ISSN 1070-4280, Russian Journal of Organic Chemistry, 2022, Vol. 58, No. 7, pp. 997–1001. © Pleiades Publishing, Ltd., 2022.
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Synthesis and Optical Properties of 3,4-Diamino-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles

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Received November 29, 2021; revised December 14, 2021; accepted December 18, 2021

Abstract—Previously unknown 3,4-diamino-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles were synthesized by reaction of 4-amino-6-aryl-2-bromopyridine-3,5-dicarbonitriles with hydrazine hydrate. Study of the optical properties of the synthesized compounds revealed their fluorescence in solution with the emission maximum located in the range of λ 484–548 nm and quantum yield of 0.9–3.9%.

Keywords: pyrazolo[3,4-*b*]pyridines, nucleophilic substitution, fluorescence

DOI: 10.1134/S1070428022070089

INTRODUCTION

Pyrazolo[3,4-*b*]pyridine ring system is an important structural fragment of many biologically active compounds, including those exhibiting antiproliferative [1], antimicrobial [2, 3], anticancer [4–6], and antiparasitic activities [7], as well as inhibitory activity against acetylcholinesterase [8], casein kinase 1 (CK1), checkpoint kinase 1 (CHK1) [9], Aurora A kinase [10], and fibroblast growth factor (FGFR) [11]. Optical properties of pyrazolo[3,4-*b*]pyridine derivatives are no less interesting. In this regard, the synthesis of efficient fluorophores [12–14] and chemosensors based thereon [15, 16] was reported.

The most widely used method for the synthesis of 3-amino-1*H*-pyrazolo[3,4-*b*]pyridines is based on nucleophilic substitution of halogens [17] or, more rarely, oxygen- [3, 5, 18–19] or sulfur-containing fragments [20–22]. Herein we report the synthesis of new 3,4-diamino-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **1** and their optical properties.

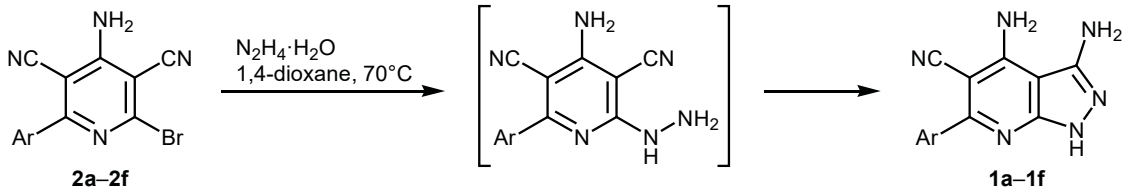
RESULTS AND DISCUSSION

We previously found that the bromine atom in 4-amino-6-aryl-2-bromopyridine-3,5-dicarbonitriles **2** [23, 24] can be readily replaced by an amino group in reactions with primary and secondary amines to produce the corresponding 2-[(di)alkylamino]pyridines [25]. In continuation of these studies, compounds **2** were reacted with hydrazine hydrate. According to published data [26–28], replacement of the halogen atom in **2** by hydrazine leads to the formation of 2-hydrazinylpyridine-3,5-dicarbonitriles which then undergo intramolecular heterocyclization to 3-amino-1*H*-pyrazolo[3,4-*b*]pyridines. As expected, the reaction of **2** with hydrazine hydrate also afforded 3,4-diamino-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **1** in 83–92% yield (Scheme 1). It should be noted that, despite all attempts, we failed to isolate intermediate 2-hydrazinylpyridines.

The ^{1}H NMR spectra of **1a**–**1f** showed signals from protons of the aryl substituent. The two amino and one NH groups gave rise to broadened singlets or exchanged with water. In the IR spectra of **1a**–**1f**, stretching vibrations of the conjugated cyano groups were observed at 2206–2218 cm^{-1}, and N–H stretching bands were observed in the region 3161–3466 cm^{-1}. In the mass spectra of **1a**–**1f**, the base peak was that of the molecular ion.

Compounds **1a**–**1f** were isolated as yellow to orange crystalline solids poorly soluble in organic solvents (except for DMSO). Using compound **1b** as an ex-

Scheme 1.



Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 3,4-$(MeO)_2C_6H_3$ (**c**), 2-ClC_6H_4 (**d**), 3,4-$Cl_2C_6H_3$ (**e**), 3-$O_2NC_6H_4$ (**f**).

ample, we found that the position of the electronic absorption maximum almost does not depend on the solvent nature. Moreover, in many cases we failed to determine its exact position because of overlap by the solvent band. The fluorescence maximum of **1a**–**1f** ranges from λ 452 to 514 nm, and it shifts to longer wavelengths as the solvent polarity increases (Table 1). Depending on the substituent in the benzene ring, the fluorescence maximum of **1a**–**1f** in DMSO appears in the range λ 484–548 nm (Table 2). Electron-donating groups generally increase the fluorescence intensity and shift its maximum to shorter wavelengths (Fig. 1). Compounds **1a**–**1f** in the solid state showed almost no fluorescence.

EXPERIMENTAL

The IR spectra were recorded on an FSM-1202 FTIR spectrometer (Russia) from samples dispersed in mineral oil. The ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (USA) using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were run on a Finnigan MAT INCOS-50 mass spectrometer (USA). Elemental analysis was performed with a Vario Micro cube CHN analyzer (Germany). The fluorescence spectra were measured on an Agilent Cary Eclipse spectrofluorometer (USA). The melting points were determined with an OptiMelt MPA100

Table 1. Optical properties of compound **1b** in different solvents

Solvent	λ_{abs}, nm	*A*	ε, L mol^{-1} cm^{-1}	logε	λ_{fl}, nm	Quantum yield Φ, %	Stokes shift, cm^{-1} (nm)
Ethanol[a,b]	271	0.135	13460	4.13	502	0.6	16980 (231)
Methylene chloride	268	0.130	13040	4.12	452	6.7	15190 (184)
Acetic acid	269	0.215	21470	4.33	–	–	–
Acetonitrile[b]	262	0.227	22740	4.36	495	4.9	17966 (233)
Ethyl acetate[b]	264	0.169	16930	4.23	480	5.3	17045 (216)
1,4-Dioxane[b]	262	0.151	15120	4.18	459	5.2	16381 (197)
DMSO[a]	274	0.167	16730	4.22	514	4.1	17041 (240)

[a] The absorption maximum was estimated roughly because of overlap by the solvent absorption.
[b] Compound **1b** is sparingly soluble in the given solvent.

Table 2. Optical properties of compounds **1a**–**1f**

Compound no.	λ_{abs}, nm	*A*	ε, L mol^{-1} cm^{-1}	logε	λ_{fl}, nm	Quantum yield Φ, %	Stokes shift, cm^{-1} (nm)
1a	273[a]	0.216	21620	4.33	517	3.9	17288 (244)
1b	274[a]	0.167	16730	4.22	514	4,1	17041 (240)
1c	274[a]	0.242	24170	4.38	484	2.7	15835 (210)
1d	295	0.122	12240	4.09	498	3.3	13818 (203)
1e	274[a]	0.228	22770	4.36	548	0.9	18248 (274)
1f	274[a]	0.205	20490	4.31	–	–	–

[a] The absorption maximum was estimated roughly because of overlap by the DMSO absorption.

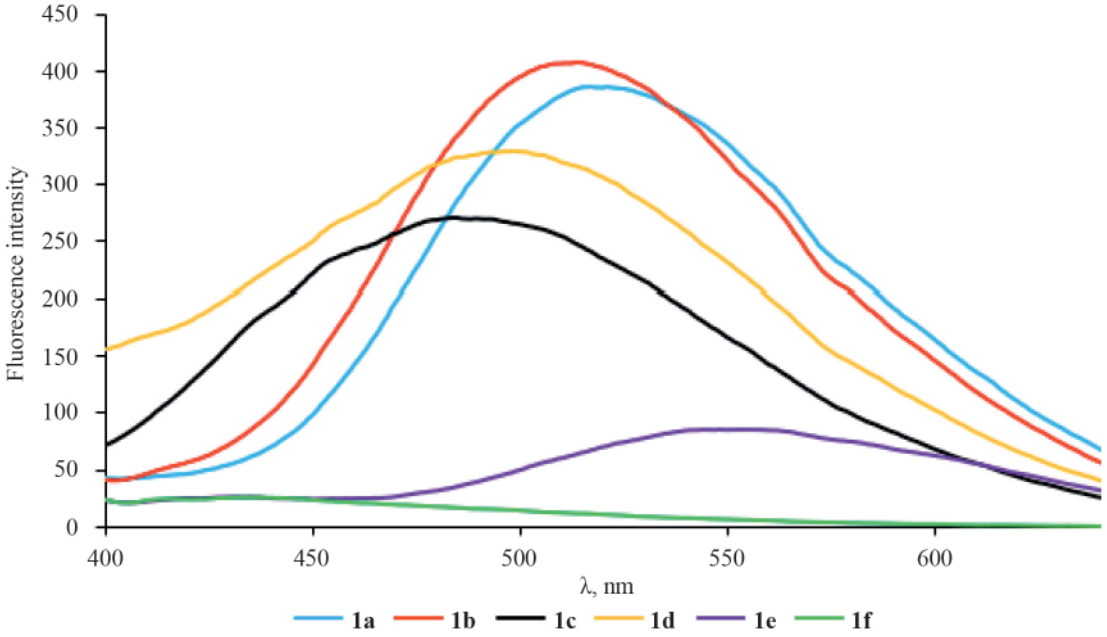


Fig. 1. Photoluminescence spectra of compounds **1a**–**1f**.

automated melting point apparatus (USA). The progress of reactions and the purity of the isolated compounds were monitored by TLC on Sorbfil PTSKh-AF-A-UF plates using ethyl acetate as eluent; visualization was done under UV light, by treatment with iodine vapor, and by thermal decomposition. Compounds **2a**–**2f** were synthesized as described in [23]. Hydrazine hydrate (100%) was commercial product (Germany).

3,4-Diamino-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (1a). A mixture of 0.299 g (1 mmol) of 4-amino-2-bromo-6-phenylpyridine-3,5-dicarbonitrile (**2a**) and 0.15 g (3 mmol) of hydrazine hydrate in 5 mL of 1,4-dioxane was refluxed for 4 h. After completion of the reaction (TLC), the mixture was diluted with 30 mL of distilled water, and the precipitate was filtered off, washed with small portions of distilled water, and recrystallized from 1,4-dioxane. Yield 0.228 g (91%), mp 291–292°C (decomp.). IR spectrum, ν, cm^{-1}: 3454, 3358, 3177 (NH, NH_2), 2206 (CN), 1654 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.72 s (2H, NH_2), 7.27 s (2H, NH_2), 7.48–7.51 m (3H, C_6H_5), 7.71–7.74 m (2H, C_6H_5), 12.20 s (1H, NH). Mass spectrum: *m*/*z* 250 (I_{rel} 100%). Found, %: C 62.45; H 4.09; N 33.46. $C_{13}H_{10}N_6$. Calculated, %: C 62.39; H 4.03; N 33.58. *M* 250.27.

Compounds **1b**–**1f** were synthesized in a similar way.

3,4-Diamino-6-(4-methylphenyl)-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitrile (1b). Yield 0.219 g (83%), mp 306–307°C (decomp.). IR spectrum, ν, cm^{-1}: 3467, 3395 (NH, NH_2), 2218 (C≡N), 1696 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.39 s (3H, CH_3), 7.38 d (2H, C_6H_4, *J* = 7.7 Hz), 7.62 d (2H, C_6H_4, *J* = 7.7 Hz), 8.78 br.s (3H, NH, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.51, 81.85, 89.97, 116.15, 129.53, 129.57, 142.14, 146.87, 148.41, 155.41, 155.51, 159.70. Mass spectrum: *m*/*z* 264 (I_{rel} 100%). Found, %: C 63.52; H 4.63; N 31.85. $C_{14}H_{12}N_6$. Calculated, %: C 63.62; H 4.58; N 31.80. *M* 264.29.

3,4-Diamino-6-(3,4-dimethoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (1c). Yield 0.276 g (89%), mp 246–247°C (decomp.). IR spectrum, ν, cm^{-1}: 3439, 3379, 3300 (NH, NH_2), 2208 (C≡N), 1662 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.82 s (3H, OCH_3), 3.83 s (3H, OCH_3), 5.70 s (2H, NH_2), 7.07 d (1H, C_6H_3, *J* = 8.3 Hz), 7.22 s (2H, NH_2), 7.32–7.38 m (2H, C_6H_3), 12.17 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 56.14, 56.20, 80.72, 91.48, 111.63, 112.91, 119.35, 122.16, 131.95, 148.74, 148.80, 150.44, 153.98, 154.15, 161.25. Mass spectrum: *m*/*z* 310 (I_{rel} 100%). Found, %: C 58.18; H 4.61; N 27.00. $C_{15}H_{14}N_6O_2$. Calculated, %: C 58.06; H 4.55; N 27.08. *M* 310.32.

3,4-Diamino-6-(2-chlorophenyl)-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitrile (1d). Yield 0.262 g (92%), mp 308–309°C (decomp.). IR spectrum, ν, cm^{-1}: 3448, 3177 (NH, NH_2), 2218 (C≡N), 1687 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.57 t (1H, C_6H_4, *J* = 7.6 Hz), 7.64 t (1H, C_6H_4, *J* = 7.4 Hz), 7.68–7.72 m (2H, C_6H_4), 8.80 br.s (5H, NH, NH_2).

^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 66.82, 83.90, 90.49, 115.15, 128.06, 130.21, 131.34, 131.91, 132.97, 146.95, 148.70, 154.93, 157.80. Mass spectrum: m/z 286/284 (I_{rel} 33/100%). Found, %: C 54.73; H 3.25; N 29.60. $C_{13}H_9ClN_6$. Calculated, %: C 54.84; H 3.19; N 29.52. M 284.71.

3,4-Diamino-6-(3,4-dichlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (1e). Yield 0.287 g (90%), mp 322–323°C (decomp.). IR spectrum, ν, cm^{-1}: 3466, 3335, 3161 (NH, NH_2), 2216 (C≡N), 1657 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.74 br.s (2H, NH_2), 7.36 s (2H, NH_2), 7.73 d.d (1H, C_6H_3, J = 8.3, 2.1 Hz), 7.77 d (1H, C_6H_3, J = 8.4 Hz), 7.95 d (1H, C_6H_3, J = 2.1 Hz), 12.27 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 80.73, 91.62, 118.54, 129.34, 130.86, 131.00, 131.39, 132.55, 139.81, 148.72, 153.50, 153.91, 158.80. Mass spectrum, m/z (I_{rel}, %): 320 (65), 318 (18), 316 (100). Found, %: C 48.80; H 2.60; N 26.39. $C_{13}H_8Cl_2N_6$. Calculated, %: C 48.92; H 2.53; N 26.33. M 319.15.

3,4-Diamino-6-(3-nitrophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (1f). Yield 0.338 g (85%), mp 243–244°C (decomp.). IR spectrum, ν, cm^{-1}: 3460, 3343, 3185 (NH, NH_2), 2210 (C≡N), 1672 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.84 t (1H, C_6H_4, J = 8.1 Hz), 8.22 d.t (1H, C_6H_4, J = 7.8, 1.4 Hz), 8.39 d.d (1H, C_6H_4, J = 8.1, 2.4 Hz), 8.56–8.61 m (1H, C_6H_4). Mass spectrum: m/z 295 (I_{rel} 100%). Found, %: C 52.77; H 3.00; N 33.32. $C_{13}H_9N_7O_2$. Calculated, %: C 52.88; H 3.07; N 33.21. M 397.44.

CONCLUSIONS

2,4-Diamino-6-arylpyridine-3,5-dicarbonitriles have been synthesized, and their electronic absorption and luminescence spectra have been recorded. The synthesized compounds show fluorescence in solution with an emission maximum located at λ 484 to 548 nm and do not fluoresce in the solid state.

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ACKNOWLEDGMENTS

A part of this study was performed in the framework of state assignment for the Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, in the field of fundamental research.

FUNDING

This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (project no. 0849-2020-0003).

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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