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Regioselective synthesis of pyrrolin-3-ones and 2,3,4,5-tetrahydro[1,3]-oxazines from *N*-vinylic amidines

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ABSTRACT

Achiral and optically active *N*-vinylic amidines are obtained by simple addition of amidines to acetylenic esters. Thermal intramolecular cyclization of these substrates containing a carboxylate group in position 3 gives pyrrolin-3-ones. The enaminone character of these compounds towards propargyl bromide, diethyl azodicarboxylate, diethyl acetylenedicarboxylate, ethyl propiolate and phenyl isocyanate is studied and functionalized pyrrolin-3-one derivatives are obtained. The reaction of the pyrrolinones prepared with diethyl ketomalonate leads to new 1,3-oxazine derivatives.

1. Introduction

Pyrrolinone derivatives are important five-membered heterocycles[1,2] because these compounds constitute the skeleton of cyclic substrates for the preparation of biologically active tetramic acid derivatives[3] **I** (Fig. 1) and antibiotics.[4] Moreover, functionalized 2-azabutadiene systems **II** (Fig. 1) represent versatile intermediates mainly for the synthesis of five- and six-membered heterocycles.[5,6] Furthermore, the presence of electron-donating groups in these substrates **III** (Fig. 1), for example, an amine group, could even favour their reactivity as enamine **IV** (Fig. 1), due to the imine–enamine prototropic rearrangement and enamines being excellent synthons for carbon–carbon bond formation.[7]

We have been involved in the chemistry of enamines[8] and in the design of new strategies for the preparation of three,[9] five[10] and six[11] nitrogen heterocyclic compounds as well as in the study of functionalized 2-azadiene systems **II** (Fig. 1) and their use in the preparation of heterocyclic compounds.[12] In this context, little is known about the reactivity of 1-amino-2-aza-1,3-butadienes as enamines **IV** (Fig. 1) and in a previous communication[13] we reported that these substrates could be used in the preparation of 5-dialkylamino-4-pyrrolin-3-one derivatives, which are starting materials for biologically active tetramic acid derivatives.[3,4] Herein, we extend the preparative scope of our methodology and report, for example, the synthesis of a variety of six- and five-membered heterocycles.

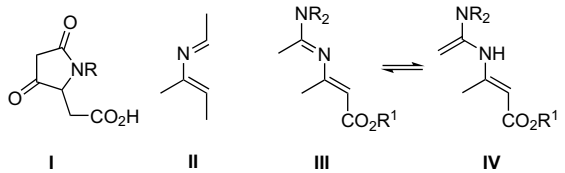
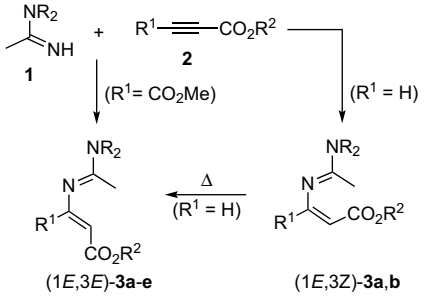


Figure 1.

2. Results and discussion

2.1. Synthesis of *N*-vinylic amidines

Conjugated amidines **3** were prepared through a conjugated addition of amidines **1**[14] to acetylenic esters **2** (Scheme 1). Initially the addition (R^1=H, R^2=Et) in $CHCl_3$ at 20 °C was performed and mixtures of *E,E* and *E,Z*-*N*-vinylic amidines **3a** (20:80) and **3b** (35:65) were obtained (Scheme 1, Table 1, entries 1 and 3). The isomerization of *E,Z* towards *E,E* isomer was observed when a solution of *E,Z* isomer of **3a** or **3b** was heated at 60 °C in $CHCl_3$.



Scheme 1.

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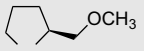
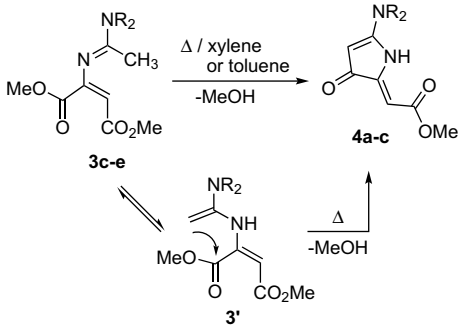
Table 1
1-Amino-2-azadienes **3** produced via Scheme 1

Entry	Compound	R_2	R^1	R^2	Conditions	3*E*/3*Z* (%)	Yield[a] (%)
1	**3a**	Et_2	H	Et	$CHCl_3$, 20 °C, 24 h	20/80[b]	98
2	**3a**	Et_2	H	Et	$CHCl_3$, 60 °C, 24 h	100/0	95
3	**3b**	$-(CH_2)_5-$	H	Et	$CHCl_3$, 20 °C, 24 h	35/65[b]	95
4	**3b**	$-(CH_2)_5-$	H	Et	$CHCl_3$, 60 °C, 4 h	100/0	90
5	**3c**	Et_2	CO_2Me	Me	$CHCl_3$, −15 °C, 4 h	100/0	97
6	**3d**	$-(CH_2)_5-$	CO_2Me	Me	$CHCl_3$, −15 °C, 2 h	100/0	95
7	**3e**		CO_2Me	Me	$CHCl_3$, −15 °C, 4 h	100/0	90

[a] Percent (%) of consumption of the starting material by NMR analysis of crude reaction mixture.
[b] Isomerization of 3*Z* towards 3*E* by heating in $CHCl_3$ at 60 °C.

In addition only *E*,*E* isomers were observed when the reaction of amidines **1** to acetylenic ester **2** was performed in $CHCl_3$ at the same temperature (Table 1, entries 2 and 4). Similar isomerizations of 2-azadienes derived from β-amino esters had been observed previously.[15] However, the addition of amidines **1** to dimethyl acetylendicarboxylate (DMAD) **2** (R^1=CO_2Me, R^2=Me) in $CHCl_3$ at −15 °C gave only *E*,*E*-azadiene isomers **3c**,**d** in excellent yields (Scheme 2, Table 1, entries 5 and 6). The higher reactivity of acetylenic diesters seems to favour the formation of the more stable *E*,*E* isomers **3c**,**d**. Compounds **3a**–**c** were unstable to distillation or chromatography and therefore were not isolated and used in situ for the subsequent reactions. The presence of the non-isolable compounds was established on the basis of the spectroscopic data of their crude reaction mixtures. The scope of this process is not restricted to the use of achiral amidines **1a** (R_2=Et_2), **1b** (R_2=$(CH_2)_5$–) (Scheme 1, Table 1, entries 1–6), given that optically active amidine **1c** derived from (*S*)-2-methoxymethylpyrrolidine gave exclusively optically active 1*E*,3*E* conjugated amidine **3e** (Scheme 1, Table 1, entry 7).



Scheme 2.

2.2. Intramolecular cyclization of *N*-vinylic amidines: synthesis of 4-pyrrolin-3-ones

The enamine character of *N*-vinylic amidines **3** (**IV**, Fig. 1, vide supra) was observed when these substrates were heated. Thermal treatment of conjugated amidine **3c** (R_2=Et_2) in xylene at 140 °C in a sealed tube led directly to cyclic derivative **4a** (Scheme 2, Table 2, entry 1). The process was extended to 1-piperidino derivative **3d** (R_2=$-(CH_2)_5-$) and optically active amidine **3e** and 2-alkylidenpyrrolin-3-ones **4b**,**c** were obtained (Scheme 2, Table 2, entries 2 and 3). Formation of compounds **4** could be explained by intramolecular cyclization of the enaminic tautomer **3′** of amidines **3** with the loss of methanol.

The structure of compounds **4** was assigned on the basis of 1D and 2D spectroscopic data. HOESY ^1H–^{13}C experiment for compound **4a** showed a cross signal between the hydrogen atom of the amino group and the carboxylate carbon atom, which suggests a hydrogen bridge bonding between amino and carboxylate groups. Moreover the IR spectra of compound **4a** showed a signal corresponding to a frequency associated with an amino group at 3409 cm^{-1} that does not change with sample dilution (0.5 M, 0.25 M, 0.12 M in $CHCl_3$). This result is consistent with the presence of the hydrogen bridge bonding between the hydrogen atom of the amino group and the oxygen atom of carboxylic group, which indicates the *Z* configuration of an exocyclic double bond.

2.3. Reactivity of 5-amino-4-pyrrolin-3-ones with electrophilic reagents

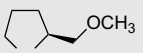
Taking into account both, the potential interest of these substrates for the preparation of functionalized pyrrolinones and that these amino-4-pyrrolin-3-ones **4** are multifunctional compounds containing two enamines, an enaminone and a secondary enamino ester, the regioselective enaminone character (reaction through the C-4) versus the enamino ester reactivity (reaction through the exocyclic carbon) was explored by the reaction of compounds **4** with electrophilic reagents such as propargyl bromide, diethyl azodicarboxylate, acetylenic esters and phenyl isocyanate.

Initially, compound **4a** reacted with propargyl bromide in refluxing $CHCl_3$ to give compound **5** (Scheme 3, Table 3, entry 1). Similarly, in the reaction of **4a** with diethyl azodicarboxylate at room temperature in $CHCl_3$, only adduct **6** (Scheme 3, Table 3, entry 2) was obtained in a regioselective fashion.

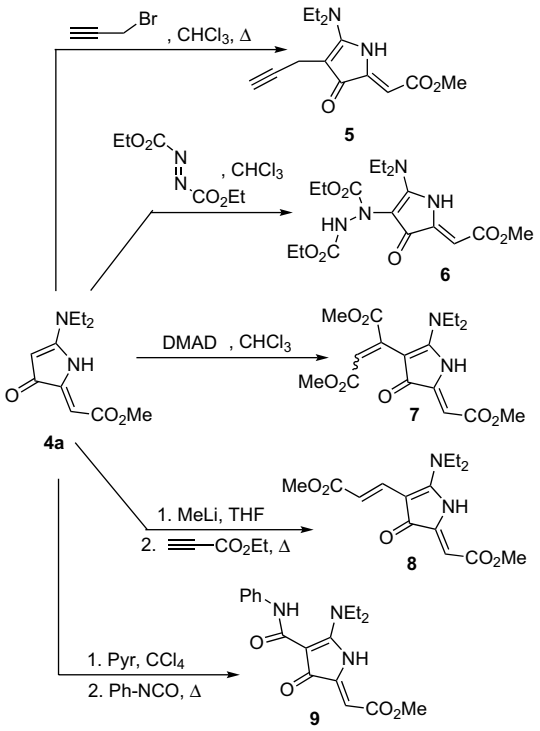
Formation of compounds **5** and **6** can be explained by nucleophilic addition of C-4 (enaminone moiety) of 5-amino-1,2-dihydropyrrol-3-one ring of **4a** to electrophilic methylenic carbon of propargyl bromide or to nitrogen of diethyl azodicarboxylate. Compounds **5** and **6** were characterized by their spectroscopic data. Thus, in ^1H NMR spectroscopic data showed the disappearance of a signal at around 4.7 ppm corresponding to the cyclic enaminic proton, while signal at around 5.8 ppm corresponding to exocyclic enaminic proton remained.

The use of acetylenic esters as electrophiles gave similar results. Thus, the reaction of **4a** with DMAD in $CHCl_3$ at room temperature led to compound **7** (Scheme 3, Table 3, entry 3) as a mixture of *Z*/*E* isomers (57:43) in relation to the newly formed exocyclic double bond. On the other hand, the reaction of **4a**,**b** (R_2=Et_2, $-(CH_2)_5-$) with methyl propiolate were inefficient even on prolonged heating and at a higher temperature. However, the metalation of the enamine by treatment of compound **4a** with MeLi increased its reactivity and thus the reaction with methyl propiolate in THF

Table 2
2-Alkyliden-pyrrolin-3-ones **4** obtained (Scheme 2)

Entry	Compound	R_2	Conditions	Yield[a] (%)
1	**4a**	Et_2	Xylene, 140 °C, 48 h	76
2	**4b**	$-(CH_2)_5-$	Toluene, 110 °C, 168 h	66
3	**4c**		Toluene, 110 °C, 144 h	49

[a] Yield of isolated compound by column chromatography.



Scheme 3.

afforded adduct **8** in a regioselective fashion (Scheme 3, Table 3, entry 4). A similar behaviour was observed when compound **4a** reacted with phenyl isocyanate, since no transformation was observed through thermal treatment. However, the corresponding pyrrolinone derivative **9** (Scheme 3, Table 3, entry 5) was obtained when the reaction was performed in refluxing CCl_4 and in the presence of 1 equiv of pyridine.

2.4. Reactivity of *N*-vinylic amidines 3 with diethyl ketomalonate: synthesis of 1,3-oxazine derivatives

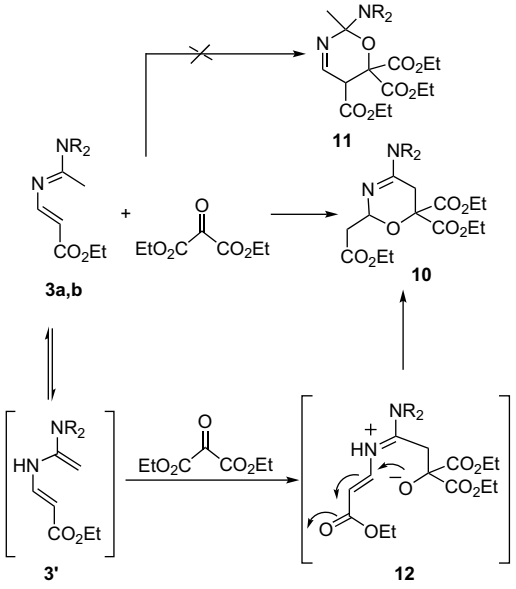
Previously, we had described the reaction of 2-azadienes with ethyl glyoxalate and diethyl ketomalonate for the synthesis of oxazine type derivatives.[12d,16] Now, we explored whether *N*-vinylic amidines **3** showed either a reactivity pattern as heterodienes (**III**, Fig. 1, vide supra) or as enamines (**IV**, Fig. 1, vide supra) with some carbonyl derivatives. In this case the reaction of azadienes **3** with ethyl glyoxalate was inefficient. Indeed, even on prolonged heating and at higher temperature no significant cycloaddition was observed.

However, reaction of conjugated amidines **3a**,**b** with ethyl ketomalonate at room temperature in $CHCl_3$ gave 1,3-oxazine derivatives **10a**,**b**, respectively (Scheme 4), in moderate yields (37% and 42%, respectively), instead of the corresponding [4+2] cycloadducts **11**. The structure of compounds **10** was assigned on the basis of the 1D and 2D spectroscopy, including HMQC and HMBC experiments and mass spectral data. The ^1H NMR spectrum of compound **10a** showed two doublets at 2.55 and 2.95 ppm with a coupling constant of $^2J_{HH}$=15.8 Hz corresponding to methylenic protons of C-5 of new formed oxazine ring, two double doublets at 2.62 and 2.81 ppm with coupling constants of $^2J_{HH}$=14.3 Hz and $^3J_{HH}$=5.3 Hz corresponding to exocyclic methylenic protons and a triplet at 5.48 ppm with coupling constant of $^3J_{HH}$=5.3 Hz corresponding to methynic proton of C-2 of oxazine ring. HMBC experiment for compound **10a** showed cross signals between the exocyclic methylenic protons and the C-2 of oxazine ring. Moreover, cross signals were observed between the methylenic protons of C-5 with the iminic carbon and the quaternary carbon C-6 of the oxazine ring.

Table 3
Compounds **5**–**9** produced via Scheme 3

Entry	Compound	Conditions	Yield[a] (%)
1	**5**	$CHCl_3$, 60 °C, 24 h	38
2	**6**	$CHCl_3$, 20 °C, 24 h	42
3	**7**	$CHCl_3$, 20 °C, 144 h	[b]
4	**8**	THF, 65 °C, 24 h	40
5	**9**	CCl_4, 75 °C, 72 h	42

[a] Yield of isolated compound by column chromatography.
[b] A mixture of *Z* isomer (21%) and *E* isomer (16%) was obtained.



Scheme 4.

Formation of compounds **10** could be explained by the nucleophilic addition of methylenic carbon of compound **3′** to carbonylic group of diethyl ketomalonate to give intermediate **12**, which cyclizes intramolecularly to lead to compound **10**. As far as we know, this strategy represents the first example of the preparation of the previously unknown, 2,3,4,5-tetrahydro[1,3]oxazine derivatives **10**.

3. Conclusion

In conclusion, *N*-vinylic amidines derived from β-amino esters **3** can be readily prepared with very high yields by conjugated addition of *N*-unsubstituted amidines to acetylenic compounds. The new family of conjugated amidines derived from β-amino esters may be important synthons in organic synthesis in the preparation of heterocycles. *N*-Vinylic amidines **3** containing a carboxylate group in position 3 cyclize to 5-amino-4-pyrrolin-3-ones **4**. These compounds (**4**) present an enaminone character reacting with electrophilic reactivities through the C-4 to give a wide range of functionalized pyrrolinone derivatives **5**–**9**. The reaction of conjugated amidines **3** with ethyl ketomalonate gives new oxazine derivatives **10**.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich, Lancaster and Acros Chemical Companies. Solvents for extraction and chromatography

were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} and aluminium oxide N/UV_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (400 MHz, 300 MHz, 250 MHz) and ^{13}C (100 MHz, 75 MHz), spectra were recorded on a Bruker Avance 400 MHz and a Varian VXR 300 MHz spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference (δ=0.00 ppm) for ^{1}H and ^{13}C NMR spectra. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Data are reported in the form m/z (intensity relative to base=100). HRMS were recorded on a MAT95S mass spectrometer. Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}.

4.2. Preparation of *N*-[2-(*S*)-methoxymethylpyrrolidinyl]-acetamidine (1c)

Compound **1c** was synthesized according to the literature procedure[14] using 15 mmol (1.48 g) of CuCl, 90.0 mmol (7.89 mL) of acetonitrile and (1.73 mL) of (*S*)-(+)-2-methoxymethylpirrolidine. The mixture was refluxed during 20 h. Yield: 0.93 g (40%) as brown oil. IR (KBr) ν 3386, 1620, 15 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.89–2.03 (m, 4H), 2.11 (s, 3H), 3.24–3.32 (m, 2H), 3.35 (s, 3H), 3.37–3.44 (m, 2H), 3.98–4.05 (m, 1H), 4.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.3, 23.7, 28.3, 47.5, 57.1, 58.9, 73.2, 163.2. $[\alpha]_D^{20}$ −36.5 (*c* 5.5 mg/mL, CH_2Cl_2). MS (EI) m/z (%) 156 (M^+, 7).

4.3. General procedure for the preparation of *N*-vinylic amidines 3

A solution of acetylenic ester (5 mmol) in $CHCl_3$ (5 mL) was added drop wise to a solution of amidine **1** (5 mmol) in $CHCl_3$ (10 mL) under N_2 and was stirred to adequate temperature until TLC indicated the disappearance of amidine. Evaporation of solvent to reduced pressure afforded *N*-vinylic amidines **3**. The reaction product is unstable during distillation and/or chromatography and was used without purification for the following reactions.

*4.3.1. (1E,3E/1E,3Z)-4-Ethoxycarbonyl-1-dietylamino-1-methyl-2-azabuta-1,3-diene (**3a**)*

The general procedure was followed using acetamidine **1a** (0.57 g) and ethyl propiolate (0.51 mL) at 20 °C for 24 h. Evaporation of solvent to reduced pressure gave **3a** as a mixture of isomers 1*E*,3*E*/1*E*,3*Z* (20/80, 98% of consumption of the starting material by NMR analysis of crude reaction mixture). Spectroscopic data of crude reaction mixture [(1*E*,3*E* and 1*E*,3*Z*) **3a**]: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (t, $^3J_{HH}$=7.2 Hz, 6H) for isomer 3*E*, 1.19–1.25 (m, 9H) for isomer 3*Z*, 1.27 (t, $^3J_{HH}$=7.2 Hz, 3H) for isomer 3*E*, 2.05 (s, 3H) for isomer 3*Z*, 2.12 (s, 3H) for isomer 3*E*, 3.43–3.50 (m, 8H), 4.10–4.21 (m, 4H), 4.97 (d, $^3J_{HH}$=8.3 Hz, 1H) for isomer *Z*, 5.50 (d, $^3J_{HH}$=12.6 Hz, 1H) for isomer *E*, 7.19 (d, $^3J_{HH}$=8.3 Hz, 1H) for isomer *Z*, 8.11 (d, $^3J_{HH}$=12.6 Hz, 1H) for isomer *E*. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3, 13.5, 13.7, 14.4, 14.5, 42.6, 42.8, 58.9, 59.1, 105.1, 105.2, 150.2, 152.7, 152.8, 162.6, 167.0, 169.8.

When the general procedure was followed at 60 °C for 24 h, isomer 1*E*,3*E* of **3a** was obtained (95% of consumption of the starting material by NMR analysis of crude reaction mixture). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.27 (t, $^3J_{HH}$=7.2 Hz, 3H), 2.12 (s, 3H), 3.44–3.50 (m, 4H), 4.16 (q, $^3J_{HH}$=7.2 Hz, 2H), 5.50 (d, $^3J_{HH}$=12.6 Hz, 1H), 8.11 (d, $^3J_{HH}$=12.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3, 13.7, 14.5, 42.8, 59.1, 105.2, 152.8, 162.6, 169.8.

*4.3.2. (1E,3E/1E,3Z)-4-Ethoxycarbonyl-1-methyl-N-piperidyl-2-azabuta-1,3-diene (**3b**)*

The general procedure was followed using acetamidine **1b** (0.63 g) and ethyl propiolate (0.51 mL) at 20 °C for 24 h. Evaporation of solvent to reduced pressure gave **3b** as a mixture of isomers 1*E*,3*E*/1*E*,3*Z* (35/65, 95% of consumption of the starting material by NMR analysis of crude reaction mixture). Spectroscopic data of crude reaction mixture [(1*E*,3*E* and 1*E*,3*Z*) **3b**]: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.26 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.42–1.73 (m, 12H), 2.03 (s, 3H), 2.11 (s, 3H), 3.43–3.68 (m, 8H), 4.08–4.17 (m, 4H), 4.98 (d, $^3J_{HH}$=8.4 Hz, 1H), 5.50 (d, $^3J_{HH}$=12.7 Hz, 1H), 7.22 (d, $^3J_{HH}$=8.4 Hz, 1H), 8.10 (d, $^3J_{HH}$=12.7 Hz, 1H).

When the general procedure was followed at 60 °C for 4 h, isomer 1*E*,3*E* of **3b** was obtained (90% of consumption of the starting material by NMR analysis of crude reaction mixture). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.42–1.63 (m, 6H), 2.11 (s, 3H), 3.43–3.62 (m, 4H), 4.15 (q, $^3J_{HH}$=7.2 Hz, 2H), 5.50 (d, $^3J_{HH}$=12.7 Hz, 1H), 8.10 (d, $^3J_{HH}$=12.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 14.5, 24.4, 25.7, 46.1, 58.9, 105.3, 152.6, 162.3, 169.4.

*4.3.3. (1E,3E)-1-Diethylamino-1-methyl-3,4-dimethoxycarbonyl-2-azabuta-1,3-diene (**3c**)*

The general procedure was followed using acetamidine **1a** (0.57 g) and DMAD (0.61 mL) at −15 °C for 4 h. Evaporation of solvent to reduced pressure gave **3c** (97% of consumption of the starting material by NMR analysis of crude reaction mixture). Spectroscopic data of crude reaction mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.89 (s, 3H), 3.35–346 (m, 4H), 3.65 (s, 3H), 3.78 (s, 3H), 6.04 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3 (m), 15.5, 42.7, 50.7, 52.4, 103.1, 151.0, 157.3, 166.4, 166.9.

*4.3.4. (1E,3E)-1-Methyl-3,4-dimethoxycarbonyl-1-N-piperidyl-2-azabuta-1,3-diene (**3d**)*

The general procedure was followed using acetamidine **1b** (0.63 g) and DMAD (0.61 mL) at −15 °C for 2 h. Evaporation of solvent to reduced pressure gave **3d** (95% of consumption of the starting material by NMR analysis of crude reaction mixture). Spectroscopic data of crude reaction mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55–1.67 (m, 6H), 1.87 (s, 3H), 3.56–3.68 (m, 4H), 3.65 (s, 3H), 3.78 (s, 3H), 6.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.7, 24.2, 25.6, 46.2, 50.8, 52.6, 103.0, 151.1, 158.2, 166.5, 166.8.

*4.3.5. (1E,3E)-1-Methyl-1-[2-(S)-methoxymethylpirrolidyl]-3,4-dimetoxycarbonyl-2-azabuta-1,3-diene (**3e**)*

The general procedure was followed using *N*-[2-(*S*)-methoxymethylpyrrolidinyl]-acetamidine **1c** (0.78 g) and DMAD (0.61 mL) at −15 °C for 4 h. Evaporation of solvent to reduced pressure gave **3e** (90% of consumption of the starting material by NMR analysis of crude reaction mixture). Spectroscopic data of crude reaction mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.89–2.15 (m, 4H), 2.05 (s, 3H), 3.24–3.39 (m, 2H), 3.40–3.59 (m, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 4.12 (s, 1H), 6.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.8, 23.6, 27.7, 47.9, 50.6, 52.4, 57.2, 58.8, 76.0, 103.3, 150.7, 156.8, 166.1, 166.6.

4.4. General procedure for preparation of 5-amino-4-pyrrolin-3-ones 4

A solution of compound **3** (5 mmol) in toluene or xylene (15 mL) under N_2, was refluxed until TLC indicated the disappearance of

compound **3**. Evaporation of solvent and chromatographic separation (silica gel, ethyl acetate) gave compounds **4**.

*4.4.1. (2Z)-5-Diethylamino-2-(1-methoxycarbonylmethylene)-1,2-dihydropyrrol-3-one (**4a**)*

The general procedure was followed using **3c** (1.28 g) in xylene for 48 h. Compound **4a** (0.85 g, 76%) was obtained as a brown solid; mp 167–168 °C (hexane/CH_2Cl_2). IR (KBr) ν 3393, 1661, 1594 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (t, $^3J_{HH}$=7.1 Hz, 6H), 3.41 (q, $^3J_{HH}$=7.1 Hz, 4H), 3.77 (s, 3H), 4.64 (s, 1H), 5.80 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.0, 14.1, 43.5, 45.9, 51.7, 80.6, 91.4, 149.5, 166.0, 169.8, 180.9. MS (EI) *m*/*z* (%) 224 (M^+, 10). Calcd for $C_{11}H_{16}N_2O_3$ [M^+] 224.1161, found [M^+−MeOH] 192.0889.

*4.4.2. (2Z)-2-(1-Methoxycarbonylmethylene)-5-(N-piperidyl)-1,2-dihydropyrrol-3-one (**4b**)*

The general procedure was followed using **3d** (1.34 g) in toluene for 168 h. Compound **4b** (0.78 g, 66%) was obtained as a brown solid; mp 164–165 °C (hexane/ethyl acetate). IR (KBr) ν 3387, 1672, 1584 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.67–1.80 (m, 6H), 3.43–3.45 (m, 4H), 3.77 (s, 3H), 4.71 (s, 1H), 5.80 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 25.4, 48.7, 51.6, 80.9, 91.9, 149.6, 165.7, 169.7, 181.1. MS (EI) *m*/*z* (%) 236 (M^+, 8). Calcd for $C_{12}H_{16}N_2O_3$ [M^+] 236.1161, found [M^+−MeOH] 204.0897.

*4.4.3. (2Z)-2-(1-Methoxycarbonylmethylene)5-[N-(2-(S)-methoxymethyl)pyrrolidinyl]-1,2-dihydropyrrol-3-one (**4c**)*

The general procedure was followed using **3e** (1.49 g) in toluene for 144 h. Compound **4c** (0.65 g, 49%) was obtained as a brown oil. R_f=0.23 (10:1, ethyl acetate/methanol). IR (KBr) ν 3399, 1702, 1666, 1578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.77–1.83 (m, 1H), 1.99–2.07 (m, 2H), 2.13–2.20 (m, 1H), 3.41–3.45 (m, 2H), 3.47 (s, 3H), 3.50–3.56 (m, 2H), 3.76 (s, 3H), 4.20 (t, $^3J_{HH}$=8.8 Hz, 1H), 4.58 (s, 1H), 5.74 (s, 1H), 9.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.6, 28.7, 50.1, 51.2, 58.8, 60.0, 75.9, 81.3, 92.3, 149.0, 167.1, 168.3, 181.5. $[\alpha]_D^{20}$ −153.3 (*c* 0.3 mg/mL, CH_2Cl_2). MS (EI) *m*/*z* (%) 266 (M^+, 8). Calcd for $C_{13}H_{18}N_2O_4$ [M^+] 266.1267, found [M^+−MeOH] 234.1011.

4.5. General procedure for preparation of 4-substituted pyrrolinones 5–7

To a solution of compound **4a** (0.45 g, 2 mmol) in $CHCl_3$ (15 mL) to 0 °C under N_2, electrophilic reactive (2 mmol) was added and the mixture was stirred to adequate temperature until TLC indicated the disappearance of compound **4a**. Evaporation of solvent and chromatographic separation (silica gel, ethyl acetate) gave compound **5**, **6** or **7**.

*4.5.1. (2Z)-5-Diethylamino-2-(1-methoxycarbonylmethylene)-4-(2-propinyl)-1,2-dihydropyrrol-3-one (**5**)*

The general procedure was followed using propargyl bromide (2.72 mL) and the reaction was warmed to 60 °C for 24 h. Compound **5** (0.20 g, 38%) was obtained as a brown oil. R_f=0.43 (ethyl acetate). IR (KBr) ν 3405, 3280, 1689, 1664 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.99 (t, $^4J_{HH}$=2.6Hz, 1H), 3.30 (d, $^4J_{HH}$=2.6Hz, 2H), 3.64 (q, $^3J_{HH}$=7.2 Hz, 4H), 3.77 (s, 3H), 5.81 (s, 1H), 8.55 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.5, 14.7, 45.1, 51.9, 68.3, 83.7, 89.3, 92.1, 147.8, 163.5, 170.1, 180.6. EM (CI, 90 V): 263 (M^++1, 100). Calcd for $C_{14}H_{18}N_2O_3$ [M^+] 262.1317, found [M^+] 262.1314.

*4.5.2. (2Z)-5-Diethylamino-4-(N,N′-diethoxycarbonyl-hidrazino)-2-(1-methoxycarbonylmethylene)-1,2-dihydropyrrol-3-one (**6**)*

The general procedure was followed using DEAD (0.34 mL) at room temperature for 24 h. Compound **6** (0.33 g, 42%) was obtained as a yellow oil. R_f=0.26 (1:1, ethyl acetate/pentane). IR (KBr) ν 3383, 1730, 1663 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, $^3J_{HH}$=7.2 Hz, 6H), 1.30–1.34 (m, 6H), 3.42–3.63 (m, 4H), 3.77 (s, 3H), 4.20 (q, $^3J_{HH}$=7.2 Hz, 4H), 5.80 (s, 1H), 7.67 (s, 1H), 8.68 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7, 14.4, 44.1, 51.8, 61.7, 63.3, 92.5, 101.2, 145.6, 156.1, 157.1, 158.9, 169.5, 176.9. EM (CI, 90 V): 399 (M^++1, 100). Calcd for $C_{17}H_{26}N_4O_7$ [M^+] 398.1802, found [M^+] 398.1805.

*4.5.3. (2Z)-5-Diethylamino-4-(1,2-dimethoxycarbonyl-ethenyl)-2-(1-methoxycarbonylmethylene)-1,2-dihydropyrrol-3-one (**7**)*

The general procedure was followed using DMAD (0.27 mL) at room temperature for 144 h. Chromatographic separation (silica gel, 1:1, pentane/ethyl acetate) gave 0.15 g (21%) of *Z* isomer of **7** as a brown oil. R_f=0.50 (ethyl acetate) and 0.12 g (16%) of *E* isomer of 7 as a brown oil. R_f=0.43 (ethyl acetate). Spectroscopic data for *Z* isomer: IR (KBr) ν 3383, 1730, 1578 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ: 1.30 (t, $^3J_{HH}$=7.2 Hz, 6H), 3.55 (q, $^3J_{HH}$=7.2 Hz, 4H), 3.74 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 5.85 (s, 1H), 6.01 (s, 1H), 8.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.4, 44.8, 51.8, 51.9, 52.6, 93.1, 121.5, 138.5, 146.5, 163.5, 165.9, 168.1, 169.6, 179.3. EM (CI, 90 V): 367 (M^++1, 95). Calcd for $C_{17}H_{22}N_2O_7$ [M^+] 366.1427, found [M^+] 366.1443.

Spectroscopic data for *E* isomer: IR (KBr) ν 3384, 1722, 1663, 1596 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, $^3J_{HH}$=7.2 Hz, 6H), 3.43 (q, $^3J_{HH}$=7.2 Hz, 4H), 3.73 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 5.83 (s, 1H), 6.92 (s, 1H), 8.80 (s, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 13.5, 44.8, 51.7, 51.8, 52.8, 92.6, 128.3, 136.0, 147.4, 163.2, 165.6, 167.2, 169.7, 178.2. EM (CI, 90 V): 367 (M^++1, 100). Calcd for $C_{17}H_{22}N_2O_7$ [M^+] 366.1427, found [M^+] 366.1427.

4.6. Procedure for preparation of (2*Z*)-5-diethylamino-4-[(*E*)-2-methoxycarbonylethenyl)-2-(1-methoxycarbonyl-methylene)-1,2-dihydropyrrol-3-one] (8)

To a solution of compound **4a** (0.45 g, 2 mmol) in THF (10 mL) at −78 °C under N_2, MeLi (2.75 mL, 4.4 mmol) was added and the mixture was stirred for 1 h. The reaction was warmed to 0 °C and a solution of methyl propiolate (0.18 mL, 2 mmol) in THF (5 mL) was added. The mixture was stirred to 65 °C for 24 h. The crude reaction mixture was washed with water, extracted with CH_2Cl_2 and dried over $MgSO_4$. Evaporation of solvent and chromatographic separation (silica gel, 1:2 pentane/ethyl acetate) gave compound **8** (0.25 g, 40%) as a red oil. R_f=0.30 (2:1, ethyl acetate/pentane). IR (KBr) ν 3367, 1695, 1664, 1583 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (t, $^3J_{HH}$=7.2 Hz, 6H), 3.63 (q, $^3J_{HH}$=7.2 Hz, 4H), 3.73 (s, 3H), 3.79 (s, 3H), 5.85 (s, 1H), 7.03 (d, $^3J_{HH}$=15.0 Hz, 1H), 7.53 (d, $^3J_{HH}$=15.0 Hz, 1H), 9.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 46.1, 51.1, 51.9, 92.5, 93.2, 111.6, 134.1, 146.3, 162.8, 169.7, 170.1, 180.4. EM (CI, 90 V) *m*/*z*: 308 (M^++1, 100). Calcd for $C_{15}H_{20}N_2O_5$ [M^+] 308.1372, found [M^+] 308.1389.

4.7. Procedure for preparation of (2*Z*)-5-diethylamino-2-(1-methoxycarbonylmethylene)-4-(phenylcarbamoyl)-1,2-dihydropyrrol-3-one (9)

To a solution of compound **4a** (0.45 g, 2 mmol) in CCl_4 (10 mL) at 0 °C under N_2, pyridine (0.18 mL, 2.2 mmol) and a solution of phenylisocyanate (0.24 mL, 2.2 mmol) in CCl_4 (5 mL) were added and the mixture was refluxed for 72 h. The crude reaction mixture was washed with HCl 1 M, water, extracted with CH_2Cl_2 and dried over $MgSO_4$. Evaporation of solvent and chromatographic separation (silica gel, 1:1 pentane/ethyl acetate) gave compound **9** (0.29 g, 42%) as a yellow solid. Mp 170–171 °C (pentane/ethyl acetate). IR (KBr) ν 3361, 1670, 1576 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41 (t, $^3J_{HH}$=7.2 Hz, 6H), 3.81 (s, 3H), 3.79–3.87 (m, 4H), 5.91 (s, 1H), 7.05 (t, $^3J_{HH}$=7.5 Hz, 1H), 7.29 (dd, $^3J_{HH}$=8.5 Hz, $^3J_{HH}$=7.5 Hz, 2H), 7.61 (d, $^3J_{HH}$=8.5 Hz, 2H), 9.14 (s, 1H), 10.85 (s, 1H). ^{13}C NMR (75 MHz,

$CDCl_3$) δ: 13.5, 47.2, 52.0, 93.4, 120.3, 123.1, 128.7, 129.0, 139.1, 146.0, 161.3, 164.4, 169.4, 181.0. EM (CI, 90 V): 344 (M^++1, 27). Calcd for $C_{15}H_{20}N_2O_5$ [M^+] 343.1532, found [M^+] 343.1525.

4.8. General procedure for the reaction of *N*-vinylic amidines 3 with diethyl ketomalonate

To a solution of compound **3** (2 mmol) in $CHCl_3$ (10 mL) under N_2 was added diethyl ketomalonate (0.30 mL, 2 mmol) and the mixture was stirred at room temperature for 24 h. Evaporation of solvent and chromatographic separation (silica gel, 2:1, pentane/ethyl acetate) gave compounds **10**.

*4.8.1. Diethyl 4-diethylamino-2-ethoxycarbonylmethyl-2,5-dihydro-[1,3]oxazine-6,6-dicarboxylate (**10a**)*

The general procedure was followed using **3a** (0.42 g) and compound **10a** (0.28 g, 37%) was obtained as a yellow oil. R_f=0.31 (2:1, hexane/ethyl acetate). IR (KBr) ν 1739, 1627 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.09 (t, $^3J_{HH}$=7.0 Hz, 6H), 1.29–1.30 (m, 9H), 2.55 (d, $^2J_{HH}$=15.8 Hz, 1H), 2.62 (dd, $^2J_{HH}$=14.3 Hz, $^3J_{HH}$=5.3 Hz, 1H), 2.81 (dd, $^2J_{HH}$=14.3 Hz, $^3J_{HH}$=5.3 Hz, 1H), 2.95 (d, $^2J_{HH}$=15.8 Hz, 1H), 3.18 (q, $^3J_{HH}$=7.0 Hz, 2H), 3.38 (q, $^3J_{HH}$=7.0 Hz, 2H), 4.12–4.18 (m, 2H), 4.25–4.31 (m, 4H), 5.48 (t, $^3J_{HH}$=5.3 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 13.8, 13.9, 14.0, 14.2, 27.9, 41.1, 43.6, 60.1, 62.3, 62.4, 78.8, 83.9, 152.2, 167.9, 168.2, 170.4. MS (EI) *m*/*z* (%) 386 (M^+, 6). Calcd for $C_{18}H_{30}N_2O_7$ [M^+] 386.2053, found [M^+] 386.2049.

*4.8.2. Diethyl 2-ethoxycarbonylmethyl-4-(N-piperidyl)-2,5-dihydro-[1,3]oxazine-6,6-dicarboxylate (**10b**)*

The general procedure was followed using **3b** (0.45 g) and compound **10b** (0.33 g, 42%) was obtained as a yellow oil. R_f=0.28 (2:1, hexane/ethyl acetate). IR (KBr) ν 1739, 1633 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25–1.30 (m, 9H), 1.48–1.61 (m, 6H), 2.49 (d, $^2J_{HH}$=15.9 Hz, 1H), 2.62 (q, $^2J_{HH}$=14.3 Hz, $^3J_{HH}$=5.8 Hz, 1H), 2.79 (q, $^2J_{HH}$=14.3 Hz, $^3J_{HH}$=5.8 Hz, 1H), 2.95 (d, $^2J_{HH}$=15.9 Hz, 1H), 3.32–3.40 (m, 4H), 4.22–4.35 (m, 6H), 5.44 (t, $^3J_{HH}$=5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 13.9, 14.1, 24.7, 25.4, 27.7, 43.4, 44.9, 60.1, 62.2, 78.7, 83.6, 153.2, 167.8, 168.0, 170.2. MS (EI) *m*/*z* (%) 398 (M^+, 8). Calcd for $C_{19}H_{30}N_2O_7$ [M^+] 398.2053, found [M^+] 398.2057.

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