A New Approach to the Synthesis of Pyrrolizines: A One-pot Procedure from 2*H*-Pyrroles

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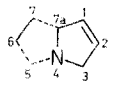
A convenient method for synthesis of the pyrrolizine nucleus is reported. The pyrrolizines were obtained through 1,3-dipolar cycloaddition on azomethine ylids **4** generated in situ from 2H-pyrroles. The new adducts were characterized by ^{1}H- and ^{13}C-N.M.R. data as well as mass spectrometry.

Pyrrolizines are part of a wide family of natural products and useful intermediates for the total synthesis of more complex compounds such as mitomycins[1]. The most important general methods for preparing the pyrrolizine nucleus start from pyrrole derivatives and can be classified into two main groups, according to the number of bonds newly formed. Methods implying one-bond formation by intramolecular cyclization of mono- or di-substituted pyrroles carrying adequate functions constitute the first group. Techniques in which two bonds are formed successively or simultaneously are placed together in the second group of methods.

In this work, we propose a new strategy for an approach to the synthesis of the pyrrolizine nucleus **1**, involving the formation of three new bonds (N–C-5, C-5–C-6 and C-7–C-7a).



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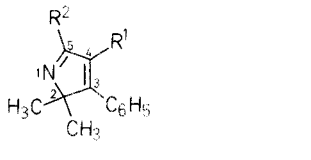
This strategy is based on a two-step reaction (but a "one-pot" process):

- nonstabilized azomethine ylids derived from 2*H*-pyrroles **2** are generated by the desilylation method; and
- cyclization is accomplished by 1,3-dipolar cycloaddition.

Thus, 2*H*-pyrroles **2a–c**[3,4] bearing different substituents at C-4 and C-5 positions were used. They were easily quaternarized by treatment with methyl(trimethylsilyl) triflate in dimethoxyethane (DME) at room temperature to give **3**.



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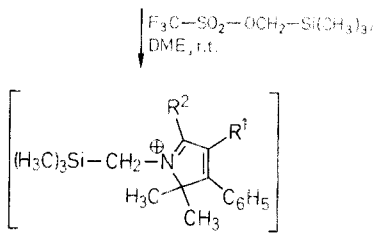

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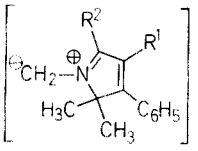

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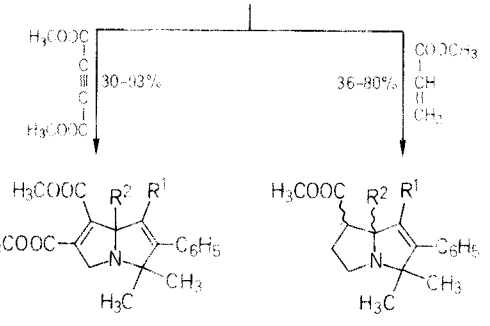
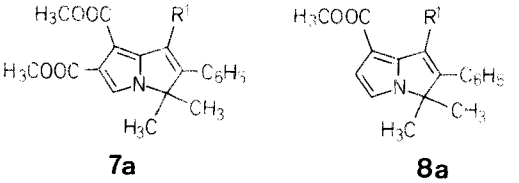


5 **6**



7a **8a**

2-8	R^1	R^2
a	C_2H_5	H
b	H	C_6H_5
c	$-(CH_2)_5-$	

Table. Compounds **5**, **6**, **7a** and **8a** Prepared

Product No.	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	I.R. (CH_2Cl_2) $\nu_{c=o}$[cm^{-1}]	^{1}H-N.M.R. (solvent/TMS) δ[ppm]	^{13}C-N.M.R. (solvent/TMS) δ[ppm]	M.S. *m/e* (rel. int., %)
5a	93[b]	–	$C_{21}H_{25}NO_4$ (355.4)	–	C_6D_6: 0.82 (t, 3H, J = 7 Hz, CH_2—C$\underline{H}_3$); 0.97 (s, 3H, CH_3); 1–10 (s, 3H, CH_3); 1.93 (q, 2H, J = 7 Hz, C$\underline{H}_2$—CH_3); 3.42 (s, 3H, OCH_3); 3.48 (s, 3H, OCH_3); 3.75 (dd, 1H, J = 16 Hz, 4 Hz, *endo*-CH—N); 4.17 (dd, 1H, J = 16 Hz, 4 Hz, *exo*-CH—N); 5.38 (dd, 1H, J = 4 Hz, 4 Hz, 7a–H); 7.2–7.5 (m, 5H, C_6H_5)		
5.b[c]	30	–	$C_{25}H_{25}NO_4$ (403.5)	1720, 1735	C_6D_6: 1.13 (s, 3H, CH_3); 1.22 (s, 3H, CH_3); 3.33 (s, 3H, OCH_3); 3.41 (s, 3H, OCH_3); 4.05 (br.s, 2H, CH_2—N); 6.48 (s, 1H, =CH); 7.0–7.5 (m, 8H_{arom}); 7.5–7.9 (m, 2H, conjugated H_{ortho})	C_6D_6: 23.0 (q, *endo*-CH_3); 30.9 (q, *exo*-CH_3); 51.5 (q, OCH_3); 51.6 (q, OCH_3); 53.5 (t, CH_2—N); 70.9 (s, 3-C); 87.7 (s, 7a-C); 120.6 (d, 1-C); 127.2 (d, C_p); 127.9 (d, C_p); 128.0, 128.1, 128.2, 128.3 (4d, $C_o + C_m$)[d], 135.0, 137.6, 143.8, 144.4, 151.2 (5s, 2-C, 6-C, 7-C + 2 C_q); 163.9 (s, CO); 164.4 (s, CO)	
5c	48	125–127° (hexane)	$C_{24}H_{29}NO_4$ (395.5)	1715, 1730	$CDCl_3$: 1.02 (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 0.8–2.2 [m, 10H, —$(CH_2)_5$—]; 3.63 (d, 1H, J = 16 Hz, CH—N); 3.70 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 3.97 (d, 1H, J = 16 Hz, CH—N); 6.9–7.5 (m, 5H, C_6H_5)	$CDCl_3$: 21.4 (q, *endo*-CH_3); 30.1 (q, *exo*-CH_3); 23.7, 25.5, 30.7, 31.3, 35.1 [5t, —$(CH_2)_5$—]; 50.6 (t, CH_2—N); 51.9 (q, OCH_3); 52.2 (q, OCH_3); 70.3 (s, 3-C); 89.5 (s, 7a-C); 126.9 (d, C_p); 127.8 (d, C_m)[d]; 129.6 (d, C_o)[d]; 132.7, 135.7, 135.8, 150.6 (4s, 1-C, 6-C, 7-C, C_q); 146.9 (s, 2-C); 163.4 (s, CO); 166.8 (s, CO)	395 (M^+, 44); 380 (M—CH_3, 16); 363 (M—CH_3OH, 11); 351 (16); 347 (10); 336 (M—$COOCH_3$, 37); 335 (100); 319 (13)
6a[b]	80	–	$C_{19}H_{23}NO_2$ (297.4)	1730	CCl_4: 0.83 (t, 3H, J = 7 Hz, CH_2—C$\underline{H}_3$); 1.07 (t, 3H, J = 7 Hz, CH_2—C$\underline{H}_3$); 1.10 (s, 6H, 2 × CH_3); 1.2–1.9 (m, 2H, 6-H); 1.82 (q, 2H, J = 7 Hz, C$\underline{H}_2$—CH_3); 2.02 (q, 2H, J = 7 Hz, C$\underline{H}_2$—CH_3); 2.6–3.2 (m, 3H, 2 × 5-H + 7-H); 3.50 (s, 3H, OCH_3); 3.58 (s, 3H, OCH_3); 4.35 (d, 1Hm J = 10.5 Hz, 7a-H); 4.53 (d, 1H, J = 12 Hz, 7a-H); 6.7–7.4 (m, 5H, C_6H_5)		
6b	36	74–75° (hexane)	$C_{23}H_{25}NO_2$ (347.4)	1725	$CDCl_3$: 1.33 (s, 6H, 2 × CH_3); 1.0–2.4 (m, 2H, 6-H); 2.8–3.6 (m, 3H, 2 × 5−H + 7−H); 3.72 (s, 3H, OCH_3); 5.73 (s, 1H, 1−H); 6.9–7.8 (m, 10H_{arom})	$CDCl_3$: 23.4 (q, *endo*-CH_3); 29.9 (t, 6-C); 31.2 (q, *exo*-CH_3); 46.6 (t, 5-C); 51.4 (q, OCH_3); 56.3 (d, 7-C); 69.2 (s, 3-C); 83.8 (s, 7a-C); 125.5, 126.0, 127.0 (3d, 1-C + 2C_p); 127.7, 127.8, 127.9, 128.1 (4d, $C_o + C_m$)[d]; 136.2 (s, C_q of 2-C_6H_5); 149.1, 149.3 (2s, 2-C + C_q of 7a-C_6H_5); 173.8 (s, CO)	347 (M^+, 16); 346 (M—H, 13); 332 (M—CH_3, 42); 316 (M—OCH_3, 10); 262 (15); 261 (83); 260 (100)

6c[e]	24	–[e]	$C_{22}H_{29}NO_2$ (339.5)	1725	C_6D_6[f]: 22.4 (q, *endo*-CH_3); 31.8 (q, *exo*-CH_3); 24.8, 25.7, 30.9, 31.7, 32.2, 43.0 [6t, $-(CH_2)_5-$ + 6-C); 45.6 (t, 5-C); 50.7 (q, OCH_3); 55.7 (d, 7-C); 69.0 (s, 3-C); 85.9 (s, 7a-C); 126.8 (d, C_p); 128.0 (d, C_m)[d]; 130.0 (d, C_o)[d]; 137.2, 137.7 (2s, C_q + 1-C); 145.5 (s, 2-C); 174.1 (s, CO).	339 (M^+, 51); 338 (M—H, 20); 337 (M—H_2, 29); 325 (24); 324 (M—CH_3, 100); 297 (15); 296 (69); 295 (25); 266 (28)
7a	23	165–166[c] (hexane)	$C_{21}H_{23}NO_4$ (353.4)	1715	C_6D_6: 0.90 (s, 6H, 2 × CH_3); 1.05 (s, 3H, J = 7 Hz, CH_3); 2.47 (q, 2H, J = 7 Hz, CH_2); 3.60 (s, 3H, OCH_3); 3.68 (s, 3H, OCH_3); 6.7–7.3 (m, 6H, C_6H_5 + 5-H) $CDCl_3$: 14.3 (q, CH_3); 19.1 (t, CH_2); 26.1 (q, *gem*-CH_3)[d]; 51.3 (q, OCH_3); 51.4 (q, OCH_3); 66.9 (s, 3C); 106.1, 118.2, 132.8, 133.5, 141.3 (5s, 1-C, 6-C, 7-C, 7a-C, C_q); 119.3 (d, 5-C); 127.9 (d, C_p); 128.3 (d, C_m)[d]; 129.2 (d, C_o)[d]; 149.9 (s, 2-C); 164.2 (s, CO); 165.1 (s, CO)	353 (M^+, 100); 324 (M—C_2H_5, 22); 322 (M—OCH_3, 33); 321 (M—CH_3OH, 50); 306 (60)
8a	12	–	$C_{19}H_{21}NO_2$ (295.4)	1725	C_6D_6: 0.97 (s, 6H, CH_3); 1.25 (t, 3H, J = 7 Hz, CH_2—CH_3); 2.78 (q, 2H, J = 7 Hz, CH_2—CH_3); 3.57 (s, 3H, OCH_3); 6.47 (d, 1H, J = 3 Hz, 6-H); 6.9–7.3 (m, 6H, C_6H_5 + 5-H)	295 (M^+, 100); 280 (M—CH_3, 20); 267 (12); 266 (M—C_2H_5, 62); 264 (M—OCH_3, 11); 248 (10); 236 (M—$COOCH_3$, 12)

[a] Satisfactory microanalyses obtained: C ± 0.39, H ± 0.15, N ± 0.35.
[b] Crude yield.
[c] Contaminated with 10% of the starting material.
[d] Signals with double intensity.
[e] Diastereomeric mixture (85/15, based on methyl signals in the ^{1}H-N.M.R. spectrum).
[f] Major isomer.

Reaction of **3** with cesium fluoride in the presence of dimethyl acetylenedicarboxylate (DMAD) allowed the trapping of the azomethine ylid intermediate **4** to yield dihydropyrrolizine **5a–c**. During the purification step, **5a** (R^2 = H) was transformed into 3*H*-pyrrolizine **7a**.

To show the regiochemistry of the 1,3-dipolar cycloaddition, we used methylacrylate as dipolarophile: only regioisomers **6a–c** were obtained from reaction with ylids **4**. If R^2 was a phenyl group, we observed the exclusive formation of isomer **6b**, in which R^2 and carboxylate are *trans* to each other. However, for **6a** and **6c**, a mixture of *trans* and *cis* isomers was formed, with *trans* isomer as the major product. As observed for **5a**, **6a** (R^2 = H) was transformed into 3H-pyrrolizine **8a** during the purification step.

Good yields of crude products were generally obtained (40–95%). Due to the poor stability of the products, yields of purified samples were lower. However, no by-product formation was observed except in the case of **6b**.

The new approach to the synthesis of the pyrrolizine nucleus described herein presents two important features:
- it is a "one-pot" procedure; and
- the desired pyrrolizine structure is reached irrespective of the kind of substitution in the starting material.

Melting points were determined on a BUCHI apparatus and are uncorrected. I. R. spectra were obtained with a PERKIN-ELMER 297 spectrophotometer. ^{1}H- and ^{13}C-N.M.R. spectra were determined with Varian spectrometers EM-360 and XL-100, respectively. Mass spectra were recorded on Varian MAT CH5 apparatus working with an ionizing energy of 70 eV.

Preparative T.L.C. were performed on Kieselgel 60F_{254} (2 mm) (Merck) or Alumina 150F_{254} (1.5 mm) (Merck) plates using mixtures of hexane and diethylether as eluents.

1-Ethyl-3,3-dimethyl-6,7-bismethoxycarbonyl-2-phenyl-5,7a-dihydro-3*H*-pyrrolizine (5a); Typical Procedure:

A solution of methyl (trimethylsilyl)triflate (320 µl, 1.6 mmol) in dimethoxyethane (5 ml) is added to a solution of 2*H*-pyrrole (**2a**[4]; 291 mg, 1.5 mmol) in dimethoxyethane (25 ml) under nitrogen. The mixture is stirred at room temperature for 23 h. Dimethyl acetylenedicarboxylate (230 mg, 1.6 mmol) dissolved in dimethoxyethane is then added followed by dry cesium fluoride (292 mg, 2.0 mmol) and the stirring is continued at room temperature for 18 h. After evaporation of solvent under reduced pressure, the mixture is diluted with water (10 ml) and extracted with ether (4 × 50 ml). The combined ether layer is dried with magnesium sulfate and concentrated under reduced pressure to give crude **5a**; yield: 492 mg (93%). The products **5b, c, 6a–c** and **8a** are prepared in the same way, except that methyl acrylate is used as the dienophile in the cases of **6a–c** and **8a**. The products are purified as given below.

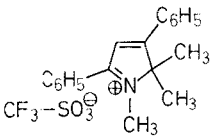
5b: Upon workup the compound is purified by preparative T.L.C. on neutral alumina using a 1:1 mixture of hexane and ether as the eluent. This gives a 3:1 mixture of **5b** and the starting material **2b**[3]. Other attempts to separate **5b** and **2b** led to decomposition of **5b**. ^{1}H-N.M.R. spectra of the crude mixture and that obtained after T.L.C. are very similar.

5c: Recrystallization from hexane yielded pure product.

6a and **8a**: ^{1}H-N.M.R. spectrum of the crude mixture from the preparation of **6a** showed that it is a mixture of *cis*- and *trans*-**6a** and traces of the 3*H*-pyrrolizine **8a**, based on the doublet signal of 7a-H at δ = 4.53 (J = 12 Hz) and 4.35 ppm (J = 10.5 Hz) and singlet signals for methoxy group at δ = 3.50 and 3.58 ppm. The crude mixture showed I. R. absorption for the carbonyl of the ester group at 1730 cm^{-1}. No Bohlmann band (2600–2800 cm^{-1}) is observed indicating that isomers **6a** are both *cis* fused ring isomers. Preparative T.L.C. of the crude mixture on neutral alumina using

hexane/ether as eluent gives a mixture of **6a** and **8a**, which is rechromatographed (T.L.C. on silica gel, ether) to yield pure unstable **8a**.

6b: The reaction mixture is extracted with dichloromethane (4 × 50 ml) and the solvent evaporated. The ^{1}H-N.M.R. spectrum of the crude product showed it to be a mixture of a single diastereoisomer **6b**, starting material **2b** and its *N*-methyl triflate derivative. The latter is insoluble in ether and separated by simple filtration (25%).



2b · $F_3C-SO_3CH_3$

N-Methyl Triflate of **2b**:
I.R. ($CHCl_3$): ν = 1615 (C=N), 1270 (SO), 1160 (CF_3) cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.78 (s, 6H, 2 × CH_3); 3.70 (s, 3H, N—CH_3); 7.27 (s, 1H, 4-H); 7.4–8.2 ppm (m, 10 H_{arom}).

The ether soluble portion is subjected to preparative T.L.C. on silica gel using ether as eluent to separate the starting material **2b** (20%) from **6b**, which is recrystallized from hexane twice.

6c: Purified by preparative T.L.C. on neutral alumina using hexane/ether (1/1) as eluent. ^{1}H-N.M.R. spectrum (Table) shows it to be a diastereoisomeric mixture (85/15 based on methyl signals).

7a: Recrystallization of **5a** from hexane thrice gives **7a**.

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