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TETRAHEDRON

Novel Pathway to 1-Aminopyrroles and other Nitrogen Heterocycles from Glyoxal Monohydrazones and Acylated Active Methylene Compounds in Solvent-Free Reactions under Microwave Irradiation

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Abstract : Heterobicyclic compounds **5** obtained by ring closure of glyoxal monophenylhydrazones **1a** with acyl active methylene compounds **2** ($R^3COCH_2CO_2R^4$), in solvent-free reaction catalyzed by piperidine, give after acidic treatment functionalized N-anilinopyrroles **6** which may also be readily obtained in a one-pot reaction starting from **1** and **2** in the presence of piperidine followed by the acidic treatment. When R^3 is an isopropyl group, the reaction follows a different course leading to new nitrogen fused heterocycles **7** and **8**. Microwave irradiation converts **5** into the isomeric N-anilinopyrroles **12** except when **5** bears two acyl groups which then leads to **6**. Starting from glyoxal N-dimethylhydrazones **1b**, N,N-dimethylamino pyrroles **9** can be prepared at room temperature or under microwaves in the presence of catalytic amounts of piperidine. Microwave irradiation converts cyclohexanones **10** into benzo-pyrrolidinones **11**. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The N-anilinopyrrole moiety is present in several natural products, which display a wide variety of biological applications, for example as antibiotics[1-3]. Usually, their preparation is achieved by reaction of diazoalkenes with 1,3-dicarbonyl compounds[4,5]. The phenyl group may be replaced by 2,4-dinitrophenyl, methoxycarbonyl[6] or amide group[7,8]. Furthermore, pyrrole nucleus is still of great interest as reported in the recent literature[9].

Microwave irradiation (MWI) and its application for dry organic reactions is currently under extensive examination and has been recently reviewed[10-16]. Solvent-free organic reactions, eventually under microwave irradiation, are one of the main research topics in our laboratory[17-19] and as part of our program to develop the synthesis of heterocyclic compounds under these conditions, we have previously reported an unusual ring closure of N-substituted glyoxal monohydrazones **1a-b** with several β-ketoesters **2a-d** or **f** in a solvent-free reaction catalyzed by piperidine. Thus, we have shown that, according to the hydrazone nitrogen substitution, we obtained either heterobicycles **5** as the kinetically controlled product or cyclohexanone **10**. Pyridazinone **4**, which results from the cyclization of the alkene intermediate **3** appears as the thermodynamically controlled product[20] (Scheme 1).

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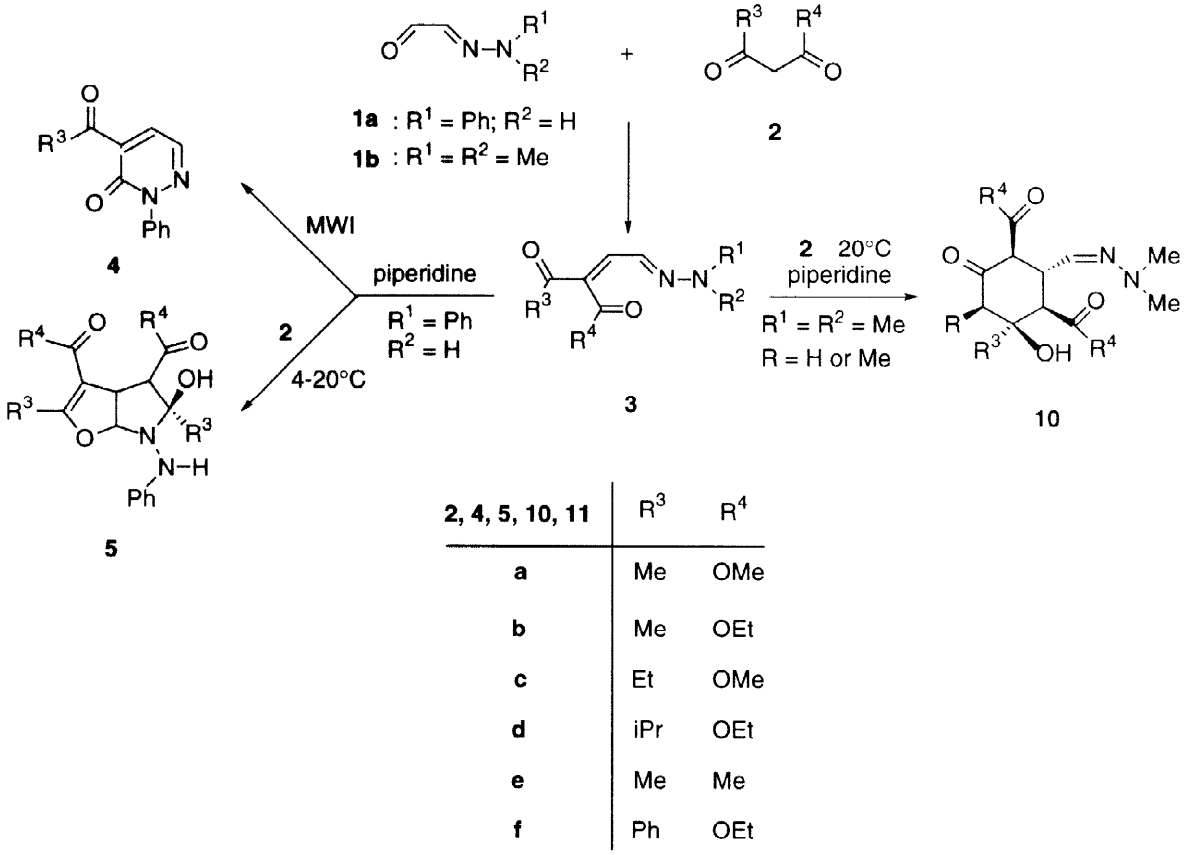


2, 4, 5, 10, 11	R^3	R^4
a	Me	OMe
b	Me	OEt
c	Et	OMe
d	iPr	OEt
e	Me	Me
f	Ph	OEt

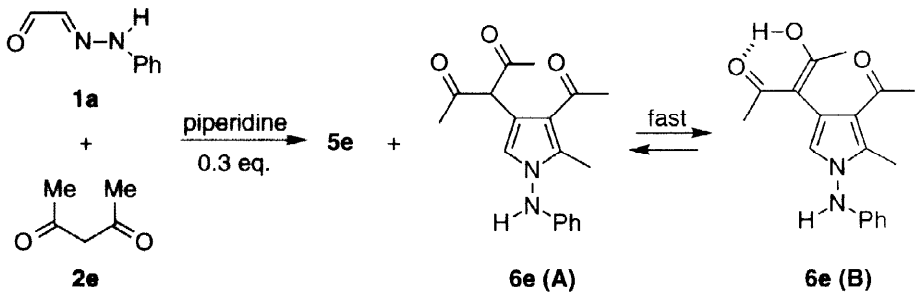
Scheme 1

In an attempt to extend these previous studies and with the aim towards the exclusive formation of the heterobicycle **5**, we studied the reaction of acetylacetone **2e** (no ester group and consequently no pyridazinone) with the monophenylhydrazone of glyoxal **1a**. The results are reported, discussed and extended here.

RESULTS AND DISCUSSION

The reaction catalyzed by piperidine (0.3 eq.) was carried out under various conditions of time and temperature (Table 1). **5e** was formed quantitatively after 1 to 4 hours at 4°C (entries 1-2). If the mixture was allowed to stand 72 hours at 4°C, N-anilinopyrrole **6e** appeared as by-product (entry 3) : the proportion of **6e** in the mixture increased with the temperature and the reaction time (entries 4-5). Microwave irradiation of the initial mixture carried out in an open focused microwave oven[21] which allows to operate at atmospheric pressure with temperature monitoring (infrared detection[22]) resulted in the formation of unidentified side-products (entry 6).

Table 1. Reaction of monophenylhydrazone of glyoxal 1a with acetylacetone 2e.



Entry	Time	T (°C)	Percent completion[a] (%)	5e[b] (%)	6e[b] (%)
1	1h	4	92	100 (78[c])	0
2	4h	4	91	100	0
3	72h	4	92	83	17
4	15 min	20	37	67	33
5	25 min	20	44	50 (13[c])	50 (17[d])
6	2 min	90[e]	90	0[f]	0[f]

[a] Estimated by ^{1}H NMR of crude reaction mixture.

[b] Relative percentages in the crude mixture estimated by ^{1}H NMR.

[c] Isolated yield after washing with diethyl ether; mp 146°C.

[d] Isolated yield after similar treatment; mp 157°C.

[e] Final temperature under 30W irradiation in a focused microwave oven MX350 Prolabo.

[f] By-products (**5e** and **6e** destroyed).

Heterobicycle **5e** isolated in pure state is slowly transformed in **6e** at room temperature (89% after 3 months). This processus could be accelerated by focused microwave irradiation (300 W ; 130°C ; 30 min) : **6e** was isolated in 61% yield after washing with diethyl ether.

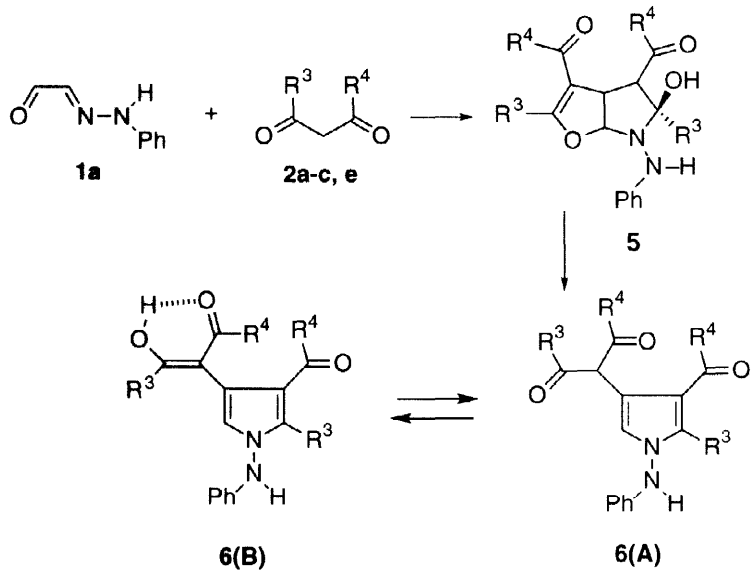
On the other hand, treatment of **5e** (600 mg diluted in 15 mL of CH_2Cl_2) with concentrated hydrochloric acid (12 N HCl : 0.5 mL) afforded pyrrole **6e** in 96% yield in a few minutes.

Structure **6e** was established by mass spectrometry, elemental analysis and spectroscopic data. ^{1}H NMR showed a single signal at 2 ppm corresponding to six protons of two acyl groups. The latter groups presented a single peak at 24 ppm in ^{13}C NMR at room temperature and were differentiated at low temperature (233K). The enol hydrogen has a considerable downfield shift (17 ppm) suggesting a strong chelation with the neighbouring acyl group. A doublet with a small value of $^3J_{CH}$ (*6.4 Hz*) was detected at 117.6 ppm and could be assigned to the carbon bearing the two acyl groups in the enol form (**6e** B). This signal became a singlet after irradiation of the pyrrolic hydrogen nucleus (δ = 6.5 ppm). The two forms A and B were in very fast equilibrium at room temperature.

In the same way, pure **5a**, **5b**, **5c** were converted to N-anilinopyrroles **6a**, **6b**, **6c** in acidic medium (Table 2 : method A). NMR data show that at room temperature in $CDCl_3$ the ketoform is largely favoured.

However, we found it more convenient to carry out the synthesis of **6** in a one-pot reaction : **1a** was first mixed with **2a**, **2c** or **2e** and carefully adjusted amounts of piperidine at room temperature or 4°C during the appropriate time. The crude mixture was then treated with concentrated hydrochloric acid. In this way, pyrroles **6** were obtained in 52-86% yields from readily available starting products (Table 2 : method B).

Table 2. Preparation of N-anilinopyrroles 6.



Method	6	R^3	R^4	Time (min)	Piperidine (%)	T (°C)	Yield (%)[a]	A/B
A[b]	**a**	Me	OMe	3	no	20	83	87/13
B[c]	**a**	Me	OMe	20	10	30[d]	86	87/13
A	**b**	Me	OEt	3	no	20	73	87/13
A	**c**	Et	OMe	3	no	20	45	92/8
B	**c**	Et	OMe	30	20	20	75	92/8
B	**e**	Me	Me	60	30	4	52[e]	0/100

[a] Yield of isolated pure product.

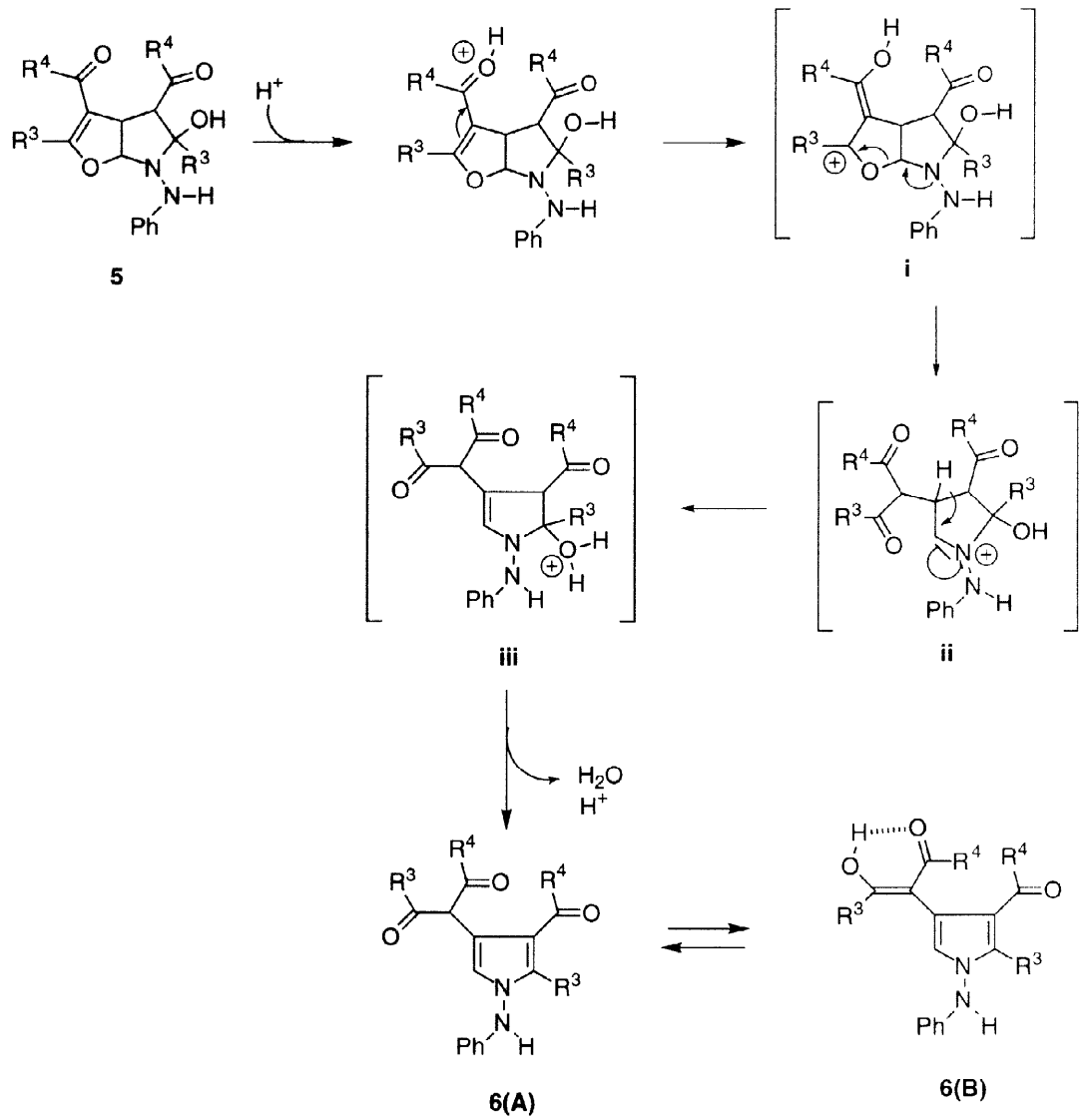
[b] From pure isolated **5** in acidic medium.

[c] From **1a** and **2** in two steps and one pot reaction.

[d] Exothermic reaction.

[e] After chromatography on silica gel.

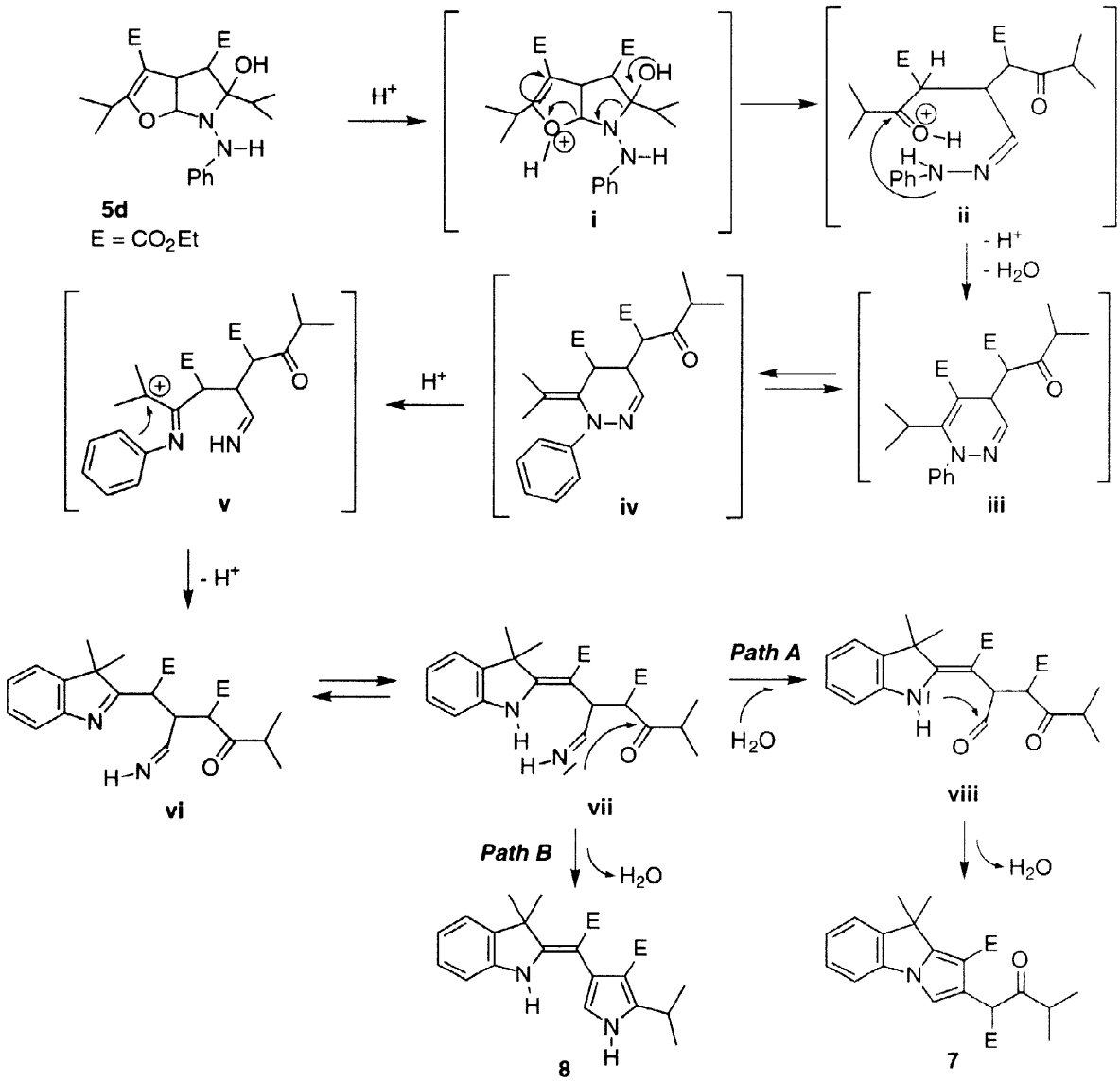
The proposed mechanism for the transformation of heterobicycles **5** into N-anilinopyrroles **6** is outlined in Scheme 2. Protonation of the carbonyl group to give a resonance stabilized cation **i** which then opens to the intermediate **ii** which rearranges to **iii** to give the aromatic N-anilinopyrrole **6(A)** ⇌ **6(B)** after an acid catalyzed dehydration.



Scheme 2

When heterobicycle **5** bears an isopropyl group (for example **5d** : R^3 = iPr ; R^4 = OEt), the acid treatment affords a mixture of two new products **7** and **8** instead of pyrrole **6**. These two compounds were separated by silica gel chromatography (**7** : 28% yield, mp = 81°C ; **8** : 53% yield, mp = 155°C). The structural assignment for **7** and **8** was achieved by ^1H and ^{13}C NMR, HRMS and elemental analysis (Molecular formula : **7** : $C_{24}H_{29}NO_4$, **8** : $C_{24}H_{30}N_2O_4$). Although all the spectroscopic data were consistent with **8**, the structure was confirmed by X-ray diffraction analysis. The ORTEP diagram is shown on Figure 1. We propose the following mechanism (Scheme 3) path A for the formation of **7** and path B for **8**. Protonation of **5d** gives **i** which rings open to **ii**. Then cyclization and dehydration lead to **iii** in equilibrium with **iv**. After protonation to **v**, a Friedel-Crafts intramolecular substitution leads to **vi** in equilibrium with **vii**. At this point, two different pathways

compete : **vii** bearing an hydrolisable imine group produces **7** after cyclization of **viii** (path A) or cyclization and dehydration leads to **8** (path B).



Scheme 3

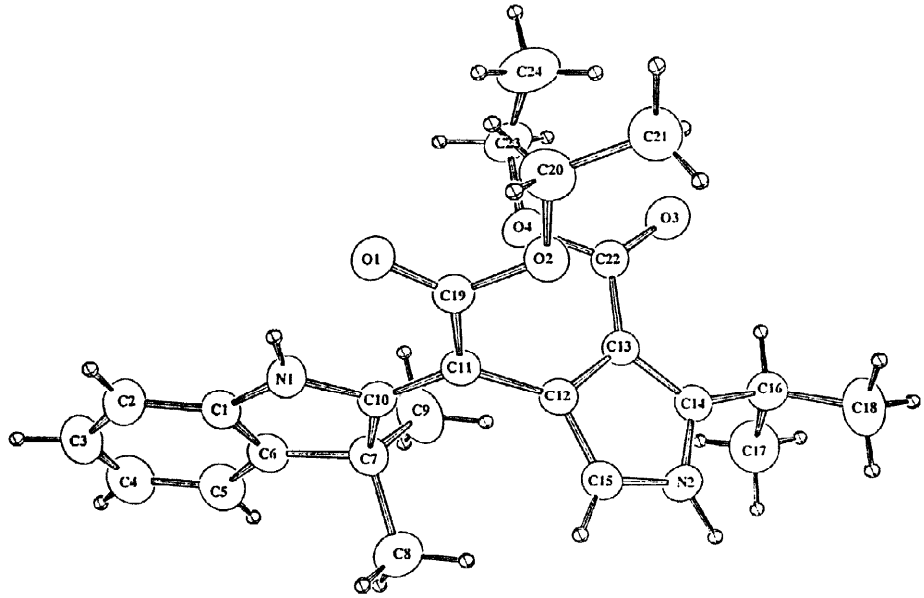


Fig. 1 : ORTEP diagram 8

On the other hand, we have recently reported that the condensation of monodimethylhydrazone of glyoxal **1b** with two equivalents of methylacetoacetate **2a** led to cyclohexanone **10a** as major product (54% isolated yield)[20].

The course of the reaction was strongly depending on the experimental conditions : the results are reported in Table 3.

Table 3. Reaction of monodimethylhydrazone of glyoxal 1b with methylacetoacetate 2a.

Entry	Time	T (°C)	P (W)	Pip. mL (%)	Percent Completion[a] (%)	**3ba**[b] %	**10a**[b] %	**9a**[b] %
1	1 h	20	no	0.15(30)	83	16	68(54[c])	16
2	24 h	20	no	0.15(30)	95	0	56	44
3	48 h	20	no	0.15(30)	96	0	50	50
4	7 d	20	no	0.01(2)	100	9	0	91(85[e])
5	12 d	20	no	no	94	36[f]	0	64
6	4 min	100[d]	30	0.15(30)	80	0	67	33
7	4 min	78[d]	30	0.01(2)	52	50	0	50

[a] Calculated by ^{1}H NMR on the crude oil and relative to major residual starting product.

[b] Relative percentages (%) **3ba** + (%) **10a** + (%) **9a** = 100.

[c] Isolated pure product after washing with ether/petroleum ether.

[d] Final temperature monitored by computer with Maxidigest MX350[21].

[e] Isolated pure product after bulb to bulb short-path distillation.

[f] Yellow oil[23].

The moderate yield of cyclohexanone **10** was due to the competing formation of N,N-dimethylamino pyrrole **9a** bearing an hydrogen in β-position of nitrogen ; the structure of which was in agreement with spectroscopic data and confirmed by X-ray analysis (Fig. 2).

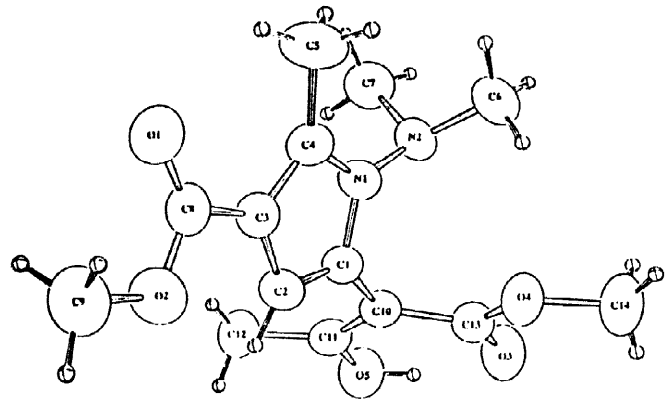


Fig. 2 : ORTEP diagram 9a.

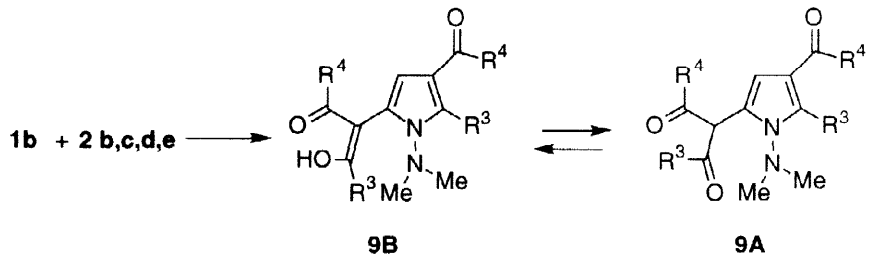
In this synthesis, we could also isolate the alkene **3ba**[23] ($R^1 = R^2 = Me$; $R^3 = Me$; $R^4 = OMe$) (entry 5), precursor of **9a** ($R^1 = R^2 = Me$; $R^3 = Me$; $R^4 = OMe$) by simply mixing **1b** and **2a**. **3ba** disappeared after 4 minutes under microwave irradiation (entry 6) or 24-48h at room temperature (entries 2-3) in presence of 30% piperidine. The percentage of **9a** increased when the reaction time was longer whereas cyclohexanone **10a** decreased.

9a was quantitavely formed after 7 days at room temperature with 2% of piperidine (entry 4). After 5 minutes under microwave irradiation at 78°C, with 2% of piperidine, cyclohexanone was transformed into pyrrole (yield : 50% ; entry 7). It is noteworthy that cyclohexanone **10** was slowly transformed into **9** on standing at room temperature during 5 months. With longer microwave irradiation time, the final products were largely degradated.

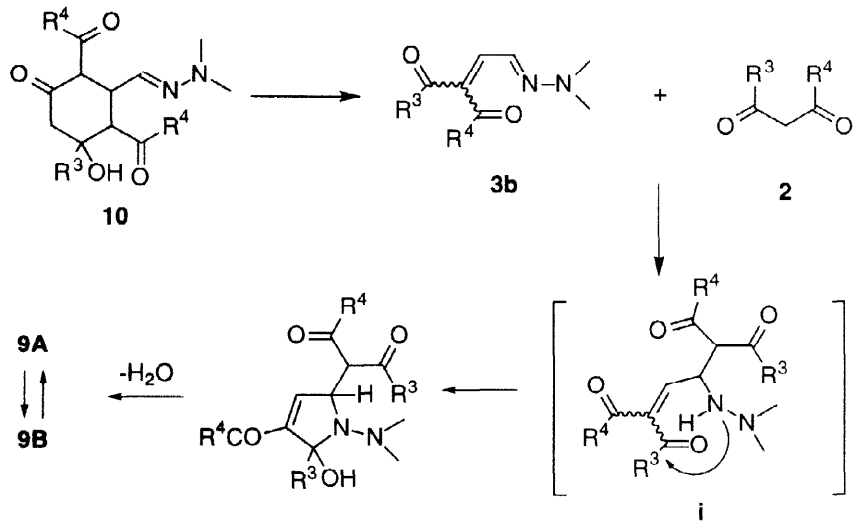
We have extended the reaction to methylene compounds **2b**, **2c**, **2d**, **2e** and obtained the corresponding pyrroles **9** at room temperature (Table 4).

Table 4. Preparation of pyrroles 9 from monodimethylhydrazone of glyoxal 1b with 2b-e in presence of piperidine (2%).

9	R^3	R^4	Reaction Time	yield (%)	A/B
b	Me	OEt	6 d	60	42/58
c	Et	OMe	13 d	43	35/65
d	iPr	OEt	33 d	21	0/100
e	Me	Me	25 h	62	100/0

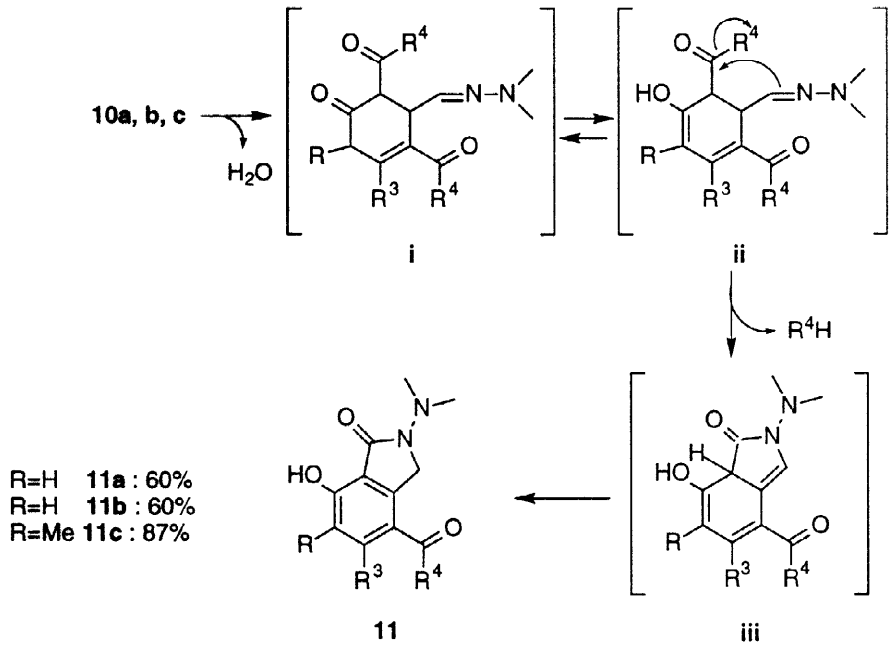


A reasonable mechanism for the transformation of cyclohexanone **10** into pyrrole **9** at room temperature is proposed in Scheme 4. Presumably, the reaction proceeds with ring opening of the cyclohexanone **10** followed by cleavage to regenerate the corresponding alkene **3b** and acyl methylene compound **2**. In absence of base and solvent, it can be assumed that monodimethyl-hydrazone moiety of **3b** acts as a base to remove the acidic proton of **2** to give an intimate ion-pair which is transformed in highly functionalized β-enone **i** by nucleophilic attack of the carbanion of **2** on the hydrazone carbon atom. The cyclization to afford pyrrole **9** took place after hydrogen displacement and dehydration to gain aromaticity in the final step. **9** exists under two forms A and B.



Scheme 4

With the aim to accelerate the formation of pyrrole **9** from cyclohexanone **10**, we decided to submit **10** to microwave irradiation. In fact, this process did not lead to **9**, formed by slow evolution at room temperature, but **10** was converted into a novel and unexpected product **11** which was identified as a benzopyrrolidinone. For example, cyclohexanone **10a** irradiated for 30 minutes at 300W (temperature monitored at 160°C) led to **11a** as yellow crystals. ^{1}H NMR showed only one methyl ester group at 3.8 ppm, a singlet at 4.66 ppm assigned to the methylene protons. In order to secure the structure **11a**, an ORTEP diagram has been established from X-Ray analysis (Fig. 3). The presumed mechanism and the isolated yields are described in the Scheme 5.



Scheme 5

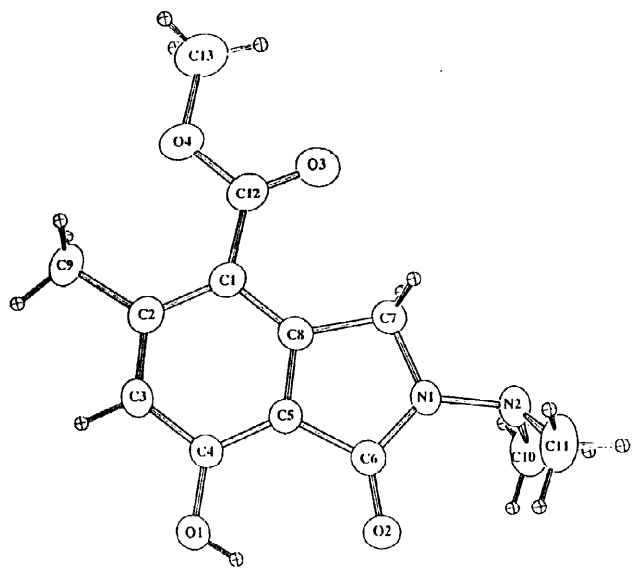
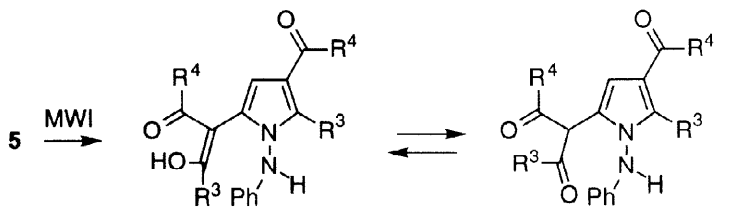


Fig. 3 : ORTEP diagram 11a.

Finally in the same way, we submitted heterobicycles **5** to focused microwaves and N-anilinopyrroles **12**, the structure of which was analogous to **9**, were obtained. For instance, **5a** at 300W (T = 150°C) during 20 minutes was converted to **12a** (73% isolated yield ; A:B = 17/83). (Scheme 6). At room temperature, several months were necessary to obtain complete conversion.

The generalization to several substituents has been realized but the pure products were not isolated and the materials were only characterized by HRMS.



12B **12A**

a	R^3 = Me	R^4 = OMe	(73%; A/B = 17/83)
b	R^3 = Me	R^4 = OEt	(HRMS calc 372.168, found 372.167)
c	R^3 = Et	R^4 = OMe	(HRMS calc 372.168, found 372.167)
d	R^3 = iPr	R^4 = OEt	(HRMS calc 428.231, found 428.232)

Scheme 6

The mechanism of the formation of pyrrole **12** may be rationalized as for pyrrole **9**. The first step being ring opening of heterobicycle **5** to generate alkene **3a** and **2**, and the following sequence is analogous.

CONCLUSION

We have described an unusual and short synthesis of pyrroles **6**, **9** and **12** from simple starting materials. These goals were accomplished through different strategies : the overall transformation of heterobicycle **5** leads to N-anilinopyrrole **6** in acid medium at room temperature. **12** is obtained under microwave irradiation of **5**. Nevertheless, in the case of R^3 = iPr, two new heterocycles **7** and **8** were isolated. A straighforward strategy to reach N-anilinopyrrole in a one-pot reaction is as follows : **1** and **2** without solvent in the presence of piperidine, followed by acidification of the reaction mixture. Cyclohexanones **10** were transformed at room temperature into N,N-dimethylpyrroles **9**, whereas microwave irradiation generated benzopyrrolidinones **11**.

Coupling dry media and focused microwave irradiation appears to be a clean, economical and environmentally benign process. If specific microwave activation is actually a matter of controversy[25,26], microwave heating presents nevertheless particular features such as volumetric character, instantaneous heating, easy monitoring and consequently remains a particularly simple and powerful tool for organic synthesis.

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

General methods : Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a PERKIN-ELMER 1420 spectrometer. ^{1}H NMR spectra were recorded on BRUKER WP 80 CW (80 MHz), BRUKER AC 300 P (300 MHz) spectrometers and ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. The mass spectra (MS) were taken on a VARIAN MAT 311 at a ionizing potential of 70 eV in the Centre de Mesures Physiques de l'Ouest (CRMPO, Rennes). Elemental analysis were performed at the Laboratoire Central de Microanalyses-CNRS (Lyon). Thin-layer chromatography (TLC) were performed on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm). For preparative column chromatography, silica gel 60 Merck (230-240 Mesh ASTM) was used. Reactions under microwave irradiation were performed in a

Prolabo Maxidigest MX350 TM (2.45 GHz) microwave reactor with a single focused system. All solvents and reagents were purchased from Janssen Chimica and Aldrich Chimie and used without further purification.

Monophenylhydrazone of glyoxal **1a** or dimethylhydrazone of glyoxal **1b** were readily prepared by literature methods [23,24].

General procedure for the preparation of N-anilinopyrrole 6 and 12.

Method A : Heterobicycle **5** (600mg) diluted with CH_2Cl_2 or $CHCl_3$ (5 mL) was treated by concentrated HCl (12 N ; 0.5 mL). Washing with H_2O, drying organic layers over anhydrous $MgSO_4$, and removal of the solvent *in vacuo*, after filtration, afforded directly the desired product which in some cases needed a purification by column chromatography on silica gel.

Method B : The pyrrole was prepared by simply mixing **1a** (5 mmol) with **2a**, **c**, **e** (10 mmol) and piperidine in catalytic amount after standing during appropriate time at room temperature. After dilution with CH_2Cl_2 addition of 1 mL of concentrated hydrochloric acid and chromatography on silica gel, pure products were isolated.

Method C : Heterobicycle **5** (600mg) was placed in a pyrex tube (diameter 1.5cm) and introduced into a Maxidigest MX350 microwave reactor fitted with a spinning system and adjustable power within 0-300W range and a wave guide (monomode T_{01}). Time and power are adjusted according to the nature of **5**. Crude products were washed or chromatographied.

3-Oxo-2-(1-anilino-5-methyl-4-methoxycarbonyl-3-pyrrolyl) methylbutanoate (6a A) and 3-hydroxy-2-(1-anilino-5-methyl-4-methoxycarbonyl-3-pyrrolyl) methylbut-2-enoate (6a B).

Method A : **6a** is obtained in 83% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 9 : 1 Rf = 0.6).

Method B : From the monohydrazone of glyoxal **1a** (0.74g, 5 mmol) and methylacetoacetate **2a** (1.16g, 10 mmol) and piperidine (0.05 mL, 0.1 eq.) at 30°C (exothermic reaction) during 20 minutes. **6a** was isolated (1.48 mg, 86%) after silica gel chromatography : (CH_2Cl_2/EtOAc, 9 : 1) then washing with ether/petroleum ether. Data of form A : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.3 (s, 3H), 2.4 (s, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 5.5 (s, 1H), 6.4-7.2 (m, 6H), 6.7 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9, 29.3, 50.8, 52.5, 57.1, 108.6, 112.6, 115.1, 121.2, 129.4, 138.5, 146.9, 165.6, 169.8, 202.7; Data of form B : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.9 (s, 3H), 2.4 (s, 3H), 3.6 (s, 3H), 3.7 (s, 3H), 6.5 (s, 1H), 6.4-7.2 (m, 6H), 12.9 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7, 19.8, 50.8, 51.6, 96.9, 110.1, 112.5, 116.6, 121.4, 129.3, 138.0, 147.1, 165.8, 172.9, 173.4; HRMS calcd for $C_{18}H_{20}N_2O_5$: 344.1372, found 344.1351. Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found : C, 63.15; H, 5.81; N, 8.17.

3-Oxo-2-(1-anilino-5-methyl-4-methoxycarbonyl-2-pyrrolyl) methylbutanoate (12a A) and 3-hydroxy-2-(1-anilino-5-methyl-4-methoxycarbonyl-2-pyrrolyl) methylbut-2-enoate (12a B).

Method C : Heterobicycle **5a** (600 mg) is submitted to focused microwave irradiation at 300W (150°C) during 20 minutes. After chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 15 : 1), **12a** was obtained with 73% yield. Data of **12a** : mp 139°C ; Rf = 0.7; Data of form A (17%) : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.1 (broad s, 3H), 2.4 (s, 3H), 3.8 (s, 3H), 3.81 (s, 3H), 4.7 (s, 1H), 6.4-7.2 (m, 6H), 6.6 (s, 1H) ; IR (neat) 3280 cm^{-1}; Unambiguous assignment of carbons of minor isomer A was not possible because of the overlaping with the carbons of major isomer B. Data of form B (83%) : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.8 (s, 3H), 2.5 (s, 3H), 3.6 (broad s, 3H), 3.8 (s, 3H), 6.4-7.2 (m, 7H), 13.0 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9, 19.9, 50.9, 51.9, 93.4, 109.4, 110.3, 112.8, 125.6, 129.2, 138.1, 165.7, 172.4, 178.8; HRMS calcd for $C_{18}H_{20}N_2O_5$: 344.1372, found 344.1361. Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found : C, 62.63; H, 5.82; N, 8.00.

3-Oxo-2-(1-anilino-3-ethoxycarbonyl-2-methyl-4-pyrrolyl) ethylbutanoate (6b A) and 3-hydroxy-2-(1-anilino-5-methyl-4-ethoxycarbonyl-3-pyrrolyl) ethylbut-2-enoate (6b B).

Method A : **6b** was obtained in 73% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 24 : 1, Rf = 0.5); Data of form A (83%) : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H), 1.3 (t, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 4.2 (q, 2H), 4.3 (q, 2H), 5.5 (s, 1H), 6.4-7.2 (m, 6H), 6.7 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9, 14.0, 14.4, 29.2, 57.3, 59.7, 61.5, 108.9, 112.7, 115.2, 121.2, 129.4, 138.3, 147.0, 165.2, 169.3, 202.8; Data of form B (17%) : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2 (t, 3H), 1.25 (t, 3H), 1.9 (s, 3H), 2.4 (s, 3H), 4.1-4.3 (2q, 4H), 6.4-7.2 (m, 6H), 6.5 (s, 1H), 13.0 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.6, 14.22, 14.27, 19.8, 59.3, 60.3, 97.4, 110.4, 112.5, 116.7, 121.2, 129.4, 137.8, 147.3, 165.5, 172.7, 173.1; HRMS calcd for $C_{20}H_{24}N_2O_5$: 372.1685, found 372.1668.

3-Oxo-2-(1-anilino-5-methyl-4-methoxycarbonyl-3-pyrrolyl) methylpentanoate (6c A) and 3-hydroxy-2-(1-anilino-5-methyl-4-methoxycarbonyl-3-pyrrolyl) methylpent-2-enoate (6c B).

Method A : **6c** was obtained in 45% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 19 : 1, Rf = 0.5). **Method B** : From the monohydrazone of glyoxal **1a** (0.74g, 5 mmol) and methyl 3-oxopentanoate **2c** (1.30g, 10 mmol) and piperidine (0.1 mL, 0.2 eq.) at 20°C during 30 minutes, **6c** was obtained with 75% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 19 : 1, Rf = 0.5); Data of form A (92%) : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.0 (t, 3H), 1.1 (t, 3H), 2.6 (q, 2H), 2.9 (q, 2H), 3.7 (s, 3H), 3.8 (s, 3H), 5.5 (s, 1H), 6.4-7.2 (m, 6H), 6.6 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.9, 14.0, 18.5, 35.3, 50.8, 52.5, 56.2, 107.6, 112.7, 115.4, 121.3, 129.3, 144.2, 147.2, 165.4, 169.9, 205.4; HRMS calcd for $C_{20}H_{24}N_2O_5$: 372.168, found 372.167. For enol form B the signals were not assigned owing to the low proportion (8%).

3-(1-Anilino-2-methyl-3-methylcarbonyl-4-pyrrolyl) pent-2,4-dione (6e).

Method A : **6e** was obtained in 96% yield. **Method B** : Heterobicycle **5e** (600 mg) is submitted to focused microwave irradiation at 300W (110°C) during 30 minutes. After washing with ether, **6e** was isolated in 61% yield. **Method B** : From the monohydrazone of glyoxal **1a** (0.74g, 5 mmol), acetylacetone **2e** (1.00g, 10 mmol) and piperidine (0.15 mL, 0.3 eq.) at 4°C during 60 minutes, **6e** was obtained in 52% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 9 : 1, Rf = 0.5). Data of **6e** : mp 157°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.0 (s, 6H), 2.3 (s, 3H), 2.5 (s, 3H), 6.5-7.45 (m, 7H), 17.0 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 24.0, 30.3, 107.5, 112.5, 117.6, 119.5, 121.5, 121.8, 129.5, 138.6, 146.9, 191.6, 195.2; HRMS calcd for $C_{18}H_{20}N_2O_3$: 312.1473, found 312.1457. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found : C, 69.34; H, 6.66; N, 8.90.

4-Methyl-3-oxo-2-(1,1-dimethyl-7-ethoxycarbonyl-6-benzo [2,3] pyrrolizinyl) ethyl pentanoate (7 A) and 3-hydroxy-4-methyl-2-(1,1-dimethyl-7-ethoxycarbonyl-6-benzo [2,3] pyrrolizinyl) ethylpent-2-enoate (7 B).

Method A : **7** was obtained in 28% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 30 : 1, Rf = 0.86); mp 81°C; Data of form A (89%) : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.1 (d, 3H), 1.2 (d, 3H), 1.3 (t, 3H), 1.4 (t, 3H), 1.65 (s, 3H), 1.66 (s, 3H), 2.9 (hept, 1H), 4.2 (q, 2H), 4.35 (q, 2H), 5.9 (s, 1H), 7.1 (s, 1H), 7.15-7.4 (m, 5H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 14.4, 18.1, 18.7, 24.7, 24.8, 40.7, 44.4, 54.4, 59.8, 61.4, 107.3, 110.4, 111.3, 121.0, 123.1, 124.9, 127.5, 137.9, 145.2, 150.0, 164.7, 169.4, 208.3 ; IR (neat) 3050 cm^{-1}; HRMS calcd for $C_{24}H_{29}NO_5$: 411.1920, found 411.1983. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found : C, 69.91; H, 7.18; N, 3.54.

2-(4-Ethoxycarbonyl-5-isopropyl-3-pyrrolyl)-3-(3-dimethyl-2-benzopyrrolidinyl) ethylprop-2-enoate (8).

Method A : **8** was obtained in 53% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 30 : 1, Rf = 0.5); mp 155°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 3H), 1.13 (t, 3H), 1.14 (t, 3H), 1.29 (d, 3H), 1.30 (d, 3H), 1.40 (s, 3H), 3.87 (hept, 1H), 3.9-4.25 (m, 4H), 6.4 (d, 1H), 6.8-7.1 (m, 4H), 8.65 (broad s, 1H), 10.8 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 14.5, 21.7, 22.4, 24.3, 26.1, 29.4, 48.3, 58.7, 59.3, 91.8, 112.1, 118.12, 118.16, 120.4, 121.6, 127.5, 138.7, 142.5, 145.3, 165.8, 166.5, 171.3 ; HRMS calcd for $C_{24}H_{30}N_2O_4$: 410.2123, found 410.2116. Anal. Calcd for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found : C, 70.27; H, 7.53; N, 6.99.

General procedure for the preparation of N-dimethylamino pyrrole 9.

The pyrrole was prepared by simply mixing **1a** (5 mmol) with **2a-e** (10 mmol) and piperidine in catalytic amount and standing during appropriate time at room temperature.

3-Oxo-2-(1-dimethylamino-5-methyl-4-methoxycarbonyl-2-pyrrolyl) methylbutanoate (9a A) and 3-hydroxy-2-(1-dimethylamino-5-methyl-4-methoxy-carbonyl-2-pyrrolyl) methylbut-2-enoate (9a B).

Piperidine 0.02 eq.(0.01 mL); 7 days (20°C); 85% yield; mp 86°C; Data of form A : ^1H NMR ($CDCl_3$, 300 MHz) δ 2.3 (s, 3H), 2.7 (s, 3H), 2.9 (d, 6H), 3.75 (s, 3H), 3.8 (s, 3H), 4.9 (s, 1H), 6.4 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 28.8, 44.9-45.0, 50.8, 52.7, 57.1, 107.2, 110.8, 124.6, 136.5, 165.4, 168.6, 200.5; Data of form B : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.9 (s, 3H), 2.6 (s, 3H), 2.8 (s, 6H), 3.7 (s, 3H), 3.8 (s, 3H), 6.2 (s, 1H), 13.1 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9, 20.1, 45.1, 50.7, 51.6, 95.4, 109.2, 109.8, 125.2, 137.1, 165.7, 173.2, 177.1; HRMS calcd for $C_{14}H_{20}N_2O_5$: 296.1372, found 296.1378. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found : C, 56.81; H, 6.75; N, 9.30.

3-Oxo-2-(1-dimethylamino-5-methyl-4-ethoxycarbonyl-2-pyrrolyl) ethylbutanoate (9b A) and 3-hydroxy-2-(1-dimethylamino-5-methyl-4-ethoxycarbonyl-2-pyrrolyl) ethyl but-2-enoate (9b B).

Piperidine 0.02 eq.(0.01 mL); 6 days (20°C); 60% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 23 : 1, Rf = 0.9); Data of form A : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2-1.4 (2t, 6H), 1.9 (s, 3H), 2.6 (s, 3H), 2.8 (s, 6H), 4.2-4.3 (2q, 4H), 6.2 (s, 1H), 13.3 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 14.1, 14.4, 20.1, 45.1, 59.0, 60.6, 95.4, 109.4, 109.9, 125.0, 136.5, 165.8, 172.8, 177.0; Data of form B : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2-1.4 (2t, 6H), 2.3 (s, 3H), 2.7 (s, 3H), 2.9 (d, 6H), 4.2-4.3 (2q, 4H), 4.9 (s, 1H), 6,4 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2, 14.0, 14.3, 28.7, 44.7-44.8, 57.0, 59.1, 61.5, 107.1, 110.9, 124.5, 136.1, 164.8, 167.9, 200.3 ; IR (neat) 2970 cm^{-1}; HRMS calcd for $C_{16}H_{24}N_2O_5$: 324.1685, found 324.1684. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found : C, 59.11; H, 7.48; N, 8.48.

3-Oxo - 2- (1 - dimethylamino - 5-ethyl - 4 - methoxycarbonyl - 2 - pyrrolyl) methyl pentanoate (9c A) and A3-hydroxy-2-(1-dimethylamino-5-ethyl-4-methoxycarbonyl-2-pyrrolyl) methylpent-2-enoate (9c B).

Piperidine 0.02 eq.(0.01 mL); 13 days (20°C); 43% yield after chromatography on silica gel (eluent CH_2Cl_2/EtOAc, 23 : 1, Rf = 0.9); mp 70°C; Data of form A : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (t, 3H), 1.12 (t, 3H), 2.6 (q, 2H), 2.7 (s, 6H), 3.0 (q, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 6.2 (s, 1H), 13.2 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9, 14.4, 18.9, 26.9, 45.0, 50.6, 51.6, 94.5, 107.9, 110.8, 124.4, 143.6, 165.4, 173.5, 181.5; Data of form B : ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, 3H), 1.28 (t, 3H), 2.2 (q, 2H),

2.9 (d, 6H), 3.0 (q, 2H), 3.7 (s, 3H), 3.75 (s, 3H), 4.9 (s, 1H), 6.4 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.9, 14.2, 19.5, 34.9, 45.7-45.9, 50.7, 52.7, 56.4, 108.1, 110.0, 124.2, 143.2, 164.8, 168.7, 203.1 : HRMS calcd for $C_{16}H_{24}N_2O_5$: 324.1685, found 324.1684. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found : C, 58.98; H, 7.49; N, 8.57.

3-Hydroxy-4-methyl-2-(1-dimethylamino-5-isopropyl-4-ethoxycarbonyl-2-pyrrolyl) ethyl pent-2-enoate (9d).

Piperidine 0.3 eq.(0.15 mL); 33 days (20°C); 21% yield after washing with ether; mp 107°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.1 (d, 3H), 1.15 (d, 3H), 1.2 (t, 3H), 1.3 (t, 3H), 1.4 (d, 6H), 2.6 (hept, 1H), 2.8 (d, 6H), 3.9 (hept, 1H), 4.1-4.3 (m, 4H), 6.3 (s, 1H), 13.5 (d, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 14.5, 17.8, 20.4, 21.3, 25.5, 31.8, 45.8-46.0, 59.3, 60.7, 93.5, 107.8, 112.0, 124.0, 146.3, 165.1, 173.5, 184.5; HRMS calcd for $C_{20}H_{32}N_2O_5$: 380.2273, found 380.2269. Anal. Calcd for $C_{20}H_{32}N_2O_5$: C, 63.13; H, 8.48; N, 7.36. Found : C, 63.18; H, 8.72; N, 7.30.

3-(1-Dimethylhydrazino-2-methyl-3-methylcarbonyl-4-pyrrolyl)pent-2,4-dione (9e).

Piperidine 0.3 eq.(0.15 mL); 25 h (20°C); 47% yield after washing with ether/petroleum ether; mp 134°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.9 (s, 6H), 2.2 (s, 3H), 2.5 (s, 3H), 2.8 (s, 6H), 6.7 (s, 1H), 17.2 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 300 MHz) δ 11.4, 23.9, 30.2, 47.4, 108.0, 113.0, 117.9, 118.1, 136.9, 191.6, 194.9 ; HRMS calcd for $C_{14}H_{20}N_2O_3$: 264.1481, found 264.1473. Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.62; N, 10.60. Found : C, 63.63; H, 7.82; N, 10.44.

General procedure for the preparation of benzopyrrolidinones 11.

Cyclohexanone **10** (500mg) was placed in a pyrex tube (diameter 1.5cm) without solvent or catalyst and introduced into the Maxidigest MX350 microwave reactor during 30 minutes at 300W (160°C). Crude products were purified by washing with ether or short-path distillation.

7-Dihydro-3-hydroxy-5-methyl-6-methoxycarbonyl benzo[3,4-c] dimethylhydrazono pyrrolidin-2-one (11a).

11a was isolated in 60% yield after short-path distllation ($Eb_{0.03}$ = 200°C); mp 166°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.6 (s, 3H), 2.8 (s, 6H), 3.8 (s, 3H), 4.7 (s, 2H), 6.7 (s, 1H), 9.0 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.2, 44.6, 47.2, 51.6, 114.9, 116.6, 118.0, 143.5, 148.3, 158.1, 166.3, 167.3 ; HRMS calcd for $C_{13}H_{16}N_2O_4$: 264.1096, found 264.1110. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found : C, 59.00; H, 6.05; N, 10.58.

7-Dihydro-3-hydroxy-6-ethoxycarbonyl-5-methyl benzo [3,4-c] dimethylhydrazono pyrrolidin-2-one (11b).

11b was obtained in 60% yield after washing with ether; mp 145°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.4 (t, 3H), 2.6 (s, 3H), 2.8 (s, 6H), 4.4 (q, 2H), 4.7 (s, 2H), 6.7 (s, 1H), 9.0 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 23.2, 44.5, 47.2, 60.6, 114.9, 116.8, 117.9, 143.4, 148.1, 157.9, 165.8, 167.3 ; HRMS calcd for $C_{14}H_{18}N_2O_4$: 278.1267, found 278.1261. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06. Found : C, 60.39; H, 6.40; N, 10.05.

7-Dihydro - 5 - ethyl - 3- hydroxy - 4 - methyl - 6 -methoxycarbonyl benzo [3,4-c] dimethylhydrazono pyrrolidin-2-one (11c).

11c was isolated in 87% yield after short-path distllation ($Eb_{0.035}$ = 150°C); mp 66°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.2 (t, 3H), 2.2 (s, 3H), 2.8 (s, 6H), 3.0 (q, 2H), 3.9 (s, 3H), 4.6 (s, 2H), 9.3 (broad s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.2, 14.4, 24.4, 44.6, 47.0, 51.7, 113.9, 116.8, 123.6, 139.7, 151.6, 156.7,

166.9, 167.9 ; HRMS calcd for $C_{15}H_{20}N_2O_4$: 292.1423, found 292.1431. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found : C, 61.82; H, 7.10; N, 9.75.

X-Ray Crystallographic Analysis Data for 8, 9a and 11a.

Crystal data for $C_{24}H_{30}O_4N_2$ **(8)**, Mr = 410.52, monoclinic, $p2_1/c$, a = 11.357(2), b = 12.299(4), c = 16.529(6) Å, β = 106.51(3)°, V = 2214(2) $Å^{-3}$, Z = 4, D_x = 1.232 $Mg.m^{-3}$, λ(MoKα) = 0.70926Å, μ = 0.783 cm^{-1}, F(000) = 880, T = 293 K, final R = 0.033 for 2447 observations. The sample (0.30*0.30*0.35 mm) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan ω/2θ = 1, t_{max} = 60 s, range HKL : H 0,13 K 0,14 L -19,19, intensity controls without appreciable decay (0.3%) gives 4315 reflections from which 2247 independant (R_{int} = 0.009) with I>2σ(I). After Lorenz and polarization corrections the structure was solved with Direct Method which reveals all the non-hydrogen atoms of the structure. After isotropic (R = 0.105), then anisotropic refinement (R = 0.086), all the hydrogen atoms are found with a Fourier Difference between 0.65 and 0.26 $e.Å^{-3}$. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude : x, y, z, β_{ij} for N, O and C atoms and x, y, z for H atoms ; 362 variables and 2447 observations ; $w = 1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R = 0.033, R_w = 0.033 and S_w = 0.723 (residual $\Delta\rho \leq 0.15$ e $Å^{-3}$). Atomic scattering factors from International Tables for X-ray Crystallography (1974)[27]. All the calculations were performed on a Digital MicroVAX3100 computer with the MOLEN package (Fair, 1990)[28]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Crystal data for $C_{14}H_{20}O_5N_2$ **(9a)**, Mr = 296.33, monoclinic, $p2_1/c$, a = 9.664(7), b = 7.335(2), c = 22.019(9) Å, β = 101.32(4)°, V = 1531(2) $Å^{-3}$, Z = 4, D_x = 1.286 $Mg.m^{-3}$, λ(MoKα) = 0.70926A, μ = 0.92 cm^{-1}, F(000) = 632, T = 293 K, final R = 0.041 for 1771 observations. The sample (0.20*0.20*0.30 mm) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan ω/2θ = 1, t_{max} = 60 s, range HKL : H 0,11 K 0,8 L -26,26, intensity controls without appreciable decay (0.4%) gives 3114 reflections from which 1771 independant (R_{int} = 0.010) with I>2σ(I). After Lorenz and polarization corrections the structure was solved with Direct Method which reveals all the non-hydrogen atoms of the structure. After isotropic (R = 0.095), then anisotropic refinement (R = 0.079), all the hydrogen atoms are found with a Fourier Difference between 0.54 and 0.32 $e.Å^{-3}$. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude : x, y, z, β_{ij} for N, O and C atoms and x, y, z for H atoms ; 251 variables and 1771 observations ; $w = 1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R = 0.044, R_w = 0.041 and S_w = 0.772 (residual $\Delta\rho \leq 0.16$ e $Å^{-3}$). Atomic scattering factors from International Tables for X-ray Crystallography (1974)[27]. All the calculations were performed on a Digital MicroVAX3100 computer with the MOLEN package (Fair, 1990)[28].

Crystal data for $C_{13}H_{16}O_4N_2$ **(11a)**, Mr = 264.28, triclinic, P-1, a = 7.110(4), b = 9.239(2), c = 10.599(2) Å, α = 100.14(2), β = 109.55(2), γ = 90.06(3)°, V = 644.4(4) $Å^{-3}$, Z = 2, D_x = 1.362 $Mg.m^{-3}$, λ(MoKα) = 0.70926Å, μ = 1.362 cm^{-1}, F(000) = 280, T = 293 K, final R = 0.043 for 1597 observations. The sample (0.25*0.25*0.30 mm) is studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan ω/2θ = 1, t_{max} = 60 s, range HKL : H 0,8 K -11,11 L -12,12, intensity controls without appreciable decay (0.4%) gives 2462 reflections from which 1597 independant (R_{int} = 0.011) with I>2σ(I). After Lorenz and polarization corrections the structure was solved with Direct Method which reveals all the non-hydrogen atoms of the structure. After isotropic (R = 0.105), then anisotropic refinement

(R = 0.085), all the hydrogen atoms are found with a Fourier Difference between 0.64 and 0.28 e.Å^{-3}. The whole structure was refined by the full-matrix least-square techniques (use of F magnitude ; x, y, z, β_{ij} for N, O and C atoms and x, y, z for H atoms ; 220 variables and 1597 observations ; $w = 1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R = 0.043, R_w = 0.044 and S_w = 0.556 (residual $\Delta\rho \leq 0.21$ e Å^{-3}). Atomic scattering factors from International Tables for X-ray Crystallography (1974)[27]. All the calculations were performed on a Digital MicroVAX3100 computer with the MOLEN package (Fair, 1990)[28].

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