

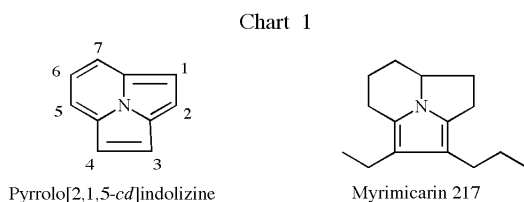
Feng Liang [a], Jiaxin Hu [a], Lande Zhang [a], Yuefei Hu*[a,b] and Hongwen Hu[a,b]

Department of Chemistry [a] and Coordination Chemistry Institute [b],
Nanjing University, Nanjing 210093, People's Republic of China
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An efficient two step route has been developed to synthesize pyrrolo[2,1,5-*cd*]indolizine derivatives. The reaction sequence proceeds *via* preparation of 3-acyl-5-methylindolizines followed by an intramolecular condensation. The procedures were carried out under convenient conditions and gave the products in high yields. It could be expected to be used to prepare a broad range of potentially interesting pyrrolo[2,1,5-*cd*]indolizine derivatives.

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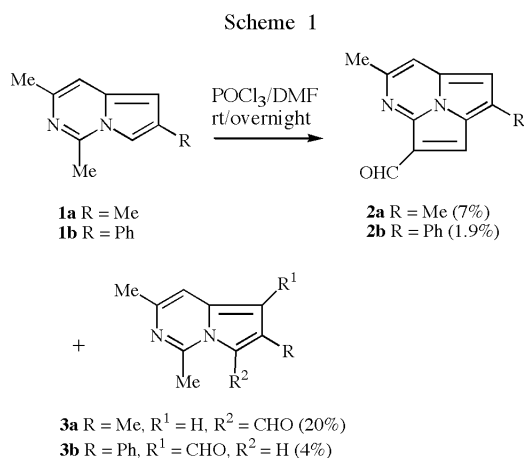
Pyrrolo[2,1,5-*cd*]indolizine is the most interesting member in the family of cyclazines, well-known as cycl[2,2,3]azine [1]. Its derivatives have received considerable attention in the field of synthetic organic chemistry due to their novel structural properties [1,2], increasing biological interests [1,3] and because their partial saturated frameworks occur in natural products [1,4] (Chart 1).



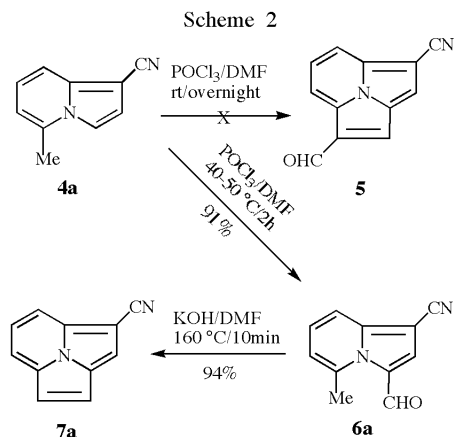
A number of methods have been developed for the preparation of pyrrolo[2,1,5-*cd*]indolizines [1,5]. Over recent years, the [8+2]-cycloaddition of indolizine with an electron-deficient acetylene has been frequently employed for this purpose. But it bears two significant drawbacks arising from inaccessible electron-deficient acetylenes and the requirement for 3-cyano- or 3-unsubstituted indolizines without electron-withdrawing substituents on C1 and C2 [6]. These drawbacks have seriously limited the range of C1-C4 functionalized pyrrolo[2,1,5-*cd*]indolizines that can be prepared by this method. So, there remains a need for a more efficient and practical route for the synthesis of pyrrolo[2,1,5-*cd*]indolizines. Herein we report an efficient route that proceeds *via* preparation of 3-acyl-5-methylindolizine followed by an intramolecular condensation and overcomes some of the limitation of published procedures.

In our previous work, a general and convenient method has been developed for the preparation of 3-unsubstituted and 3-acylindolizines [7]. These results prompted us to explore their further conversions into the corresponding pyrrolo[2,1,5-*cd*]indolizines. By survey of literature, the procedure for the preparation of pyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (2) [8] draw our attention because its third ring can be constructed in a single step from 5-methyl-6-

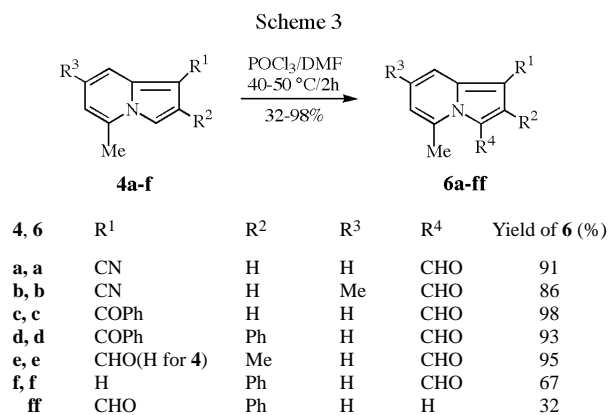
azaindolizine (**1**) under Vilsmeier conditions, even though with very low yields (Scheme 1). Following that procedure, a mixture of 5-methylindolizine-1-carbonitrile (**4a**) and phosphorus oxychloride in *N,N*-dimethylformamide was stirred at room temperature overnight. After normal work-up, a white solid was obtained by recrystallization. Unfortunately, it was not the expected product 1-cyano-pyrrolo[2,1,5-*cd*]indolizine-4-carboxaldehyde (**5**) and its structure was assigned as 1-cyano-5-methylindolizine-3-carboxaldehyde (**6a**) by its ir, ¹H nmr and mass spectroscopy. This result may reason the fact that 5-Me in compound **4a** is much less active than that of compound **1**. By optimizing conditions, the formylation of **4a** was completed at 40-50 °C within 2 hours and yielded **6a** in 91% yield.



Intramolecular condensation of 3-acyl-5-methylindolizine can be used for the preparation of pyrrolo[2,1,5-*cd*]indolizine. But this convenient method has almost been ignored because it suffered seriously from very low yields under several conditions [5h,8]. However, when **6a** was treated with potassium hydroxide in *N,N*-dimethylformamide at 160 °C for 10 minutes, the condensation occurred and yielded the desired pyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (**7a**) in 94% yield (Scheme 2).

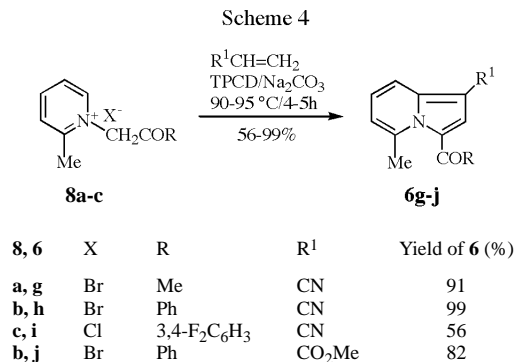


To explore the scope of this novel route, 5-methylindolizine-3-carboxaldehydes **6a-f** and other 3-acyl-5-methylindolizines **6g-j** were tested. By known procedures, 3-unsubstituted 5-methylindolizines **4a-f**, which are starting materials for **6a-f**, were prepared [5j][7c][11]. Compounds **4a-d** were formylated with Vilsmeier reagent to give the corresponding compounds **6a-d** in 86-98% yields smoothly. However, compound **4e** was diformylated and yielded 2,5-dimethylindolizine-1,3-dicarboxaldehyde (**6e**) in 95% yield when two equivalents of phosphorus oxychloride was used. Whereas compound **4f** gave the 3-carboxaldehyde compound **6f** (67%) and 1-carboxaldehyde compound **6ff** (32%) when one equivalent of phosphorus oxychloride was used. These results are in agreement with literature data on the order of reaction activities of C1 and C3 on indolizine derivatives [7b,8] (Scheme 3). As shown in Scheme 4, 3-acyl-5-

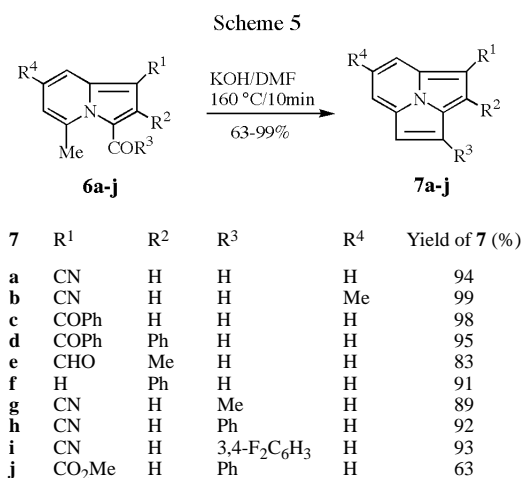


methylindolizines **6g-j** were obtained conveniently by oxidant promoted 1,3-dipolar cycloaddition between salts **8a-c** (precursors of *N*-ylides) and electron-deficient alkenes, acrylonitrile and methyl acrylate [7a].

Using the procedure reported for the preparation of **7a**, 3-carboxaldehyde compounds **6b-f** were converted to 3-unsubstituted pyrrolo[2,1,5-*cd*]indolizines **7b-f** in high yields. Under similar conditions, other 3-acyl derivatives



6g-j gave 3-substituted pyrrolo[2,1,5-*cd*]indolizines **7g-j** in 63-93% yields (Scheme 5).



EXPERIMENTAL

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. The IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with potassium bromide pellets. The ¹H NMR spectra were recorded on a Bruker ACF-300 spectrometer in chloroform-*d* with trimethylsilane as internal reference. The J values are given in Hz. The MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV. The elemental analyses were performed on a Perkin-Elmer 240C instrument. PE is light petroleum (60-90 °C).

General Procedure for Preparation of 5-Methylindolizine-3-carboxaldehydes (6a-ff).

To a stirred mixture of compound **4** (4 mmol) in *N,N*-dimethylformamide (4 mL) was added dropwise Vilsmeier reagent (650 mg, 4.4 mmol) of phosphorus oxychloride in 4 mL of *N,N*-dimethylformamide) at 40-50 °C. Two hours later, it was poured into ice-water. Then 25% aqueous solution of sodium hydroxide (6 mL, 50 mmol) was added and the mixture was refluxed for 15 minutes. After it was cooled to room temperature, the solid was collected by filtration. The crude product was purified by chromatography [silica gel, 20% ethyl acetate in PE] to give pure product **6**.

Cyano-5-methylindolizine-3-carboxaldehyde (**6a**).

This compound was obtained as a white solid, mp 148-150 °C; ir: ν_{\max} 2230, 1640 cm^{-1} ; ^1H nmr: δ 9.90 (1H, s, CHO), 7.92 (1H, s, ArH), 7.72 (1H, d, J = 8.7, ArH), 7.43 (1H, t, J = 7.9, ArH), 6.96 (1H, d, J = 7.0, ArH), 2.93 (3H, s, CH_3); ms: m/z (%) 184 (M^+ , 37), 167 (79), 155 (100), 129 (9), 128 (23), 127 (8), 101 (14), 77 (8).

Anal. Calcd. for $\text{C}_{11}\text{H}_8\text{N}_2\text{O}$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.68; H, 4.42; N, 15.51.

1-Cyano-5,7-dimethylindolizine-3-carboxaldehyde (**6b**).

This compound was obtained as a white solid, mp 155-156 °C; ir: ν_{\max} 2200, 1620 cm^{-1} ; ^1H nmr: δ 9.81 (1H, s, CHO), 7.88 (1H, s, ArH), 7.50 (1H, s, ArH), 6.82 (1H, s, ArH), 2.92 (3H, s, CH_3), 2.49 (3H, s, CH_3); ms: m/z (%) 198 (M^+ , 55), 197 (9), 182 (15), 181 (100), 169 (15), 166 (29), 77 (4).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.75; H, 5.16; N, 14.22.

1-Benzoyl-5-methylindolizine-3-carboxaldehyde (**6c**).

This compound was obtained as a white solid, mp 134-135 °C; ir: ν_{\max} 1640, 1630 cm^{-1} ; ^1H nmr: δ 9.91 (1H, s, CHO), 8.67 (1H, d, J = 8.7, ArH), 7.97 (1H, s, ArH), 7.90-7.84 (2H, m, 2 x ArH), 7.64-7.52 (4H, m, 4 x ArH), 7.04 (1H, d, J = 6.9, ArH), 2.98 (3H, s, CH_3); ms: m/z (%) 263 (M^+ , 100), 262 (5), 246 (27), 234 (3), 186 (46), 105 (46), 77 (23).

Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.59; H, 4.91; N, 5.41.

1-Benzoyl-2-phenyl-5-methylindolizine-3-carboxaldehyde (**6d**).

This compound was obtained as a yellowish solid, mp 123-124 °C (Lit. [9], 126 °C).

2,5-Dimethylindolizine-1,3-dicarboxaldehyde (**6e**).

In this experiment, two equivalent of phosphorus oxychloride was used. Compound **6e** was obtained as a white solid, mp 173-174 °C; ir: ν_{\max} 1660, 1630 cm^{-1} ; ^1H nmr: δ 10.25 (1H, s, CHO), 10.18 (1H, s, CHO), 8.48 (1H, d, J = 8.5, ArH), 7.54 (1H, t, J = 7.9, ArH), 7.02 (1H, d, J = 7.1, ArH), 2.90 (3H, s, CH_3), 2.88 (3H, s, CH_3); ms: m/z (%) 201 (M^+ , 100), 200 (21), 184 (19), 173 (26), 172 (18), 156 (72), 144 (46), 143 (15), 141(31), 77 (10).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.63; H, 5.56; N, 6.86.

2-Phenyl-5-methylindolizine-3-carboxaldehyde (**6f**).

This compound was obtained as a white solid, mp 70-71 °C; ir: ν_{\max} 1620 cm^{-1} ; ^1H nmr: δ 9.42 (1H, s, CHO), 7.64-7.62 (2H, m, 2 x ArH), 7.53-7.46 (4H, m, 4 x ArH), 7.37 (1H, t, J = 7.7, ArH), 6.89 (1H, d, J = 7.0, ArH), 6.74 (1H, s, ArH), 2.89 (3H, s, CH_3); ms: m/z (%) 235 (M^+ , 62), 234 (19), 218 (100), 206 (19), 77 (4).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.48; H, 5.72; N, 5.94.

2-Phenyl-5-methylindolizine-1-carboxaldehyde (**6ff**).

This compound was obtained as a white solid, mp 97-99 °C; ir: ν_{\max} 1640 cm^{-1} ; ^1H nmr: δ 10.07 (1H, s, CHO), 8.44 (1H, d, J = 8.9, ArH), 7.65-7.40 (6H, m, 6 x ArH), 7.25 (1H, s, ArH), 6.79 (1H, d, J = 6.8, ArH), 2.65 (3H, s, CH_3); ms: m/z (%) 235 (M^+ , 90), 234 (100), 218 (14), 206 (17), 205 (11), 204 (22), 191 (8), 178 (13), 77 (6).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.63; H, 5.55; N, 5.93.

General Procedure for the Preparation of 3-Acyl-5-methylindolizines (**6g-j**).

A mixture of 2-methylpyridine (9.3 g, 100 mmol) and the corresponding halide (100 mmol) in ethyl acetate (60 mL) was stirred at room temperature for 4 hours. Crude salt **8** [**8a**, 87%, mp 190-192 °C; **8b**, 96%, mp 209-211 °C (Lit. [7a] 214 °C); **8c**, 83%, mp 202-205 °C] was filtrated, rinsed with ethyl acetate and dried in air. It was used for the next step without further purification and characterization.

The mixture of **8** (10 mmol), alkene **9** (50 mmol), tetrakis-pyridine cobalt (II) dichromate (4 g, 6.5 mmol) and sodium carbonate (1.1 g, 10 mmol) in *N,N*-dimethylformamide (30 mL) was stirred at 90-95 °C for 4-5 hours (monitored by tlc). The resultant mixture was then cooled to room temperature and poured into 5% hydrochloric acid. Crude solid **6** was filtrated and purified by chromatography [20% ethyl acetate in PE].

3-Acetyl-5-methylindolizine-1-carbonitrile (**6g**).

This compound was obtained as a yellowish solid from salt **8a** and had mp 145-146 °C; ir: ν_{\max} 2200, 1640 cm^{-1} ; ^1H nmr: δ 7.85 (1H, s, ArH), 7.72 (1H, d, J = 8.6, ArH), 7.44 (1H, t, J = 7.8, ArH), 6.95 (1H, d, J = 6.9, ArH), 2.67 (3H, s, COCH_3), 2.64 (3H, s, CH_3); ms: m/z (%) 198 (M^+ , 64), 183 (100), 181 (46), 155 (63), 129 (8), 77 (13), 43 (22).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.60; H, 5.20; N, 14.13.

3-Benzoyl-5-methylindolizine-1-carbonitrile (**6h**).

This compound was obtained as a yellowish solid from salt **8b** and had mp 160-161 °C (Lit. [7a] 160-162 °C).

3-(3,4-Difluorobenzoyl)-5-methylindolizine-1-carbonitrile (**6i**).

This compound was obtained as a yellow-green solid from salt **8c** and had mp 146-147 °C; ir: ν_{\max} 2200, 1625 cm^{-1} ; ^1H nmr: δ 7.91 (1H, d, J = 9.9, ArH), 7.86-7.78 (1H, m, ArH), 7.54 (1H, s, ArH), 7.50 (1H, d, J = 8.6, ArH), 7.40-7.34 (2H, m, 2 x ArH), 7.02 (1H, d, J = 6.9, ArH), 2.60 (3H, s, CH_3); ms: m/z (%) 296 (M^+ , 55), 295 (9), 279 (100), 183 (15), 155 (13), 141 (14), 113 (27), 77 (4).

Anal. Calcd. for $\text{C}_{17}\text{H}_{10}\text{N}_2\text{OF}_2$: C, 68.92; H, 3.40; N, 9.46. Found: C, 69.01; H, 3.57; N, 9.54.

Methyl 3-Benzoyl-5-methylindolizine-1-carboxylate (**6j**).

This compound was obtained as a yellowish solid from salt **8b** and had mp 117-118 °C (Lit. [10], 115-116 °C).

General Procedure for Preparation of Pyrrolo[2,1,5-*cd*]indolizines (**7a-j**).

To a mixture of potassium hydroxide (1.2 g, 20 mmol), toluene (20 mL) and *N,N*-dimethylformamide (10 mL) at 160 °C was added compound **6** (1 mmol) and the resultant mixture was stirred for another 10 minutes. It was then cooled to room temperature and poured into water. The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine. After it was dried over sodium sulfate, the solvent was removed to give a residue, which was purified by chromatography [silica gel, 20% ethyl acetate in PE] to give pure product **7**.

Pyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (**7a**).

This compound was obtained as a yellow solid, mp 67-68 °C; ir: ν_{\max} 2200 cm^{-1} ; ^1H nmr: δ 8.18 (1H, d, J = 7.9, ArH), 8.06

(1H, d, J = 7.7, ArH), 7.96-7.90 (2H, m, 2 x ArH), 7.71 (1H, d, J = 4.7, ArH), 7.49 (1H, d, J = 4.7, ArH); ms: m/z (%) 166 (M⁺, 100), 165 (7), 139 (11).

Anal. Calcd. for C₁₁H₆N₂: C, 79.50; H, 3.64; N, 16.86. Found: C, 79.33; H 3.52; N, 16.75.

6-Methylpyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (7b).

This compound was obtained as a yellow solid, mp 87-88 °C; ir: ν_{max} 2200 cm⁻¹; ¹H nmr: δ 8.02 (1H, s, ArH), 7.87 (1H, s, ArH), 7.84 (1H, s, ArH), 7.66 (1H, d, J = 4.7, ArH), 7.39 (1H, d, J = 4.7, ArH), 2.86 (3H, s, CH₃); ms: m/z (%) 180 (M⁺, 100), 179 (99), 154 (2).

Anal. Calcd. for C₁₂H₈N₂: C, 79.98; H, 4.48; N, 15.55. Found: C, 79.95; H, 4.54; N, 15.26.

1-Benzoylpyrrolo[2,1,5-*cd*]indolizine (7c).

This compound was obtained as a yellow solid, mp 88-89 °C; ir: ν_{max} 1610 cm⁻¹; ¹H nmr: δ 8.52 (1H, d, J = 7.7, ArH), 8.05-7.93 (5H, m, 5 x ArH), 7.70 (1H, d, J = 4.7, ArH), 7.67-7.54 (3H, m, 3 x ArH), 7.44 (1H, d, J = 4.7, ArH); ms: m/z (%) 245 (M⁺, 52), 168 (100), 140 (38), 77 (8).

Anal. Calcd. for C₁₇H₁₁NO: C, 83.25; H, 4.52; N, 5.71. Found: C, 83.36; H, 4.66; N, 5.68.

1-Benzoyl-2-phenylpyrrolo[2,1,5-*cd*]indolizine (7d).

This compound was obtained as a yellow solid, mp 124-125 °C; ir: ν_{max} 1620 cm⁻¹; ¹H nmr: δ 8.11 (1H, d, J = 7.9, ArH), 8.01 (1H, d, J = 7.7, ArH), 7.88 (1H, t, J = 7.8, ArH), 7.78-7.75 (3H, m, 3 x ArH), 7.62-7.60 (2H, m, 2 x ArH), 7.47 (1H, d, J = 4.6, ArH), 7.40 (1H, d, J = 7.4, ArH), 7.31-7.26 (5H, m, 5 x ArH); ms: m/z (%) 321 (M⁺, 0.42), 216 (48), 215 (100), 166 (10), 139 (2).

Anal. Calcd. for C₂₃H₁₅NO: C, 85.96; H, 4.70; N, 4.36. Found: C, 86.01; H, 4.73; N, 4.15.

2-Methylpyrrolo[2,1,5-*cd*]indolizine-1-carboxaldehyde (7e).

This compound was obtained as a yellow solid, mp 102-103 °C; ir: ν_{max} 1640 cm⁻¹; ¹H nmr: δ 10.38 (1H, s, CHO), 8.35 (1H, d, J = 5.6, ArH), 7.94-7.89 (2H, m, 2 x ArH), 7.70 (1H, d, J = 4.7, ArH), 7.37 (1H, d, J = 4.7, ArH), 3.02 (3H, s, CH₃); ms: m/z (%) 183 (M⁺, 94), 182 (100), 154 (25).

Anal. Calcd. for C₁₂H₉NO: C, 78.67; H, 4.95; N, 7.65; O, 8.73. Found: C, 78.52; H, 4.88; N, 7.56.

2-Phenylpyrrolo[2,1,5-*cd*]indolizine (7f).

This compound was obtained as a yellow solid, mp 89-90 °C (Lit. [11], 93.5-94.5 °C).

3-Methylpyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (7g).

This compound was obtained as a yellow solid, mp 75-76 °C; ir: ν_{max} 2230, 1370 cm⁻¹; ¹H nmr: δ 8.08 (1H, t, J = 4.3, ArH), 7.88-7.84 (3H, m, 3 x ArH), 7.19 (1H, s, ArH), 2.75 (3H, s, CH₃); ms: m/z (%) 180 (M⁺, 89), 179 (100), 178 (21), 177 (11), 154 (2).

Anal. Calcd. for C₁₂H₈N₂: C, 79.98; H, 4.48; N, 15.55. Found: C, 79.77; H, 4.33; N, 15.29.

3-Phenylpyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (7h).

This compound was obtained as a yellow solid, mp 118-120 °C; ir: ν_{max} 2200 cm⁻¹; ¹H nmr: δ 8.17-8.12 (2H, m, 2 x ArH), 8.03-8.00 (3H, m, 3 x ArH), 7.94 (1H, t, J = 7.8, ArH), 7.68 (1H, s, ArH), 7.60-7.55 (2H, m, 2 x ArH), 7.47 (1H, s, ArH); ms: m/z (%) 242 (M⁺, 100), 241 (8), 240 (17), 216 (6), 166 (4).

Anal. Calcd. for C₁₇H₁₀N₂: C, 84.28; H, 4.16; N, 11.56. Found: C, 84.27; H, 4.35; N, 11.43.

3-(3,4-Difluorophenyl)pyrrolo[2,1,5-*cd*]indolizine-1-carbonitrile (7i).

This compound was obtained as a yellow solid, mp 222-223 °C; ir: ν_{max} 2200 cm⁻¹; ¹H nmr: δ 8.19 (1H, d, J = 7.8, ArH), 8.09 (1H, s, ArH), 8.04 (1H, d, J = 7.7, ArH), 7.96 (1H, t, J = 7.8, ArH), 7.81-7.72 (2H, m, 2 x ArH), 7.61 (1H, s, ArH), 7.37 (1H, d, J = 9.9, ArH); ms: m/z (%) 278 (M⁺, 100), 277 (6), 258 (4), 252 (3), 250 (3), 139 (3).

Anal. Calcd. for C₁₇H₈N₂F₂: C, 73.38; H, 2.90; N, 10.07. Found: C, 73.40; H, 3.13; N, 10.07.

Methyl 3-Phenylpyrrolo[2,1,5-*cd*]indolizine-1-carboxylate (7j).

This compound was obtained as a yellow solid, mp 109-110 °C; ir: ν_{max} 1705 cm⁻¹; ¹H nmr: δ 8.41-8.33 (2H, m, 2 x ArH), 8.08-8.05 (2H, m, 2 x ArH), 7.95-7.86 (2H, m, 2 x ArH), 7.61 (1H, s, ArH), 7.58-7.53 (2H, m, 2 x ArH), 7.45 (1H, d, J = 7.2, ArH), 4.06 (3H, s, CH₃); ms: m/z (%) 275 (M⁺, 94), 244 (100), 216 (33), 215 (32), 122 (15), 107 (8).

Anal. Calcd. for C₁₈H₁₃NO₂: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.56; H, 4.88; N, 5.12.

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