1,3-Dipolar Cycloadditions of Azomethine Ylides with Dipolarophiles. II. Synthesis of Pyrrolizidines

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Received April 1, 1988

Substituted pyrrolizidines have been synthesized by 1,3-dipolar cycloaddition of various dipolarophiles with the azomethine ylide generated by treatment of proline with benzaldehyde in dimethylsulfoxide. The regio- and stereochemical outcome of the reaction as well as the stability of the isomers obtained are discussed.

J. Heterocyclic Chem., **25**, 1665 (1988).

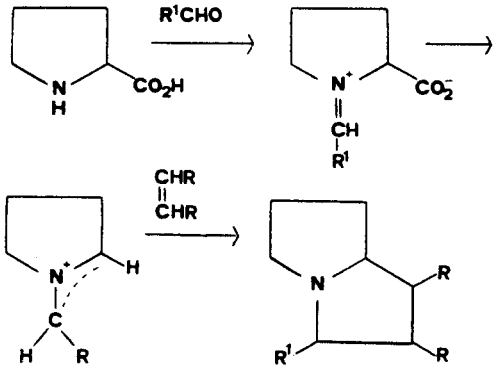
1,3-Dipolar cycloadditions represent a good method for the synthesis of five-membered rings. Since the pyrrolizidine ring occurs widely in many natural compounds such as alkaloids, azomethine ylides have received growing attention in recent years [1a-1b].

In a preceding paper [2a] we reported the synthesis of 1-oxapyrrolizidines by cycloaddition of azomethine ylides with carbonyl compounds.

To develop a more versatile method for forming five-membered heterocyclic rings under mild conditions we also tested the dipolar cycloaddition reaction of azomethine ylides with ethylenic and acetylenic dipolarophiles, and preliminary results have already been reported [2b].

The azomethine ylides were generated as previously described [1,2,3] by treatment of proline with benzaldehyde, *p*-nitrobenzaldehyde, 4-pyridinecarboxaldehyde and phenylglyoxal in dimethylsulfoxide.

Scheme 1



Results and Discussion.

When methyl acrylate, methyl fumarate and methyl maleate are used and reacted with the azomethine ylides, generated as mentioned above, pyrrolizidines were obtained in good yields. In most cases one stereoisomer is predominant (Figure 1).

Dimethyl acetylenedicarboxylate and methyl propiolate added quickly to the aminoacid affording unidentified high molecular weight compounds and leaving unreacted aldehyde [4].

When the reactivities of ethylenic and carbonyl dipolarophiles are comparable a variable amount of oxapyrrolizidine is obtained.

Due to the importance of heterocyclic 4-5 fused systems, the behaviour of (*S*)-(-)-2-azetidinecarboxylic acid was also investigated: The results are summarized in the Figure 2.

Elucidation of the structure and stereochemistry of adducts **1-7** was based on a) X-Ray diffraction analysis of **2a** (whose structure and stereochemistry is as depicted below, b) correlation of spectroscopic data, and c) thermodynamic stability tests.

The molecular structure of compound **2a**, as derived from the X-ray analysis, is shown in Figure 3. The stereochemistry of **2a** is clearly evident from the figure: the H atom at C-4 and the phenyl substituent at C-3 are on the same side of the plane through the atoms of the proline ring, while the two $COOCH_3$ groups lie on the other side. The junction between the five-membered rings is *cis*, the torsion angles C(3)-N(1)-C(4)-C(1) and C(7)-N(1)-C(4)-C(5) being 3.4(2)° and 2.1(2)° respectively. Both rings exhibit

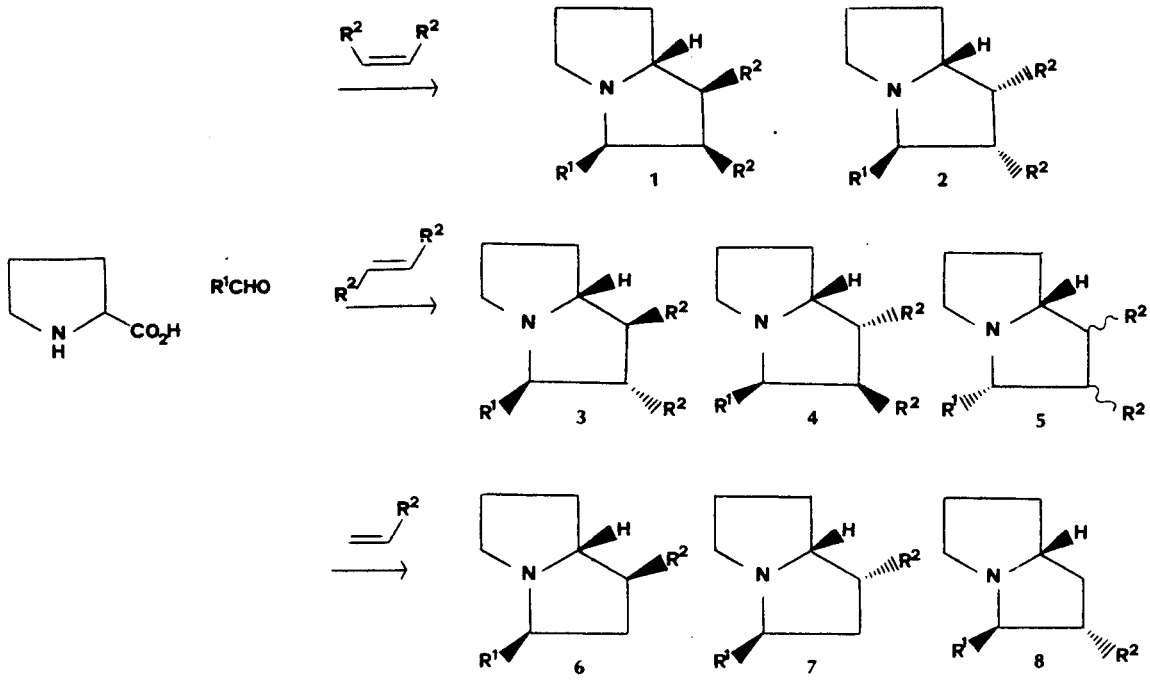


Figure 1 R^2 = COOMe

a) R^1 = Phenyl
b) R^1 = *p*-NO_2Phenyl
c) R^1 = 4-Pyridyl
d) R^1 = Benzoyl

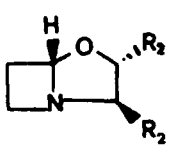
an envelope conformation; the puckering parameters [5] for the proline ring are q_2 = 0.380(2) Å and ϕ_5 = -3.4(3)°; for the other ring the puckering amplitute q_2 amounts to 0.399(2) Å and the phase angle ϕ_2 is -3.7(3)°.

The conformation around the bonds C(1)-C(2) and C(2)-C(3) is closer to a staggered than to an eclipsed conformation; the average torsion angle involving the closest substituents at C(1) and C(2) is 38.6(6)° and the same average torsion angle around the C(2)-C(3) bond is 44.1(7)°. There are no unusual bond distances and angles for a compound of this type; the closest intermolecular contact is between O(1) and H(11)B (at 1/2-x, 1/2+y, 1/2-z), the distance being 2.50(3) Å.

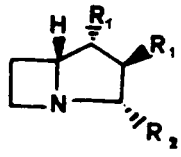
Due to the presence of a bridged nitrogen atom, the junction of the two five-membered rings is not necessarily the same in solution and in the solid state. To define this point, the one-bond ^{13}C-H coupling constants have been evaluated for C-3 and C-8, as it is well-known their dependence on the relative geometry between the nitrogen lone-pair and the vicinal proton [6,7]. The observed value of 149 Hz and 137 Hz are consistent with a synperiplanar arrangement for H-8 and an antiperiplanar arrangement for H-3. This allows assignment of the stereochemistry at C-3 and C-8. The absence of Bohlmann bands [8] in the ir spectrum (chloroform solution) is also in agreement with a *cis* junction between the two rings. As it is well-known the shielding effect of the phenyl group on syn-vicinal hydrogens [9a,b,c], the stereochemistry at C-2 is therefore determined.

On the other hand the phenyl group has a deshielding effect on 1,3 syn-hydrogens while the carbomethoxy group has a deshielding effect on 1,3 syn-hydrogens (Figure 4).

The analysis of the anisotropic effect of the substituents and the comparison of the chemical shifts of compounds **1a-4a** lead to the assignment of the stereochemistry at C-1. This is supported by inspection of the Dreiding molecular models which also evidences the falling of the H-7 in the shielding cone of -COOMe at C-1 when it is in an *endo* arrangement. This is consistent with the upfield shift observed for H-7 in **2a** and **3a**. As expected in the ^{13}C-nmr spectrum a γ-gauche effect on C-7 is observed in **2a** and **4a**. As already stressed in the preceding paper [2a] vicinal proton coupling constants are not discriminating in these compounds since J_{cis} varies in the range 6.5-9.5 Hz, while the J_{trans} varies between 8.5 and 10 Hz. Further evidence for the proposed stereochemistry for C-3 and C-8 in pyrrolizidines **1-4** comes from nuclear Overhauser effect exhibited by the ammonium salt 15 (Figure 5). By saturation of the



9 (10%)



10 (74%)

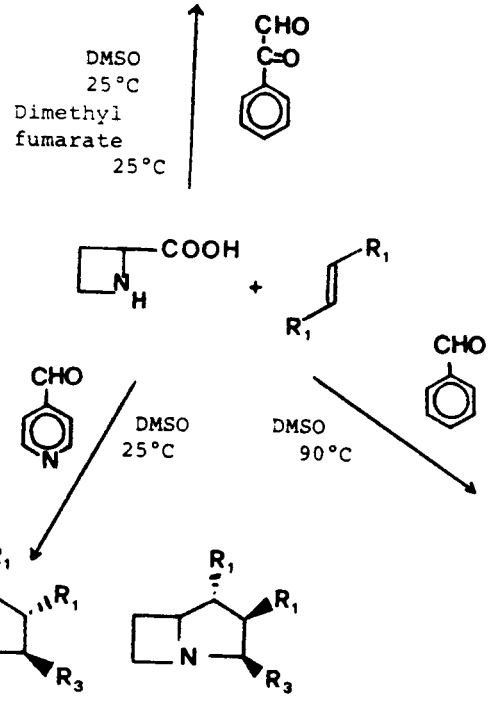


Figure 2

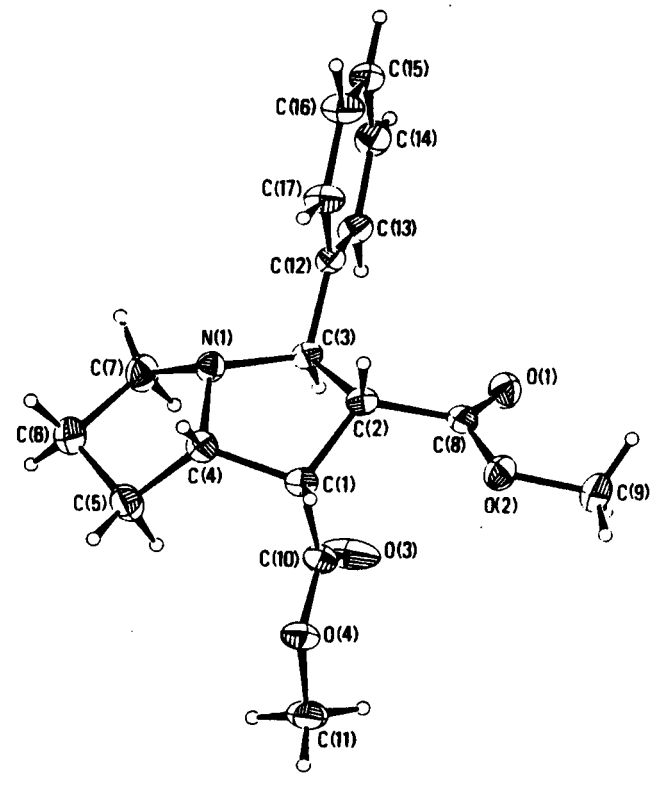


Figure 3. Perspective view of the molecule of **2a** with the numbering scheme adopted for the X-ray analysis. The thermal ellipsoids are drawn at a 20% probability level. The H atoms are on an arbitrary scale and were numbered according to the atom to which they are bonded.

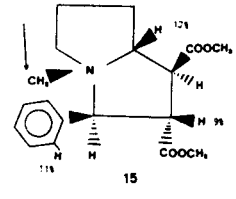
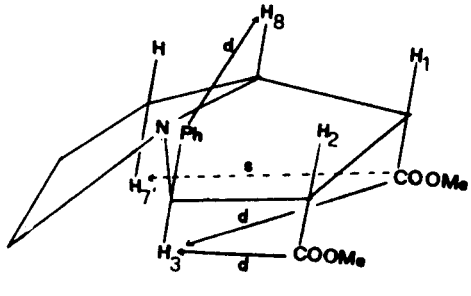


Figure 5



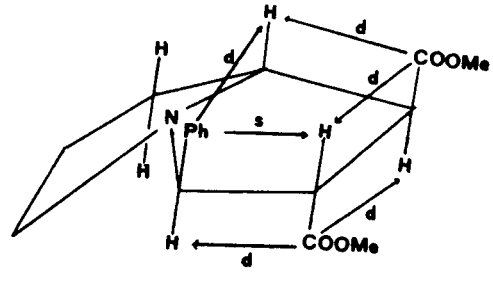


Figure 4 s = shielding d = deshielding

Table 1

	1a	2a	3a	4a	3b	4b	3c	4c
H1	2.92	3.56	3.13	3.72	3.11	3.80-3.60	3.05	3.69-3.74
H2	3.62	3.37	3.39	3.66	3.33	3.80-3.60	3.30	3.69-3.74
H3	4.16	4.34	3.92	4.29	4.04	4.39	3.90	4.26
H5	2.92	2.84	2.81	3.21	2.83	3.16	2.80	3.17
H5'	2.50	2.67	2.65	2.67	2.57	2.62	2.53	2.61
H5-7	1.8-1.6	2.0-1.8	2.2-1.8	2.1-1.7	2.1-1.7	2.1-1.7	2.2-1.7	2.2-1.7
H7'	1.8-1.6	1.59	2.2-1.8	1.40	2.1-1.7	1.40	2.2-1.7	1.37
H8	4.35	4.06	3.85	4.12	3.85	4.11	3.80	4.08
COOMe1	3.68	3.69	3.71	3.70	3.70	3.70	3.66	3.69
COOMe2	3.22	3.55	3.58	3.33	3.60	3.33	3.57	3.33
J1,2	6.5	8.0	10.0	*	11.0	*	11.0	*
J2,3	6.5	10.0	10.0	8.0	10.0	8.0	10.0	7.5
J1,8	9.0	8.0	8.5	9.5	8.0	*	9.0	9.5
C1	54.0	49.4	53.7	47.7	53.7	47.8	53.8	47.8
C2	56.1	57.1	57.2	50.4	57.4	50.9	57.0	50.6
C3	72.5	69.9	73.3	71.1	72.2	70.5	71.8	70.0
C5	52.9	52.7	53.9	55.4	53.6	55.2	53.3	55.2
C6	26.4	27.0	25.2	26.0	25.5	26.2	25.4	26.1
C7	33.5	28.4	32.2	28.8	32.0	28.7	31.9	28.7
C8	65.1	66.2	67.2	65.7	67.5	65.9	67.6	65.9
COO	172.8	172.4	172.5	172.5	171.9	172.1	171.8	172.2
COO	171.2	171.0	172.5	171.0	171.7	170.5	171.8	170.4
OMe	51.7	51.4	52.1	51.7	52.1	51.9	52.1	51.8
OMe	51.6	51.3	51.9	51.3	52.0	51.6	52.1	51.5
IJC3		136.8	134.5	138.8	136.4	143.0		
IJC3		148.8	147.9	150.4	147.9	151.2		

	3d	4d	2d		5d
H1	3.11	3.90	3.45	H1	3.31
H2	4.19	3.68	4.23	H2	4.00
H3	4.64	4.78	4.99	H3	4.08
H5	3.20	3.43	*	H5	2.68
H5'	2.78	2.75	2.85	H5'	2.00
H6,7	2.1-1.8	2.1-1.8	1.9-1.8	H6,7	2.2-1.9
H7	2.1-1.8	1.42	1.55	H7'	1.32
H8	3.72	3.90	4.02	H8	3.03
COOMe1	3.72	3.73	3.72	COOMe1	3.70
COOMe2	3.61	3.55	3.45	COOME2	3.11
J1,2	10.0	10.5	7.0	J1,2	8.0
J2,3	7.0	7.0	9.0	J2,3	9.5
J1,8	10.0	*	7.0	J1,8	10.0
C1	53.2	48.8	51.9	C1	57.6
C2	50.5	46.0	49.6	C2	48.1
C3	71.6	69.7	67.8	C3	70.8
C5	54.5	56.2	54.6	C5	45.6
C6	24.8	26.1	23.7	C6	27.3
C7	29.9	26.2	27.4	C7	27.8
C8	68.5	65.0	67.7	C8	65.2
COO	173.0	172.8	173.4	COO	172.5
COO	172.0	171.2	171.2	COO	171.0
OMe	52.1	51.7	51.9		
OMe	52.0	51.6	51.6		

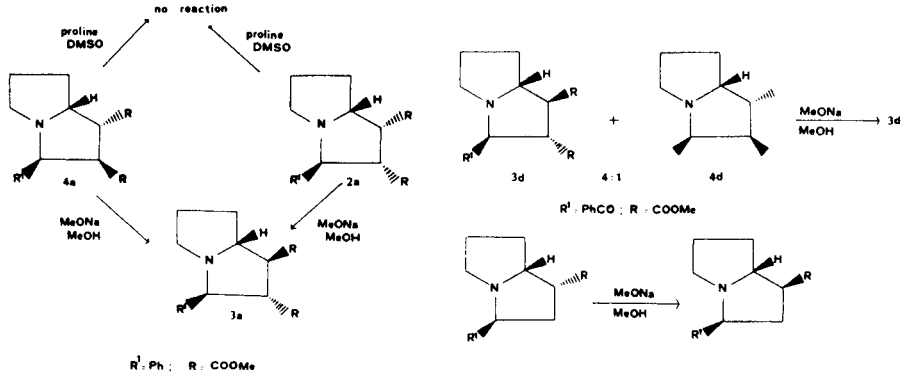


Figure 6

methyl group on the nitrogen atom a 17% increase of the intensity of the H-8 and a 9% increase of the hydrogen atom at C-2 have been observed, consistent with the depicted stereochemistry.

Structure and stereochemistry of pyrrolizidines **3b-c** and **4b-c** were easily determined by analogy with the corresponding phenyl derivatives. In compounds **6-8** the assignments of the hydrogens at C-1, C-2, C-3 and C-8 has been based on spin decoupling experiments on H-1, H-2, H-3 and H-8 (Table 2). The chemical shift of H-7′ (δ 1.40) in **7a**, in comparison with **6a** is consistent with an *endo* disposition of the carbomethoxyl group in **7a** and an *exo* disposition in **6a**. The chemical shift of H-1 in **7a** and **6a** is consistent with the depicted stereochemistry at C-3. In **7a** H-2 and H-2′ are well differentiated (δ 1.98 and δ 2.75) due to the opposite anisotropic effects of the vicinal phenyl and carbomethoxy groups [10b].

The change of configuration at C-1 in **6a** shifts H-2 and H-2′ in opposite directions with respect to **7a**.

Table 2

^{1}H-NMR and ^{13}C-NMR Data for Pyrrolizidines **5-8**

	6a	**7a**	**8a**	**7d**	**8d**
H1	2.71	3.24	2.40	3.31	2.34
H1′	-	-	2.1-1.5	-	2.1-1.7
H2	2.24	1.98	3.04	2.19	3.60
H2′	2.43	2.57	-	2.47	-
H3	3.74	4.01	3.91	4.48	4.66
H5	2.87	3.01	2.80	3.31	3.14
H5′	2.63	2.67	2.63	2.69	2.79
H6,7	2.0-1.7	2.0-1.7	2.1-1.5	2.0-1.7	2.1-1.7
H7′	2.0-1.7	1.40	2.1-1.5	1.36	1.60
H8	3.86	3.98	3.76	3.93	3.70
COOMe	3.70	3.69	3.57	3.68	3.59
J1,2	12.0	8.0	7.0	7.7	6.5
J1,2′	6.0	8.0	-	8.4	-
J2,3	11.5	8.0	10.0	4.2	8.0
J2′,3	6.0	7.0	-	8.0	-
J1,8	8.5	5.0	7.0	*	*
C1		45.6	37.1		36.0
C2		37.0	54.8		47.9
C3		68.7	73.1		71.6
C5		53.7	53.1		54.7
C6		26.4	25.7		26.7
C7		28.4	32.9		31.1
C8		67.1	64.3		65.3
COO		174.2	173.7		174.4
OMe		51.3	51.5		52.0

Table 3

^{1}H-NMR Data for Azetidines

	9	**10**	**11**	**12**
H1	-	3.78	3.78	4.29
H2	5.98	4.27	3.37	3.62
H3	5.18	4.55	4.15	4.28
H5	3.81	3.90	3.86	3.89
H5′	3.42	3.55	3.46	3.26
H6	2.47	2.62	2.70	2.54
H6′	2.11	2.10	2.21	2.00
H7	5.47	4.11	4.23	4.66
COOMe	-	3.71	3.72	3.70
COOMe	-	3.70	3.68	3.53
J1,2	-	9.5	10.5	1.8
J2,3	3.0	7.0	9.0	9.6
J1,7	-	7.5	8.0	*

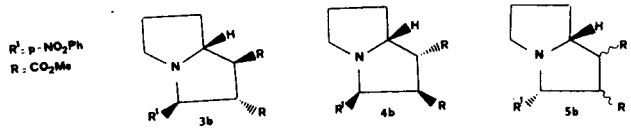
Concerning pyrrolizidines **1-8d** it should be pointed out that the benzoyl group is expected to behave as the carbomethoxy group and exerts a deshielding anisotropic effect both on 1,2 and 1,3 syn-hydrogens [10a,b].

The isomers which have been isolated are sterically stable under the reaction conditions but undergo isomerization in the presence of sodium methoxide in methanol affording the most thermodynamically stable product (Figure 6). This result is noteworthy since: a) In this case the most stable product can easily be assumed to be the "all *trans*" one (this is also inferred by inspection of Dreiding molecular models), thus affording a chemical proof to the assignments of configurations; b) only one product can easily be obtained from a mixture of stereoisomers; c) the reaction mixture is a "kinetic" one, thus

the stereochemistry of the obtained products give information on the mechanism of the cycloadditions.

Table 4

Solvent and Temperature Influence on the Stereoisomers Ratio



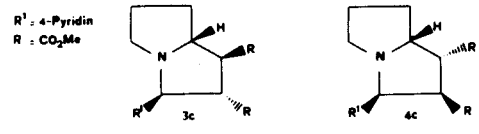
Solvent	Temperature °C	Time (hours)	Stereoisomers ratio 3b	4b	5b	Yields (%)
DMSO	25	1	1.4	1	1.5	77
DMSO	55	0.3	1.7	1	1.9	90
DMSO	90	0.3	1.7	1	2.1	90
THF	25	168	2.3	1	0.5	87
Toluene	25	168	1.7	1	0.4	85
Methanol	25	6	1.6	1	0.9	60

As expected the stereoisomers ratios are scarcely influenced by the temperature and the solvent. Temperature and solvent are, on the contrary, effective on the rate of the reaction. This observation suggests that the rate determining step is the one before cycloaddition (Tables 4, 5, 6).

A rough scale of dipolarophilicity can be traced from the obtained results. Dimethyl fumarate is always the most effective dipolarophile. Maleate and acrylate compare effectively only with benzaldehyde and phenylglyoxal: when *p*-nitrobenzaldehyde or pyridinaldehyde are treated with proline and maleate or fumarate (even in large excess) only traces of pyrrolizidines are obtained.

Table 5

Solvent and Temperature Influence on the Stereoisomers Ratio

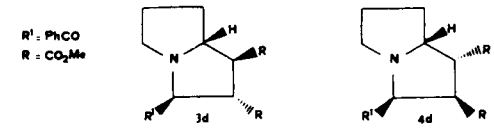


Solvent	Temperature °C	Time (hours)	Stereoisomers ratio 3c	4c	Yields %
DMSO	25	4	53	47	75
THF	25	72	63	37	92

The stereochemical outcome of the reaction is consistent with the stereoselective formation of an intermediate anti azomethine ylide (a) which could arise from the decarboxylation of a previously formed immonium salt [2,3]. Very recently, MNDO calculations indicate that the decarboxylative route to azomethine [11] ylides involves an intermediate oxazolidin-5-one which undergoes a stereospecific 1,3-dipolar cycloreversion.

Table 6

Solvent and Temperature Influence on the Stereoisomers Ratio



Solvent	Temperature °C	Time (hours)	Stereoisomers ratio 3d	4d	Yields %
DMSO	25	1.5	80	20	75
DMSO	80	0.2	100	0	[a]
THF	25	72	90	10	80
Toluene	25	24	78	22	85 [b]
Toluene	90	2	79	21	63 [b]

[a] Determined by ^{1}H-nmr in DMSO-d_6 [b] Significant amounts of **1d** (45 and 13% respectively) have been detected in the crude material.

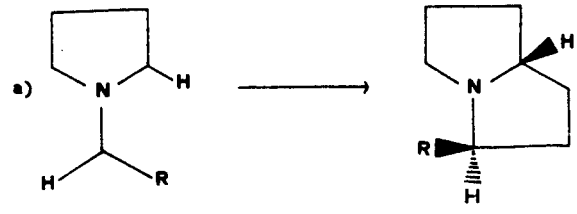


Figure 7

EXPERIMENTAL

Proline was supplied by Merck and was used without any further treatment: its purity was checked by hplc using methanol-water 1/1 as eluent with an RP8 column and an uv detector at 204 nm. Dimethyl sulfoxide (from Carlo Erba) was distilled from calcium hydride under reduced pressure and stored over 3 Å Molecular sieves (from Merck) in a nitrogen atmosphere. Benzaldehyde was washed with an aqueous potassium carbonate solution, dried on the same reagent and distilled under reduced pressure from zinc powder and stored in the dark in a nitrogen atmosphere. *p*-Methoxybenzaldehyde was distilled under reduced pressure and stored in a nitrogen atmosphere. *p*-Nitrobenzaldehyde was supplied from Carlo Erba and directly used. Dimethyl maleate, dimethyl fumarate and 4-pyridinaldehyde were supplied from Aldrich and used without any further treatment. The ^{13}C-nmr spectra were recorded on a Varian XL-100 and XL-200 spectrometer in deuteriochloroform with TMS as the internal standard. The ^{1}H-nmr spectra were recorded in deuteriochloroform solutions on a Brucker WP-80 or on a Varian XL-200 spectrometer. Chemical shifts are expressed in (ppm) relative to TMS and coupling constant in Hz. The ir spectra refer to chloroform solutions and were recorded with a Perkin Elmer 681 spectrophotometer (data expressed in cm^{-1}). Mass spectra were recorded on a VG 7070 EQ spectrometer. The uv spectra refer to ethanolic solutions and were recorded on a Perkin Elmer 551 spectrophotometer: λ nm (ϵ molar). The hplc analyses were performed on a Perkin Elmer series 2 Liquid Chromatograph equipped with a RP8 column and a LC75 detector. Melting points are uncorrected.

Typical Procedure.

a) Proline (2.5 mmoles) and a later specified amount of ethylenic dipolarophile were stirred in anhydrous DMSO (5 ml). The aldehyde (1 equivalent) was added in small portions. After the disappearance of the suspended proline the reaction was poured into diethyl ether-water and

extracted three times. The combined organic extracts were dried (magnesium sulfate) and the solvent removed under reduced pressure. Crude product was examined by nmr spectroscopy and then chromatographed on silica gel with the procedure developed by Still [12].

b) The same reaction was performed with 1 equivalent of ethylenic dipolarophile at different temperatures (as shown in the Tables 4, 5, 6) and with different solvents. Mixture compositions were determined by ^{1}H-nmr and hplc analysis on the crude reaction mixture or (in the case of deuterated DMSO) directly on deuterated reaction mixture without evaporation of the solvent.

1,2-Dicarbomethoxy-3-phenylpyrrolizidines **1a** and **2a**.

The reaction was performed at 80° for 1 hour with 4 equivalents of methyl maleate. From the extracted crude material, the excess of maleate was distilled under reduced pressure (70°, 2mm Hg). The remaining thick yellow oil (72% by weight, composition by ^{1}H-nmr analysis: **2a**, 59%, **1a**, 17%, **3a**, 12%, **4a**, 12%) was chromatographed on silica gel (hexane/ethyl acetate 2/1 and then 3/2) affording **2a** as colorless prism (45%), mp 83°; ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1490, 1450, 1430; λ (ϵ) 296 (320); ms: m/z 303 (M^+), 272, 244, 159.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; N, 4.62. Found: C, 67.17; H, 6.91; N, 4.64.

Compound **1a** was recovered as 1:1 mixture with **2a**; ^{1}H-nmr and ^{13}C-nmr (by difference) as listed.

1,2-Dicarbomethoxy-3-phenylpyrrolizidines **3a** and **4a**.

The reaction was performed at 90° for 0.5 hour with 2.0 equivalents of methyl fumarate. Ether extraction afforded 83% by weight of yellow oil (composition by ^{1}H-nmr analysis: **3a**, 50%, **4a**, 50%). Chromatography on silica gel (hexane/ethyl acetate 7/2 and then 7/3) afforded **3a** as colorless oil (40%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1490, 1450, 1440; λ (ϵ) 290 (750); ms: m/z 303 (M^+), 288, 272, 244, 212, 184, 159.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; N, 4.62. Found: C, 67.16; H, 6.95; N, 4.60.

Compound **4a**.

This compound was obtained as a colorless oil (40%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1490, 1450, 1440; λ (ϵ) 302 (650); ms: m/z 303 (M^+), 288, 272, 244, 212, 184, 159.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; N, 4.62. Found: C, 67.22; H, 6.91; N, 4.62.

1-Carbomethoxy-3-phenylpyrrolizidines **6a**, **7a** and 2-Carbomethoxy-3-phenylpyrrolizidine **8a**.

The reaction was run at 75° for 1 hour with 3 equivalents of methyl acrylate. After extraction the excess of acrylate was removed under reduced pressure affording 95% by weight crude mixture as a thick pale yellow oil (composition by ^{1}H-nmr analysis **6a**, 11%, **7a** 63%, **8a** 26%). Flash chromatography on silica gel (hexane/ethyl acetate 6/4 with 0.5% of diethylamine) afforded **7a** as pale yellow oil (60%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1450, 1430; λ (ϵ) 298 (800); ms: m/z 245 (M^+), 230, 214, 186, 159.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.75; N, 5.71. Found: C, 73.58; H, 7.72; N, 5.73.

Compound **8a**.

This compound was obtained as a pale yellow oil (25%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1450, 1430; λ (ϵ) 306 (400); ms: m/z 245 (M^+), 159.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.75; N, 5.71. Found: C, 73.56; H, 7.78; N, 5.69.

Compound **6a**.

This compound was obtained as a pale yellow oil (10%). It was further purified by semipreparative hplc (silica gel chloroform/2-propanol 9/1); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1590, 1450, 1430; λ (ϵ) 290 (510); ms: m/z 245 (M^+), 159.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.75; N, 5.71. Found: C, 73.26; H, 7.77; N, 5.74.

1,2-Dicarbomethoxy-3-(4'-nitro)phenylpyrrolizidines **3b**, **4b** and **5b**.

The reaction was performed at room temperature for 1 hour with 1 equivalent of methyl fumarate; 77% by weight of an orange solid crude mixture was recovered (composition by ^{1}H-nmr analysis; **3b**, 36%, **4b**, 26%, **5b** 38%). Column chromatography (hexane/ethyl acetate 3/1 and then 2/1) afforded **3b** as an orange amorphous powder solid (34%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1520, 1435, 1350; λ (ϵ) 266 (13100); ms: m/z 348 (M^+), 333, 317, 289, 204.

Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.75; N, 8.05. Found: C, 58.47; H, 5.77; N, 8.00.

Compound **4b**.

This compound was obtained as an orange amorphous powder (20%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1520, 1435, 1350; λ (ϵ) 266 (11600); ms: m/z 348 (M^+), 333, 317, 289, 204.

Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.75; N, 8.05. Found: C, 58.48; H, 5.73; N, 8.01.

Compound **5b**.

This compound was obtained as an orange amorphous powder (30%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1520, 1435, 1350; λ (ϵ) 266 (12400); ms: m/z 348 (M^+), 333, 317, 289, 204.

Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.75; N, 8.05. Found: C, 58.45; H, 5.73; N, 8.07.

1,2-Dicarbomethoxy-3-(4'pyridinyl)pyrrolizidines **3c** and **4c**.

The reaction was performed at room temperature for 4 hours with 1 equivalent of methyl fumarate. Extraction afforded 75% by weight of a crude mixture (composition by ^{1}H-nmr analysis, **3c**, 53%, **4c**, 47%). Column chromatography on silica gel (chloroform and then chloroform with 5% methanol) afforded **3c** as a colorless amorphous solid (40%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1550, 1430, 1410; λ (ϵ) 224 (3000) 254 (330); ms: m/z 304 (M^+), 289, 273, 245, 160.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.16; H, 6.58; N, 9.21. Found: C, 62.97; H, 6.56; N, 9.23.

Compound **4c**.

This compound was obtained in 35% yield as white crystals, mp 115-116°; ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1550, 1430, 1410; λ (ϵ) 218 (2800) 254 (2200); ms: m/z 304 (M^+), 289, 273, 245, 160.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.16; H, 6.58; N, 9.21. Found: C, 63.08; H, 6.55; N, 9.18.

1,2-Dicarbomethoxy-3-benzoylpyrrolizidines **3d** and **4d**.

The reaction was performed at room temperature for 1 hour with 3 equivalents of methyl fumarate. Ether extraction afforded 90% by weight of a solid compound (composition by ^{1}H-nmr analysis; **3d**, 80%, **4d**, 20%). Column chromatography on silica gel (hexane/ethyl acetate 2/1 and then 1/1) afforded **3d** as yellow crystals (72%), mp 99.5-100.5°; ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1690, 1600, 1450, 1440; λ (ϵ) 240 (14400), 278 (2600); ms: m/z 331 (M^+), 300, 254, 226, 194, 166.

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.26; H, 6.34; N, 4.23. Found: C, 65.39; H, 6.36; N, 4.20.

Compound **4d**.

This compound was obtained as yellow crystals (18%), mp 149-150°; ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1690, 1600, 1450, 1440; ms: m/z 331 (M^+), 300, 254, 226, 194.

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.26; H, 6.34; N, 4.23. Found: C, 65.28; H, 6.32; N, 4.25.

1,2-Dicarbomethoxy-3-benzoylpyrrolizidine **2d**.

The reaction was performed at room temperature for 1.5 hours using 2.2 equivalents of methyl maleate. The excess of methyl maleate was evaporated under reduced pressure affording 72% by weight of crude

material (composition by ^{1}H-nmr analysis; **2d**, 72%, oxapyrrolizidine derivative (see compound **2d** in reference [1]) 13%; unidentified products 15%). Column chromatography on silica gel (hexane/ethyl acetate 1/1) afforded **2d** as a yellow oil (50%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1690, 1600, 1580, 1450, 1440; λ (ϵ) 244 (13100), 280 (3100); ms: m/z 331 (M^+), 300, 272, 254, 240, 226, 194, 166.

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.26; H, 6.34; N, 4.23. Found: C, 65.08; H, 6.35; N, 4.26.

1-Carbomethoxy-3-benzoylpyrrolizidine **7d** and 2-Carbomethoxy-3-benzoylpyrrolizidine **8d**.

The reaction was performed at room temperature for 3 hours with 5 equivalent of methyl acrylate. Extraction afforded 63% by weight of crude mixture (composition by ^{1}H-nmr analysis; **8d**, 26%, oxapyrrolizidine derivative (see compound **2d** in reference [1] 26%, **7d**, 48%). Column chromatography on silica gel (hexane/ethyl acetate 2/8 and then 1/9 afforded the oxapyrrolizidine **8d** as a yellow amorphous powder (17%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1685, 1600, 1580, 1445, 1430; λ (ϵ) 240 (6500), 284 (3100); ms: m/z 273 (M^+), 242, 168, 108.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.17; H, 6.94; N, 5.11.

Compound **7d**.

This compound was obtained as a yellow solid (31%), ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1685, 1600, 1580, 1445, 1435; λ (ϵ) 226 (10900), 304 (5900); ms: m/z 273 (M^+), 242, 168, 108.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.36; H, 6.96; N, 5.15.

Reaction of Azetidinecarboxylic Acid with Phenylglyoxal and Methyl Fumarate.

The reaction was performed at room temperature for 1 hour with 1 equivalent of methyl fumarate. Extraction afforded 71% by weight of a yellow solid (composition by ^{1}H-nmr analysis **9**, 10%, **10**, 74%, other products 16%). Flash chromatography on silica gel (hexane/ethyl acetate 7/3 then 8/2 then 1/1) afforded **9** as a yellow amorphous solid (7%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1685, 1600, 1580, 1500, 1450; λ (ϵ) 246 (14600); ms: m/z 307 (M^+), 279, 202, 174.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.38; H, 5.52; N, 4.53.

Compound **10**.

This compound was obtained as a yellow solid (60%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1735, 1685, 1600, 1580, 1450, 1440; λ (ϵ) 242 (10600); ms: m/z 317 (M^+), 286, 258, 226, 212, 180.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.35; H, 5.99; N, 4.42. Found: C, 64.16; H, 5.99; N, 4.45.

Reaction of Azetidinecarboxylic Acid with 4-Pyridinecarbaldehyde and Methyl Fumarate.

The reaction was performed at room temperature for 20 hours, then extracted with chloroform. DMSO was distilled off under reduced pressure (55° at 4 mm Hg) obtaining 20% by weight of crude reaction mixture (composition by ^{1}H-nmr analysis; **11**, 35%, **12**, 65%). The crude material was purified by semipreparative hplc on silica gel (chloroform/2-propanol 8/2) and afforded **11** as an orange thick oil (7%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1550, 1430, 1410; λ (ϵ) 257 (2500); ms: m/z 290 (M^+), 259, 231, 199, 146.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.21; N, 9.65. Found: C, 62.17; H, 6.23; N, 9.61.

Compound **12**.

This compound was obtained as an orange oil (13%); ^{1}H-nmr and ^{13}C-nmr as listed; ν max 1730, 1600, 1550, 1430; λ (ϵ) 255 (2400); ms: m/z 290 (M^+), 259, 231, 199, 146.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.21; N, 9.65. Found: C, 61.98; H, 6.19; N, 9.68.

X-Ray Analysis of Compound **2a** [13].

Data for the substance under study are: $C_{17}H_{21}NO_4$, M_r = 303.4; crystal of approximate dimension 0.30 x 0.30 x 0.30 mm, monoclinic, space group $P2_1/n$, a = 5.768(2), b = 15.300(8), c = 18.276(6) Å, β = 93.06(3)°, V = 1611(1) Å^3, Z = 4, D_{calc} = 1.251 g/cm^3, μ (MoKα) = 0.831 cm^{-1}, F(000) = 648.

All measurements were carried out at room temperature on an Enraf-Nonium CAD-4 diffractometer, using graphite-monochromated MoKα radiation (λ = 0.71073 Å). Intensity data were collected up to 2θ = 50° by variable-rate θ-2θ scan technique. Out of the 2818 independent reflections collected 2542 with $I > 0$ were considered observed. The observational variances $\sigma^2(I)$ were estimated including counting statistic for the scans and the additional term $(0.0351)^2$. Three standard reflections were periodically checked and no significant variation of the intensities were observed. The data were corrected for the Lorentz and polarization factors but not for absorption. The structure was solved by direct method using the program MULTAN [14]. Preliminary positions for the H atoms were derived from the difference maps and geometrical arguments.

The full matrix least-squares refinement was minimization of the quantity $\Sigma w(\Delta F)^2$, with weights $w = 4F_o^2/\sigma^2(F_o^2)$ for the reflections classified as observed. In the final cycles the 284 variables simultaneously adjusted included coordinates and atomic displacement parameters for the C, N and O atoms, coordinates and isotropic B's for the H atoms, a scale factor and a secondary extinction coefficient [final value = 6(1) x 10^{-7}]. Convergence was reached at R = 0.057, wR = 0.052, for 2818 reflections with $I > 0$ R = 0.042 and wR = 0.049 for 2021 reflections with $I > 2\sigma(I)$; maximum Δ/σ = 0.09; no residual peaks higher than 0.21 e/Å^3 were found on the final difference map.

REFERENCES AND NOTES

[1a] J. J. Tufariello, H. Meckler, and A. Senaratana, *Tetrahedron*, **41**, 3447 (1985) [b] During the preparation of the manuscript the following papers were published on this subject: O. Tsuge, S. Kanemasa, M. Ohe, K. Yorozu, S. Takenaka, and K. Ueno, *Bull. Chem. Soc. Japan.*, **60**, 4067 (1987); *ibidem*, **60**, 4079 (1987); F. M. Aly, H. Ardill, R. Grigg, S. Leong-Ling, S. Rajviroongit, and S. Surendrakumar, *Tetrahedron Letters*, **28**, 6077 (1987); D. A. Barrin, R. Grigg, H. Q. N. Gunaratne, J. Kemp, P. McMeekin, and V. Sridharan, *Tetrahedron*, **44**, 557 (1988).

[2a] F. Orsini, F. Pelizzoni, M. Forte, P. Gariboldi, and R. Destro, *Tetrahedron*, **44**, 519 (1987). [b] F. Orsini, F. Pelizzoni, and M. Forte, *Gazz. Chim. Ital.*, **115**, 569 (1985).

[3] "Synthetic Application of Dipolar Cycloaddition Reactions", *Tetrahedron*, **41**, 3447 (1985); G. P. Rizzi, *J. Org. Chem.*, **35**, 2069 (1970); R. Grigg and S. Thianapatanagul, *J. Chem. Soc., Chem. Commun.*, 182 (1984); R. Grigg, M. F. Ally, V. Shridaran, and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 182 (1984).

[4] Reaction of proline derived azomethine ylides (from formaldehyde) with methyl propiolate and dimethylacetylenedicarboxylate in toluene at 100° give ring-expanded products: H. Ardill, R. Grigg, V. Sridharan, and J. Malone, *J. Chem. Soc., Chem. Commun.*, 1296 (1987).

[5] D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, **97**, 1354 (1975).

[6] G. Toth, J. Frank, Z. Bende, L. Weber, and K. Simon, *J. Chem. Soc., Perkin Trans. I*, 1961 (1983).

[7] J. L. Marshall, "Carbon-Carbon and Carbon-Proton NMR Couplings", Verlag Chemie International, 1983.

[8] A. Bohlmann, *Angew. Chem.*, **69**, 541 (1957); *Chem. Ber.*, **91**, 2157 (1958).

[9a] R. P. Ossorio, P. Alcaide, and L. Mardomingo, *J. Heterocyclic Chem.*, **19**, 45 (1982); [b] M. Gelbke, M. Baudet, J. Hoyois, G. Van De Vlied, and M. Deleers, *Nouv. J. Chim.*, **7**, 41 (1983); [c] J. Engel, *Chem. Z.*, 427 (1982).

[10a] R. Huisgen, V. Martin Ramos, and W. Scheer, *Tetrahedron Letters*, 477 (1971); [b] L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed, Pergamon Press, 1969.

[11] R. Grigg, J. Idle, P. McMeekin, and D. Vipond, *J. Chem. Soc., Chem. Commun.*, 49 (1987) and references cited therein.

[12] W. C. Still, M. Kahu, and A. Mitra, *J. Am. Chem. Soc.*, **14**, 2923 (1978).

[13] Lists of atomic coordinates and displacement parameters, together with a table of distances and angles, and calculated structure factors have been deposited with Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, UK.

[14] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, **A27**, 368 (1971).