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Synthesis of 1,2,3-triazoles linked into chains with other carbo- and heterocycles by a reaction between β-azolyl enamines and azides

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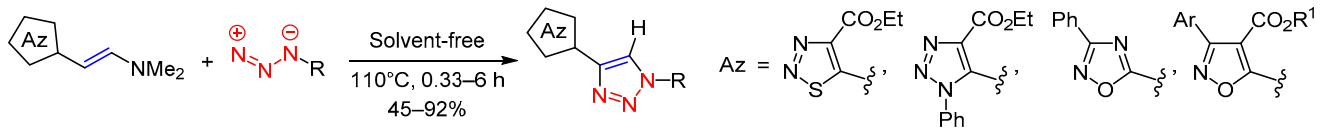


R = Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, CH_2CO_2Et, Bn; Ar = Ph, 2,6-$Cl_2C_6H_3$; R^1 = Me, Et

The reactions of β-azolyl enamines with azides proceeded under solvent-free conditions in the absence of base at 110°C by one of the possible routes, selectively forming 1,4-disubstituted 1,2,3-triazoles. The proposed reaction mechanism includes cycloaddition of the starting reagents, leading to 1,2,3-triazoline intermediates, followed by elimination of dimethylamine and the formation of aromatic triazole ring.

Keywords: azides, enamines, linear chains of ring systems, 1,2,3-triazoles, triazolines.

Heterocyclic compounds containing chains of several linked rings have shown various types of biological activity,[1–8] are used for the purposes of organic synthesis,[9–11] in materials chemistry,[12–17] and are recognized as promising objects for organic chemistry research. They can be considered as rod-like molecules, representing a new class of materials for organic electronics.[18,19]

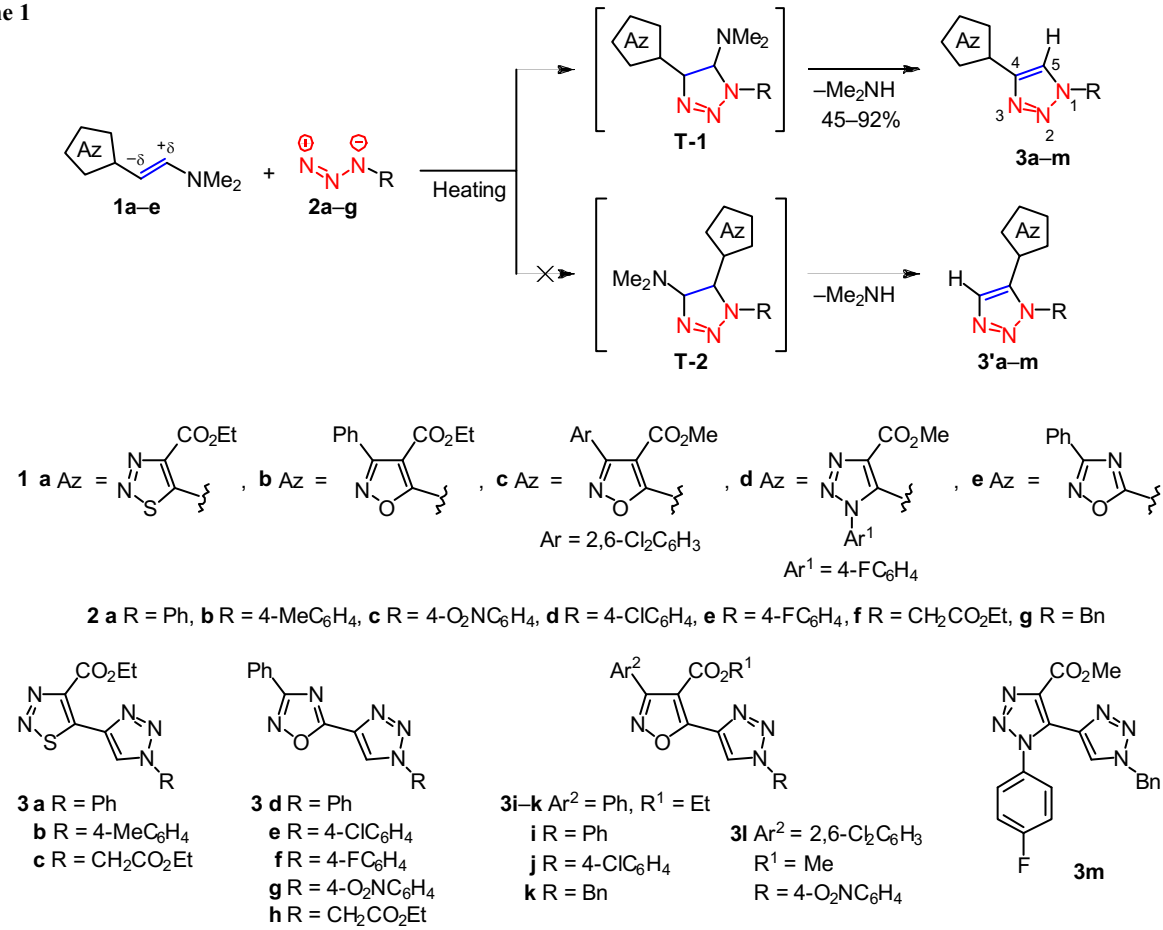
The copper-catalyzed cycloaddition of azides to acetylenes (CuAAC) discovered by Meldal and Sharpless[20,21] has attracted the interest of many synthetic chemists toward studying the properties of 1,2,3-triazole derivatives.[1,22–24] The use of CuAAC reactions has provided access to a large number of various compounds belonging to this class, including bioconjugates,[2] chemosensors,[3] ligands,[4] and anion receptors.[5] These developments have led to increased role of 1,2,3-triazoles in medicine, technology, and organic synthesis.[13,22–24]

The main methods for the synthesis of 1,2,3-triazoles include the addition of azides to acetylenes,[20,21,25] the reaction of azides with compounds containing activated methylene groups,[26,27] intramolecular cyclization of diazoimines according to the heteroelectrocyclic mechanism,[28,29] reactions of α-diazoacetonitriles with amines and hydrogen halides,[30,31] and electrophilic substitution reactions in 1,2,3-triazoles synthesized by other methods.[32] Our attention was focused on the reaction between azides and enamines, which also led to regiospecific formation of 1,4-disubstituted 1,2,3-triazoles as a result of the high reactivity of enamines toward azides, relative to other alkenes in analogous reactions.[33,34] Our preferred method for the synthesis of azolyl-1,2,3-triazoles was based on the use of β-azolyl enamines,[33–35] due to their better availability compared to azolylacetylenes. The reactions of β-azolyl enamines with aromatic and aliphatic azides have not been described in the literature, except for our preliminary report.[33]

In order to develop an effective and convenient preparative method for the synthesis of bicyclic 1,2,3-triazoles linked in linear chains with 1,2,3-thiadiazole, isoxazole, 1,2,3-triazole, or 1,2,4-oxadiazole rings, we studied the reactions of β-azolyl enamines **1a**–**e** with aromatic azides **2a**–**e**, ethoxycarbonylacetazide (**2f**), and benzyl azide (**2g**) (Scheme 1). The starting enamines **1a**–**e** were synthesized from the respective 5-methylazoles by a reaction with dimethylformamide dimethyl acetal according to previously published procedures.[34,35] Their structures were assigned as *trans*-isomers on the basis of spin-spin coupling constants (J = 13.0–13.6 Hz) of the vicinal protons in ^{1}H NMR spectra of compounds **1a**–**e**.

Aromatic azides **2a**–**e** were obtained by treatment of aromatic diazonium salts with sodium azide,[36] while 2-azidoacetate (**2f**) and benzyl azide (**2g**) were obtained by

Scheme 1



a reaction of 2-bromoacetate and benzyl bromide with sodium azide.[37]

In order to find the optimum conditions for the preparation of azolyl-1,2,3-triazoles, we studied the reaction of β-(oxadiazol-5-yl)enamine **1e** with 4-nitrophenyl azide (**2c**) in different solvents and at different temperatures (Table 1). As indicated by Table 1, the type of solvent had a minor effect on the yield of azolyltriazole **3g**.

It was shown that increasing the temperature of the process (entries 2, 3) shortened the reaction time and at the same time improved the yield of triazole **3g**. We found that rapid heating of the starting material mixture to 110°C under solvent-free conditions and maintaining for 20 min at this temperature followed by rapid cooling allowed to increase the target product yield to 92%. Thus, the optimum reaction conditions involve the use of starting materials in equivalent amounts and performing the reaction in the absence of solvent at 110°C. The same conditions were used in all our subsequent experiments for the preparation of 1,2,3-triazoles **3a**–**m**. We demonstrated that all of the synthesized enamines **1a**–**e** smoothly reacted with azides **2a**–**g** providing 45–92% yields of 1,2,3-triazoles **3a**–**m** containing 1,2,3-thiadiazole, isoxazole, 1,2,3-triazole, or oxadiazole rings in their molecules (Scheme 1).

It should be noted that analysis by TLC and ^{1}H NMR spectroscopy did not reveal the formation of 1,5-di-substituted 1,2,3-triazoles **3'** representing isomers of compounds **3**. When comparing our studied reaction of azolyl enamines and azides with the CuAAC reaction, which also led to the formation of 1,4-disubstituted 1,2,3-triazoles, it can be concluded that β-azolyl enamines can be viewed as synthetic equivalents of monosubstituted acetylenes.

Table 1. Optimization of conditions for the reaction of enamine **1e** with azide **2c*** and yields of triazole **3g**

Entry	Solvent	Temperature, °C	Time, h	Yield, %
1	DMSO	70	10	40
2	DMF	110	2.5	70
3	DMSO	110	0.5	65
4	*m*-Xylene	110	0.66	70
5	Melt	110	0.33	92

* Experiments 1–4 were performed with 0.33 mmol of the starting compounds in 1 ml of the indicated solvent, while experiment 5 was performed with the same amount of the starting materials under solvent-free conditions.

The structures of the obtained 4-(azol-5-yl)-1,2,3-triazoles **3a**–**m** were confirmed by the results of ^{1}H and ^{13}C NMR spectroscopy, as well as by X-ray structural analysis of compound **3i** (Fig. 1). It should be noted that a

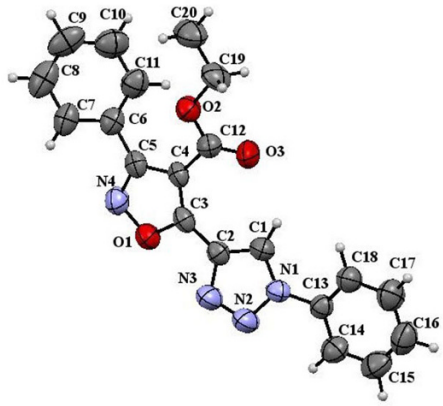


Figure 1. The molecular structure of triazole **3i** with atoms represented by thermal vibration ellipsoids of 50% probability.

characteristic feature of all obtained triazoles **3a**–**m** was the presence of ^{1}H NMR signal due to the H-5 proton of triazole ring in the range of 8.21–10.12 ppm and ^{13}C NMR signals due to the C-4 carbon atom in the range of 134.7–139.9 ppm.

The integral values for ^{1}H NMR signals belonging to the enamine moiety allowed us to determine the extent to which enamines **1a**,**b** were converted to the corresponding triazoles in reactions with azides **2a**–**d**, when heated in DMSO-d_6 solution at 110°C for 120 min (Table 2). As shown in Table 2, the conversion of both enamines decreased along with weaker electron-withdrawing properties of substituents in the aryl azide molecule (NO_2 > Cl > H > Me). Thus, we can conclude that the introduction of electron-withdrawing substituents in azide molecules increases the rate of reactions with enamines.

The reactions of aromatic azides with enamines are recognized as reactions with inverse electron demand, since the introduction of electron-withdrawing substituents in the molecule of azide (the dipole component) and electron-donating substituents in the molecule of enamine (the dipolarophile component) facilitates the cycloaddition reaction.[38] This interpretation is in agreement with our obtained data on the conversion of β-azolyl enamines achieved in reactions with aromatic azides. The expected mechanism of the reaction between enamines **1** and azides **2** involves 1,3-dipolar cycloaddition with the formation of nonaromatic 1,2,3-triazoline intermediate **T-1**, but not **T-2** (Scheme 1).

1,2,3-Triazolines are generally unstable compounds. Some compounds of this type have been isolated and identified by using NMR spectroscopy[38] and X-ray structural analysis.[39] The process leading to the formation of aromatic 1,2,3-triazoles was concluded by the elimination of dimethylamine molecule.

Thus, by studying the reaction of azolyl enamines with aromatic and aliphatic azides we have developed an effective and convenient preparative method for regioselective and atom-economical synthesis of 4-azolyl-1,2,3-triazoles.

Table 2. The degree of conversion for enamines **1a**,**b** in reactions with azides **2a**–**d** in DMSO-d_6 over 120 min, %

Enamine	Azide 4-$RC_6H_4N_3$			
	2a (R = H)	**2b** (R = Me)	**2c** (R = NO_2)	**2d** (R = Cl)
1a	20	15	78	41
1b	6	2	63	13

Experimental

IR spectra were recorded on a Bruker Alpha FTIR spectrometer equipped with a ZnSe ATR accessory. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II 400 spectrometer (400 and 100 MHz, respectively). Solvents: 1:1 DMSO-d_6–CCl_4 system (^{1}H NMR spectra of compounds **3a**,**i**,**j**,**l**,**m**), $CDCl_3$ (^{1}H and ^{13}C NMR spectra of compounds **3b**,**k**), or DMSO-d_6 (the rest of the spectra); TMS was used as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP2010 Ultra mass spectrometer (EI ionization, 70 eV). Elemental analysis (C, H, N) was performed on a PerkinElmer 2400 II automatic analyzer. Melting points were determined on a Stuart SMP3 apparatus. Reaction progress and purity of the obtained compounds were controlled by a TLC method on Sorbfil UV-254 plates using 1:1 EtOAc–hexane system. Column chromatography was performed on silica gel with 60–120 μm particle size.

The starting enamines **1a**–**e**[34,35] and azides **2a**–**g**[36,37] were obtained according to standard literature procedures. Enamines **1a**–**e** were obtained by using commercially available dimethylformamide dimethyl acetal (Sigma-Aldrich).

Preparation of 4-(azol-5-yl)-1,2,3-triazoles 3a–m (General method). A mixture of azolyl enamine **1a**–**e** (1 mmol) and azide **2a**–**g** (1 mmol) was stirred at 110°C for 0.33–6 h. The reaction mixture was then cooled to room temperature and diluted with hexane. The obtained precipitate was filtered off, dried, and recrystallized from EtOH (compound **3i** was purified by column chromatography, eluent 1:1 EtOAc–hexane).

Ethyl 5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-carboxylate (3a). Yield 0.22 g (73%), light-beige powder, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3156, 1706 (C=O), 1462, 843, 755. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.54 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.45–7.59 (1H, m, H Ph); 7.63 (2H, d, *J* = 7.8, H Ph); 7.94 (2H, d, *J* = 7.8, H Ph); 9.33 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 14.4 ($OCH_2\underline{C}H_3$); 62.6 ($O\underline{C}H_2CH_3$); 120.9 (C Ph); 123.6 (C-5); 129.7 (C Ph); 130.0 (C Ph); 136.5 (C Ph); 136.8 (C-4); 146.5 (C-5'); 152.6 (C-4'); 161.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 301 $[M]^+$ (4), 217 (27), 104 (100), 77 (80), 69 (68). Found, %: C 51.84; H 4.05; N 23.61. $C_{13}H_{11}N_5O_2S$. Calculated, %: C 51.82; H 3.68; N 23.24.

Ethyl 5-[1-(4-methylphenyl)-1*H*-1,2,3-triazol-4-yl]-1,2,3-thiadiazole-4-carboxylate (3b). Yield 0.16 g (52%), light-beige powder, mp 205–207°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.45 (3H, s, $ArCH_3$); 4.58 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.36 (2H, d,

J = 8.5, H Ar); 7.69 (2H, d, *J* = 8.5, H Ar); 9.22 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 14.4 ($OCH_2\underline{C}H_3$); 21.3 ($ArCH_3$); 62.6 ($O\underline{C}H_2CH_3$); 120.8 (C Ar); 123.5 (C-5); 130.5 (C Ar); 134.1 (C Ar); 136.7 (C Ar); 139.9 (C-4); 146.4 (C-5'); 152.7 (C-4'); 161.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 315 $[M]^+$ (5), 287 (37), 270 (53), 242 (40), 91 (100). Found, %: C 53.47; H 3.87; N 22.48. $C_{14}H_{13}N_5O_2S$. Calculated, %: C 53.32; H 4.16; N 22.21.

Ethyl 5-[1-(2-ethoxyethyl-2-oxo)-1*H*-1,2,3-triazol-4-yl]-1,2,3-thiadiazole-4-carboxylate (3c). Yield 0.14 g (45%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.38 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.20 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.48 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.58 (2H, s, NCH_2); 9.05 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 14.4 ($OCH_2\underline{C}H_3$); 14.5 ($OCH_2\underline{C}H_3$); 51.3 (NCH_2); 62.2 ($O\underline{C}H_2CH_3$); 62.4 ($O\underline{C}H_2CH_3$); 128.3 (C-5); 135.3 (C-4); 146.6 (C-5'); 152.5 (C-4'); 160.9 (C=O); 167.4 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 311 $[M]^+$ (6), 283 (44), 211 (26), 125 (17). Found, %: C 42.28; H 4.30; N 22.71. $C_{11}H_{13}N_5O_4S$. Calculated, %: C 42.44; H 4.21; N 22.50.

3-Phenyl-5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1,2,4-oxadiazole (3d). Yield 0.21 g (69%), colorless powder, mp 183–184°C. IR spectrum, ν, cm^{-1}: 3136, 1640, 1303, 1040, 745. ^{1}H NMR spectrum, δ, ppm: 7.48–7.67 (6H, m, H Ph); 8.03–8.09 (2H, m, H Ph); 8.09–8.16 (2H, m, H Ph); 9.82 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 120.6; 125.8 (C-5); 125.9; 127.1; 129.2; 129.4; 129.9; 131.7; 133.8; 135.8; 168.1 (C-3'); 168.8 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 289 $[M]^+$ (5), 144 (31), 128 (12), 118 (17), 103 (16), 77 (100), 51 (50). Found, %: C 66.61; H 3.47; N 24.61. $C_{16}H_{11}N_5O$. Calculated, %: C 66.43; H 3.83; N 24.21.

5-[1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-3-phenyl-1,2,4-oxadiazole (3e). Yield 0.24 g (75%), colorless powder, mp 250–252°C. IR spectrum, ν, cm^{-1}: 3120, 1638, 1487, 833, 742. ^{1}H NMR spectrum, δ, ppm: 7.50–7.69 (5H, m, H Ar); 8.03–8.18 (4H, m, H Ar); 9.87 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 122.4; 125.8 (C-5); 126.3; 127.1; 129.3; 129.9; 131.8; 133.9; 134.0; 134.7; 168.2 (C-3'); 168.8 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 325 $[M(^{37}Cl)]^+$ (8), 323 $[M(^{35}Cl)]^+$ (22), 180 (30), 179 (20), 178 (100), 177 (38), 176 (31), 164 (17), 150 (28), 128 (23), 118 (59), 113 (19), 111 (59), 77 (60), 76 (18), 75 (45). Found, %: C 59.12; H 2.72; N 21.60. $C_{16}H_{10}ClN_5O$. Calculated, %: C 59.36; H 3.11; N 21.63.

5-[1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl]-3-phenyl-1,2,4-oxadiazole (3f). Yield 0.24 g (78%), beige powder, mp 225–227°C. IR spectrum, ν, cm^{-1}: 3125, 1639, 1511, 1225, 827, 744. ^{1}H NMR spectrum, δ, ppm: 7.34–7.44 (2H, m, H Ar); 7.53–7.62 (3H, m, H Ar); 8.08–8.16 (4H, m, H Ar); 9.82 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 116.8 (d, *J* = 23.0); 123.6 (d, *J* = 9.0); 125.8 (C-5); 126.3; 127.1; 129.3; 131.8; 132.4 (d, *J* = 3.0); 133.9; 162.1 (d, *J* = 244.0, C–F); 168.1 (C-3'); 168.8 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 307 $[M]^+$ (18), 162 (100), 161 (47), 160 (41), 146 (17), 134 (46), 128 (26), 119 (16), 118 (73), 95 (92), 77 (71), 76 (15), 75 (46). Found, %: 62.48; H 3.08; N 22.82. $C_{16}H_{10}FN_5O$. Calculated, %: C 62.54; H 3.28; N 22.79.

5-[1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl]-3-phenyl-1,2,4-oxadiazole (3g). Yield 0.30 g (92%), colorless powder, mp 288–290°C. IR spectrum, ν, cm^{-1}: 3120, 1639, 1522, 1337, 1039, 853, 745. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.52–7.64 (3H, m, H Ph); 8.12–8.15 (2H, m, H Ph); 8.43 (2H, d, *J* = 9.3, H Ar); 8.50 (2H, d, *J* = 9.3, H Ar); 10.12 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 122.0; 126.0 (C-5); 126.3; 127.3; 127.7; 129.9; 132.4; 134.9; 140.7; 147.9; 168.7 (C-3'); 169.1 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 334 $[M]^+$ (8), 189 (18), 143 (25), 128 (19), 118 (37), 103 (34), 91 (23), 77 (100), 76 (82), 75 (39). Found, %: C 57.65; H 2.90; N 25.52. $C_{16}H_{10}N_6O_3$. Calculated, %: C 57.49; H 3.02; N 25.14.

Ethyl 2-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)-1*H*-1,2,3-triazol-1-yl]acetate (3h). Yield 0.21 g (70%), colorless powder, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3070, 1707, 1513, 1220, 852. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.26 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.49 (2H, s, NCH_2); 7.52–7.58 (3H, m, H Ph); 8.08–8.14 (2H, m, H Ph); 9.03 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 13.8 ($OCH_2\underline{C}H_3$); 50.6 (NCH_2); 61.5 ($O\underline{C}H_2CH_3$); 126.1 (C-5); 126.9 (2C Ph); 128.7 (2C Ph); 128.8; 131.1; 132.9; 166.0 (C=O); 167.9 (C-3'); 168.7 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 299 $[M]^+$ (4), 240 (19), 223 (35), 145 (28), 135 (63), 77 (100). Found, %: C 56.51; H 4.72; N 23.17. $C_{14}H_{13}N_5O_3$. Calculated, %: C 56.18; H 4.38; N 23.40.

Ethyl 3-phenyl-5-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-1,2-oxazole-4-carboxylate (3i). Yield 0.20 g (56%), colorless prisms, mp 153–154°C. IR spectrum, ν, cm^{-1}: 3180, 2926, 1714, 1618, 1131. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.25 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.46–7.76 (8H, m, H Ph); 8.00 (2H, d, *J* = 8.0, H Ph); 9.42 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 13.6 ($OCH_2\underline{C}H_3$); 61.4 ($O\underline{C}H_2CH_3$); 108.5 (C-4'); 120.8; 125.4 (C-5); 127.5; 128.4; 129.0; 129.6; 130.1; 130.3; 135.2; 136.0; 160.9 (C=O); 162.3 (C-3'); 163.7 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 360 $[M]^+$ (4), 286 (17), 259 (17), 144 (95), 143 (94), 116 (22), 104 (25), 77 (100). Found, %: C 66.69; H 4.61; N 15.79. $C_{20}H_{16}N_4O_3$. Calculated, %: C 66.66; H 4.48; N 15.55.

Ethyl 5-[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]-3-phenyl-1,2-oxazole-4-carboxylate (3j). Yield 0.24 g (61%), light-beige powder, mp 130–133°C. IR spectrum, ν, cm^{-1}: 3173, 1718, 1500, 1135, 824. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.25 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 7.26–7.56 (3H, m, H Ar); 7.56–7.85 (4H, m, H Ar); 8.03–8.06 (2H, m, H Ar); 9.46 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 13.5 ($OCH_2\underline{C}H_3$); 61.3 ($O\underline{C}H_2CH_3$); 108.5 (C-4'); 122.4; 125.3 (C-5); 127.4; 128.3; 128.9; 129.9; 130.1; 133.8; 134.8; 135.2; 160.8 (C=O); 162.1 (C-3'); 163.5 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 396 $[M(^{37}Cl)]^+$ (4), 394 $[M(^{35}Cl)]^+$ (10), 368 (27), 366 (39), 217 (33), 145 (42), 113 (27), 111 (100), 77 (38), 76 (18), 75 (41). Found, %: C 60.86; H 3.64; N 14.28. $C_{20}H_{15}ClN_4O_3$. Calculated, %: C 60.84; H 3.83; N 14.19.

Ethyl 5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3-phenyl-1,2-oxazole-4-carboxylate (3k). Yield 0.22 g (62%), colorless

powder, mp 161–163°C. IR spectrum, ν, cm^{-1}: 3116, 1624, 1067, 696. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.66 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 3.77 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.25 (2H, s, NCH_2); 6.88–7.11 (8H, m, H Ph); 7.18–7.20 (2H, m, H Ph); 8.21 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 13.6 ($OCH_2\underline{C}H_3$); 54.4 (NCH_2); 61.1 ($O\underline{C}H_2CH_3$); 108.0 (C-4'); 126.4; 127.9; 128.0; 128.4; 129.0; 129.2; 129.3; 129.7; 134.0; 136.0; 161.8 (C=O); 162.6 (C-3'); 164.8 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 374 $[M]^+$ (5), 91 (100), 77 (17), 65 (15). Found, %: C 67.07; H 5.15; N 14.61. $C_{21}H_{18}N_4O_3$. Calculated, %: C 67.37; H 4.85; N 14.96.

Methyl 3-(2,6-dichlorophenyl)-5-[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]-1,2-oxazole-4-carboxylate (3l). Yield 0.38 g (82%), cream-colored powder, mp 205–207°C. IR spectrum, ν, cm^{-1}: 3188, 1732, 1522, 1504, 1346, 780. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.71 (3H, s, OCH_3); 7.59 (3H, s, H Ar); 8.37 (2H, d, *J* = 9.1, H Ar); 8.49 (2H, d, *J* = 9.1, H Ar); 9.75 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 52.5 (OCH_3); 108.9 (C-4'); 121.6; 125.5; 126.4; 126.7; 128.3; 132.7; 134.3; 135.1; 140.2; 147.3; 158.9 (C=O); 160.0 (C-3'); 163.9 (C-5'). Mass spectrum, *m*/*z* (I_{rel}, %): 459 $[M(^{35}Cl)]^+$ (4), 399 (19), 398 (15), 396 (42), 213 (65), 211 (100), 189 (25), 146 (18), 143 (45), 76 (43). Found, %: C 49.41; H 2.53; N 14.93. $C_{19}H_{11}Cl_2N_5O_5$. Calculated, %: C 49.59; H 2.41; N 15.22.

Methyl 1-benzyl-(4-fluorophenyl)-1*H*,3'*H*-4,4'-bis(1,2,3-triazole)-5'-carboxylate (3m). Yield 0.22 g (59%), colorless powder, mp 160–162°C. IR spectrum, ν, cm^{-1}: 3070, 1707, 1513, 1220, 852. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.33 (3H, s, OCH_3); 5.22 (2H, br. s, NCH_2); 6.55–6.84 (2H, m, H Ar); 6.90 (5H, br. s, H Ar); 7.09 (2H, br. s, H Ar); 8.23 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 52.5 (OCH_3); 53.3 (NCH_2); 116.5 (d, *J* = 23.0); 127.4; 128.2; 128.3; 128.6 (d, *J* = 9.0); 128.8; 132.3; 132.5 (d, *J* = 4.0); 133.0; 135.7; 136.1; 160.7 (C=O); 162.5 (d, *J* = 246.0, C–F). Mass spectrum, *m*/*z* (I_{rel}, %): 378 $[M]^+$ (3), 228 (59), 226 (36), 158 (18), 95 (100). Found, %: C 60.44; H 3.85; N 22.06. $C_{19}H_{15}FN_6O_2$. Calculated, %: C 60.31; H 4.00; N 22.21.

X-ray structural study of compound 3i. Crystals of compound **3i** ($C_{20}H_{16}N_4O_3$, *M* 360.12) suitable for X-ray structural analysis were obtained by slowly evaporating an ethanol solution of compound **3i**. A fragment of colorless crystal was studied on an Xcalibur 3 monocrystal X-ray diffractometer according to the standard procedure (MoKα radiation, graphite monochromator, ω-scanning with a step of 1°, 295(2) K). The structure was solved and refined by using the SHELXTL software suite.[40] The structure was solved by direct method with the ShelXS program and refined by full-matrix method of least squares by F^2 with the ShelXL program in anisotropic approximation for non-hydrogen atoms. The hydrogen atom positions were calculated and included in the refinement according to the "rider" model. The complete dataset obtained by X-ray structural analysis for compound **3i** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1580192).

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References

1. De Carvalho da Silva, F.; Cardoso, M. F. C.; Ferreira, P. G.; Ferreira, V. F. *Top. Heterocycl. Chem.* **2015**, *40*, 117.
2. Leban, J.; Baumgartner, R.; Saeb, W.; Chevrier, C. WO Patent 2012101261.
3. Li, W.-T.; Wu, W.-H.; Tang, C.-H.; Tai, R.; Chen, S.-T. *ACS Comb. Sci.* **2011**, *13*, 72.
4. Olesen, P. H.; Sørensen, A. R.; Ursø, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. *J. Med. Chem.* **2003**, *46*, 3333.
5. Lu, R. J.; Pickens, J. C.; Tucker, J. A.; Zinevitch, T.; Sviridov, S.; Konoplev, V. WO Patent 2007103456.
6. Leclerc, J.-P.; Li, C. S.; Ramtohul, Y. K. WO Patent 2010025553.
7. Hirose, T.; Sunazuka, T.; Noguchi, Y.; Yamaguchi, Y.; Hanaki, H.; Sharpless, K. B.; Omura, S. *Heterocycles* **2006**, *69*, 55.
8. Sapountzis, I.; Ettmayer, P.; Klein, C.; Mantoulidis, A.; Steegmaier, M.; Steurer, S.; Waizenegger, I. WO Patent 2009003998.
9. Patil, P.; Madhavachary, R.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Dömling, A. *Org. Lett*. **2017**, *19*, 642.
10. Sinn, S.; Biedermann, F.; De Cola, L. *Chem.–Eur. J.* **2017**, *23*, 1965.
11. Kaur, T.; Gautam, R. N.; Sharma, A. *Chem.–Asian J.* **2016**, *11*, 2938.
12. Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389.
13. Watkinson, M. *Top. Heterocycl. Chem*. **2012**, *28*, 109.
14. Potratz, S.; Mishra, A.; Bäuerle, P. *Beilstein J. Org. Chem*. **2012**, *8*, 683.
15. van Steenis, D. J. V. C.; David, O. R. P.; van Strijdonck, G. P. F.; van Maarseveen, J. H.; Reek, J. N. H. *Chem. Commun*. **2005**, 4333.
16. Kulhánek, J.; Ludwig, M.; Bureš, F.; Tydlitát, J. *Chem. Heterocycl. Compd*. **2017**, *53*, 46. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 46.]
17. Kostyuchenko, A. S.; Drozdova, E. A.; Fisyuk, A. S. *Chem. Heterocycl. Compd*. **2017**, *53*, 92. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 92.]
18. Horčic, M.; Kozmík, V.; Svoboda, J.; Novotná, V.; Pociecha, D. *J. Mater. Chem. C* **2013**, *1*, 7560.
19. Kim, M.-H.; Nam, Y.-K.; Choi, E.-J. *J. Inf. Disp.* **2017**, *18*, 31.
20. Tornøe, C. W.; Chistensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.
21. Rostovtsev, V. V.; Green, L. G., Fokin V. V.; Sharpless, B. K. *Angew. Chem., Int. Ed*. **2002**, *41*, 2596.
22. Crowley, J. D.; McMorran, D. A. *Top Heterocycl. Chem*. **2012**, *28*, 31.
23. Lee, S.; Flood, A. H. *Top Heterocycl. Chem*. **2012**, *28*, 85.
24. Zheng, T.; Rouhanifard, S. H.; Jalloh, A. S.; Wu, P. *Top Heterocycl. Chem*. **2012**, *28*, 163.
25. Bakulev, V. A.; Dehaen, W. *The Chemistry of 1,2,3-Thiadiazoles*; John Wiley & Sons Inc.: Hoboken, Heidelberg, New York, Dordrecht, London, 2004, 241 pp.
26. Mignani, S.; Zhou, Y.; Lecourt, T.; Micouin, L. *Top Heterocycl. Chem*. **2012**, *28*, 185.
27. Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev*. **2005**, *74*, 339. [*Usp. Khim.* **2005**, *74*, 369.]
28. Bakulev, V. A.; Morzherin, Yu. Yu.; Lebedev, A. T.; Dankova, E. F.; Kolobov, M. Yu.; Shafran, Yu. M. *Bull. Soc. Chim. Belg*. **1993**, *102*, 493.
29. Bakulev, V. A. *Rus. Chem. Rev.* **1995**, *64*, 99. [*Usp. Khim.* **1995**, *64*, 107.]
30. Shafran, Yu. M.; Bakulev, V. A.; Mokrushin, V. S.; Alexeev, S. G. *Chem. Heterocycl. Compd.* **1984**, *20*, 1038. [*Khim. Geterotsikl. Soedin.* **1984**, 1266.]
31. Bakulev, V. A.; Chiang, Y.; Kresge, A. J.; Meng, Q.; Morzherin, Y. Y.; Popik, V. V. *J. Am. Chem. Soc.* **2001**, *123*, 2681.
32. Bakulev, V. A.; Beryozkina, T. V. *Chem. Heterocycl. Compd.* **2016**, *52*, 4. [*Khim. Geterotsikl. Soedin.* **2016**, *52*, 4.]

33. Bakulev, V. A.; Efimov, I. V.; Belyaev, N. A.; Rozin, Yu. A.; Volkova, N. N.; El'tsov, O. S. *Chem. Heterocycl. Compd*. **2012**, *47*, 1593. [*Khim. Geterotsikl. Soedin.* **2011**, 1900.]
34. Bakulev, V. A.; Efimov, I. V.; Belyaev, N. A.; Zhidovinov, S. S.; Rozin, Yu. A.; Volkova, N. N.; Khabarova, A. A.; El'tsov, O. S. *Chem. Heterocycl. Compd.* **2013**, *48*, 1880. [*Khim. Geterotsikl. Soedin.* **2012**, 2002.]
35. Beryozkina, T. V.; Zhidovinov, S. S.; Shafran, Y. M.; Eltsov, O. S.; Slepukhin, P. A.; Leban, J.; Marquez, J.; Bakulev, V. A. *Tetrahedron* **2014**, *70*, 3915.
36. Maruani, A.; Alom, S.; Canavelli, P.; Lee, M. T. W.; Morgan, R. E.; Chudasama, V; Caddick, S. *Chem. Commun*. **2015**, *51*, 5279.
37. Berry, M. T.; Castrejon, D.; Hein, J. E. *Org. Lett*. **2014**, *16*, 3676.
38. Bakulev, V. A.; Beryozkina, T. V.; Tomas, J.; Dehaen, W. *Eur. J. Org. Chem*. **2018**, 262.
39. Murata, S.; Mori, Y.; Satoh, Y.; Yoshidome, R.; Tomioka, H. *Chem. Lett*. **1999**, 597.
40. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A: Found. Crystallogr.* **2008**, *A64*, 112.