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SHORT COMMUNICATIONS

An Effective Synthetic Approach to of 2-([5'-Aryl-2,2'-bipyridin]-6-yl)-5-aryl-1,3,4-oxadiazoles

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Abstract—A convenient synthetic approach to 2-(2,2'-bipyridin-6-yl)-1,3,4-oxadiazole derivatives is proposed, which involves the preparation of 5-aryl-2,2'-bipyridine-6-carboxylic acid esters by the "1,2,4-triazine" methodology and the subsequent construction of the 1,3,4-oxadiazole ring via the modification of the ester group.

Keywords: 2-(2,2'-bipyridin-6-yl)-1,3,4-oxadiazoles, heterocyclization, dehydration, "1,2,4-triazine" methodology

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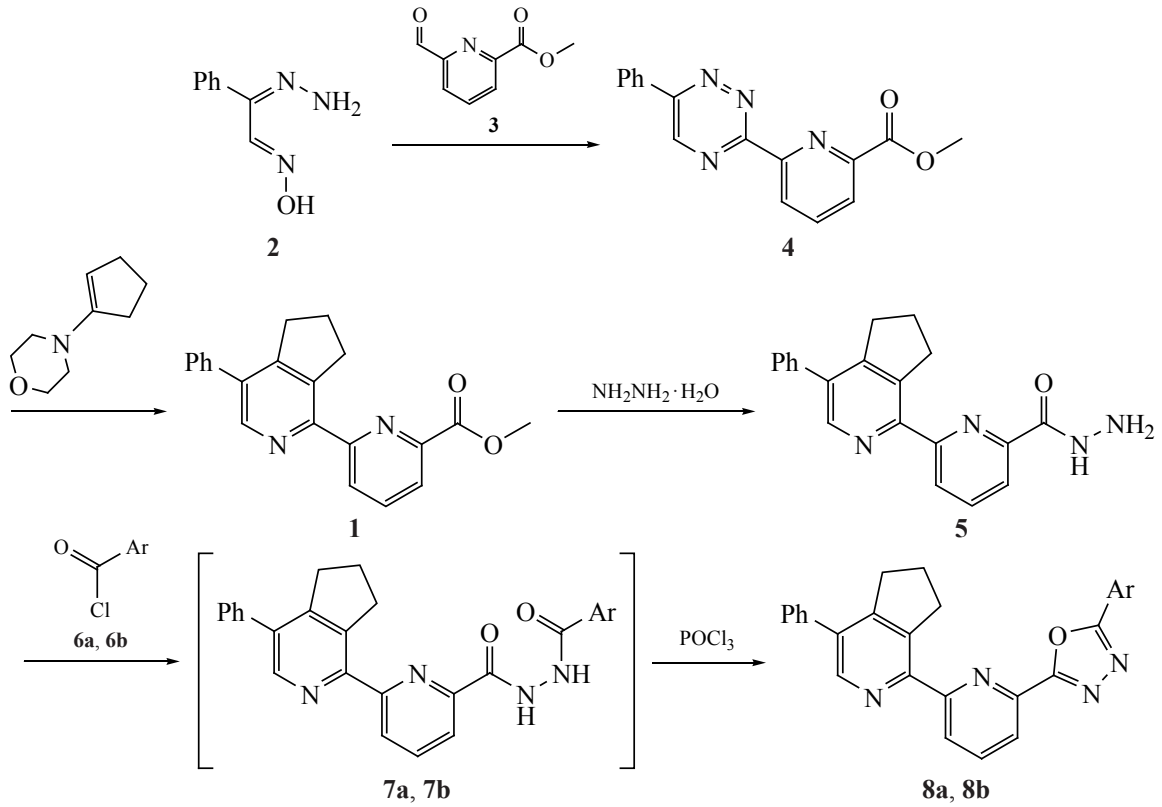
1,3,4-Oxadiazole derivatives are of interest due to their biological activity [1, 2]. At the same time, the activity of 2-(2,2'-bipyridin-6-yl)-1,3,4-oxadiazole derivatives studied in this work has scarcely been studied. Thus, of their closest analogues we can mention 7-[5-(4-fluorobenzyl)-1,3,4-oxadiazol-2-yl]-5-(pyridin-2-yl)-1,6-naphthyridin-8-ol, which showed activity as an antiviral agent against HIV [3, 4]. Another example of a similar structure is oligomeric biosimilar ion channels, including a fragment of (1,10-phenanthrolin-2-yl)-1,3,4-oxadiazole [5]. Thus, oligomers based on 2,6-bis[2-(1,10-phenanthrolin-2-yl)-1,3,4-oxadiazol-5-yl]pyridine proved to be selective toward potassium cations, while a derivative of 2,5-bis(1,10-phenanthrolin-2-yl)-1,3,4-oxadiazole did not show selectivity toward potassium and sodium cations [6].

By now the reported methods for the synthesis of such structures have been mainly limited to the use of compounds that are not easily accessible. Thus, the formation of the 1,3,4-oxadiazole ring via the reaction of compounds containing the 2*H*-tetrazol-5-yl fragment with carboxylic acid chlorides has been described [7–10]. The assembly of this system by Suzuki cross-coupling, specifically the addition of the 2-pyridyl residue, has been reported [3]. In addition, an example of the dehydration of the bishydrazide fragment is available [6, 11]. The proposed method features the simultaneous use of reagents and solvents, such as triethylamine, triphenylphosphine, chloroform, and carbon tetrachloride. It should be noted that the simultaneous use of these compounds at the last stage of synthesis complicates the subsequent medical application of the resulting product because of the risk that it may contain highly toxic impurities [12].

In this work, we developed a much simplified method for preparing such structures. The key compound was 2,2'-bipyridine-6-carboxylic acid ester **1** synthesized by the 1,2,4-triazine methodology [13–15]. Thus, the condensation of isonitrosoacetophenone hydrazone (**2**) with 6-(methoxycarbonyl)pyridine-2-carbaldehyde (**3**) gave a triazine intermediate **4** (Scheme 1). As shown in [14], the reactions of 1,2,4-triazines with dienophiles, such as enamines, allow to annulate an aliphatic carbocycle to the newly formed pyridine ring. In accordance with this, we reacted compound **4** with 1-morpholinocyclopentene to obtain ester **1**, whose subsequent reaction with hydrazine hydrate led to hydrazide **5**, and the latter, in its turn, served as a

Scheme 1.



Ar = Ph (**a**), 4-FC_6H_4 (**b**).

substrate for constructing the 1,3,4-oxadiazole ring. This process was accomplished in two stages: first compound **5** was reacted with acid chlorides **6** to form intermediates **7**.

As known, the dehydration/heterocyclization of such compounds is one of the main approaches to the construction of the 1,3,4-oxadiazole ring. Various dehydrating agents (in particular, thionyl chloride, polyphosphoric acid, P_2O_5, etc.) were proposed in the literature [16]. In this work, we did not isolate compounds **7** and immediately involved them in heterocyclization/dehydration in a $POCl_3$ medium. The yields of target products **8** reached 70%.

The structure of compounds **8** was confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. In particular, the ^1H NMR spectra contain proton signals of the cyclopentene fragment in the resonance region of aliphatic protons, two aromatic substituents, as well the bipyridine fragment (singlet of the 6,7-dihydro-5*H*-cyclopenta[*c*]pyridine proton and signals of the pyridine ABC protons). The ^1H NMR spectrum of intermediate hydrazide **5** shows two broadened singlets of the hydrazine fragment at 4.49–4.64 and 9.17–9.22 ppm.

6-(4-Phenyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-1-yl)picolinohydrazide (5). 2,2'-Bipyridine **1** (204 mg, 0.62 mmol) was dissolved in ethanol (40 mL) under heating. Hydrazine hydrate (0.15 mL, 3.09 mmol) was added to the resulting solution, the reaction mixture was refluxed for 8 h, was cooled to room temperature, and concentrated under reduced pressure to 10 mL. The precipitate that formed was filtered, washed with ethanol, and dried. The product was used in the next step without further purification. Yield 179 mg (0.54 mmol, 88%). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.07–2.17 m (2H, 6-CH_2), 3.07 t (2H, 7-CH_2, ^3J 7.2 Hz), 3.07 t (2H, 5-CH_2, ^3J 7.2 Hz), 4.49–4.64 br.s [2H, C(O)NHN$\underline{H}_2$], 7.39–7.45 m (1H, Ph), 7.48–7.57 m (4H, Ph), 8.02–8.11 m (2H, py), 8.04 d.d (1H, H^3, py, ^3J 7.6, ^4J 1.2 Hz), 8.09 d.d (1H, H^4, ^3J 7.6, 7.6 Hz), 8.50 s {1H, H^3 (cyclopenta[*c*]pyridine)}, 9.17–9.22 br.s [1H, C(O)N$\underline{H}$NH_2]. Mass spectrum, *m/z* (I_{rel}, %): 331.16 (100) $[M + H]^+$.

Synthesis of oxadiazoles 8 (*general procedure*). Triethylamine (0.13 mL, 0.90 mmol) was added to a

solution of hydrazide **5** (100 mg, 0.3 mmol) in 40 mL of 1,4-dioxane, after which acid chloride **6** (0.3 mmol) was added. The resulting solution was heated three times to 90°C, cooled to room temperature, and the solvent was removed under reduced pressure. $POCl_3$ (10 mL) was added to the residue, and the reaction mixture was heated with stirring to 90°C for 8 h and then $POCl_3$ was removed under reduced pressure. Ice was added to the residue, and then aqueous ammonia was added dropwise to the mixture until neutral pH. The precipitate that formed was filtered off, washed with water, and dried. The product was purified by column chromatography (hexane–ethyl acetate, 1 : 1, R_f 0.5). An analytically pure sample was obtained by recrystallization from ethanol.

2-Phenyl-5-{6-(4-phenyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-1-yl)pyridin-2-yl}-1,3,4-oxadiazole (8a). Yield 87 mg (0.21 mmol, 70%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.14–2.23 m (2H, 6-CH_2), 3.10 t (2H, 7-CH_2, ^3J 7.6 Hz), 3.74 t (2H, 5-CH_2, ^3J 7.6 Hz), 7.39–7.46 m (1H, Ph), 7.48–7.54 m (4H, Ph), 7.55–7.62 m (3H, Ph), 8.04 d.d [1H, H^4 (C_5H_3N), ^3J 7.6, 8.0 Hz], 8.20–8.25 m (2H, Ph), 8.29 d and 8.53 d [1H, H^3 and H^5 (C_5H_3N), ^3J 8.0 Hz], 8.58 s {1H, H^3 (cyclopenta[*c*]-pyridine)}. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.4, 32.6, 33.8, 122.0, 124.0, 124.7, 127.2, 127.9, 128.5, 128.7, 129.2, 131.9, 134.4, 137.7, 137.7, 140.1, 142.3, 146.7, 149.5, 153.6, 158.7, 164.3, 165.4. Mass spectrum, *m/z* (I_{rel}, %): 417.17 (100) [M + H]$^+$. Found, %: C 77.75; H 4.71; N 13.27. $C_{27}H_{20}N_4O$. Calculated, %: C 77.87, H 4.84, N 13.45.

2-(4-Fluorophenyl)-5-{(4-phenyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-1-yl)pyridin-6-yl}-1,3,4-oxadiazole (8b). Yield 86 mg (0.198 mmol, 66%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.13–2.22 m (2H, 6-CH_2), 3.10 t (2H, 7-CH_2, ^3J 7.6 Hz), 3.71 t (2H, 5-CH_2, ^3J 7.6 Hz), 7.22–7.30 m (2H, C_6H_4F), 7.40–7.46 m (1H, Ph), 7.47–7.55 m (4H, Ph), 8.04 d.d [1H, H^4 (C_5H_3N), ^3J 7.6, 7.6 Hz], 8.19–8.25 m (2H, C_6H_4F), 8.29 d and 8.53 d [1H, H^3 and H^5 (C_5H_3N), ^3J 8.0 Hz], 8.58 s {1H, H^3 (cyclopenta[*c*]pyridine). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm: –106.50 s (1F, C_6H_4F). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.4, 32.6, 33.8, 116.5 d (*J* 22.4 Hz), 120.3 d (*J* 2.9 Hz), 122.0, 124.8, 127.9, 128.6, 128.7, 129.4 d (*J* 9.0 Hz), 134.4, 137.7, 137.7, 140.1, 142.3, 146.8, 153.6, 158.7, 164.3, 164.6, 165.0 d (*J* 252.2 Hz). Mass spectrum, *m/z* (I_{rel}, %): 435.16 (100) [M + H]$^+$. Found, %: C 74.51; H 4.53; N 12.74. $C_{27}H_{19}FN_4O$. Calculated, %: C 74.64, H 4.41, N 12.90.

The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400, 376.5, and 100 MHz, respectively, internal standards TMS (for ^{1}H and ^{13}C) or $CFCl_3$ (for ^{19}F). The ESI mass spectra were recorded on a Bruker Daltonics MicrOTOF-Q II instrument. Elemental analysis was performed on a Perkin–Elmer PE 2400 II CHN analyzer. 6'-Methoxycarbonyl-5-phenyl-2,2'-bipyridine **1** was prepared by the procedure described in [13]. All other reagents were obtained from commercial sources.

CONCLUSIONS

A simple and efficient synthetic approach to 2-([2,2'-bipyridin]-6-yl)-1,3,4-oxadiazoles derivatives, involving the preparation of 2,2'-bipyridine-6-carboxylic acid esters by the "1,2,4-triazine" methodology and the subsequent formation of the 1,3,4-oxadiazole ring via the modification of the ester group.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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