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1,3 DIPOLAR CYCLOADDITIONS OF AZOMETHINE YLIDES WITH AROMATIC ALDEHYDES. SYNTHESES OF 1-OXAPYRROLIZIDINES AND 1,3-OXAZOLIDINES.

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Abstract - Substituted 1-oxapyrrolizidines have been synthetized by cycloaddition of azomethine ylides, generated by aldehydes induced decarboxylation of proline, with carbonyl dipolarophyles. The stereochemistry of the cycloadducts indicate that they arise from the stereospecific formation of one isomer of the azomethine ylide.

INTRODUCTION

1,3 Dipolar cycloadditions often represent a good method for the synthesis of five membered rings. Since pyrrolizidine ring has a widespread occurrence in many natural compounds, namely alkaloids, azomethine ylides have received a growing attention in recent years[1].

Different methods have been envisaged for the in situ generation of non aromatic and not (or scarcely) stabilized iminium dipoles[2].

The photochemical or thermal opening of aziridines usually work well in the presence of electron-withdrawing substituents at the three membered ring. Desilylation of α-trimethylsilyliminium salts with fluoride ions, on the contrary, afford unstabilized dipoles which undergo intra- or intermolecular cycloadditions with various dipolarophyles. A limited number of examples deal with the generation of the ylide by deprotonation of iminium salts formed "in situ", or previously synthesized, in the presence or not of bases. A carbanion

stabilizing group such as carbomethoxy or phenyl is present. Azomethine ylides can also be formed by aldehydes a ketones induced decarboxylation of aminoacids; 1,2H shifts in imines of α-aminoacid esters and generation from primary or secondary amines and carbonyl compounds containig the O=C-C=X moiety [3].

The present paper deals with similarly generated dipoles and subsequent cyclization on carbonylic dipolarophyles to obtain oxazolidines and 1-oxapyrrolizidines [4].

RESULTS AND DISCUSSION

Addition of p-nitrobenzaldehyde, 4-pyridin aldehyde or phenylglyoxal to a suspension of proline in DMSO results in a rapid dissolution of the aminoacids and formation of stereisomeric 1-oxapyrrolizidine derivatives 1a-d and 2a-d whose structures were assigned on the basis of their spectral data. (Fig. 1)

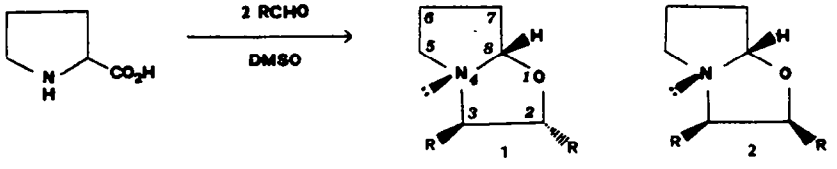


Figure 1. a) R = Ph; b) R = p-NO_2Ph; c) R = p-MeOPh; d) R = PhCO; e) R = Ph;

The stereochemistry of the chiral centers (C-2, C-3 and C-8) could not be assessed by a simple analysis of the values of the vicinal coupling constants. As known from the literature and after inspection of the molecular models, the conformational mobility of the oxazolidine ring is such as to humper any straightward choice between cis and trans stereochemistry by measuring the torsion angle of H-2 and H-3.

The stereochemical elucidation was therefore based on the use of different methods such as a) X-Ray diffraction analysis, performed on compound 1b and b) correlation of ^{1}H-NMR and ^{13}C-NMR data.

The molecular model of 1 is depicted in Figure 2 , while some details of the geometry are reported in Table 9. It is evident from the figure that the hydrogen atoms at C1 and C3, and the phenyl group at C2 all lie on the same side of the plane through atoms C1, C2, N1 and C3, while the hydrogen atom at C2 and and the phenyl group at C-1 lie on the opposite side. The values of the torsion angles listed in Table 9 indicate that the arrangement of the substituents at C-1

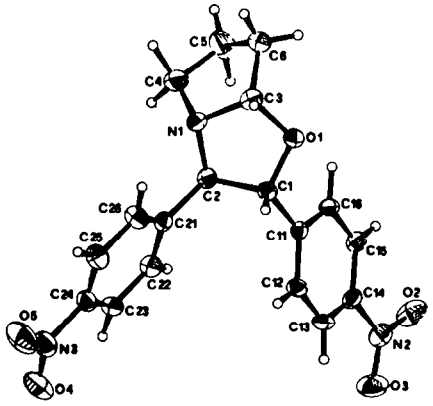


Figure 2. Perspective view of the molecule of 1b. The thermal ellipsoids are drawn at a 20% probability level. The nonlabeled hydrogen atoms were numbered according to the carbon atom to which they are bonded. The molecule is seen along the C2-H2 bond.

and C2 is midway between staggered and eclipsed. Both five-membered rings assume a twist conformation with axis through atom N1. For the proline ring, the puckering parameters[5] are q_2 =0.313(5) Å and ϕ_2=263.6(6)° ,while for the other ring the puckering amplitude q_2 is 0.335(3) Å and the puckering phase ϕ amounts to 271.8(5)° .

As seen by visual inspection of the ellipsoids plot, very high thermal motion affects the carbon atom C-5. Consequently, the derived geometry for the fragment of the molecule that includes this atom is of rather low accuracy, showing apparent distances as short as 1.433(7) Å for the C4-C5 bond, and 1.484(7) Å for the C5-C6 bond.

The two phenyl groups therefore have a trans arrangement and are almost perpendicular to the oxazolidine ring. The junction between the two pentaatomic

rings is cis. The absence of Bohlmann bands in the IR spectrum ($CHCl_3$ solution) show that the cis junction is mantained in the solvated state. Comparison of the ^{1}H-NMR spectrum of 1b and 2b shows a downfield shift of H-2 (4,71 to 5.37 δ) and H-3 (3,86 δ to 4.53 δ) accompanied by a small decrease of coupling constant (Table 1) passing from 1b to 2b.

This result is consistent with the well known[7] anisotropic effect reported for

TABLE 1: ^{1}H-NMR and ^{13}C-NMR data for 1-oxapyrrolizidines 1-2

	1a	1b	1c	1d	1e	2a	2b	2e
H2	4.76	4.71	4.60	5.73	4.55	5.30	5.37	5.24
H3	3.88	3.86	3.70	5.23	3.72	4.38	4.53	4.31
H5	3.20	3.18	3.10	3.32	3.05	3.40	3.40	3.35
H5'	2.96	2.88	2.90	2.90	2.80	2.95	2.92	2.90
H8	5.36	5.36	5.25	5.02	5.22	5.64	5.69	5.58
J2,3	8.0	8.0	8.5	3.5	7.6	6.0	6.0	6.0
J7,8	2.2	2.4	2.5	2.5	2.6	3.2	3.3	3.0
J7',8	4.1	4.0	4.2	2.5	3.8	5.3	5.7	5.1
C2	88.5	87.2	88.3	78.9	86.5	80.2	79.1	*
C3	78.7	78.1	78.1	70.1	77.3	73.3	72.8	72.4
C5	55.6	55.7	55.5	53.8	55.7	55.4	55.4	55.4
C6	23.9	24.1	23.9	23.5	24.1	23.9	23.9	23.9
C7	31.6	31.6	31.8	30.4	31.4	33.0	32.9	32.9
C8	98.2	99.2	97.8	99.8	99.3	98.3	99.2	99.3

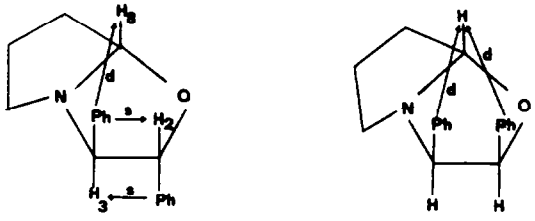
* Undetermined

the phenyl group on 1,2 (shielding) and 1,3 (deshielding) hydrogen atoms and summarized in Fig. 3.

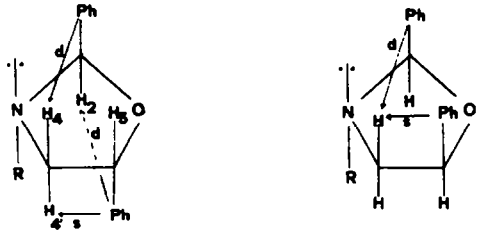
These results are in agreement with the upfield shift observed for C-2 and C-3 in the ^{13}C-NMR spectrum, due to a larger steric overcrowding of 2b with respect to 1b in the former.

The anisotropic effect exerted by both exo-phenyl groups in 2b accounts for the downfield shift of H-8 (δ 5.69) respect to 1b (δ 5.36).

The anisotropic effect of the carbonyl group, which is opposite to the one induced by the phenyl moiety, is consistent with the stereochemistry depicted for 1d. In this case a smaller $J_{4,5}$ is observed, most likely related to a conformational change due to a less severe overcrowding in 1d then in 1a-c and to the higher inductive electron attracting power of the C=O moiety.



s=shielding



d=deshielding

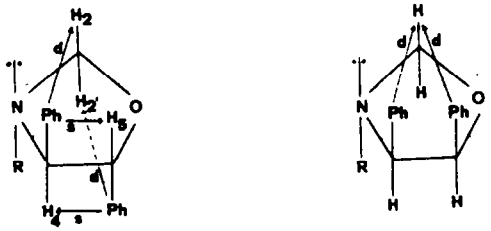
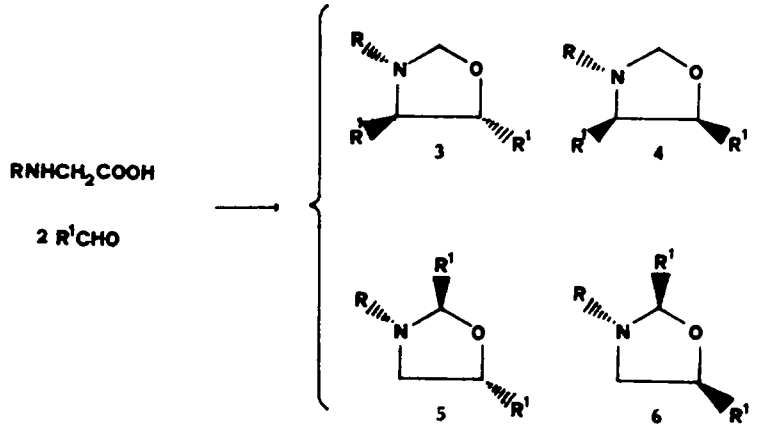


Figure 3. Anisotropic effect of the substituents on the chemical shifts in 1-oxapyrrolizidines, 2,5- and 4,5-disubstituted oxazolidines.

The use of N-substituted aminoacids as methyl glycine and N-benzylglycine afforded a mixture of stereisomeric 4,5 disubstituted-1,3-oxazolidines 3-4 and 2,5-disubstituted-1,3-oxazolidines 5-6 (Fig. 4).

Figure 4



a) R = Benzyl, R^1 = Phenyl; b) R = Benzyl, R^1 = p-NO_2 Phenyl;
c) R = Methyl R^1 = Phenyl; d) R = Methyl, R^1 = p-NO_2 Phenyl

Assuming the substituents at nitrogen and at C-4 in a anti relationship, compound 3 and 4 can only display cis-trans isomerism. The comparison of the chemical shifts of H-4 and H-5 allow to distinguish between the two stereoisomers, the cis one having both hydrogens more downfield shifted for the anisotropic effect of the phenyl group. Also the hydrogens at C-2 are discriminant .

In the cis-isomer one of them is in a 1,3 syn-relationship with both phenyl groups and it is consequentely most downfield shifted (Table 2).

TABLE 2: H-NMR and C-NMR data for 4,5-disubstituted 1,3-oxazolidines 3-4

	3a	3b	3d	4b	4d
H2	4.86	4.92	5.05	5.05	5.14
H2'	4.46	4.59	4.44	4.36	4.25
H4	3.61	3.70	3.36	4.32	4.02
H5	4.84	4.89	4.85	5.46	5.41
H6	3.95	3.88	2.27	3.92	2.28
H6'	3.42	3.57	--	3.44	--
J2,2'	2.8	3.4	2.5	2.6	2.1
J4,4'	8.3	8.7	8.4	7.9	7.9
J6,6'	13.4	13.7	--	13.5	--
C2	--	87.6	89.3	87.2	88.8
C4	--	75.4	77.1	70.5	72.5
C5	--	86.6	87.0	82.7	83.0
C6	--	56.4	36.9	55.1	35.9

Concerning 2,5-disubstituted-1,3-oxazolidines 5-6 it should be pointed out that the hydrogens at C-4 are more differentiated in the trans isomer due to the shielding effect of the phenyl group at C-5 on H-4 and to the deshielding effect of the phenyl at C-1 on H-4 (Fig. 4). Also in this case the substituent at the nitrogen atom and R are assumed to be in a trans relationship. Another feature which differentiates the stereoisomer is the coupling constant between H-4 and H-5 which is generally smaller for the cis- than the trans-isomer with larger values in the 4,5-disubstituted derivatives (Table 3).

TABLE 3: ^{1}H-NMR and ^{13}C-NMR data for 2,5-disubstituted 1,3-oxazolidines 5-6

	5a	5b	5c	5d	6a	6b	6c	6d
H2	5.26	5.42	4.96	5.01	5.23	5.42	4.87	4.92
H4	2.57	2.64	2.65	2.50	3.10	3.12	3.19	3.15
H4'	3.58	3.64	3.74	3.70	3.21	3.31	3.36	3.22
H5	5.31	5.36	5.38	5.21	5.21	5.33	5.17	5.35
H6	3.87	3.80	2.33	4.92	3.94	3.94	2.30	*
H6'	3.34	3.45	--	*	3.48	3.67	--	--
J2,4	9.2	8.5	9.4	9.5	7.5	5.7	7.8	7.0
J2,4'	6.0	6.2	5.7	6.0	5.0	7.2	4.3	4.5
J6,6'	13.0	13.0	--	--	13.2	13.0	--	--
C2		96.4	99.1	97.5		96.8	99.4	98.0
C4		59.7	63.5	62.6		58.8	61.8	61.2
C5		77.8	78.6	77.8		77.2	77.6	76.8
C6		56.3	38.5	37.5		56.9	38.3	38.3

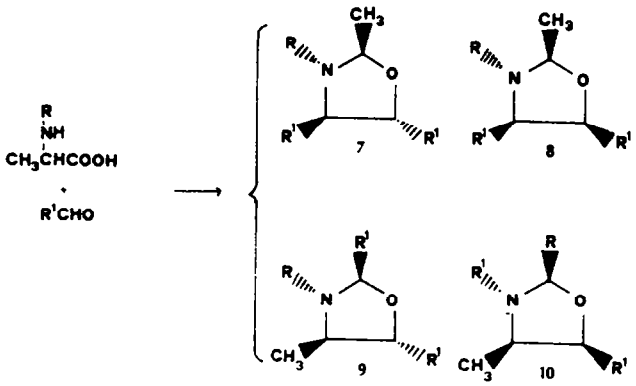
* Undetermined

Analogously N-benzylalanine treated with 2 equivalents of benzaldehyde or p-NO_2-benzaldehyde afforded a complex mixture of regio and stereoisomeric oxazolidines 7-10 (Fig. 5).

It should be pointed out that the composition of the crude reaction mixture has been evaluated by ^{1}H-NMR and does not reflect the products distribution after chromatography.

This discrepancy could be most likely related to the low stability of some oxazolidines on silica gel and to decomposition patways as, for example, the

Figure 5



a) R = Benzyl R^1 = Phenyl

b) R = Benzyl R^1 = p-NO_2Phenyl

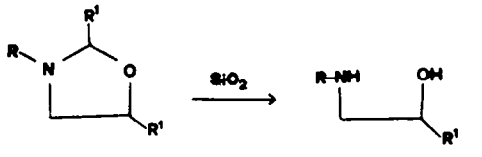
ones depicted in scheme 1.

TABLE 4: ^{1}H-NMR and ^{13}C-NMR data for trisubstituted 1,3-oxapyrrolizidines 7-10

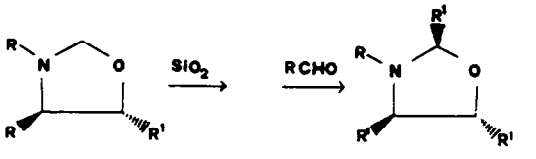
	7a	7b	7	12a		9a	10a
H2	4.72	4.82	4.62	5.21	H2	5.37	5.16
H4	3.66	3.70	4.33	3.60	H4	2.90	3.33
H5	4.86	4.90	5.33	5.11	H5	4.75	5.17
H6	3.89	3.79	3.85	2.16	H6	3.95	3.92
H6'	3.46	3.60	3.75	-	H6'	3.63	3.65
Me	1.25	1.35	1.53	-	Me	1.15	0.64
J4,4'	8.6	8.5	8.2	8.6	J4,5	8.3	7.5
J6,6'	13.8	13.5	13.5	-	J6,6'	14.2	14.2
					C2	97.2	94.0
C2	93.5	94.0	95.0	99.2	C4	67.2	76.4
C4	77.0	76.4	73.1	78.3	C5	86.2	84.9
C5	85.6	84.9	83.4	86.9	C6	54.3	55.1
C6	54.5	55.1	56.5	35.2	Me	16.0	*
Me	21.9	21.5	20.6	-			

The course of the reaction is consistent with the intermediacy of an azomethine ylide 13 by previous formation of an immonium salt which undergoes decarboxylation (Scheme 2).

Scheme 1



11a: R=Me; R¹=Ph
11b: R=Me; R¹=Ph



12a: R=Me; R¹=Ph
12b: R=Me; R¹=p-NO_2Ph

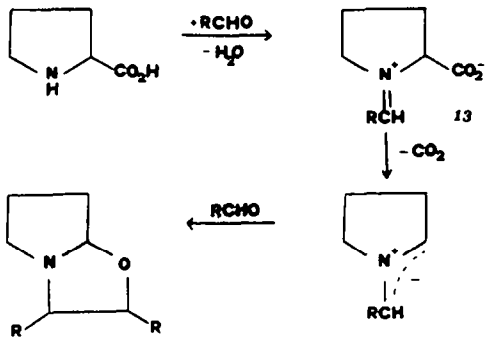
This hypothesis is supported by literature reports[7], but any attempt to detect by spectroscopycal means the intermediate 1,3-dipole failed. Reaction of proline with benzaldehyde in the presence of LiBr to stabilize the ylide as lithium complex did not work at room temperature and afforded poor yields of 1a-2a at higher temperature.

Azomethine ylide would then undergo cycloaddition with a second mole of carbonyl compound acting as dienophyle. It is widely accepted that the transitions states of 1,3-dipolar cycloadditions lay early on the reaction coordinate and that the reaction is kinetically controlled. Therefore the diastereoselection of the reaction is not dictated by the thermodinamic stability of the products, but on the activation energy necessary to form each of the products. If it is not easy to predict which of the activation energies is the lowest, we can however assume the transition states to be closer in energy to the reacting

ylide than to the products. Invoking the Hammond postulate we can reasonably assume that the geometries of the transition states resemble those of the starting ylide and aldehyde[8] and speculate on the interplay of attractive, repulsive and steric factors as they approach.

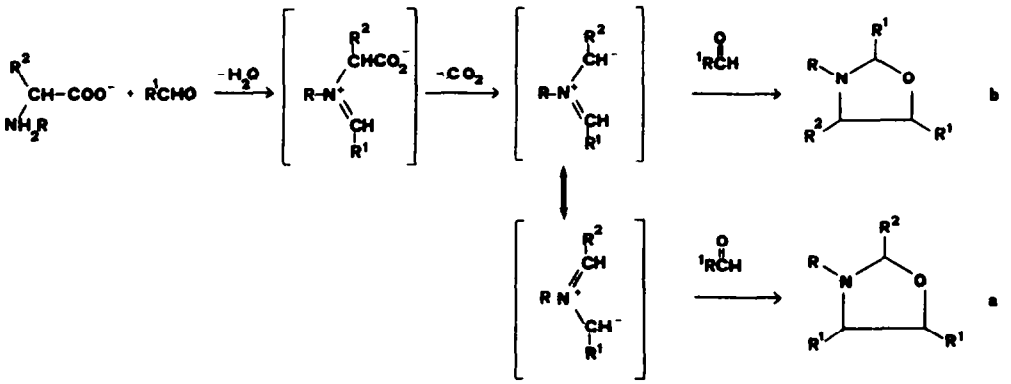
Regioselectivity can be explained by a lower activation energy for the approach a) with respect to b), as depicted in Scheme 3, for aromatic aldehydes with proline.

Scheme 2



Since it is known that the major lobe of the LUMO of the aldehyde lays on C atom, the major lobe of the HOMO of the dipolarophyle should be placed (for the principle of the maximum orbital overlap) on the aryl or benzoyl substituted carbon atom[9].

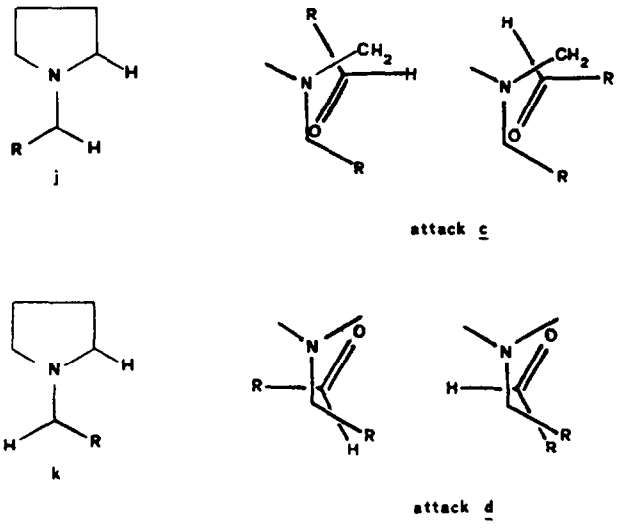
Scheme 3



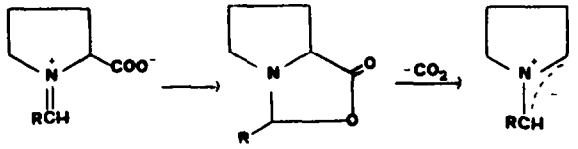
With N-substituted aminoacids the b) pathway becomes competitive except for p-NO$_2$-benzaldehyde where the presence of the p-electron withdrawing group better stabilize the resonance formula 15.

Stereoselectivity is directly dependent on the ylide stereochemistry (j or k) and on the mutual orientation of the dipole and dipolarophyle c and d as depicted in Fig. 6.

Figure 6



Our experimental data indicate k as the preferred dipole. Concerning the ylides stereochemistry recently published MNDO calculations supported by the stereochemical outcome of the reactions indicates that the decarboxylative route to azomethine ylides involves an intermediate oxazolidin-5-one: subequent loss of carbon dioxide, by 1,3-dipolar cycloversion, would generate an azomethine ylide stereospecifically [10]:



No stereoselectivity is observed with the N-substituted aminoacids where the substituents of the dipole and the dipolarophyle are far apart in the transition states and no significant energy difference can be expected for the two

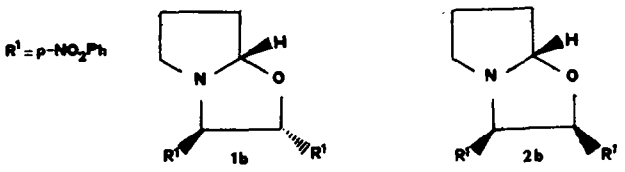
orientations.

The low enthalpic requirements of the cycloadditive step are consistent with the scarce influence of the temperature and the solvent on the regio- and stereochemical outcome of the reaction. Solvent and temperature do however influence the rate of the reactions (Table 5).

Higher rates are observed for electron attracting aldehydes: these results suggest that the rate determining step is the decarboxilative one so that a major ease of formation of a carbonium ion (by raising the temperature or by stabilizing the ylide charge) fasten the reaction without dramatic change in the ratio of the products.

This method represents an easy, mild and cheap procedure to obtain, from proline, 1-oxapyrrolizidines with a rationable regio- and stereochemistry

TABLE 5



Solvent	Temper. (hrs)	1b	2b	yields
DMSO	25 (2)	66	34	95
DMSO	96 (2)	78	22	*
THF	25 (72)	78	22	83
THF	67 (6)	75	25	85
Toluene	25 (168)	75	25	95
Toluene	90 (1)	79	21	**
Methanol	25 (1,5)	63	37	***

* Determined by ^{1}H-NMR (DMSOd$_6$)

** 70 of Starting aldehyde was recovered

*** 70% of starting aldehyde recovered; prolonged reaction times afforded unidentified side products

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. Dimethylsulfoxide (from Carlo Erba) was distilled from Calcium hydride under reduced pressure and stored over 3A Molecular sieves (from Merck) in a nitrogen atmosphere. Benzaldehyde was washed an aqueous K_2CO_3 solution, dried on the same reagent and distilled under reduced pressure from zinc powder and stored in the dark in a nitrogen atmosphere. p-Methoxybenzaldeyde was distilled under reduced pressure and stored in a nitrogen atmosphere. p-Nitrobenzaldehyde was supplied from Carlo Erba and directly used. 4-Pyridinaldehyde was supplied from Aldrich and used without any further treatment.

^{13}C-NMR spectra were recorded on a Varian XL-100 and XL-200 spectrometers in $CDCl_3$ with TMS as internal standart. ^{1}H-NMR spectra were recorded in $CDCl_3$ 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. IR spectra refer to $CHCl_3$ solutions and were recorded with a Perkin Elmer 681 spectrophotometer (data expressed in cm^{-1}). Mass spectra were recorded on a Varian mat 112 spectrometer. UV spectra refer to ethanolic solutions and were recorded on a Perkin Elmer 551 spectrophotometer: λ nm (ε molar). HPLC analyses were performed on a Perkin Elmer series 2 Liquid Chromatography equipped with a RP8 column and a LC75 detector. Melting points are uncorrected.

Typical procedure for the synthesis of 1-oxapyrrolizidines.

In a typical experiment 2.5 mmols of proline, anhydrous DMSO (5 ml) and 5,0 mmols of aldehyde were stirred in a nitrogen atmosphere. When no more suxpended proline was observed the reaction mixture was partitioned between ether and water and extracted three times. The combined organic extracts were dried over sodium sulfate and the solvent removed under reduced pressure. The crude product was examined by 1H-NMR spectroscopy and then flash chromatographed on silica gel [11].

Reaction between proline and benzaldehyde.

The reaction was run for 0.5 hrs at 95° C. Extraction as described above afforded 84% by weight of crude material (composition by 1H-NMR analysis: mostly 1a accompanied by traces of 2a). The crude reaction product was purified by flash chromatography on silica gel (hexane/ethylacetate 9/1) and afforded 1a as pale yellow oil (63%), ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 81.28; H, 7.11; N, 5.38. Calcd. for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.39). $\nu_{max.}$ 1600, 1490, 1450, 1190-1010. λ (ε) 247-273 (780). MS m/z 265 (M^+), 159.

2a , pale yellow oil (2%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1490, 1450, 1190-1010. λ(ε) 245-275 (700). MS m/z 265 (M+) 159.

Reaction between proline and p-nitrobenzaldehyde.

The reaction was performed at room temperature for 2 hrs. After extraction 95% by weight of the crude material was recovered (composition by ^{1}H-NMR analysis 1b: 66%, 2b 34%). The crude material was purified by flash chromatography (hexane/ethylacetate 1/1). Both products were further crystallized from hexane - ethylacetate.

1b (60%), pale yellow needles, mp 110.5-111° C, ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 60.65; H, 4.83; N, 11.64. Calcd. for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83). $\nu_{max.}$ 1600, 1520, 1345, 1190-1010. λ(ε): 279 (19300) MS m/z 355 (M^+), 354, 204.

2b, yellow crystals (30%), mp 109-110° C; ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 60.53; H, 4.88; N, 11.77. Calcd. for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83). $\nu_{max.}$ 1605, 1515, 1345, 1190-1050. λ (ε) 270 (16000). MS m/z 355 (M^+), 204.

Reaction between proline and p-methoxybenzaldehyde.

The reaction was performed at 80-100° C for 2.5 hrs. After extraction 76% of the crude reaction mixture was recovered. ^{1}H-NMR analysis showed that 1c was present as the unique reaction product toghether with unreacted aldehyde. The crude material was purified by flash chromatography (hexane/ethylacetate 8/2).

1c ,pale yellow oil (37%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1610, 1510, 1465, 1250, 1170, 1130-1070, 1030. λ (ε) 226 (13060), 274 (2710), 280 (2300). MS m/z 325 (M^{+}), 189.

Reaction between proline and 4-pyridinaldehyde.

The reaction was performed at room temperature for 3 hrs. Extraction afforded 50% by weight of crude material (composition by ^{1}H-NMR analysis 1e 80%, 2e 20%). The reaction mixture was purified by chromatography on silica gel (chloroform, then chloroform/methanol 9/1, then chloroform/methanol 8/2) affording 1e as an orange amorphous powder (35%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1560 cm^{-1}. λ (ε) 256 (5000). MS m/z 2e, orange amorphous powder (8%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1560, 1410 cm^{-1}. λ (ε) 256 (4100).

Reaction between proline and phenylglyoxal

The reaction was performed at room temperature for 1.5 hrs. Extraction afforded 86% by weight of crude material. ^{1}H-NMR analysis showed that 1d was the unique reaction product. Purification of the crude mixture by chromatography on silica gel hexane/ethylacetate 3/1) afforded 1d as yellow amorphous substance (85%): ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 74.58; H, 5.40; N, 4.26. Calcd. for $C_{20}H_{9}NO_{3}$: C, 74.77; H, 5.29; N, 4.36) ^{1}H-NMR and ^{13}C-NMR as listed $\nu_{max.}$ 1685, 1600, 1580, 1450 cm^{-1}. λ (ε) 242 (25100), 273 (3200), 322 (600). MS m/z 321 (M^{+}), 216, 187.

N-Benzyl alanine with p-nitrobenzaldehyde

After extraction 87% by weight of crude mixture was recovered (Composition: 7b 90%; 8b 10% ; minor amounts of other unidentified diastereoisomers were also present)

7b: pale yellow amorphous substance (60% yields), ^{1}H-HNMR and ^{13}C-NMR as listed. (Found C, 66.12, H, 4.91; N, 9.86. Calcd. for $C_{23}H_{21}N_{3}O_{5}$: C, 65.87; H, 5.01; N, 10.02) $\nu_{max.}$ 1600, 1520, 1345, 1190-1010. λ (ε) 268 (16 230). MS

m/z 419 (M^+), 404, 268, 177.

8b: orange amorphous substance, (6%); ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1520, 1190-1010. λ (ε) 270 (16.200). MS m/z 419 (M^+) 404, 268.

N-Benzyl alanine with benzaldehyde

After extraction 78% by weight was recovered (Composition by ^{1}H-NMR analysis: 7a 30%; 9a 42%; unidentified isomer 12%)

7a: colorless oil (20%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600 ,1490, 1450, 1190-1010. λ (ε) 242-278 (900). MS m/z 329 (M^+), 223, 132.

9a: pale yellow oil (41%), ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 84.00; H, 6.77; N, 4.28: Calcd for $C_{23}H_{23}NO$ C, 83.89; H 6.99; N, 4.25). $\nu_{max.}$ 1600, 1450, 1190-1010. λ (ε) 240-270 (1140). Ms m/z 329 (M^+), 328, 252, 223, 132.

N-methylglycine with p-nitrobenzaldehyde

After extraction 95% by weight was recovered. (Composition by ^{1}H-NMR: 3d 48%, 4d 19%; 5d 17% 6d 17%): Compounds were separated by flash chromatography on silica gel (hexane/ ethyl acetate 8/2, then 6/4, then 4/6).

3d: pale yellow crystals, m.p.=115.5-116.5°C (35%), ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 58.31; H, 4.60; N, 12.68: Calcd. for $C_{16}H_{15}N_3O_5$:C, 58.36; H, 4.56; N, 12.76). $\nu_{max.}$ 1600, 1515, 1345, 1190-1010. λ (ε) 267 (16.620). Ms m/z 329 (M^+), 178, 177, 163.

4d: orange amorphous solid (19%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1515, 1345, 1190-1010. λ (ε) 222 (8900), 267 (13700). MS m/z 329 (M^+), 178, 177.

12a: pale yellow crystals, m.p. 150-150.5°C (3%), ^{1}H-NMR and ^{13}C-NMR as listed. (Found C, 58.42; H 4.15; N 12.39. Calcd for $C_{22}H_{18}N_4O_7$:C, 58.67; H, 4.00; N 12.44). $\nu_{max.}$ 1600, 1515, 1345, 1190-1010. λ (ε) 266 (22 800). MS m/z 450 (M^+), 328, 299, 284.

5d and 6d were not isolated ^{1}H-NMR and ^{13}C-NMR are as listed and were calculated by difference from the crude reaction mixture.

N-Methylglycine with benzaldehyde

After extraction 92% by weight was recovered. (Composition by ^{1}H-NMR analysis: Benzaldehyde 23%; 12a 19%; 5c 33%; 6c 24%). Benzaldehyde was removed under reduced pressure. The residue was flash chromatographed (hexane with 8% of diisopropyl ether), affording benzaldehyde and 12a: The columnn was then washed with methanol and 11a was recovered.

12a: pale yellow needles (hexane-diisopropyl ether: 7%), m.p.= 83-83.5°C. 1H-NMR and 13C-NMR as listed. (Found C, 83.60; H, 6.49; N, 4.41: Calcd. for $C_{22}H_{21}NO$: C, 83.81: H, 6.67:4; N, 4.44). $\nu_{max.}$1600, 1490, 1450, 1190-1010. $\lambda(\varepsilon)$ 246-266 (600). MS m/z 315 (M^+), 209, 194.

11a: higly hygroscopic white needles (30%); ^{1}H-NMR 7.34 (5H, m), 4.76 (1H, dd, J=6-7Hz), 3.06 (2H, bs, disappears with D2O), 2.76 (2H, bs), 2.41 (3H,s). $\nu_{max.}$ 3500, 3300, 1600, 1490, 1450. λ (ε) 44-262 (200). MS m/z 151 (M+), 133, 107,105,91,77.

Reaction between N-benzyl glicine and p-nitrobenzaldehyde.

After extraction 81% by weight was recovered (Composition by ^{1}H-NMR analysis: 3b 38%; 4b 23%; 5b 19%; 6b 21%). Flash chromatography on silica gel (hexane/ethylacetate 3/1 and then 2/1) afforded:

3b: yellow oil (31%). ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1515, 1345, 1190-1010. λ (ε) 266 (13600). MS m/z 405 (M^+), 254, 163.

4b: yellow oil (15%), ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$1600, 1515, 1345, 1190-1010. $\lambda(\varepsilon)$ 266 (15400). MS m/z 405 (M+), 254, 163.

5b and 6b: mixture (4%), yellow needles from ethylacetate-hexane. ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$ 1600, 1515, 1345, 1190-1010. $\lambda(\varepsilon)$ 264 (15600). MS m/z 405 (M+), 283, 254, 163.

Reaction between N-benzylglicine and benzaldehyde.

After extraction 80% by weight of crude mixture was recovered. Flash chromatography (hexane with 4% of diisopropyl ether) afforded:

3a: yellow oil (6%). ^{1}H-NMR and ^{13}C-NMR as listed. $\nu_{max.}$1600, 1490, 1450, 1190-1010. $\lambda(\varepsilon)$ 242-278 (15009). MS m/Z 315 (M^+), 209, 118.

Washing the column with methanol afforded 10b: colorless prisms (ethylacetate), mp= 94.5-95.5° C. (Found C, 79.06; H, 7.53; N, 6.18. Calcd. for $C_{15}H_{17}N$ O: C, 79.29; H, 7.49; N, 6.18) 1H-NMR: 7.33 (10H, m), 4.72 (1H, 4.3, J=8.3 Hz), 3.82 (2H, s), 2.95 (1H, dd, J=4.3, 12 Hz), 2.72 (1H, dd, J=12, 4.3), 2.7 (br, disappears with D_2O). $\nu_{max.}$ 3500-3200, 1600, 1490, 1450, 1110. λ (ε) 251-262 (300). MS m/z 227(M+), 209, 120, 91.

X-Ray analysis of compound 1

Crystal data and details of data collection and refiment are summarized in Tables 6 and 7. All measurement were performed at room temperature (293 + 2 K)

Table 6. Crystal data for compound 1b

Formula	$C_{18}H_{17}N_3O_5$
molecular mass	355.3
crystal dimensions (mm)	0.30×0.13×0.12
system	monoclinic
space group	$P2_1/c$
a (Å)	6.023(2)
b (Å)	11.386(2)
c (Å)	24.973(5)
β (deg)	90.48(2)
V (Å^3)	1712.5(7)
Z	4
D_{obs} (g cm^{-3})	1.38
D_{calc} (g cm^{-3})	1.378
F(000)	744
μ(Mo Kα) (cm^{-1})	0.96

with an Enraf-Nonius CAD-4 diffractometer, using graphite-monochromatized Mo K radiation (λ =0.71073 Å). Reflections with net intensity I<0 were classified as unobserved and were given zero weight. All other reflections were assigned variances $\sigma^2(I)$ based on counting statistic plus the additional term $(0.03\ S)^2$ where S is the scan count. Diffraction data were corrected for Lorentz and polarization factors but not for absorpion.

The structure was solved by direct methods using the program MULTAN[12], and refined by least square techniques. Preliminary positions for the hydrogen atoms were derived from difference maps and geometrical arguments. The refinement was done by minimization of the quantity $\Sigma w(\Delta F)^2$, with weights $\underline{w} = 4F_o^2/\sigma^2(F_o^2)$ for the reflections classified as observed. In the final cycles, the set of parameters simultaneously adjusted included: coordinates and anisotropic temperature coefficients for non hydrogen atoms, coordinates and isotropic B's for hydrogen atoms, a scale factor, and a secondary coefficient g. Final atomic coordinates are given in Table 8[13]. A selected portion of the molecular geometry is given in Table 9.

Table 7. Details of X-ray data collection and refinement for compound 1b

scan type	ω
scan rate (deg min^{-1})	1.5 - 10
scan width (deg)	1.1+0.35tanθ
max. 2θ	50
no. of independent reflections measured	2992
M = no. of reflections included in the refinement (I>0)	2460
M_1 = no. of reflections with I>2σ(I)	1373
P = no. of parameters refined	304
g (isotropic extinction coeff.) $\times 10^7$	3.0(6)
R^a (on M)	0.091
R (on M_1)	0.060
$R_{\underline{w}}^b$ (on M)	0.063
S^c	1.26
convergence, largest shift	0.10σ

[a] $R = \Sigma\left|\,|F_o|-|F_c|\,\right|/\Sigma|F_o|$; [b] $R_{\underline{w}} = \left[\Sigma\underline{w}(|F_o|-|F_c|)^2/\Sigma\underline{w}F_o^2\right]^{\frac{1}{2}}$

[c] $S = \left[\Sigma\underline{w}(|F_o|-|F_c|)^2/(M-P)\right]^{\frac{1}{2}}$

TABLE 8. Positional parameters for the non-hydrogens atom of 1b with estimated standart deviations in parentheses

Atom	x	y	z
O1	0.0979(4)	0.0852(2)	0.1840(1)
O2	-0.5448(4)	0.5563(2)	0.2449(1)
O3	-0.3304(5)	0.6742(2)	0.2038(1)
O4	0.4568(5)	0.4905(3)	-0.0841(1)
O5	0.7139(5)	0.3589(3)	-0.0834(1)
N1	0.1206(5)	0.0184(2)	0.0963(1)
N2	-0.3823(5)	0.5771(3)	0.2176(1)
N3	0.5379(6)	0.3981(3)	-0.0687(1)
C1	0.1404(5)	0.1850(3)	0.1521(1)
C2	0.0766(5)	0.1454(3)	0.0954(1)
C3	0.1593(6)	-0.0140(3)	0.1525(2)
C4	-0.0657(8)	-0.0542(4)	0.0772(2)
C5	-0.1681(9)	-0.1033(4)	0.1237(2)
C6	0.0114(8)	-0.1169(4)	0.1643(2)
C11	0.0122(5)	0.2894(3)	0.1717(1)
C12	0.0829(5)	0.4027(3)	0.1626(1)
C13	-0.0440(6)	0.4968(3)	0.1775(2)
C14	-0.2445(6)	0.4769(3)	0.2016(1)
C15	-0.3170(5)	0.3653(3)	0.2124(1)
C16	-0.1900(6)	0.2713(3)	0.1969(1)
C21	0.1953(5)	0.2098(3)	0.0511(1)
C22	0.1060(6)	0.3103(3)	0.0290(1)
C23	0.2149(7)	0.3719(3)	-0.0104(2)
C24	0.4186(6)	0.3310(3)	-0.0268(1)
C25	0.5114(6)	0.2322(4)	-0.0063(2)
C26	0.3974(6)	0.1712(3)	0.0331(2)

TABLE 9. Selected portion of the molecular geometry of 1b

a) Bond lengths (Å)

C1-C2	1.532(4)	N1-C4	1.470(5)
C1-O1	1.412(4)	C4-C5	1.433(7)
C1-C11	1.502(5)	C5-C6	1.484(7)
C2-N1	1.470(4)	C6-C3	1.502(6)
C2-C21	1.511(4)	C3-O1	1.428(5)
N1-C3	1.468(5)		

b) Bond angles (deg)

C2-C1-O1	103.9(2)	C3-N1-C4	106.4(3)
C2-C1-C11	114.1(2)	N1-C4-C5	106.8(4)
O1-C1-C11	110.9(2)	C4-C5-C6	106.2(4)
C1-C2-N1	103.3(3)	C4-C6-C3	102.4(4)
C1-C2-C21	114.7(3)	C6-C3-N1	107.1(4)
N1-C2-C21	113.7(3)	C6-C3-O1	110.6(3)
C2-N1-C3	106.9(2)	N1-C3-O1	106.7(3)
C2-N1-C4	114.3(3)	C3-O1-C1	106.0(3)

c) Torsion angles (deg)

C11-C1-C2-N1	-150.4(2)	C4-N1-C2-C1	128.7(3)
C11-C1-C2-C21	85.3(3)	C4-N1-C2-C21	-106.3(3)
C11-C1-C2-H2	-32(2)	C4-N1-C2-H2	13(2)
H1-C1-C2-N1	90(2)	C4-N1-C3-O1	-111.9(3)
H1-C1-C2-C21	-34(2)	C4-N1-C3-H3	139(2)
H1-C1-C2-H2	-152(2)	C1-O1-C3-H3	84(2)
O1-C1-C2-C21	-153.9(2)	C3-O1-C1-C11	160.0(3)

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