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Selectivity in domino reaction of *ortho*-carbonyl azides with malononitrile dimer leading to [1,2,3]triazolo[1,5-*a*]pyrimidines

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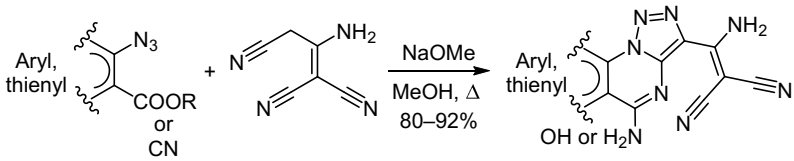


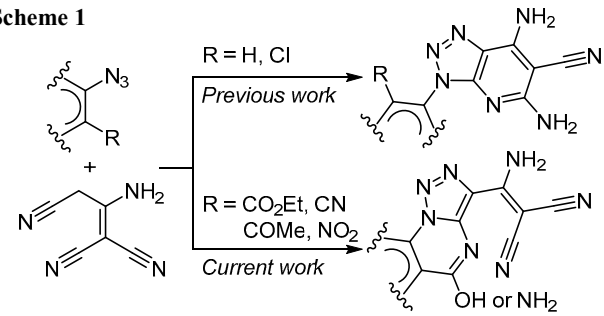
The selectivity of the domino reaction of the (het)aryl azides, containing the carbonyl center in the *ortho* position to the azido group, with malonodinitrile dimer was studied. It has been shown that in the case of aromatic azides bearing a carboxy or nitrile function in the *ortho* position, the reaction occurred with the formation of exclusively [1,2,3]triazolo[1,5-*a*]pyrimidine instead of [1,2,3]triazolo[4,5-*b*]pyridine system. Thus, new [1,2,3]triazolo[1,5-*a*]quinazolines, thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine, and thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]-pyrimidines, having polyfunctional 1-amino-2,2-dicyanovinyl fragment, were prepared in short time in high yields.

Keywords: azides, malononitrile dimer, [1,2,3]triazolo[1,5-*a*]pyrimidines, domino reaction, selectivity.

The malononitrile dimer is an attractive organic reagent containing several reactive centers with different nature allowing to construct a diversity of polyfunctional derivatives. For example, some recent works were dedicated to the application of malononitrile dimer in synthesis of new condensed heterocyclic systems, such as furo[3,2-*c*]-isothiazole,[1] furo[3,2-*c*]isoselenazole,[2] pyrido[3',2':5,6]-pyrano[3,2-*c*]carbazoles,[3] 1,8-naphthyridines,[4] chromeno-[2,3-*b*]pyridines,[5] pyrido[3,2-*c*]pyridazines,[6] and pyrido-[3,2-*a*]indolizines.[7] These studies demonstrated the large potential of malononitrile dimer for preparation of new ring systems, which can be studied and developed further.

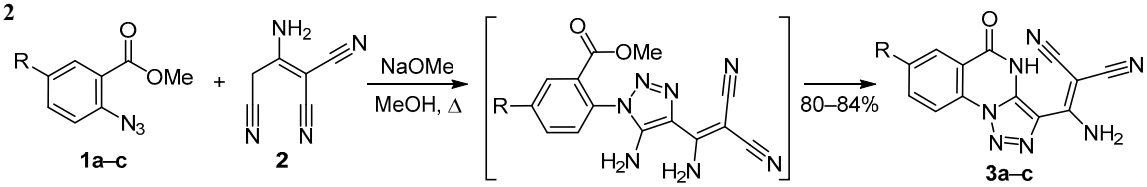
Recently, we reported a new variation of domino process providing access to polyfunctional [1,2,3]triazolo-[4,5-*b*]pyridines *via* the reaction of aryl azides with malononitrile dimer.[8] The reaction occurred in two steps through the formation of 5-aminotriazole intermediate, which underwent spontaneous cyclization leading to the pyridine ring annulation. The scope of the reaction was demonstrated on 9 compounds with various substituents in the aromatic ring. However, aryl or hetaryl azides that have carbonyl center in *ortho* position to azide moiety have not been studied in the reaction with malononitrile dimer. It was previously shown that such azides reacted with activated acetonitriles to form condensed [1,2,3]triazolo-[1,5-*a*]pyrimidines.[9] Such reaction proceeds rapidly (generally during the mixing of the reagents) and leads to the triazolopyrimidine formation in excellent yields, as it was described in a number of our articles.[9] Therefore, we decided to examine *ortho*-substituted aryl azides in the reaction with malononitrile dimer to identify the direction of reaction and to find out which system, [1,2,3]triazolo-[1,5-*a*]pyrimidine or [1,2,3]triazolo[4,5-*b*]pyridine, will be formed preferably (Scheme 1).

Scheme 1



The reactions of azides **1a–g** with malononitrile dimer (**2**) were carried out under standard protocol[8] by refluxing their solutions in methanol with sodium methylate until the precipitate was formed. It was found, that in the case of *o*-alkoxycarbonyl azides **1a**–**c**, reaction proceeds in a chemoselective manner leading to only one of the two

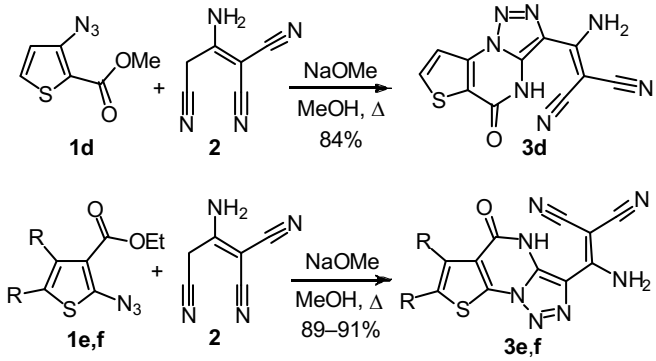
Scheme 2



possible fused heterocyclic compounds. Thus, [1,2,3]triazolo[1,5-*a*]quinazolines **3a**–**c** (Scheme 2) were isolated in excellent yields after 1 min refluxing.

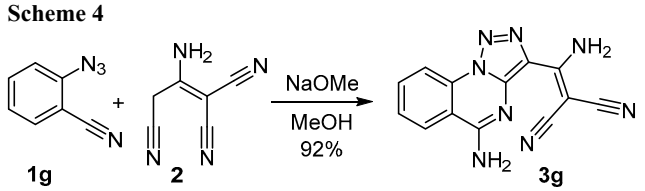
The reaction occurred similarly in the case of alkyl azidothiophenecarboxylates **1d**–**f**, allowing to obtain thieno-[2,3-*e*]- or [3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **3d**–**f** in high yields (Scheme 3).

Scheme 3



The structure of the *o*-alkoxycarbonyl azides had only a slight effect on the reaction yields. Replacement of the alkoxycarbonyl group with nitrile group did not change the course of reaction. Thus, the interaction of 2-azidobenzonitrile **1g** with malononitrile dimer (**2**) led to the selective formation of 5-amino[1,2,3]triazolo[1,5-*a*]-quinazoline **3g** in high yield (Scheme 4). But the reaction of *ortho*-nitro and acetyl azides resulted in the formation of tarry mixtures.

Scheme 4



The HPLC-MS analysis data confirmed that compounds **3a**–**g** were the single products of the reaction, pointing to the good selectivity of the process.

It should be noted that in the ^{1}H NMR spectra of compounds **3a**–**f**, signals of NH protons of pyrimidinone ring were not observed. It can be explained by the fact that due to the electron-withdrawing effect of 1,2,3-triazole ring the NH proton apparently has a significant acidity and a tautomeric equilibrium of 5-oxo and hydroxy forms is formed. Moreover, compounds **3a**–**f** are poorly soluble in most organic solvents, particularly in DMSO. Thus, an additional heating of samples in DMSO-d_6 was required to homogenize the solution. Under these conditions, NH protons were exchanged rapidly with deuterium atoms of the surrounding deuterated solvent. And as a result, the NH proton signal is not observed in spectra. Enamine proton signals (=C–NH_2) in compounds **3a**–**g** were found as two broad signals at 8.08–8.18 and 8.23–8.96 ppm.

^{13}C NMR spectra and ^{1}H–^{13}C HMBC experiments clearly indicate the formation of [1,2,3]triazolo[1,5-*a*]-pyrimidines by the presence of the signal of central carbon atom in the dicyanomethylene fragment (=$C(CN)_2$) with the chemical shift in 42.2–42.6 ppm range. Other characteristic carbon chemical shifts for compounds **3a**–**f** are given in Figure 1. Due to the amine-imine tautomerism in the (aminomethylidene)malononitrile fragment, which leads to easy rotation of malonodinitrile moiety, carbon atoms of two CN groups give a common signal (compounds **3a**–**c**). It is interesting that the non-equivalence of both CN groups is observed in the carbon NMR spectra of compounds **3d**–**f**, containing the thiophene ring. Probably the electron-rich thiophene ring increases the electron density on nitrogen atom of the pyrimidine ring leading to the formation of stable hydrogen bonds with the hydrogen atom of the amino group (=C–NH_2). As a result, tautomeric shifts and conformation conversions (rotation of malonodinitrile fragment) were inhibited to form stable configuration with nonequivalent CN groups. In ^{13}C NMR spectra of compounds **3d**–**f**, two neighboring signals are detected at 118.2–118.5 ppm with the chemical shifts difference of 0.2 ppm.

The assignment of downfield signals in carbon NMR spectra of compounds **3a**–**f**, in particular, of carbonyl (C=O) signal at 160.2–166.3 ppm, was carried out by comparing the spectra of compounds **3a**–**f** with those of

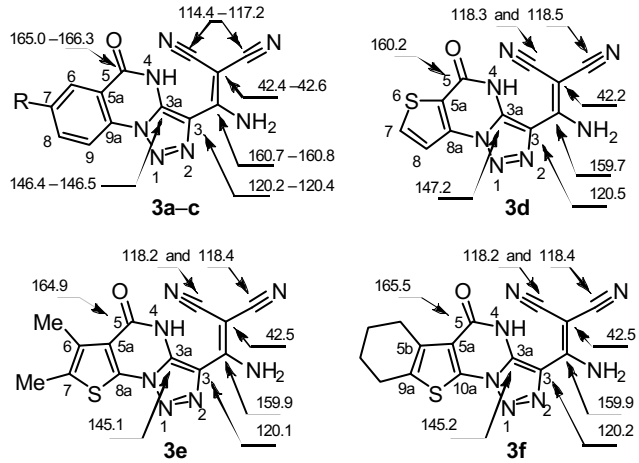


Figure 1. Characteristic chemical shifts (ppm) in ^{13}C NMR spectra of triazolopyrimidines **3a**–**f**.

[1,2,3]triazolo[1,5-*a*]pyrimidines prepared previously.[9] Enamine carbon signals (=C–NH_2) in compounds **3a**–**f** were found at 159.7–160.8 ppm.

In summary, the selectivity of the domino reaction of the (het)aryl azides, containing the carbonyl center in the *ortho* position to the azido group, with malononitrile dimer was studied and new [1,2,3]triazolo[1,5-*a*]quinazolines, thieno-[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine, and thieno[3,2-*e*]-[1,2,3]triazolo[1,5-*a*]pyrimidines, having polyfunctional aminodicyanovinyl fragment at position 4 of triazole ring were synthesized.

Experimental

^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively), and ^{1}H–^{13}C HMBC spectra were acquired on a Varian Mercury 400 instrument in DMSO-d_6 with TMS as internal standard. HPLC-MS analysis was performed by using an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode array and mass-selective Agilent LC/MSD SL detector, chemical ionization at atmospheric pressure (ionization agent NH_4^+). Elemental analysis was performed on a Carlo Erba 1106 analyzer. Melting points were measured on a Boetius apparatus.

Starting azides **1a**–**g** were prepared from the corresponding amines as was described in our previous work.[9a,b,d]

Synthesis of [1,2,3]triazolo[1,5-*a*]pyrimidines 3a–**g** (General method). Malononitrile dimer (**2**) 1.32 g (10.0 mmol) was dissolved in a minimal quantity of methanol under reflux. Then the obtained solution was added to a solution of appropriate azide **1a**–**g** (10.0 mmol) and NaOMe (540 mg, 10.0 mmol) in dry MeOH (25 ml), and the mixture was refluxed until the precipitate was formed. When TLC monitoring (DCM–MeOH, 10:1) indicated that starting azide had disappeared, the suspension was filtered and the solid product was washed with H_2O and MeOH to give the target triazole as a white, crystalline solid.

[Amino(5-oxo-4,5-dihydro[1,2,3]triazolo[1,5-*a*]quinazolin-3-yl)methylidene]propanedinitrile (3a). Yield 2.22 g (80%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.96 (1H, s, NH_2); 8.35–8.06 (3H, m, H-6,9, NH_2); 7.83 (1H, t, *J* = 6.6, H-8); 7.57 (1H, t, *J* = 6.6, H-7). ^{13}C NMR spectrum, δ, ppm: 166.3 (CO); 160.8 (=C–NH_2); 146.5 (C-3a); 134.8 (C-9a); 133.2 (C-8); 128.8 (C-7); 127.1 (C-6); 121.8 (C-5a); 120.2 (C-3); 118.9 (C-9); 114.4 (2CN); 42.3 (<u>C</u>$(CN)_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 278 $[M+H]^+$ (100). Found, %: C 56.37; H 2.59; N 35.28. $C_{13}H_7N_7O$. Calculated, %: C 56.32; H 2.55; N 35.37.

[Amino(7-chloro-5-oxo-4,5-dihydro[1,2,3]triazolo[1,5-*a*]quinazolin-3-yl)methylidene]propanedinitrile (3b). Yield 2.58 g (83%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.60 (2H, s, NH_2); 8.20 (1H, d, *J* = 7.8, H-8); 8.19 (1H, s, H-6); 8.09 (1H, s, NH); 7.86 (1H, d, *J* = 7.8, H-9). ^{13}C NMR spectrum, δ, ppm: 165.2 (CO); 160.7 (=C–NH_2); 146.4 (C-3a); 134.2 (C-7) 133.6 (C-9a); 133.3 (C-9); 131.6 (C-8); 128.1 (C-6); 120.4 (C-3); 120.4 (C-5a); 117.0 (2CN); 42.6 (<u>C</u>$(CN)_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 312 $[M+H]^+$ (100). Found, %: C 50.17; H 1.85; N 31.41. $C_{13}H_6ClN_7O$. Calculated, %: C 50.10; H 1.94; N 31.46.

[Amino(7-bromo-5-oxo-4,5-dihydro[1,2,3]triazolo[1,5-*a*]quinazolin-3-yl)methylidene]propanedinitrile (3c). Yield 2.98 g (84%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.86 (1H, s, NH_2); 8.22 (1H, s, H-6); 8.18 (1H, s, NH_2); 8.14 (1H, d, *J* = 8.7, H-9); 7.99 (1H, d, *J* = 8.7, H-8). ^{13}C NMR spectrum, δ, ppm: 165.0 (CO); 160.7 (=C–NH_2); 146.4 (C-3a); 136.8 (C-9a); 136.0 (C-8); 133.9 (C-4); 131.1 (C-6); 120.7 (C-9); 120.4 (C-3); 119.7 (C-5a); 117.2 (2CN); 42.6 (<u>C</u>$(CN)_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 356 $[M(^{79}Br)+H]^+$ (100), 358 $[M(^{81}Br)+H]^+$ (97). Found, %: C 43.75; H 1.75; N 27.58. $C_{13}H_6BrN_7O$. Calculated, %: C 43.84; H 1.70; N 27.53.

[Amino(5-oxo-4,5-dihydrothieno[2,3-*e*][1,2,3]triazolo-[1,5-*a*]pyrimidin-3-yl)methylidene]propanedinitrile (3d). Yield 2.38 g (84%). Mp 258–259°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.63 (1H, s, NH_2); 8.12 (2H, br. s, H-7, NH_2); 7.27 (1H, d, *J* = 5.2, H-8). ^{13}C NMR spectrum, δ, ppm: 160.2 (CO); 159.7 (=C–NH_2); 152.3 (C-8a); 147.2 (C-3a); 136.3 (C-7); 124.3 (C-8); 120.5 (C-3); 118.5 (CN); 118.3 (CN); 110.4 (C-5a); 42.2 (<u>C</u>$(CN)_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 284 $[M+H]^+$ (100). Found, %: C 46.71; H 1.72; N 34.72. $C_{11}H_5N_7OS$. Calculated, %: C 46.64; H 1.78; N 34.61.

[Amino(6,7-dimethyl-5-oxo-4,5-dihydrothieno[3,2-*e*]-[1,2,3]triazolo[1,5-*a*]pyrimidin-3-yl)methylidene]propanedinitrile (3e). Yield 2.77 g (89%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm: 8.23 (1H, s, NH_2); 8.09 (1H, s, NH_2); 2.41 (3H, s, CH_3); 2.27 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 164.9 (CO); 159.9 (=C–NH_2); 152.9 (C-8a); 145.1 (C-3a); 128.0 (C-6); 123.2 (C-7); 120.1 (C-3); 118.4 (CN); 118.2 (CN); 112.8 (C-5a); 42.5 (<u>C</u>$(CN)_2$); 13.8 (CH_3); 13.1 (CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 312 $[M+H]^+$ (100). Found, %: C 50.08; H 2.93; N 31.44. $C_{13}H_9N_7OS$. Calculated, %: C 50.15; H 2.91; N 31.49.

[Amino(5-oxo-4,5,6,7,8,9-hexahydrobenzo[4,5]thieno-[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidin-3-yl)methylidene]-propanedinitrile (3f). Yield 3.07 g (91%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm: 8.28 (1H, s, NH_2); 8.08 (1H, s, NH_2); 2.92 (2H, br. s, CH_2); 2.64 (2H, br. s, CH_2); 1.78 (4H, br. s, CH_2). ^{13}C NMR spectrum, δ, ppm: 165.5 (CO); 159.9 (=C–NH_2); 152.6 (C-10a); 145.2 (C-3a); 130.4 (C-5b); 126.3 (C-11); 120.2 (C-3); 118.4 (CN); 118.2 (CN); 111.9 (C-5a); 42.5 (<u>C</u>$(CN)_2$); 26.2 (CH_2); 25.1 (CH_2); 23.1 (CH_2); 22.5 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 338 $[M+H]^+$ (100). Found, %: C 53.49; H 3.23; N 29.00. $C_{15}H_{11}N_7OS$. Calculated, %: C 53.40; H 3.29; N 29.06.

[Amino(5-amino[1,2,3]triazolo[1,5-*a*]quinazolin-3-yl)-methylidene]propanedinitrile (3g). Yield 2.54 g (92%). Mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.68 (2H, s, NH_2); 8.44 (2H, d, *J* = 7.8, H-6,9); 8.23 (1H, s, NH_2); 8.06 (1H, t, *J* = 7.5, H-8); 7.78 (1H, t, *J* = 7.5, H-7). ^{13}C NMR spectrum, δ, ppm: 160.4 (=C–NH_2(C-5)); 158.9 (C-5(=C–NH_2)); 141.9 (C-3a); 135.7 (C-8); 133.6 (C-9a); 128.6 (C-7); 126.4 (C-6); 123.3 (C-3); 117.4 (C-9); 115.8 (2CN); 112.0 (C-5a); 45.7 (<u>C</u>$(CN)_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 277 $[M+H]^+$ (100). Found, %: C 56.49; H 2.97; N 40.51. $C_{13}H_8N_8$. Calculated, %: C 56.52; H 2.92; N 40.56.

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