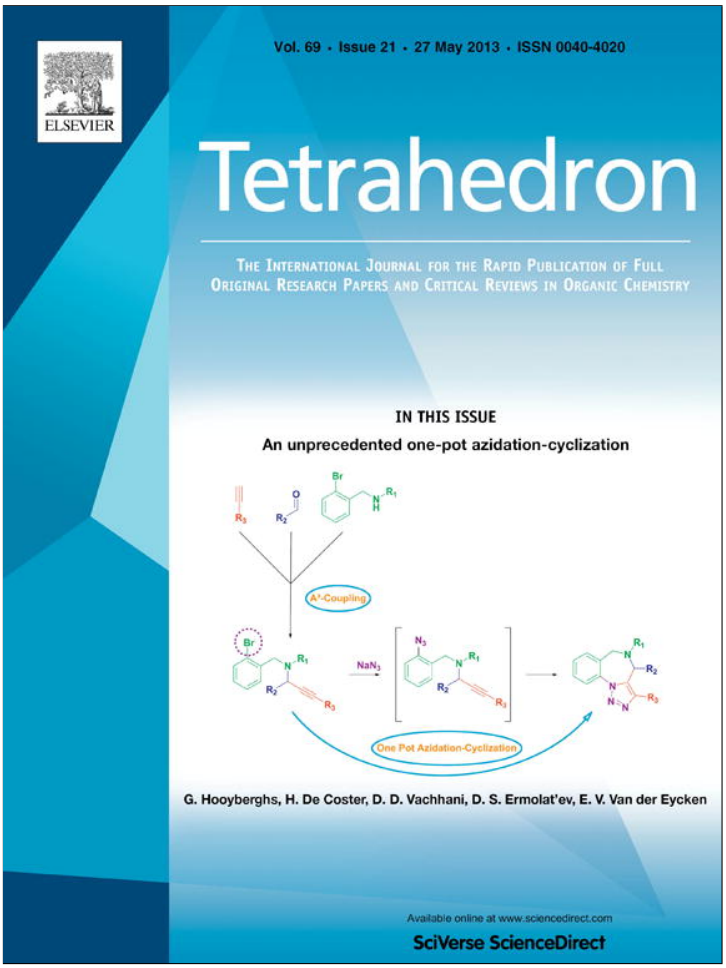

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Simple stepwise route to 1-substituted 2-amino-3-ethoxycarbonylindolizines

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ABSTRACT

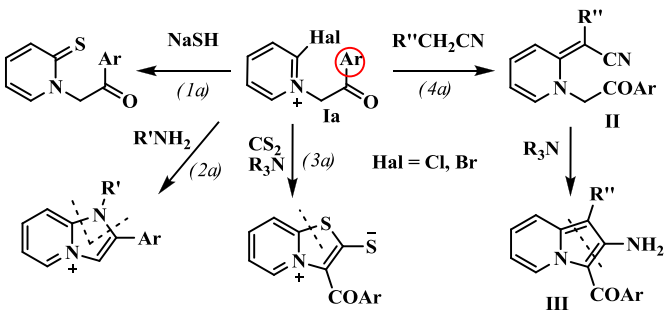
2-Chloro-*N*-ethoxycarbonylmethylpyridinium bromide reacts with substituted acetonitriles in two steps; the initially formed pyridine anhydro baseses undergo further ring closure to 2-amino-3-ethoxycarbonylindolizines.

1. Introduction

2-Chloro(bromo)pyridinium salts **I** with a potentially ylidic N–CH_2COR-group are important precursors of various pyrido-annelated heterocycles with bridgehead nitrogen atom.[1] The structure of the products formed from these salts strictly depends on the nature of the CH_2COR group. Thus, the salts with methylketone residue **Ia** (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 **Ib** with more reactive acetic ester group CH_2CO_2Et 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 **Ib**.

Kröhnke demonstrated that the reaction *4a* (Scheme 1) between 2-chloropyridinium salt **Ia** 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 **Ia** in reactions *4a* with diversely substituted acetonitriles (R′=α-heteroaryl group).[9]



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

Similar reaction *4b* of the salts **Ib** 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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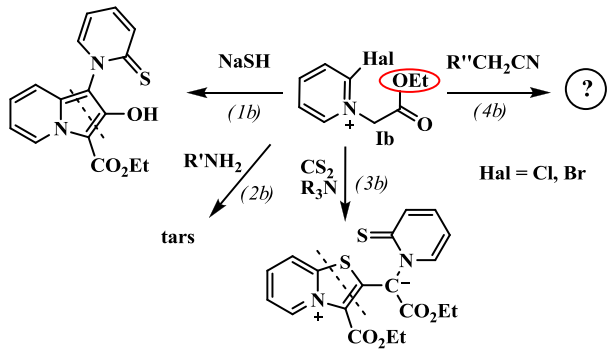
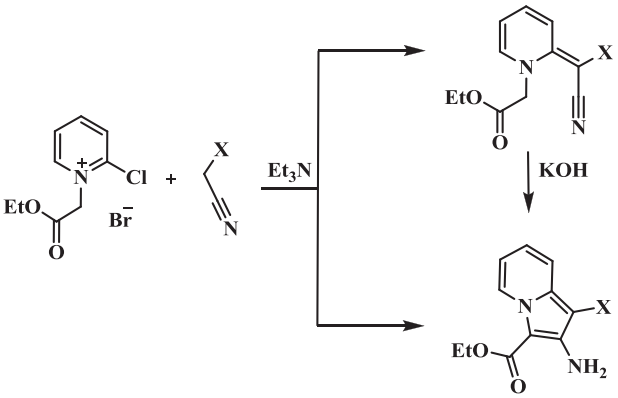


Scheme 2. The reactions of 2-halopyridinium salts **Ib**.

Tables 1 and 2). In the case of cyanoacetic ester **2a** (X=CO_2Et) 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.

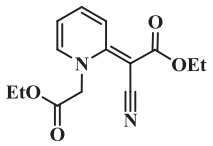
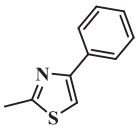
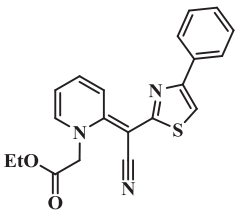
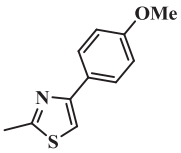
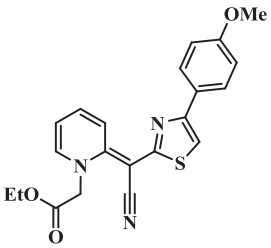
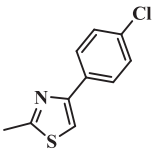
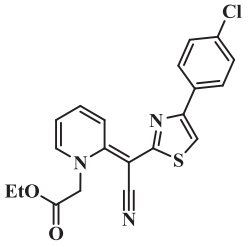
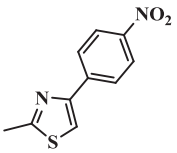
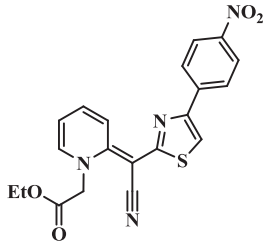
Thiazolyl-substituted acetonitriles **2b**–**e** (X=α-thiazolyl) gave either pure pyridine anhydro bases **3d**,**e** (in cases **2d**,**e**) or mixtures of anhydro bases **3b**, **3c** with minor amounts of indolizines **4b**, **4c** (**3**:**4** ~ 85:15 by ^{1}H NMR spectroscopy). All the anhydro bases **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 ^{1}H NMR spectra a broad singlet for the NH_2-group appeared at ~7 ppm (6.5 for **4a**). The signal of proton H-5, appeared as a doublet (for **4b**,**c**,**f** J 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-CO_2Et 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-CO_2Et 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 ^{1}H NMR spectroscopy: in all cases the singlet of the methylene NCH_2 group appeared at δ=5.18–5.29 ppm for all

Table 1
Characteristics of dihydropyridines **3a**–**e** (Scheme 3)

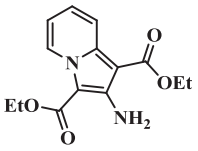
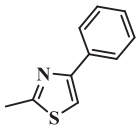
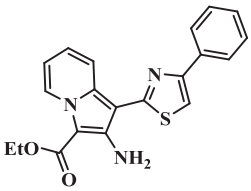
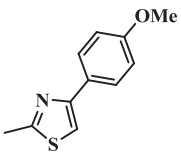
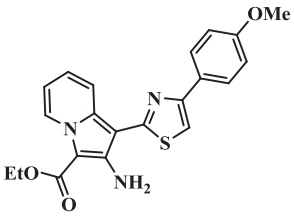
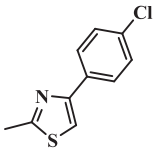
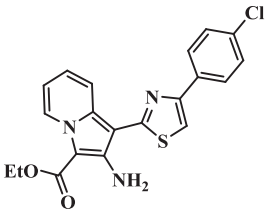
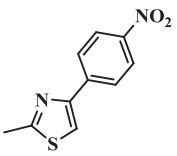
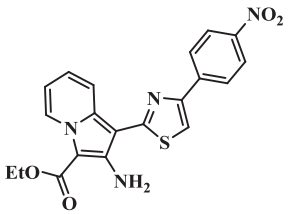
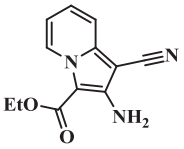
Compd	X	Product	Yield (%)
3a	CO_2Et		47
3b			71
3c			42
3d			76
3e			58

structures **3** and at δ=48–50 ppm in the ^{13}C 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 CO_2Et 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 ^{1}H NMR spectra. In our opinion, it is instructive to compare the isostructutral parts of anhydro bases **3** and of indolizines **4**, as shown on Scheme 4.

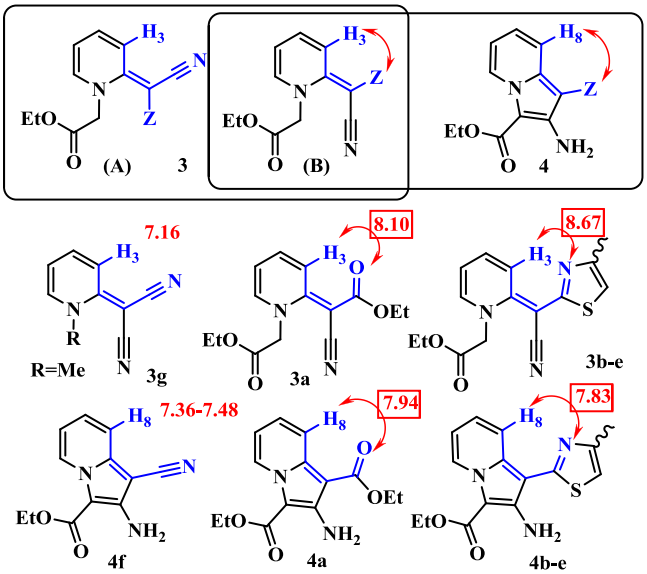
As was shown above, the chemical shift of proton H-8 in indolizines **4** is very sensitive to the nature of the substituent in position 1 due to the *peri*-effect. In the isostructural anhydro bases **3** the proton H-3 (spatially corresponding to proton H-8 in **4**) should definitely undergo a similar ('*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_2Et		69
4b			85
4c			86
4d			89
4e			41
4f	CN		67

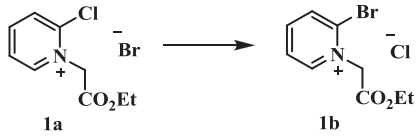
influence from the CN group). This expectation is completely confirmed (as shown by chemical shifts of the protons H-3 and H-8 labeled by squares in Scheme 3). Therefore, the observed high values (δ>8) for H-3 in the spectra of anhydro bases **3** clearly indicate their E configuration (B) (since the data for 'ideal' reference dicyano-structure **3f** with R=CH_2CO_2Et 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 NCH_2CO_2Et residue expected to be cis-oriented to each other. On the other hand, this spatial vicinity of the CN and CH_2CO_2Et 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=CO_2Et 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 **Ia**,[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 ^{1}H 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 **I**).[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 bifunctional scaffold—aminoindolizine esters **4** with various groups at C-1. In contrast to earlier observed (and somewhat complex, Scheme 2) behavior of the salts **Ib**, 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 literature[13] as a precursor of biologically active pyrido[2,3-*b*]indolizines. Several *N*-alkyl-[14,15] and *N*-tosyl-[16] derivatives with a 3-CO_2R 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. ^{1}H and ^{13}C 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 (±0.01%) and for other compounds using Euro Vector EA 300 (±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; ν_{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$_2$CH_3 (**1a**+**1b**)); δ_C (100 MHz, CCl_4–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]acetonitriles (**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**).* Anhydro 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. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%]; ν_{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$_2$CH_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)acetonitrile (**3b**).* Orange solid, mp 164–165 °C (EtOH); [found: C, 66.1; H, 4.5; N, 11.6; S 8.8. $C_{20}H_{17}N_3O_2S$ requires C, 66.10; H, 4.71; N, 11.56; S 8.82%]; ν_{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, $H_{thiazolyl}$), 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$_2$CH_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]acetonitrile (**3c**).* Orange solid, mp 158–159 °C (EtOH); [found: C, 64.1; H, 4.7; N, 10.7; S 8.1. $C_{21}H_{19}N_3O_3S$ requires C, 64.10; H, 4.87; N, 10.68; S 8.15%]; ν_{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, $H_{thiazolyl}$), 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$_2$CH_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]acetonitrile (**3d**).* Orange solid, mp 183–184 °C (EtOH); [found: C, 60.41; H, 4.11; N, 10.61. $C_{20}H_{16}ClN_3O_2S$ requires C, 60.37; H, 4.05; N, 10.56%]; ν_{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, $H_{thiazolyl}$), 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$_2$CH_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]acetonitrile (**3e**).* Orange solid, mp 221 °C (EtOH);[found: C, 58.6; H, 4.2; N, 13.6; S 7.8. $C_{20}H_{16}N_4O_4S$ requires C, 58.81; H, 3.95; N, 13.72; S 7.85%]; ν_{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, $H_{thiazolyl}$), 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$_2$CH_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. $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.84; N, 10.14%]; ν_{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$_2$CH_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. $C_{20}H_{17}N_3O_2S$ requires C, 66.10; H, 4.71; N, 11.56; S 8.82%]; ν_{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, $H_{thiazolyl}$), 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$_2$CH_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. $C_{21}H_{19}N_3O_3S$ requires C, 64.10; H, 4.87; N, 10.68; S 8.15%]; ν_{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, $H_{thiazolyl}$), 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$_2$CH_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%]; ν_{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]; ν_{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: 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]; ν_{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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