Synthesis of 2,3-Dihydropyrrolizines from Weinreb 3-(Pyrrolidin-2-ylidene)propionamides or Weinreb *N*-Vinylprolinamides

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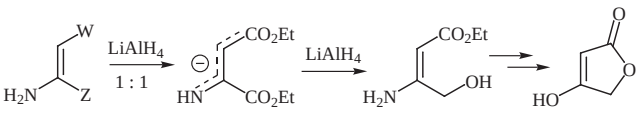
Abstract: Weinreb 3-(pyrrolidin-2-ylidene)propionamides and Weinreb *N*-vinylprolinamides were used for the synthesis of 2,3-dihydropyrrolizines. The selective reaction of the carboxamide group with organometallic compounds allowed us to obtain a great variety of carbonyl intermediates, analogous to the Hantzsch and Knorr pyrrole synthesis, which were thermally cyclized.

Key words: Weinreb amides, cyclizations, amines, pyrroles, bicyclic pyrrolizines

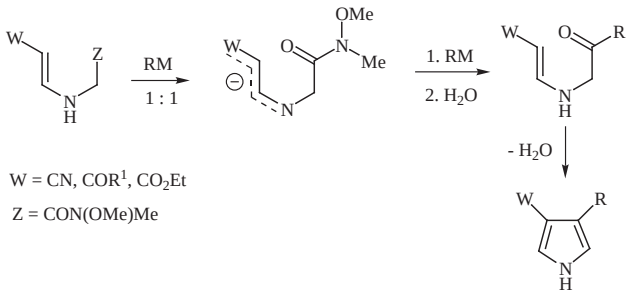
β-Functionalized enamines have been widely used with great success in the synthesis of a great variety of heterocycles.[1,2] However, there are few procedures in which one of the key stages is based on the use of these substrates as deactivated and inert systems towards determinate reagents. For example, the tetronic acid was prepared starting from diethyl aminomaleate by selective reduction of only one of the two ester groups present in the molecule[3] (Scheme 1). More recently, we have described a modified Knorr synthesis starting from Weinreb α-enamino carboxamides (Scheme 2) in which organometallic reagents selectively attack the carboxamide group, and the W function (ketone, ester or nitrile) remains untransformed.[4] In both schemes, the intermediate anion deactivates the conjugated W function with the enamine and, if an excess of the organometallic compound is used, this allows the selective reaction of other Z functions present in the molecule.



W = Z = CO_2Et

Scheme 1

The characteristics of the final heterocycles will depend, among other factors, on the nature and position of the chain which links the Z function with the enamine. In Figure 1 we show three general synthons of which one type C was used for the formation of the tetronic acid and one type B in the synthesis of pyrroles. Among the multiple possibilities of the above, in this paper we have developed two complementary procedures for the synthesis of 2,3-dihydro-1*H*-pyrrolizines starting from type A or B structures. In both, we started from pyrrolidine derivatives and the processes were completed with the formation of C6–N7 or C4–C5 bonds (Scheme 3). They are, respectively, variations of the Hantzsch and Knorr pyrrole synthesis in which the versatile Weinreb amides were precursors of the traditional carbonyl intermediates. Our objective with this type of key synthon was not to obtain entirely new synthetic designs, but rather to modify some of the procedural stages already described with the aim of increasing their potential with simple chemical processes.



W = CN, COR^1, CO_2Et

Z = CON(OMe)Me

Scheme 2

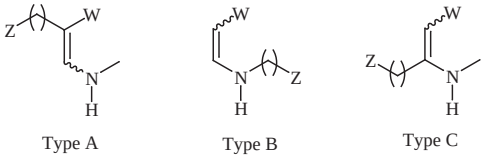
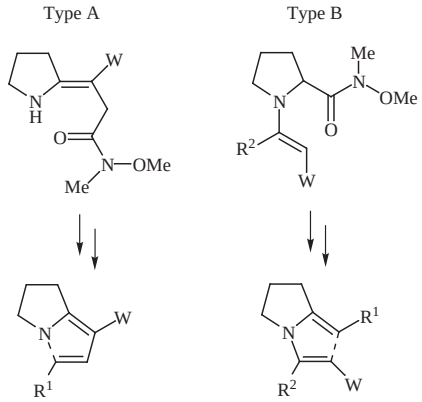


Figure 1



Scheme 3

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Method A

This procedure (Scheme 4) is referable to those described by other authors for the synthesis of pyrrolizinones starting from ethyl pyrrolidin-2-ylideneacetate (**3**) and ethyl bromoacetate.[5] In our case *N*-methoxy-*N*-methyl-α-bromoacetamide (**4**) was used, which, in THF–LDA, chiefly produced *C*-alkylation in the enamine derivatives **1**–**3** to give the key intermediates **5**–**7** (55–70%, Table 1). In the said intermediates, which are secondary enamines, the deactivation of the W function (**8**–**10**) was complete in the presence of organometallic compounds (R^1MgX, R^1Li, DIBAL) and the Weinreb amide reacted selectively to give the carbonyl compounds **11**–**13** without limitations in the nature of the incorporated substituent (R^1 = H, alkyl, ethenyl, ethynyl, aryl or masked function). Normally, a strict control of the temperature and proportion of reagents is unnecessary and it is advisable to use tetrahydrofuran as the solvent.

The ketonic intermediates **11**–**13** were obtained as a mixture of *Z*/*E* isomer olefins in a push–pull equilibrium. Their partial or total cyclization to **14**–**16** took place spontaneously and, consequently, no attempt was made to isolate **11**–**13** from the reaction mixture and the process was continued at reflux in chloroform in the presence of silica gel in order to obtain a complete transformation to pyrrolizines **14**–**16** (Table 2).

Although substrates analogous to **1**–**3** have been described in which W is a carbonyl group,[6] we have not used them as starting products for the synthesis of 7-acyl-2,3-dihydropyrrolizine derivatives **17**–**18**. These were prepared by reaction of their analogous cyano derivatives **14** with organolithium reagents (Scheme 5). The adequate selection of the two stages in which organometallic compounds are used, potentially gives great versatility to this simple synthetic sequence.

Method B

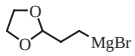
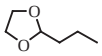
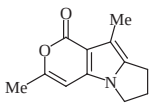
The second procedure (Scheme 6) is an extension of our own method developed from β-functionalized enamines

Table 1 Preparation and Physical Data of Enamines[a] **5**–**7, 25**–**29**

Start	Conditions	Product (% Yield)	Mp (°C)	IR (KBr) (cm^{-1})	^1H NMR or ^{13}C NMR ($CDCl_3$), δ, *J* (Hz)
1 + **4**	LDA–THF –78→0 °C	**5** (70)	90	2181,1668, 1622	^1H NMR: 2.03 (m, 2 H, *J* = 7.4), 2.77 (t, 2 H, *J* = 7.4), 3.17 (s, 2 H), 3.19 (s, 3 H), 3.49 (t, 2 H, *J* = 7.4), 3.81 (s, 3 H), 6.61 (br s, 1 H, NH)
2 + **4**	LDA–THF –78→0 °C	**6** (77)	67	1659, 1596	^1H NMR: 1.95 (m, 2 H, *J* = 7.5), 2.59 (t, 2 H, *J* = 7.5), 3.15 (s, 3 H), 3.27 (s, 2 H), 3.51 (t, 2 H, *J* = 7.5), 3.60 (s, 3 H), 3.69 (s, 3 H), 8.21 (br s, 1 H, NH)
3 + **4**	LDA–THF –78→0 °C	**7** (65)	87	1662, 1590	^1H NMR: 1.23 (t, 3 H, *J* = 7.1), 1.99 (m, 2 H, *J* = 7.4), 2.64 (t, 2 H, *J* = 7.4), 3.19 (s, 3 H), 3.30 (s, 2 H), 3.54 (t, 2 H, *J* = 7.4), 3.73 (s, 3 H), 4.09 (q, 2 H, *J* = 7.1), 8.25 (br s, 1 H, NH)
19 + **24**	MeOH, reflux, 36 h	**25** (31)	62	2194,1670, 1621	^{13}C NMR: 23.4 (CH_3), 30.0 (CH_2), 32.3 (CH_3), 48.1 (br, CH_2), 61.0 (br, CH), 61.4 (CH_3), 62.0 (CH), 121.7 (C), 149.9 (CH), 171.9 (C)
20 + **24**	MeOH, reflux, 7 h	**26** (82)	75	2178,1680, 1572	^{13}C NMR: 18.9 (CH_3), 23.2 (CH_2), 30.5 (CH_2), 32.6 (CH_3), 49.1 (CH_2), 58.8 (CH), 61.6 (CH_3), 62.3 (CH), 122.4 (C), 159.2 (C), 172.8 (C)
21 + **24**	MeOH, reflux, 48 h	**27** (52)	133	1666,1538 1222, 759, 711	^{13}C NMR:[c] 17.6 (CH_3), 22.7 and 23.2 (CH_2), 30.0 (CH_2), 32.5 (CH_3), 48.9 and 49.2 (CH_2), 58.7 (CH), 61.4 (CH_3), 93.2 and 93.9 (CH), 127.1 (2 CH), 127.8 (2 CH), 130.1 (CH), 142.7 (C), 160.7 (C), 172.7 (C)
22 + **24**	MeOH, reflux, 40 h	**28** (51)	oil	1680,1610, 1143[b]	^{13}C NMR: 13.9 (CH_3), 22.8 (CH_2), 29.4 (br, CH_2), 31.6 (CH_3), 46.6 (br, CH_2), 57.9 (CH_2), 60.8 (CH_3), 61.0 (br, CH), 147.4 (CH), 168.4 (C), 171.7 (br, C)
23 + **24**	Et_3N–CH_2Cl_2 r.t., 24 h	**29** (48)	89	1695,1646, 1541	^{13}C NMR: 20.0 (CH_3), 22.9 (CH_2), 29.9 and 30.1 (CH_2), 32.2 (CH_3), 48.1 and 48.4 (CH_2), 58.1 (CH), 61.4 (CH_3), 81.5 and 82.1 (CH), 96.3 and 97.0 (CH), 155.7 (C), 161.4 (C), 164.6 (C), 171.5 and 172.4 (C)

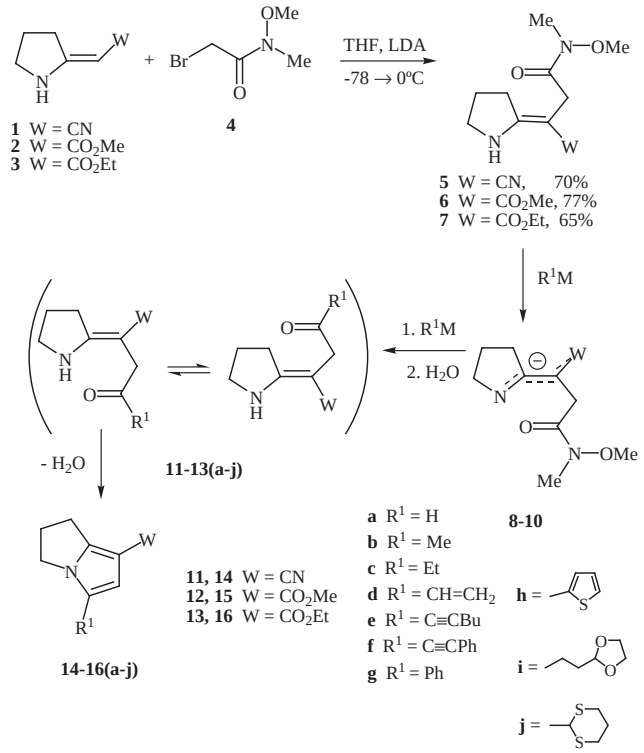
[a] Satisfactory microanalyses were obtained: C ± 0.30, H ± 0.30, N ± 0.30.
[b] Film.
[c] Undetected C=O.

Table 2 Preparation of 2,3-Dihydropyrrolizines (**14–16, 35–39**) from **5–7, 19–23**

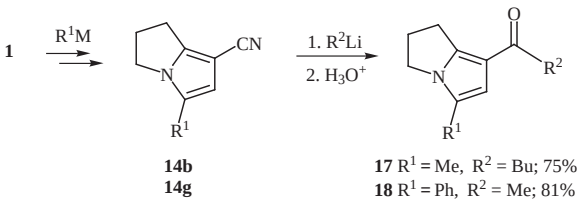
Reaction with organometallic compounds					Cyclization					
Start	R^1M	Ratio	Temp (°C)	Time (min)	Solvent reflux	Time (min)	W	R^1	R^2	Pyrrolizine (% Yield)[a]
5	DIBALH	1:2.5	–40	15	-[c]	–	CN	H	–	**14a** (50)
5	MeLi	1:2.5	–40	15	$CHCl_3$	45	CN	Me	–	**14b** (83)
5	EtBrMg	1:3	0→20	60[b]	$CHCl_3$	45	CN	Et	–	**14c** (40)
5	PhC≡CLi	1:2.5	0	30	$CHCl_3$	45	CN	PhC≡C	–	**14f** (60)
5	PhLi	1:2.5	–40	15	$CHCl_3$	120	CN	Ph	–	**14g** (56)
5		1:3	0→20	60[b]	$CHCl_3$	45	CN		–	**14i** (49)
5		1:2.5	–40	15	$CHCl_3$	45	CN		–	**14j** (99)
6	CH_2=CHLi	1:2.5	–30	30	$CHCl_3$	45	CO_2Me	CH_2=CH	–	**15d** (44)
6	BuC≡CLi	1:3	–40	30	$CHCl_3$	45	CO_2Me	BuC≡C	–	**15e** (75)
6		1:2.5	–40	30	$CHCl_3$	45	CO_2Me		–	**15h** (80)
7	DIBALH	1:2.5	–40	15	-[c]	–	CO_2Et	H	–	**16a** (53)
7	MeLi	1:2.5	–40	15	-[c]	–	CO_2Et	Me	–	**16b** (74)
7	PhLi	1:2.5	–40	10	$CHCl_3$	90	CO_2Et	Ph	–	**16g** (67)
19	MeLi	1:1.5	–40	25	Toluene	60	CN	Me	H	**35b** (92)
19	PhC≡CLi	1:2.5	0	90	Toluene	60	CN	PhC≡C	H	**35f** (65)
20	MeLi	1:1.5	–40	30	$CHCl_3$	60	CN	Me	Me	**36b** (81)
20	BuC≡CLi	1:3	0	40	$CHCl_3$	60	CN	BuC≡C	Me	**36e** (95)
20	PhC≡CLi	1:2.5	0	80	$CHCl_3$	60	CN	PhC≡C	Me	**36f** (72)
20	HC≡CLi	1:3	r.t.	60	$CHCl_3$	60	CN	HC≡C[b]	Me	**36k** (87)
21	MeLi	1:3	–40	60	$CHCl_3$	30	COPh	Me	Me	**37b** (67)
22	MeLi	1:1.5	–40	20	Toluene	60	CO_2Et	Me	H	**38b** (61)
22	PhC≡CLi	1:2.5	0	90	Toluene	60	CO_2Et	PhC≡C	H	**38f** (53)
23	MeLi	1:1.5	–40	15	Xylene	60				**39b** (79)

[a] Yield from **5**–**7**, **19**–**23**.
[b] Ultrasonic bath.
[c] Spontaneous cyclization.

and Weinreb α-amino amides[4] (Scheme 2). The principal difference is that the key intermediates **25**–**29** are tertiary enamines and that the deactivation of the W group toward the organometallic reagents is only partial (compare structures **8**–**10** in Scheme 4 with **25′**–**29′** in Scheme 6). As a consequence, control of the selective reaction of the Weinreb amide group with organometallic reagents was less satisfactory than with the secondary enamines **5**–**7**. Only the less basic organolithium compounds at –40 °C (e.g. MeLi and RC≡CLi) allowed us to prepare the ketones **30**–**34**. The rest of the organolithium (PhLi, BuLi) or dialkylmagnesium compounds (Bu_2Mg) led to complex reaction mixtures in which the transposition of the methoxy group occurred in a high proportion.[4] Moreover, neither were the results of the alkylmagnesium halides effective, given that at low temperatures no evolution of **25**–**29** was observed and at high temperatures the process could not be controlled.

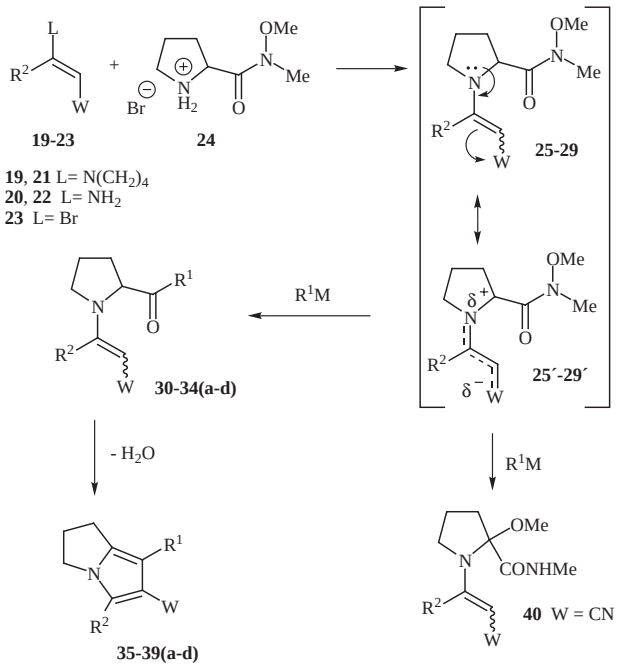


Scheme 4



Scheme 5

As in the Method A the ketonic intermediates **30**–**34** were not isolated from the reaction mixture. Their cyclization conditions to pyrrolizines **35**–**39** not only depended on the reactivity of the carbonyl group (COMe > COCCR), but also on the nature of R^2. The structures with R^2 = H required more vigorous cyclization conditions (reflux of toluene in the presence of silica gel) than their analogues with R^2 = Me (reflux of chloroform in the presence silica-gel). A simple explanation for this phenomenon can be found in the conformational stability with regard to theenamine bond C–N: as the size of R^2 increases, the adequate conformation for cyclization is favoured. On the other hand, the pyrrolizine **39**, fused to a pyranone, was only obtained at high temperatures by means of xylene reflux.



19, 25, 30, 35 W= CN, R^2= H
20, 26, 31, 36 W= CN, R^2= Me
21, 27, 32, 37 W= COPh, R^2= Me
22, 28, 33, 38 W= CO_2Et, R^2= H
23, 29, 34, 39 W-R^2= CO_2CMe=CH

b R^1= Me
e R^1= C≡CBu
f R^1= C≡CPh
k R^1= C≡CH

Scheme 6

In short, Method B presented greater limitations than Method A in the incorporation of the R^1 group via organometallic reagents. However, the advantage was that enamines **19**–**23** were more accessible and varied than the 2-methylidenepyrrolidines **1**–**3**, in which the nitrogenated exchange to **25**–**28** occurred easily in refluxing methanol. In the 4-amino-6-methyl-2*H*-pyran-2-one the amino substituent was an inefficient leaving group. Consequently, the 4-bromo derivative **23** was used and its reaction with the α-aminocarboxamide **24** was carried out at 20 °C in dichloromethane–triethylamine to give **29**.

Table 3 Physical Data[a] for Pyrrolizines **14**–**18**, **35**–**39** and Enamino Nitrile **40**[b]

Product	Mp or bp (°C)	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ
14a	62	2217, 1550, 1300	2.55 (m, 2 H, *J* = 7.3), 2.93 (t, 2 H, *J* = 7.3), 3.97 (t, 2 H, *J* = 7.3), 6.36 (d, 1 H, *J* = 2.8), 6.53 (d, 1 H, *J* = 2.8)	24.1 (CH_2), 27.0 (CH_2), 47.2 (CH_2), 83.7 (C), 115.1 (CH), 115.2 (CH), 117.2 (C), 145.1 (C)
14b	73	2208, 1532, 1428, 1303	2.16 (s, 3 H), 2.55 (m, 2 H, *J* = 7.4), 2.96 (t, 2 H, *J* = 7.4), 3.86 (t, 2 H, *J* = 7.4), 6.07 (s, 1 H)	11.6 (CH_3), 24.6 (CH_2), 27.0 (CH_2), 45.2 (CH_2), 82.9 (C), 111.8 (CH), 117.7 (C), 124.6 (C), 143.9 (C)

Table 3 Physical Data[a] for Pyrrolizines **14**–**18**, **35**–**39** and Enamino Nitrile **40**[b] (continued)

Product	Mp or bp (°C)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ
14c	84	2206, 1529, 1305	1.20 (t, 3 H, *J* = 7.5), 2.50 (q, 2 H, *J* = 7.5), 2.56 (m, 2 H, *J* = 7.2), 2.96 (t, 2 H, *J* = 7.2), 3.88 (t, 2 H, *J* = 7.2), 6.08 (s, 1 H)	12.7 (CH_3), 19.6 (CH_2), 24.4 (CH_2), 27.0 (CH_2), 45.3 (CH_2), 82.9 (C), 110.4 (CH), 117.7 (C), 131.0 (C), 143.9 (C)
14f	112	2219, 1474, 1144, 755, 691	2.61 (m, 2 H, *J* = 7.2), 3.04 (t, 2 H, *J* = 7.2), 4.09 (t, 2 H, *J* = 7.2), 6.67 (s, 1 H), 7.34–7.41 (m, 5 H, Ar)	25.0 (CH_2), 26.6 (CH_2), 46.5 (CH_2), 78.0 (C), 84.8 (C), 92.3 (C), 110.9 (C), 116.3 (C), 120.2 (CH), 122.3 (C), 128.3 (2 CH), 128.4 (CH), 131.1 (2 CH), 145.0 (C)
14g	102	2221, 1601, 1488, 1153, 757, 692	2.59 (m, 2 H, *J* = 7.5), 3.03 (t, 2 H, *J* = 7.5), 4.15 (t, 2 H, *J* = 7.5), 6.55 (s, 1 H), 7.26–7.43 (m, 5 H, Ar)	24.3 (CH_2), 27.2 (CH_2), 47.7 (CH_2), 84.8 (C), 112.8 (CH), 117.1 (C), 126.0 (2 CH), 127.1 (CH), 128.8 (2 CH), 130.0 (C), 131.4 (C), 146.3 (C)
14i	101	2207, 1530, 1396, 1142, 1031	1.93 (m, 2 H), 2.55 (m, 2 H, *J* = 7.4), 2.61 (m, 2 H), 2.96 (t, 2 H, *J* = 7.4), 3.82–4.01 (m, 4 H, AA′BB′), 3.88 (t, 2 H, *J* = 7.4), 4.90 (t, 1 H, *J* = 4.5), 6.10 (s, 1 H)	20.6 (CH_2), 24.5 (CH_2), 27.0 (CH_2), 32.6 (CH_2), 45.4 (CH_2), 64.9 ($2CH_2$), 83.1 (C), 103.2 (CH), 111.2 (CH), 117.6 (C), 128.4 (C), 144.1 (C)
14j	186	2214, 1420, 1300, 767	1.82–2.20 (m, 2 H), 2.55 (m, 2 H, *J* = 7.3), 2.86–3.05 (m, 4 H), 2.96 (t, 2 H, *J* = 7.3), 4.15 (t, 2 H, *J* = 7.4), 5.18 (s, 1 H), 6.44 (s, 1 H)	24.4 (CH_2), 24.9 (CH_2), 26.9 (CH_2), 31.3 (2 CH_2), 42.0 (CH), 47.1 (CH_2), 84.2 (C), 114.4 (CH), 116.9 (C), 125.6 (C), 146.1 (C)
15d	oil	1701, 1228, 1085, 774[c]	2.52 (m, 2 H, *J* = 7.4), 3.04 (t, 2 H, *J* = 7.4), 3.77 (s, 3 H), 4.01 (t, 2 H, *J* = 7.4), 5.00 (d, 1 H, *J* = 11.5), 5.37 (d, 1 H, *J* = 17.8), 6.43 (dd, 1 H, *J* = 11.5, 17.8), 6.62 (s, 1 H)	25.2 (CH_2), 26.6 (CH_2), 46.4 (CH_2), 50.7 (CH_3), 107.1 (C), 109.9 (CH_2), 111.9 (CH), 126.1 (CH), 127.3 (C), 144.8 (C), 165.3 (C)
15e	185/0.1 mmHg	1711, 1229, 1087, 722 [c]	0.94 (t, 3 H, *J* = 7.2), 1.47 (m, 2 H), 1.54 (m, 2 H), 2.41 (t, 2 H, *J* = 7.0), 2.52 (m, 2 H, *J* = 7.3), 3.07 (t, 2 H, *J* = 7.3), 3.77 (s, 3 H), 3.96 (t, 2 H, *J* = 7.3), 6.68 (s, 1 H)	13.6 (CH_3), 19.2 (CH_2), 21.9 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 30.7 (CH_2), 46.0 (CH_2), 50.9 (CH_3), 71.3 (C), 92.9 (C), 106.8 (C), 110.8 (C), 117.4 (CH), 144.0 (C), 165.1 (C)
15h	143	1686, 1206, 1093, 767	2.59 (m, 2 H, *J* = 7.3), 3.13 (t, 2 H, *J* = 7.3), 3.81 (s, 3 H), 4.16 (t, 2 H, *J* = 7.3), 6.78 (s, 1 H), 7.01–7.27 (m, 3 H, Ar)	25.6 (CH_2), 26.9 (CH_2), 47.1 (CH_2), 50.9 (CH_3), 107.5 (C), 111.5 (CH), 122.4 (CH), 123.3 (C), 123.4 (CH), 127.5 (CH), 134.8 (C), 144.9 (C), 165.4 (C)
16a	27	1699, 1246, 1122, 714	1.32 (t, 3 H, *J* = 7.1), 2.51 (m, 2 H, *J* = 7.4), 3.04 (t, 2 H, *J* = 7.4), 3.94 (t, 2 H, *J* = 7.4), 4.24 (q, 2 H, *J* = 7.1), 6.52 (d, 1 H, *J* = 2.9), 6.58 (d, 1 H, *J* = 2.9)	14.4 (CH_3), 25.4 (CH_2), 26.9 (CH_2), 46.7 (CH_2), 59.1 (CH_2), 106.9 (C), 113.3 (CH), 114.5 (CH), 143.8 (C), 165.1 (C)
16b	58	1697, 1210, 1081, 767	1.31 (t, 3 H, *J* = 7.1), 2.16 (s, 3 H), 2.50 (m, 2 H, *J* = 7.3), 3.05 (t, 2 H, *J* = 7.3), 3.83 (t, 2 H, *J* = 7.3), 4.22 (q, 2 H, *J* = 7.1), 6.26 (s, 1 H)	11.6 (CH_3), 14.5 (CH_3), 25.8 (CH_2), 26.8 (CH_2), 44.8 (CH_2), 59.0 (CH_2), 106.1 (C), 109.9 (CH), 123.9 (C), 142.5 (C), 165.3 (C)
16g	94	1693, 1248, 1184, 1090, 761, 697	1.34 (t, 3 H, *J* = 7.1), 2.52 (m, 2 H, *J* = 7.4), 3.11 (t, 2 H, *J* = 7.4), 4.12 (t, 2 H, *J* = 7.4), 4.27 (q, 2 H, *J* = 7.1), 6.79 (s, 1 H), 7.21–7.46 (m, 5 H, Ar)	14.5 (CH_3), 25.5 (CH_2), 27.1 (CH_2), 47.4 (CH_2), 59.3 (CH_2), 107.7 (C), 111.3 (CH), 125.8 (2 CH), 126.4 (CH), 128.6 (2 CH), 129.3 (C), 132.4 (C), 145.2 (C), 165.1 (C)
17	195/1 mmHg	1645, 1523, 1428[c]	0.91 (t, 3 H, *J* = 7.3), 1.36 (m, 2 H, *J* = 7.3 and *J* = 7.4), 1.64 (m, 2 H, *J* = 7.4 and *J* = 7.5), 2.16 (s, 3 H), 2.52 (m, 2 H, *J* = 7.4), 2.62 (t, 2 H, *J* = 7.5), 3.08 (t, 2 H, *J* = 7.4), 3.82 (t, 2 H, *J* = 7.4), 6.26 (s, 1 H)	11.5 (CH_3), 13.9 (CH_3), 22.5 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 27.0 (CH_2), 39.4 (CH_2), 44.6 (CH_2), 109.5 (CH), 116.5 (C), 124.2 (C), 141.8 (C), 196.0 (C)
18	109	1643, 763, 694	2.42 (s, 3 H), 2.60 (m, 2 H, *J* = 7.3), 3.19 (t, 2 H, *J* = 7.3), 4.17 (t, 2 H, *J* = 7.3), 6.77 (s, 1 H), 7.25–7.49 (m, 5 H, Ar)	26.2 (CH_2), 27.2 (CH_2), 27.7 (CH_3), 47.2 (CH_2), 111.1 (C), 118.0 (C), 126.0 (2 CH), 126.8 (CH), 128.8 (2 CH), 129.6 (C), 132.3 (C), 144.7 (C), 193.4 (C)

Table 3 Physical Data[a] for Pyrrolizines **14**–**18**, **35**–**39** and Enamino Nitrile **40**[b] (continued)

Product	Mp or bp (°C)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), δ
35b	67	2210, 1718, 1504, 770	2.08 (s, 3 H), 2.50 (m, 2 H, *J* = 7.2), 2.73 (t, 2 H, *J* = 7.2), 3.94 (t, 2 H, *J* = 7.2), 6.99 (s, 1 H)	9.8 (CH_3), 22.6 (CH_2), 27.6 (CH_2), 46.8 (CH_2), 96.2 (C), 112.6 (C), 117.0 (C), 120.3 (CH), 135.0 (C)
35f	86	2218, 1689, 751, 689	2.56 (m, 2 H, *J* = 7.3), 2.95 (t, 2 H, *J* = 7.3), 4.01 (t, 2 H, *J* = 7.3), 7.04 (s, 1 H), 7.30–7.52 (m, 5 H, Ar)	23.8 (CH_2), 27.1 (CH_2), 47.5 (CH_2), 80.9 (C), 91.9 (C), 98.6 (C), 99.5 (C), 115.5 (C), 121.4 (CH), 123.2 (C), 127.8 (CH), 128.1 (2 CH), 131.2 (2 CH), 141.9 (C)
36b	88	2202, 1428	2.04 (s, 3 H), 2.28 (s, 3 H), 2.48 (m, 2 H, *J* = 7.1), 2.72 (t, 2 H, *J* = 7.1), 3.79 (t, 2 H, *J* = 7.1)	9.9 (CH_3), 11.2 (CH_3), 22.9 (CH_2), 27.5 (CH_2), 44.7 (CH_2), 94.2 (C), 111.2 (C), 117.4 (C), 131.3 (C), 132.5 (C)
36e	98	2211, 1423	0.94 (t, 3 H, *J* = 7.2), 1.48 (m, 2 H), 1.58 (m, 2 H), 2.29 (s, 3 H), 2.40 (t, 2 H, *J* = 7.0), 2.51 (m, 2 H, *J* = 7.1), 2.86 (t, 2 H, *J* = 7.1), 3.83 (t, 2 H, *J* = 7.1)	11.2 (CH_3), 13.7 (CH_3), 19.3 (CH_2), 21.9 (CH_2), 24.0 (CH_2), 27.1 (CH_2), 31.0 (CH_2), 45.4 (CH_2), 72.0 (C), 92.4 (C), 96.1 (C), 98.9 (C), 116.3 (C), 132.0 (C), 139.2 (C)
36f	120	2213, 1489, 758, 692	2.28 (s, 3 H), 2.51 (m, 2 H, *J* = 7.3), 2.90 (t, 2 H, *J* = 7.3), 3.84 (t, 2 H, *J* = 7.3), 7.27–7.49 (m, 5 H, Ar)	11.2 (CH_3), 24.1 (CH_2), 26.9 (CH_2), 45.4 (CH_2), 81.4 (C), 91.6 (C), 96.0 (C), 97.9 (C), 116.0 (C), 123.4 (C), 127.7 (CH), 128.1 (2 CH), 131.1 (2 CH), 132.6 (C), 140.1 (C)
36k	149	3253, 2209, 2101, 1405, 615	2.31 (s, 3 H), 2.54 (m, 2 H, *J* = 7.3), 2.90 (t, 2 H, *J* = 7.3), 3.14 (s, 1 H), 3.87 (t, 2 H, *J* = 7.3)	11.2 (CH_3), 24.0 (CH_2), 26.9 (CH_2), 45.5 (CH_2), 75.7 (CH), 79.6 (C), 96.5 (C), 96.9 (C), 115.7 (C), 132.5 (C), 141.1 (C)
37b	109	1623, 1421, 1375, 730, 699	1.93 (s, 3 H), 2.09 (s, 3 H), 2.45 (m, 2 H, *J* = 7.2), 2.74 (t, 2 H, *J* = 7.2), 3.79 (t, 2 H, *J* = 7.2), 7.36–7.69 (m, 5 H, Ar)	11.6 (CH_3), 12.6 (CH_3), 22.7 (CH_2), 27.1 (CH_2), 44.3 (CH_2), 106.3 (C), 123.8 (C), 128.0 (2 CH), 128.8 (2 CH), 129.7 (C), 130.9 (CH), 133.2 (C), 141.8 (C), 193.9 (C)
38b	175/0.4 mmHg[d]	1703, 1233, 1079[c]	1.31 (t, 3 H, *J* = 7.1), 2.19 (s, 3 H), 2.41 (m, 2 H, *J* = 7.2), 2.69 (t, 2 H, *J* = 7.2), 3.86 (t, 2 H, *J* = 7.2), 4.21 (q, 2 H, *J* = 7.1), 7.16 (s, 1 H)	10.7 (CH_3), 14.0 (CH_3), 22.1 (CH_2), 27.1 (CH_2), 46.0 (CH_2), 58.6 (CH_2), 110.8 (C), 117.2 (C), 119.0 (CH), 135.0 (C), 165.3 (C)
38f	86	3135, 2213, 1694, 1212	1.36 (t, 3 H, *J* = 7.1), 2.51 (m, 2 H, *J* = 7.3), 2.95 (t, 2 H, *J* = 7.3), 3.98 (t, 2 H, *J* = 7.3), 4.30 (q, 2 H, *J* = 7.1), 7.22 (s, 1 H), 7.23–7.53 (m, 5 H, Ar)	14.4 (CH_3), 24.0 (CH_2), 27.1 (CH_2), 47.2 (CH_2), 59.7 (CH_2), 83.7 (C), 90.8 (C), 96.8 (C), 120.0 (CH), 120.2 (C), 124.4 (C), 127.3 (CH), 128.1 (2CH), 131.2 (2 CH), 143.0 (C), 164.2 (C)
39b	168	1703, 1630, 1485, 1312	2.24 (s, 3 H), 2.28 (s, 3 H), 2.54 (m, 2 H, *J* = 7.2), 2.80 (t, 2 H, *J* = 7.2), 3.90 (t, 2 H, *J* = 7.2), 6.08 (s, 1 H)	10.0 (CH_3), 19.8 (CH_3), 22.2 (CH_2), 27.6 (CH_2), 44.0 (CH_2), 94.0 (CH), 108.4 (C), 109.3 (C), 134.6 (C), 137.2 (C), 154.2 (C), 161.2 (C)
40	oil	3353, 2194, 1680, 1582, 1539 [c]	2.04 (m, 2 H), 2.14 (s, 3 H), 2.24 (m, 2 H), 2.84 (d, 3 H, *J* = 4.8), 3.25 (s, 3 H), 3.50 (m, 2 H), 4.07 (s, 1 H), 7.01 (q, 1 H, NH, *J* = 4.8)	18.0 (br, CH_3), 21.9 (CH_2), 25.8 (CH_3), 35.8 (CH_2), 49.5 (CH_3), 51.1 (CH_2), 66.6 (CH), 95.2 (C), 121.1 (C), 159.1 (C), 171.5 (C).

[a] Satisfactory microanalyses were obtained: C ± 0.30, H ± 0.30, N ± 0.30.
[b] Compound selected from series **40**.
[c] Film.
[d] With decomposition.

The NMR spectra of the **25**–**29** series presented broad signals with a low magnetic response and, on occasions, duplicated. The *Z*/*E* push–pull equilibrium appears to be insufficient for the explanation of this phenomenon, given that this was also observed in the cyclic compound **29,** with a single configuration. This suggests that the equilibrium between the two pseudo-planar conformations of the enamine group ($C{=}CNR_2$) plays an important role in the number and type of NMR signals. Only the chemical behaviour of the enamines **25**–**29**, capable of transforming to **35**–**39** via **30**–**34**, allowed us to confirm their structure and to overcome the ambiguity and difficulty of the spec-

troscopic assignment. For this reason, in the characterization of the compounds **25**–**29** (Table 1) only the ^{13}C NMR spectra are included which are simpler and better defined than the ^{1}H NMR spectra.

Mps were measured on a Reichert–Jung Thermo Galen and are uncorrected. IR spectra were obtained on a Perkin–Elmer 1720 X spectrometer. NMR spectra were recorded on a Bruker AC300 spectrometer, and chemical shifts are given downfield from $SiMe_4$ as an internal standard; ^{13}C NMR spectra were carried out with complete ^{1}H decoupling and the assignments were made by additional DEPT experiments.

The starting compounds were purchased from the usual suppliers (**20**) or prepared by literature procedures. Pyrrolidin-2-ylideneacetonitrile (**1**) was synthesized from 5-ethoxy-3,4-dihydro-2*H*-pyrrole and methyl cyanoacetate;[7] methyl pyrrolidin-2-ylideneacetate (**2**) from 5-ethoxy-3,4-dihydro-2*H*-pyrrole and Meldrum's acid,[7,8] and ethyl pyrrolidin-2-ylideneacetate (**3**) from pyrrolidine-2-thione and ethyl bromoacetate.[5]The preparation of enamines **19, 21, 22** involves the condensation of ammonia or pyrrolidine with corresponding β-keto nitriles, β-keto esters or β-diketones.[2] The halogenation of 4-hydroxy-6-methyl-2*H*-pyran-2-one with phosphorus tribromide gives 4-bromo-6-methyl-2H-pyran-2-one (**23**).[9] The *N*-methoxy-*N*-methylprolinamide (hydrobromide derivative) (**24**) was obtained from their Cbz-derivative[10] by deprotection with HBr in HOAc (33%) and precipitation in anhyd Et_2O.[11]

N-Methoxy-*N*-methyl-3-(pyrrolidin-2-ylidene)propionamides 5–7 from 1–3; General Procedure

To a solution at –78 °C of pyrrolidine derivative **1**–**3** (7.10 mmol) in THF (7 mL) was added dropwise LDA (10.65 mmol) in THF (10 mL) over a 40 min period followed by a 30 min stirring period. Then *N*-methoxy-*N*-methylbromoacetamide (**4**) (2.20 g, 12.07 mmol, in 10 mL of THF) was added slowly and stirring was continued for 2 h at –78 °C. The reaction mixture was allowed to warm to 0 °C, stirred for another 6 h, hydrolyzed with aq HCl (5%), and neutralized with solid $NaHCO_3$. The THF was removed with a rotary evaporator and the residue was extracted with CH_2Cl_2 (3 × 70 mL). The combined CH_2Cl_2 layers were washed twice with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel; CH_2Cl_2–Et_2O, 5: 1).

Weinreb *N*-Vinylprolinamides 25–28 from 19–22; General Procedure

A mixture of enamine **19**–**22** (10.5 mmol) and *N*-methoxy-*N*-methylprolinamide (hydrobromide derivative) (**24**) (2.51 g, 10.5 mmol) in MeOH (25 mL) was stirred at 40 °C for the times given in Table 1. At the end of the reaction, monitored by TLC, the solution was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2–H_2O (1:1; 100 mL). The aq layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed (silica gel; CH_2Cl_2–Et_2O; 10:1 for **25**, **26** and **28**; 1:1 for **27**).

N-(6-Methyl-2-oxo-2*H*-pyran-4-yl)proline *N*′-Methoxy-*N*′-methylamide (29)

A mixture of 4-bromo-2*H*-pyran-2-one (2 g, 10.6 mmol), *N*-methoxy-*N*-methylprolinamide (hydrobromide derivative) (**24**) (2.77 g, 11.6 mmol) and Et_3N (3.08 mL, 22.2 mmol) in anhyd CH_2Cl_2 (40 mL) was stirred at r.t. for 24 h. H_2O (40 mL) was added, then decanted, and the aq layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed (silica gel; CH_2Cl_2–THF, 5:1) to give **29**.

Yield: 1.35 g (5.1 mmol, 48%).

2,3-Dihydropyrrolizines 14–16(a–j) from 5–7 or 35–39(b–k) from 25–29; General Procedure

To a magnetically stirred solution of amides **5**–**7, 25**–**29** (2.22 mmol) in anhyd THF (35 mL) was added dropwise the organometallic compound under nitrogen (see Table 2). At the end of the reaction (monitored by TLC), the mixture was hydrolyzed. The organic layer was decanted, washed with water, dried (Na_2SO_4) and evaporated. The carbonyl intermediates **11**–**13(a–j)** or **30**–**34(b–k)** were not isolated and the concentrate underwent cyclization treatment.

The previously mentioned reaction mixtures of **11**–**13(a–j)** or **30**–**34(b–k)** (ca. 2.2 mmol) and silica gel (5 × w/w) in appropriate solvent (50 mL) were heated in a rotary evaporator, slowly distilling the solvent (see Table 2). The silica gel was filtered off and washed thoroughly with hot acetone. The solvent was removed in vacuo, and the concentrate was recrystallized from hexane–toluene (**36e, 36f, 36k, 39b**) or chromatographed [silica gel; CH_2Cl_2 (**35b**, **35f**, **38b**, **38f**); or CH_2Cl_2–Et_2O (10:1) (**36b**, **37b**)].

4-Acyl-3,4-dihydropyrrolizines (17–18) from 14b,g

To a magnetically stirred solution of **14** (5.5 mmol) in anhyd THF (100 mL) was added dropwise (30 min) the organolithium compound (11 mmol) under nitrogen. At the end of the reaction (30–60 min, monitored by TLC), aq HCl (10%; 5 mL) was added, and the mixture was stirred rapidly at r.t. overnight. Then it was extracted with CH_2Cl_2 (2 × 50 mL), dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed (silica gel using; CH_2Cl_2–Et_2O, 15:1).

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