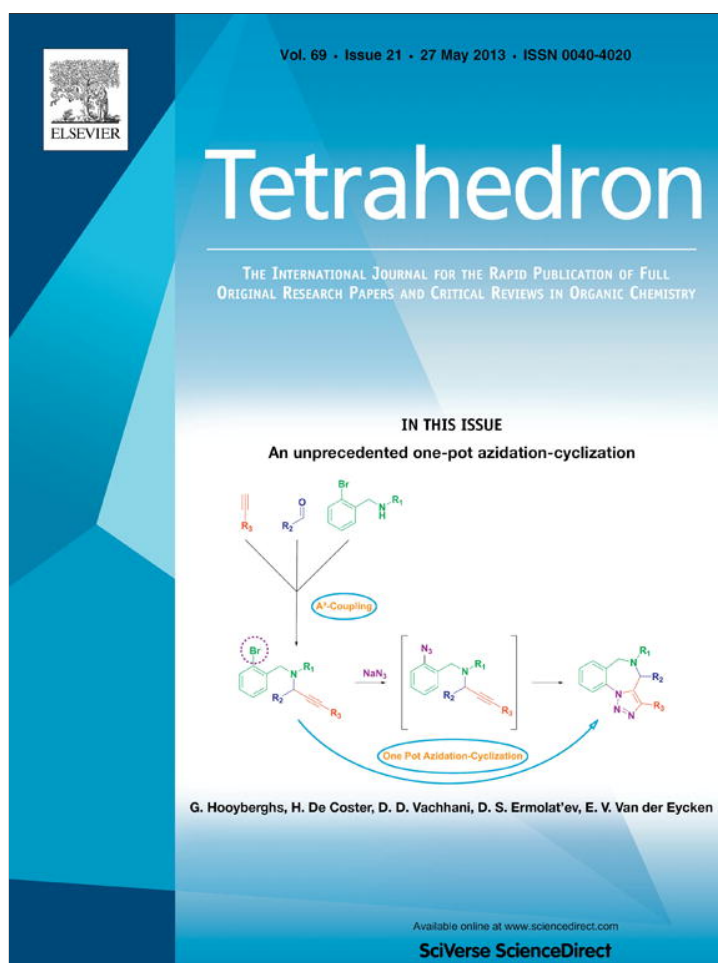




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Simple stepwise route to 1-substituted 2-amino-3-ethoxycarbonylindolizines



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ABSTRACT

2-Chloro-N-ethoxycarbonylmethylpyridinium bromide reacts with substituted acetonitriles in two steps; the initially formed pyridine anhydro bases undergo further ring closure to 2-amino-3-ethoxycarbonylindolizines.

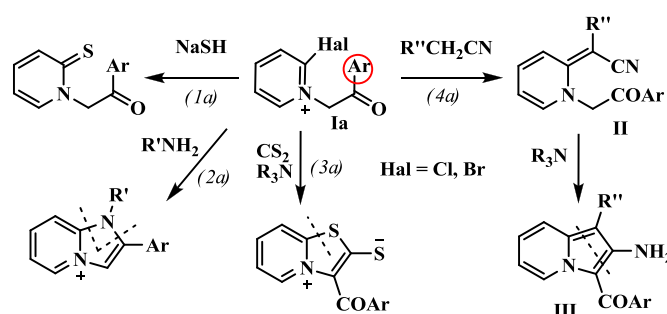
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1. Introduction

2-Chloro(bromo)pyridinium salts **I** with a potentially ylidic N-CH₂COR-group are important precursors of various pyrido-annulated heterocycles with bridgehead nitrogen atom.¹ The structure of the products formed from these salts strictly depends on the nature of the CH₂COR group. Thus, the salts with methylketone residue **1a** (R=Ar, Scheme 1), smoothly react with nucleophiles (reactions 1a, 2a)^{2,3} or dipolarophiles (reaction 3a)⁴ giving the expected products of ring closure.

In contrast, analogous salts **1b** with more reactive acetic ester group CH₂CO₂Et react with the same reagents in a more complicated way (reactions 1b, 2b, 3b),^{5–7} see Scheme 2, so that the products involve two structural units of the parent salt **1b**.

Kröhnke demonstrated that the reaction 4a (Scheme 1) between 2-chloropyridinium salt **1a** and either malononitrile or ethyl cyanoacetate in the presence of Hunig's base yielded anhydro bases **II**, which may undergo further cyclization to 2-aminoindolizines **III**.⁸ Recently we have expanded this novel synthetic route to indolizines **III** by involving salts **1a** in reactions 4a with diversely substituted acetonitriles (R'=α-heteroaryl group).⁹



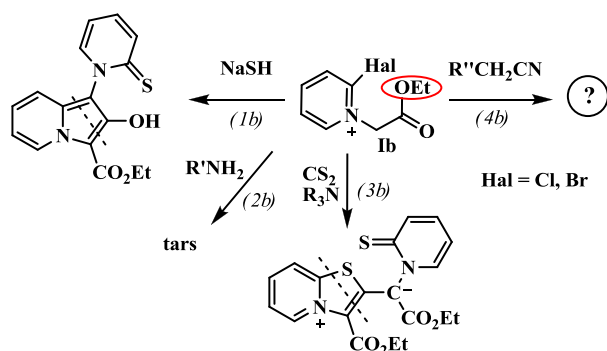
Scheme 1. The reactions of 2-halopyridinium salts **1a**.

Similar reaction 4b of the salts **1b** toward CH-acidic acetonitriles may result in the interesting class of bifunctional 2-aminoindolizines bearing ester groups at position 3. This reaction, however, was never studied before and is the goal of the present communication.

2. Results and discussion

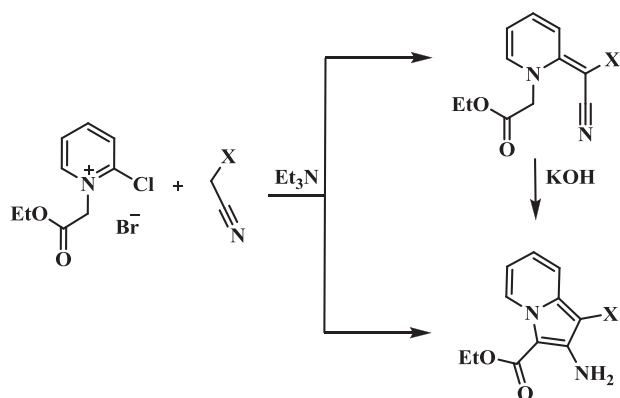
We found that 2-chloro-1-(2-ethoxy-2-oxoethyl)pyridinium bromide **1** readily reacts with various acetonitrile derivatives **2a–e** in the presence of 2 equiv of a tertiary amine, and the structure of product strongly depends on the nature of the CH-acid (Scheme 3,

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Scheme 2. The reactions of 2-halopyridinium salts **1b**.

Tables 1 and 2). In the case of cyanoacetic ester **2a** (X=CO₂Et) the product was the pyridine anhydro base **3a**, whereas malononitrile **2f** (X=CN) gave aminoindolizine **4f**.



Scheme 3. The reaction of 2-chloro-1-(2-ethoxy-2-oxoethyl)pyridinium bromide **1** with methylene active nitriles.

Thiazolyl-substituted acetonitriles **2b–e** (X=α-thiazolyl) gave either pure pyridine anhydro bases **3d,e** (in cases **2d,e**) or mixtures of anhydro bases **3b, 3c** with minor amounts of indolizines **4b, 4c** (**3:4** ~ 85:15 by ¹H NMR spectroscopy). All the anhydro bases **3a–e** smoothly underwent ring closure to indolizines **4a–e** upon treatment with 10% KOH in DMF.

In the IR spectra of all of the aminoindolizines **4** the characteristic frequency of amino group was observed at 3316–3485 cm^{−1}, and in their ¹H NMR spectra a broad singlet for the NH₂-group appeared at ~7 ppm (6.5 for **4a**). The signal of proton H-5, appeared as a doublet (for **4b,c,f** 6.7–7.2 Hz) or a broad singlet (for **4a,d,e**), and is strongly downshifted (δ=9.32–9.39) due to the well-known *peri*-effect of the magnetically anisotropic 3-CO₂Et group, typical for indolizines.¹⁰

Additional to *peri*-effect from position 3 toward proton H-5, an analogous downfield shift was observed for proton H-8 from similar groups located at *peri*-position 1. Thus, the chemical shift of proton H-8 in the indolizine **4a** with 1-CO₂Et groups appeared at 7.94 ppm, whereas in the analogous 1-cyanoderivative **4f** (where the CN group is incapable to *peri*-effect) the signal for H-8 is located at 7.36–7.48 ppm. A similar downfield location for the signal of H-8 in 1-(2-thiazolyl)-derivatives **4b–e** (at 7.79–7.85 ppm) clearly indicates the *peri*-influence of the C=N bond of the thiazolyl ring, which has the same nature as the C=O bond of the ester group in the indolizine **4a** (see also Scheme 3 and discussion below).

The isomeric anhydro bases **3** can be clearly distinguished from the indolizines **4** by ¹H NMR spectroscopy: in all cases the singlet of the methylene NCH₂ group appeared at δ=5.18–5.29 ppm for all

Table 1

Characteristics of dihydropyridines **3a–e** (Scheme 3)

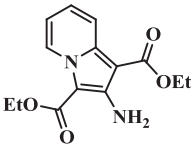
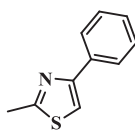
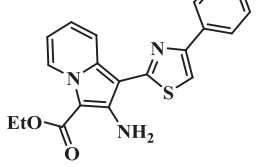
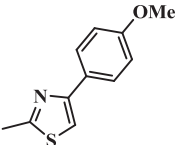
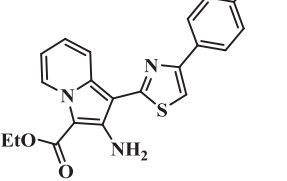
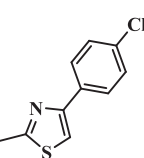
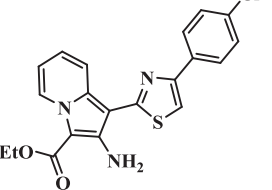
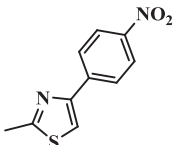
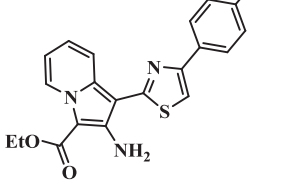
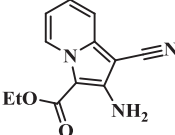
Compd	X	Product	Yield (%)
3a	CO ₂ Et		47
3b			71
3c			42
3d			76
3e			58

structures **3** and at δ=48–50 ppm in the ¹³C NMR spectra. Since the CN-group in anhydro bases **3** was preserved, it can be observed in the IR spectra as a broad vibrational band at 2169–2179 cm^{−1}. The frequency of the non-conjugated carbonyl function of the ester group (1726–1747 cm^{−1}) in anhydro bases **3** dramatically differed from the frequency of the conjugated CO₂Et group in indolizines **4** (ν 1665–1673 cm^{−1}).

It is an interesting problem to establish the configuration of the non-symmetrical double bond in anhydro bases **3** only from their ¹H NMR spectra. In our opinion, it is instructive to compare the isostructural parts of anhydro bases **3** and of indolizines **4**, as shown on Scheme 4.

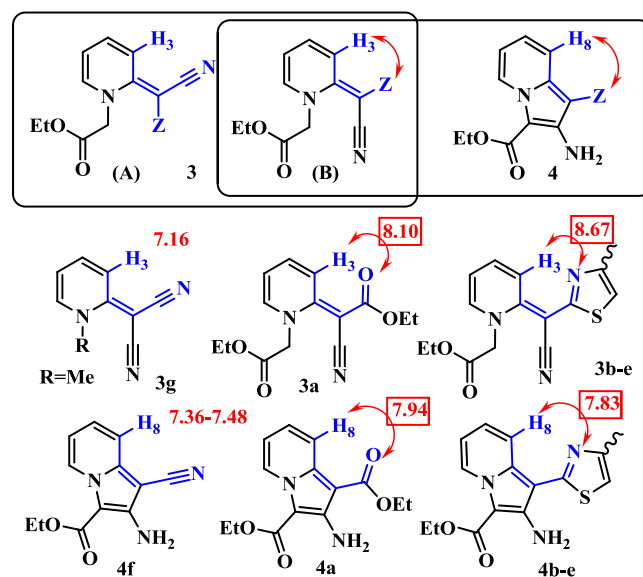
As was shown above, the chemical shift of proton H-8 in indolizines **4** is very sensitive to the nature of the substituent in position 1 due to the *peri*-effect. In the isostructural anhydro bases **3** the proton H-3 (spatially corresponding to proton H-8 in **4**) should definitely undergo a similar ('*peri*-like') effect from the group (X or CN) located at the end of the double bond. Therefore, one might expect that in the E-isomers (B on Scheme 4), the signals H-3 should be much more downfielded (due to the influence of the ester or thiazolyl group X) than in the Z-isomers A (without such

Table 2
Characteristics of indolizines **4a–f** (Scheme 3)

Compd	X	Product	Yield (%)
4a	CO ₂ Et		69
4b			85
4c			86
4d			89
4e			41
4f	CN		67

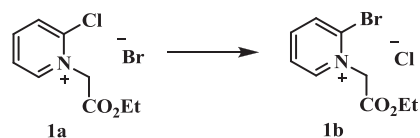
influence from the CN group). This expectation is completely confirmed (as shown by chemical shifts of the protons H-3 and H-8 labeled by squares in Scheme 3). Therefore, the observed high values ($\delta > 8$) for H-3 in the spectra of anhydro bases **3** clearly indicate their E configuration (B) (since the data for 'ideal' reference dicyano-structure **3f** with R=CH₂CO₂Et were not available due to its spontaneous ring closure to **4f**, the NMR data were taken for simplest structure **3g** with R=Me).¹¹

The observed Z-configuration of anhydro bases **3** may be clearly understood for steric reasons, since the less bulky CN group and NCH₂CO₂Et residue expected to be cis-oriented to each other. On the other hand, this spatial vicinity of the CN and CH₂CO₂Et groups strongly favor the next step—Thorpe–Ziegler cyclization to form the pyrrole ring of indolizines **4**. Concerning the differences in behavior of different CH-acids (formation of **3**, **4** or their mixtures) one may suppose that the stronger is the acceptor properties of the groups X in **3**, the easier is the final cyclization step to **4** (cf. where X=CN or nitrophenyl-substituted thiazole against X=CO₂Et and other thiazolyl radicals).



Scheme 4. The peri-like effect in the series of compounds **3** and **4**.

One interesting observation on the structure of the parent pyridinium salt **1** cannot be neglected: its mass spectrum displayed two peaks of molecular ions corresponding both to 2-chloro (**1a**) and 2-bromo (**1b**) pyridinium cations, Scheme 5. This effect was also observed in the spectra of the analogous 2-chloropyridinium bromides **1a**,¹ and can be rationalized by the higher nucleophilicity of the bromide ion versus chloride.



Scheme 5. Isomeric compounds **1a** and **1b**.

According to the ¹H NMR spectra, the ratio **1a**:**1b** (~70:30) is not influenced by further heating of the parent salt. In our opinion, this fact does not influence the nature and distribution of the products **3,4**, but may be dramatic if the halogen is preserved (like in cycloadditions of the ylides from salts **1**).^{1,12}

To conclude, the reaction of readily available pyridinium salt **1** (having an acetic ester residue at nitrogen atom) with various acetonitriles **2**, provides a smooth route to an interesting bi-functional scaffold—aminoindolizine esters **4** with various groups at C-1. In contrast to earlier observed (and somewhat complex, Scheme 2) behavior of the salts **1b**, the discovered transformation of **1** to **4** occurs smoothly, and in many cases, interesting stable multifunctional anhydro bases **3** can be isolated as intermediates.

It should be mentioned that indolizines bearing 2-amino and 3-alkoxycarbonyl groups are poorly investigated; the only known structure is an indolizine (obtained from α -pyridyl acetonitrile and bromoacetate) described in patent literature¹³ as a precursor of biologically active pyrido[2,3-*b*]indolizines. Several *N*-alkyl-^{14,15} and *N*-tosyl-¹⁶ derivatives with a 3-CO₂R group were obtained via cycloaddition to pyridinium ylides (frequently as side products).

3. Experimental section

3.1. General

IR spectra were measured with a Perkin–Elmer spectrometer in dry KBr pellets. ¹H and ¹³C NMR spectra were recorded with Bruker

DRX-200 (200 MHz), Bruker AVANCE II-400 (400 MHz) and Bruker AC-400 (400 MHz) spectrometers. The purity of the products was monitored by TLC on Silufol UV-254 plates (acetone–hexane, 3:5). Mass spectra were measured on MX-1321 (EY, 70 eV) mass spectrometer. Melting points were determined on a Kofler hot stage. The elemental analysis data were obtained for **3a**, **3d**, **4d** using Carlo Erba 11-06 ($\pm 0.01\%$) and for other compounds using Euro Vector EA 300 ($\pm 0.1\%$).

3.1.1. A mixture of 2-chloro-1-(2-ethoxy-2-oxoethyl)pyridinium bromide 1a and 2-bromo-1-(2-ethoxy-2-oxoethyl)pyridinium chloride 1b. A mixture of 2-chloropyridine (30.0 mmol) and ethyl 2-bromoacetate (32.0 mmol) was heated without solvent at 80–85 °C for 3 h. After cooling, the mixture was diluted with acetone (40 mL) and kept for 24 h at ambient temperature. The residue was filtered and washed with acetone. Yield: 2.5 g (30%), white solid, mp 186 °C; $\nu_{\max}$ (KBr): 1741 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 9.25 (1H, d, J 6.2 Hz, H-6 (**1b**)), 9.21 (1H, d, J 6.2 Hz, H-6 (**1a**)), 8.76 (1H, td, J 8.2, 1.7 Hz, H-4 (**1a**)), 8.66–8.56 (2H, m, H-3, H-4 (**1b**)), 8.52 (1H, d, J 8.3 Hz, H-3 (**1a**)), 8.30–8.21 (1H, m, H-5 (**1a**+**1b**)), 5.83 (2H, s, NCH_2 (**1a**+**1b**)), 4.27 (2H, qd, J 7.1, 2.0 Hz, CH_2CH_3 (**1a**+**1b**)), 1.25 (3H, td, J 7.1, 0.9 Hz, CH_2CH_3 (**1a**+**1b**)); δ_{C} (100 MHz, CDCl_3 –DMSO- d_6) 164.63, 164.56, 149.3, 149.0, 147.8, 139.8, 139.4, 133.8, 129.9, 126.8, 126.6, 119.1, 62.4, 61.9, 60.6, 59.4, 13.80, 13.76; m/z (EI, 70 eV) 525 (4.2), 481 (4.7), 244 (36, M–1) (**1b**), 200 (100%, M–1) (**1a**).

3.1.2. 2-[1-(2-Ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetoneitriles (3a–e), 2-amino-1-cyano-3-ethoxycarbonylindolizine (4f). The salt **1** (2.0 mmol) and corresponding acetonitrile **2** (2.0 mmol) were dissolved in ethanol (15 mL). To the stirred mixture, 2 equiv of triethylamine was added, and the solution was stirred for 4 h at rt and kept for 24 h in the fridge (–10 °C). The residue was filtered, washed with cold ethanol and recrystallized (for solvents, see Tables 1 and 2).

3.1.3. 2-Amino-1-(R)-3-ethoxycarbonylindolizine (4a–e). Anhydrous base **3** (1.0 mmol) was dissolved in DMF (5–7 mL). To the stirred solution the aqueous 10% KOH (1.0 mmol) was added. After stirring for 3–4 h the mixture was mixed with 5–7 mL of distilled water and kept for 24 h in the fridge. The residue was filtered, washed with distilled water, then with ethanol and recrystallized (for solvent, see Table 1).

3.1.4. Ethyl (E)-2-cyano-2-[1-(2-ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetate (3a). Yellow solid, mp 115 °C (MeOH); [found: C, 60.77; H, 5.82; N, 10.18. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$ requires C, 60.86; H, 5.84; N, 10.14%]; $\nu_{\max}$ (KBr): 2179, 1746, 1655 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 8.10 (2H, d, J 8.50 Hz, H-3, H-6), 7.84–7.75 (1H, m, H-4), 7.11–7.03 (1H, m, H-5), 5.18 (2H, s, NCH_2), 4.17 (2H, q, J 7.11 Hz, CH_2CH_3), 4.04 (2H, q, J 7.08 Hz, CH_2CH_3), 1.13–1.29 (6H, m, CH_2CH_3); δ_{C} (100 MHz, DMSO- d_6) 167.3, 166.5, 157.6, 143.5, 138.6, 125.7, 121.6, 115.6, 96.1, 61.9, 59.1, 58.1, 15.0, 14.3; m/z (EI, 70 eV) 276 (97.5, M⁺), 158 (87), 132 (100%).

3.1.5. (E)-2-[1-(2-Ethoxy-2-oxoethyl)pyridin-1(2H)-ylidene]-2-(4-phenylthiazol-2-yl)acetoneitrile (3b). Orange solid, mp 164–165 °C (EtOH); [found: C, 66.1; H, 4.5; N, 11.6; S 8.8. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ requires C, 66.10; H, 4.71; N, 11.56; S 8.82%]; $\nu_{\max}$ (KBr): 2172, 1726 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 8.67 (1H, d, J 9.2 Hz, H-3), 7.95–7.87 (3H, m, H-6, H_{Ar}), 7.71 (1H, s, $H_{\text{thiazolyl}}$), 7.69–7.60 (1H, m, H-4), 7.48 (1H, t, J 7.5 Hz, H_{Ar}), 7.42 (2H, t, J 7.5 Hz, H_{Ar}), 6.86–6.76 (1H, m, H-5), 5.27 (2H, s, NCH_2), 4.14 (2H, q, J 7.1 Hz, CH_2CH_3), 1.1 (3H, t, J 7.1 Hz, CH_2CH_3); δ_{C} (100 MHz, DMSO- d_6) 167.7, 167.1, 153.8, 153.1, 142.8, 137.2, 134.9, 129.0, 128.9, 127.9, 126.5, 126.3, 113.3, 109.1, 62.0, 59.6, 57.7, 14.4; m/z (EI, 70 eV) 363 (100%, M⁺).

3.1.6. (E)-2-[4-(4-Methoxyphenyl)thiazol-2-yl]-2-[1-(2-ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetoneitrile (3c). Orange solid, mp

158–159 °C (EtOH); [found: C, 64.1; H, 4.7; N, 10.7; S 8.1. $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ requires C, 64.10; H, 4.87; N, 10.68; S 8.15%]; $\nu_{\max}$ (KBr): 2171, 1747 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 8.65 (1H, d, J 9.0 Hz, H-3), 7.88–7.82 (3H, m, H-6, H_{Ar}), 7.65–7.57 (1H, m, H-4), 7.54 (1H, s, $H_{\text{thiazolyl}}$), 6.97 (2H, d, J 8.7 Hz, H_{Ar}), 6.77 (1H, t, J 6.7 Hz, H-5), 5.26 (2H, s, NCH_2), 4.15 (2H, q, J 7.1 Hz, CH_2CH_3), 3.78 (3H, s, OCH_3), 1.19 (3H, t, J 7.1 Hz, CH_2CH_3); δ_{C} (100 MHz, DMSO- d_6) 171.3, 170.4, 162.7, 157.0, 156.3, 146.3, 141.0, 131.2, 131.0, 127.4, 118.5, 118.0, 117.8, 116.9, 110.7, 65.5, 61.2, 58.9, 17.7; m/z (EI, 70 eV) 393 (100%, M⁺).

3.1.7. (E)-2-[4-(4-Chlorophenyl)thiazol-2-yl]-2-[1-(2-ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetoneitrile (3d). Orange solid, mp 183–184 °C (EtOH); [found: C, 60.41; H, 4.11; N, 10.61. $\text{C}_{20}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}$ requires C, 60.37; H, 4.05; N, 10.56%]; $\nu_{\max}$ (KBr): 2173, 1740 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 8.65 (1H, d, J 9.3 Hz, H-3), 7.95–7.87 (3H, m, H-6, H_{Ar}), 7.78 (1H, s, $H_{\text{thiazolyl}}$), 7.64 (1H, dd, J 9.3, 6.7 Hz, H-4), 7.47 (2H, d, J 8.5 Hz, H_{Ar}), 6.82 (1H, t, J 6.7 Hz, H-5), 5.27 (2H, s, NCH_2), 4.15 (2H, q, J 7.1 Hz, CH_2CH_3), 1.19 (3H, t, J 7.1 Hz, CH_2CH_3); δ_{C} (100 MHz, DMSO- d_6) 167.5, 167.2, 152.6, 152.1, 142.6, 137.5, 133.3, 132.1, 128.7, 127.61, 127.57, 123.6, 123.2, 113.4, 109.5, 61.7, 57.4, 13.9; m/z (EI, 70 eV) 397 (100%, M⁺).

3.1.8. (E)-2-[4-(4-Nitrophenyl)thiazol-2-yl]-2-[1-(2-ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetoneitrile (3e). Orange solid, mp 221 °C (EtOH); [found: C, 58.6; H, 4.2; N, 13.6; S 7.8. $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$ requires C, 58.81; H, 3.95; N, 13.72; S 7.85%]; $\nu_{\max}$ (KBr): 2169, 1727 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 8.70 (1H, d, J 9.5 Hz, H-3), 8.28 (2H, d, J 8.9 Hz, H_{Ar}), 8.17 (2H, d, J 8.9 Hz, H_{Ar}), 8.09 (1H, s, $H_{\text{thiazolyl}}$), 7.96 (1H, d, J 7.1 Hz, H-6), 7.74–7.64 (1H, m, H-4), 6.88 (1H, t, J 7.1 Hz, H-5), 5.29 (2H, s, NCH_2), 4.16 (2H, q, J 7.2 Hz, CH_2CH_3), 1.19 (3H, t, J 7.2 Hz, CH_2CH_3); δ_{C} (100 MHz, DMSO- d_6) 168.1, 167.7, 153.2, 151.6, 146.7, 143.0, 140.9, 137.7, 127.4, 127.1, 124.5, 124.3, 113.9, 113.5, 96.0, 62.1, 57.7, 14.3; m/z (EI, 70 eV) 408 (100%, M⁺).

3.1.9. 2-Amino-1,3-di(ethoxycarbonyl)indolizine (4a). White solid, mp 113 °C (MeOH); [found: C, 60.9; H, 5.9; N, 10.1. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$ requires C, 60.86; H, 5.84; N, 10.14%]; $\nu_{\max}$ (KBr): 3515, 3387, 1666 cm^{-1} ; δ_{H} (400 MHz, DMSO- d_6) 9.32 (1H, s, H-5), 7.94 (1H, d, J 8.8 Hz, H-8), 7.41 (1H, t, J 7.8 Hz, H-7), 7.02 (1H, t, J 6.4 Hz, H-6), 6.48 (2H, s, NH_2), 4.31 (4H, dq, J 14.3, 7.1 Hz, CH_2CH_3), 1.34 (6H, t, J 7.1 Hz, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 165.6, 165.5, 161.8, 138.7, 128.2, 126.8, 117.3, 112.8, 99.9, 90.3, 59.6, 59.4, 14.7, 14.6; m/z (EI, 70 eV) 276 (73.2, M⁺), 158 (100%).

3.1.10. 2-Amino-1-(4-phenylthiazol-2-yl)-3-ethoxycarbonylindolizine (4b). Yellow solid, mp 139–140 °C (EtOH); [found: C, 66.1; H, 5.1; N, 11.6; S 8.8. $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$ requires C, 66.10; H, 4.71; N, 11.56; S 8.82%]; $\nu_{\max}$ (KBr): 3485, 3329, 1668 cm^{-1} ; δ_{H} (200 MHz, DMSO- d_6) 9.37 (1H, d, J 6.8 Hz, H-5), 8.03 (2H, d, J 7.0 Hz, H_{Ar}), 7.98 (1H, s, $H_{\text{thiazolyl}}$), 7.81 (1H, d, J 8.8 Hz, H-8), 7.52–7.31 (4H, m, H-7, H_{Ar}), 7.07 (2H, s, NH_2), 6.99 (1H, t, J 6.8 Hz, H-6), 4.36 (2H, q, J 7.1 Hz, CH_2CH_3), 1.37 (3H, t, J 7.1 Hz, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 170.0, 166.4, 162.0, 153.8, 153.4, 134.5, 134.1, 128.7, 128.0, 126.3, 125.8, 125.4, 118.4, 115.0, 111.5, 107.1, 59.6, 14.8; m/z (EI, 70 eV) 363 (100%, M⁺).

3.1.11. 2-Amino-1-(4-methoxyphenylthiazol-2-yl)-3-ethoxycarbonylindolizine (4c). Yellow solid, mp 157 °C (EtOH); [found: C, 64.1; H, 5.0; N, 10.7; S 8.0. $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ requires C, 64.10; H, 4.87; N, 10.68; S 8.15%]; $\nu_{\max}$ (KBr): 3464, 3313, 1670 cm^{-1} ; δ_{H} (200 MHz, DMSO- d_6) 9.36 (1H, d, J 6.7 Hz, H-5), 7.95 (2H, d, J 8.8 Hz, H_{Ar}), 7.83–7.79 (2H, m, H-8, $H_{\text{thiazolyl}}$), 7.44 (1H, t, J 9.0 Hz, H-7), 7.10–6.95 (5H, m, H_{Ar} , NH_2 , H-6), 4.36 (2H, q, J 7.1 Hz, CH_2CH_3), 3.80 (3H, s, OCH_3), 1.37 (3H, t, J 7.1 Hz, CH_2CH_3); δ_{C} (100 MHz, CDCl_3) 166.5, 160.8, 158.3, 152.3, 144.5, 133.8, 127.4, 126.4, 124.6, 113.8, 112.8, 110.3,

104.2, 100.0, 99.6, 94.3, 58.4, 54.2, 13.6; m/z (EI, 70 eV) 393 (100%, M^+).

3.1.12. 2-Amino-1-(4-chlorophenylthiazol-2-yl)-3-ethoxycarbonyl-indolizine (4d). Yellow solid, mp 175–176 °C (EtOH); [found: C, 60.39; H, 4.10; N, 10.59. $C_{20}H_{16}ClN_3O_2S$ requires C, 60.37; H, 4.05; N, 10.56%]; $\nu_{\max}$ (KBr): 3470, 3316, 1673 cm^{-1} ; δ_H (400 MHz, DMSO- d_6) 9.39 (1H, s, H-5), 8.10–8.04 (3H, m, H_{Ar} , $H_{thiazolyl}$), 7.83 (1H, d, J 8.9 Hz, H-8), 7.53 (2H, d, J 8.5 Hz, H_{Ar}), 7.51–7.44 (1H, m, H-7), 7.05 (2H, s, NH_2), 7.01 (1H, t, J 6.5 Hz, H-6), 4.37 (2H, q, J 7.1 Hz, CH_2CH_3), 1.38 (3H, t, J 7.1 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 166.4, 162.2, 161.9, 152.6, 135.4, 133.7, 133.0, 128.8, 128.7, 127.5, 125.9, 115.0, 111.6, 107.5, 106.1, 99.7, 59.6, 14.8; m/z (EI, 70 eV) 397 (100%, M^+).

3.1.13. 2-Amino-1-(4-nitrophenylthiazol-2-yl)-3-ethoxycarbonyl-indolizine (4e). Brown solid, mp 203–204 °C (EtOH); [found: C, 58.1; H, 3.6; N, 13.6; S, 7.7. $C_{20}H_{16}N_4O_4S$ requires C, 58.81; H, 3.95; N, 13.72; S, 7.85]; $\nu_{\max}$ (KBr): 3499, 3359, 1667 cm^{-1} ; δ_H (400 MHz, DMSO- d_6) 9.38 (1H, s, H-5), 8.38 (1H, s, $H_{thiazolyl}$), 8.31 (4H, s, H_{Ar}), 7.85 (1H, d, J 8.9 Hz, H-8), 7.54–7.44 (1H, m, H-7), 7.10–6.95 (3H, m, H-6, NH_2), 4.38 (2H, q, J 7.1 Hz, CH_2CH_3), 1.39 (3H, t, J 7.1 Hz, CH_2CH_3); δ_C (100 MHz, DMSO- d_6) 172.5, 161.1, 158.1, 146.6, 139.8, 138.6, 134.8, 128.2, 126.9, 124.1, 120.3, 114.7, 113.2, 112.5, 109.7, 99.5, 59.4, 14.6; m/z (EI, 70 eV) 408 (100%, M^+).

3.1.14. 2-Amino-1-cyano-3-ethoxycarbonylindolizine (4f). Colorless solid, mp 151 °C (MeOH); [found: C, 62.9; H, 4.9; N, 18.3. $C_{12}H_{11}N_3O_2$ requires: C, 62.87; H, 4.84; N, 18.33]; $\nu_{\max}$ (KBr): 3469, 3343, 2207, 1675 cm^{-1} ; δ_H (200 MHz, DMSO- d_6) 9.25 (1H, d, J 7.2 Hz, H-5), 7.48–7.36 (2H, m, H-7, H-8), 7.06–6.98 (1H, m, H-6), 6.49 (2H, s, NH_2), 4.33 (2H, q, J 7.0 Hz, CH_2CH_3), 1.32 (3H, t, J 7.0 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 163.7, 161.2, 139.4, 128.7, 126.9, 115.3, 115.0, 113.3, 100.0, 93.1, 60.1, 14.7; m/z (EI, 70 eV) 229 (100%, M^+).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.tet.2013.02.049>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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