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Straightforward synthesis of pyrrolizidines

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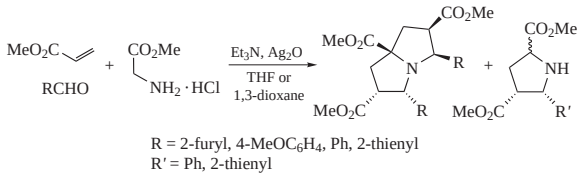
A one-pot synthesis of new multi-functional pyrrolizidines from simple starting compounds was carried out by a double 1,3-dipolar cycloaddition protocol.

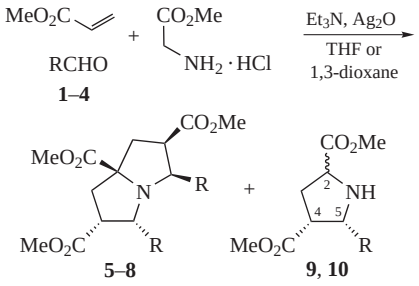


Pyrrolizidine alkaloids manifest a specific spectrum of biological activity (hepatotoxic and mutagenic properties, toxic and genotoxic effects).[1] Some of them are used for the treatment of bacterial and viral infections, cancer, and as glycosidase inhibitors.[2]

The syntheses of pyrrolizidine (1-azabicyclo[3.3.0]octane) derivatives are diverse[3] and involve side functionalization of proline derivatives followed by intramolecular ring closure.[4] Among them, reactions of 1,3-dipolar cycloaddition of nitrones[5] and prolinate-derived azomethine ylides[6] are the most important. 1,3-Dipolar cycloaddition of azomethine ylides to activated multiple bonds is also used in the synthesis of pyrrolidines.[7] The *in situ* generated pyrrolidines were subjected to subsequent condensations towards pyrrolizidines.[8,9]

The purpose of this work was to develop a direct synthesis of new pyrrolizidines by the 'double' 1,3-dipolar cycloaddition of azomethine ylides and dipolarophiles using a twofold or greater excess of the aldehyde component. Methyl glycinate hydrochloride, methyl acrylate and aldehydes **1**–**4** were used in the reactions under typical coupling conditions, and Ag_2O was used as the activator (Scheme 1).

The cycloaddition reactions were carried out with a twofold molar excess of the aldehyde and methyl acrylate with respect to the amine with the aid of 0.1 equiv. Ag_2O. As expected, the reaction proceeded smoothly in the case of furfural at 20 °C in THF solution to give pyrrolizidine **5** in 65% yield.† Similarly, the reaction starting from anisic aldehyde **2** in dioxane gave adduct **6** in 59% yield. In both experiments, no corresponding intermediate pyrrolidines were detected. Benzaldehyde **3** and



1, **5** R = 2-furyl
2, **6** R = 4-MeOC$_6$H$_4$
3, **7**, **9** R = Ph
4, **8**, **10** R = 2-thienyl

Scheme 1

† NMR spectra were recorded on a Bruker AVANCE-500 spectrometer (500.13 MHz) using TMS as the internal standard. IR spectra were recorded on an IR Prestige-21 Fourier Transform Shimadzu spectrophotometer from samples prepared as thin films or dispersed in Nujol. Mass spectra were recorded on an LCMS-2010EV mass spectrometer (Shimadzu) (sample solution in chloroform–acetonitrile were injected by a syringe at a flow rate of 0.1 ml min^{-1}; eluent, acetonitrile–water, 95 : 5) in the register mode of positive ions when the ionizing potential of the needle electrode was 4.5 kV. The temperature of capillary interface was 250 °C, the voltage of capillary interface was 5 V. Flow rate of atomizing gas (nitrogen) was 1.5 dm^3 min^{-1} for chemical ionization at atmospheric pressure. The reaction course was monitored by TLC on 'Sorbfil' plates (Russia) with visualization of compounds in the ethanol solution of anisaldehyde acidified with sulfuric acid with subsequent heating at 120–150 °C. The products were isolated by column chromatography on silica gel (30–60 g of adsorbent per 1 g of compound); freshly distilled solvents were used as eluents.

Pyrrolizidines **5**–**8** *(general procedure)*. Triethylamine (0.75 ml, 5.4 mmol) was added to a solution of glycine methyl ester hydrochloride (0.29 g, 2.32 mmol) in THF or 1,3-dioxane (30 ml). The mixture was stirred for 30 min, then the appropriate aldehyde **1**–**4** (4.64 mmol) was added. The reaction mixture was stirred for 30 min, then methyl acrylate (0.42 ml, 4.64 mmol) and Ag_2O (0.054 g, 0.23 mmol) were added. The stirring was continued for 24 to 48 h at room temperature or under reflux. The mixture was filtered through silica gel and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a column with SiO_2 using EtOAc–light petroleum (1 : 10, then 1 : 5, 1 : 3) as the eluent.

*Trimethyl (2*R**,3*S**,5*S**,6*R**)-3,5-di(2-furyl)tetrahydro-1*H*-pyrrolizine-2,6,7a(5*H*)-tricarboxylate* **5**. The double cycloaddition reaction was conducted in THF at 20 °C for 24 h, yield 65%, oil. IR (ν_{max}/cm^{-1}): 2996, 2952, 2845, 1739, 1735, 1733, 1456, 1436, 1370, 1337, 1293, 1259, 1202, 1178, 1150, 1097, 1066, 1029, 1011, 920, 736, 600. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 2.31 (dd, 1H, CH_2, *J* 7.8, 13.6 Hz), 2.92 (dd, 1H, CH_2, *J* 8.4, 13.5 Hz), 2.42 (dd, 1H, CH_2, *J* 6.4, 12.9 Hz), 2.64 (t, 1H, CH_2, *J* 13.0 Hz), 3.33 (q, 1H, H^2, *J* 8.0 Hz), 3.67–3.71 (m, 1H, H^6), 3.39 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.75 (s, 3H, OMe), 4.17 (d, 1H, H^3, *J* 7.7 Hz), 4.84 (d, 1H, H^5, *J* 8.1 Hz), 6.18 (s, 1H, =CH$_{furyl}$), 6.19 (d, 1H, =CH$_{furyl}$, *J* 1.7 Hz), 6.24 (d, 1H, =CH$_{furyl}$, *J* 3.2 Hz), 6.30 (dd, 1H, =CH$_{furyl}$, *J* 1.8, 3.1 Hz), 7.19 (s, 1H, =CH$_{furyl}$), 7.39 (s, 1H, =CH$_{furyl}$). ^{13}C NMR (125.47 MHz, $CDCl_3$) δ: 36.23, 38.56 (CH_2), 49.00, 49.03 (C^2, C^6), 51.57, 51.63, 52.89 (OMe), 60.09, 60.82 (C^5, C^3), 76.00 (C^{7a}), 106.87, 110.04, 110.21, 111.57 (C$^3_{furyl}$, C$^4_{furyl}$), 141.50, 142.99 (C$^5_{furyl}$), 151.57, 154.33 (C$^2_{furyl}$), 171.04, 171.55 and 176.59 (*C*O$_2$Me). MS (EI), *m*/*z* (%): 418 [M + H]$^+$ (100).

thiophene-2-carbaldehyde **4** turned out to be less reactive giving pyrrolizidines **7** and **8** in 30–35% yields. Simultaneously, the corresponding pyrrolidines **9** and **10** were isolated in 35–40% yields (see Scheme 1).

Structures of products **5**–**8** were confirmed by spectral data. NOE data were recorded for compound **5** (Figure 1), and X-ray single crystal diffraction data were obtained for adduct **6** (Figure 2).‡

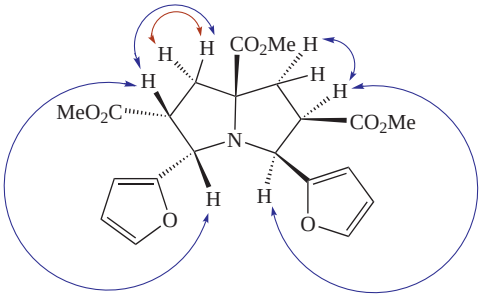


Figure 1 Characteristic NOE-coupling in pyrrolizidine **5**.

*Trimethyl (2*R*,*3*S*,*5*S*,*6*R*)-3,5-bis(4-methoxyphenyl)tetrahydro-1*H*-pyrrolizine-2,6,7a(5*H*)-tricarboxylate* **6** was obtained by keeping the mixture of anisic aldehyde, methyl acrylate and glycine methyl ester in dioxane for 48 h. Yield 59%, mp 142–144 °C (EtOAc–light petroleum, 1:5). IR (ν_{max}/cm^{-1}): 2952, 2917, 2852, 1737, 1612, 1514, 1464, 1455, 1435, 1377, 1297, 1288, 1260, 1252, 1238, 1202, 1175, 1165, 1138, 1064, 1029, 820. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 2.19 (dd, 1H, CH_2, J 7.6, 13.2 Hz), 3.03 (d, 1H, CH_2, J 13.2 Hz), 2.38 (dd, 1H, CH_2, J 6.6, 13.1 Hz), 2.53 (t, 1H, CH_2, J 13.2 Hz), 3.08 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.39 (t, 1H, H^2, J 7.5 Hz), 3.74 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.95 (m, 1H, H^6), 4.31 (d, 1H, H^3, J 7.8 Hz), 4.67 (d, 1H, H^5, J 8.8 Hz), 6.72 (d, 2H, H_{Ar}, J 8.6 Hz), 6.73 (d, 2H, H_{Ar}, J 8.3 Hz), 6.88 (d, 2H, H_{Ar}, J 8.4 Hz), 7.12 (d, 2H, H_{Ar}, J 8.5 Hz). ^{13}C NMR (125.47 MHz, $CDCl_3$) δ: 38.60, 39.44 (CH_2), 51.09, 51.32 (C^2, C^6), 52.04, 52.25, 55.11 (CO_2*Me*), 53.46 (OMe), 64.18, 65.13 (C^5, C^3), 71.08 (C^{7a}), 113.12, 113.28, 128.22, 130.24 (C^2_{Ar}, C^6_{Ar}), 128.84, 132.52 (C^1_{Ar}), 158.52, 158.91 (C^4_{Ar}), 171.91, 172.92, 177.54 (*C*O_2Me). MS (EI), *m*/*z* (%): 498 [M + H]$^+$ (100).

*Trimethyl (2*R*,*3*S*,*5*S*,*6*R*)-3,5-diphenyltetrahydro-1*H*-pyrrolizine-2,6,7a(5*H*)-tricarboxylate* **7** was prepared from benzaldehyde, glycine methyl ester and methyl acrylate along with pyrrolidine **9**, and was isolated by column chromatography on SiO_2 (EtOAc–light petroleum, 1:10). Yield 30%, mp 102–103 °C (EtOAc–light petroleum, 1:5). IR (ν_{max}/cm^{-1}): 2952, 2851, 2727, 1735, 1729, 1718, 1464, 1456, 1447, 1436, 1377, 1320, 1304, 1248, 1237, 1217, 1209, 1194, 1175, 1148, 1098, 1078, 1037, 1027, 764, 746, 705. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 2.23 (dd, 1H, CH_2, J 7.6, 13.3 Hz), 2.57 (t, 1H, CH_2, J 13.2 Hz), 2.41 (dd, 1H, CH_2, J 6.7, 13.2 Hz), 3.06 (d, 1H, CH_2, J 12.9 Hz), 3.02 (s, 3H, OMe), 3.18 (s, 3H, OMe), 3.44 (dt, 1H, H^2, J 1.3, 7.8 Hz), 3.85 (s, 3H, OMe), 3.99 (ddd, 1H, H^6, J 6.3, 8.7, 13.1 Hz), 4.37 (d, 1H, H^3, J 7.8 Hz), 4.75 (d, 1H, H^5, J 8.7 Hz), 7.19 (m, 10H, Ph). ^{13}C NMR (125.47 MHz, $CDCl_3$) δ: 38.53, 39.48 (CH_2), 50.94, 51.20 (C^2, C^6), 52.15, 52.21, 53.51 (OMe), 64.72, 65.62 (C^5, C^3), 76.74 (C^{7a}), 126.86, 127.06, 127.69, 127.91, 127.93, 129.04, 136.76, 140.44 (Ph), 171.77, 172.72, 177.44 (*C*O_2Me). MS (EI), *m*/*z* (%): 438 [M + H]$^+$ (48).

*Trimethyl (2*R*,*3*S*,*5*S*,*6*R*)-3,5-di(2-thienyl)tetrahydro-1*H*-pyrrolizine-2,6,7a(5*H*)-tricarboxylate* **8**. Yield 30%, oil. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 2.22 (dd, 1H, CH_2, J 7.0, 13.0 Hz), 3.0 (m, 1H, CH_2), 2.48 (t, 1H, CH_2, J 13.2 Hz), 2.69 (ddd, 1H, CH_2, J 7.7, 13.3 Hz), 3.25 (s, 3H, OMe), 3.29 (m, 1H, H^2), 3.36 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.95 (m, 1H, H^6), 4.59 (d, 1H, H^3, J 7.9 Hz), 5.16 (d, 1H, H^5, J 7.9 Hz), 6.78 (d, 1H, =CH, J 7.0 Hz), 6.89 (m, 2H, =CH), 7.09 (d, 1H, =CH, J 4.4 Hz), 7.17 (d, 1H, =CH, J 4.8 Hz), 7.25 (t, 1H, =CH, J 4.9 Hz). ^{13}C NMR (125.47 MHz, $CDCl_3$) δ: 37.78, 38.76 (CH_2), 49.43, 51.24 (C^2, C^6), 51.40, 51.58, 52.73 (OMe), 60.66, 61.67 (C^5, C^3), 76.30 (C^{7a}), 124.06, 124.12, 125.82, 126.53 ($C^3_{thienyl}$, $C^4_{thienyl}$), 128.85 ($C^5_{thienyl}$), 139.93, 145.75 ($C^2_{thienyl}$), 171.28, 172.09, 176.56 (*C*O_2Me). MS (EI), *m*/*z* (%): 472 [M + Na]$^+$ (100), 450 [M + H]$^+$ (53).

*Dimethyl (2*RS,*4*R*,*5*S*)-5-phenylpyrrolidine-2,4-dicarboxylate* **9** was obtained in 40% yield. Oil, a mixture of diastereomers (~3:1, ^{1}H NMR), which were separated by column chromatography. IR (ν_{max}/cm^{-1}): 2952, 1738, 1734, 1454, 1436, 1376, 1269, 1246, 1205, 1171, 1033, 753, 702. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: major isomer: 2.24 (ddd, 1H, CH_2, J 4.3, 7.8, 13.4 Hz), 2.52 (br. s, 1H, NH), 2.68 (ddd, 1H, CH_2, J 5.7, 8.9, 13.5 Hz), 3.22 (s, 3H, OMe), 3.31 (q, 1H, H^4, J 7.8 Hz), 3.76 (s, 3H, OMe), 4.29 (dd, 1H, H^2, J 4.3, 8.8 Hz), 4.73 (d, 1H, H^5, J 7.8 Hz), 7.24 (m, 5H, Ph); minor isomer: 2.24 (t, 2H, CH_2, J 7.1 Hz), 3.02 (br. s, 1H, NH), 3.15 (s, 3H, OMe), 3.27 (t, 1H, H^4, J 7.3 Hz), 3.75 (s, 3H, OMe), 3.93 (t, 1H, H^2, J 8.1 Hz), 4.48 (d, 1H, H^5, J 7.7 Hz), 7.26 (m, 5H, Ph). ^{13}C NMR (125.47 MHz, $CDCl_3$) δ: major isomer: 32.06 (CH_2), 49.37 (C^4), 51.26, 52.28 (OMe), 59.20, 64.46 (C^5, C^2), 126.90, 127.53, 128.07, 139.89 (Ph), 172.88, 175.70 (*C*O_2Me); minor isomer: 33.18 (CH_2), 49.58 (C^4), 51.17, 52.25 (OMe), 59.67, 65.63 (C^5, C^2), 126.65, 127.59, 128.15, 138.76 (Ph), 172.92, 173.61 (*C*O_2Me). MS (EI), *m*/*z* (%): 264 [M + H]$^+$ (100).

*Dimethyl (2*RS,*4*R*,*5*S*)-5-(2-thienyl)pyrrolidine-2,4-dicarboxylate* **10**. Yield 35%, oil, a mixture of diastereomers (~4:1, ^{1}H NMR). IR (ν_{max}/cm^{-1}): 3345, 3104, 2996, 2952, 2848, 1728, 1716, 1610, 1459, 1434, 1376, 1304, 1203, 1172, 1082, 1038, 964, 852, 833, 706. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: major isomer: 2.22 (ddd, 1H, CH_2, J 4.0, 7.7, 13.4 Hz), 2.71 (ddd, 1H, CH_2, J 7.2, 9.0, 13.5 Hz), 2.81 (br. s, 1H, NH), 3.30 (q, 1H, H^4, J 7.5 Hz), 3.42 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.25 (dd, 1H, H^2, J 4.0, 9.0 Hz), 5.03 (d, 1H, H^5, J 7.7 Hz), 6.87 (d, 1H, =CH, J 3.5 Hz), 6.91 (dd, 1H, =CH, J 3.5, 5.0 Hz), 7.18 (dd, 1H, =CH, J 1.1, 5.0 Hz); minor isomer: 2.38 (m, 2H, CH_2, J 5.3, 7.5, 13.1 Hz), 2.80 (br. s, 1H, NH), 3.29 (q, 1H, H^4, J 7.4 Hz), 3.34 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.93 (t, 1H, H^2, J 8.1 Hz), 4.73 (d, 1H, H^5, J 7.5 Hz), 6.89 (dd, 1H, =CH, J 3.7, 5.0 Hz), 6.94 (d, 1H, =CH, J 3.5 Hz), 7.15 (dd, 1H, =CH, J 1.0, 5.0 Hz). ^{13}C NMR (125.47 MHz, $CDCl_3$) δ: major isomer: 31.36 (CH_2), 49.38 (C^4), 51.61, 52.24 (OMe), 58.63, 59.98 (C^5, C^2), 124.17, 124.38, 126.51 (C^3, C^4, C^5 thienyl), 144.47 ($C^2_{thienyl}$), 172.09, 175.35 (*C*O_2Me); minor isomer: 32.40 (CH_2), 49.81 (C^4), 51.49, 52.24 (OMe), 59.40, 62.79 (C^5, C^2), 124.47, 124.55, 126.60 (C^3, C^4, C^5 thienyl), 143.21 ($C^2_{thienyl}$), 172.28, 173.50 (*C*O_2Me). MS (EI), *m*/*z* (%): 270 [M + H]$^+$ (100).

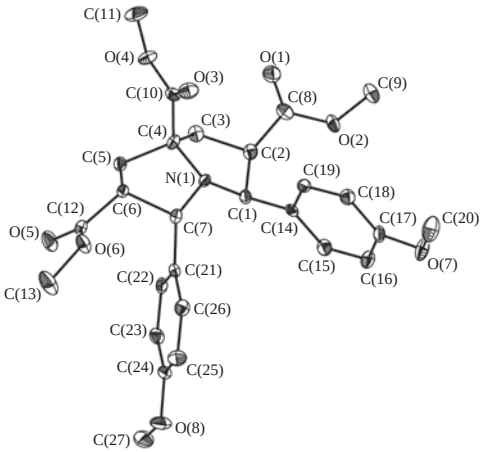
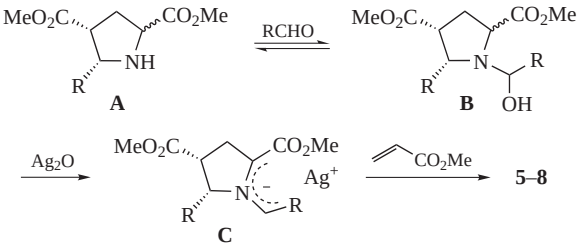


Figure 2 X-ray structure of adduct **6**.

‡ *Crystallographic data for* **6**: crystals of $C_{54}H_{62}N_2O_{16}$ (M = 995.05) are monoclinic, space group $P2_1$ (no. 4) at 120(2) K: a = 10.8153(15), b = 6.3799(9) and c = 17.985(3) Å, β = 91.439(4)°, V = 1240.6(3) Å^3, Z = 1, d_{calc} = 1.332 g cm^{-3}, μ(MoKα) = 0.098 mm^{-1}, F(000) = 528. Total of 18711 reflections were measured (6° ⩽ 2θ ⩽ 60°) and 6015 independent reflections (R_{int} = 0.0952) were used in all calculations. The refinement converged to wR_2 = 0.1046 and GOF = 0.979 for all independent reflections [R_1 = 0.0542 was calculated against F for 3991 observed reflections with $I > 2\sigma(I)$]. The measurements were made on a Bruker SMART APEX2 CCD diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXL[10] using a full-matrix least-squares procedure based on F_{hkl}. The hydrogen atom positions were fixed geometrically at calculated distances and allowed them to ride on the parent atoms.

CCDC 1524732 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 2

The possible pathways for formation of compounds **5**–**8** are rather obvious under the assumption that pyrrolidines **A** are initially formed (Scheme 2). They would react with the second molecule of the aldehyde to give aminals **B**. Under the action of Ag_2O, the latter generate ylide **C** which reacts with the dipolarophile.

In conclusion, we have developed a simple one-pot syntheses of symmetric racemic pyrrolizidines from simple starting compounds.

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