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Three-Component Synthesis and Optical Properties of Nicotinic Acid Esters Containing Buta-1,3-dien-1,1,3-tricarbonitrile Fragment

I. N. Bardasov[a],* A. Yu. Alekseeva[a], S. S. Chunikhin[a], and O. V. Ershov[a]

[a] *I.N. Ul'yanov Chuvash State University, Moskovskii pr. 15, Cheboksary, 428015 Russia*
**e-mail: bardasov.chem@mail.ru*

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Abstract—Three-component synthesis of ethyl 4-aryl-2-methyl-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylates was developed consisting in the reaction of acetoacetic ester, aromatic aldehydes, and malononitrile dimer in the presence of sodium nitrite. Optical properties of synthesized compounds were investigated and it was demonstrated that they possessed intensive fluorescence in solution and in solid state with emission maxima in the yellow and green region of the visible light.

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Derivatives of nicotinic acid play a significant role in biological processes and find application in different areas of medicine, science, and technology [1, 2]. These compounds are interesting not only because of a broad spectrum of biological activity, but also by properties discovered in the latest years. Applications were described of nitriles of nicotinic acids as special fluorescent markers [3], new promising compounds for WOLED-technologies [4], as fluorescent chemosensors for biologically important ions of Fe(III) and Hg(II) [5].

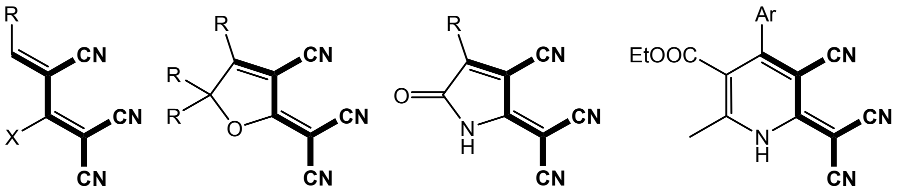
In this study we present a three-component synthesis of nicotinic acid esters **1**, containing buta-1,3-dien-1,1,3-tricarbonitrile (BDTC) fragment [6–10]. The most known compounds possessing such structural element are 3-cyano-2-(dicyanomethylidene)-2,5-dihydrofuranes (TCF) [11] and 2-oxo-4-cyano-5-(dicyanomethylidene)-3-pyrrolines (TCP) [12, 13] (Scheme 1).

The fragment BDTC is a promising component of organic donor-acceptor chromophores that find application in molecular electronics [11] and nonlinear optics [12–17].

The synthesis of target ethyl 4-aryl-2-methyl-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylates **1a–1g** is underlain by a polycomponent reaction between acetoacetic ester, aromatic aldehydes, and malononitrile dimer in the presence of sodium nitrite that functions as a base catalyzing the addition and as an oxidizer (Scheme 2). Yields of compounds **1a–1g** reached 65–76%.

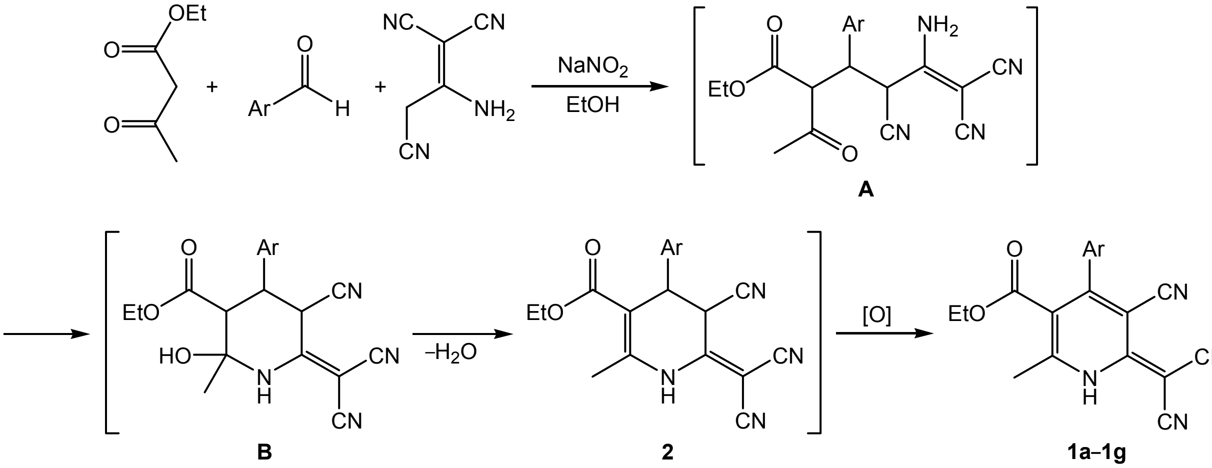
The reaction apparently starts by tandem occurring Knoevenagel and Michael reactions and the intermediate **A** formation. Further intermolecular cyclization of the amino group with the carbonyl results in the forming of a piperidine cycle **B**. After that the dehydration leads to derivatives of tetrahydropyridine **2** that may be isolated in low yields

Scheme 1.



BDTC TCF TCP **1**

Scheme 2.



Ar = Ph (**a**), 4-MeC$_6$H$_4$ (**b**), 4-FC$_6$H$_4$ (**c**), 2-ClC$_6$H$_4$ (**d**), 4-Me$_2$NC$_6$H$_4$ (**e**), 4-MeOC$_6$H$_4$ (**f**), 2-MeOC$_6$H$_4$ (**g**).

Table 1. Effect of a solvent on optical properties of ethyl 2-methyl-4-phenyl-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate **1a**

Solvent	λ_{abs}, nm	A_{max}	ε_{max}	λ_{fl}, nm	I_{max}
Ethyl acetate	338	0.5187	47587	520	1.2769
Ethanol	335	1.0839	94250	520	1.2894
Acetonitrile	336	1.1650	92458	521	2.6862
Benzene	335	0.3390	31387	514	0.4056
Acetic acid	329	0.9515	93280	456	0.0478
Dioxane	333	0.6762	61476	516	0.3183
DMSO	340	1.0708	101984	520	3.3929
Pyridine	344	0.9171	90802	519	3.4421

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

Compound no.	λ_{abs}, nm	A_{max}	ε_{max}	λ_{fl}, nm[a]	I_{max}[b]	λ_{fl}, nm[c]	RI[d]
1a	334	1.0708	10708	521	3.4211	526	1.00
1b	332	0.6730	67298	518	6.2761	533	0.70
1c	346	0.7520	75200	518	4.7947	524	1.57
1d	334	0.7914	79141	512	16.1677	529	1.82
1e	339	0.4491	44910	506	12.2428	561	0.64
1f	334	0.4417	44170	512	8.0319	528	1.24
1g	339	0.4381	43810	508	11.8309	521	1.27

[a] Maximum fluorescence emission in DMSO.
[b] Intensity of fluorescence in DMSO.
[c] Maximum fluorescence emission in solid phase.
[d] Intensity of solid phase fluorescence relatively to compound **1a**.

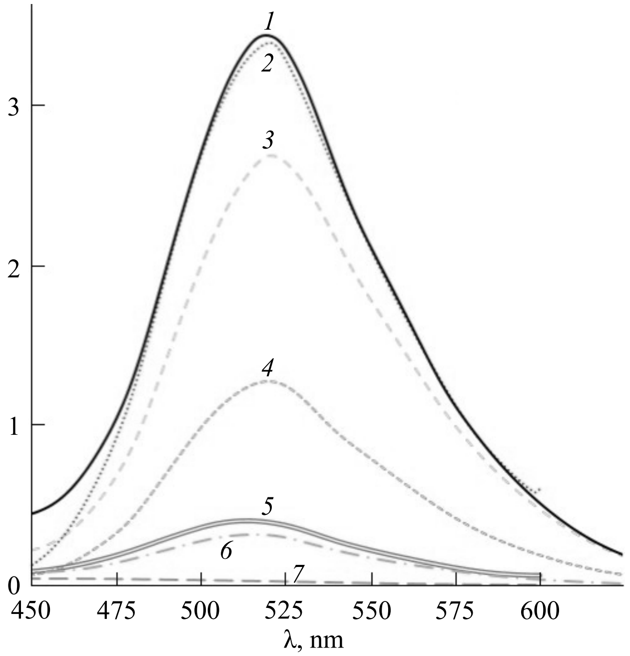


Fig. 1. Fluorescence spectra of ethyl 2-methyl-4-phenyl-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate **1a** in different solvents: *1*, pyridine; *2*, DMSO; *3*, acetonitrile; *4*, ethyl acetate; *5*, benzene; *6*, dioxane; *7*, acetic acid.

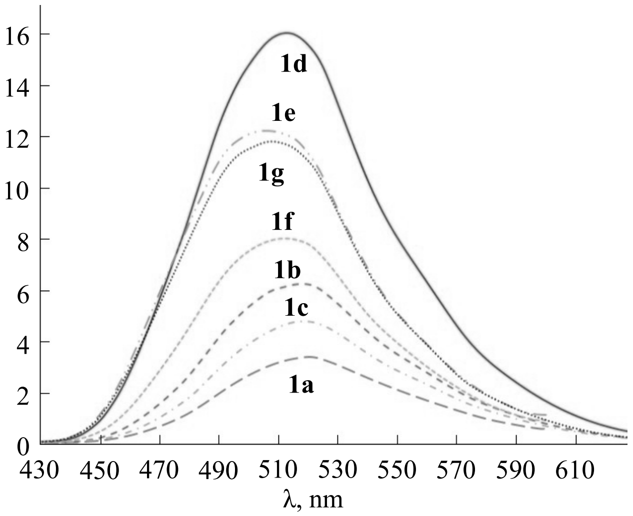


Fig. 2. Fluorescence spectra of compounds **1a–1g** in DMSO.

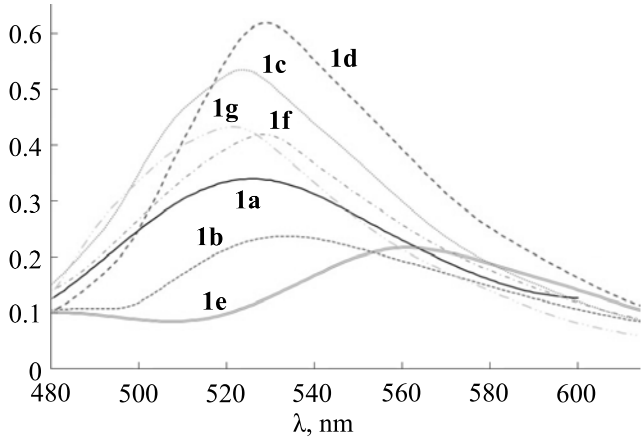


Fig. 3. Fluorescence spectra of compounds **1a–1g** in solid state.

at acidifying the reaction mass. Their oxidation with sodium nitrite completes the process.

Structure of synthesized compounds **1a–1g** is confirmed by IR, ^{1}H NMR, and mass spectra.

The obtained derivatives of the nicotinic acid **1a–1g** exhibit fluorescence both in solution and solid state, therefore we have investigated their optical properties. As a first step the effect of a solvent on absorption and fluorescence properties of compound **1a** was investigated (Table 1).

In polar solvents the optical density is higher than in low-polar and non-polar solvents. In going from a solution in acetic acid to solutions in basic solvents, like pyridine and DMSO, a red shift is observed. The intensity of fluorescence is also affected by the polarity and acid-base properties of solvents. The maximal fluorescence is observed for solutions in pyridine and DMSO, a little lower in acetonitrile, low in dioxane and benzene and practically no fluorescence in acetic acid (Fig. 1).

Further we investigated optical properties of all synthesized compounds **1a–1g** in DMSO (Table 2). As it is evident from the table data, a change in the nature of substituent in the aromatic ring affects the optical density and strongly affects the fluorescence intensity, while the wavelengths of maxima remain almost unchanged. From the spectral data it can be seen that the intensity of fluorescence increases in the presence of a substituent in the position *2* of the benzene ring (Fig 2).

Further we investigated the solid phase fluorescence of compounds **1a–1g**. The most intensive fluorescence was observed in 2-chlorosubstituted compound **1d**. In general an intensive fluorescence in solid state is observed in halogen- and methoxy-substituted compounds. The fluorescence maximum appears in the range 520–530 nm, except for compound with 4-dimethylamine substituent, whose maximum of is shifted to 561 nm (Table 2, Fig. 3).

Hence we synthesized a series of nicotinic acid derivatives containing BDTC fragment and investigated their optical properties.

EXPERIMENTAL

IR spectra were registered on Fourier spectrometer FSM-1202 in thin layer (suspension in mineral oil). ^{1}H NMR spectra were registered on a spectrometer Bruker DRX-500 in DMSO-d_6, internal reference TMS. Mass spectra were recorded on an instrument Finnigan MAT INCOS-50 (EI, 70 eV). Elemental analysis was carried out on a CHN-analyzer vario Micro cube. Melting points were determined on automatic apparatus OptiMelt MPA100. Monitoring of the reactions progress and purity of synthesized compounds was performed by TLC method on Sorbfil PTLC-AF-A-UV plates (eluent EtOAc, development under UV irradiation, by iodine vapor and thermal decomposition).

Ethyl 2-methyl-4-phenyl-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate (1a). A mixture of 0.264 g (2 mmol) of 2-aminoprop-1-en-1,1,3-tricarbonitrile and 0.212 g (2 mmol) of benzaldehyde was stirred in 10 ml of ethanol in the presence of catalytic amount of piperidine acetate at 60°C till components dissolved, then into the reaction mixture was added 0.260 g (2 mmol) of acetoacetic ester and 0.152 g (2.1 mmol) of sodium nitrite. After the end of reaction (TLC) the reaction mixture was cooled, conc. HCl was added dropwise till pH 3–4, the precipitate was filtered off, washed with a small amount of 2-propanol and with distilled water. The product was recrystallized from a mixture 2-propanol–dioxane. Yield 0.462 g (70%), mp 224–225°C (decomp.) {224–225°C (decomp.) [6]}.

Compounds **1b–1g** were obtained similarly.

Ethyl 2-methyl-4-(4-tolyl)-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate (1b). Yield 68%, mp 238–239°C (decomp.). IR spectrum, ν, cm^{-1}: 3250–3100 (NH), 2220, 2196 (C≡N), 1725 (C=O), 1625 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.78 t (3H, $CH_2C\underline{H}_3$, *J* 7.1 Hz), 2.36 s (3H, CH_3), 2.39 s (3H, CH_3), 3.85 q (2H, $C\underline{H}_2CH_3$, *J* 7.1 Hz), 7.15 d (2H, C_6H_4, *J* 8.1 Hz), 7.26 d (2H, C_6H_4, *J* 8.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 344 $[M]^+$ (22), 299 $[M-45]^+$ (100). Found, %: C 69.65; H 4.75; N 16.36. $C_{20}H_{16}N_4O_2$. Calculated, %: C 69.76; H 4.68; N 16.27. *M* 344.37.

Ethyl 2-methyl-4-(4-fluorophenyl)-5-cyano-6-(dicyano-methylidene)-1,6-dihydropyridine-3-carboxylate (1c). Yield 74%, mp 227–228°C (decomp.) {197–198°C (decomp.) [6]}.

Ethyl 2-methyl-4-(2-chlorophenyl)-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate (1d). Yield 76%, mp 238–239°C (decomp.) {218–219°C (decomp.) [6]}.

Ethyl 2-methyl-4-(4-dimethylaminophenyl)-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate (1e). Yield 65%, mp 231–232°C (decomp.) {209–210°C (decomp.) [6]}.

Ethyl 2-methyl-4-(4-methoxyphenyl)-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate (1f). Yield 68%, mp 211–212°C (decomp.). IR spectrum, ν, cm^{-1}: 3260–3110 (NH), 2227, 2200 (C≡N), 1729 (C=O), 1607 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.82 t (3H, $CH_2C\underline{H}_3$, *J* 7.1 Hz), 2.38 s (3H, CH_3), 3.80 s (3H, OCH_3), 3.88 q (2H, $C\underline{H}_2CH_3$, *J* 7.1 Hz), 7.02 d (2H, C_6H_4, *J* 8.7 Hz), 7.21 d (2H, C_6H_4, *J* 8.7 Hz). Mass spectrum, *m/z* (I_{rel}, %): 360 $[M]^+$ (13), 315 $[M-45]^+$ (100). Found, %: C 66.54; H 4.59; N 15.68. $C_{20}H_{16}N_4O_3$. Calculated, %: C 66.66; H 4.48; N 15.55. *M* 360.37.

Ethyl 2-methyl-4-(2-methoxyphenyl)-5-cyano-6-(dicyanomethylidene)-1,6-dihydropyridine-3-carboxylate (1g). Yield 70%, mp 215–216°C (decomp.). IR spectrum, ν, cm^{-1}: 3268–3100 (NH); 2223, 2202 (C≡N), 1725 (C=O), 1604 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.74 t (3H, $CH_2C\underline{H}_3$, *J* 7.1 Hz), 2.41 s (3H, CH_3), 3.72 s (3H, OCH_3), 3.81 q (2H, $C\underline{H}_2CH_3$, *J* 7.1 Hz), 6.99 t (1H, C_6H_4, *J* 7.2 Hz), 7.04 d.d (1H, C_6H_4, *J* 7.5, 1.8 Hz), 7.15 d (1H, C_6H_4, *J* 8.3 Hz), 7.39–7.43 m (1H, C_6H_4). Mass spectrum, *m/z* (I_{rel}, %): 360 $[M]^+$ (32), 315 $[M-45]^+$ (100). Found, %: C 66.51; H 4.57; N 15.68. $C_{20}H_{16}N_4O_3$. Calculated, %: C 66.66; H 4.48; N 15.55. *M* 360.37.

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