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SHORT COMMUNICATIONS

Reaction of 3-(Pyridin-2-yl)-1,2,4-triazine-5-carbonitriles with 2-Amino-4-aryl-1,3-oxazoles in Anhydrous Medium[1]

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Abstract—We previously reported the solvent-free reaction of 5-aryl-3-(pyridin-2-yl)-1,2,4-triazine-5-carbonitriles with 2-amino-4-aryl-1,3-oxazoles, which afforded 4,5-diaryl-3-hydroxy-2,2′-bipyridine-6-carbonitriles. Similar reaction in anhydrous medium led to the formation of two products, previously described 4,5-diaryl-3-hydroxy-2,2′-bipyridine-6-carbonitriles (up to 44%) and 4,5-diaryl-2,2′-bipyridine-6-carbonitriles (up to 32%).

Keywords: 5-cyano-1,2,4-triazines, 2-aminooxazoles, solvent-free reaction, anhydrous conditions, aza-Diels–Alder reaction, 4,5-diaryl-3-hydroxy-2,2′-bipyridines

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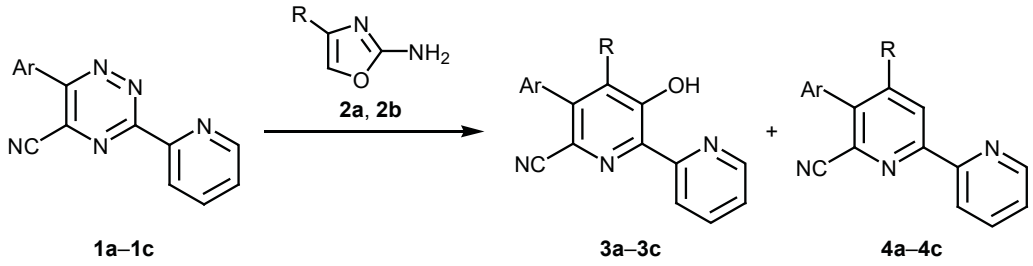
Reactions of substituted 1,2,4-triazines with various dienophiles [1] provide a promising method for the synthesis of pyridine [2, 3], cycloalkapyridine [4], isoquinoline [5], pyrido[1,2-*a*]indole [6], and other derivatives. We have recently shown that 2-amino-4-aryl-1,3-oxazoles as dienophiles can be involved in these reactions under different conditions (solvent-free or in a solvent) [7, 8] to obtain 4,5-diaryl-3-hydroxy-2,2′-bipyridine-6-carbonitriles. The latter are of practical interest since they exhibit antibiotic and antitumor activities [9, 10] and are used as enzyme inhibitors [11]. In the present work we studied the reaction of 5-aryl-3-(pyridin-2-yl)-1,2,4-triazine-5-carbonitriles with 2-amino-4-aryl-1,3-oxazoles in the absence of even traces of water in the reaction mixture.

The reactants were dried by azeotropic removal of water via distillation with anhydrous toluene. The subsequent reaction of dried compounds **1** and **2** under solvent-free conditions led to the formation of two products (Scheme 1) which can be easily separated by column chromatography. According to the ^{1}H NMR and mass spectra and elemental analysis, one of the products was previously described 4,5-diaryl-3-hydroxy-2,2′-bipyridine-6-carbonitrile **3a**–**3c**; the spectral and analytical data for compounds **3a**–**3c** fully coincided with those reported by us previously [7]. The other product was 4,5-diaryl-2,2′-bipyridine-6-carbonitrile **4a**–**4c** bearing no hydroxy group at the 3-position. The ^{1}H NMR spectra of **4a**–**4c** showed signals from protons in the two aromatic substituents and pyridine fragments, and a singlet at δ 8.70– 8.83 ppm due to the 3-H proton. However, the ^{1}H NMR spectra of **4a**–**4c** did not allow us to unambiguously determine the position of the newly introduced aromatic substituent because of significant electron-withdrawing effect of the cyano group, which is comparable with that of the pyridine nitrogen atom; as a result, the chemical shifts of protons on C^3 and C^4 could be

[1] Dedicated to the 125th anniversary of Academician I.Ya. Postovsky.

Scheme 1.



1a–1c **3a–3c** **4a–4c**

Ar = 4-MeC_6H_4, R = 4-ClC_6H_4 (**a**); Ar = Ph, R = 4-ClC_6H_4 (**b**); Ar = 4-MeC_6H_4, R = naphthalen-2-yl (**c**).

similar. Compounds **4a**–**4c** were unambiguously identified as 4,5-diaryl-2,2′-bipyridine-6-carbonitriles on the basis of the X-ray diffraction data for **4a** (Fig. 1). We can conclude that in this reaction 2-amino-4-aryl-1,3-oxazoles act as synthetic equivalents of arylacetylenes, but the addition is regioselective, whereas the reactions with acetylenes generally produce two isomers [12, 13]. Likewise, the formation of two isomers was described previously in the reactions of 1,2,4-triazines with enolates [14] or enamines [15] generated in situ from acetophenones.

[2,2′-Bipyridine]-6-carbonitriles 3a–3c and 4a–4c (*general procedure*). The corresponding 2-aminooxazole **2** (0.4 mmol) and 1,2,4-triazine-5-carbonitrile **1** (0.37 mmol) were dissolved in anhydrous toluene (20 mL), and the solvent was removed under reduced pressure. The residue was heated at 155°C under argon with stirring on a magnetic stirrer for 8 h. The products were separated by column chromatography on silica gel using methylene chloride as eluent:

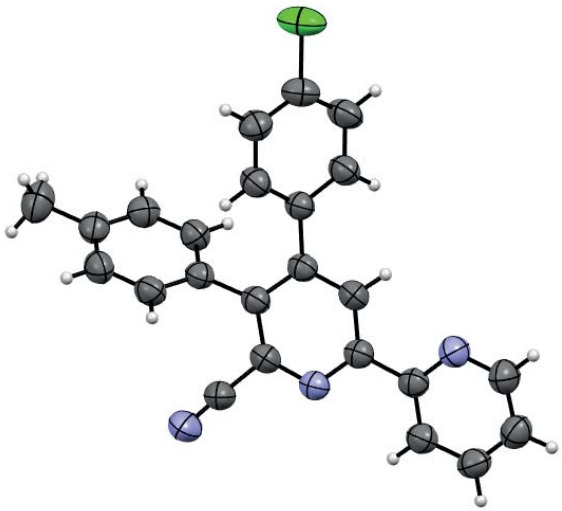


Fig. 1. Structure of the molecule of compound **4a** according to the X-ray diffraction data. Non-hydrogen atoms are shown as anisotropic displacement ellipsoids with a probability of 50%.

R_f 0.7 (**3a**–**3c**), 0.4 (**4a**–**4c**). Analytical samples were obtained by recrystallization from ethanol.

4-(4-Chlorophenyl)-3-hydroxy-5-(4-methylphenyl)[2,2′-bipyridine]-6-carbonitrile (3a). Yield 64 mg (44%), mp >250°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.36 s (3H, CH_3), 7.07–7.09 m (2H, $C_6\mathbf{H}_4Me$), 7.10–7.12 m (2H, C_6H_4Cl), 7.12–7.14 m (2H, $C_6\mathbf{H}_4Me$), 7.26–7.28 m (2H, C_6H_4Cl), 7.47–7.50 m (1H, 5′-H), 8.05 d.d.d (1H, 4′-H, ^3J = 7.6, 7.6, ^4J = 1.6 Hz), 8.52 d (1H, 6′-H, ^3J = 4.8 Hz), 8.75 d (1H, 3′-H, ^3J = 8.0 Hz), 15.77 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.3, 117.6, 121.9, 123.5, 124.2, 128.3, 129.2, 129.9, 131.2, 131.6, 131.7, 133.9, 136.8, 137.2, 138.7, 138.7, 143.1, 144.9, 156.5, 156.9. Mass spectrum: *m*/*z* 398.11 (I_{rel} 100%) $[M + H]^+$. Found, %: C 72.32; H 4.18; N 10.79. $C_{24}H_{16}ClN_3O$. Calculated, %: C 72.45; H 4.05; N 10.56. *M* + H 398.11.

4-(4-Chlorophenyl)-3-hydroxy-5-phenyl[2,2′-bipyridine]-6-carbonitrile (3b). Yield 58 mg (41%), mp 235–237°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.06–7.10 m (2H, C_6H_4Cl), 7.16–7.20 m (2H, Ph), 7.22–7.26 m (2H, C_6H_4Cl), 7.29–7.34 m (3H, Ph), 7.45–7.49 m (1H, 5′-H), 8.04 d.d.d (1H, 4′-H, ^3J = 8.0, 8.0, ^4J = 1.8 Hz), 8.49–8.52 m (1H, 6′-H), 8.72–8.75 m (1H, 3′-H), 15.80 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 117.5, 121.7, 123.3, 124.4, 128.2, 128.4, 128.8, 130.0, 131.4, 131.8, 134.0, 134.3, 136.9, 137.4, 138.7, 143.0, 145.0. Mass spectrum: *m*/*z* 384.09 (I_{rel} 100%) $[M + H]^+$. Found, %: C 71.83; H 3.52; N 11.12. $C_{23}H_{14}ClN_3O$. Calculated, %: C 71.97; H 3.68; N 10.95. *M* + H 384.09.

3-Hydroxy-5-(4-methylphenyl)-4-(naphthalen-2-yl)[2,2′-bipyridine]-6-carbonitrile (3c). Yield 58 mg (38%), mp >250°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.28 s (3H, CH_3), 7.06–7.09 m (2H, $C_6\mathbf{H}_4Me$), 7.11–7.14 m (2H, $C_6\mathbf{H}_4Me$), 7.18 d.d (1H, 3-H_{Np}, ^3J = 8.0, ^4J = 1.2 Hz), 7.44–7.51 m (2H, 6-H_{Np}, 7-H_{Np}), 7.65–7.68 m (1H, 5′-H), 7.70 s (1H, 1-H_{Np}), 7.71–7.76 m (2H, 5-H_{Np}, 8-H_{Np}), 7.82 d (1H, 4-H_{Np}, ^3J =

8.0 Hz), 8.22 d.d.d (1H, 4′-H, ^3J = 8.0, 8.0, ^4J = 1.6 Hz), 8.67 d (1H, 6′-H, ^3J = 4.8 Hz), 8.70 d (1H, 3′-H, ^3J = 8.0 Hz), 15.76 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.2, 117.6, 122.5, 124.0, 124.7, 126.1, 126.5, 127.6, 127.9, 128.2, 128.6, 128.8, 129.1, 129.9, 130.0, 130.1, 130.9, 131.2, 132.6, 132.8, 136.7, 138.4, 138.5, 140.2, 143.7, 144.3, 154.6, 156.5. Mass spectrum: *m*/*z* 414.16 (I_{rel} 100%) $[M + H]^+$. Found, %: C 81.47; H 4.51; N 10.31. $C_{28}H_{19}N_3O$. Calculated, %: C 81.34; H 4.63; N 10.16. *M* + H 414.16.

4-(4-Chlorophenyl)-5-(4-methylphenyl)[2,2′-bipyridine]-6-carbonitrile (4a). Yield 45 mg (32%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (1H, CH_3), 7.10–7.16 m (4H, C_6H_4Cl, $C_6\mathbf{H}_4Me$), 7.17–7.22 m (2H, C_6H_4Cl), 7.23–7.30 m (2H, $C_6\mathbf{H}_4Me$), 7.38–7.43 m (1H, 5′-H), 7.90 d.d.d (1H, 4′-H, ^3J = 7.6, 7.6, ^4J = 1.6 Hz), 8.55–8.59 m (1H, 3′-H), 8.69–8.73 m (2H, 3-H, 6′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.3, 117.2, 121.6, 124.6, 124.7, 128.6, 129.5, 130.0, 130.6, 133.9, 134.7, 135.9, 139.0, 140.3, 149.3, 149.7, 153.9, 156.3. Mass spectrum: *m*/*z* 382.12 (I_{rel} 100%) $[M + H]^+$. Found, %: C 75.51; H 4.21; N 10.97. $C_{24}H_{16}ClN_3$. Calculated, %: C 75.49; H 4.22; N 11.00. *M* + H 382.12.

The crystallographic data for compound **4a** were deposited at the Cambridge Crystallographic Data Centre (CCDC entry no. 2190817) and are available at http://www.ccdc.cam.ac.uk. Molecular weight 381.85; triclinic crystal system, space group *P*-1; temperature 293(2) K; radiation wavelength λ 0.71073 Å; unit cell parameters: a = 9.2854(4), b = 10.2006(3), c = 11.6576(3) Å; α = 72.799(2)°, β = 74.884(2)°, γ = 71.024(3)°; V = 980.48(5) Å^3; Z = 2; d_{calc} = 1.293 g cm^{-3}; F(000) = 396.0; μ = 0.209 mm^{-1}; 3.702 ≥ 2θ ≤ 49.482; total number of reflections: 84277; number of independent reflections: 5217 (R_{int} = 0.0560); number of reflections with $I > 2\sigma(I)$: 3103; number of refined parameters: 254; R_1 = 0.0482 [reflections with $I > 2\sigma(I)$]; wR_2 = 0.1636 (all independent reflections); goodness of fit with respect to F^2:1.006; maximum and minimum residual electron density peaks: 0.23/–0.31.

4-(4-Chlorophenyl)-5-phenyl[2,2′-bipyridine]-6-carbonitrile (4b). Yield 41 mg (30%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.08–7.13 m (2H, C_6H_4Cl), 7.20–7.28 m (4H, Ph, C_6H_4Cl), 7.36–7.43 m (4H, Ph, 5′-H), 7.89 d.d.d (1H, 4′-H, ^3J = 7.6, 7.6, ^4J = 1.6 Hz), 8.53–8.58 m (1H, 3′-H), 8.67–8.72 m (2H, 3-H, 6′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 117.0, 121.7, 124.7, 124.8, 128.6, 128.7, 129.0, 130.1, 130.6, 133.8, 134.0, 134.8, 135.8, 137.3, 140.2, 149.3, 149.8, 153.9, 156.2. Mass spectrum: *m*/*z* 368.10 (I_{rel} 100%) $[M + H]^+$. Found, %: C 75.11; H 3.86; N 11.45. $C_{23}H_{14}ClN_3$. Calculated, %: C 75.10; H 3.84; N 11.42. *M* + H 368.10.

5-(4-Methylphenyl)-4-(naphthalen-2-yl)[2,2′-bipyridine]-6-carbonitrile (4c). Yield 40 mg (0.10 mmol, 27%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.33 s (1H, CH_3), 7.09–7.13 m (3H, $C_6\mathbf{H}_4Me$, 3-H_{Np}), 7.16–7.19 m (2H, $C_6\mathbf{H}_4Me$), 7.37–7.40 m (1H, 5′-H), 7.47–7.52 m (2H, 6-H_{Np}, 7-H_{Np}), 7.64 d (1H, 4-H_{Np}, ^3J = 8.5 Hz), 7.77–7.80 m (2H, 5-H_{Np}, 8-H_{Np}), 7.83–7.85 m (1H, 1-H_{Np}), 7.89 d.d.d (1H, 4′-H, ^3J = 7.6, 7.6, ^4J = 1.6 Hz), 8.56–8.59 m (1H, 3′-H), 8.69–8.71 m (1H, 6′-H), 8.81 s (1H, 3-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.4, 117.4, 121.7, 124.7, 125.2, 126.5, 126.6, 127.7, 127.8, 128.3, 128.9, 130.1, 131.2, 132.8, 133.1, 133.9, 135.2, 137.3, 138.8, 140.6, 149.3, 150.9, 154.2, 156.2. Mass spectrum: *m*/*z* 398.15 (I_{rel} 100%) $[M + H]^+$. Found, %: C 84.63; H 4.81; N 10.56. $C_{28}H_{19}N_3$. Calculated, %: C 84.61; H 4.82; N 10.57. *M* + H 398.15.

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-400 and Bruker Avance-600 spectrometers (400 and 600 MHz for ^{1}H and 100 and 150 MHz for ^{13}C, respectively) using tetramethylsilane as internal standard. The mass spectra (electrospray ionization) were recorded on a Bruker Daltonics MicrOTOF-Q II instrument (Bremen, Germany). Elemental analysis was performed with a Perkin Elmer 2400 Series II CHN analyzer. The X-ray diffraction study was carried out at the X-Ray Analysis Department, Testing Center of Nanotechnologies and Promising Materials, Institute of Metal Physics, Ural Branch, Russian Academy of Sciences. Initial 5-cyanotriazines **1** [16] and 2-aminooxazoles **2** [17] were synthesized according to known procedures. All other reagents were commercial products.

CONCLUSIONS

The reaction of 5-aryl-3-(pyridin-2-yl)-1,2,4-triazine-5-carbonitriles and 2-amino-4-aryloxazoles in anhydrous medium was found to produce mixtures of previously described 4,5-diaryl-3-hydroxy-2,2′-bipyridine-6-carbonitriles and 4,5-diaryl-2,2′-bipyridine-6-carbonitriles containing no hydroxy group on C^3. The structure of the latter was confirmed by X-ray analysis.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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