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Highly Fluorescent Pyrido[2,3-*b*]indolizine-10-Carbonitriles through Pseudo Three-Component Reactions of *N*-(Cyanomethyl)pyridinium Salts

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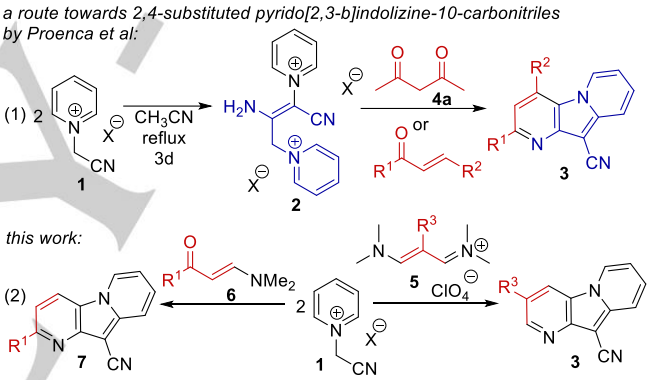
Abstract: An interaction of *N*-(cyanomethyl)pyridinium salts with vinamidinium perchlorates or enaminones proceeds as a pseudo-three component process and results in the formation of 3- or 2-substituted pyrido[2,3-*b*]indolizine-10-carbonitriles, respectively. Optical properties of these compounds have been evaluated, revealing effective green light emission with fluorescence quantum yields of up to 0.81.

Introduction

Domino and multicomponent reactions allow rapid and efficient construction of molecular complexity;[1–5] they are widely used for the synthesis of natural products and analogues,[6,7] pharmaceutical substances,[8–11] functional materials,[12,13] macrocyclizations[14,15]. Employing these tools for the preparation of fluorophores and electrophores emerged as a useful technique,[16–19] enabling fast creation of numerous scaffolds with diverse structure and needful properties. Indolizines are indeed sought-for heterocycles,[20,21] which have various applications as biologically active compounds,[22–25] dyes,[26–28] molecular probes and sensors [29–33]. They are also well-known fluorophores,[34] with some recent examples of multicomponent syntheses.[35–39] Pyrido[2,3-*b*]indolizine-10-carbonitrile scaffold **3** has been firstly prepared by Proença *et al* through a domino cyclization of dimerized pyridinium salts **2** with acetylacetone **4a** or chalcones (Scheme 1, eq. 1),[40,41] although their potential as fluorophores was not recognized. This method is also limited to the synthesis of pyridoindolizines, bearing substituents at C(2) and C(4) positions only. Moreover, the preliminary preparation of dimerized salt is needed. Following our interest in the chemistry of *N*-(cyanomethyl)azinium quaternary salts,[42–47] we have concurrently discovered, that this reaction might be carried out without initial dimerization of the pyridinium salts, prompting us to investigate its potential in the transformations with other 1,3-difunctionalized compounds. Herein we report a pseudo three-component reaction of *N*-(cyanomethyl)pyridinium **1** (2 equiv) and vinamidinium salts or enaminones, to form hitherto unknown 3- or 2-substituted pyrido[2,3-*b*]indolizines **3** with prominent optical properties (fluorescence quantum yields of up to 0.81) (Scheme 1, eq. 2).



Scheme 1. An outline for the synthesis of pyrido[2,3-*b*]indolizines.

Results and Discussion

Synthesis of pyrido[2,3-*b*]indolizines

Firstly, we envisioned 1,3-dialdehydes to work analogously to acetylacetone (Table 1, entry 1), to give target pyridoindolizines, unsubstituted at C(2) and C(4) positions. Unfortunately, these reactions were ineffective, producing target molecule **3b** in 5% yield (Table 1, entry 2). It turned out, that the reaction of synthetic precursors of malondialdehydes, vinamidinium salts **5**, furnished corresponding pyridoindolizine **3b** with 20% yield (Table 1, entry 3). The reaction conditions optimization allowed to increase the yield of this pseudo three-component reaction to 30% (Table 1, entry 4). Under standard conditions, the reactants were refluxed in absolute EtOH for 25 h in the presence of Et_3N. The use of different bases or solvents, as far as varying reaction time or performing the reaction under MW conditions did not improve the yield of product **3b**.

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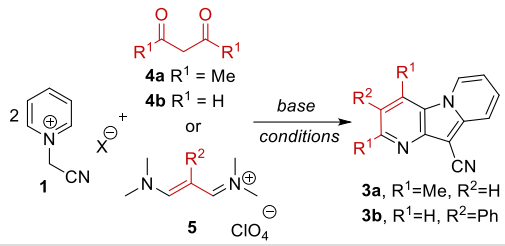


Table 1. Reaction Optimization.

Entry	Substrate	Base	Conditions	Product, Yield, %
1	**4a**	K_2CO_3 (3 equiv)	MeOH-H_2O (3:1), reflux, 3 h	**3a**, 91
2	**4b**	K_2CO_3 (3 equiv)	MeOH-H_2O (3:1), reflux, 3 h	**3b**, 5
3	**5**	K_2CO_3 (3 equiv)	MeOH, reflux, 18 h	**3b**, 20
4[a]	**5**	Et_3N	EtOH, reflux, 25 h	**3b**, 30
5	**5**	NH_4OAc	EtOH, reflux, 25 h	**3b**, 21
6[b]	**5**	NH_4OAc	EtOH, MW, 150 °C, 30 min	**3b**, 28

[a] Reaction conditions: *N*-(cyanomethyl)pyridinium chloride **1** (1.19 mmol), vinamidinium perchlorate **5** (0.40 mmol), NEt_3 (1.98 mmol), EtOH (9 mL).

[b] Reactions were run in microwave reactor Monowave 300 (Anton Paar GmbH) in a closed vial, and the reaction temperature was monitored by an IR sensor.

Despite high reactivity of vinamidinium perchlorates, and consequent formation of complex mixtures, the reaction scope investigation showed the possibility to employ vinamidinium salts with various aryl substituents. Thus, phenyl, *p*-chlorophenyl, *p*-fluorophenyl pyridoindolizines were obtained with poor to moderate yields (Figure 1). Besides *N*-(cyanomethyl)pyridinium chloride, 4-substituted pyridinium salts were tested. The reaction worked for 4-methyl, ethyl, and phenyl-substituted pyridinium salts. The structure of compound **3l** was unambiguously determined by X-ray diffraction study (CCDC #1938370). The use of 3-substituted pyridinium salts resulted in the formation of isomeric mixtures and were not listed in the scheme.

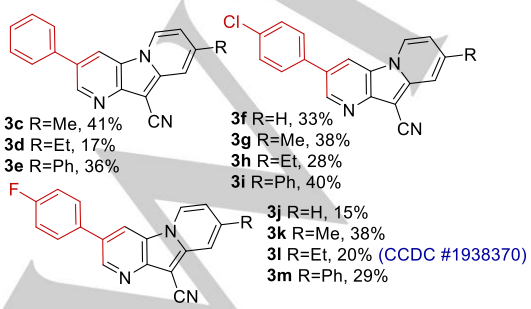


Figure 1. Scope of pseudo three-component reaction of vinamidinium and *N*-(cyanomethyl)pyridinium (2 equiv) salts. Reaction conditions: Table 1, Entry 4.

In search for a better coupling partner, we put our attention to another well-known 1,3-dielectrophiles – enaminones. The interaction of enaminone **6a** with pyridinium salt under standard conditions furnished target indolizine **7a** with negligible 4% yield (Table 2, Entry 1). Carrying out the reaction in ethanol-water mixture raised the yield to 31% (Table 2, Entry 2), while changing the alcohol to *i*-PrOH resulted in 44% of the target product (Table 2, Entry 3). Screening of the bases (Table 2, Entries 4-8) revealed sodium acetate to be the best choice, delivering compound **7a** with 51% yield (Table 2, Entry 6). The structure of compound **7a** was determined by single crystal X-ray diffraction study (CCDC #1938369), displaying the process to be regioselective.

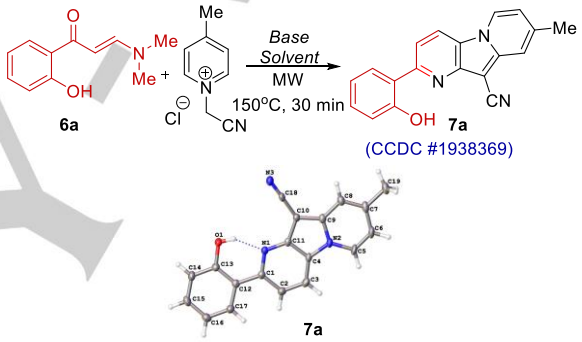


Table 2. Enaminone **6a** in a reaction with pyridinium salt[b]

Entry	Base	Solvent	Yield, %
1	Et_3N	EtOH	4
2	Et_3N	EtOH-H_2O (3:1)	31
3	Et_3N	*i*-PrOH-H_2O (3:1)	44
4	DIPEA	*i*-PrOH-H_2O (3:1)	36
5	NH_4OAc	*i*-PrOH-H_2O (3:1)	43
6[a]	**NaOAc**	***i*-PrOH-H_2O (3:1)**	**51**
7	K_2CO_3	*i*-PrOH-H_2O (3:1)	5
8	Cs_2CO_3	*i*-PrOH-H_2O (3:1)	21

[a] Reaction conditions: *N*-(cyanomethyl)pyridinium chloride **1** (1.19 mmol), vinamidinium perchlorate **5** (0.40 mmol), NEt_3 (1.98 mmol), EtOH (9 mL).

[b] Reactions were run in microwave reactor Monowave 300 (Anton Paar GmbH) in a closed vial, and the reaction temperature was monitored by an IR sensor.

The selected conditions were used to perform the scope studies. Enaminone **6a** reacted with unsubstituted, 4-ethyl-, 4-phenyl-*N*-(cyanomethyl)pyridinium chlorides to produce target molecules

7b-d with moderate yields (Figure 2). Phenyl substituent could be successfully installed on a pyridoindolizine moiety with the help of the corresponding enaminone, producing compounds **7e-h**. Aliphatic enaminones could also be used to generate 2-methyl and 2-ethyl substituted pyridoindolizines **7i-l**, and **7m, n**, respectively. We were also happy to find that pyridine rings could be also incorporated in pyridoindolizine scaffolds **7o-s** with moderate yields.

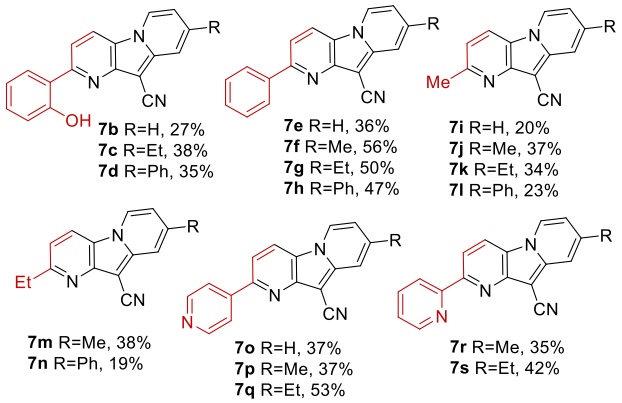
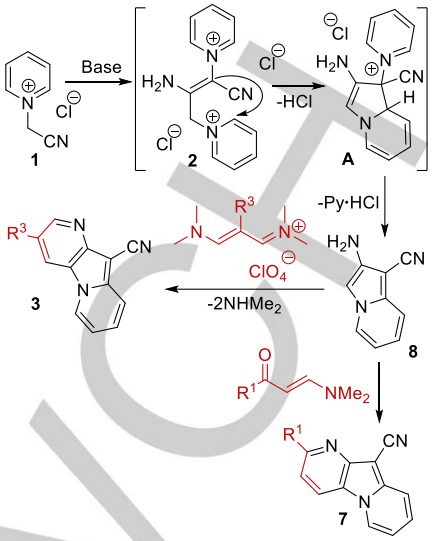


Figure 2. Reaction scope for enaminones and pyridinium salts. Reaction conditions: Table 2, Entry 6.

According to the literature,[40,41] the following pathway for the formation of pyrido[2,3-*b*]indolizines can be suggested. At first, the base-promoted dimerization of pyridinium salt **1** takes place. The dimerized salt **2** undergoes a cyclization to an intermediate **A**, which can aromatize through the elimination of pyridinium hydrochloride. The formed aminoindolizine **8** can condense with 1,3-dielectophiles, forming pyridoindolizines **3** or **7** (Scheme 2). This key intermediate **8** might be isolated from the reaction mixture and transformed into corresponding product in a two-component manner, providing evidence for the suggested reaction pathway. It needs to be noted that four new bonds and two rings are formed in one synthetic operation, supporting high effectiveness of the discovered process.



Scheme 2. Proposed mechanism for the formation of pyridoindolizines **3** and **7**.

Optical properties of pyrido[2,3-*b*]indolizines. The fluorophoric indolizine system offers versatile possibilities for construction of various derivatives with intense emission in the desired ranges of the visible spectrum.[48] The above synthesized compounds exhibit a visibly strong green-light fluorescence with quantum yields of 0.4–0.8 determined with respect to coumarin 153 in ethanol as the reference (quantum yield of 0.546[49]). In Figure 3, we present UV/Vis absorption and emission spectra for a representative selection of pyrido[2,3-*b*]indolizines. The parent compound **7m** shows a strong absorption band with partial vibrational resolution in the region of 350–470 nm. Extension of the π-system of **7m** with various phenyl substituents leads to a red shift of the absorption spectrum. The effect is more pronounced when there is a phenyl moiety at the position 8 of the core pyridoindolizine (**3i** and **7n**) while in the 2- and 3-sustituted compounds **3b** and **7g** it is weaker. The lowest excitation energy is observed in the 3,8-substituted **3i** where the absorption threshold emerges at 2.4 eV. (Figure 3 and Table 3).

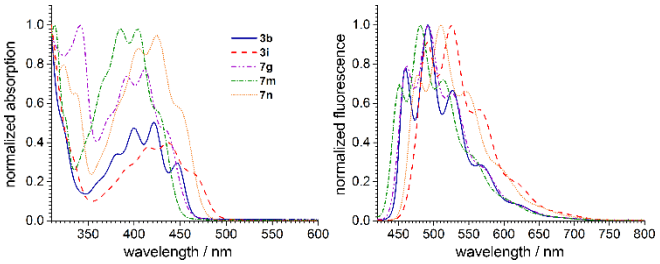


Figure 3. UV/Vis absorption (left) and fluorescence (right, excitation wavelength 400 nm) spectra for the selected pyrido[2,3-*b*]indolizines in dichloromethane.

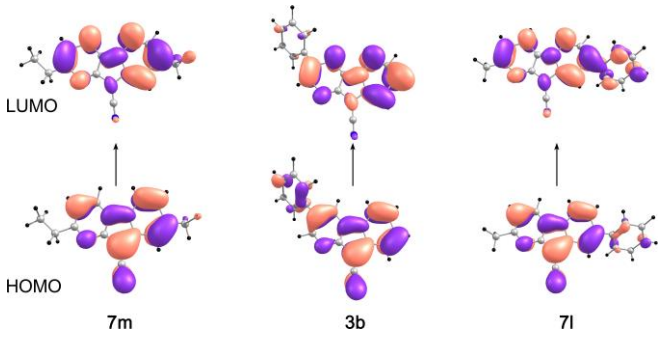


Figure 4. Frontier molecular orbitals in the compounds **3b**, **7m** and **7l** show relatively limited effect of the phenyl substituents.

To rationalize the observed spectra, we have performed geometry optimization of the compounds synthesized at the PBE0/Def2-TZVPP level and calculated the vertical excitation spectra using the TDDFT-PBE0/Def2-TZVPP approach. The calculations were carried out with the use of the Firefly v. 8.2 software[50] which is partly based on the GAMESS(US) package.[51] It was found that the observed absorption corresponds to the *S1* state dominated by the HOMO→LUMO excitation, and the calculated vertical absorption wavelengths are in a reasonable agreement with the measured spectra. The structures of the HOMO and the LUMO in the selected compounds are shown on Fig. 4. One can see that the frontier orbitals only moderately vary upon addition of the phenyl substituents. Yet, as can be seen from Table 3, the substituents can induce some 2-3-fold increase in the oscillator strength (compare, e.g., **7m, 7n**, and **3i**).

Fluorescence of eleven compounds was measured mostly in ethanol with the excitation at 400 nm (Table 3). For five selected compounds (**3b**, **3i**, **7g**, **7m** and **7n**), the absorption and emission spectra were also measured in dichloromethane and toluene. The partly resolved vibrational progressions allow for certain liberty in defining the Stokes shift. Measuring it between the first vibrational peaks yields rather small values of 600–1200 cm^{-1} while the distance between the center-of-mass of the absorption and emission bands reaches several thousands of cm^{-1}. Both in the ground and the excited states, the compounds are polar, the dipole moment of ca. 8-9 D in S_0 and ca. 6-7 D S_1 being oriented more or less parallel to the nitrile moiety. As a result, the emission band shifts to the red in the less polar solvents together with a drop in the fluorescence quantum yield. Introduction of a fluorine atom into a peripheral phenyl ring (**3j**, **3k**) has no effect on the emission properties while the chlorine substituents can cause significant fluorescence quenching. Thus, compound **3g** demonstrates the lowest quantum yield in ethanol of 0.46.

TDDFT-PBE0 optimization of the S_1 state shows good agreement with experimental emission wavelength (see Table 3). The stationary point of S_1 reveals, together with anticipated redistribution of the bond lengths in the conjugated system, certain decrease in the dihedral angles between the pyridoindolizine and its phenyl substituents. The computational estimates of the 0-0 transition energy taken as the difference between the stationary points of the S_0 and S_1 agrees quite well with the experimental estimates obtained as the crossing point of the normalized absorption and emission spectra.

Table 3. Experimental absorption (wavelength and absorption edge) and fluorescence (emission wavelength, quantum yield, Stokes shift) data together with the respective TD-DFT estimates for a series of pyrido[2,3-*b*]indolizines.

Compound	solvent	λ_{abs}, nm	λ_{em}, nm	Φ_f	Stokes shift, cm^{-1}	E_g^{opt}, eV	TDDFT absorption wavelength, nm	f_{01} (TDDFT)	TDDFT emission wavelength, nm	f_{01} (TDDFT)	0-0 transition energy exp., cm^{-1}	TDDFT 0-0 transition energy, cm^{-1}
3b	EtOH	443	459	0.66	790	2.6	405	0.09	501	0.07	22200	22300
	DCM	447	460	0.69	630						22100	
	Toluene	454	465	0.47	520						21800	
3c	EtOH	438	462	0.81	1190	2.6	399	0.11	494	0.08	22200	22600
3g	EtOH	440	463	0.46	1130	2.6	401	0.12	495	0.08	22100	22600
3i	EtOH	461	487	0.74	1160	2.4	429	0.26	528	0.21	21100	21100
	DCM	467	490	0.74	1010						20900	
	Toluene	473	471	0.52	0						21200	
3j	EtOH	443	459	0.65	790	2.6	406	0.09	502	0.07	22200	22300
3k	EtOH	438	462	0.68	1190	2.6	400	0.11	495	0.08	22200	22600

7f	EtOH	431	456	0.74	1270	2.6	394	0.08	508	0.05	22500	22500
7g	EtOH	431	456	0.64	1270	2.6	392	0.09	483	0.06	22500	23100
	DCM	435	460	0.66	1250						22300	
	Toluene	442	466	0.48	1170						22000	
7l	EtOH	446	471	0.69	1190	2.6	410	0.18	518	0.14	21800	21900
7m	EtOH	422	448	0.58	1380	2.7	388	0.08	488	0.05	23000	23100
	DCM	426	450	0.64	1250						22800	
	Toluene	435	457	0.44	1110						22400	
7n	EtOH	447	472	0.75	1190	2.6	415	0.17	520	0.14	21800	21700
	DCM	450	475	0.76	1170						21600	
	Toluene	458	482	0.56	1090						21300	

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Conclusions

We have revealed that the interaction of readily available starting materials: *N*-(cyanomethyl)pyridinium salts and vinamidinium perchlorates or enaminones, leads to the formation of 3-substituted or 2-substituted pyrido[2,3-*b*]indolizine-10-carbonitriles, respectively. The synthesized indolizines are prominent fluorophores with emission ranging from blue to green regions and Φ_f from 0.46 to 0.81. We believe these compounds to find interesting applications in biology in the nearest future, as well as in the fabrication of OLED devices.

Experimental Section

General details can be found in the online Supporting Information. This document also contains detailed procedures and analytical data for novel compounds as well as copies of NMR spectra.

Representative procedure for the synthesis of 3-substituted pyrido[2,3-*b*]indolizine-10-carbonitriles (3b, 3j, 3l)

To a stirred solution of a pyridinium salt **1** (1.19 mmol) and vinamidinium perchlorate **5** (0.40 mmol) in dry ethanol (9 ml), NEt_3 (1.98 mmol) was added in five portions over 2 hours at reflux. The reaction mixture was heated at reflux for 25-30 hours. The reaction mixture was diluted with water (75 ml) and extracted with DCM. The combined organic layer was dried over Na_2SO_4. After filtration, the solvent was then evaporated under reduced pressure. Products were isolated by column chromatography on neutral aluminium oxide, eluent ethyl acetate-hexane 1:5.

3-Phenylpyrido[2,3-*b*]indolizine-10-carbonitrile (3b). Yellow solid; 32 mg; 30% yield, m.p. 208-209 (dec); ^{1}H NMR (400 MHz, DMSO-d6): δ = 7.16 (t, *J* = 6.8 Hz, 1H; H-7); 7.44 (t, *J* = 7.4 Hz, 1H; Ph-H); 7.55 (t, *J* = 7.4 Hz, 2H; Ph-H); 7.62-7.64 (m, 1H; H-8); 7.86-7.87 (m, 3H; H-9, Ph-H); 9.10 (d, *J* = 1.7 Hz,1H; H-4); 9.15 (d, *J* = 1.7 Hz, 1H; H-2); 9.30 (d, *J* = 6.8 Hz,1H; H-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 73.5; 112.5; 115.4; 117.1; 118.4; 123.4; 127.1 (3C); 127.7; 128.4; 129.2 (2C); 130.4; 137.5; 143.0; 144.2; 147.6; IR (KBr): ν = 2205 cm-1 (C≡N); ESI MS: m/z 270 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{11}N_3$: C 80.28; H 4.12; N 15.60; found: C 80.22; H 4.07; N 15.73.

Representative procedure for the synthesis of 2-substituted pyrido[2,3-*b*]indolizine-10-carbonitriles (7a-f, 7p-s)

A mixture of pyridinium salt **1** (1.19 mmol), enaminone **6** (0.40 mmol), and sodium acetate (1.98 mmol) in isopropyl alcohol (3 ml) and water (1 mL) was heated to 150 °C for 30 min in a closed vial in the microwave reactor Monowave 300. After cooling to rt, the precipitate was filtered-off and washed with isopropyl alcohol, water (2 times) and isopropyl alcohol again; dried on air.

2-(2-Hydroxyphenyl)-8-methylpyrido[2,3-*b*]indolizine-10-carbonitrile (7a). Brown solid; 61 mg; 51% yield, m.p. > 300°C (dec); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.44 (s, 3H; C_8-C<u>H</u>$_3$); 6.94-6.97 (m, 2H; Ph-<u>H</u>); 7.00 (d, *J* = 6.6 Hz, 1H; H-7); 7.33 (t, *J* = 7.5 Hz, 1H; Ph-H); 7.60 (s, 1H; H-9); 8.11 (d, *J* = 7.5 Hz, 1H; Ph-<u>H</u>); 8.15 (d, *J* = 8.8 Hz, 1H; H-4); 8.85 (d, *J* = 8.8 Hz, 1H; H-3); 9.10 (d, *J* = 6.6 Hz, 1H; H-6); 14.04 (s, 1H; O<u>H</u>); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3; 71.3; 112.8; 115.0; 115.1; 115.6; 118.0; 119.0; 119.5; 122.0; 122.6; 127.5; 127.8; 131.4; 142.4; 142.6; 143.3; 155.8; 159.0; IR (KBr): ν = 2203 cm^{-1}

(C≡N); ESI MS: m/z 300 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{13}N_3O$: C 76.24; H 4.38; N 14.04; found: C 76.19; H 4.32; N 14.17.

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Keywords: indolizine • multicomponent reaction • fluorescence • pyridinium salt • heterocycles

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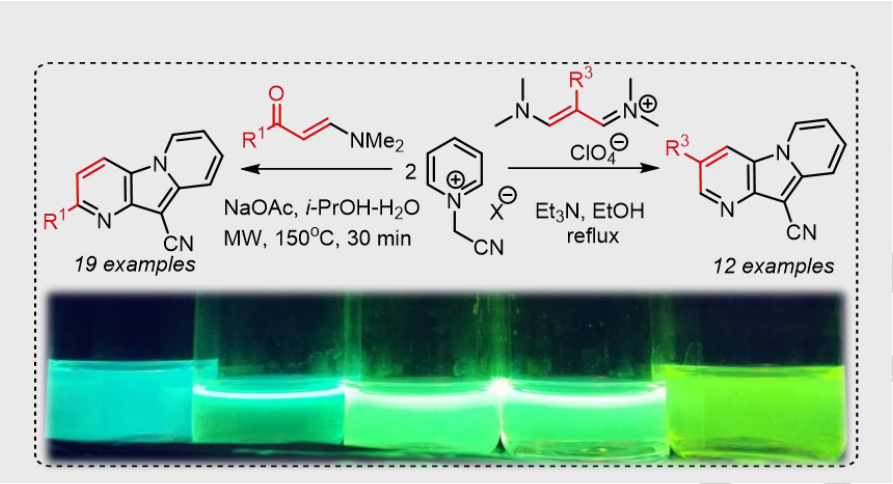

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Highly Fluorescent Pyrido[2,3-*b*]indolizine-10-Carbonitriles through Pseudo Three-Component Reactions of *N*-(Cyanomethyl)pyridinium Salts

TOC text: A novel class of effective fluorophores, incorporating pyrido[2,3-*b*]indolizine scaffold, has been discovered. The synthesis of pyridoindolizines involves one synthetic step from readily available starting materials.
KEY topic: Multicomponent reactions