



Synthesis of 1-vinylpyrrole-2-carbonitriles

Boris A. Trofimov*, Alexander M. Vasil'tsov, Al'bina I. Mikhaleva, Andrey V. Ivanov, Elena V. Skital'tseva, Elena Yu. Schmidt, Elena Yu. Senotrusova, Igor A. Ushakov, Konstantin B. Petrushenko

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

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ABSTRACT

A new highly synthetically potent series of bifunctional pyrroles, 1-vinylpyrrole-2-carbonitriles, were synthesized from readily available 1-vinylpyrrole-2-carbaldehyde oximes by two methods: (1) reaction with acetylene (KOH/DMSO, 70 °C, 10 min, yields 58–67%) and (2) reaction with acetic anhydride (90–100 °C, 5 h, yields 83–93%). Starting from 2-phenyl-1-vinylpyrrole, the one-pot synthesis of the corresponding 1-vinyl-2-carbonitrile was accomplished directly by successive treatment with a DMF/(COCl)₂ complex, NH₂OH·HCl/NaOAc, and acetic anhydride (yield 58%).

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Pyrrolicarbonitriles are important intermediates in various research fields.¹ They are precursors of diverse heterocyclic ensembles² possessing high and often specific biological activity, which makes them prospective candidates for applications in medicine. Their derivatives include nonpeptide Angiotensin II receptor antagonists,³ 5-HT₃ receptor agonists,⁴ nonpeptide Bradykinin B₂ receptor antagonists,⁵ the nonsteroidal progesterone receptor agonist Tanaproget,⁶ the insulin-like growth factor I receptor (IGF-IR) inhibitor AEW541,⁷ and progesterone receptor modulators.⁸

Some of their representatives (Chlorfenapyr, Fludioxonil) exhibit high insecticidal activity and are applied extensively in agriculture.⁹ Pyrrole-2-carbonitrile was used for the synthesis of bis-(2-pyrrolyl)-1,2,4,5-tetrazine, a monomer for the preparation of organic conductors with low band gaps and fluorescent and non-linear optical materials.¹⁰

Pyrrole-2-carbonitriles are currently synthesized by dehydration of pyrrole-2-carbaldehyde oximes under the action of acidic reagents (e.g., acetic anhydride,¹¹ *p*-TsOH¹¹ and diethyl chlorophosphate¹²). They can also be obtained from pyrrole-2-carbaldehyde hydrazone salts in the presence of hydrogen chloride,¹³ by the reaction of pyrroles with chlorosulfonylisocyanate,¹⁴ cyanation of pyrroles with 1-cyanobenzotriazole,¹⁵ and also with a derivative of hypervalent iodine,¹⁶ as well as iodopyrroles and CuCN in the presence of a palladium catalyst (tris(dibenzylideneacetone)dipalladium).¹⁷ Syntheses of pyrrole-2-carbonitriles from nonpyrrolic precursors have also been published.¹⁸

Despite the advances in pyrrolicarbonitrile chemistry, pyrroles containing both cyano and vinyl groups remain poorly understood, the difficulty in their preparation being a limitation. Meanwhile, the combination of cyano and vinyl groups on the pyrrole moiety provides a series of bifunctional pyrroles of considerably higher synthetic utility, particularly for the design of pyrrole polymers, organic conductors, and optoelectronic materials.

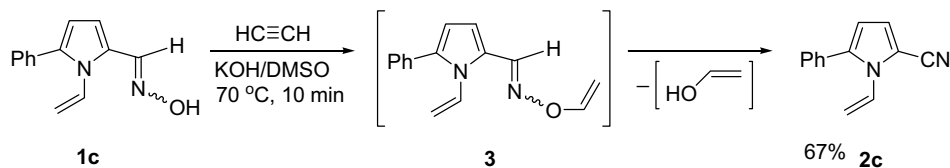
Herein, we report the synthesis of 1-vinylpyrrole-2-carbonitriles starting from 1-vinylpyrrole-2-carbaldehydes.¹⁹ As we had previously noted, the easy dehydration of 5-phenyl-1-vinylpyrrole-2-carbaldehyde oxime **1c** may occur upon direct vinylation with acetylene in KOH/DMSO to afford 5-phenyl-1-vinylpyrrole-2-carbonitrile **2c** in 67% yield (20–22 atm, 70 °C, 10 min).^{20,21} The reaction is likely to proceed via the intermediate *O*-vinyl oxime **3** by elimination of vinyl alcohol (Scheme 1).

Based on this result, we next attempted, using pyrrole-2-carbaldehyde oxime **4**, to combine dehydration of the oxime function with vinylation of the N-angular position in a one-pot procedure and, hence to synthesize 1-vinylpyrrole-2-carbonitriles directly from 1-pyrrole-2-carbaldehyde oximes (Scheme 2).

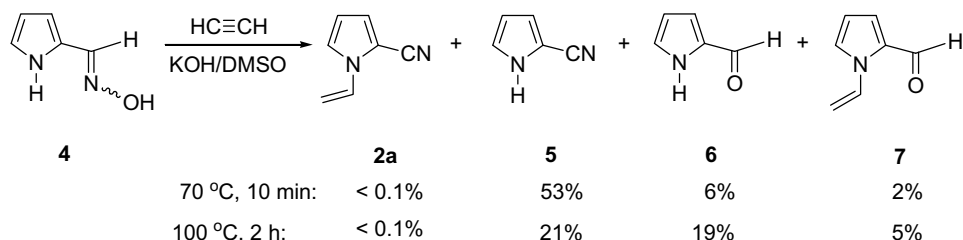
However, the expected pyrrole **2a** was not discernible (yield < 0.1%) among the reaction products, the synthesis being carried out both under the conditions shown in Scheme 1 (20–22 atm, 70 °C, 10 min) or at a higher temperature (100 °C) for a longer period of time (2 h). The major product was found to be pyrrole-2-carbonitrile, **5**, in keeping with the easy dehydration of oximes with KOH/DMSO in the presence of acetylene.²²

Under the studied conditions, pyrrole **5**, due to its high acidity and hence lower nucleophilicity of the corresponding anion, proved to be inert toward acetylene.

* Corresponding author. Tel.: +7 395251 19 26; fax: +7 395241 93 46.
E-mail address: boris_trofimov@iriokh.irk.ru (B. A. Trofimov).



Scheme 1.



Scheme 2.

Using known $pK_a - \sigma_I$ (where σ_I is an inductive constant for the pyrrole substituent) correlations for substituted pyrroles,^{22,23} we have estimated the pK_a value of pyrrole **5** to be 14.4 which is 9 orders higher than that for unsubstituted pyrrole (23.3).²³ Pyrrole-2-carbaldehyde **6** obviously resulted from the starting oxime **4** after deoxygenation of the latter.

An advantage of the method of oxime dehydration with the KOH/DMSO–acetylene system is that it can be applied to oximes possessing functional groups sensitive to acidic reagents.²² However, the limitations of this method are the requirement for special equipment (autoclave) and acetylene under pressure. To elaborate a complimentary method, we have modified the dehydration of oximes under the action of acetic anhydride such that it is applicable to 1-vinylpyrrole-2-carbaldehyde oximes.

Application of the reported protocol for dehydration of pyrrole-2-carbaldehyde oximes by reflux in acetic anhydride (137 °C, 20 min)²⁴ to 1-vinylpyrrole-2-carbaldehyde oximes turned out to be of low efficacy: the yields of pyrroles **2a** and **2c** were 39% and 37%, respectively. This is as a result of the known sensitivity of 1-vinylpyrroles toward acids.²²

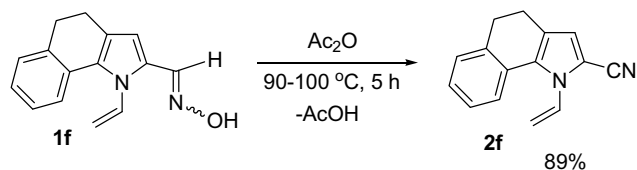
We have managed to substantially increase the yields (up to 83–93%) of the target 1-vinylpyrrole-2-carbonitriles **2a–f** by carrying out the acetic anhydride-mediated dehydration of oximes **1a–f** at a lower reaction temperature (90–100 °C) and over a longer period of time (5 h).²⁵

The formation of 1-vinylpyrrole-2-carbonitriles **2a–e** was apparently preceded by acylation of the starting oximes **1a–e**, the intermediate acetates **8a–e**, then eliminating acetic acid (Scheme 3).

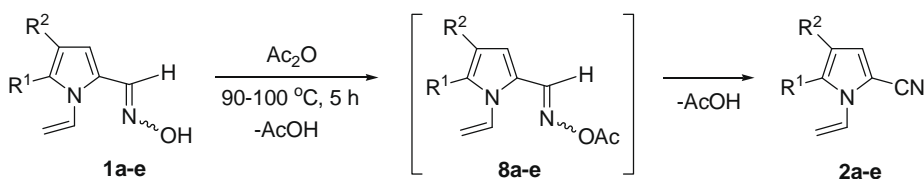
Under the same conditions, 1-vinyl-4,5-dihydrobenzo[g]indole-2-carbonitrile **2f** was obtained from oxime **1f** in 89% yield (Scheme 4).²⁵

It is noteworthy that both starting oximes **1a–f** and product nitriles **2a–f** were fairly stable on extended heating (90–100 °C, 5 h) in the presence of acetic acid, which easily oligomerizes other 1-vinylpyrroles (20 °C, 2 h).^{22,26} This is indicative of the sharp drop in electron density both in the pyrrole nucleus and in the vinyl group under the effect of a strong electron-withdrawing nitrile substituent.

To compare the synthetic utility of the two methods (Scheme 1 and 3), we have synthesized pyrrole **2f** by dehydration of oxime **1f**

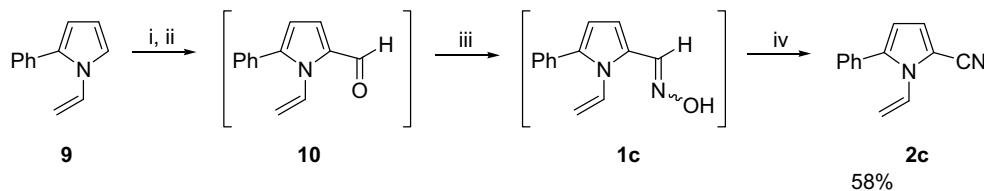


Scheme 4.



Nitrile	R ¹	R ²	Yield, %
2a	H	H	93
2b		(CH ₂) ₄	83
2c	Ph	H	85
2d	4-EtC ₆ H ₄	Me	84
2e	2-Naphthyl	H	92

Scheme 3.



Scheme 5. Reagents and conditions: (i). DMF/(COCl)₂/CH₂Cl₂, 10–20 °C, 40 min; (ii) NaOAc/H₂O, rt, 30 min; (iii) H₂NOH·HCl, 40–50 °C, 10 min; (iv) Ac₂O, 90–100 °C, 5 h.

in the KOH/DMSO–acetylene system, the yield of nitrile **2f** being only 53% (vs 89% according to Scheme 4).^{21,25}

Of interest is the one-pot, multi-component synthesis of 1-vinylpyrrole-2-carbonitriles which involves treatment of pyrroles with the complex DMF/(COCl)₂ and hydroxylamine hydrochloride in pyridine.²⁷ However, when applied to vinylpyrroles, this method (according to our experiments) proved to be inefficient (resinification).

Nevertheless, we found that the direct one-pot synthesis of 1-vinylpyrrole-2-carbonitriles **2a–f** from 1-vinylpyrroles occurred when pyridine was replaced by sodium acetate and when acetic anhydride was added. Under these modified conditions, 2-phenyl-1-vinylpyrrole **9** gave nitrile **2c** in 58% yield,²⁸ which is 8% higher than that obtained with isolation of the intermediate 1-vinylpyrrole-2-carbaldehyde **10** (Scheme 5).¹⁷

The structures of nitriles **2a–f** were consistent with their IR, NMR (¹H, ¹³C, ¹⁵N), and UV/Vis spectra and elemental analysis (see the Supplementary data). In the IR spectra of nitriles **2a–f**, intensive C≡N and C=C stretching vibrations (2200–2215 cm⁻¹ and 1637–1646 cm⁻¹, respectively) were observed. The C≡N groups appeared in the region of 112–114 ppm in the ¹³C NMR spectra and at –113 to –110 ppm in the ¹⁵N NMR spectra. In the UV/Vis spectra of nitriles **2a–f**, absorption bands at 256–315 nm (log ε 3.95–4.07) were observed (Table 1). Nitriles **2b–f** fluoresced (λ_{max} of emission 337–378 nm, Stokes shift 57–81 nm) on irradiation at their absorption maximum (Table 1).

Comparison of the UV spectra of pyrrole **9**²⁹ and nitrile **2c** showed that the introduction of the C-2 nitrile group resulted in a bathochromic shift (10 nm) and in a hypochromic effect (decrease of log ε from 4.18 to 4.03) due to extension of the π-conjugated system. The same trends were observed for other nitriles when compared with the corresponding unsubstituted 1-vinylpyrroles^{22,29} (Table 1).

In conclusion, two expedient methods for the synthesis of 1-vinylpyrrole-2-carbonitriles, a new series of bifunctionalized pyrroles, have been developed. The key reaction of the methods is dehydration of 1-vinylpyrrole-2-carbaldehyde oximes under the action of KOH/DMSO–acetylene (method 1) or acetic anhydride (method 2). Also, the one-pot synthesis of 1-vinylpyrrole-2-carbonitriles directly from 1-vinylpyrroles has been realized.

The synthesized 1-vinylpyrrole-2-carbonitriles are promising building blocks for the preparation of new pyrrole-based compounds and the design of materials for optoelectronic devices.

Table 1
UV/vis and fluorescence spectra of nitriles **2a–f** (in hexane)

Nitrile	Absorption		Emission λ _{max} (nm)	Stokes shift (nm)
	λ _{max} (nm)	log ε		
2a	260	3.97	None	—
2b	256	4.01	337	81
	280	3.95	337	57
2c	280	4.03	352	72
2d	284	4.05	355	71
2e	310	4.02	370	60
2f	315	4.07	378	63

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.104.

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21. A mixture of 5-phenyl-1-vinylpyrrole-2-carbaldehyde oxime **1c** (0.50 g, 2.4 mmol), KOH·0.5H₂O (0.16 g, 2.4 mmol), and DMSO (50 mL) was placed into a 0.25 L steel rotating autoclave, saturated with acetylene at room temperature (initial pressure 14 atm), and heated (70 °C, 10 min, maximal pressure of acetylene ~20–22 atm). After cooling (20–25 °C), the reaction mixture was diluted with water (100 mL) and extracted with CH₂Cl₂ (20 mL × 6). The extract was washed with water (30 mL × 4) and dried over K₂CO₃. After removal of CH₂Cl₂, 0.68 g of a crude residue was obtained. Column chromatography (basic Al₂O₃, hexane) gave 0.31 g (67%) of nitrile **2c**. Pyrrole **2f** was prepared in the same manner (yield 53%).
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28. *One-pot procedure for the synthesis of 3c*. To DMF (0.9 g, 12 mmol) was added a solution of oxalyl chloride (1.5 g, 12 mmol) under cooling (10 °C) for 2–3 min. To the white crystals of the DMF/(COCl)₂ reagent was added a solution of 1-vinyl-2-phenylpyrrole **9** (2.0 g, 12 mmol) in CH₂Cl₂ (15 mL) at room temperature with stirring for 10 min. The mixture was stirred for 30 min, and then a solution of sodium acetate (3.1 g, 38 mmol) and water (0.2 mL) were added at room temperature. The mixture was stirred additionally for 30 min, then H₂NOH·HCl (0.92 g, 13 mmol) was added and then CH₂Cl₂ was distilled off. To the residue was added acetic anhydride (6.5 g, 63 mmol) in one portion and the mixture was heated (90–100 °C for 5 h). After cooling (20–25 °C) benzene (50 mL), water (20 mL) and solid NaHCO₃ were added with stirring until the evolution of gas stopped. The organic layer was separated and dried over K₂CO₃. After removal of the solvent, the crude product was purified by column chromatography (Al₂O₃, benzene) to afford 1.35 g (58%) of **3c**.
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