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Microwave-assisted synthesis of pyridylpyrroles from *N*-acylated amino acids

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ABSTRACT

A small library of 3- and 4-pyridyl-substituted pyrroles was prepared from *N*-acylated amino acids. Nicotinoyl or isonicotinoyl chloride was used for the N-acylation of benzyl esters of amino acids. Debenzylation by palladium-catalyzed hydrogenation gave *N*-acylated amino acids. Dehydration of the acylated amino acids gave cyclic intermediates, münchnones or azlactones, which were treated in situ with alkynes in 1,3-dipolar cycloadditions. The starting materials were prepared in a parallel fashion, and microwave irradiation was used to facilitate the cycloaddition reactions. The regiochemistry of the cycloaddition was studied.

1. Introduction

Pyrroles are interesting aromatic heterocycles, widely present in nature. The pyrrole ring appears in many natural compounds including marine alkaloids,[1] bacterial prodigiosins,[2] and porphyrins.[3] Some of these naturally occurring pyrroles have shown antitumor activity.[4] Additionally, commercial drugs such as cholesterol-reducing atorvastatin[5] and anti-inflammatory ketorolac[6] contain the pyrrole ring. Pyridylpyrroles, in turn, have shown antidiabetic,[7] anti-inflammatory,[8] antioxidant,[9] antiprotozoal,[10] and antiviral[11] activities, and they are also found in tobacco alkaloids.[12]

There are various methods to prepare pyrroles.[13] One of the methods involves 1,3-dipolar cycloaddition of azomethine ylides and alkynes.[14] The cycloaddition reaction of azomethine ylide-type mesoionic dipoles, münchnones[15] or azlactones,[16] with alkynes was first reported by Huisgen et al. Münchnones are obtained from secondary amino acids and are highly reactive toward alkynes, whereas azlactones, which are obtained from primary amino acids, require tautomeric proton shift before cycloaddition.[17] Mesoionic azomethine ylide-type dipoles can be obtained from *N*-acylated amino acids with a dehydrating agent. Typically the water-removing agent has been acetic anhydride used simultaneously for the acylation of the amino acid, but other reagents, such as *N*,*N*′-dicyclohexylcarbodiimide (DCC),[18] *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC),[19] and *N*,*N*′-diisopropylcarbodiimide (DIC),[20] have been used for the dehydration of *N*-acylated amino acids in the cycloaddition. The chemistry of the münchnones and azlactones has recently been reviewed,[21] and some mesoion-mediated syntheses of pyrroles have also been reported,[22] including one microwave-assisted synthesis.[23]

1,3-Dipolar cycloaddition is an efficient reaction carried out with simple building blocks. Amino acids are readily available reagents with a wide variety of functional groups. Another substituent is easily added to the pyrrole ring structure through acylation of the amino acid. Pyrroles with various substituents are then readily obtained when the mesoionic compounds are reacted with alkynes. Microwaves can be used to enhance the reaction rate, and a compound library can be conveniently obtained with parallel methods. We describe here a microwave-assisted synthesis of various pyridyl pyrroles.

2. Results and discussion

N-Acylated amino acid benzyl esters were prepared in a parallel fashion on a Radleys 12-place carousel reaction station from benzyl esters of amino acids **1** and acyl chlorides (Scheme 1). Parallel catalytic hydrogenation in Radleys reaction tubes gave pyridyl-substituted amino acids **2**. Cycloaddition with a dehydrating reagent and dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate led to highly functionalized pyrroles **4a**–**4m**. Several dehydrating agents were tested and acetic anhydride gave the highest yields. The yields with EDC and polymer-bound *N*-benzyl-*N*′-cyclohexylcarbodiimide were lower than those obtained with acetic anhydride. DCC and DIC gave urea as side-product, which was difficult to remove.

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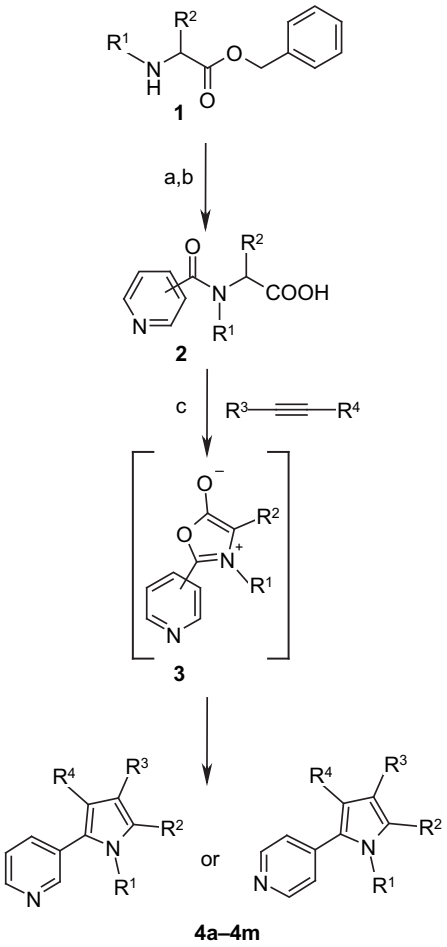

Scheme 1. Synthesis of pyridylpyrroles **4**. Reagents and conditions: (a) amino acid benzyl ester **1** (1 equiv), nicotinoyl or isonicotinoyl chloride (1 equiv), prepared in situ from nicotinic or isonicotinic acid, Et_3N (3.2 equiv), DCM; 0 °C, 2 h; rt, 15–20 h; (b) H_2, 1 atm, 10 wt % Pd on activated carbon (catalytic amount), MeOH, rt, 5 h; (c) Ac_2O, alkyne (1 equiv), MW irradiation, 130 °C, 5 min.

A series of pyrroles was subsequently synthesized with acetic anhydride as the dehydrating agent. Two alkynes, DMAD and methyl propiolate, were used in microwave-assisted 1,3-dipolar cycloaddition, and a small library of pyridylpyrroles was obtained (Fig. 1). The yields and purities of the pyrroles are listed in Table 1. Methyl propiolate gave two regioisomers. The regiochemistry of the münchnone cycloaddition has been studied, and the regiochemical outcome depends on the substituents.[24] The amino acids behaved quite differently, and gave varying regiochemical results. Compounds **4b** and **4e**, which were prepared via azlactones, were obtained regioselectively, whereas compounds obtained via münchnones were mixtures of regioisomers. Pyrrole **4k** was an inseparable mixture of two regioisomers, while pyrroles **4h** and **4i** were a separable mixture of regioisomers. The regiochemistry of the cycloaddition was verified with NMR experiments. The pyrrole C*H* proton appeared at 6.67–6.93 ppm when the proton was closer to the pyridyl ring and at 6.38–6.40 ppm when it was closer to the alkyl substituent. Additionally, NOESY experiments revealed close proximity of the aromatic pyrrole C*H* proton, either between the nearest aromatic pyridyl protons and the pyrrole proton (Fig. 2, compound **4h**) or between the closest alkyl protons and the pyrrole proton (Fig. 2, compound **4i**).

In summary, we have developed a fast method to prepare new functionalized pyridylpyrroles starting from amino acids. Parallel methods and microwave irradiation were utilized. This facile method can be used to synthesize highly substituted pyrroles, containing two substituents from the amino acid, one from the acyl chloride, and two from the alkyne.

3. Experimental

3.1. General

Dichloromethane (DCM) was freshly distilled over calcium hydride. Parallel reactions were performed on a Radleys 12-place carousel reaction station. Microwave reactions were carried out with the Biotage Microwave Initiator EXP EU in 2–5 mL sealed reaction tubes with normal (PhMe) or high (Ac_2O) solvent affinity, fixed reaction time on, and pre-stirring for 30 s. 1,1,1-Trifluorotoluene (TFT) was used as a polar cosolvent with toluene to enable efficient heating. TLC plates were Merck TLC aluminum sheets coated with silica gel 60 F_{254}. Flash chromatography was performed with a Biotage SP1-A2C with 12+M or 25+M silica cartridges. Melting points were measured with an Electrothermal IA9100 digital melting point apparatus and are uncorrected. NMR spectra were recorded with a Varian Mercury 300 Plus spectrometer. Chemical shifts (δ) are reported in ppm relative to residual

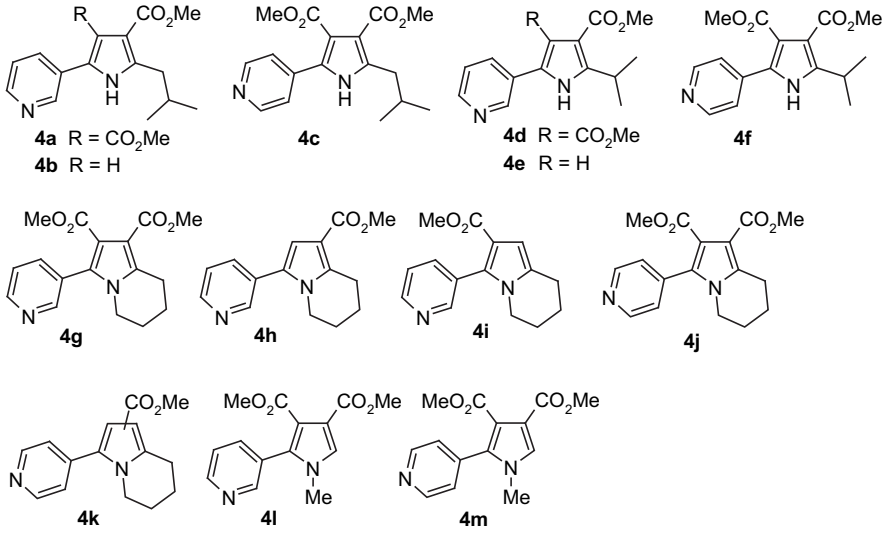

Figure 1. Pyridylpyrroles **4a**–**4m** prepared from DMAD and methyl propiolate.

Table 1
Yields and purities of pyridylpyrroles **4a**–**4m** prepared with Ac_2O as dehydrating agent

Entry	Product	Yield %[a]	Purity %[b]
1	**4a**	49	93
2	**4b**	43	93
3	**4c**	32	>98
4	**4d**	18	~95
5	**4e**	48	>98
6	**4f**	28	>98
7	**4g**	78	>98
8	**4h**+**4i**	85[c]	>98
9	**4j**	63	>98
10	**4k**	70[d]	>98
11	**4l**	34	~95
12	**4m**	21	~95

[a] Isolated yield.
[b] Purities were evaluated on the basis of LC–MS, ^{1}H NMR and elemental analyses.
[c] Combined yield of regioisomers, ratio of **4h**: **4i** ~1:2.
[d] ~1:1 mixture of regioisomers.

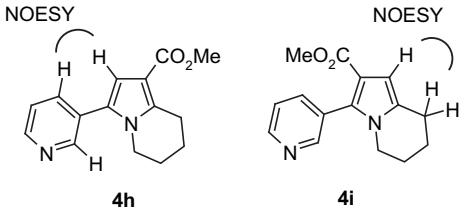

Figure 2. Analysis of the regiochemistry of **4h** and **4i** with NOESY experiment.

NMR solvent peaks (DMSO-d_6 2.5 and 39.51 ppm, $CDCl_3$ 7.26 and 77.16 ppm). Signals were assigned on the basis of DEPT, HSQC, and HMBC experiments. Secondary *N*-acylated amino acid benzyl esters and *N*-acylated amino acids were obtained as mixtures of two rotamers. Only the NMR data of the major rotamer obtained from the HSQC and HMBC experiments is reported. FTIR spectra were measured with a Bruker Vertex 70 FTIR spectrometer by KBr technique; oily samples were measured between two KBr pellets. LC–MS analyses were carried out with an HP 1100 series instrument and an Esquire-LC Bruker Daltonik ion trap mass spectrometer with positive mode ESI ion source, UV detector wavelength of 210 nm, column XTerra MS RP18 (4.6×30 mm, 2.5 μm), eluent gradient of 0.1% formic acid in water–acetonitrile from 10% to 90%, and flow rate 0.7 mL/min. Q-TOF Micro (quadrupole time-of-flight) mass spectrometer (The Waters Micromass) with electrospray ionization in positive ion mode was used for accurate LC–MS analyses (HRMS). Elemental analyses were done at Robertson Microlit Laboratories, Inc., Madison, NJ.

3.2. General preparation of benzyl esters of amino acids[25]

The solution of L-leucine or DL-pipecolinic acid (30 mmol, 1 equiv), benzyl alcohol (6.2 mL, 60 mmol, 2 equiv), and *p*-toluenesulfonic acid (6.9 g, 36 mmol, 1.2 equiv) in toluene (60 mL) was refluxed for 20 h under Dean–Stark apparatus to remove water. The reaction mixture was cooled and stored in a freezer. The precipitated salt was filtered, washed with toluene, and dried. The obtained products were used as such in the next reaction step. L-Valine benzyl ester *p*-toluenesulfonate [16652-76-9] and sarcosine benzyl ester *p*-toluenesulfonate [54384-06-4] were purchased from Chem-Impex International, Inc, Wood Dale, IL.

3.3. General preparation of *N*-acylated amino acid benzyl esters[26,27]

The reactions were performed in a parallel fashion with a Radleys carousel. Nicotinic acid or isonicotinic acid (0.5 g, 4 mmol, 1 equiv) was placed in the reaction tube under argon in DCM. Oxalyl chloride (0.4 mL, 4.5 mmol, 1.1 equiv) and a catalytic amount of DMF (2–3 drops) were added, and the reaction mixture was stirred at room temperature for 2 h. Benzyl ester (4 mmol, 1 equiv) was added to the reaction mixture. Triethylamine (1.8 mL, 13 mmol, 3.2 equiv) was added dropwise at 0 °C, and the reaction mixture was stirred for 2 h at 0 °C, and overnight (15–20 h) at room temperature. The solution was washed with saturated $NaHCO_3$ (2×) and with water (2×), dried with Na_2SO_4, and evaporated. The crude products were purified by flash chromatography.

3.4. General preparation of *N*-acylated amino acids

The reactions were performed in a parallel fashion with a Radleys carousel. Palladium 10 wt% on activated carbon (~100 mg) was placed in the reaction tube. Benzyl ester of amino acid (~2–3 mmol) was added in MeOH (20 mL), and the reaction mixture was stirred at room temperature under a hydrogen balloon for about 5 h. The mixture was filtered through Celite, the Celite was rinsed with methanol, and the filtrate was evaporated and dried in vacuo. The products were used as such in the following cycloaddition.

3.5. General preparation of pyridinyl-1*H*-pyrroles

N-Acylated amino acid (0.6 mmol, 1 equiv) and alkyne (0.6 mmol, 1 equiv) were placed in a microwave reaction tube. Acetic anhydride (3 mL) was added. The reaction mixture was purged with argon, and the microwave tube was irradiated at 130 °C for 5 min. Water was added and the solvent was evaporated. The crude product was purified by flash chromatography.

3.5.1. 2-(2-Methylpropyl)-5-(3-pyridinyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester ***4a****.* Yield 93 mg (49%, purity 93%), white solid, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.14 (br s, 1H), 8.64 (dd, *J*=2.1 Hz and 0.6 Hz, 1H), 8.43 (dd, *J*=4.8 Hz and 1.5 Hz, 1H), 7.87 (ddd, *J*=8.1 Hz, 2.1 Hz, and 1.5 Hz, 1H), 7.27 (ddd, *J*=8.1 Hz, 4.8 Hz, and 0.9 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.75 (d, *J*=7.2 Hz, 2H), 1.92–2.06 (m, 1H), 0.93 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7, 165.2, 148.2 (Ar*C*H), 147.9 (Ar*C*H), 139.9, 135.9 (Ar*C*H), 128.2, 127.9, 123.8 (Ar*C*H), 115.5, 113.3, 52.3 (*C*H$_3$), 51.5 (*C*H$_3$), 35.9 (*C*H$_2$), 29.5 (*C*H), 22.5 (2×*C*H$_3$). FTIR (KBr, cm^{-1}): 1707 (C=O). LC–MS: $[M+H]^+$, *m*/*z* 317 (t_R=4.7 min). HRMS $[M+H]^+$ found 317.1494, $C_{17}H_{21}N_2O_4$ requires 317.1501.

3.5.2. 2-(2-Methylpropyl)-5-(3-pyridinyl)-1H-pyrrole-3-carboxylic acid methyl ester ***4b****.* Yield 67 mg (43%, purity 93%), white solid, R_f=0.2 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.68 (br s, 1H), 8.90 (d, *J*=1.8 Hz, 1H), 8.38 (d, *J*=4.5 Hz, 1H), 8.02 (dt, *J*=8.1 Hz and 1.8 Hz, 1H), 7.37 (dd, *J*=8.1 Hz and 4.8 Hz, 1H), 6.93 (d, *J*=2.7 Hz, 1H), 3.70 (s, 3H), 2.80 (d, *J*=7.2 Hz, 2H), 1.95–2.06 (m, 1H), 0.88 (d, *J*=6.6 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.7, 146.9 (Ar*C*H), 145.0 (Ar*C*H), 141.2, 130.6 (Ar*C*H), 127.7, 126.6, 123.7 (Ar*C*H), 112.1, 107.9 (Ar*C*H), 50.4 (*C*H$_3$), 35.2 (*C*H$_2$), 28.9 (*C*H), 22.2 (2×*C*H$_3$). FTIR (KBr, cm^{-1}): 1698 (C=O). LC–MS: $[M+H]^+$, *m*/*z* 259 (t_R=4.3 min). HRMS $[M+H]^+$ found 259.1444, $C_{15}H_{19}N_2O_2$ requires 259.1447.

3.5.3. 2-(2-Methylpropyl)-5-(4-pyridinyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester ***4c****.* Yield 61 mg (32%), white solid, mp 165–166 °C, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.29 (br s, 1H), 8.44 (d, *J*=6.3 Hz, 2H), 7.39 (dd, *J*=4.8 Hz

and 2.1 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.79 (d, J=7.2 Hz, 2H), 1.93–2.07 (m, 1H), 0.93 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.2, 164.7, 149.6 (ArCH), 141.1, 139.0, 127.3, 121.4 (ArCH), 117.3, 113.4, 52.6 (CH_3), 51.6 (CH_3), 36.1 (CH_2), 29.5 (CH), 22.6 (2×CH_3). FTIR (KBr, cm^{-1}): 1735, 1709 (C=O). LC–MS: $[M+H]^+$, m/z 317 (t_R=4.2 min). Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54%; H, 6.37%; N, 8.85%, found C, 64.28%; H, 6.13%; N, 8.84%.

3.5.4. 2-(1-Methylethyl)-5-(3-pyridinyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester ***4d***. Yield 33 mg (18%, purity ~95%), white solid, mp 207–209 °C, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.73 (br s, 1H), 8.68 (d, J=1.8 Hz, 1H), 8.54 (dd, J=4.8 Hz and 1.2 Hz, 1H), 7.87 (ddd, J=7.8 Hz, 2.4 Hz, and 1.2 Hz, 1H), 7.46 (ddd, J=7.8 Hz, 4.8 Hz, and 0.9 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 3.55 (sept, J=6.9 Hz, 1H), 1.27 (d, J=7.2 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 165.8, 164.6, 148.6 (ArCH), 148.4 (ArCH), 144.8, 135.4 (ArCH), 128.6, 126.9, 123.3 (ArCH), 114.0, 110.7, 51.6 (CH_3), 51.2 (CH_3), 25.5 (CH), 21.8 (2×CH_3). FTIR (KBr, cm^{-1}): 1710 (C=O). LC–MS: $[M+H]^+$, m/z 303 (t_R=4.1 min). HRMS $[M+H]^+$ found 303.1331, $C_{16}H_{19}N_2O_4$ requires 303.1345.

3.5.5. 2-(1-Methylethyl)-5-(3-pyridinyl)-1H-pyrrole-3-carboxylic acid methyl ester ***4e***. Yield 70 mg (48%), white solid, R_f=0.2 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.85 (br s, 1H), 8.77 (d, J=1.8 Hz, 1H), 8.44 (dd, J=4.8 Hz and 1.5 Hz, 1H), 7.75 (ddd, J=8.1 Hz, 2.1 Hz, and 1.8 Hz, 1H), 7.29 (dd, J=7.8 Hz and 4.8 Hz, 1H), 6.88 (d, J=2.7 Hz, 1H), 3.87 (sept, J=6.9 Hz, 1H), 3.83 (s, 3H), 1.34 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.5, 147.54 (ArCH), 147.48, 145.3 (ArCH), 131.4 (ArCH), 128.2, 126.6, 123.9 (ArCH), 112.1, 109.2 (ArCH), 51.1 (CH_3), 26.3 (CH), 22.1 (2×CH_3). FTIR (KBr, cm^{-1}): 1699 (C=O). LC–MS: $[M+H]^+$, m/z 245 (t_R=3.8 min). Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83%; H, 6.60%; N, 11.47%, found C, 68.57%; H, 6.64%; N, 11.32%.

3.5.6. 2-(1-Methylethyl)-5-(4-pyridinyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester ***4f***. Yield 50 mg (28%), mp 177–178 °C, white solid, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.86 (br s, 1H), 8.44 (br s, 2H), 7.37 (br s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.73 (sept, J=6.9 Hz, 1H), 1.31 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.0, 164.7, 149.7 (ArCH), 146.7, 138.8, 127.4, 121.5, 117.1, 111.9, 52.6 (CH_3), 51.7 (CH_3), 26.2 (CH), 22.2 (2×CH_3). FTIR (KBr, cm^{-1}): 1733, 1700 (C=O). LC–MS: $[M+H]^+$, m/z 303 (t_R=3.7 min). Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57%; H, 6.00%; N, 9.27%, found C, 63.47%; H, 5.89%; N, 8.99%.

3.5.7. 3-(3-Pyridinyl)-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylic acid dimethyl ester ***4g***. Yield 147 mg (78%), white solid, mp 123–124 °C, R_f=0.2 (EtOAc–*n*-hexane 7:3). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.60 (d, J=4.5 Hz, 1H), 8.56 (s, 1H), 7.83 (ddd, J=8.1 Hz, 2.1 Hz, and 1.8 Hz, 1H), 7.48 (dd, J=8.1 Hz and 5.1 Hz, 1H), 3.73 (t, J=6.0 Hz, 2H), 3.70 (s, 3H), 3.56 (s, 3H), 2.96 (t, J=5.7 Hz, 2H), 1.78–1.84 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 165.4, 164.0, 150.2 (ArCH), 149.2 (ArCH), 137.6 (ArCH), 136.5, 130.0, 126.0, 123.2 (ArCH), 115.5, 109.6, 51.5 (CH_3), 51.0 (CH_3), 44.3 (CH_2), 23.2 (CH_2), 22.3 (CH_2), 19.0 (CH_2). FTIR (KBr, cm^{-1}): 1733, 1697 (C=O). LC–MS: $[M+H]^+$, m/z 315 (t_R=4.3 min). Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96%; H, 5.77%; N, 8.91%, found C, 64.89%; H, 5.57%; N, 9.01%.

3.5.8. 3-(3-Pyridinyl)-5,6,7,8-tetrahydroindolizine-1-carboxylic acid methyl ester ***4h*** *and 3-(3-pyridinyl)-5,6,7,8-tetrahydroindolizine-2-carboxylic acid methyl ester* ***4i***. Yield 131 mg (85%, ~1:2 ratio of regioisomers **4h** and **4i**).

3.5.9. 3-(3-Pyridinyl)-5,6,7,8-tetrahydroindolizine-1-carboxylic acid methyl ester ***4h***. Analytical sample (38 mg) separated from the mixture of regioisomers, white solid, mp 125–126 °C, R_f=0.2 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.65 (s, 1H), 8.54 (d, J=3.9 Hz, 1H), 7.68 (dt, J=7.5 Hz and 1.8 Hz, 1H), 7.32 (dd, J=7.5 and 4.5 Hz, 1H), 6.67 (s, 1H), 3.91 (t, J=6.0 Hz, 2H), 3.80 (s, 3H), 3.18 (t, J=6.0 Hz, 2H) 1.88–1.96 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.6, 149.5 (ArCH), 148.3 (ArCH), 138.6, 136.0 (ArCH), 129.3, 128.6, 123.4 (ArCH), 111.1, 110.7 (ArCH), 50.9 (CH_3), 45.2 (CH_2), 24.2 (CH_2), 23.4 (CH_2), 19.9 (CH_2). FTIR (KBr, cm^{-1}): 1695 (C=O). LC–MS: $[M+H]^+$, m/z 257 (t_R=3.8 min). Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29%; H, 6.29%; N, 10.93%, found C, 69.95%; H, 6.37%; N, 10.90%.

3.5.10. 3-(3-Pyridinyl)-5,6,7,8-tetrahydroindolizine-2-carboxylic acid methyl ester ***4i***. Analytical sample (61 mg) separated from the mixture of regioisomers, white solid, mp 85–87 °C, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.59–8.61 (m, overlapping 2H), 7.72 (dt, J=7.8 Hz and 1.8 Hz, 1H), 7.36 (dd, J=7.5 Hz and 4.8 Hz, 1H), 6.40 (t, J=0.9 Hz, 1H), 3.68 (t, J=6.3 Hz, 2H), 3.64 (s, 3H), 2.84 (t, J=6.3 Hz, 2H), 1.82–1.91 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3, 151.1 (ArCH), 149.0 (ArCH), 138.6 (ArCH), 132.8, 130.5, 128.3, 122.9 (ArCH), 113.6, 107.0 (ArCH), 51.0 (CH_3), 44.8 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 20.8 (CH_2). FTIR (KBr, cm^{-1}): 1699 (C=O). LC–MS: $[M+H]^+$, m/z 257 (t_R=4.0 min). Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29%; H, 6.29%; N, 10.93%, found C, 70.05%; H, 6.23%; N, 10.75%.

3.5.11. 3-(4-Pyridinyl)-5,6,7,8-tetrahydroindolizine-1,2-dicarboxylic acid dimethyl ester ***4j***. Yield 119 mg (63%), white solid, mp 139 °C, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.64 (d, J=4.8 Hz, 2H), 7.38 (dd, J=4.8 Hz and 1.8 Hz, 2H), 3.82 (t, J=6.0 Hz, 2H), 3.70 (s, 3H), 3.60 (s, 3H), 2.98 (t, J=5.7 Hz, 2H), 1.78–1.84 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 165.6, 163.8, 149.6 (ArCH), 137.5, 137.1, 129.9, 124.3 (ArCH), 116.2, 109.5, 51.7 (CH_3), 51.0 (CH_3), 44.6 (CH_2), 23.3 (CH_2), 22.3 (CH_2), 18.9 (CH_2). FTIR (KBr, cm^{-1}): 1703 (C=O). LC–MS: $[M+H]^+$, m/z 315 (t_R=3.7 min). Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96%; H, 5.77%; N, 8.91%, found C, 64.64%; H, 5.54%; N, 8.79%.

3.5.12. 3-(4-Pyridinyl)-5,6,7,8-tetrahydroindolizine-1-carboxylic acid methyl ester and 3-(4-pyridinyl)-5,6,7,8-tetrahydroindolizine-2-carboxylic acid methyl ester ***4k***. Yield 108 mg (70%, ~1:1 mixture of regioisomers), white solid, R_f=0.1 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1-carboxylic acid 8.59 (d, J=4.2 Hz, 2H), 7.27–7.30 (m, overlapping 2H), 6.80 (s, 1H), 4.02 (t, J=5.7 Hz, 2H), 3.81 (s, 3H), 3.18 (t, J=5.7 Hz, 2H), 1.83–1.93 (m, overlapping 4H); 2-carboxylic acid 8.66 (d, J=5.7 Hz, 2H), 7.27–7.30 (m, overlapping 2H), 6.38 (t, J=0.9 Hz, 1H), 3.68 (t, J=5.7 Hz, 2H), 3.64 (s, 3H), 2.83 (t, J=5.7 Hz, 2H), 1.83–1.93 (m, overlapping 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 1-carboxylic acid 165.5, 150.0 (ArCH), 139.9, 139.6, 130.2, 122.4 (ArCH), 111.9 (ArCH), 111.5, 51.0 (CH_3), 45.8 (CH_2), 24.3 (CH_2), 23.4 (CH_2), 19.8 (CH_2); 2-carboxylic acid 165.2, 149.5 (ArCH), 140.2, 133.3, 130.8, 125.6 (ArCH), 113.4, 107.2 (ArCH), 51.0 (CH_3), 44.9 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 20.8 (CH_2). FTIR (KBr, cm^{-1}): 1684 (C=O). LC–MS: $[M+H]^+$, m/z 257 (t_R=3.6 min). Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29%; H, 6.29%; N, 10.93%, found C, 70.11%; H, 6.17%; N, 11.04%.

3.5.13. 1-Methyl-2-(3-pyridinyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester ***4l***. Yield 56 mg (34%, purity ~95%), off-white solid, mp 113–114 °C, R_f=0.1 (EtOAc–*n*-hexane 7:3). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.63 (dd, J=4.8 Hz and 1.2 Hz, 1H), 8.58 (d, J=2.4 Hz, 1H), 7.86 (ddd, J=8.4 Hz, 2.1 Hz, and 0.6 Hz, 1H), 7.64 (s, 1H), 7.50 (dd, J=7.5 Hz and 4.8 Hz, 1H), 3.72 (s, 3H), 3.57 (s, 3H), 3.53 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.8, 163.2, 150.2 (ArCH), 149.5 (ArCH), 137.6 (ArCH), 132.9, 129.1 (ArCH), 125.9, 123.3 (ArCH), 115.5, 113.5, 51.5 (CH_3), 51.2 (CH_3), 35.0 (CH_3). FTIR (KBr, cm^{-1}): 1717, 1698 (C=O). LC–MS: $[M+H]^+$, m/z 275

(t_R=3.0 min). HRMS $[M+H]^+$ found 275.1019, $C_{14}H_{15}N_2O_4$ requires 275.1032.

3.5.14. 1-Methyl-2-(4-pyridinyl)-1H-pyrrole-3,4-dicarboxylic acid dimethyl ester ***4m****.* Yield 35 mg (21%, purity ~95%), off-white solid, mp 158 °C, R_f=0.05 (EtOAc–*n*-hexane 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.69 (d, J=5.7 Hz, 2H), 7.28–7.30 (m, overlapping 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 163.8, 150.0 (ArCH), 138.4, 133.7, 128.9 (ArCH), 124.8 (ArCH), 116.8, 115.3, 52.1 (CH_3), 51.7 (CH_3), 35.6 (CH_3). FTIR (KBr, cm^{-1}): 1713 (C=O). LC–MS: $[M+H]^+$, m/z 275 (t_R=2.4 min). HRMS $[M+H]^+$ found 275.1025, $C_{14}H_{15}N_2O_4$ requires 275.1032.

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Supplementary data

Characterization data of the intermediates, and ^{1}H and ^{13}C NMR spectra of the products. The supplementary data associated with this article can be found in the on-line version at doi:10.1016/j.tet.2009.09.094.

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