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A one-pot synthesis of substituted pyrido[2,3-*b*]indolizines

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ABSTRACT

An efficient and novel approach to the synthesis of substituted pyrido[2,3-*b*]indolizine-10-carbonitriles was developed. These structures are practically unavailable through previously described methods. The cascade transformation involves the reaction of α,β-unsaturated carbonyl compounds with a stable dimer prepared from 1-(cyanomethyl)pyridinium chloride. The reaction was performed under reflux conditions in ethanol/water and in the presence of sodium acetate. This procedure represents a eco-friendly regioselective approach to the pyrido[2,3-*b*]indolizine core structure.

1. Introduction

The indolizine nucleus is present in a diversity of biologically active compounds and can be considered an important scaffold for the preparation of new pharmaceuticals. In fact, many natural and synthetic derivatives have been identified as anticancer,[1] antiviral,[2] anti-inflamatory,[3] anti-tuberculosis,[4] analgesic,[5] and antioxidant[6] agents. As a result, different approaches have been reported in the literature for their synthesis.[7]

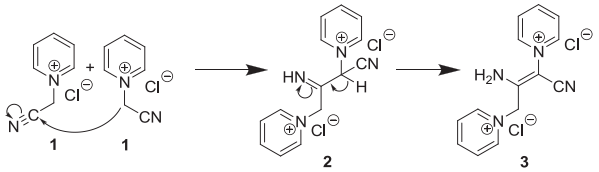
Fused tricyclic structures combining the indolizine and pyridine moieties are rather uncommon. To our knowledge, the only synthesis of pyrido[2,3-*b*]indolizines reported in the literature uses the reaction of 2-amino-3-(arylcarbonyl)indolizine-1-carbonitrile with substituted acetophenones.[8] Poor yields of the product (5–20%) have been reported when the reaction was performed in DMF, at 80 °C and in the presence of potassium *tert*-butoxide. The yield was improved (29–65%) when the reaction was carried out at room temperature, with no solvent and using a large excess of acetophenone (34–86 M equiv).

In recent years, the need to use eco-friendly synthetic methodologies has emerged, especially in the pharmaceutical industry. The use of polar aprotic solvents, such as DMF is problematic for the environment and has human reproductive risks. The search for solvents with reduced environmental impact is one of the major goals recently identified by pharmaceutical manufacturers.[9] In our research group, this concern prompted us to use green solvents, such as water and ethanol, to improve safety of the synthetic processes.[10]

The present work reports the synthesis of substituted pyrido[2,3-*b*]indolizine-10-carbonitriles from the reaction of the dipyridinium dichloride **3** with α,β-unsaturated carbonyl compounds, in ethanol and water, using sodium acetate as catalyst.

2. Results and discussion

A recent study on the synthesis of 1-(cyanomethyl) pyridinium chlorides[11] from substituted pyridines and chloroacetonitrile, revealed the competitive formation of compound **3** when the reflux in acetonitrile was extended for 1 day. After 4 days under reflux conditions, the dipyridinium salt **3** was isolated as a cream solid in 57% yield. The formation of this product can be rationalized by nucleophilic attack of the methylene carbon atom of a pyridinium salt molecule to the cyano group of another molecule, followed by tautomerization (Scheme 1).



Scheme 1. Proposed reaction mechanism for the dimerization of 1-(cyanomethyl) pyridinium chloride **1**.

Compound **3** proved to be stable at room temperature for at least 6 months and no special requirements were necessary for storage. In the infrared spectrum of this compound, multiple bands in the 3500–1800 cm^{-1} region were associated with different

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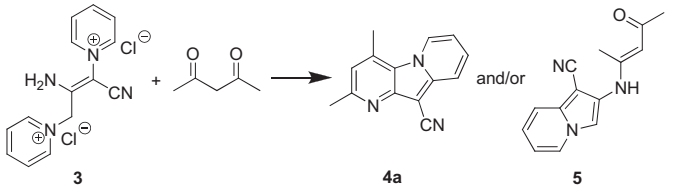
C–H/N–H stretching vibrations of the dipyridinium salt. The cyano group leads to a clear, medium intensity band at 2195 cm^{-1}. In the ^1H NMR spectrum, the amino group generates two broad singlets centered at δ 8.5 and δ 9.0 ppm, reflecting a hindered rotation barrier across the C–N bond.

The formation of the pyrido[2,3-*b*]indolizine core was initially detected in the reaction of the dipyridinium dichloride **3** with acetylacetone. The reagents were combined in a 1:2 M ratio, in aqueous sodium carbonate solution and a small amount of solid material, identified as **4a**, was isolated after 3 h at 60 °C (Table 1, entry 1).

Table 1
Experimental conditions used in the reaction of dipyridinium dichloride **3** and acetylacetone



Entry	Reaction conditions	Product, Yield
1	Na_2CO_3 aq (0.05 M), 60 °C (3 h)	**4a**, 3%
2	H_2O, Na_2CO_3 (1 equiv), reflux (60 min)	**4a**, 30%
3	H_2O, reflux (18 h)	—[a]
4	EtOH, *N*-methylpiperazine (2 equiv), reflux (21 h)	**4a**, 35% **5**, 12%

[a] No reaction, by TLC.

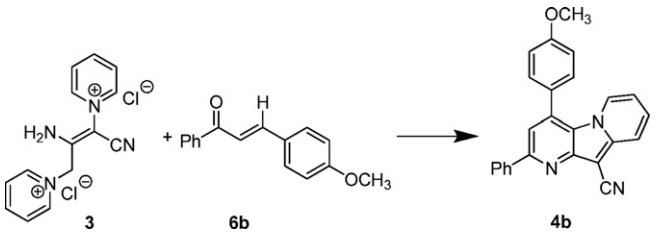
The use of reflux conditions (entry 2) led to an improved yield of the product (30%). The reaction only proceeds in the presence of base, considering that no evolution was detected by TLC after 18 h under reflux in aqueous media (entry 3). Reflux in ethanol and *N*-methylpiperazine resulted in the isolation of **4a** (35%) and a compound identified as **5** (12%) was collected from the mother liquor (entry 4). Indolizine **5** partially evolved to **4a** when a DMSO-d_6 solution of this compound and *N*-methylpiperazine (1.2 M equiv) was kept at 60 °C for 19 h.

The reaction of the dipyridinium dichloride **3** with 1-phenylbutane-1,3-dione in aqueous Na_2CO_3 (1.1 M equiv), led to a complex mixture after 19 h under reflux conditions. A major product could not be isolated from this reaction and the difficulty was partially associated with the poor selectivity of the nucleophilic attack to the carbonyl group. To overcome this problem, α,β-unsaturated dicarbonyl compounds were reacted with the dipyridinium dichloride **3**. The experimental conditions were selected from a study using 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **4b**, summarized in Table 2.

The use of aqueous sodium carbonate solution (entry 1) led to an isolated yield of 67% of product **4b** after refluxing for 8 h. The low solubility of compound **6b** in water was considered a problem and ethanol was selected as an alternative solvent, using *N*-methylpiperazine as base (entry 2). After refluxing the solution for 15 h, a complex mixture was formed and the pure product **4b** was isolated in only 38% yield. A mixture of ethanol and water was used, in combination with a base soluble in both these solvents (sodium acetate). The pure product **4b** was isolated in 91% yield after refluxing the solution for 4 days (entry 3).

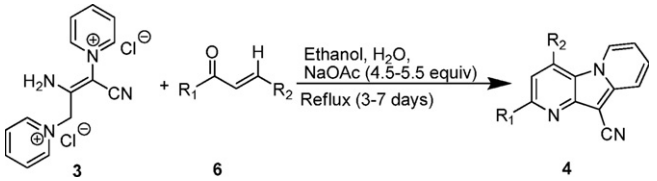
This combination of solvents and base was selected for all the reactions between compounds **6** and the dimer **3**. The isolated yield of the products **4b**–**i** is summarized in Table 3. The reaction of compound **3** with acetylacetone was also performed under these optimized experimental conditions, leading to the product **4a** in 79% yield.

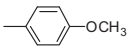
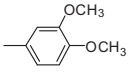
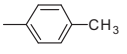
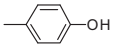
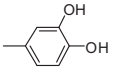
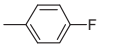
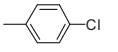
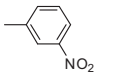
Table 2
Optimization of the reaction conditions for the synthesis of pyrido[2,3-*b*]indolizine-10-carbonitrile **4b**



Entry	Equiv **3**:**6b**	Reaction conditions	Product, yield (%)
1	1:1	H_2O, Na_2CO_3 (1.2 equiv), reflux (8 h)	**4b**, 67%
2	1:1	EtOH, *N*-methylpiperazine (2 equiv), reflux (15 h)	**4b**, 38%
3	1.4:1	EtOH, H_2O, NaOAc (5 equiv), reflux (4 days)	**4b**, 91%
4	1:1	H_2O, Na_2CO_3 (1.2 equiv), reflux (8 h)	**4b**, 67%

Table 3
Synthesis of pyrido[2,3-*b*]indolizine-10-carbonitrile **4**



Compd **4**	R_1	R_2	Equiv **3**:**6**	Time (days)	Yield (%)
4a	CH_3	CH_3	1:2[a]	4	79
4b	Ph		1.4:1	4	91
4c	Ph		1.1:1	4	77
4d	Ph		1.2:1	4	63
4e	Ph		1.3:1	4	77
4f	Ph		1.3:1	3	90
4g	Ph		1.2:1	4	85
4h	Ph		1.2:1	4	90
4i	Ph		1:1.1	7	75

[a] Acetylacetone was used in this case.

All the compounds were fully characterized by the usual spectroscopic techniques and the preparation of a crystal of **4b** from dichloromethane provided the X-ray for this structure (Fig. 1). The data collected confirms the structure of the isolated products and indicates that, in compound **4b**, the three fused rings are co-planar, with the phenyl ring twisted out of this plane by 25.2° and the aryl ring by 66.1°. The bond length for C3–C19 (1.508 Å) further supports the poor conjugation between the aryl and the pyridine rings. The bond length for C5–C6 (1.331 Å) and for C7–C8 (1.321 Å) is similar to the value reported in the literature for the C=C bond in

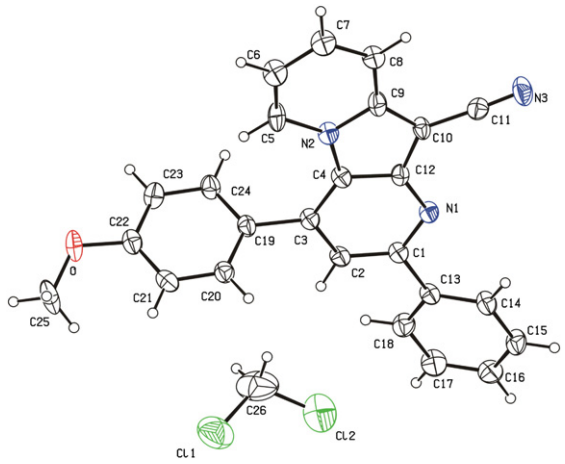
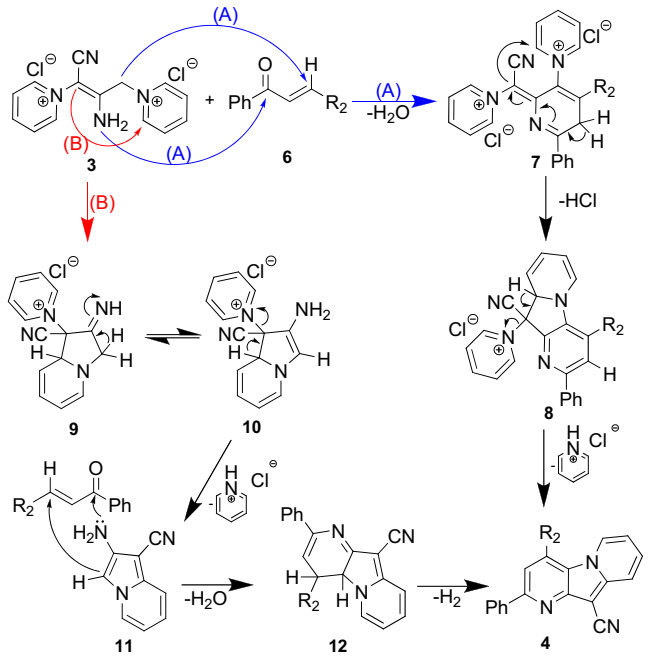


Fig. 1. Crystal structure for pyrido[2,3-*b*]indolizine-10-carbonitrile **4b**.

cyclohexadiene (1.332 Å).[12] The bond length for C4–N2 (1.376 Å) also reflects the single bond character of this linkage.[12]

The formation of the pyrido[2,3-*b*]indolizine-10-carbonitriles **4b–i** is probably the result of nucleophilic attack of the active methylene group in dimer **3** to the beta carbon of **6** and of the amino group of **3** to the carbonyl carbon atom of **6** (Scheme 2, pathway A). Intramolecular cyclization in the intermediate species 7 leads directly to the final structure **4** after elimination of HCl and pyridinium chloride.



Scheme 2. Proposed mechanism for the synthesis of pyrido[2,3-*b*]indolizine-10-carbonitrile **4b–i**.

An alternative pathway is equally plausible (Scheme 2, pathway B) starting with intramolecular cyclization of compound **3** to generate a substituted indolizine **11** after tautomerization and elimination of pyridinium chloride. Reaction of **11** with the α,β-unsaturated compound **6** through nucleophilic attack by the enamine moiety leads to the isolated product **4** after dehydration followed by oxidation.

In order to understand the feasibility of pathway B, the dimer **3** was combined with sodium acetate and refluxed in ethanol (Table 4, entry 1). These conditions were previously selected for the efficient synthesis of the tricyclic product **4**. In this case, the ^{1}H NMR spectrum of the reaction mixture was analyzed after 25 h of reflux and showed no evidence for the formation of indolizine **11**. Different bases (sodium carbonate or *N*-methylpiperazine) and solvents (water, methanol or acetonitrile) were also used, leading usually to complex reaction mixtures (Table 4, entries 2–5). This observation may indicate that pathway A is favored or, alternatively, that indolizine **11** is unstable and can only be isolated when a substituent is incorporated in the amino group. The fact that compound **5** was identified in the reaction of **3** with acetylacetone supports this assumption.

Table 4
Experimental conditions used for the intramolecular cyclization of compound **3**

Entry	Reaction conditions	Product
1	EtOH, NaOAc (4.5 equiv), reflux (25 h)	Complex mixture[a]
2	Na_2CO_3 aq (0.05 M), rt (7 h)	No reaction[b]
3	EtOH, *N*-methylpiperazine (2.2 equiv), reflux (23 h)	Complex mixture[a]
4	MeOH, $NaOCH_3$ (1.1 M, 1.3 equiv), rt (1 h)	Complex mixture[a]
5	Acetonitrile, DBU, reflux (2 days)	**3**, 29%[c]

[a] By ^{1}H NMR.
[b] By TLC.
[c] Mother liquor was a complex mixture, by ^{1}H NMR.

3. Conclusion

A new and simple one-pot procedure was developed for the synthesis of substituted pyrido[2,3-*b*]indolizine-10-carbonitriles from easily available α,β-unsaturated carbonyl compounds and a stable dimer generated from 1-(cyanomethyl)pyridinium chloride. The reaction proceeded in a combination of water and ethanol, with sodium acetate catalysis. The products were isolated by simple filtration in a high purity form and in yields ranging from 63 to 91%.

4. Experimental section

4.1. General

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded on a Varian Unity Plus at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Bruker Avance 3400 at 400 MHz for ^{1}H and 100 MHz for ^{13}C, including the ^{1}H–^{13}C correlation spectra (HMQC and HMBC). Deuterated DMSO was used as solvent. The chemical shifts are expressed in δ (ppm) and the coupling constants (J) in Hertz (Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet, and br, broad. IR spectra were recorded on an FT-IR Bomem MB using Nujol mulls and NaCl cells. The reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F_{254} (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus. Elemental analysis was performed on a LECO CHNS-932 instrument. Crystallographic information files of compound **4b** were obtained from the C.A.C.T.I. — Universidade de Vigo.

4.2. Synthesis of 1,1′-[2-amino-1-cyanoprop-1-ene-1,3-diyl] dipyridinium dichloride 3

1-(Cyanomethyl)pyridinium chloride **1** (4.79 mmol) was refluxed in CH_3CN (80 mL) for 4 days. The off-white solid was filtered and washed with CH_3CN, leading to the pure product **3** (1.36 mmol). Mp 245–246 °C; IR (Nujol mull) 3500–1800 (broad, fringed), 2195, 1667, 1662, 1598, 1461 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.90 (s, 2H), 8.27 (t, J=6.9 Hz, 2H), 8.34 (t, J=6.9 Hz, 2H), 8.40–8.58 (br s, 1H), 8.70–8.80 (m, 2H), 8.92–9.12 (br s, 1H), 9.36

(d, J=6.9 Hz, 2H), 9.44 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 58.6, 88.1, 116.6, 128.2, 130.0, 145.9, 146.9, 148.4, 148.0, 153.3. Anal. Calcd for $C_{14}H_{14}N_4Cl_2\cdot 0.8H_2O$: C, 51.95; H, 4.82; N, 17.32. Found: C, 51.91; H, 4.88; N, 17.71.

4.3. General procedure for the synthesis of pyrido[2,3-*b*] indolizine-10-carbonitrile 4a–i

α,β-Unsaturated dicarbonyl compound (0.21 mmol) was added to a solution of 1,1′-[2-amino-1-cyanoprop-1-ene-1,3-diyl]dipyridinium dichloride **3** (0.29 mmol) and sodium acetate (1.10 mmol) in EtOH (6 mL) and water (1 mL). The yellow solution was refluxed for 3–7 days and then concentrated in the rotary evaporator. After cooling in an ice-bath, the solid started to precipitate. The solid was filtered and washed with water, leading to the pure product **4**.

*4.3.1. 2,4-Dimethylpyrido[2,3-b]indolizine-10-carbonitrile (**4a**).* Brown solid. Mp 270–272 °C; IR (Nujol mull) ν 2197, 1636, 1595, 1571, 1519, 1462 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.60 (s, 3H), 2.88 (s, 3H), 7.05 (td, J=7.0, 1.2 Hz, 1H), 7.10 (s, 1H), 7.56 (td, J=6.8, 0.8 Hz, 1H), 7.82 (dt, J=7.6, 1.2 Hz, 1H), 9.01 (d, J=7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.3, 24.1, 73.9, 112.3, 115.7, 116.8, 119.6, 120.9, 128.9, 130.2, 134.2, 142.2, 145.2, 157.0. Anal. Calcd for $C_{14}H_{11}N_3\cdot 0.2H_2O$: C, 74.80; H, 5.08; N, 18.70. Found: C, 74.72; H, 4.87; N, 18.91.

*4.3.2. 4-(4-Methoxyphenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4b**).* Greenish-yellow solid. Mp higher than 300 °C; IR (Nujol mull) ν 2205, 1638, 1609, 1578, 1557, 1513, 1461 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 6.89 (td, J=6.8, 1.2 Hz, 1H), 7.20 (dd, J=6.8, 2.0 Hz, 2H), 7.45–7.57 (m, 4H), 7.62 (dd, J=6.8, 2.4 Hz, 2H), 7.73 (s, 1H), 7.86 (dt, J=8.8, 1.2 Hz, 1H), 8.02 (dt, J=7.6, 0.8 Hz, 1H), 8.26 (dd, J=8.4, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.4, 74.9, 112.3, 114.7 (2C), 115.5, 116.3, 117.3, 119.7, 127.2 (2C), 127.6, 128.1, 128.8 (2C), 129.3, 129.7, 130.2 (2C), 137.6, 138.4, 143.5, 146.1, 154.7, 160.1. Anal. Calcd for $C_{25}H_{17}N_3O.0.5H_2O$: C, 78.12; H, 4.69; N, 10.94. Found: C, 78.16; H, 4.54; N, 10.81.

*4.3.3. 4-(3,4-Dimethoxyphenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4c**).* Green solid. Mp 262–264 °C; IR (Nujol mull) ν 2207, 1634, 1606, 1588, 1558, 1508, 1465 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H), 3.88 (s, 3H), 6.91 (td, J=7.2, 1.2 Hz, 1H), 7.21 (s, 2H), 7.30 (s, 1H), 7.45–7.58 (m, 4H), 7.77 (s, 1H), 7.87 (dd, J=8.4, 0.8 Hz, 1H), 8.08 (d, J=7.2 Hz, 1H), 8.27 (d, J=7.8, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.6, 55.7, 74.9, 112.2, 112.27, 112.33, 115.5, 116.3, 117.2, 119.7, 121.1, 127.2 (2C), 127.7, 128.4, 128.8 (2C), 129.3, 129.8, 137.8, 138.5, 143.5, 146.1, 149.2, 149.6, 154.6. Anal. Calcd for $C_{26}H_{19}N_3O_2$: C, 77.04; H, 4.69; N, 10.37. Found: C, 77.36; H, 4.69; N, 10.31.

*4.3.4. 4-(4-Methylphenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4d**).* After Green solid. Mp 229–231 °C; IR (Nujol mull) ν 2204, 1635, 1578, 1557, 1513, 1463 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H), 6.87 (td, J=6.8, 1.6 Hz, 1H), 7.44–7.58 (m, 8H), 7.72 (s, 1H), 7.85 (dt, J=8.8, 1.2 Hz, 1H), 7.95 (dd, J=7.2, 1.6 Hz, 1H), 8.24 (dd, J=7.2, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.0, 75.0, 112.3, 115.4, 116.1, 117.3, 119.5, 127.2 (2C), 128.0, 128.6 (2C), 128.8 (2C), 129.3, 129.7, 129.8 (2C), 132.7, 137.7, 138.4, 139.0, 143.4, 146.0, 154.6. Anal. Calcd for $C_{25}H_{17}N_3$: C, 83.56; H, 4.74; N, 11.70. Found: C, 83.62; H, 4.71; N, 11.64.

*4.3.5. 4-(4-Hydroxyphenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4e**).* Green solid. Mp higher than 300 °C; IR (Nujol mull) ν 3328, 2194, 1637, 1616, 1588, 1571, 1513, 1462 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (td, J=6.8, 1.6 Hz, 1H), 7.01 (dd, J=6.8, 2.0 Hz, 2H), 7.44–7.55 (m, 6H), 7.70 (s, 1H), 7.84 (dt, J=8.8, 1.2 Hz, 1H), 8.06 (dd, J=6.6, 1.2 Hz, 1H), 8.24 (dd, J=7.6, 1.6 Hz, 2H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 74.9, 112.2, 115.5, 116.1 (2C), 116.2, 117.2, 119.8, 125.8, 127.2 (2C), 128.1, 128.8 (2C), 129.3, 129.6, 130.1 (2C), 138.0, 138.5, 143.4, 146.0, 154.6, 158.4. Anal. Calcd for $C_{24}H_{15}N_3O$: C, 79.78; H, 4.16; N, 11.63. Found: C, 79.71; H, 4.20; N, 11.54.

*4.3.6. 4-(3,4-Dihydroxyphenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4f**).* Green solid isolated after reflux for 3 days (0.10 g, 90%). Mp higher than 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88–6.93 (m, 2H), 6.97–7.00 (m, 2H), 7.44–7.50 (m, 4H), 7.69 (s, 1H), 7.84 (dd, J=8.6, 0.8 Hz, 1H), 8.10 (d, J=7.2 Hz, 1H), 8.24 (dd, J=7.8, 1.2 Hz, 2H), 9.45 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 74.9, 112.2, 115.5, 115.8, 116.1, 116.3, 117.2, 119.7, 119.8, 126.3, 127.2 (2C), 128.2, 128.8 (2C), 129.3, 129.6, 138.2, 138.5, 143.4, 146.0, 146.7, 154.6. IR (Nujol mull) ν 3600–3000 (broad), 2196, 1634, 1599, 1558, 1511, 1461 cm^{-1}. Anal. Calcd for $C_{24}H_{15}N_3O_2\cdot 0.8H_2O$: C, 73.58; H, 4.24; N, 10.73. Found: C, 73.52; H, 4.22; N, 11.09.

*4.3.7. 4-(4-Fluorophenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4g**).* Yellow solid. Mp higher than 300 °C; IR (Nujol mull) ν 2208, 1638, 1609, 1593, 1568, 1533, 1509, 1464 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.87 (td, J=7.2, 1.2 Hz, 1H), 7.44–7.58 (m, 6H), 7.70–7.79 (m, 3H), 7.85 (dt, J=9.0, 1.2 Hz, 1H), 7.90 (dt, J=6.9, 1.2 Hz, 1H), 8.26 (dd, J=8.2, 1.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 75.0, 112.1, 114.9, 115.97, 116.0 (d, J=21.4 Hz, 2C), 117.0, 119.3, 127.0 (2C), 127.9, 128.5, 129.0 (2C), 129.4 (2C), 130.8 (d, J=8.2 Hz, 2C), 131.8 (d, J=3.2 Hz), 136.4, 138.2, 143.3, 145.8, 154.6, 162.5 (d, J=245.4 Hz). Anal. Calcd for $C_{24}H_{14}N_3F\cdot 0.09H_2O$: C, 78.99; H, 3.89; N, 11.52. Found: C, 79.22; H, 3.98; N, 11.53.

*4.3.8. 4-(4-Chlorophenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4h**).* Greenish-yellow solid. Mp 272–275 °C; IR (Nujol mull) ν 2211, 1636, 1599, 1573, 1555, 1534, 1514, 1461 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (t, J=6.4 Hz, 1H), 7.46–7.57 (m, 4H), 7.69–7.75 (m, 4H), 7.76 (s, 1H), 7.86 (d, J=8.8 Hz, 1H), 7.93 (d, J=7.2 Hz, 1H), 8.25 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 75.0, 112.5, 115.4, 116.1, 117.3, 119.3, 127.2 (2C), 128.3, 128.8 (2C), 129.3 (2C), 129.4, 129.8, 130.8 (2C), 134.3, 134.5, 136.4, 138.3, 143.5, 146.0, 154.6. Anal. Calcd for $C_{24}H_{14}N_3Cl\cdot 0.2H_2O$: C, 75.18; H, 3.76; N, 10.96. Found: C, 75.15; H, 3.97; N, 11.03.

*4.3.9. 4-(3-Nitrophenyl)-2-phenylpyrido[2,3-b]indolizine-10-carbonitrile (**4i**).* Greenish solid. Mp higher than 300 °C; IR (Nujol mull) ν 2206, 1637, 1578, 1561, 1530, 1515, 1501, 1460 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 (dt, J=6.6, 1.2 Hz, 1H), 7.46–7.58 (m, 4H), 7.86–7.96 (m, 4H), 8.16 (dt, J=8.2, 1.6 Hz, 1H), 8.29 (dd, J=8.4, 1.2 Hz, 2H), 8.49 (dq, J=8.4, 1.2 Hz, 1H), 8.60 (t, J=1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 75.0, 112.6, 115.4, 116.2, 117.2, 119.3, 123.9, 124.2, 127.2 (2C), 128.6, 128.8, 129.5 (2C), 129.9, 130.8, 135.3, 135.6, 137.2, 138.2, 143.6, 146.1, 148.2, 154.7. Anal. Calcd for $C_{24}H_{14}N_4O_2\cdot 0.6H_2O$: C, 71.86; H, 3.79; N, 13.97. Found: C, 71.78; H, 3.86; N, 13.98.

4.4. Synthesis of 2-{[4-oxopent-2-en-2-yl]amino}indolizine-1-carbonitrile 5

Compound **5** was isolated from the mother liquor, in the synthesis of compound **4a** under the conditions referred in Table 1, entry 4. Green solid. Mp 165–167 °C; IR (Nujol mull) ν 3136, 2191, 1633, 1614, 1594, 1546, 1524, 1460 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04 (s, 3H), 2.22 (s, 3H), 5.40 (s, 1H), 6.61 (s, 1H), 6.94 (td, J=7.0, 1.2 Hz, 1H), 7.16 (td, J=7.8, 1.2 Hz, 1H), 7.56 (dt, J=8.8, 1.2 Hz, 1H), 8.34 (dd, J=6.8, 0.8 Hz, 1H), 12.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.0, 29.1, 87.0, 94.1, 99.4, 112.6, 113.4,

118.4, 123.8, 125.7, 135.7, 136.8, 158.4, 196.5. Anal. Calcd for $C_{14}H_{13}N_3O \cdot 0.1H_2O$: C, 69.77; H, 5.48; N, 17.44. Found: C, 69.63; H, 5.39; N, 17.67.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.12.047.

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