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Versatility of Weinreb Amides in the Knorr Pyrrole Synthesis

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Abstract. *N*-Methoxy-*N*-methyl-α-enaminocarboxamides were prepared starting from enamines and Weinreb α-aminoamides. Their reaction with oganometallic compounds and subsequent cyclization constitute a versatile alternative in the Knorr pyrrole synthesis.

Keywords: Knorr pyrrole synthesis; Weinreb amides.

Introduction

One of the most important limitations of the Knorr pyrrole synthesis is the easy autocondensation of starting α-aminoketones.[1,2] They are frequently prepared *in situ* by reduction of an α-oximino ketone or by deprotection of either a masked carbonyl group (*e.g.* a ketal derivative) or a masked amino group (*e.g.* a phthalimide derivative). We have developed a synthetic method starting from Weinreb α-aminoamides. Their low tendency to autocondensation and the possibility of transformation into several ketones,[3-5] make them useful synthetic equivalents and potentially more versatile than the α-oximino ketones or the α-amino ketals.

Although the Weinreb amides have already been used by other authors[5] in the synthesis of pyrroles, our method is different (Scheme 1). Here, *N*-methoxy-*N*-methyl-α-enaminocarboxamides **8-16**, obtained from enamines (**1-4**) and from *N*-methoxy-*N*-methyl-α-aminocarboxamides **5-7**, react with organometallic compounds or diisobutylaluminium hydride to give carbonyl derivatives **17-20**, which can later cyclize to give pyrroles **21-24**.

The transformation of **8-16** into **17-20** is the key stage in the process. The organometallic reagent selectively attacks the carboxamide group. The Z function remains untransformed (nitrile, ester or ketone). In this paper we study the influence of Z, R^1 and the organometallic compound, and the scope and limitations of the synthetic method is indicated.

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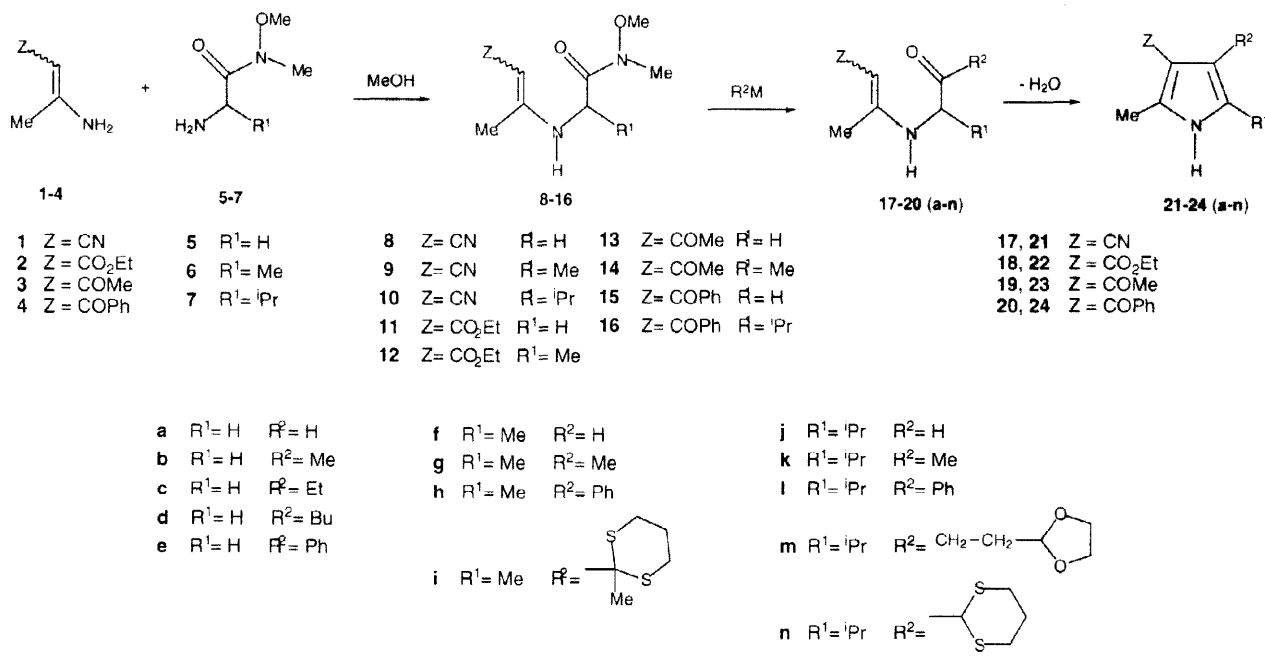


Scheme 1

Synthesis of Weinreb α-Vinylaminoamides

In the first stage β-aminocrotonitrile **1**, ethyl-β-aminocrotonate **2** and β-aminoenones **3** and **4** react with *N*-methoxy-*N*-methyl-α-aminocarboxamides **5-7** (hydrobromide derivatives) by conjugate addition-elimination leading with good yields to the α-vinylaminoamides **8-16** (Table 1). The interchange of nitrogenated substituents[6,7] is produced by gentle heating of a dissolution of the reagents in methanol. Autocondensation of the α-amino amides was not observed.

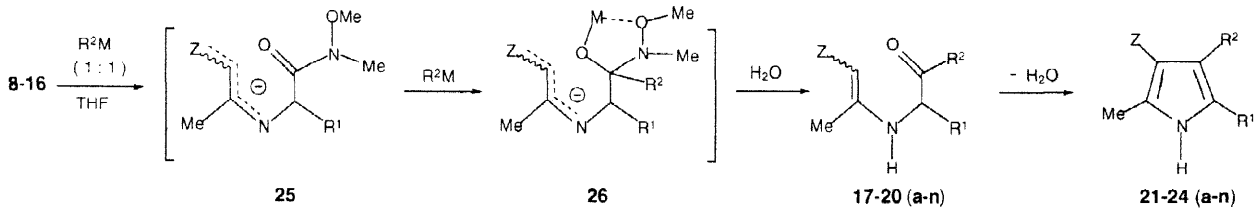
Table 1. Preparation of Weinreb α-Vinylaminoamides **8-16**.

Start	Amide[a]	Z	R^1	T (°C)	Time (h)	Product	Yield (%)
1	**5**	CN	H	30	6	**8**	79
1	**6**	CN	Me	35	6	**9**	85
1	**7**	CN	ⁱPr	35	15	**10**	83
2	**5**	CO_2Et	H	20	12	**11**	75
2	**6**	CO_2Et	Me	20	20	**12**	85
3	**5**	COMe	H	35	10	**13**	81
3	**6**	COMe	Me	30	12	**14**	72
4	**5**	COPh	H	35	10	**15**	73
4	**7**	COPh	ⁱPr	35	15	**16**	72

(a) Hydrobromide derivative.

Reaction of Weinreb α-Vinylaminoamides with Organolithium and Grignard Compounds.

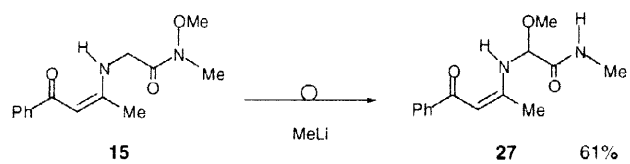
When the secondary enamines **8-16** react with an equimolar amount of the organometallic compound (R^2MgBr, R^2Li) they form a conjugated anion **25** which deactivates the electrophilic function Z.[8-10] If an excess of reagent is used, only the *N*-methoxy-*N*-methyl-carboxamide group is transformed into a carbonyl group (Scheme 2). Normally, a strict control of the temperature and proportion of reagents is unnecessary and it is advisable to use tetrahydrofuran as the solvent.[11] In the preparation of the enaminoesters **18**, which are very unstable in medium acid, the hydrolysis should take place in neutral conditions.



Scheme 2

The success achieved in the preparation of compounds **17-20**[12] depends essentially on Z and R^1. When R^1 is different from hydrogen, the reaction with organomagnesium or organolithium compounds occurs satisfactorily, irrespective of the nature of Z. However, if R^1 = H, a significant influence of Z can be observed: the results are still good for enaminonitriles (Z= CN), but may deteriorate for enaminoesters (Z= CO_2Et) and are irrelevant for enaminones (Z= COR).

This latter phenomenon is not due to a reaction of the Z group with the organometallic compound, but rather to other processes which affect the α-aminocarboxamide group. Thus, in the reaction of **15** with methyllithium (or MeMgI) we have been able to identify **27** as the main product (Scheme 3). The compound is the result of a rearrangement of the methoxy group. This rearrangement would not take place or would be more difficult when R^1 is different from hydrogen.

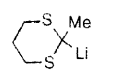
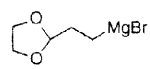
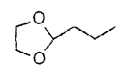


Scheme 3

The hydrolysis of the metallic intermediates **26** (Scheme 2) occurs with total or partial simultaneous cyclization to **21-24**. Consequently, no attempts were made to isolate **17-20** from the reaction mixture[12] and the process was continued with basic catalysis (EtONa/EtOH) in order to obtain a complete transformation to pyrroles **21-24** (Table 2). In these conditions, the secondary enamines increase their nucleophilicity in the intramolecular condensation. In the case of **20n**, in which the basic treatment was unsuccessful, we proceeded to a reflux in toluene in the presence of silica gel. When the same treatment is applied to **19i**, the cyclization-aromatization occurs mainly with deacetylation to give 2,5-dimethyl-3-(2-methyl-1,3-dithiolan-3-yl) pyrrole **28**.

In the results (Table 2), due to the nature of Z, R^1 and R^2, we have not observed Fischer-Fink-type cyclizations to α-acyl pyrroles. Among the examples chosen, the compounds **24m** and **24n** show the potential use of the synthetic method in the preparation of pyrroles with functionalized substituents.

Table 2. Preparation of Pyrroles **21-24** from Weinreb α-Vinylaminoamides **8-16**.

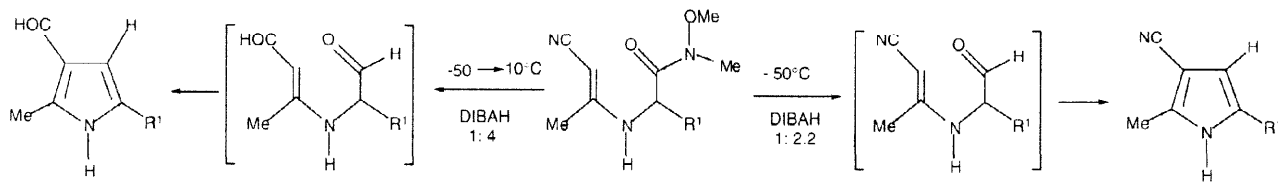
			Reaction with organometallic compounds					Cyclization		
Start	Z	R^1	Organometallic	R^2	Ratio	T (°C)	Time (h)	Meth.[a]	Time (h)	Product (%)
8	CN	H	DIBAL-H	H	1 : 2.2	-50	0.5	A		**21a** (73)
8	CN	H	DIBAL-H	H	1 : 4	-50 → 10	4	A		**21a** (62) **29a**[c] (0)
8	CN	H	EtMgBr	Et	1 : 3	18	1	B	1	**21c** (68)
8	CN	H	BuLi	Bu	1 : 3	0	1	A[b]		**21d** (65)
8	CN	H	PhMgBr	Ph	1 : 3	-10 → 0	2	B	3	**21e** (63)
9	CN	Me	DIBAL-H	H	1 : 2.2	-50	1	A		**21f** (92)
9	CN	Me	DIBAL-H	H	1 : 4	-50 → 10	4	A		**21f** (27) **29f**[c] (35)
10	CN	^{i}Pr	DIBAL-H	H	1 : 2.2	-50	0.5	A		**21j** (75)
10	CN	^{i}Pr	DIBAL-H	H	1 : 4	-50 → 10	8	A		**21j** (15) **29j**[c] (65)
10	CN	^{i}Pr	MeLi	Me	1 : 3	18	2	A[b]		**21k** (76)
11	CO_2Et	H	DIBAL-H	H	1 : 2.2	-20	1	A		**22a** (68)
11	CO_2Et	H	MeLi	Me	1 : 3	-10	1	A[b]		**22b** (62)
11	CO_2Et	H	PhLi	Ph	1 : 3	-10	1	B	2	**22e** (47)
12	CO_2Et	Me	DIBAL-H	H	1 : 2.2	-20	1	A		**22f** (74)
12	CO_2Et	Me	MeLi	Me	1 : 3	0	1	A[b]		**22g** (80)
12	CO_2Et	Me	PhLi	Ph	1 : 3	0	1	B	2	**22h** (83)
13	COMe	H	DIBAL-H	H	1 : 3	-50	5	A		**23a** (62)
13	COMe	H	MeLi	Me	1 : 3	-10	1	A[b]		**23b** (10)[d]
14	COMe	Me	DIBAL-H	H	1 : 3	-10 → 20	3	_		**14** (85)
14	COMe	Me	PhMgBr	Ph	1 : 3	18	1	B	1	**23h** (71)
14	COMe	Me			1 : 3	-20 → 0	1	C	1	**28**[e] (48)
15	COPh	H	DIBAL-H	H	1 : 2.2	-50	2	A		**24a** (28) **30** (36)
15	COPh	H	MeLi	Me	1 : 3	-5 → 10	2	_		**24b** (12) **27** (61)
16	COPh	^{i}Pr	DIBAL-H	H	1 : 3	-10 → 20	3	_		**16** (88)
16	COPh	^{i}Pr	MeLi	Me	1 : 3	0	0.5	B	2	**24k** (69)
16	COPh	^{i}Pr	PhMgBr	Ph	1 : 3	18	2	B	5	**24l** (62)
16	COPh	^{i}Pr			1 : 3	18	1	B	5	**24m** (65)
16	COPh	^{i}Pr			1 : 3	-20 → 0	2	C	1	**24n** (59)

(a) Methods: A spontaneous, B EtONa/EtOH, C silica gel/toluene. (b) The basic conditions of the hydrolysis (LiOH) makes the cyclization process easier. (c) Z = COH. (d) The remainder is degraded. (e) Z = H.

Reaction of Weinreb α-Vinylaminoamides with Diisobutylaluminium Hydride.

The reaction of aminonitriles **8-10** and aminoesters **11-12** with diisobutylaluminium hydride needs stricter control conditions than with organolithium or organomagnesium compounds. In general, at -50°C and with a ratio of substrate/DIBAL-H 1 : 2.2, excellent yields of **17-20** were obtained, which were spontaneously cyclized to pyrroles (Table 2). At higher temperatures, and with a greater proportion of hydride, other processes take place which decrease the yields of **21-23**.

In the experiments starting from **10** (Z= CN, R^1=^{i}Pr), very interesting results were achieved: depending on the temperature and the proportion of reagents, the reaction can be stopped at **21j** (75%) or continue to **29j** (65%) by simultaneous reduction of the amide and nitrile groups. Unfortunately, the effectiveness of the control conditions can not be extended to their homologues **8** and **9**, in which the size of R^1 may decisively influence the double reduction. The yields of the 3-pyrrolcarboxaldehyde derivatives **29a,f,j** decrease in the order ^{i}Pr > Me > H (Scheme 4).



29a R^1 = H 0%
29f R^1 = Me 35%
29j R^1 = ^{i}Pr 65%

8 R^1 = H
9 R^1 = Me
10 R^1 = ^{i}Pr

21a R^1 = H 73%
21f R^1 = Me 92%
21j R^1 = ^{i}Pr 75%

Scheme 4

The influence of R^1 in the reduction of the β-aminoenones **13-16** with DIBAL-H is very different to that observed in their reactions with organometallic compounds (R^2Li and R^2Mg^iPr). Surprisingly, **14** and **16**, with $R^1 \neq H$, are resistent to the reduction. When R^1=H (**13** and **15**), even though the expected pyrroles are produced, reductions in the enone group may take place. For example, starting from **15**, together with **24a**, the 1-phenyl-2-buten-1-one (30-55%) is produced by a conjugated reduction-elimination.[13,14] Once again, the β-aminoenones are the substrates which present the greatest limitations in our synthetic method.

Conclusion

In the Knorr pyrrole synthesis, as in many other organic processes, Weinreb amides have been shown to be very versatile starting compounds. They are especially useful in the preparation of pyrrole derivatives in which we wish to vary systematically the β-substituent, whether this be H, alkyl, aryl and even some functionalized substituents.

Experimental

Melting points were measured on a Reichert-Jung Thermo Galen and are uncorrected. Boiling points correspond to the oven temperature in a Kugelrohr GKR-51. 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 ^1H decoupling and the assignments were made by additional DEPT experiments. Mass spectra were measured on a Hewlett-Packard 5988A mass spectrometer.

The starting enamines were purchased from the usual suppliers (**1** and **2**) or synthesized by literature procedure[15] (**3** and **4**). The *N*-methoxy-*N*-methyl-α-aminocarboxamides **5-7** (hydrobromide derivatives) were prepared from their corresponding BOC-α-amino derivatives[16] (or CBZ-α-amino derivatives) by deprotection with HBr in AcOH (33%) and precipitation in dry ether.[17]

Preparation of compounds 8-16 from enamines 1-4 and amides 5-7. General procedure. A mixture of **1-4** (12.18 mmol) and **5-7** (14.62 mmol) in 25 cm^3 of methanol was stirred at 40°C for the times given in the Table 1. At the end of the reaction, monitored by TLC, the solution was concentrated *in vacuo*. The hydrobromides present in the mixture were removed by successive washings with water when the residue was a solid. Otherwise, when an oil was obtained, the residue was dissolved in dry THF, filtered and evaporated to dryness. The product was recrystallized from toluene or dichloromethane/diethyl ether (**8**, **10**, **11**, **13** and **14**), or chromatographed on silica gel with dichloromethane/diethyl ether (10 : 1) as eluent (**9**,**15** and **16**), or used in the later processes without purifying[18] (**12**).

The chemical yields and the physical and spectral characteristics of these products are given below.

2-(2-Cyano-1-methylvinylamino)-N-methoxy-N-methylacetamide (**8**): 79%, colorless crystals, mp. 98°C. IR (KBr) 3338, 2192, 1667, 1592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.17 (s, 3H), 3.25 (s, 3H), 3.75 (s, 3H), 3.76 (s, 1H), 3.81 (d, J=4.0, 2H), 5.35 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 20.10 (CH_3), 32.42 (CH_3), 43.54 (CH_2), 61.63 (CH_3), 61.63 (CH), 121.41 (C), 159.15 (C), 168.39 (C); MS: m/z 183 (M^+, 63), 95 (100). (Found: C, 52.56; H, 7.17; N, 22.87. $C_8H_{13}N_3O_2$ requires C, 52.44; H, 7.15; N, 22.94%).

2-(2-Cyano-1-methylvinylamino)-N-methoxy-N-methylpropionamide (**9**): 85%, pale-yellow oil. IR (film) 3319, 2197, 1661, 1604, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.27 (d, J=6.8, 3H), 2.02 (s, 3H), 3.14 (s, 3H), 3.68 (s, 3H), 3.69 (s, 1H), 4.18 (m, 1H), 5.48 (d, J=6.5, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 17.14 (CH_3), 20.12 (CH_3), 32.22 (CH_3), 48.32 (CH), 60.58 (CH_3), 61.59 (CH), 121.57 (C), 158.74 (C), 172.51 (C); MS: m/z 197 (M^+, 13), 109 (100).

2-(2-Cyano-1-methylvinylamino)-N,3-dimethyl-N-methoxybutyramide (**10**): 83%, colorless crystals, mp. 115°C. IR (KBr) 3289, 2198, 1652, 1607, 1545 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.89 (d, J=6.8, 3H), 0.90 (d, J=6.8, 3H), 2.01 (m, J=6.8, 1H), 2.08 (s, 3H), 3.17 (s, 3H), 3.70 (s, 3H), 3.90 (s, 1H), 4.06 (dd, J=8.5 and 6.8, 1H) 5.10 (d, J=8.5, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 17.90 (CH_3), 19.46 (CH_3), 20.45 (CH_3), 31.64 (CH), 31.90 (CH_3), 57.21 (CH), 61.11 (CH_3), 61.42 (CH), 121.54 (C), 160.05 (C), 171.83 (C); MS: m/z 225 (M^+, 13), 137 (100). (Found: C, 58.65; H, 8.47; N, 18.73; $C_{11}H_{19}N_3O_2$ requires C, 58.65; H, 8.50, N, 18.65%).

Ethyl 3-((N-methoxy-methylcarbamoyl) methylamino) crotonate (**11**): 75%, colorless crystals, mp. 68°C. IR (film) 3316, 1678, 1600, 1292, 1272, 1180, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.25 (t, J=7.2,

3H), 1.92 (s, 3H), 3.21(s, 3H), 3.72 (s, 3H), 4.10 (q, J=7.2, 2H), 4.14 (d, J=5.78, 2H), 4.55 (s, 1H), 8.88 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 14.64 (CH_3), 19.68 (CH_3), 32.48 (CH_3), 43.96 (CH_2), 58.46 (CH_2), 61.53 (CH_3), 84.07 (CH), 160.63 (C), 168.77 (C), 170.22 (C); MS: m/z 230 (M^+, 12), 96 (100). (Found: C, 52.03; H, 7.92; N, 12.13. $C_{10}H_{18}N_2O_4$ requires C, 52.16; H, 7.88; N, 12.17 %).

Ethyl 3-(1-(N-methoxy-methylcarbamoyl) ethylamino) crotonate (**12**): 85%, pale-yellow oil. IR (film) 3310, 1683, 1659, 1290, 1170 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.19 (t, J=7.1, 3H), 1.36 (d, J=6.9, 3H), 1.85 (s, 3H), 3.16 (s, 3H), 3.68 (s, 3H), 4.04 (q, J=7.1, 2H), 4.44 (s, 1H), 4.49 (m, 1H), 8.80 (d, J=8.4, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 14.47 (CH_3), 19.26 (CH_3), 19.36 (CH_3), 32.29 (CH_3), 48.95 (CH), 58.27 (CH_2), 61.39 (CH_3), 83.87 (CH), 159.35 (C), 169.99 (C), 173.22 (C); MS: m/z 244 (M^+, 11), 110 (100).

2-(2-Acetyl-1-methylvinylamino)-N-methoxy-N-methylacetamide (**13**): 81%, colorless crystals, mp. 98°C. IR (KBr) 3403, 1674, 1628, 1610, 1555 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.88 (s, 3H), 1.97 (s, 3H), 3.16 (s, 3H), 3.69 (s, 3H), 4.13 (d, J=6.0, 2H), 5.02 (s, 1H), 10.83 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.97 (CH_3), 28.76 (CH_3), 32.33 (CH_3), 43.87 (CH_2), 61.40 (CH_3), 96.31 (CH), 162.42 (C), 169.28 (C), 195.48 (C); MS: m/z 200 (M^+, 28), 112 (100). (Found: C, 53.90; H, 8.08; N, 13.95. $C_9H_{16}N_2O_3$ requires C, 53.99; H, 8.05; N, 13.99%).

N-Methoxy -N-methyl-2-(1-methyl-3-oxo-1-butenylamino) propionamide (**14**): 72%, pale-yellow oil. IR (film) 3321, 1668, 1613, 1574, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.40 (d, J=7.0, 3H), 1.86 (s, 3H), 1.96 (s, 3H), 3.16 (s, 3H), 3.67 (s, 3H), 4.52 (m, J=7.0, 1H), 4.96 (s, 1H), 10.86 (d, J=7.0, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 18.54 (CH_3), 18.55 (CH_3), 28.42 (CH_3), 31.90 (CH_3), 48.74 (CH), 61.07 (CH_3), 95.65 (CH), 160.32 (C), 172.16 (C), 194.73 (C); MS: m/z 214 (M^+, 16), 126 (100).

N-Methoxy-N-methyl-2-(1-methyl-3-oxo-3-phenyl-1-propenylamino) acetamide (**15**): 73%, colorless crystals, mp. 115°C. IR (KBr) 3410, 1668, 1602, 1593, 1533 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.07 (s, 3H), 3.22 (s, 3H), 3.74 (s, 3H), 4.25 (d, J=6.0, 2H), 5.76 (s, 1H), 7.37-7.89 (m, 5H), 11.51 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 19.70 (CH_3), 32.49 (CH_3), 44.22 (CH_2), 61.56 (CH_3), 93.07 (CH), 127.04 (CH), 128.09 (CH), 130.48 (CH), 140.38 (C), 164.16 (C), 169.18 (C), 188.34 (C); MS (CI): m/z 263 (M+1, 100). (Found: C, 64.23; H, 6.89; N, 10.66. $C_{14}H_{18}N_2O_3$ requires C, 64.10; H, 6.92; N, 10.68%).

N,3-Dimethyl-N-methoxy-2-(1-methyl-3-oxo-3-phenyl-1-propenylamino) butyramide (**16**): 72%, pale-yellow oil. IR (film) 3320, 1667, 1600, 1582, 1554, 1323, 1297 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.98 (d, J= 6.7, 3H), 1.03 (d, J=6.7, 3H), 1.99 (s, 3H), 2.20 (m, J=6.7, 1H), 3.12 (s, 3H), 3.62 (s, 3H), 4.33 (dd, J=9.6 and 6.7, 1H), 5.67 (s, 1H), 7.30-7.90 (m, 5H), 11.68 (d, J=9.6, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 17.91 (CH_3), 19.62 (CH_3), 19.74 (CH_3), 31.51 (CH), 32.03 (CH_3), 58.98 (CH), 61.37 (CH_3), 92.70 (CH), 126.91 (CH), 128.03 (CH), 130.42 (CH), 140.27 (C), 163.46 (C), 171.43 (C), 187.63 (C); MS: m/z 304 (M^+, 5), 216 (100).

Reaction of Weinreb amides 8-16 with organometallic compounds. Preparation of carbonyl intermediates 17-20. To a magnetically stirred solution of amides **8-16** (2.22 mmol) in 25 cm^3 of dry THF was added dropwise (15 min) 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 **17-20** were not isolated and the concentrate underwent cyclization treatment.

Cyclization of 17-20 to pyrroles 21-24. Method B. The previously mentioned reaction mixtures of **17-20** (approximately 2.2 mmol) and 0.151 g (2.22 mmol) of EtONa were stirred in 15 cm^3 of ethanol at room temperature for the times given in Table 2. At the end of the reaction, the mixture was poured into 50 cm^3 of water and extracted with dichloromethane (3 x 50 cm^3). The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The product was chromatographed on silica gel, using dichloromethane or dichloromethane/diethyl ether (in a variable proportion from 10 : 1 to 20 : 1) as eluent.

Cyclization of 19i and 20n to pyrroles 23i and 24n. Method C. The reaction mixture of **19i** or **20n** (approximately 2.2 mmol) and silica gel (5 x w/w) was refluxed in toluene (50 cm^3) for 1 h. The silica gel was filtered off and washed thoroughly with hot chloroform. The solvent was removed and the concentrate was recrystallized from hexane/ethyl acetate or chromatographed on silica gel using dichloromethane as eluent.

2-Methylpyrrole-3-carbonitrile (**21a**): 73%, colorless crystals, mp.131°C (lit.,[19] 131-132°C). IR (KBr) 3274, 2222, 1576, 1462, 1376, 1098, 900, 765, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.41 (s, 3H), 6.33 (t, J=2.8, 1H), 6.61 (t, J=2.8, 1H), 8.94 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.01 (CH_3), 90.65 (C), 111.05 (CH), 117.46 (CH), 117.46 (C), 137.49 (C); MS: m/z 106 (M^+, 54), 105 (100). (Found: C, 67.89; H, 5.68; N, 26.43. $C_6H_6N_2$ requires C, 67.90; H, 5.70; N, 26.40%).

4-Ethyl-2-methylpyrrole-3-carbonitrile (**21c**): 68%, colorless oil, bp. 177-180°C at 1 mmHg. IR (film) 3310, 2218, 1580, 1458, 1430, 1375, 1095, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.21 (t, J=7.5, 3H), 2.38 (s, 3H), 2.54 (q, J=7.5, 2H), 6.39 (m, 1H), 8.74 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.28 (CH_3), 14.47 (CH_3), 19.16 (CH_2), 91.17 (C), 113.74 (CH), 117.32 (C), 128.79 (C), 137.34 (C); MS: m/z 134 (M^+, 37), 119 (100).

4-Butyl-2-methylpyrrole-3-carbonitrile (**21d**): 65%, colorless oil, bp. 185-190°C at 1 mmHg. IR (film) 3300, 2212, 1575, 1460, 1429, 1372, 1095, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.91 (t, J=7.2, 3H), 1.34 (m, 2H), 1.56 (m, 2H), 2.37 (s, 3H), 2.49 (t, J=7.6, 2H), 6.37 (m, 1H), 8.69 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.17 (CH_3), 13.76 (CH_3), 22.22 (CH_2), 25.47 (CH_2), 32.23 (CH_2), 91.23 (C), 114.21 (CH), 117.42 (C), 127.05 (C), 137.19 (C); MS: m/z 162 (M^+, 18), 119 (100).

2-Methyl-4-phenylpyrrole-3-carbonitrile (**21e**): 63%, colorless crystals, mp.161°C. IR (KBr) 3271, 2214, 1606, 1538, 1466, 752, 738, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.46 (s, 3H), 6.82 (d, J=2.6, 1H), 7.25-7.63 (m, 5H), 8.63 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.33 (CH_3), 90.05 (C), 114.49 (CH), 117.39 (C), 126.26 (CH), 126.70 (C), 126.95 (CH), 128.77 (CH), 133.06 (C), 138.91 (C); MS: m/z 182 (M^+, 100). (Found: C, 79.06; H, 5.51; N, 15.43. $C_{12}H_{10}N_2$ requires C, 79.10; H, 5.53; N, 15.37%).

2,5-Dimethylpyrrole-3-carbonitrile (**21f**): 92%, colorless crystals, mp. 89°C (lit.,[20] 89°C). IR (KBr) 3303, 2215, 1602, 1533, 1458, 1432, 788, 766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.20 (s, 3H), 2.36 (s, 3H), 5.96 (d, J=1.6, 1H), 8.42 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.05 (CH_3), 12.50 (CH_3), 90.36 (C), 107.89 (CH), 117.70 (C), 127.45 (C), 136.42 (C); MS: m/z 120 (M^+, 48), 119 (100). (Found: C, 70.03; H, 6.68; N, 23.29. $C_7H_8N_2$ requires C, 69.98; H, 6.71; N, 23.31%).

5-Isopropyl-2-methylpyrrole-3-carbonitrile (**21j**): 75%, colorless crystals, mp. 86°C. IR (KBr) 3268, 2219, 1600, 1525, 1463, 788, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.24 (d, J=6.9, 6H), 2.39 (s, 3H), 2.87 (m, J=6.9, 1H), 5.97 (m, 1H), 9.28 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.82 (CH_3), 22.13 (CH_3), 26.65 (CH), 88.91 (C), 104.74 (CH), 118.28 (C), 136.89 (C), 138.99 (C); MS: m/z 148 (M^+, 22), 133 (100). (Found: C, 72.91; H, 8.14; N, 18.95. $C_9H_{12}N_2$ requires C, 72.94; H, 8.16; N, 18.90%).

2,4-Dimethyl-5-isopropylpyrrole-3-carbonitrile (**21k**): 76%, colorless crystals, mp. 123°C. IR (KBr) 3256, 2220, 1607, 1540, 1468, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.20 (d, J=7.0, 6H), 2.05 (s, 3H), 2.35 (s, 3H), 2.95 (m, J=7.0, 1H), 8.45 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 9.47 (CH_3), 12.12 (CH_3), 22.28 (CH_3), 25.20 (CH), 91.96 (C), 114.48 (C), 117.71 (C), 133.19 (C), 134.75 (C); MS: m/z 162 (M^+, 17), 147 (100). (Found: C, 74.14; H, 8.68; N, 17.18. $C_{10}H_{14}N_2$ requires C, 74.03; H, 8.70; N, 17.27%).

Ethyl 2-methylpyrrole-3-carboxylate (**22a**): 67%, colorless crystals, mp. 78°C (lit.,[21] 78-79°C). IR (KBr) 3289, 1673, 1575, 1444, 1322, 1267, 1201, 1122, 1095, 1050, 779, 719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.35 (t, J=7.0, 3H), 2.51 (s, 3H), 4.28 (q, J=7.0, 2H), 6.54 (m, 1H), 6.55 (m, 1H), 9.15 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.07 (CH_3), 14.35 (CH_3), 59.37 (CH_2), 110.12 (CH), 111.29 (C), 115.92 (CH), 135.40 (C), 166.15 (C); MS: m/z 153 (M^+, 48), 108 (100). (Found: C, 62.70; H, 7.26; N, 9.16. $C_8H_{11}NO_2$ requires C, 62.73; H, 7.24; N, 9.14%).

Ethyl 2,4-dimethylpyrrole-3-carboxylate (**22b**): 62%, colorless crystals, mp. 76°C (lit.,[22] 74-75°C). IR (KBr) 3310, 1665, 1582, 1439, 1326, 1262, 1130, 1091, 786, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.36 (t, J=7.1, 3H), 2.25 (s, 3H), 2.50 (s, 3H), 4.28 (q, J=7.1, 2H), 6.36 (d, J=1.0, 1H), 8.00 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.60 (CH_3), 14.09 (CH_3), 14.49 (CH_3), 59.04 (CH_2), 110.80 (C), 114.12 (CH), 121.59 (C), 135.83 (C), 166.28 (C). (Found: C, 64.70; H, 7.82; N, 8.40. $C_9H_{13}NO_2$ requires C, 64.64; H, 7.84; N, 8.38%).

Ethyl 2-methyl-4-phenylpyrrole-3-carboxylate (**22e**): 47%, colorless crystals, mp. 109°C (lit.,[23] 108°C). IR (KBr) 3365, 1673, 1444, 1288, 1232, 1126, 755, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.08 (t, J=7.1, 3H), 2.41 (s, 3H), 4.09 (q, J=7.1, 2H), 6.43 (d, J=2.5, 1H), 7.13-7.33 (m, 5H), 8.49 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.89 (CH_3), 14.06 (CH_3), 59.34 (CH_2),109.71 (C), 115.47 (CH), 126.11 (CH), 127.01 (C), 127.45 (CH), 129.25 (CH), 135.81 (C), 136.16 (C), 165.93 (C); MS: m/z 229 (M^+, 100). (Found: C, 73.28; H, 6.61; N, 6.12. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%).

Ethyl 2,5-dimethylpyrrole- 3-carboxylate (**22f**): 74%, colorless crystals, mp. 113°C (lit.,[24] 116-117°C). IR (KBr) 3293, 1666, 1436, 1224, 1087, 800, 775, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.33 (t, J=7.2, 3H), 2.19 (s, 3H), 2.47 (s, 3H), 4.25 (q, J=7.2, 2H), 6.20 (m, 1H), 8.17 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.57 (CH_3), 13.10 (CH_3), 14.48 (CH_3), 59.21 (CH_2), 107.35 (CH), 111.49 (C), 125.59 (C), 134.25 (C), 165.84 (C); MS: m/z 167 (M^+, 68), 138 (100). (Found: C, 64.54; H, 7.87; N, 8.41. $C_9H_{13}NO_2$ requires C, 64.64; H, 7.84; N, 8.38%).

Ethyl 2,4,5-trimethylpyrrole-3-carboxylate (**22g**): 80%, colorless crystals, mp. 105°C (lit.,[25] 103-105°C). IR (KBr) 3286, 1655, 1465, 1431, 1268, 1250, 1150, 995, 784, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.34 (t, J=7.1, 3H), 2.11 (s, 3H), 2.15 (s, 3H), 2.45 (s, 3H), 4.26 (q, J=7.1, 2H), 8.02 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 10.44 (CH_3), 10.92 (CH_3), 13.82 (CH_3), 14.48 (CH_3), 58.93 (CH_2), 110.62 (C), 115.90 (C), 121.96 (C), 133.61 (C), 166.50 (C); MS: m/z 181 (M^+, 39), 152 (100). (Found: C, 66.27; H, 8.32; N, 7.72. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 8.34; N, 7.73%).

Ethyl 2,5-dimethyl-4-phenylpyrrole-3-carboxylate (**22h**): 83%, colorless crystals, mp.126°C (lit.,[26] 127-128°C). IR (KBr) 3259, 1658, 1445, 1425, 1290, 1164, 1091, 785, 755, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.05 (t, J=7.1, 3H), 2.12 (s, 3H), 2.52 (s, 3H), 4.08 (q, J=7.1, 2H), 7.21-7.36 (m, 5H), 7.94 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.17 (CH_3), 13.62 (CH_3), 13.97 (CH_3), 59.04 (CH_2), 110.57 (C), 122.43 (C), 123.40 (C), 125.83 (CH), 127.29 (CH), 130.35 (CH), 133.83 (C), 136.14 (C), 165.80 (C); MS:

m/z 243 (M^+, 70), 214 (100). (Found: C, 74.04; H, 7.04; N, 5.78. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%).

3-Acetyl-2-methylpyrrole (**23a**): 62%, colorless crystals, mp. 87°C (lit.,[27] 87-88°C). IR (KBr) 3212, 1625, 1569, 1451, 943, 892, 730, 674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 2.52 (s, 3H), 6.48 (m, 1H), 6.54 (m, 1H), 9.84 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.80 (CH_3), 28.31 (CH_3), 110.43 (CH), 115.85 (CH), 120.45 (C), 135.36 (C), 195.59 (C); MS: m/z 123 (M^+, 47), 108 (100). (Found: C, 68.29; H, 7.35; N, 11.33. C_7H_9NO requires C, 68.27; H, 7.37; N, 11.37%).

3-Acetyl-2,4-dimethylpyrrole (**23b**): 10%, colorless crystals, mp. 138°C (lit.,[7] 138°C). IR (KBr) 3216, 1617, 1473, 1442, 943, 800, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.27 (d, J=1, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 6.37 (m, 1H), 8.98 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.66 (CH_3), 15.13 (CH_3), 30.82 (CH_3), 114.98 (CH), 120.44 (C), 120.46 (C), 136.07 (C), 195.90 (C); MS: m/z 137 (M^+, 18), 122 (100). (Found: C, 69.94; H, 8.12; N, 10.22. $C_8H_{11}NO$ requires C, 70.05; H, 8.08; N, 10.21%).

3-Acetyl-2,5-dimethyl-4-phenylpyrrole (**23h**): 71%, pale-yellow crystals, mp. 134°C (lit.,[7] 135°C). IR (KBr) 3230, 1631, 1604, 1584, 1525, 1446, 1412, 964, 808, 759, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.92 (s, 3H), 2.09 (s, 3H), 2.52 (s, 3H), 7.23-7.42 (m, 5H), 8.40 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.02 (CH_3), 14.08 (CH_3), 30.63 (CH_3), 121.34 (C), 122.14 (C), 123.42 (C), 126.51 (CH), 128.11 (CH), 130.40 (CH), 133.37 (C), 136.70 (C), 196.99 (C); MS: m/z 213 (M^+, 72), 198 (100). (Found: C, 78.90; H, 7.07; N, 6.54. $C_{14}H_{15}NO$ requires C, 78.84; H, 7.09; N, 6.57%).

3-Benzoyl-2-methylpyrrole (**24a**): 28%, colorless crystals, mp. 121°C. IR (KBr) 3310, 1600, 1570, 1555, 1449, 1368, 1280, 885, 790, 745, 720, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.53 (s, 3H), 6.40 (t, J=2.6, 1H), 6.53 (dd, J=3.0 and 2.6, 1H), 7.42-7.83 (m, 5H), 9.44 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.70 (CH_3), 112.42 (CH), 115.76 (CH), 119.43 (C), 127.99 (CH), 128.92 (CH), 131.13 (CH), 136.94 (C), 140.53 (C), 192.99 (C); MS: m/z 185 (M^+, 7), 77 (100). (Found: C, 77.86; H, 5.92; N, 7.52. $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56%).

3-Benzoyl-2,4-dimethylpyrrole (**24b**): 12%, colorless crystals, mp.129°C (lit.,[7] 128-129°C). IR (KBr) 3215, 1604, 1572, 1462, 1426, 1348, 903, 800, 756, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.00 (s, 3H), 2.13 (s, 3H), 6.37 (s, 1H), 7.39-7.70 (m, 5H), 8.71 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.17 (CH_3), 13.75 (CH_3), 115.23 (CH), 120.46 (C), 120.65 (C), 128.15 (CH), 128.85 (CH), 131.33 (CH), 134.89 (C), 141.35 (C), 194.83 (C); MS: m/z 199 (M^+, 70), 198 (100). (Found: C, 78.36; H, 6.60; N, 7.05. $C_{13}H_{13}NO$ requires C, 78.36; H, 6.58; N, 7.03%).

3-Benzoyl-2,4-dimethyl-5-isopropylpyrrole (**24k**): 69 %, colorless crystals, mp. 134°C. IR (KBr) 3255, 1590, 1578, 1466, 1429, 1380, 753, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.20 (d, J=7.0, 6H), 1.96 (s, 3H), 2.07 (s, 3H), 3.01 (m, J=7.0, 1H), 7.36-7.71 (m, 5H), 8.35 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 10.57 (CH_3), 13.67 (CH_3), 22.30 (CH_3), 24.73 (CH), 113.67 (C), 120.85 (C), 128.04 (CH), 128.92 (CH), 131.12 (CH), 132.40 (C), 133.06 (C), 141.57 (C), 194.63 (C); MS: m/z 241 (M^+, 46), 226 (100). (Found: C, 79.72; H, 7.90; N, 5.78. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80%).

3-Benzoyl-5-isopropyl-2-methyl-4-phenylpyrrole (**24l**): 62%, pale-yellow crystals, mp. 185°C. IR (KBr) 3241, 1610, 1598, 1562, 1527, 1451, 1418, 763, 737, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.23 (d, J=7.0, 6H), 2.39 (s, 3H), 3.11 (m, J=7.0, 1H), 6.96-7.58 (m, 10H), 8.22 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.21 (CH_3), 23.07 (CH_3), 24.70 (CH), 120.14 (C), 120.92 (C), 125.36 (CH), 127.39 (CH),

127.51 (CH), 129.50 (CH), 130.09 (CH), 131.12 (CH), 133.18 (C), 133.56 (C), 135.66 (C), 139.81 (C), 194.22 (C); MS: m/z 303 (M^+, 100). (Found: C, 83.14; H, 6.95; N, 4.63. $C_{21}H_{21}NO$ requires C, 83.13; H, 6.98; N, 4.62%).

3-Benzoyl-4-(3,3-ethylenedioxypropyl)-5-isopropyl-2-methylpyrrole (**24m**): 65%, pale-yellow crystals, mp. 158°C. IR (KBr) 3247, 1591, 1425, 1333, 1043, 889, 750, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.22 (d, J=7.0, 6H), 1.76 (m, 2H), 1.99 (s, 3H), 2.64 (m, 2H), 3.09 (m, J=7.0, 1H), 3.75-3.93 (m, AA'BB', 4H), 4.73 (t, J=5.0, 1H), 7.37-7.70 (m, 5H), 7.89 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.89 (CH_3), 19.29 (CH_2), 22.91 (CH_3), 24.47 (CH), 35.67 (CH_2), 64.65 (CH_2), 104.34 (CH), 118.40 (C), 120.11 (C), 128.10 (CH), 128.90 (CH), 131.23 (CH), 132.10 (C), 133.38 (C), 141.49 (C), 194.45 (C); MS: m/z 327 (M^+, 30), 105 (100). (Found: C, 73.38; H, 7.73; N, 4.29. $C_{20}H_{25}NO_3$ requires C, 73.36; H, 7.70; N, 4.28%).

3-Benzoyl-4-(1,3-dithiolan-2-yl)-5-isopropyl-2-methylpyrrole (**24n**): 59%, yellow crystals, mp. 271°C. IR (KBr) 3295, 1608, 1590, 1569, 1445, 1421, 1284, 1168, 950, 736, 718, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.27 (d, J=7.0, 6H), 1.82 (m, 1H), 2.00 (s, 3H), 2.04 (m, 1H), 2.76 (m, 4H), 3.88 (m, J=7.0, 1H), 5.44 (s, 1H), 7.37-7.74 (m, 5H), 8.16 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 13.87 (CH_3), 23.27 (CH_3), 25.35 (CH_2), 25.41 (CH), 33.09 (CH_2), 43.26 (CH), 116.21 (C), 118.15 (C), 128.16 (CH), 128.99 (CH), 131.55 (CH), 132.74 (C), 138.58 (C), 141.04 (C), 193.76 (C); MS: m/z 347 (M+2, 4), 345 (M^+, 33), 239 (100). (Found: C, 66.07; H, 6.73; N, 4.06. $C_{19}H_{23}NOS_2$ requires C, 66.05; H, 6.71; N, 4.05%).

2-Methoxy-N-methyl-2-(1-methyl-3-oxo-3-phenyl-1-propenylamino) acetamide (**27**): 61%, brown oil. IR (film) 3392, 1674, 1600, 1581, 1542, 1477, 1320, 1063, 750, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.18 (s, 3H), 2.86 (d, J=5.0, 3H, N-CH_3), 3.40 (s, 3H), 5.07 (d, J=9.0, 1H), 5.82 (s, 1H), 6.78 (m, 1H, NH), 7.30-7.90 (m, 5H), 11.41 (d, J=9.0, 1H, N'H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 19.81 (CH_3), 26.07 (CH_3), 54.72 (CH_3), 83.17 (CH), 94.95 (CH), 127.15 (CH), 128.25 (CH), 131.08 (CH), 139.72 (C), 163.07 (C), 168.10 (C), 189.49 (C); MS): m/z 262 (M^+, 10), 204 (100).

2,5-Dimethyl-3-(2-methyl-1,3-dithiolan-2-yl) pyrrole (**28**): 48%, colorless crystals, mp. 147°C. IR (KBr) 3311, 1411, 1270, 1141, 1064, 788, 738, 676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.95 (m, 1H), 2.05 (m, 1H), 2.06 (s, 3H), 2.19 (s, 3H), 2.49 (s, 3H), 2.78 (ddd, J=14.4, 6.8 and 3.1, 1H), 3.05 (ddd, J=14.4, 9.9 and 2.9, 1H), 6.00 (m, 1H), 7.65 (br, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 12.75 (CH_3), 13.89 (CH_3), 25.11(CH_2), 28.39 (CH_2), 29.85 (CH_3), 47.81 (C), 106.23 (CH), 121.21 (C), 123.86 (C), 124.49 (C); MS: m/z 229 (M+2, 2), 227 (M^+, 22), 120 (100). (Found: C, 58.06; H, 7.51; N, 6.14. $C_{11}H_{17}NS_2$ requires C, 58.10; H, 7.54; N, 6.16%).

2,5-Dimethylpyrrole-3-carboxaldehyde (**29f**): 35%, colorless crystals, mp. 144°C (lit.,[28] 145°C). IR (KBr) 3231, 3181, 1636, 1602, 1578, 1480, 1372, 1270, 1153, 998, 840, 811, 657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.20 (s, 3H), 2.49 (s, 3H), 6.19 (m, 1H), 9.10 (br, 1H, NH), 9.76 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.49 (CH_3), 12.57 (CH_3), 105.07 (CH), 122.01 (C), 128.32 (C), 138.18 (C), 185.15 (CH); MS: m/z 123 (M^+, 97), 122 (100). (Found: C, 68.26; H, 7.40; N, 11.38. C_7H_9NO requires C, 68.27; H, 7.37; N, 11.37%).

5-Isopropyl-2-methylpyrrole-3-carboxaldehyde (**29j**): 65%, colorless crystals, mp. 124°C. IR (KBr) 3253, 1627, 1595, 1486, 1369, 1307, 1178, 1118, 1060, 813, 755, 655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.22 (d, J=6.9, 6H), 2.51 (s, 3H), 2.85 (m, J=6.9, 1H), 6.25 (d, J=2.4, 1H), 9.64 (br, 1H, NH), 9.77 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 11.40 (CH_3), 22.12 (CH_3), 26.68 (CH), 101.93 (CH), 121.47 (C), 138.87

(C), 139.87 (C), 185.23 (CH); MS: m/z 151 (M^+, 9), 108 (100). (Found: C, 71.46; H, 8.69; N, 9.23. $C_9H_{13}NO$ requires C, 71.49; H, 8.67; N, 9.26%).

References and Notes

1. Sundberg, R. J. Pyrroles and their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry* ; Katritzky, A. R. and Rees, C. W. Eds.; Pergamon Press: Oxford, **1984**, Vol. 4, part 3, pp 324, 325, 331-334, 341-343.
2. Bean, G. P. Pyrroles: The Synthesis of 1*H*-Pyrroles. In *The Chemistry of Heterocyclic Compounds;* Jones, R. A.; Taylor, E. C. and Weissbergen, A. Eds.; John Wiley and Sons: New York, **1990**, Vol. 48, part 1, pp 108, 189.
3. Nahm, S. and Weinreb, S. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
4. O'Neill, B. T. Nucleophilic Addition to Carboxylic Acid Derivatives. In *Comprehensive Organic Synthesis*; Trost, M. and Fleming, I. Eds.; Pergamon Press: Oxford, **1991**, Vol. 1, part 1, pp 399-407.
5. Nagafuji, P. and Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999-5003.
6. Kashima, C. and Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1735-1737.
7. Alberola, A.; Andrés, J. M.; González Ortega, A. and Pedrosa, R. *Heterocycles* **1989**, *29*, 1983-1991. *ibid* **1990**, *31*, 1049-1058.
8. Proll, T. and Walter, W. *Chem. Ber.* **1983**, *116*, 1564-1572.
9. Greenhill, J. V.; Ramli, M. and Tomassini, T. *J. Chem. Soc. Perkin 1* **1975**, 588-591.
10. The secondary β-aminoenones only react with organometallic compounds when the process is catalysed with $CeCl_3$. Bartoli, J.; Marcantoni, E.; Petrini, M. and Sambri, L. *Chem. Eur. J.* **1996**, *2*, 913-918.
11. In other solvents, such as toluene or diethyl ether, the amides **8-16** and their metallic derivatives are very insoluble.
12. The yield of **17-20** in the reaction mixture was estimated by ^{1}H-NMR spectroscopy.
13. Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 286 and 290.
14. Kuckländer, U. The Chemistry of Enaminones. In *The Chemistry of Functional Groups;* Rappoport, Z. Ed.; John Wiley and Sons: New York, **1994**, Part 1, pp 576, 577, and 599.
15. Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277 and 278.
16. Fahrentz, J. A. and Castro, B. *Synthesis* **1983**, 676-678.
17. Ben-Ishai, D. *J. Org. Chem.* **1954**, 62-66.
18. Due to its thermal instability and ease of hydrolysis in silica gel, it has been impossible to purify compound **12** by distillation or chromatography. We considered the reaction mixture, with a purity of over 89%, technically adequate for use in the later stages.
19. Padwa, A.; Gasdaska, J. R.; Tomas, M.; Turro, N. J.; Cha, Y. and Gould, Y. R. *J. Am. Chem. Soc.* **1986**, *108*, 6739-6746.
20. Bilton, J. A. and Linstead, R. P. *J. Chem. Soc.* **1937**, 922-929.
21. Benary, E. *Chem. Ber.* **1911**, *44*, 493-496.
22. Angelini, G.; Illuminati, G.; Monaci, A.; Sleter, G. and Speranza, M. *J. Am. Chem. Soc.* **1980**, *102*, 1377-1382.
23. Cusmano, S. and Sprio, V. *Gazz. Chim. Ital.* **1952**, *82*, 567-575.
24. Sprio, V. and Madonia, P. *Ann. Chim. (Rome)* **1960**, *50*, 1627-1634.
25. Treibs, A.; Schmidt, R. and Zeinsmeister, R. *Chem. Ber.* **1957**, *90*, 79-84.
26. Patterson, J. M. and Soedigdo, S. *J. Org. Chem.* **1968**, *33*, 2057-2061.
27. Ducker, J. W. and Gunter, M. J. *Aust. J. Chem.* **1973**, *26*, 1551-1569.
28. Gardner, T. S.; Weins, E. and Lee, J. *J. Org. Chem.* **1958**, *23*, 823-827.