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.

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

In contrast, analogous salts Ib with more reactive acetic ester group CH2CO2Et react with the same reagents in a more complicated way (reactions 1b, 2b, 3b, 4b) see Scheme 2, so that the products involve two structural units of the parent salt Ib.

Krohnke 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 = -heteroaryl group).9

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 I 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,
In the case of cyanoacetic ester 2a (X=CO$_2$Et) the product was the pyridine anhydro base 3a, whereas malononitrile 2f (X=CN) gave aminoindolizine 4f.

Additional to peri-effect from position 3 toward proton H-5, an analogous downfield shift was observed for proton H-5 due to the peri-effect from the CO$_2$Et group (1726–1747 cm$^{-1}$) or a broad singlet for H-8 (6.5 for 4a). The signal of proton H-5, appeared as a doublet (for 4b,c,f) at 6.7–7.2 Hz or a broad singlet (for 4a,d,e), and is strongly downshifted ($\delta$=9.32–9.39) due to the well-known peri-effect of the magnetically anisotropic 3-CO$_2$Et group, typical for indolizines.

Additional to peri-effect from position 3 toward proton H-5, an analogous downfield shift was observed for proton H-5 from similar groups located at peri-position 1. Thus, the chemical shift of proton H-8 in the indolizine 4a with 1-CO$_2$Et groups appeared at 7.94 ppm, whereas in the analogous 1-cyanoderivative 4f (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 $\delta$=5.18–5.29 ppm for all structures 3 and at $\delta$=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$_2$Et group in indolizines 4 ($\nu$ 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 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
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 conformation (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).

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 a acetic ester residue at nitrogen atom) with various acetonitriles 2, provides a smooth route to an interesting bifunctional scaffold—aminoundolizidine 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-alkoxy carbonyl 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
8.3 Hz, dissolved in ethanol (15 mL). To the stirred mixture, 2 equiv of (2-oxoethyl)pyridin-2(1H)-ylidene]acetonitrile (58.1, 15.0, 14.3; C, 66.10; H, 4.71; N, 11.56; S 8.82%; (40 mL) and kept for 24 h at ambient temperature. The residue was filtered, washed with water, then with ethanol and recrystallized (for solvent, see Table 1). 3.1.2. 2-[[(2-Ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetottonitrile (3a–e). 2-amino-cyano-3-ethoxy carbonylindolizine (4f). The salt 1 (2.0 mmol) and corresponding acetottonitrile 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 room temperature 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-(1R)-3-ethoxy carbonylindolizine (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-[(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. C12H16N2O2 requires C, 60.68; H, 5.84; N, 10.14%]; vmax (KBr) : 1709, 1746, 1655 cm−1; δ7 (400 MHz, DMSO-d6) : 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, NCH2), 4.21 (2H, q, J 7.11 Hz, CH2CH3), 4.04 (2H, q, J 7.08 Hz, CH2CH3), 1.13–1.29 (6H, m, CH2CH3); δc (100 MHz, DMSO-d6) : 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 (El, 70 eV) : 276 (M+75), 158 (87), 132 (100%). 3.1.5. (E)-2-[[(2-Ethoxy-2-oxoethyl)pyridin-1(2H)-ylidene]-2-[(2-phenylthiazol-2-yl)acetetitrile (3b). Orange solid, mp 166–165 °C (EtOH); [found: C, 66.1; H, 4.5; N, 11.6; S 8.88%. C13H12N2O2S requires C, 66.10; H, 4.71; N, 11.56; S 8.82%; vmax (KBr) : 2172, 1726 cm−1; δ7 (400 MHz, DMSO-d6) : 6.67 (1H, d, J 9.2 Hz, H-3), 7.95–7.87 (7H, m, H-6, H-5), 7.11 (1H, s, Hhazaolyl), 7.69–7.60 (1H, m, H-4), 7.48 (1H, t, J 7.5 Hz, Hg), 4.72 (2H, t, J 7.5 Hz, Hg), 6.86–6.76 (1H, m, H-5), 5.27 (2H, s, NCH2), 4.14 (2H, q, J 7.1 Hz, CH2CH3), 1.1 (3H, t, J 7.1 Hz, CH2CH3); δc (100 MHz, DMSO-d6) : 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 (El, 70 eV) : 363 (100%). 3.1.6. (E)-2-[[(4-Methoxyphenyl)thiazol-2-yl-2-[(1-[(2-ethoxy-2-oxoethyl)pyridin-2(1H)-ylidene]acetetonitrile (3c). Orange solid, mp 158–159 °C (EtOH); [found: C, 64.1; H, 4.7; N, 10.7; S 8.1. C12H12N2O2S requires C, 64.10; H, 4.87; N, 10.68; S 8.15%]; vmax (KBr) : 3146, 3313, 1670 cm−1; δ7 (200 MHz, DMSO-d6) : 9.36 (1H, d, J 6.7 Hz, H-5), 7.95 (2H, d, J 8.8 Hz, Hg), 7.83–7.79 (2H, m, H-6, Hhazaolyl), 7.44 (1H, t, J 9.0 Hz, H-7), 7.10–6.95 (5H, m, Hg, HN-Ar, HN-H, H-7), 4.36 (2H, q, J 7.1 Hz, CH2CH3), 3.80 (3H, s, OCH3), 1.37 (3H, t, J 7.1 Hz, CH2CH3); δc (100 MHz, DMSO-d6) : 166.5, 166.0, 158.3, 152.3, 144.5, 133.8, 127.4, 126.4, 124.6, 113.8, 112.8, 110.3, 108.5, 110.8, 107.8, 105.7, 103.1, 101.5, 101.0, 100.6, 97.4, 96.0, 95.9, 92.3, 85.4, 83.5, 83.4, 81.5, 76.0, 69.2, 62.1, 59.3, 40.3, 37.9, 35.7, 34.9, 33.9, 31.2, 29.9, 28.9, 22.1, 19.7, 15.5, 13.6, 13.5, 10.0, 9.7, 9.5, 9.2, 8.6; δc (100 MHz, DMSO-d6) : 167.5, 167.2, 152.6, 142.6, 142.5, 137.5, 133.3, 132.1, 128.7, 126.7, 125.7, 123.6, 123.2, 113.4, 105.9, 61.6, 57.4, 13.9; m/z (El, 70 eV) : 397 (100%).
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 (4f). Yellow solid, mp 175–176 °C (EtOH); [found: C, 60.39; H, 4.10; N, 10.59. C23H22ClN3O2S requires C, 60.37; H, 4.05; N, 10.56%]; δH (400 MHz, DMSO-d6) 9.39 (1H, s, H-5), 6.10–8.04 (3H, m, HAr, Hthiazolyl). 7.83 (1H, d, J 8.9 Hz, H-8), 7.53 (2H, d, J 8.5 Hz, HAr), 7.51–7.44 (1H, m, H-7), 7.05 (2H, s, NH2), 7.01 (1H, t, J 6.5 Hz, H-6), 4.37 (2H, q, J 7.1 Hz, CH2CH3). 1.38 (3H, t, J 7.1 Hz, CH2CH3); δC (100 MHz, CDCl3) 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. C20H16N3O2S requires C, 58.81; H, 3.95; N, 13.72; S, 7.85%]; δmax (KBr): 3470, 3316, 1673 cm⁻¹; δH (400 MHz, DMSO-d6) 9.38 (1H, s, H-5), 8.38 (1H, s, Hthiazolyl). 8.31 (4H, s, HAr), 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, NH2), 4.38 (2H, q, J 7.1 Hz, CH2CH3), 1.39 (3H, t, J 7.1 Hz, CH2CH3); δC (100 MHz, DMSO-d6) 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. C12H12N3O2 requires C, 62.87; H, 4.84; N, 18.33%]; δmax (KBr): 3489, 3359, 1667 cm⁻¹; δH (400 MHz, DMSO-d6) 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, NH2), 4.33 (2H, q, J 7.0 Hz, CH2CH3), 1.32 (3H, t, J 7.0 Hz, CH2CH3); δC (100 MHz, CDCl3) 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.

References and notes
6. According to unpublished data of the authors, salts Ib react with primary amines giving unidentified tars.