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Acid-Induced Dimerization of Imidates Derived from Glycine: Synthesis of Methyl *N*-(1,2,5-Trisubstituted-4-imidazoyl)glycinates

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ABSTRACT

A number of N-(1,2,5-trisubstituted-4-imidazoyl)-glycinates **4** *were prepared in 60–95% yield from imidates* **1** *derived from α-amino esters by cyclodimerization without solvent at 70°C in acetic acid medium. According to this process, the reaction of imidate* **1a** *as a 1,3-dipole generated in situ by thermal 1,2-prototropy with the free ethyl benzimidate as the dipolarophile has been investigated for the first time and gave directly the methyl imidazole-4-carboxylate in moderate yield by regioselective [3 + 2] cycloaddition. © 1996 John Wiley & Sons, Inc.*

INTRODUCTION

Recently, it was shown in our laboratory that imidates **1** derived from methyl glycinate are in equilibrium with azomethine ylides **1′** by thermal 1,2-prototropy [1] and undergo regioselective cycloadditions with aldimines or with imino-alcohols [2] at 70°C without solvent. This 1,3-dipolar cycloaddition reaction leads to 4-yliden-2-imidazoline-5-ones after the successive loss of ethanol [3] and methanol via an intramolecular rearrangement [4].

In some cases, with less-reactive dipolarophiles or after long storage at 4°C, we have found that imidates **1** slowly dimerize [5–7] to imidazoles **4**. The main goals of this study were to establish the mechanism of this dimerization and eventually the nature of the intermediates. We now report the results of our studies that describe the 1,3-dipolar activity of imidates **1** in cyclodimerization, providing novel substituted imidazoles [8] with preparative procedures, including the characterization of these new compounds.

RESULTS AND DISCUSSION

The starting imidates **1** (Table 1) were readily prepared by our previous method [2] in good yields from the appropriate imidate hydrochloride [9] and commercial methyl glycinate hydrochloride (except for **1c**, which was obtained from 2-propynyl glycinate hydrochloride: this α-amino ester was prepared according to standard esterification procedure from glycine and thionyl chloride). Compounds **1** were purified by distillation under reduced pressure as sweet-smelling mobile oils.

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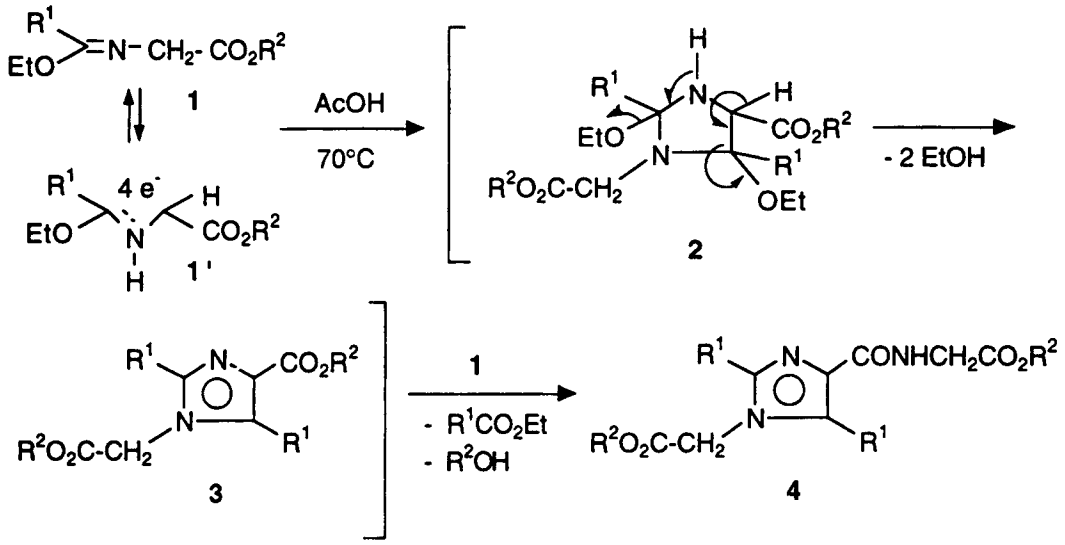
TABLE 1 Synthesis of Imidates **1(a–g)**

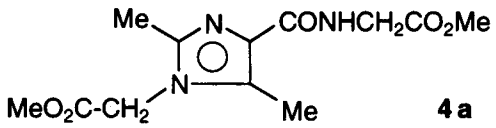
Compound	*R^1*	*R^2*	*Conditions*	*bp (°C/torr)*	*Yield (%)*[a]
1a	Me	Me	24 h; 25°C	93–94/16	(98) 87
1b	Me	Et	24 h; 25°C	46–47/0.1	(80) 70
1c	Me	CH_2–C≡C–H	18 h; 25°C	oil	(94)[b]
1d	Et	Me	24 h; 25°C	41–42/0.1	(78) 64
1e	Me_2CH	Me	18 h; 25°C	50–51/0.05	(75) 70
1f	$PhCH_2$	Me	24 h; 25°C	96–97/0.01	(98) 84
1g	Ph	Me	170 h; 41°C	65–66/0.02	(90) 80

[a]Yield (%) for crude product by ^1H NMR spectroscopy and isolated product.
[b]Bp with decomposition: 38–41°C/0.1 torr.



SCHEME 1

TABLE 2 Effect of Catalyst on Reaction Time for the Formation of **4a**(R^1 = R^2 = Me)



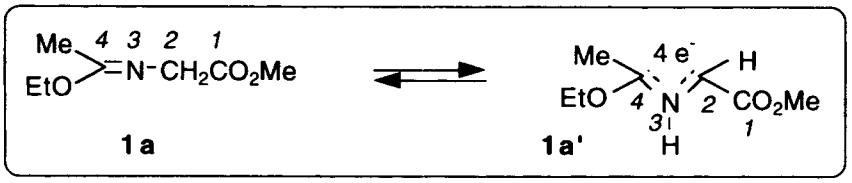
4a

Entry	*Catalyst*	*Conditions*[a]	*Reaction Time (h)*	*Yield (%)*[b]
1	AcOH	25°C, 10%	120	98
2	AcOH	70°C, 10%	24	95
3	AcOH	70°C, 0.33 eq	5	97
4	AcO^-, NH_4^+	70°C, 3%	24	95

[a]Reactions were run in a thermostated oil bath: temperature variation ±1°C.
[b]Estimated by ^1H NMR spectroscopy.

From **1a**, after long storage in the refrigerator, a pale yellow crystalline product **4a** (Scheme 1) was obtained and was separated from **1a** by precipitation in ether. The substituted imidazole structure of **4a** was established by ^1H and ^{13}C spectroscopic data and MS analyses. For example, **4a** (R^1, R^2 = Me) exhibits a doublet at δ = 4.13 (CH_2NH, ^3J = 6.2 Hz); a singlet at low field (4.41 CH_2); and in the ^{13}C NMR spectrum, two signals at δ = 115.31 (C-4) and 144.83 (C-5) that can be assigned to the C,C double bond, also another signal at δ = 156.63 (C-2): these resonances are in agreement with an imidazole structure [10]. The methyl group on C-5 (δ = 13.60) was confirmed by identification of a small coupling constant (^5J = 5.5 Hz) between NH and the protons of the Me group (C-5); no coupling constant was observed for the Me group on C-2.

TABLE 3 Calculated Frontier Orbital Energies, HOMO and LUMO Coefficients, Net Atomic Charges for Imidates **1a**, **1a'** and Frontier Orbital (FO) Differences Between **1a** and **1a'** via the Intermediate **2a**.



	Imidate **1a**				*Imidate* **1a'**			
	NAC[a]	*HOMO*	*LUMO*	*ΔE*[b]	*NAC*[a]	*HOMO*	*LUMO*	
E/eV	—	−10.11	0.59	ΔE_1 = 7.38	—	−7.97	−0.25	E/eV
N-3	−0.416	−0.446	−0.535	ΔE_2 = 9.86	−0.722	−0.711	−0.313	C-2
C-4	0.064	−0.368	0.591		−0.312	0.533	−0.600	C-4
ΔH_f[c]	−118.88				ΔH_f[c]	103.95		

[a]NAC: Net Atomic Charge.
[b]ΔE_1 = $HOMO_{1a'}$ − $LUMO_{1a}$ and ΔE_2 = $HOMO_{1a}$ − $LUMO_{1a'}$ in eV.
[c]kcal.

Then it became of interest to accelerate the cyclodimerization of imidates **1** by use of a Brönsted acid as a catalyst [11]. Dimerization of **1a** (R^1, R^2 = Me) was carried out at 70°C under nitrogen with acetic acid as catalyst using solvent-free conditions (Table 2).

This reaction was monitored by ^{1}H NMR spectroscopy: analysis of the crude reaction mixture indicated the formation of **4a** in 97% yield, together with alcohols (EtOH, MeOH) and ethyl acetate. This observation suggests a mechanism for the conversion of **1a** to **4a** involving initial (3 + 2) cycloaddition between azomethine ylide **1a'** and dipolarophile **1a** to give **3a** as an intermediate (after ethanol elimination) that then undergoes an amidation reaction to afford the substituted imidazole **4a** by a nucleophilic attack at the methyl ester group of **3a** by methyl glycinate (arising from hydrolysis of **1a**). Identification of a small amount of **3a** (4%, estimation) in the ^{1}H NMR spectrum of the crude reaction mixture of **1a** was confirmed by a singlet at δ = 4.37 (CH_2) and another signal at δ = 3.75 for the Me ester group on C-4. But attempts to isolate **3a** by chromatography on silica gel from the crude reaction mixture were unsuccessful.

The formation of a single regioisomer is consistent with a regioselective dimerization and elimination of ethanol, suggesting that imidate **1a** is synthetically equivalent to the corresponding nitrile ylide. The reactivity order could be studied by consideration of frontier molecular orbitals (FMOs). Semi-empirical PM3 calculations [12] using the MOPAC program (version 6.0) for compound **1a** showed that the first step of this dimerization (Scheme 1) is controlled by the interaction of the $HOMO_{1a'}$-$LUMO_{1a}$ (ΔE_1 = 7.38 eV, Table 3).

Finally, we have extended this process to the preparation of *N*-(4-imidazoyl)glycinates **4(b–g)** from imidates **1(b–g)**: a mixture of distilled imidate **1** and freshly distilled glacial acetic acid (0.33 equivalent) was heated at 70°C under nitrogen with vigorous stirring. After elimination of the corresponding alcohols (EtOH, R^2OH) and ester ($R^1CO_2R^2$) in vacuo, the crude reaction mixture was triturated with ether for 30 minutes. Then, after having been allowed to stand 24 hours, compounds **4** were separated from ether solution and recrystallized from ether/methylene chloride as needles. The cyclodimerization afforded the seven compounds **4** shown in Table 4 in yields ranging from 60 to 97%. The structures assigned to these compounds **4(b–g)** are identical to **4a**.

Furthermore, we have also studied the addition reactivity of imidate **1a** (R^1, R^2 = Me) to ethyl benzimidate [13] **5a** as a dipolarophile according to Scheme 2 (**5a** having been used previously as an electron-rich dienophile in the synthesis of 1,2,4 triazines [14]). The free imidate **5a** readily underwent a reaction (at 70°C under nitrogen with AcOH) with **1a** to produce the expected methyl imidazole-4-carboxylate **6a**. Chromatography of the crude reaction product over silica gel gave **6a** in 35% yield.

The ^{1}H NMR spectrum showed two singlets at δ = 2.30 and 3.77 as expected for the methyl (C-2) and the carbomethoxy protons and a broad signal (δ = 9.78, 1H), exchangeable with deuterium oxide, due to the nitrogen proton (N-1, N-3). In addition, the ^{13}C NMR spectrum exhibited a signal at high field (δ =

TABLE 4 Synthesis of *N*-(1,2,5-Trisubstituted-4-imidazoyl)glycinate **4(a–g)** by Dimerization of Imidates **1(a–g)**

Compound	R^1	R^2	*Time (h)*[a]	*mp (°C)*	*Yield (%)*[b]
4a	Me	Me	5	172–173	95
4b	Me	Et	50	73–74	70
4c	Me	CH_2–C≡C–H	100[c]	114–115	60
4d	Et	Me	30	139–140	97
4e	Me_2CH	Me	200[d]	oil	70
4f	$PhCH_2$	Me	160[d]	122–123	65
4g	Ph	Me	100[d]	191–192	65

[a]Reaction time.
[b]Isolated yield after recrystallization.
[c]With 5% of AcOH at 40°C.
[d]Reaction time was monitored by TLC.

121.44, C-4) and another at δ = 143.00 (C-5); for the carbonyl ester group, we have found only one peak at δ = 162.29. Also, the mass spectrometric molecular weight determination was in agreement with the above structure.

The reaction of imidate **1a** with the N-isobutyl derivative of ethyl acetimidate **5b** as the dipolarophile was unsuccessful. In fact, the reaction gave a mixture of products after 30 hours, from which only the substituted imidazole **4a** could be isolated (10% yield) together with the N-acylated compounds [15] of methyl glycinate and isobutylamine.

CONCLUSION

In summary, this work contributes to the study of the 1,3-dipolar activity of imidates **1** derived from α-amino esters. In acid medium, imidates **1** give new N-(1,2,5-trisubstituted-4-imidazoyl)glycinates **4** by cyclodimerization. Moreover, we have found that extension of the [3 + 2] cycloaddition reaction of imidate **1a** to the unsubstituted imidate **5a** as dipolarophile may be useful for the synthesis of the corresponding methyl imidazole-4-carboxylate. Further investigations to determine the synthetic utility of this process are underway in our laboratory.

EXPERIMENTAL

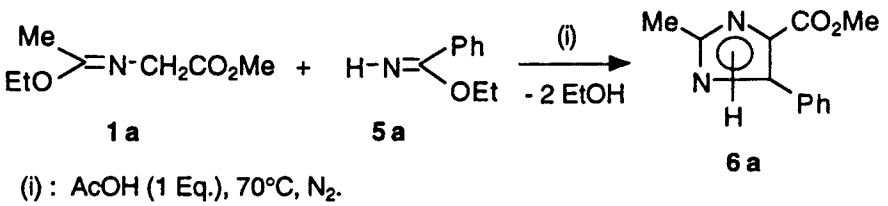
Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm). For preparative column chromatography, silica gel 60 Merck (230–240 Mesh ASTM) was used. Melting points were determined on a Kofler melting point apparatus and are uncorrected.

The IR spectra were taken with a Perkin Elmer 157G spectrometer. ^1H NMR spectra were recorded on Bruker WP 80 CW (80 MHz) and Bruker AC 300 P (300 MHz) spectrometers, and ^{13}C NMR spectra on a 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 instrument at an ionizing potential of 70 eV in the Centre de Mesures Physiques de l'Ouest (CRMPO, Rennes).

Acetonitrile and methylene chloride were distilled over calcium chloride, after having been allowed to stand over the drying agent overnight, and stored over molecular sieves (3Å). Absolute ethanol was distilled over magnesium after standing overnight and stored over molecular sieves (3Å). Ether was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Solvents were evaporated with a Buchi rotary evaporator.

All reagents were purchased from Janssen Chimica and Aldrich Chimie and used without further purification. N-Substituted imidates **1(a–b)** and **1(d–g)** were synthetized according to our previous method [2] from the appropriate ethyl imidate hydrochloride and commercial ethyl or methyl glycinate hydrochloride. Ethyl imidate hydrochlorides obtained from phenylacetonitrile [16], propionitrile [17], and

SCHEME 2



1a **5a** **6a**

(i) : AcOH (1 Eq.), 70°C, N_2.

2-methylpropionitrile [18] were prepared by methods described in the literature.

Methyl 2-(1-Ethoxyethyliden)aminoethanoate (**1a**)

Reaction time: 24 hours at 25°C, Rf = 0.86 in AcOEt, colorless viscous oil, bp = 93–94°C/16 torr, in 87% yield (Ref. [19] = 68%). ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.25 (t, 3H, J = 7.2 Hz); 1.87 (s, 3H); 3.72 (s, 3H); 4.04 (s, 2H); 4.09 (q, 2H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.22 (qt, J = 126 Hz); 15.19 (q, J = 129 Hz); 51.09 (t, J = 136 Hz); 51.18 (q, J = 147 Hz); 60.97 (tq, J = 146 Hz); 164.80 (C=N); 171.60 (C=O); IR (cm^{-1}): 1720, 1665.

Ethyl 2-(1-Ethoxyethyliden)aminoethanoate (**1b**)

Reaction time: 24 hours at 25°C, Rf = 0.14 in MeCN/AcOEt (9:1), colorless viscous oil, bp = 46–47°C/0.1 torr, in 70% yield. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.25 (t, 3H, J = 7.1 Hz); 1.26 (t, 3H, J = 7.2 Hz); 1.85 (s, 3H); 4.01 (s, 2H); 4.10 (q, 2H, J = 7.1 Hz); 4.17 (q, 2H, J = 7.2 Hz); IR (cm^{-1}): 1725, 1665.

2-Propynyl Glycinate Hydrochloride

To a suspension of glycine (7 g, 93.2 mmol.) in 100 mL of propargyl alcohol was added dropwise with vigorous stirring freshly distilled thionyl chloride (13.31 g, 111.9 mmol) during 0.5 hours. After having been stirred at room temperature (2 hours), the resulting mixture was heated at 50°C during 2.5 hours. The solution was allowed to warm to room temperature, and 150 mL of dry ether was added to the reaction mixture. After vigorous stirring during 0.5 hours at 25°C, the precipitate that had formed was filtered off, washed with anhydrous ether (3 × 40 mL), and vacuum dried in a desiccator over $CaCl_2$ to give 10.31 g (74% yield) of the expected 2-propynyl glycinate hydrochloride as white needles (mp = 161–162°C). This salt was further used without purification and was stored at 4°C under nitrogen. ^{1}H NMR (80 MHz, D_2O/MeCN as internal ref.) δ: 2.95 (t, 1H, J = 2.3 Hz); 3.90 (s, 2H); 4.80 (d, 2H, J = 2.3 Hz).

2-Propynyl 2-(1-Ethoxyethyliden)aminoethanoate (**1c**)

To a suspension of ethyl acetimidate hydrochloride (4.96 g, 40.1 mmol) and 2-propynyl glycinate hydrochloride (6.0 g, 40.1 mmol) in 200 mL of dry methylene chloride, cooled to 0°C with vigorous stirring, a solution of dry triethylamine (4.51 g, 44.6 mmol) in 50 mL of dry methylene chloride was added dropwise during 0.5 hours. Then the resulting mixture was stirred at 25°C during 18 hours. The solvent was removed in vacuo, ether (150 mL) was added to the reaction mixture, and the suspension was filtered through filter paper. The filtrate was concentrated in vacuo to give an oil (6.9 g, 94% yield). (Bp with decomposition = 38–41°C/0.1 torr.) Compound **1c** was rapidly stored under nitrogen at 0°C and was used further without purification. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.23 (t, 3H, J = 7.1 Hz); 1.85 (t, 1H, J = 2.4 Hz); 4.05 (s, 2H); 4.10 (q, 2H, J = 7.1 Hz); 4.72 (d, 2H, J = 2.4 Hz), IR (cm^{-1}): 3100, 2110, 1720, 1670.

Methyl 2-(1-Ethoxypropyliden)aminoethanoate (**1d**)

Reaction time: 24 hours at 25°C, Rf = 0.30 in MeCN, colorless viscous oil, bp = 41–42°C/0.1 torr, in 64% yield, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.05 (t, 3H, J = 7.5 Hz); 1.20 (t, 3H, J = 7.1 Hz); 2.17 (q, 2H, J = 7.1 Hz); 3.70 (s, 3H); 4.02 (s, 2H); 4.07 (q, 2H, J = 7.5 Hz), IR (cm^{-1}): 1720, 1665.

Methyl 2-(1-Ethoxy-2-methylpropyliden)aminoethanoate (**1e**)

Reaction time: 18 hours at 25°C, Rf = 0.40 in MeCN, colorless viscous oil, bp = 50–51/0.05 torr, in 70% yield, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.12 (d, 6H, J = 7.6 Hz); 1.25 (t, 3H, J = 7.1 Hz); 2.75 (m, 1H, J = 7.6 Hz); 3.71 (s, 3H); 4.07 (q, 2H, J = 7.1 Hz); 4.10 (s, 2H), IR (cm^{-1}): 1725, 1660.

Methyl 2-(1-Ethoxy-2-phenyl-ethyliden)aminoethanoate (**1f**)

Reaction time: 24 hours at 25°C, Rf = 0.33 in AcOEt, colorless viscous oil, bp = 96–97/0.01 torr, in 84% yield, ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.21 (t, 3H, J = 7.1 Hz); 3.55 (s, 2H); 3.65 (s, 3H); 4.05 (s, 2H); 4.13 (q, 2H, J = 7.1 Hz); 7.20 (broad s, 5H, Ar), IR (cm^{-1}): 2840, 1715, 1665, 1575, 1440.

Methyl 2-(1-Ethoxy-phenyl-methyliden)aminoethanoate (**1g**)

Reaction time: 170 hours at 41°C, Rf = 0.38 in AcOEt, pale yellow viscous oil, bp = 65–66/0.02 torr, in 80% yield [20], ^{1}H NMR (80 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J = 7.2 Hz); 3.67 (s, 3H); 4.05 (s, 2H); 4.30 (q, 2H, J = 7.2 Hz); 7.35 (s, 5H, Ar), IR (cm^{-1}): 2835, 1720, 1660, 1575, 1445.

General Procedure for Dimerization of Imidates **1(a–g)**

A mixture of freshly distilled imidate 1 (40 mmol) and freshly distilled glacial acetic acid (13.2 mmol, 0.79 g) was heated at 70°C under dry nitrogen with vigorous stirring for an appropriate reaction time (the reaction time being monitored by TLC with precoated plates of silica gel 60F-254). After elimination of the corresponding alcohols and ester under reduced pressure, the crude reaction mixture was triturated with dry ether. After standing (24 hours) at 4°C, the precipitated product **4** was filtered off, washed with ether (4 × 15 mL), dried in a desiccator over $CaCl_2$, and recrystallized from a mixture of Et_2O/CH_2Cl_2 (eventually purified by chromatography on silica gel 60F-254). Then the compounds **4(a–g)** were characterized by ^1H NMR, ^{13}C NMR, and HRMS analyses.

Methyl N-(2,5-Dimethyl-l-methoxycarbonylmethyl-4-imidazoyl)aminoethanoate **(4a)**

Reaction time = 5 hours, Rf = 0.27 in AcOEt, white needles, mp = 172–173°C from Et_2O/CH_2Cl_2 (9:1), in 95% yield, ^1H NMR (300 MHz, $CDCl_3$) δ: 2.20 (s, 3H); 2.33 (s, 3H); 3.75 (s, 3H); 3.78 (s, 3H); 4.13 (d, 2H, J = 6.2 Hz); 4.41 (s, 2H); 9.25 (broad t, 1H, J = 6.2 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.60 (qd, J = 129.4, 5.5 Hz); 14.50 (q, J = 128.6 Hz); 41.10 (t, J = 141 Hz); 44.65 (td, J = 140, 2.6 Hz); 52.28 (q, J = 148 Hz); 52.65 (q, J = 148 Hz); 115.31 (C-4, C=C); 144.83 (C-5, C=C); 156.63 (C-2, C=N); 166.33 (t, J = 2.9 Hz, CO, CONH); 168.66 (CO); 169.29 (CO), HRMS, m/z = 283.1150 found (calculated for $C_{12}H_{17}N_3O_5$: 283.1168), $M^{\cdot+}$, $M^{\cdot+}$-CO_2Me found: 224.1034, calc 224.1035.

Ethyl N-(2,5-Dimethyl-1-ethoxycarbonylmethyl-4-imidazoyl)aminoethanoate **(4b)**

Reaction time = 50 hours, Rf = 0.34 in MeCN/AcOEt (9:1), white needles, mp = 73–74°C from Et_2O/CH_2Cl_2 (9:1), in 70% yield, ^1H NMR (300 MHz, $CDCl_3$) δ: 1.19 (2 × t, 6H, J = 7.1 Hz); 2.11 (s, 3H); 2.24 (s, 3H); 4.01 (d, 2H, J = 6.1 Hz); 4.13 (2 × q, 4H, J = 7.1 Hz); 4.30 (s, 2H); 9.16 (broad t, 1H, J = 6.1 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.46 (q, J = 128 Hz); 14.00 (q, J = 128 Hz); 14.05 (q, J = 128 Hz); 14.38 (q, J = 128 Hz); 41.07 (t, J = 141 Hz); 44.66 (t, J = 140 Hz); 61.53 (t, J = 148 Hz); 61.64 (t, J = 148 Hz); 115.22 (C-4, C=C); 144.68 (C-5, C=C); 156.33 (C-2, C=N); 166.22 (t, J = 2.9 Hz, CO, CONH); 168.05 (CO); 168.62 (CO), HRMS, m/z = 311.1476 found (calculated for $C_{14}H_{21}N_3O_5$: 311.1481), $M^{\cdot+}$, $M^{\cdot+}$-CO_2Et found 238.1191, calc 238.1185.

2-Propynyl N-(2,5-Dimethyl-1-(2-propynyl)oxycarbonylmethyl-4-imidazoyl)aminoethanoate **(4c)**

Reaction time = 100 hours at 40°C with 5% of AcOH, mp = 114–115°C from Et_2O/CH_2Cl_2 (8:2), in 60% yield, ^1H NMR (300 MHz, $CDCl_3$) δ: 2.21 (s, 3H); 2.33 (s, 3H); 2.55 (t, 1H, J = 2.23 Hz); 2.57 (t, 1H, J = 2.35 Hz); 4.19 (d, 2H, J = 6.2 Hz); 4.46 (s, 2H); 4.76 (d, 2H, J = 2.36 Hz); 4.78 (d, 2H, J = 2.40 Hz); 9.22 (broad t, 1H, J = 6.2 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.65 (qd, J = 129, 5.5 Hz); 14.43 (q, J = 129 Hz); 41.03 (t, J = 141 Hz); 44.56 (td, J = 127, 2.6 Hz); 53.02 (tt, J = 154, 4.0 Hz); 53.07 (tt, J = 154, 4.0 Hz); 75.79 (dt, J = 153, 5.61 Hz); 76.81–76.84 (C≡C); 115.19 (C-4, C=C); 144.94 (C-5, C=C); 156.77 (C-2, C=N); 166.18 (t, J = 2.9 Hz, CO, CONH); 167.52 (CO); 168.28 (CO), HRMS, m/z = 331.1149 found (calculated for $C_{16}H_{17}N_3O_5$: 331.1168), $M^{\cdot+}$.

Methyl N-(2,5-Diethyl-1-methoxycarbonylmethyl-4-imidazoyl)aminoethanoate **(4d)**

Reaction time = 30 hour, Rf = 0.68 in MeCN, white needles, mp = 139–140°C from Et_2O/CH_2Cl_2 (8:2), in 97% yield, ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (2 × t, 6H, J = 7.5 Hz); 2.48 (q, 2H, J = 7.5 Hz); 2.78 (q, 2H, J = 7.5 Hz); 3.75 (s, 3H); 3.79 (s, 3H); 4.15 (d; 2H, J = 6.2 Hz); 4.41 (s, 2H); 9.25 (broad t, 1H, J = 6.2 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.04 (qt, J = 128, 5.1 Hz); 12.47 (qt, J = 128, 5.4 Hz); 20.62 (tq, J = 131, 5.0 Hz); 21.49 (tq, J = 127, 4.4 Hz); 41.05 (t, J = 140 Hz); 44.40 (td, J = 138, 2.3 Hz); 52.53 (q, J = 148 Hz); 56.65 (q, J = 148 Hz); 114.56 (C-4, C=C); 148.87 (C-5, C=C); 161.32 (C-2, C=N); 167.06 (t, J = 2.9 Hz, CO, CONH); 168.83 (CO); 169.38 (CO), HRMS, m/z = 311.1476 found (calculated for $C_{14}H_{21}N_3O_5$: 311.1481), $M^{\cdot+}$, $M^{\cdot+}$-CO_2Me found 252.1365, calc 252.1348.

Methyl N-(2,5-Dimethylethyl-1-methoxycarbonylmethyl-4-imidazoyl)aminoethanoate **(4e)**

Reaction time = 200 hours, Rf = 0.70 in MeCN, colorless viscous oil in 70% yield after purification on silica gel 60F-254, ^1H NMR (300 MHz, $CDCl_3$) δ: 1.15 (d, 6H, J = 6.9 Hz); 1.16 (d, 6H, J = 6.9 Hz); 2.48 (m, 2 × 1H, J = 6.9 Hz); 3.72 (s, 3H); 3.73 (s, 3H); 4.00 (d, 2H, J = 5.6 Hz); 4.37 (s, 2H); 9.53

(broad t, 1H, J = 5.6 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.33 (qdm, J = 132, 5.0 Hz); 20.06 (qm, J = 130 Hz); 26.83 (dm, J = 126 Hz); 35.02 (dm, J = 128 Hz); 40.96 (t, J = 140 Hz); 41.08 (td, J = 140 Hz); 52.07 (q, J = 147 Hz); 52.32 (q, J = 148 Hz); 113.94 (C-4, C=C); 142.50 (C-5, C=C); 152.50 (C-2, C=N); 165.40 (CO, CONH); 169.01 (CO); 169.61 (CO); HRMS, m/z = 339.1381 found (calculated for $C_{16}H_{25}N_3O_5$: 339.1490), M^+.

Methyl N-(2,5-Diphenylmethyl-1-methoxycarbonylmethyl-4-imidazoyl)aminoethanoate (**4f**)

Reaction time = 160 hour, Rf = 0.57 in AcOEt, white needles, mp = 122–123°C from Et_2O/CH_2Cl_2 (19:1), in 65% yield, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.60 (s, 3H); 3.65 (s, 3H); 3.94 (s, 2H); 3.97 (d, 2H, J = 6.1 Hz); 4.23 (s, 2 × 2H); 7.20–7.30 (m, 2 × 5H, Ar); 9.32 (broad t, 1H, J = 6.1 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.37 (tm, J = 131, 2.1 Hz); 33.55 (tm, J = 131, 2.1 Hz); 41.32 (t, J = 141 Hz); 44.70 (td, J = 140, 2.1 Hz); 52.39 (q, J = 148 Hz); 52.51 (q, J = 148 Hz); 116.41 (C-4, C=C); 127.03–127.06–128.51–128.79–128.92–135.39–135.42 (Ar); 146.86 (C-5, C=C); 157.39 (C-2, C=N); 167.21 (t, J = 3.1 Hz, CO, CONH); 168.45 (CO); 169.02 (CO), HRMS, m/z = 435.1834 found (calculated for $C_{24}H_{25}N_3O_5$: 435.1794), M^+.

Methyl N-(2,5-Diphenyl-l-methoxycarbonylmethyl-4-imidazoyl)aminoethanoate (**4g**)

Reaction time = 100 hour, Rf = 0.67 in AcOEt, white needles, mp = 191–192°C from Et_2O/CH_2Cl_2 (9:1), in 65% yield, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.72 (s, 2 × 3H); 4.00 (d, 2H, J = 6.2 Hz); 4.53 (s, 2H); 7.34–7.36 (m, 2 × 3H, Ar); 7.45–7.49 (m, 2 × 2H, Ar); 9.62 (broad t, 1H, J = 6.2 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.81 (t, J = 141 Hz); 46.18 (td, J = 141, 2.5 Hz); 52.54 (q, J = 148 Hz); 52.55 (q, J = 148 Hz); 116.96 (C-4, C=C); 128.16–128.56–128.66–129.45–129.58–130.27–130.30–130.39 (Ar); 148.23 (C-5, C=C); 158.74 (C-2, C=N); 168.55 (t, J = 3.1 Hz, CO, CONH); 168.92 (CO); 169.59 (CO), HRMS, m/z = 407.1475 found (calculated for $C_{22}H_{21}N_3O_5$: 407.1481), M^+.

Methyl 2-Methyl-5-phenyl-imidazole-4-carboxylate (**6a**)

A mixture of imidate **1a** (0.64 g, 4.0 mmol.) and 1.19 g (8.0 mmol) of freshly distilled ethyl benzimidate **5a** [13] was heated at 70°C with freshly distilled glacial acetic acid (0.24 g, 0.23 mL, 0.4 mmol), during 6 hours under nitrogen and with vigorous stirring. After addition of methylene chloride (2 mL), the mixture was filtered. Removal of the solvents from the filtrate in vacuo gave an oil that solidified on trituration with ether (15 mL). This was dissolved in a solution of $MeCN/CH_2Cl_2/MeOH$: 10/9/1 (Rf = 0.69) that was submitted to chromatography on silica gel 60F-254 (Ø: 15 mm; H: 30 cm). Solvent evaporation gave the desired compound **6a** (0.13 g, 35% yield) as an oil that crystallized on standing. The purity of **6a** was further confirmed by HRMS examination, m/z = 216.0900 found (calculated for $C_{12}H_{12}N_2O_2$: 216.0899), M^+, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3H); 3.77 (s, 3H); 7.29–7.38 (m, 3H, Ar); 7.70–7.74 (m, 2H, Ar); 9.78 (broad s, 1H, NH), ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.73 (q, J = 129 Hz); 51.51 (q, J = 147 Hz); 121.44 (C-4, C=C); 127.96–128.48–129.09–131.54 (Ar); 143.00 (C-5, C=C); 146.33 (C-2); 162.29 (CO).

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