base peak. During fragmentation by the electron impact, the molecular ion emits two molecules of N_2, followed by the elimination of the HCN molecule. Product **2** can be stored both in crystalline form and as a solution in organic solvents with different dielectric permittivity values: PhH, CCl_4, 1,4-dioxane, EtOH, Me_2CO, DMF, without being subject to azido-tetrazole tautomeric transformation (IR spectra data).

We used the Staudinger reaction[29] to mildly reduce the azido groups. Diazide **2** reacts with PPh_3 at room temperature in PhH solution. PPh_3 was introduced into the reaction mixture in small portions with vigorous stirring. A rapid release of nitrogen could be observed during this time. Using elemental analysis, ^{1}H NMR spectroscopy, and mass spectrometry, it was found that one azido group enters the reaction, forming the corresponding monoiminophosphorane, while the second azido group forms the tetrazole ring (IR spectrum). NOESY experiments were used to establish the structure of the obtained compound **3**. The ^{1}H–^{1}H NOESY spectrum contains the cross peaks of the interaction of the *ortho*-protons of the phenyl ring (7.90–7.95 ppm) with the H-6 proton (5.69 ppm). The presence of the latter indicates that these protons are spatially close, that is, the iminophosphorane fragment is in the C-5 position of the tetrazolopyridine system (Scheme 2, Fig. 1).

The structure of compound **3** was additionally confirmed by its ^{31}P NMR spectrum, as well as by the ^{13}C DEPTQ NMR experiment (Supplementary information file). The ^{31}P NMR spectrum contains a single signal at 14.1 ppm, which is typical of iminophosphoranes.[30] The ^{13}C DEPTQ NMR spectrum of compound **3** demonstrates the splitting of ^{13}C signals at the ^{31}P nucleus, while carbon C-6 appears as a doublet at 102.6 ppm with coupling constant of $^3J_{PC}$ = 8.4 Hz.

Tetrazolopyridine **3** is a high-melting crystalline substance of light-yellow color, soluble in DMF and $CHCl_3$, moderately soluble in DMSO. The mass spectrum of compound **3** exhibits the molecular ion peak M^+ with a

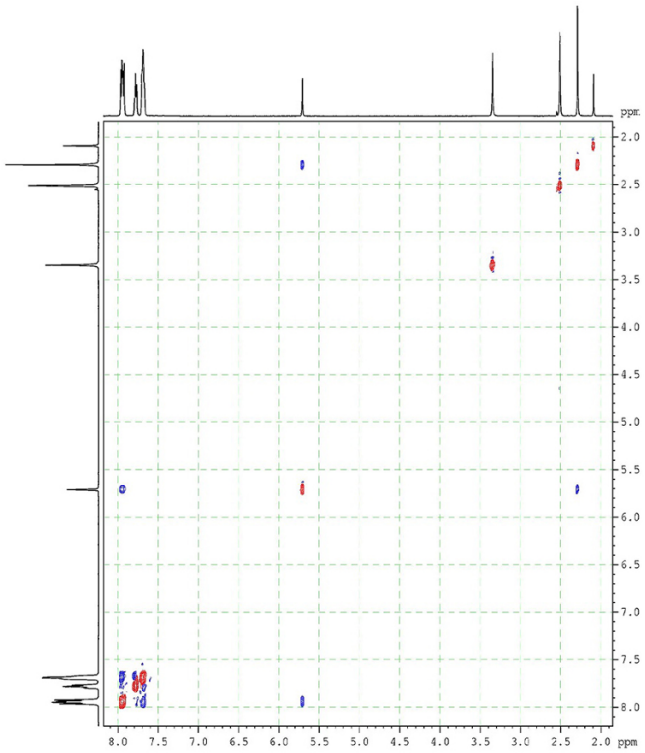


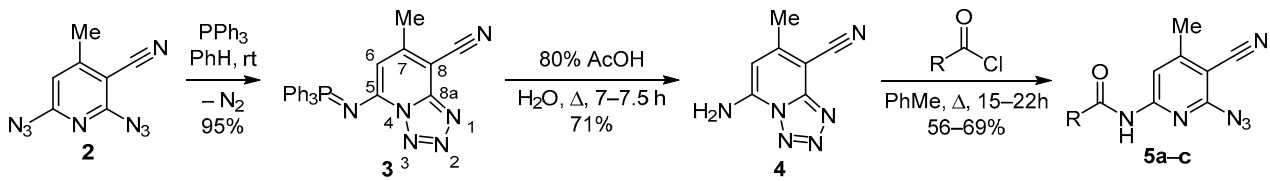
Figure 1. ^{1}H–^{1}H NOESY spectrum of compound **3**.

mass of 434, corresponding to a monoiminophosphorane derivative. It is interesting to note that the fragmentation of the molecular ion of this compound is characterized by only one route, namely, the splitting of the P–N bond, while the positive charge is completely localized on the $[PPh_3]^+$ fragment, which has the maximum intensity. This fragment then consecutively loses two C_6H_5 radicals. Iminophosphoranes are converted to the corresponding amines by heating with dilute acids.[31,32] In our case, the most suitable conditions for the reduction of compound **3** to 6-amino derivative **4** were refluxing with 80% AcOH for 7–7.5 h (Scheme 2).

5-Amino-7-methyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (**4**) is a white crystalline substance, poorly soluble in most organic solvents, except DMSO. In the IR spectrum of amine **4**, the absorption bands of the NH_2 group at 3425 and 3328 cm^{-1} are evident. Valence vibrations of the azido group in the IR spectrum are not observed, which indicates the preservation of the tetrazole ring in the molecule.

When studying the nucleophilic properties of the amino group of product **4**, it was established that the latter has a very low activity in acylation reactions due to the strong conjugation of the free electron pair of nitrogen with the

Scheme 2



5 a R = 2,6-$F_2C_6H_3$, **b** R = Cy, **c** R = cyclopropyl

heterocyclic system. 5-Amino-7-methyltetrazolo[1,5-*a*]-pyridine-8-carbonitrile (**4**) does not react with isocyanates and isothiocyanates even upon prolonged heating in high-boiling solvents. The compound is acylated with carboxylic acid chlorides in anhydrous PhMe medium by heating at the boiling point of the reaction mixture for 15–22 h (Scheme 2). It is interesting to note that the tetrazole ring opens during the reaction, and the acylation products already contain an azido group, as evidenced by the characteristic band at 2119–2126 cm^{-1} in the IR spectra of compounds **5a**–**c**. In addition, the IR spectra of compounds **5a**–**c** contain stretching vibration bands of the C=O and N–H at 1695–1711 cm^{-1} and 3255–3410-cm^{-1}, respecttively.

The NMR spectra of the acylation products indicate that in DMSO-d_6 solution, compounds **5a**–**c** exist as a mixture of tetrazolopyridine and 2-azidopyridine tautomers with the latter predominating (Fig. 2). The assignment of signals is made on the basis of the observed shift of the signal of the C(O)NH proton of the tetrazole tautomer in the downfield region ($\Delta\delta \approx 0.9$–1.1 ppm) relative to the analogous signal of the azide tautomer due to the formation of an intramolecular hydrogen bond between the NH proton and the N-3 atom of the tetrazole ring. The ratio of tautomers varies widely: from trace amounts of tetrazole (less than 5%) in the case of compound **5a** to a tetrazole:azide ratio of ≈1:5 in the case of compound **5c**.

Organic azides are known to enter the Dimroth cycloaddition reaction with active methylene ketones and nitriles in the presence of a base to form substituted 1,2,3-triazoles.[8,33] We studied the reactions of azides **5a**,**b** with acetylacetone and ethyl acetoacetate. In reactions with acetylacetone, the best results were obtained by keeping the reactants for a prolonged period of time (48–50 h) at room temperature in MeCN solution in the presence of Et_3N (Scheme 3).

In reactions with ethyl acetoacetate, the conditions were similar, but to complete the reaction it was necessary to heat the reaction mixture at 50–55°C for 30–40 min. In the IR spectra of compounds **6a**–**d**, compared with the spectra of compounds **5a**,**b**, the absorption band of the azido group disappears, which indicates its participation in the formation of a new ring. At the same time, the second absorption band of the C=O group appears (in the region of 1690–1711 cm^{-1}).

The structure of compounds **6a-d** was confirmed by a set of spectral methods (^{19}F NMR spectra, ^{13}C DEPTQ, COZY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC). As an illustrative example, Figure 3 shows the major correlations and chemical shifts for compounds **6a**,**d**. The set of heteronuclear correlations for compounds **6a**,**d** is given in Table 1. Two-dimensional spectra and correlation tables for

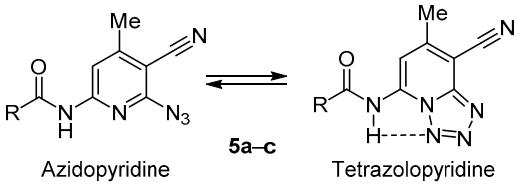
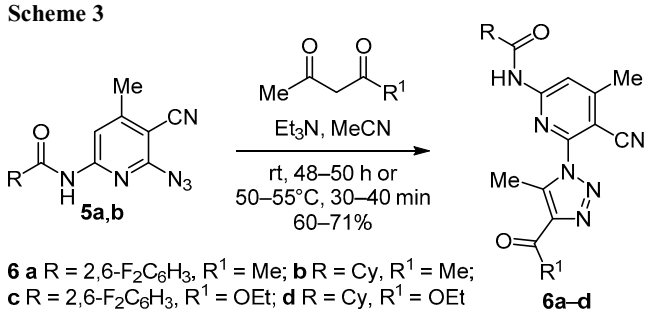


Figure 2. Tautomeric forms of compounds **5a**–**c**.

Scheme 3



6 a R = 2,6-$F_2C_6H_3$, R^1 = Me; **b** R = Cy, R^1 = Me; **c** R = 2,6-$F_2C_6H_3$, R^1 = OEt; **d** R = Cy, R^1 = OEt

the remaining compounds **6** are given in the Supplementary information file.

The synthesized compounds **5a**–**c**, **6a**–**d** were evaluated as potential growth regulators of winter wheat in field conditions. Growth regulators are used in crop production as a means of controlling the main physiological and biochemical processes in order to increase crop yield, improve its quality, facilitate care when growing plants and reduce losses during harvesting and storage.[34] It should be noted that the growth-regulating effect of 1,2,3-triazole derivatives is still little studied.[34]

The experiments were carried out on the experimental field of the All-Russian Research Institute of Biological Plant Protection (Krasnodar) on plants of winter wheat of Kalym variety, zoned in Krasnodar Krai. Vegetative plants were twice treated with an aqueous solution of the tested substances: in the tillering stage (dose 30 g/ha) and in the flag leaf phase (dose 30 g/ha). The growth-regulating effect was estimated by the crop yield increase relative to the control variant (untreated plants). Data were subjected to statistical processing using HCP_{05} (the smallest significant difference for 5% significance level).[35] According to the results of the experiments, the use of compounds **5c** and **6b** provided a reliable increase in the yield of winter wheat relative to the control by 5.0 and 4.7 cwt/ha, respectively, which is an increase by 10.2 and 9.6%, respectively (Table 2).

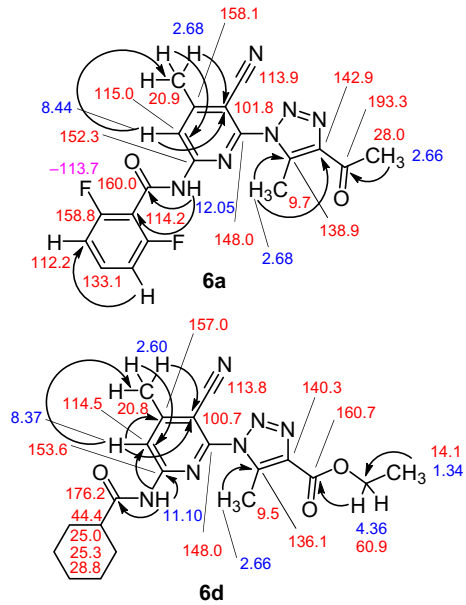


Figure 3. Chemical shifts and major heteronuclear correlations in ^{1}H–^{13}C HMBC spectra of compounds **6a**,**d**.

Table 1. Heteronuclear correlations obeserved in ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra ofr compounds **6a**,**d**

Signals in ^{1}H NMR spectrum, δ, ppm	Heteronuclear correlations, δ, ppm	
	^{1}H–^{13}C HSQC	^{1}H–^{13}C HMBC
Compound **6a**		
2.66 (3H, s, CH_3CO)	28.0	193.3
2.68 (6H, br. s, $2CH_3$ signals overlap)	9.7; 20.9	101.8; 113.9; 115.0; 138.9; 142.9; 158.1
7.25–7.29 (2H, m, H-3,5 Ar)	112.2	112.2; 114.2
7.59–7.67 (1H, m, H-4 Ar)	133.1	112.2; 158.8
8.44 (1H, s, H-3 Py)	115.0	20.9; 101.8
12.05 (1H, br. s, C(O)NH)	–	114.2; 160.0
Compound **6d**		
1.14–1.41 (5H, m, CH_2 Cy)	25.0; 25.3; 28.8	25.0; 25.3; 28.8
1.34 (3H, t, $CO_2CH_2C\underline{H}_3$)	14.1	60.9
1.62–1.82 (5H, m, CH_2 Cy)	25.0; 25.3; 28.8	25.0; 25.3; 28.8; 44.4
2.51–2.54 (1H, m, CHC=O)	44.4	28.8
2.60 (3H, s, CH_3 Py)	20.8	100.7; 114.5; 157.0
2.66 (3H, s, CH_3 triazole)	9.5	136.1; 140.3
4.36 (2H, q, $CO_2C\underline{H}_2CH_3$)	60.9	14.1; 160.7
8.37 (1H, s, H-5 Py)	114.5	20.8; 100.7; 157.0
11.10 (1H, br. s, C(O)NH)	–	114.5; 153.6; 176.2

Table 2. Effect of novel compounds **5c** and **6b** on the yield of winter wheat of Kalym variety

Compound (dose, g/ha)	Grain yield, cwt/ha	Increase *vs* control	
		cwt/ha	%
5c (30 + 30)	53.8	5.0	10.2
6b (30 + 30)	53.5	4.7	9.6
Control	48.8	–	–
HCP_{05}	2.44	0.89	–

To conclude, new methods for the transformation of 2,6-diazido-4-methylnicotinonitrile were developed and derivatives of tetrazolo[1,5-*a*]pyridine and 1,2,3-triazole were obtained. *N*-(6-Azido-5-cyano-4-methylpyridin-2-yl)-cyclopropanecarboxamide and *N*-[6-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-5-cyano-4-methylpyridin-2-yl]cyclohexanecarboxamide have a marked growth-regulating activity.

Experimental

IR spectra were registered on a Bruker Vertex 70 FT-IR spectrometer in 4000–350 cm^{-1} range using the attenuated total reflectance attachment on a diamond crystal. ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR spectra and two-dimensional NMR experiments (COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, DEPTQ) were acquired on a Bruker Avance III 400 spectrometer (400, 101, 162, and 377 MHz for ^{1}H, ^{13}C, ^{31}P, and ^{19}F nuclei, respectively) in DMSO-d_6 or $CDCl_3$. TMS was used as internal standard. For ^{31}P and ^{19}F NMR spectra, respectively H_3PO_4 (0.0 ppm) and CF_3CO_2H (–78.5 ppm) were used as external standards. ^{1}H–^{1}H NOESY spectrum was recorded on a Bruker WM-500 spectrometer at 500 MHz in DMSO-d_6. Mass spectra (EI ionization, 70 eV) were registered on a Finnigan MAT Incos 50 mass spectrometer. HPLC-MS (ESI) for compounds **2** and **3** were recorded on a Thermo TSQ Access Max triple quadrupole HPLC-MS/MS system coupled to a Dionex Ultimate-3000 LC system. Elemental analysis was performed on a Carlo-Erba 1106 Elemental analyzer. Melting points were determined on a Kofler bench and are uncorrected. Monitoring of the reaction progress and assessment of the purity of synthesized compounds was done by TLC on Silufol UF-254 plates, eluent hexane–Me_2CO, 1:1, visualization in iodine chamber.

Precursor 2,6-dichloro-4-methylnicotinonitrile **1** was synthesized by a published method.[24]

2,6-Diazido-4-methylnicotinonitrile (2). Method I. Solution of 2,6-dichloro-4-methylnicotinonitrile **1** (0.75 g, 4 mmol) in DMF (10 ml) was combined with a solution of NaN_3 (1.06 g, 16 mmol) in the minimum amount of water, and the mixture stirred at room temperature for 6–7 h. H_2O (15 ml) was added to the reaction mixture, the formed precipitate was filtered off, washed with H_2O, and dried.

Method II. A mixture of nicotinonitrile **1**, NaN_3 (amounts the same as in method I), and MeCN (15 ml) was heated under reflux for 3 h. After the completion of the reaction, MeCN was evaporated under reduced pressure on the rotary evaporator, the inorganic salts were dissolved in water, and the product filtered off and dried. Yield 0.77 g (86%, method I), 0.65 g (77%, method II), shiny colorless crystals, mp 126–127°C (hexane, decomposes with explosion). IR spectrum, ν, cm^{-1}: 2220 (C≡N), 2124, 2104 ($2N_3$), 1585, 1543 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.42 (3H, s, 4-CH_3); 6.90 (1H, s, H-5). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm: 19.9* (CH_3); 94.8 (C-3); 111.2* (C-5); 113.8 (C≡N); 155.5 (C-4); 155.6 (C-2); 157.3 (C-6). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 200 $[M]^+$ (100), 144 $[M–2N_2]^+$ (9); 117 $[M–2N_2–HCN]^+$ (93). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 208 $[M–2N_2+Na+MeCN]^+$ (56), 200 (10), 167 $[M–2N_2+Na]^+$ (100). Found, %: C 41.74; H 2.16; N 56.29. $C_7H_4N_8$. Calculated, %: C 42.00; H 2.01; N 55.98.

7-Methyl-5-[(triphenylphosphoranyliden)amino]tetrazolo[1,5-*a*]pyridine-8-carbonitrile (3). 2,6-Diazido-4-methylnicotinonitrile (**2**) (1.20 g, 6 mmol) was dissolved in PhH (40 ml), then PPh_3 powder (1.80 g, 7 mmol) was added in small portions with stirring at room temperature. Stirring of the reaction mixture was continued until evolution of gaseous products ceases. The formed copious precipitate was filtered off, washed with PhH, and dried. Yield 2.35 g (95%), light-yellow crystals, mp 224–226°C (Me_2CO). IR spectrum, ν, cm^{-1}: 2214 (C≡N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 5.69 (1H, s, H-6); 7.65–7.69 (6H, m, H Ph); 7.75–7.79 (3H, m, H Ph); 7.90–7.95 (6H, m, H Ph). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 (3H, s, CH_3); 5.52 (1H, s, H-6); 7.54–7.58 (6H, m, H Ph); 7.64–7.68 (3H, m, H Ph); 7.79–7.84 (6H, m, H Ph). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 20.2* (CH_3); 95.7 (C-8); 102.6* (C-6); 115.9 (C≡N); 125.7 (d, $^1J_{PC}$ = 102.7, C-1 Ph); 129.7* (d, $^3J_{PC}$ = 13.2, C-3,5 Ph); 132.6* (d, $^2J_{PC}$ = 11.7, C-2,6 Ph); 133.7* (d, $^4J_{PC}$ = 2.9, C-4 Ph); 145.9 (C-7); 152.2 (C-5);

* Here and hereinafter in the experimental part, antiphase signals are marked with an asterisk (*).

157.9 (C-8a). ^{13}C DEPTQ NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 20.7 (CH_3); 83.0* (C-8); 102.6 (d, $^3J_{PC}$ = 8.4, C-6); 115.0* (C≡N); 126.4* (d, $^1J_{PC}$ = 103.6, C-1 Ph); 129.4 (d, $^3J_{PC}$ = 12.8, C-3, C-5 Ph); 132.6 (d, $^2J_{PC}$ = 10.5, C-2,6 Ph); 133.4 (d, $^4J_{PC}$ = 2.9, C-4 Ph); 147.0* (d, $^2J_{PC}$ = 10.5, C-5); 149.9* (d, $^4J_{PC}$ = 1.3, C-7); 151.8* (C-8a). ^{31}P NMR spectrum ($CDCl_3$), δ, ppm: 14.1 (Ph_3P=N). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 434 $[M]^+$ (21), 262 $[P(C_6H_5)_3]^+$ (100), 185 $[P(C_6H_5)_2]^+$ (80), 108 $[PC_6H_5]^+$ (40). Mass spectrum (ESI), *m*/*z*: 435 $[M+H]^+$, 279 $[PPh_3+NH_4]^+$. Found, %: C 68.96; H 4.53; N 19.48. $C_{25}H_{19}N_6P$. Calculated, %: C 69.12; H 4.41; N 19.34.

5-Amino-7-methyltetrazolo[1,5-*a*]pyridine-8-carbonitrile (4). A mixture of iminophosphorane **3** (3.0 g, 6.9 mmol) and 80% aqueous AcOH (60 ml) was heated under reflux for 7–7.5 h. The reaction mixture was concentrated to dryness on the rotary evaporator, the residue was treated with MeOH, the product filtered off, and dried. Yield 0.85 g (71%), white crystals, mp 260–262°C (DMF, decomposes with explosion). IR spectrum, ν, cm^{-1}: 3425, 3328 (NH_2), 2217 (C≡N), 1646, 1614 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.51 (3H, s, CH_3); 6.25 (1H, s, H-6); 8.67 (2H, br. s, NH_2). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm: 20.4* (CH_3); 79.7 (C-8); 96.3* (C-6); 115.3 (C≡N); 144.7 (C-7); 149.2 (C-5); 153.1 (C-8a). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 174 $[M]^+$ (69), 148 $[M–CN]^+$ (25), 146 $[M–N_2]^+$ (95), 131 $[M–N_2–CH_3]^+$ (37), 118 $[M–2N_2]^+$ (35), 92 $[M–2N_2–CN]^+$ (100). Found, %: C 48.55; H 3.32; N 48.46. $C_7H_6N_6$. Calculated, %:C 48.27; H 3.47; N 48.25.

Synthesis of *N*-(6-azido-5-cyano-4-methylpyridin-2-yl)-acylamides 5a–c (General method). A suspension of 5-aminotetrazolo[1,5-*a*]pyridine **4** (1.00 g, 5.7 mmol), the corresponding acid chloride (8.6 mmol), Et_3N (5.7 mmol), and anhydrous PhMe (20 ml) was heated under reflux for 15–22 h. The precipitate formed after cooling of the reaction mixture was filtered off, washed with H_2O, dried, and recrystallized from a EtOH–MeCN, 1:1 mixture.

***N*-(6-Azido-5-cyano-4-methylpyridin-2-yl)-2,6-difluorobenzamide (5a)**. Yield 1.00 g (56%), white powder, mp 216–217°C. IR spectrum, ν, cm^{-1}: 3410, 3325 (N–H), 2217 (C≡N), 2128 (N_3), 1695 (C=O), 1620, 1580 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: azide tautomer: 2.49 (3H, s, CH_3); 7.21–7.25 (2H, m, H-3,5 Ar); 7.56–7.64 (1H, m, H-4 Ar); 8.01 (1H, br. s, H-3); 11.83 (1H, br. s, NH); tetrazole tautomer (<5%): 2.73 (3H, s, CH_3); 8.12 (1H, br. s, H-3); 12.96 (1H, br. s, NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): azide tautomer: 20.4* (CH_3); 94.3 (CCN); 110.5* (C-3); 112.1* (dd, $^2J_{FC}$ = 25.0, $^4J_{FC}$ = 5.9, C-3,5 Ar); 114.1 (C≡N); 114.5 (t, $^2J_{FC}$ = 22.0, C-1 Ar); 132.7* (t, $^3J_{FC}$ = 10.3, C-4 Ar); 152.4 (C-4); 155.4 (C-6); 156.9 (C-2); 158.8 (dd, $^1J_{FC}$ = 249.4, $^3J_{FC}$ = 7.3, C-2,6 Ar); 159.9 (br. s, C=O); tetrazole tautomer: 20.9* (CH_3). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: azide tautomer: –113.98 (br. s, 2,6-$F_2C_6H_3$); tetrazole tautomer: –113.42 (br. s, 2,6-$F_2C_6H_3$). Found, %: C 53.64; H 2.68; N 26.61. $C_{14}H_8F_2N_6O$. Calculated, %: C 53.51; H 2.57; N 26.74.

***N*-(6-Azido-5-cyano-4-methylpyridin-2-yl)cyclohexanecarboxamide (5b)**, the ratio of azide and tetrazole tautomers ~7:1. Yield 1.10 g (67%), white powder, mp 194–195°C. IR spectrum, ν, cm^{-1}: 3255 (N–H), 2929, 2850 (C–H), 2231 (C≡N), 2119 (N_3), 1708 (C=O), 1562, 1522 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): azide tautomer: 1.10–1.38 (5H, m, CH_2 Cy); 1.61–1.89 (5H, m, CH_2 Cy); 2.41 (3H, s, CH_3); 2.51–2.57 (1H, m, CHC=O); 7.92 (1H, s, H-3); 10.78 (1H, br. s, C(O)NH); tetrazole tautomer: 2.66 (3H, s, CH_3); 2.87–2.93 (1H, m, CHC=O); 7.98 (1H, s, H-3); 11.69 (1H, br. s, C(O)NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm: azide tautomer: 20.8* (CH_3); 25.5 (CH_2); 25.8 (CH_2); 29.3 (CH_2); 44.7* (CHC=O); 93.3 (CCN); 110.4* (C-3); 114.7 (C≡N); 153.9 (C-4); 155.6 (C-6); 156.5 (C-2); 176.5 (C=O); tetrazole tautomer: 21.4* (CH_3); 25.5 (CH_2); 29.5 (CH_2); 44.6* (CHC=O); 105.8* (C-6); 114.3 (C≡N); 137.0 (C-7); 148.8 (C-8a); 154.8 (C-5); 176.9 (C=O). Found, %: C 59.31; H 5.63; N 29.64. $C_{14}H_{16}N_6O$. Calculated, %: C 59.14; H 5.67; N 29.56.

***N*-(6-Azido-5-cyano-4-methylpyridin-2-yl)cyclopropanecarboxamide (5c)**, the ratio of azide and tetrazole tautomers ~5:1. Yield 0.96 g (69%), white powder, mp 189–190°C. IR spectrum, ν, cm^{-1}: 3285 (N–H), 2225 (C≡N), 2126 (N_3), 1702 (C=O), 1575, 1534 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: azide tautomer: 0.83–0.89 (4H, m, $(CH_2)_2$); 2.04–2.10 (1H, m, CHC=O); 2.39 (3H, s, CH_3); 7.88 (1H, s, H-3); 11.14 (1H, br. s, C(O)NH); tetrazole tautomer: 0.93–1.00 (4H, m, $(CH_2)_2$); 2.51–2.55 (1H, m, CHC=O); 2.65 (3H, s, CH_3); 7.97 (1H, s, H-6); 12.05 (1H, br. s, C(O)NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm: azide tautomer: 8.6 ($(CH_2)_2$); 14.4* (CHC=O); 20.3* (CH_3); 92.9 (CCN); 110.0* (C-3); 114.2 (C≡N); 153.2 (C-4); 155.2 (C-6); 156.0 (C-2); 173.6 (C=O); tetrazole tautomer: 9.6 ($(CH_2)_2$); 14.5* (CHC=O); 20.9* (CH_3); 90.1 (CCN); 105.4* (C-3); 113.7 (C≡N); 136.0 (C-7); 148.3 (C-8a); 154.3 (C-5); 173.9 (C=O). Found, %: C 54.72; H 4.21; N 34.51. $C_{11}H_{10}N_6O$. Calculated, %: C 54.54; H 4.16; N 34.69.

Synthesis of 1,2,3-triazoles 6a–d (General method). A solution of the respective 1,3-dicarbonyl compound (20 mmol) and Et_3N (2 mmol) in MeCN (5 ml) was added to a suspension of the respective 2-azidonicotinonitrile **5a**,**b** (2 mmol) in MeCN (5 ml) with stirring at room temperature, and kept for 46–50 h (TLC control). In the case of ethyl acetoacetate, the mixture was additionally heated at 50–55°C for 30–40 min to complete the reaction. Then, the reaction mixture was poured in cold water (50 ml), the formed precipitate was filtered off, dried, and recrystallized from a suitable solvent.

***N*-[6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-5-cyano-4-methylpyridin-2-yl]-2,6-difluorobenzamide (6a)**. Yield 0.50 g (62%), white powder, mp 201–203°C (EtOAc). IR spectrum, ν, cm^{-1}: 3245 (N–H), 2220 (C≡N), 1710 (C=O), 1692 (C=O), 1590, 1542 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.66 (3H, s, CH_3CO); 2.68 (6H, br. s, 2CH_3 singlets overlap); 7.25–7.29 (2H, m, H-3,5 Ar); 7.59–7.67 (1H, m, H-4 Ar); 8.44 (1H, s, H-3 Py); 12.05 (1H, br. s, C(O)NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.7* (CH_3 triazole); 20.9* (CH_3 Py); 28.0* (CH_3CO); 101.8 (CCN); 112.2* (dd,

$^2J_{FC}$ = 19.1, $^4J_{FC}$ = 4.4, C-3,5 Ar); 113.9 (C≡N); 114.2 (t, $^2J_{FC}$ = 22.0, C-1 Ar); 115.0* (C-3 Py); 133.1* (t, $^3J_{FC}$ = 10.3, C-4 Ar); 138.9 (C triazole); 142.9 (C triazole); 148.0 (C-6 Py); 152.3 (C-2 Py); 158.1 (C-4 Py); 158.8 (dd, $^1J_{FC}$ = 249.4, $^3J_{FC}$ = 7.3, C-2,6 Ar); 160.0 (C(O)NH); 193.3 ($CH_3\underline{C}O$). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –113.68 (m, 2,6-$F_2C_6H_3$). Found, %: C 57.56; H 3.98; N 21.26. $C_{19}H_{14}F_2N_6O_2$. Calculated, %: C 57.58; H 3.56; N 21.20.

***N*-[6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-5-cyano-4-methylpyridin-2-yl]cyclohexanecarboxamide (6b)**. Yield 0.52 g (71%), white powder, mp 162–163°C (cyclohexane). IR spectrum, ν, cm^{-1}: 3291 (NH), 2220 (C≡N), 1702 (C=O), 1690 (C=O), 1620, 1589 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.15–1.41 (5H, m, CH_2 Cy); 1.62–1.82 (5H, m, CH_2 Cy); 2.51–2.54 (1H, m, CHC=O); 2.61 (3H, s, CH_3 Py); 2.66 (6H, m, 2CH_3 singlets overlap); 8.37 (1H, s, H-3 Py); 11.08 (1H, br. s, C(O)NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm: 9.6* (CH_3 triazole); 20.8* (CH_3 Py); 25.0 (CH_2 Cy); 25.3 (CH_2 Cy); 28.0* ($\underline{C}H_3C$(O)); 28.8 (CH_2 Cy); 44.4* ($\underline{C}$HC=O); 100.6 ($\underline{C}$CN); 113.9 (C≡N); 114.5* (C-3 Py); 138.7 (C triazole); 142.8 (C triazole); 148.0 (C-6 Py); 153.5 (C-2 Py); 157.1 (C-4 Py); 176.2 (C(O)NH); 193.3 ($CH_3\underline{C}$(O)). Found, %: C 62.04; H 6.12; N 22.92. $C_{19}H_{22}N_6O_2$. Calculated, %: C 62.28; H 6.05; N 22.94.

Ethyl 1-{3-cyano-6-[(2,6-difluorophenyl)carbonyl]amino-4-methylpyridin-2-yl}-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6c). Yield 0.51 g (60%), white powder, mp 180–181°C (EtOAc). Solvate **6c** : EtOAc = 1:1 was obtained after recrystallization from EtOAc. IR spectrum, ν, cm^{-1}: 3420 (N–H), 2206 (C≡N), 1718 (2 C=O), 1690 (C=O), 1620, 1543 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.16 (3H, t, ^3J = 7.2, EtOAc); 1.34 (3H, t, ^3J = 7.2, CO_2Et); 1.98 (3H, s, EtOAc); 2.68 (3H, s, CH_3 triazole); 2.68 (3H, s, CH_3 Py); 4.02 (2H, quin, ^3J = 7.2, EtOAc); 4.36 (2H, quin, ^3J = 7.2, CO_2Et); 7.24–7.28 (2H, m, H-3,5 Ar); 7.59–7.66 (1H, m, H-4 Ar); 8.44 (1H, s, H-5 Py); 12.03 (1H, br. s, C(O)NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.6 (CH_3 triazole); 14.1 (2C, CO_2Et, EtOAc); 20.7 (CH_3 Py); 20.8 (EtOAc); 59.7 (EtOAc); 60.8 (O$\underline{C}H_2CH_3$); 101.9 ($\underline{C}$CN); 112.1 (dd, $^2J_{FC}$ = 20.0, $^4J_{FC}$ = 5.3, C-3,5 Ar); 113.7 (C≡N); 114.1 (t, $^2J_{FC}$ = 21.8, C-1 Ar); 115.0 (C-5 Py); 133.0 (t, $^3J_{FC}$ = 8.8, C-4 Ar); 136.2 (C triazole); 140.4 (C triazole); 148.0 (C-2 Py); 152.3 (C-6 Py); 157.9 (C-4 Py); 158.8 (dd, $^1J_{FC}$ = 249.4, $^3J_{FC}$ = 7.3, C-2,6 Ar); 159.9 (C(O)NH); 160.6 (CO_2Et); 170.3 (EtOAc). Found, %: C 56.23; H 4.80; N 16.44. $C_{24}H_{24}F_2N_6O_5$. Calculated, %: C 56.03; H 4.70; N 16.34.

Ethyl 1-{3-cyano-6-[(cyclohexylcarbonyl)amino]-4-methylpyridin-2-yl}-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6d). Yield 0.48 g (61%), white powder, mp 129–130°C (cyclohexane). IR spectrum, ν, cm^{-1}: 3382 (N–H), 2210 (C≡N), 1737 (C=O), 1711 (C=O), 1589, 1537 (C=C, C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.14–1.41 (5H, m, CH_2 Cy); 1.34 (3H, t, ^3J = 7.1, CO_2Et); 1.62–1.82 (5H, m, CH_2 Cy); 2.51–2.54 (1H, m, CHC=O); 2.60 (3H, s, CH_3 Py); 2.66 (3H, s, CH_3 triazole); 4.36 (2H, quin, ^3J = 7.1, CO_2Et); 8.37 (1H, s, H-5 Py); 11.10 (1H, br. s, C(O)NH). ^{13}C DEPTQ NMR spectrum (DMSO-d_6), δ, ppm: 9.5* (CH_3 triazole); 14.1* (O$CH_2\underline{C}H_3$); 20.8* (CH_3 Py); 25.0 (CH_2 Cy); 25.3 (CH_2 Cy); 28.8 (CH_2 Cy); 44.4* ($\underline{C}$HC=O); 60.9 (O$\underline{C}H_2CH_3$); 100.7 ($\underline{C}$CN); 113.8 (C≡N); 114.5* (C-5 Py); 136.1 (C triazole); 140.3 (C triazole); 148.0 (C-2 Py); 153.6 (C-6 Py); 157.0 (C-4 Py); 160.7 (CO_2Et); 176.2 (C(O)NH). Found, %: C 60.40; H 6.24; N 20.36. $C_{20}H_{24}N_6O_3$. Calculated, %: C 60.59; H 6.10; N 21.20.

Supplementary information file containing spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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