Effect of a Substituent in the Fourth Position on the Optical Properties of 2-Oxonicotinonitriles

S. P. Sorokin*, S. V. Fedoseev*, and O. V. Ershov*

*I.N. Ulyanov Chuvash State University, Cheboksary, 428015 Russia
*e-mail: oleg.ershov@mail.ru

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Abstract—Based on six representatives of 2-oxonicotinonitriles, the effect of the nature of the substituent in the fourth position of the pyridine system on the photophysical characteristics was studied. The role of the donor/acceptor nature of the substituent and the solvent nature in the absorbing and fluorescent properties of the compounds was shown.

Keywords: pyridines, nicotinonitrile, fluorescence, nitriles, trifluoromethyl, isonicotinic acid

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INTRODUCTION

2-Oxonicotinonitrile derivatives (2-oxo-1,2-dihydropyridine-3-carbonitrile, 3-cyanopyrid-2-one) are of considerable interest due to their diverse applications in various fields of science and technology. Among them, substances were found that are used in pharmaceuticals [1–14], agrochemistry [15], as agents of reducing steel corrosion [16], and in the creation of organic functional materials [17–28]. Substituted 2-oxonicotinonitriles are well known for their versatile biological activity. For example, they exhibit antitumor [3,4], anti-tuberculosis [5], anti-inflammatory [6], antipyretic [7], cytotoxic [8], and antimicrobial activity [9]. The possibility of their use as inhibitors of SARS-CoV-2 protease [10], aggregation of α-synuclein [11],

In addition, 2-oxonicotinonitrile derivatives are known for their unique photophysical properties and a wide range of potential applications based on them, for example, as dyes and pigments [17–21], nonlinear optical (NLO) and photorefractive materials [22], dye-sensitized solar cells (DSSC) [23, 24], an emitter in a device with a host–guest configuration in the manufacture of OLED displays [25], a fluorescent probe for visualizing lipid droplets to distinguish between dead and live zebrafish [26], a fluorescent dye for visualizing latent fingerprints and detecting nitrite ion (NO2–) [27], a multisensitive sensor for Ru3+, Fe3+, CrO42–, Cr2O72– and MnO4– ions [28]. Many of the above properties are based on the luminescence phenomenon.

The pyridone fragment, in particular, the 2-oxonicotinonitrile one, causes the appearance of fluorescent properties in the molecule [25–36]. However, there is practically no information in the literature on the systematic study of the effect of an individual substituent on the photophysical properties of such compounds, despite the fact that the optical properties can be finely tuned by introducing individual functional groups. In this regard, this work was devoted to comparing the fluorescent properties of 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitriles 1a–1f differing by a substituent in the fourth position of the pyridine system (Scheme 1). Pyridine 1a was chosen as the model structure. Molecule 1b contains an electron-donating methyl group. Perfluoroalkyl groups (compounds 1c and 1d) were studied as electron-withdrawing substituents with a strong negative inductive effect. The ester group (1e) and cyano group (1f) were studied as substituents with the conjugation effect.

RESULTS AND DISCUSSION

Compound 1a was synthesized by reacting enamino-ketone 2 with cyanoacetamide in acetonitrile (Scheme 2). Compounds 1b–1e were obtained from the corresponding β-diketones 3 and cyanoacetamide in refluxing ethanol in the presence of 1,4-diazobicyclo[2.2.2]octane (DABCO) (Scheme 3).
Compound 1f was prepared according to a previously developed procedure [37] based on the intramolecular cyclization of 4-oxopentane-1,1,2,2-tetracarbonitrile 4 in the presence of pyruvic acid in acetone at room temperature (Scheme 4).

Compounds 1a–1c, 1e, and 1f have been reported earlier, their structure was confirmed by IR and mass spectrometry data, as well as by $^1$H, $^{13}$C, and $^{19}$F NMR for pyridone 1e, which was not previously described.

Photophysical properties of compounds 1a–1f were studied in three solvents of different nature: acetonitrile, acetic acid and pyridine (Table 1, Figs. 1–3). It was found that, as a rule, for all the studied compounds, changing the solvent from acetonitrile to acetic acid leads to a
For all the compounds obtained, with the exception of 1a and 1b, there is a tendency to a decrease in the value of the molar light absorption coefficient when pyridine or acetic acid is used instead of acetonitrile. The maxima of the absorption and fluorescence bands for compounds substituted with acceptor substituents...
with the conjugation effect in all the studied solvents are bathochromic relative to all others and are in the range of 360–380 and 439–447 nm, respectively, for compound 1e, 366–384 and 431–437 nm for 1f. Compounds 1a and 1b have the most hypsochromic shifts in the electronic spectra, with absorption and emission band maxima in the range of 329–346 and 385–390 nm, respectively, for 1a, 323–338 and 379–386 nm for 1b. The maxima of the absorption and photoluminescence bands for fluoroalkyl-substituted derivatives 1c and 1d have intermediate values relative to those described above.

The maximum quantum yield for all the tested compounds is observed in acetic acid solution. Pyridine, having a basic nature, can lead to deprotonation of the NH acid center and the process of salt formation [38]. Apparently, therefore, the minimum values of the fluorescence quantum yield are observed in it. In contrast, acetic acid suppresses the dissociation process, which affects the efficiency of the radiative process of pyridones 1 in its solution.

It was found that the introduction of an electron-withdrawing substituent into the molecule of 2-oxonicotinonitrile 1a leads to a significant increase in the quantum yield (more than 3 times), the leader is compound 1f containing a cyano group, \( \Phi_F(\text{AcOH}) = 85\% \). On the contrary, if the fourth position of the pyridine ring contains an electron-donating substituent (compound 1b), then a sharp decrease in the efficiency of the radiative process is observed in all the studied solvents (Table 1, Fig. 3).

### EXPERIMENTAL

IR spectra were recorded in a thin layer (suspension in mineral oil) on a FSM-2201 IR Fourier spectrometer. NMR spectra were recorded on a Bruker DRX-500 spectrometer, operating frequency 500.13 (\(^1\)H), 125.76 (\(^{13}\)C), 470.59 MHz (\(^{19}\)F), using DMSO-\(d_6\) as a solvent and TMS as an internal standard. Mass spectra were taken on a Shimadzu GCMS-QP2020 spectrometer (energy of ionizing electrons was 70 eV). Elemental analysis was performed on a FlashEA 1112 CHN analyzer. Progress of reactions and purity of the synthesized substances were monitored by TLC on Sorbfil PTSKh-AF-A-UV plates (detecting with UV irradiation, iodine vapor, thermal decomposition). Melting points of the substances were determined on an OptiMelt MPA100 instrument. Absorption spectra were recorded on an Agilent Cary 60 UV-Vis Spectrophotometer. Fluorescence spectra were recorded on an Agilent Cary Eclipse spectrometer. Fluorescence quantum yield for all solutions was measured relative to 7-hydroxy-4-methylcoumarin in phosphate buffer with \( pH = 10 \) (\( \Phi_F = 0.7 \)) [39]. The excitation wavelength is 330 nm.

6-Methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1a). Cyanoacetamide (0.372 g, 4.4 mol) was added to solution of enaminoketone 2 (0.5 g, 4.4 mmol) in 15 mL of acetonitrile, and the mixture was refluxed for 4 h with stirring. The formed precipitate was filtered off and recrystallized from a mixture of ethanol–water (1 : 1). Yield 83%, mp 294–296°C. IR spectrum, \( \nu, \text{cm}^{-1} \): 3291 (N–H), 2223 (C≡N), 1666 (C=O). Mass spectrum, \( m/z \) (I\(_{rel}\) %): 134 (100) [\( M \] + ), 119 (4) [\( M – \text{CH}_3 \] + ), 106 (30) [\( M – \text{CO} \] + ), 105 (73) [\( M – \text{CO} – \text{H} \] + ). Found, %: C 62.76; H 4.55; N 20.79. C \(_7\) H\(_6\) N\(_2\)O. Calculated, %: C 62.68; H 4.51; N 20.88.

**General procedure for the synthesis of 6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitriles 1b–1e.** The corresponding diketone 3 (4.4 mmol) was dissolved in 15 mL of propanol-2, then 0.372 g (4.4 mol) of cyanoacetamide and 1 g of 1,4-diazabicyclo[2.2.2]-octane (8.9 mmol) were added. The mixture was stirred at reflux for 2–4 h (monitoring by TLC). After completion of the reaction, the reaction mixture was cooled to room temperature, poured into cold water (30 mL), and acidified with 2 M HCl solution until acidic. The resulting precipitate was filtered off, washed with water, recrystallized from the appropriate solvent, and dried in a vacuum desiccator over CaCl\(_2\) to constant weight.
4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (1b). Yield 90%, mp 293–295°C. IR spectrum, ν, cm⁻¹: 3291 (N–H), 2219 (C≡N), 1664 (C=O). Mass spectrum, m/z (Irel, %): 148 (100) [M⁺], 133 (2) [M – CH₃]⁺, 120 (35) [M – CO]⁺, 119 (80) [M – CO – H]⁺. Found, %: C 65.01; H 5.40; N 18.82. C₈H₈N₂O. Calculated, %: C 64.85; H 5.44; N 18.91.

6-Methyl-2-oxo-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile (1c). Yield 92%, mp 234–236°C. IR spectrum, ν, cm⁻¹: 3324 (N–H), 2221 (C≡N), 1746 (C=O). Mass spectrum, m/z (Irel, %): 202 (100) [M⁺], 187 (2) [M – CH₃]⁺, 174 (45) [M – CO]⁺, 173 (67) [M – CO – H]⁺, 105 (26) [M – CF₃ – CO]⁺. Found, %: C 47.47; H 2.50; N 13.79. C₆H₅F₃N₂O. Calculated, %: C 47.54; H 2.49; N 13.86.

6-Methyl-2-oxo-4-(pentfluoroethy)-1,2-dihydropyridine-3-carbonitrile (1d). Yield 84%, mp 293–295°C. IR spectrum, ν, cm⁻¹: 3306 (N–H), 2223 (C≡N), 1675 (C=O). Mass spectrum, m/z (Irel, %): 252 (100) [M⁺], 225 (5) [M – HCN]⁺, 224 (39) [M – CO]⁺, 223 (12) [M – CO – H]⁺, 155 (94) [M – CF₃ – CO]⁺. Found, %: C 60.29; H 3.14; N 26.46. C₆H₅F₅N₂O. Calculated, %: C 60.38; H 3.17; N 26.40.

CONCLUSIONS

In conclusion, six derivatives of 2-oxonicotinonitrile were obtained. The effect of the nature of the substituent in the fourth position of the pyridine system on the photophysical properties was studied. It was shown that the introduction of a cyano group leads to the maximum values of the fluorescence quantum yield among the studied functional groups and reaches 85%.

AUTHOR INFORMATION

S.P. Sorokin, ORCID: https://orcid.org/0000-0003-2959-9101
S.V. Fedoseev, ORCID: https://orcid.org/0000-0002-0749-2613
O.V. Ershov, ORCID: https://orcid.org/0000-0002-0938-4659

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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