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SHORT COMMUNICATIONS

Aqueous-Phase Synthesis and Solid-Phase Fluorescence of 3-(Methoxyphenyl)-2-cyanoacrylamides

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Abstract—Reactions of methoxybenzaldehydes with cyanoacetamide in water in the presence of cocamidopropylamine oxide afforded 84–94% of 3-(methoxyphenyl)-2-cyanoacrylamide which showed solid-phase fluorescence with the emission maxima located at λ 421–469 nm.

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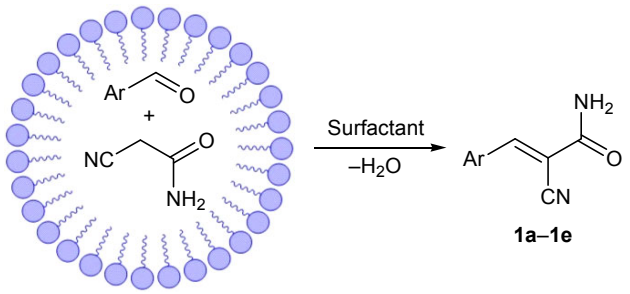
The use of aqueous medium in organic synthesis is related to obvious advantages of water compared to organic solvents, in particular to its accessibility, cheapness, safety, and the lack of toxicity. In some cases, the use of water as solvent increases the reaction rate and affects the selectivity of a wide series of organic reactions [1–3]. Therefore, water plays an important role as an alternative solvent which can replace hazardous organic solvents in the synthesis of various compounds [1–5]. However, the application of water as reaction medium is limited since most reagents are poorly soluble therein. This drawback can be overcome by adding surfactants capable of aggregating reacting species in micelles [5–7].

Alkoxybenzylidene derivatives of malononitrile dimer can be obtained in water in the presence of a nonionic surfactant, Triton X-100 [5]. Depending on the number and position of alkoxy groups in the aromatic ring, the synthesized compounds showed solid-phase fluorescence at λ_{max} 491–560 nm [5]. In continuation of our works on the development of environmentally safe methods of synthesis of organic compounds with potentially practically important properties, herein we describe the Knoevenagel condensation of methoxy-substituted benzaldehydes with cyanoacetamide in water in the presence of surfactants.

Methoxybenzylidene derivatives of cyanoacetamide are precursors to various heterocyclic structures and inhibitors of thyrosinase [8] and serine proteases (NS2B-NS3) [9]; they exhibit fluorescence [10] and reversible mechanochromism [11, 12]. Therefore, search for new simple, environmentally benign, and efficient methods of their preparation is an important problem.

(*E*)-3-Aryl-2-cyanoacrylamides **1a**–**1e** can be synthesized by mixing the corresponding substituted benzaldehyde with cyanoacetamide in water in the presence of a surfactant at room temperature. Depending on the surfactant used, the yields attained 94%. Furthermore, the reaction was stereoselective, and only one of the possible isomers was formed.

Various surfactants were tried in order to find optimal conditions for the condensation of cyanoacetamide with aromatic aldehydes, namely sodium lauryl sulfate (SLS, a traditional anionic surfactant), Triton X-100 (nonionic surfactant), and cocamidopropylamine oxide (CAPO, *Oksipav AP*, nonionic surfactant with weak cationic properties). The model reaction was the condensation of cyanoacetamide with 4-methoxybenzaldehyde. The yields of **1a** in the presence of SLS, Triton X-100, and CAPO were 23, 86%, and



1a–1e

Ar = 4-$MeOC_6H_4$ (**a**), 3-$MeOC_6H_4$ (**b**), 2-$MeOC_6H_4$ (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 3,4,5-$(MeO)_3C_6H_2$ (**e**).

93%, respectively. Presumably, the high yield of **1a** with the use of CAPO is determined by the presence in solution of free (unoxidized) amine molecules containing a long hydrophobic "tail." Unoxidized amines act as a catalyst; they facilitate the reaction via abstraction of proton from the methylene group of cyanoacetamide, and the long alkyl radical solubilizes the reactants in a micelle.

Compounds **1a**–**1e** were isolated as colorless or light yellow crystalline solids which showed fluorescence in the crystalline state. The emission range depended on the number and position of methoxy groups in the benzene ring and was located in the violet to blue region (λ_{max} 421–469 nm, Table 1). The highest fluorescence intensity was observed for 3,4-dimethoxyphenyl derivative **1d**.

Thus, we have developed a new method of synthesis of 3-aryl-2-cyanoacrylamides in aqueous medium in the presence of a surfactant. The proposed method is advantageous due to simple experimental procedure, high yields, cheap reactants, and no need of using catalysts and organic solvents. Methoxy-substituted 3-aryl-2-cyanoacrylamides show solid-phase fluorescence with their emission maxima at λ 421–469 nm.

2-Cyano-3-(4-methoxyphenyl)prop-2-enamide (1a). Cocamidopropylamine oxide, 0.069 g (0.15 mmol), 4-methoxybenzaldehyde, 0.136 g (1 mmol), and cyanoacetamide, 0.084 g (1 mmol), were added to 5 mL of water. The mixture was stirred for 1.5 h at room temperature, and the precipitate was filtered off, washed with water, and recrystallized from propan-2-ol. Yield 93%, mp 212–213°C. IR spectrum, ν, cm^{-1}: 3420, 3304 (N–H), 2204 (C≡N), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.86 s (3H, OCH_3), 7.14 d (2H, C_6H_4, J = 8.9 Hz), 7.67 br.s and 7.80 br.s (1H each, NH_2), 7.97 d (2H, C_6H_4, J = 8.9 Hz), 8.11 s (1H, CH). Mass spectrum: m/z 202 (I_{rel} 100%) $[M]^+$. Found, %: C 65.28; H 5.02; N 13.92. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.34; H 4.98; N 13.85. M 202.21.

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

2-Cyano-3-(3-methoxyphenyl)prop-2-enamide (1b). Yield 94%, mp 144–145°C. IR spectrum, ν, cm^{-1}: 3391, 3311 (N–H), 2221 (C≡N), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.81 s (3H, OCH_3), 7.16–7.19 m (1H, C_6H_4), 7.48 d (1H, C_6H_4, J = 7.6 Hz), 7.50–7.54 m (2H, C_6H_4), 7.78 br.s and 7.92 br.s (1H each, NH_2), 8.16 s (1H, CH). Mass spectrum: m/z 202 (I_{rel} 100%) $[M]^+$. Found, %: C 65.41; H 4.95; N 13.91. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.34; H 4.98; N 13.85. M 202.21.

Table 1. Relative intensities and positions of emission maxima in the solid-phase fluorescence spectra of compounds **1a**–**1e**

Compound no.	$\lambda_{fl.}$, nm	Intensity,[a] relative units
1a	442	1.00
1b	421	3.61
1c	451	3.23
1d	469	7.34
1e	448	1.70

[a] Relative to **1a**; fluorescence excitation wavelength λ 365 nm.

2-Cyano-3-(2-methoxyphenyl)prop-2-enamide (1c). Yield 93%, mp 165–166°C. IR spectrum, ν, cm^{-1}: 3398, 3273 (N–H), 2209 (C≡N), 1688 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H, OCH_3), 7.11 t (1H, C_6H_4, J = 7.6 Hz), 7.19 d (1H, C_6H_4, J = 8.3 Hz), 7.56–7.60 m (1H, C_6H_4), 7.75 br.s and 7.90 br.s (1H each, NH_2), 7.99 d.d (1H, C_6H_4, J = 7.8, 1.6 Hz), 8.40 s (1H, CH). Mass spectrum: m/z 202 (I_{rel} 100%) $[M]^+$. Found, %: C 65.28; H 4.96; N 13.91. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.34; H 4.98; N 13.85. M 202.21.

2-Cyano-3-(3,4-dimethoxyphenyl)prop-2-enamide (1d). Yield 84%, mp 191–192°C. IR spectrum, ν, cm^{-1}: 3392, 3314 (N–H), 2211 (C≡N), 1692 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.81 s (3H, OCH_3), 3.86 s (3H, OCH_3), 7.16 d (1H, C_6H_3, J = 8.5 Hz), 7.57 d.d (1H, C_6H_3, J = 8.5, 2.0 Hz), 7.66 br.s (1H, NH_2), 7.67 d (1H, C_6H_3, J = 2.0 Hz), 7.79 br.s (1H, NH_2), 8.11 s (1H, CH). Mass spectrum: m/z 232 (I_{rel} 100%) $[M]^+$. Found, %: C 61.97; H 5.18; N 12.11. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.06; H 5.21; N 12.06. M 232.24.

2-Cyano-3-(3,4,5-trimethoxyphenyl)prop-2-enamide (1e). Yield 90%, mp 197–192°C. IR spectrum, ν, cm^{-1}: 3404, 3322 (N–H), 2223 (C≡N), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.77 s (3H, OCH_3), 3.83 s (6H, OCH_3), 7.36 s (2H, C_6H_2), 7.73 br.s and 7.84 br.s (1H each, NH_2), 8.13 s (1H, CH). Mass spectrum: m/z 262 (I_{rel} 100%) $[M]^+$. Found, %: C 59.45; H 5.34; N 10.74. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.38; N 10.68. M 262.26.

The IR spectra were recorded on an FSM-1202 spectrometer with Fourier transform from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker DRX-500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were recorded on a Finnigan MAT INCOS-50 instrument. The solid-phase fluorescence spectra were measured with a Flyuorat-02

Panorama spectrofluorometer equipped with a "Frog" accessory for measurements outside the cell compartment. The elemental analyses were obtained on a Perkin Elmer-2400 CHN analyzer. The melting points were measured with an OptiMelt MPA100 melting point apparatus. The progress of reactions and the purity of products were monitored by TLC on Sorbfil PTSKh-AF-A-UF plates; spots were visualized under UV light, by treatment with iodine vapor, or by thermal decomposition.

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