Synthesis and Reactivity of New β-Enamino Acid Derivatives: A Simple and General Approach to β-Enamino Esters and Thioesters

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A new strategy has been developed for the synthesis of several β-enamino acid derivatives. *N*,*N*′-Carbonyldiimidazole has been used as C-acylating agent of methyl ketimines, providing a direct and simple route to new β-enamino carbonyl imidazole derivatives **2**. These derivatives **2** were cleanly and efficiently transformed into β-enamino esters **4** (X = O) and thioesters **4** (X = S) by reaction with a great variety of alcohols and thiols, including tertiary ones. Alternative and complementary routes to compounds **4** were also investigated. In addition, β-keto esters **6** have been obtained by mild acid hydrolysis of β-enamino esters **4**.

Introduction

The study of the synthesis and reactivity of β-amino acids has been especially an active area of investigation since in 1991 it was discovered that the anti-cancerous activity of the diterpene natural taxol mainly depends on the presence in its framework of an *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine moiety.[1] Currently, in a more general context, the increasing interest in this field is based on obtaining proteinogenic and nonproteinogenic amino acids and peptide analogues with preestablished conformational properties and biological functions.[2,3] In addition, β-amino acids are useful intermediates for preparing chiral ligands, chiral buildings blocks, and chiral auxiliaries as well as for synthesis of β-lactams.[4]

The importance and interest in this class of derivatives can be shown through the number of procedures recently developed for their preparation. Asymmetric Michael addition of amines or lithium amides to α,β-unsaturated esters,[5] ester enolate addition to imines,[6] enzymatic resolution of racemates,[7] and chemoselective reduction of β-enamino esters[8] are some of the more efficient methodologies and are used extensively. Due to the simplicity of the procedure and availability of the starting materials, the last strategy represents one of the most convenient and promising approaches for the synthesis of β-amino acids. Therefore, the development of new and simple methodologies for the synthesis of β-enamino acid derivatives is always desirable for access to biologically important compounds which contain and/or derive from this structural subunit.[9]

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‡ X-ray analyses.

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β-Enamino acid derivatives are also valuable and versatile building blocks in organic synthesis. These systems have especially been used in asymmetric synthesis of α-[10] and β-amino acids,[8] in obtaining a wide number of natural products such as alkaloids, generally through aza-annulation processes,[11] and other biologically active compounds.[12] More recently, they have been involved in the preparation of conformationally restricted dipeptides.[9] Although several routes for the synthesis of these derivatives have been reported,[13−19] most of them suffer limitations related usually to their low chemical yield and/or general applicability. In addition to the classical condensation reaction between β-keto esters and amines,[13] β-enamino esters have also been obtained in moderate to good yield by routes involving lithium, magnesium, and zinc ester or amide enolates with nitriles,[14] tosyl imines,[15] imino ethers,[16] and imidoyl halides,[17] Michael addition of amines to alkynyl esters,[5,12,18] or more recently by reaction of imines with activated carbonic acid derivatives.[19] In this context, we have developed a simple route to protected *N*-unsubstituted and *N*-substituted β-enamino acid derivatives starting from 2-alkyl-2-oxa(thia)zolines with nitriles and imidoyl halides, respectively.[20] Alternative approaches leading to γ-fluorinated β-enamino acid derivatives have also been described.[17b,19,21]

In this paper, we wish to describe a new and simple method for the synthesis of *N*-substituted β-enamino imidazole carbonylic derivatives **2** by reaction of ketimines **1**, derived from aliphatic or aromatic amines, with *N*,*N*′-carbonyldiimidazole (CDI).[22] In addition, one- and two-step general procedures for preparing *N*-substituted β-enamino esters and thioesters **4** have been developed.

Since its discovery in 1957,[23] CDI has been widely used in organic synthesis as a transfer reagent of both the imidazole ring and the carbonyl group. In the first case the significance of this reagent can be shown by the activation of the carboxylic function, through the formation of acylimidazolides, which have been extensively used as intermediates in the preparation of a variety of carbonylic and carboxylic acid derivatives including peptide synthesis,[24] as well as in C-acylation reactions of methylene active compounds.[25] One of the most versatile and efficient applications of CDI is as a carbonylating agent. This ability has been mainly used in processes which imply formation of two carbon−heteroatom bonds. As examples we can mention the synthesis of chiral hydantoins,[26] isocyanates,[27] and unsymmetrically substituted carbonic acid derivatives[24a,28] and, more recently, the preparation of urea dipeptides.[29]

In contrast, the utility of CDI in CO transfer reactions with formation of one or two carbon−carbon bonds has been less extensively studied and exploited. To the best of our knowledge only three examples have been reported related to such processes. In 1979,[30] Smith reported a simple synthesis of tetronic acid derivatives from CDI and α-hydroxy ketones with moderate yields. Closely related to this process, Weinreb[31] described a second example of the application of this methodology in the key step of the synthesis of (+)-actinoboline, an antibiotic which also shows moderate antitumoral activity. Both processes proceed *via* the formation of one C−C bond and another C−O bond. Finally, Barluenga et al.[32] reported, for the first time, a carbonylating processes with exclusive formation of carbon−carbon bonds. The described procedure allowed the synthesis of 4(1*H*)-pyridones from 2-aza-1,3-dienes and CDI, and involves a [5+1] heterocyclization with formation of two new carbonyl−carbon bonds.

In addition, very little is known about the ability of CDI as transfer reagent of the *CO−Im* grouping and simultaneous carbon−carbon bond formation. Therefore, one of the primary goals of this work was to determine this behavior by studying its reaction with ketimines.[22]

Results and Discussion

Synthesis of β-Enamino Carbonyl Imidazole Derivatives 2. β-Enamino carbonyl imidazole derivatives

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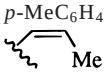
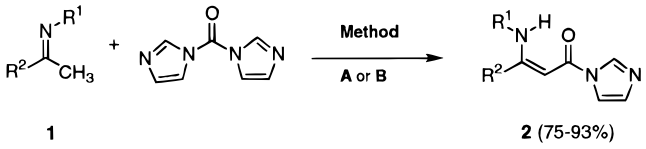
Table 1. β-Enamino Carbonyl Imidazol Derivatives 2 Obtained by Reaction of Ketimines 1 and *N,N′*-Carbonyldiimidazole (CDI)

entry	R^1	R^2	method[a]	mp (°C)[b]	product	yield (%)[c]
1	*n*-Bu	*t*-Bu	A	oil	**2a**	75 (62)
2			B			86 (78)
3	*n*-Bu	*i*-Pr	A	oil	**2b**	80 (76)
4	*n*-Bu	*c*-C_3H_5	A	oil	**2c**	80 (78)
5	*n*-Bu	Ph	A	oil	**2d**	88 (73)
6			B			92 (85)
7	*n*-Bu	*p*-$MeOC_6H_4$	A	oil	**2e**	91 (77)
8	*n*-Bu	2-furyl	A	oil	**2f**	60 (47)
9	*n*-Bu	2-thiophenyl	A	oil	**2g**	93 (70)
10	*c*-C_6H_{11}	Ph	A	163−165	**2h**	82 (66)
11	*c*-C_6H_{11}	*p*-$EtO_2CC_6H_4$	A	oil	**2i**	95 (79)
12	*c*-C_6H_{11}	Et	A	oil	**2j** + **2j′**	85[d,e]
13			B			80[d] (68)[f]
14	Ph	Ph	A	146−148	**2k**	90 (84)
15	*p*-MeC_6H_4	Ph	A	137−139	**2l**	87 (75)
16		Ph	A	141−143	**2m**	93 (88)
17	$(CH_2)_3$		A			no reaction
18			B	149−151	**2n**	75 (68)
19	(±)-$C_6H_5(Me)CH$	*i*-Pr	A	oil	**2o**	76 (59)
20	(±)-$C_6H_5(Me)CH$	Ph	A	oil	**2p**	75 (69)
21			B			84 (73)
22	(*R*)-(+)-$C_6H_5(Me)CH$	*i*-Pr	A	96−98	**2q**	71 (58)
23	(*S*)-(−)-$C_6H_5(Me)CH$	*i*-Pr	A	96−98	**2r**	86 (61)

[a] Method A: Ketimine **1** (1.0 equiv), CDI (1.1 equiv), $BF_3{\cdot}OEt_2$ (1.1 equiv), THF, Δ. Method B: Ketimine **1** (1.0 equiv), LDA (2.0 equiv), CDI (1.1 equiv), THF, −78 °C to rt. [b] Melting points are uncorrected. [c] Yields after purification are given in parentheses. [d] Overall yield **2j** + **2j′**. [e] Isolated yield of **2j** (43%) and **2j′** (29%). [f] Isolated yield of **2j** (Method B).

2 can be obtained from methyl ketimines **1** and CDI by different and complementary pathways (Scheme 1).

Scheme 1



1 **2** (75-93%)

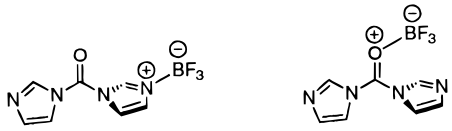
Thus, the reaction of methyl ketimines with *N,N′*-carbonyldiimidazole was first carried out in tetrahydrofuran (THF) at reflux for several hours (12−24 h) and required the presence of a Lewis acid, specifically, boron trifluoride ($BF_3{\cdot}OEt_2$) as catalyst (molar ratio **1**/CDI/$BF_3{\cdot}OEt_2$ of 1:1.1:1.1). The process afforded, cleanly, after standard workup, the corresponding β-enamino carbonyl imidazole derivatives **2** in good to excellent yields (Method A, Scheme 1). The results of this study are summarized in Table 1 (Method A; for Method B see below).

Additionally, we have investigated several aspects of the reaction conditions closely and have found that factors such as nature of the reagents, of the solvents, and particularly of the Lewis acid together with the order of addition markedly affected the course of the process. Thus, the highest yields were obtained when THF was used as solvent, while other solvents such as CH_2Cl_2, ether, or toluene gave a dramatic decrease in the amount of **2** obtained. In the same way, the use of Lewis acids, with the exception of $BF_3{\cdot}OEt_2$, such as $AlCl_3$, $TiCl_4$, and $ZnCl_2$ or an absence of catalyst, completely inhibited the course of the reaction, with recovery of the unreacted starting ketimine **1** only.

We have also observed that the order of addition has remarkable influence on the chemical yield. Thus, the best results were obtained when a THF solution of CDI was allowed to react first with $BF_3{\cdot}OEt_2$ followed by slow addition of the corresponding ketimine. In contrast, reactions carried out by initial addition of the Lewis acid to a THF solution of ketimine **1** were less efficient and resulted in a marked decrease in the yield.

We presume that the initial formation of the complex CDI→BF_3 (**3**) can take place in two different ways; either *via* an imidazolium intermediate (**3A**), as was recently suggested by Ohta,[28b] or through coordination of the boron atom with the carbonyl oxygen (**3B**) in a similar way as in the case of carbonyl derivatives (Chart 1).[33]

Chart 1



3A **3B**

To determine the preferred structure for the complex (**3A** vs **3B**, Chart 1), we carried out ab initio calculations at the HF/6-31G* level of theory.[34] The results of this study showed a marked preference for complex **3A**, which was 12.1 kcal/mol more stable than **3B**. In the favored complex **3A** the length of the N−B forming bond is 1.669 Å, a value similar to that calculated for the O−B bond (1.648 Å) in **3B**. A degree of twisting of the imidazole rings was also observed in each case.

Nevertheless, in both cases the electrophilicity of the carbonyl carbon was increased, permitting the CDI to become much more reactive toward ketimines. Thus,

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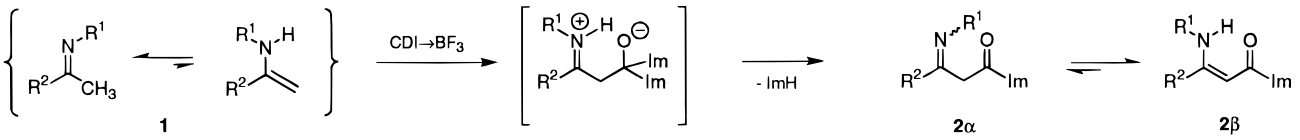
Scheme 2

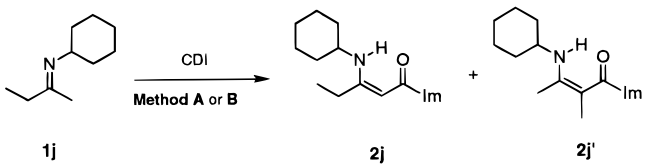


ketimines **1** react through the enamino forms with the complex CDI→BF_3 (**3**) in an addition−elimination process, involving the formation of a new carbon−carbon bond and loss of an equivalent of imidazole. In all cases, compounds **2** were isolated in the more stable enamino tautomeric form **2*β*** (Scheme 2).

Further examination of Table 1 (Method A) reveals that the reaction is also affected by the substitution pattern of the ketimine. As shown in Table 1, the described procedure is rather general as regards the amine and ketone (R^1 and R^2 respectively) residues in **1**. However, from experiments carried out within our group, the process appears to be suitable only for acyclic methyl ketimines. In contrast, cyclic methyl ketimines (entry 17, Table 1) and other nonmethyl derivatives, for instance ketimines derived from propiophenone,[22] were unreactive under the same reaction conditions.

One exception to this general behavior is the case of unsymmetrical alkyl methyl ketimines such as *N*-(2-butylidene)cyclohexylamine **1j** (entry 12, Table 1). In this example, two regioisomers **2j** and **2j′** resulting from the competitive addition of **1** to the complex CDI→BF_3 by the C_α-methyl or C_α-methylene groups respectively, were obtained in an almost equimolecular mixture (Scheme 3). Both compounds were easily separated by MPLC

Scheme 3



Method	2j / 2j'
A	55 / 45
B	>95 / 5

chromatography obtaining **2j** and **2j′** as pure material in 43 and 29% yield, respectively (see entry 12, Table 1, and Experimental Section).

Another characteristic feature of this procedure is the total C−C vs C−N regioselectivity. In fact, no products corresponding to the *N*-acylation have currently been detected being the derivatives **2** the sole isolated products.[35]

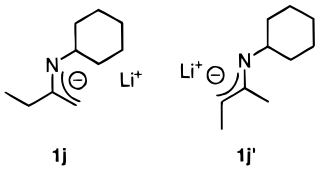
The lack of the reactivity of cyclic methyl ketimines can be circumvented by using an alternative and complementary method, in which the key step is the increase of the nucleophilicity of the starting ketimine through the formation of the corresponding azaenolate (Method B, Table 1 and Scheme 1). Thus, the reaction was accomplished by treatment of ketimines **1** (1.0 equiv) with LDA (2.0 equiv) in THF at 0 °C, followed by addition, at −78 °C, of a THF solution of CDI (1.1 equiv). After a few hours (2−4 h) at room temperature and aqueous workup, *β*-enamino carbonyl imidazole derivatives **2** were isolated as the only products and in slightly higher yields than through Method A (see entries 2, 6, 18, and 21, Table 1). The process also takes place with total C−C vs C−N regioselectivity. As in previous reports,[17b,19,20b] 2 equiv of LDA were necessary in order to increase the final yield.

Two main advantages are noteworthy in this method. First, this route is particularly useful for cyclic methyl ketimines such as **1n** (entry 18, Table 1). Thus, whereas compound **2n** was easily obtained in the reaction of azaenolate of **1n** with CDI in 68% isolated yield (Method B), no reaction was observed using the complex CDI→BF_3 (see above, Method A, and entry 17, Table 1).

Another significant difference was in the case of unsymmetrical alkyl methyl ketimines such as **1j** (entry 12, Table 1). In this example it was possible to increase the regioselectivity of the process in favor of the thermodynamically controlled derivative **2j**. Thus, if the azaenolate was generated by slow addition of ketimine **1j** to a THF solution of LDA at −10 °C for 1 h, compound **2j** was produced in 68% isolated yield along with a small amount of its regioisomer **2j′** (=5% determined by ^{1}H NMR of the crude mixture).

Attempts devoted to control the regioselectivity of the process by formation of the appropriate azaenolate (**1j-Li** or **1j′-Li**) (Chart 2) using reaction conditions described

Chart 2



by Bergbreiter et al.[36a] were unsuccessful, obtaining in all cases predominantly (>9:1) the compound **2j** corresponding to the thermodynamically controlled azaenolate.[36b]

The structures of compounds **2** were supported by NMR spectroscopy, elemental analysis, and/or high-resolution mass spectrometry (HRMS). For example, for **2n** (entry 18, Table 1) characteristic signals in the ^{1}H NMR spectrum were observed at δ 5.16 (s, 1H), 7.02 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 8.09 (s, 1H), and 9.13 (br s, 1H) which were assigned to the vinylic proton and the protons from the imidazole ring and NH group, respectively. Indeed, the carbonyl group appears at δ 171.2 (*C*O) in the ^{13}C NMR spectrum. These signals along with the downfield shift of the NH group suggest a six-membered intramolecular hydrogen bond −N−H···O=C−, supporting the presence of the tautomeric form **2*β***, as was mentioned before.

(35) In sharp contrast with these results other carbonic acid derivatives such as triphosgene [bistrichloromethyl carbonate (BTC)] afforded in its reaction with ketimines, exclusively, the corresponding C−N acyl derivatives. Fustero, S.; García de la Torre, M. Unpublished results.

(36) (a) Smith, J. K.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1983**, *105*, 4396. (b) Deprotonation experiments were run for various times (1−4 h) at −78, −10, and 25 °C, respectively.

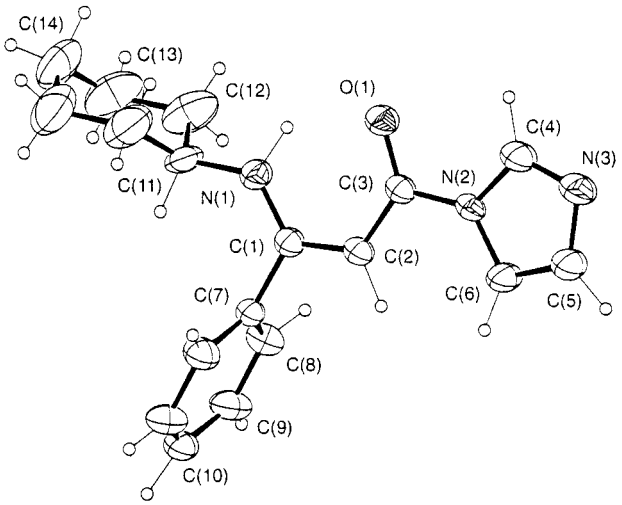
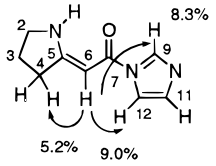


Figure 1. Perspective ORTEP plot of compound **2h** showing the intramolecular O(1)···H interaction. Arbitrary numbering system.

The (*Z*)-*s*-*cis* structure **2(*β*)n** was also established by NOE experiments, as depicted in Chart 3, because an

Chart 3



2n

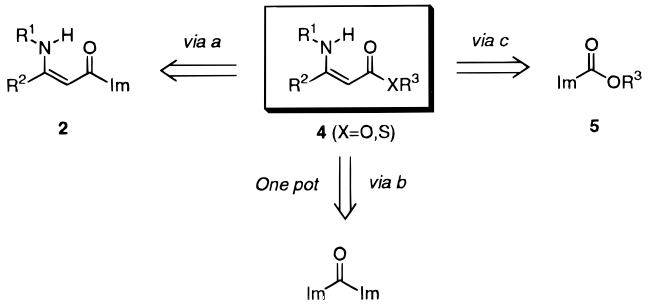
enhancement of 5.2% (H-4), 8.3% (H-9), and 9.0% (H-12) in intensity of the signals of pyrrolidine and imidazole protons, respectively, was observed, upon irradiation of the vinylic proton (H-6). Furthermore, saturation of the triplet at *δ* 2.72 ppm showed a positive NOE (7.5%) with the vinylic proton at 5.16 ppm.

Finally, the structure and the *Z* configuration of compounds **2** were unambiguously confirmed by single-crystal X-ray diffraction of **2h** (entry 10, Table 1), which was obtained by recrystallization from hexane/chloroform mixtures, to give pale yellow prismatic crystals.[37]

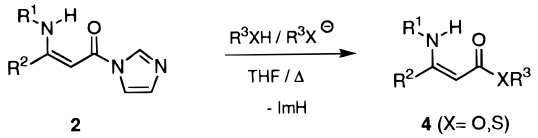
A perspective ORTEP plot of **2h** is given in Figure 1, which shows that the aromatic and cyclohexane rings are almost perpendiculars to the plane of the enamino carbonyl moiety, with the imidazole ring being coplanar to the enamino framework. The structure (Figure 1) also reveals a strong intramolecular interaction between O1 and H100 (O1−H100, 1.91 Å), as was also suggested by ^{1}H NMR.

Synthesis of *β*-Enamino Esters (4). As mentioned before *β*-enamino esters represent an interesting and useful class of compounds of great importance in organic synthesis.[9−12] To demonstrate the utility of the newly obtained derivatives **2**, we first examined the behavior of **2** toward heteronucleophiles, particularly alcohols and thiols (*via* path *a*, Scheme 4). Alternative routes (*via* paths *b* and *c*, Scheme 4) have been also tested.

Scheme 4



Scheme 5



As illustrated in Scheme 5, the reaction of derivatives **2** with alcohols was carried out by using an excess of alcohol[38] in the presence of sodium alkoxide[39] in refluxing THF for 6−24 h and provided the corresponding *β*-enamino esters **4** (X = O) (Method C, Table 2) in good to high yields after aqueous workup and purification of the crude mixture by recrystallization, flash chromatography, or MPLC on silica gel.

Table 2 summarizes the *β*-enamino esters **4** synthesized, the yields and the method used to obtain them (for explanation see below). As can be seen from Table 2, the process works well, independently of the nature of the alcohol, and high yields are generally obtained. Exceptions to this trend are related with the steric hindrance of the starting alcohol. Thus, alcohols containing bulky groups such as 1-adamantanol (entry 12, Table 2) or *tert*-butyl alcohol (entries 1, 8, 9, 18, 19, 23, and 27, Table 2) showed a tendency for lower (=20%) yields.

Indeed, it is interesting to note that the reaction is general and applicable to all types of alcohols, including tertiary ones.[28e] Thus, simple and reactive primary alcohols such as methanol or allyl alcohol (entries 2, 3, 21, 25, 26, and 28, Table 2) or others including more complex structures such as terpenes, geraniol, (+)-menthol, or (−)-8-phenylmenthol (entries 11, 14, 17, and 29, Table 2), steroids such as 5α-cholestane-3*β*-ol (entry 16, Table 2), or protected carbohydrates such as 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (entry 15, Table 2) were successfully used.

The (*Z*)-*s*-*cis* configuration shown for *β*-enamino esters **4** was inferred on the basis of their ^{1}H and ^{13}C NMR and HRMS data (see Experimental Section). Characteristic signals of the vinylic proton (*δ* 4.5−5.1 ppm) and NH grouping (*δ* 8.3−10.3 ppm) in the ^{1}H NMR spectra corroborate the proposed structure.

Alternatively, to simplify the method and to verify the feasibility of the reaction, we examined the possibility of obtaining *β*-enamino esters **4** in a *one-pot* sequence from ketimines **1** without isolation of the derivatives **2** (*via* path *b*, Scheme 4). Consequently, when the reaction was

(37) The authors have deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request, from the Director Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(38) The best results have been obtained with a molar ratio **2**/R^3-OH of 1:3 or higher, although for more expensive alcohols such as (−)-8-phenylmenthol a stoichiometric amount of alcohol could be used without significant loss in the final chemical yield. However, longer reaction times were required.

(39) Although, in general, the use of sodium alkoxide is not necessary, the presence significantly enhanced the rate of the reaction.

Table 2. *β*-Enamino Esters (X = O) and Thioesters (X = S) 4 Synthesized from Derivatives 2 or Ketimines 1

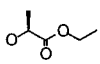
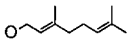
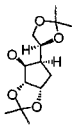
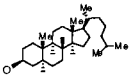
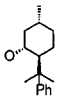
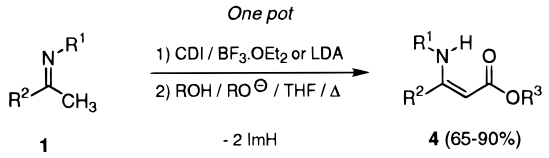
entry	R^1	R^2	XR^3	method[a]	mp (°C)[b]	4	yield (%)[c]
1	*n*-Bu	*i*-Pr	*t*-BuO	C	oil	**4a**	89 (75)
2	*n*-Bu	*i*-Pr	MeO	C	oil	**4b**	94 (88)
3				D			86 (72)
4	*n*-Bu	*i*-Pr	CF_3CH_2O	D	oil	**4c**	80 (65)
5	*n*-Bu	*i*-Pr		D	oil	**4d**	92 (85)
6	*n*-Bu	*i*-Pr	BnS	C	oil	**4e**	99 (78)
7	*n*-Bu	*i*-Pr	AllylS	C	oil	**4f**	97 (86)
8	*n*-Bu	Ph	*t*-BuO	D	oil	**4g**	77 (68)
9				E			70 (55)
10				F			No reaction
11	*n*-Bu	Ph		D	oil	**4h**	95 (80)
12	*n*-Bu	Ph		D	oil	**4i**	78 (50)
13	*n*-Bu	Ph		D	70-2	**4j**	95 (75)
14	*n*-Bu	Ph		D	oil	**4k**	90 (80)
15	*n*-Bu	Ph		D	oil	**4l**	91 (82)
16	*n*-Bu	Ph		D	oil	**4m**	80 (74)
17	*n*-Bu	Ph		D	oil	**4n**	94 (71)
18	*c*-C_6H_{11}	Ph	*t*-BuO	C	118-120	**4o**	70 (58)
19				D			65 (40)
20	*c*-C_6H_{11}	Ph	*t*-BuS	C	124-6	**4p**	72 (70)
21	Ph	Ph	MeO	C	84-6	**4q**	98 (94)
22	Ph	Ph	*i*-PrO	C	82-4	**4r**	86 (71)
23	Ph	Ph	*t*-BuO	C	oil	**4s**	88 (75)
24	Ph	Ph	BnO	C	70-2	**4t**	93 (84)
25	$(CH_2)_3$		MeO	D	95-7	**4u**	86(50)
26	(±)-C_6H_5(Me)CH	Ph	AllylO	C	oil	**4v**	88 (76)
27	(±)-C_6H_5(Me)CH	Ph	*t*-BuO	E	oil	**4w**	95 (75)
28	(*R*)-(+)-C_6H_5(Me)CH	*i*-Pr	MeO	D	oil	**4x**	75 (68)

Table 2 (Continued)

entry	R^1	R^2	XR^3	method[a]	mp (°C)[b]	4	yield (%)[c]
29	(*R*)-(+)-C_6H_5(Me)CH	*i*-Pr		C	oil	**4y**	85 (75)
30	(*S*)-(-)-C_6H_5(Me)CH	*i*-Pr	EtO	D	oil	**4z**	87 (64)

[a] Method C: Two-step reaction *via* **2** and RXH/RX^- (1.0−3.0 equiv), THF, reflux. Method D: One-pot reaction from ketimines **1** (1.0 equiv), CDI (1.1 equiv), BF_3·OEt_2 (1.1 equiv), and RXH (1.0−3.0 equiv), THF, reflux. Method E: Ketimine **1** (1.0 equiv), LDA (2.0 equiv), R^3OCOIm (1.3 equiv), THF, −78 °C to rt. Method F: Ketimine **1** (1.0 equiv), BF_3·OEt_2 (1.1 equiv), R^3OCOIm (1.1 equiv), THF, reflux. [b] Melting points are uncorrected. [c] Yields after purification are given in parentheses.

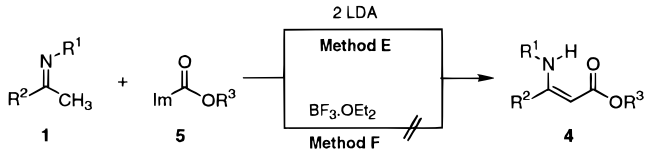
Scheme 6



carried out by sequential treatment of a THF solution of the ketimine **1** (or the corresponding lithium azaenolate), with the complex CDI→BF_3 (or CDI) followed by the appropriate alcohol, the expected compounds **4** were synthesized successfully (Scheme 6). Optimization of the reaction conditions and purification of the crude mixture allowed us to obtain pure derivatives **4** in 40−90% overall yields (Method D, Table 2).

A third alternative route for obtaining derivatives **4** involved the direct condensation between ketimines **1** and alkoxy carbonyl imidazole derivatives **5** (*via* path *c*, Scheme 4). We have explored this possibility to examine the effect of the type of carbonic acid derivative[40] (Scheme 7). As in the aforementioned studies, the reaction was

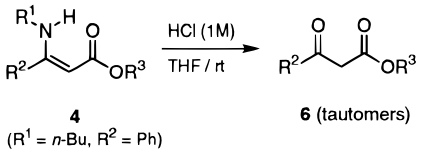
Scheme 7

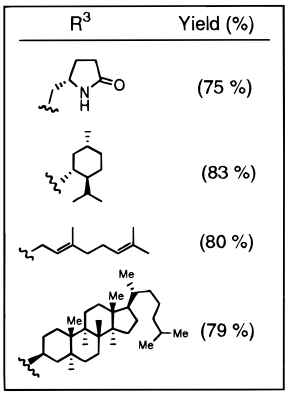


accomplished either through formation of the ketimine azenolates (Method E, Table 2) or alternatively by activation of the alkoxy carbonyl imidazole derivatives using BF_3·OEt_2 (Method F, Table 2). In sharp contrast to the above-mentioned results, the process was found to be highly dependent on the method used. Thus, whereas the reaction proceeded smoothly using preformed lithium azaenolate (Method E, entries 9 and 27, Table 2) showing no significant differences with respect to Methods C and D (Table 2), no reaction was observed when the complex **5**→BF_3 (Method F) was used as starting material (entry 10, Table 2). This inhibition could be explained by the lower electrophilicity of the carbonyl group in the complex **5**→BF_3 in comparison with CDI→BF_3.

Subsequently, we turned our attention to the reaction of derivatives **2** with other heteronucleophiles such as

Scheme 8





thiols. 2-Propene-1-thiol, α-toluenethiol, and 2-methyl-2-propanethiol were chosen as representative examples. The reaction proceeded under similar conditions to those discussed previously using RS^-/RSH as starting heteronucleophile (Scheme 5). The reaction time was shorter for these compounds and the yields were comparable to those described for the alcohols. In all cases, the corresponding β-enamino thioesters **4** (X = S) were obtained (entries 6, 7, and 20, Table 2). It is worth noting that the process is also completely regioselective with derivatives **4** (X = O, S) corresponding to a C-acylation as the sole identified products.

Finally, β-enamino esters **4** underwent a mild acid hydrolysis (1 M HCl) leading, in good yields, to the corresponding β-keto esters **6**. Some selected examples are included in Scheme 8. Because derivatives **6** can be easily synthesized in a *one-pot* reaction starting from ketimines, CDI, and a variety of alcohols, the described procedure appears as an alternative, versatile, and, in our opinion, more efficient route to synthesize β-keto esters[41] than the methodology previously developed by Mander[42] which uses alkyl cyanoformates as starting carbonic acid derivatives.

(40) Other carbonic acid derivatives such as methyl cyanoformate, diethyl carbonate or benzyl chloroformate have been recently used for several authors for the synthesis of β-enamino esters in moderate yields; see: (a) Bennet, R. B.; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 5437. (b) Reference 19.

(41) For related reactions of β-keto esters formation from ketones, see: Mander, L. N. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley & Sons: New York, 1995; Vol. 4, p 3466 and references cited therein.

(42) (a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256.

In summary, a new strategy for the synthesis of several 1,3-difunctionalized derivatives, such as β-enamino carbonyl imidazoles (**2**), β-enamino esters, and thioesters (**4**), starting from ketimines, *N*,*N*′-carbonyldiimidazole, and alcohols or thiols has been developed. The described procedure appears to be general and represents an efficient, simple, and alternative route to β-keto esters and derivatives.

Experimental Section

General Methods. All reactions were run under argon atmosphere. Solvents were dried and distilled upon standard procedures before use. Commercial *N*,*N*′-carbonyldiimidazole was purchased from Aldrich Co. and stored under argon atmosphere. Boron trifluoride was distilled and stored under argon atmosphere. Ketimines were prepared from ketones by conventional procedures.[36a] Diisopropilamine was distilled from sodium hydride and stored over 4 Å molecular sieves. All other reagents were of the best commercial grade available and were used without further purification. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates and visualized by UV irradiation and/or iodine. Flash column chromatography and medium-pressure liquid chromatography (MPLC) were performed using silica gel 60 (0.040−0.063 and 0.015−0.040 mm, respectively). Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 250, 300, and 400 MHz spectrometers, in $CDCl_3$ with tetramethylsilane as internal standard. Chemical shift values and coupling constants, *J*, are reported in δ (ppm) and in Hz, respectively. Carbon multiplicities were established by DEPT. Infrared spectra (IR) are reported in cm^{-1}. Mass spectral data, low-resolution mass spectroscopy (electron impact) (LRMS/EI) and high-resolution mass spectroscopy (HRMS), were obtained at 70 eV by electron impact. Elemental analyses were performed in the Microanalyses Service CID-CSIC of Barcelona and Microanalytical Service of the University of Zaragoza.

***N*-Substituted β-Enamino Imidazole Carbonylic Derivatives 2. General Procedure. Method A.** To a solution of *N*,*N*′-carbonyldiimidazole (2.0 g, 12.3 mmol) in THF (15 mL) at room temperature was added boron trifluoride (1.52 mL, 12.3 mmol) in THF (5 mL). The resulting mixture was stirred for 30 min, and then a solution of the desired ketimine **1** (11.2 mmol) in THF (15 mL) was added dropwise. The reaction mixture was stirred for several hours (12−24) at reflux under argon atmosphere. The reaction was monitored by TLC. The reaction was quenched with 3 N NaOH and extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, washed with brine and dried over Na_2SO_4. After filtration, the solvents were removed under reduced pressure to provide the crude product **2**. Purification was carried out as indicated in each case.

Method B. To a solution of diisopropylamine (2.6 mL, 20 mmol) in 10 mL of THF at 0 °C was dropwise added *n*-butyllithium (2.5 M in hexane, 8.0 mL, 20 mmol). After being stirred for 10 min, ketimine **1** (10.0 mmol) in THF (15 mL) was added. The resulting mixture was stirred at 0 °C for 30 min. The solution was cooled to −78 °C and *N*,*N*′-carbonyldiimidazole (1.8 g, 11.0 mmol) in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 1 h. The solution was allowed to warm to room temperature for 2−4 h. The reaction was quenched by addition of saturated ammonium chloride solution. Workup of the reaction followed the procedure described in Method A.

(*Z*)-3-Butylamino-1-(1*H*-1-imidazolyl)-4,4-dimethyl-2-penten-1-one (2a). MPLC (cyclohexanes−EtOAc (1:1)) on silica gel gave a brown oil (62%): ^{1}H NMR (250 MHz) 0.93 (t, *J* = 7.2, 3H), 1.33 (s, 9H), 1.48 (m, 2H), 1.66 (m, 2H), 3.53 (q, *J* = 6.4, 2H), 5.19 (s, 1H), 7.03 (d, *J* = 1.6, 1H), 7.41 (d, *J* = 1.6, 1H), 8.12 (s, 1H), 10.40 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.7 (q), 19.8 (t), 28.8 (q), 32.5 (t), 36.4 (s), 45.7 (t), 78.6 (d), 115.7 (d), 129.7 (d), 135.3 (d), 163.0 (s), 178.0 (s). HRMS calcd for $C_{14}H_{23}N_3O$: 249.1841. Found: 249.1838. Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.44; H, 9.30; N, 16.85. Found: C, 67.53; H, 9.42; N, 17.00.

(*Z*)-3-Butylamino-1-(1*H*-1-imidazolyl)-4-methyl-2-penten-1-one (2b). MPLC (*n*-hexanes−EtOAc (2:3)) on silica gel gave a yellow oil (76%): ^{1}H NMR (250 MHz) 0.90 (t, *J* = 7.2, 3H), 1.23 (d, *J* = 7.2, 6H), 1.42 (m, 2H), 1.65 (m, 2H), 2.80 (m, 1H), 3.31 (q, *J* = 6.4, 2H), 5.11 (s, 1H), 7.00 (d, *J* = 1.6, 1H), 7.30 (d, *J* = 1.6, 1H), 8.16 (s, 1H), 10.12 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.1 (q), 19.3 (t), 20.4 (q), 28.5 (d), 31.5 (t), 41.8 (t), 76.3 (d), 115.3 (d), 128.9 (d), 134.7 (d), 163.4 (s), 176.4 (s). HRMS calcd for $C_{13}H_{21}N_3O$: 235.1684. Found: 235.1677. Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 8.99; N, 17.86. Found: C, 65.97; H, 9.18; N, 17.93.

(*Z*)-3-Butylamino-3-cyclopropyl-1-(1*H*-1-imidazolyl)-2-propen-1-one (2c). Flash chromatography (EtOAc) on silica gel gave a yellow oil (78%): ^{1}H NMR (250 MHz) 0.88 (t, *J* = 7.2, 3H), 1.01−1.03 (m, 5H), 1.45 (m, 2H), 1.68 (m, 2H), 3.52 (q, *J* = 6.4, 2H), 4.80 (s, 1H), 7.03 (d, *J* = 1.6, 1H), 7.39 (d, *J* = 1.6, 1H), 8.10 (s, 1H), 10.12 (br s, 1H); ^{13}C NMR (62.8 MHz) 8.3 (t), 13.3 (q), 14.4 (t), 20.7 (d), 32.6 (t), 43.6 (t), 78.2 (d), 116.4 (d), 130.2 (d), 135.9 (d), 164.6 (s), 172.3 (s); IR (KBr) 3233, 1628, 1587, 1135. HRMS calcd for $C_{13}H_{19}N_3O$: 233.1528. Found: 233.1529. Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.21; H, 8.40; N, 18.23.

(*Z*)-3-Butylamino-1-(1*H*-1-imidazolyl)-3-phenyl-2-propen-1-one (2d). MPLC (*n*-hexanes−EtOAc (1:1)) on silica gel gave a yellow oil (73%): ^{1}H NMR (250 MHz) 0.82 (t, *J* = 7.2, 3H), 1.35 (m, 2H), 1.51 (m, 2H), 3.19 (q, *J* = 6.4, 2H), 5.09 (s, 1H), 7.00 (d, *J* = 1.6, 1H), 7.30 (d, *J* = 1.6, 1H), 7.41 (m, 5H), 8.10 (s, 1H), 9.96 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.1 (q), 19.2 (t), 32.1 (t), 44.3 (t), 83.2 (d), 115.4 (d), 127.0 (d), 128.3 (d), 129.4 (d), 129.5 (d), 134.5 (d), 135.0 (s), 163.1 (s), 168.7 (s). HRMS calcd for $C_{16}H_{19}N_3O$: 269.1528. Found: 269.1529 Anal. Calcd for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 70.92; H, 7.21; N, 15.48.

(*Z*)-3-Butylamino-1-(1*H*-1-imidazolyl)-3-(4-methoxyphenyl)-2-propen-1-one (2e). MPLC (*n*-hexanes−EtOAc (1:1)) on silica gel gave a yellow oil (77%): ^{1}H NMR (250 MHz) 0.82 (t, *J* = 7.2, 3H), 1.36 (m, 2H), 1.51 (m, 2H), 3.20 (q, *J* = 6.4, 2H), 3.81 (s, 3H), 5.06 (s, 1H), 6.91 (d, *J* = 8.6, 2H), 6.94 (d, *J* = 1.6, 1H), 7.29 (d, *J* = 8.6, 2H), 7.38 (d, *J* = 1.6, 1H), 8.08 (s, 1H), 9.98 (br s, 1H); ^{13}C NMR (62.8 MHz) 14.3 (q), 20.4 (t), 33.3 (t), 45.5 (t), 56.1 (q), 84.2 (d), 114.7 (d), 116.4 (d), 127.8 (s), 129.7 (d), 130.6 (d), 136.1 (d), 160.0 (s), 165.0 (s), 169.7 (s). HRMS calcd for $C_{17}H_{21}N_3O_2$: 299.1633. Found: 299.1627 Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.22; H, 7.02; N, 14.04. Found: C, 68.01; H, 7.23; N, 14.14.

(*Z*)-3-Butylamino-3-(2-furyl)-1-(1*H*-1-imidazolyl)-2-propen-1-one (2f). Flash chromatography (cyclohexanes−EtOAc (1:4)) on silica gel gave a brown oil (47%): ^{1}H NMR (250 MHz) 0.82 (t, *J* = 7.2, 3H), 1.45 (m, 2H), 1.64 (m, 2H), 3.53 (q, *J* = 6.4, 2H), 5.50 (s, 1H), 6.54 (dd, *J* = 1.7, 3.4, 1H), 6.82 (d, *J* = 3.4, 1H), 7.00 (d, *J* = 1.6, 1H), 7.41 (d, *J* = 1.6, 1H), 7.55 (d, *J* = 1.7, 1H), 8.13 (s, 1H), 10.00 (br s, 1H); ^{13}C NMR (62.8 MHz) 14.0 (q), 20.2 (t), 32.6 (t), 45.8 (t), 80.9 (d), 112.3 (d), 115.3 (d), 116.2 (d), 130.1 (d), 135.7 (d), 145.2 (d), 147.4 (s), 156.2 (s), 164.2 (s). HRMS calcd for $C_{14}H_{17}N_3O_2$: 259.1320. Found: 259.1315. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 65.33; H, 6.78; N, 16.41.

(*Z*)-3-Butylamino-1-(1*H*-1-imidazolyl)-3-(2-thienyl)-2-propen-1-one (2g). Flash chromatography (*n*-hexanes−EtOAc (3:1)) on silica gel gave a pale green oil (70%): ^{1}H NMR (250 MHz) 0.86 (t, *J* = 7.2, 3H), 1.33 (m, 2H), 1.48 (m, 2H), 3.32 (q, *J* = 6.4, 2H), 5.26 (s, 1H), 7.07 (d, *J* = 1.6, 1H), 7.10 (dd, *J* = 2.5, 3.7, 1H), 7.22 (d, *J* = 2.5, 1H), 7.30 (d, *J* = 1.6, 1H), 7.42 (d, *J* = 3.7, 1H), 8.07 (s, 1H), 9.98 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.7 (q), 19.9 (t), 32.6 (t), 45.2 (t), 84.3 (d), 115.8 (d), 127.6 (d), 128.6 (d), 129.4 (d), 130.1 (d), 135.1 (s), 135.5 (d), 161.3 (s), 163.5 (s). HRMS calcd for $C_{14}H_{17}N_3OS$: 275.1092. Found: 275.1094. Anal. Calcd for $C_{14}H_{17}N_3OS$: C, 61.07; H, 6.22; N, 15.26; S, 11.63. Found: C, 61.34; H, 6.30; N, 15.57; S, 11.70.

(*Z*)-3-Cyclohexylamino-1-(1*H*-1-imidazolyl)-3-phenyl-2-propen-1-one (2h). Recrystallization (*n*-hexane−chloro-

form (3:1)) gave a yellowish solid (66%): mp 163−165 °C; ^{1}H NMR (250 MHz) 1.10−1.80 (m, 10H), 3.24 (m, 1H), 5.09 (s, 1H), 7.00 (d, J = 1.6, 1H), 7.20−7.50 (m, 5H), 7.31 (d, J = 1.6, 1H), 8.12 (s, 1H), 10.00 (br s, 1H); ^{13}C NMR (62.8 MHz) 24.2 (t), 25.0 (t), 34.1 (t), 53.1 (d), 89.7 (d), 115.7 (d), 127.2 (d), 128.7 (d), 129.8 (d), 129.9 (d), 135.3 (s), 135.4 (d), 163.4 (s), 168.0 (s); IR (KBr) 3241, 1626, 1576, 1209. HRMS calcd for $C_{18}H_{21}N_3O$: 295.1684. Found: 295.1684. Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.73; H, 7.35; N, 14.33.

Ethyl-4-[(*Z*)-1-cyclohexylamino-3-(1*H*-1-imidazolyl)-3-oxo-1-propenyl] Benzoato (2i). Flash chromatography (*n*-hexanes−ether (1:6)) on silica gel gave a yellow oil (79%): ^{1}H NMR (300 MHz) 1.10−1.90 (m, 10H), 1.46 (t, J = 7.2, 3H), 3.24 (m, 1H), 4.43 (q, J = 7.2, 2H), 5.12 (s, 1H), 7.00 (d, J = 1.6, 1H), 7.43 (d, J = 1.6, 1H), 7.51 (d, J = 8.7, 2H), 8.12 (s, 1H), 8.15 (d, J = 8.7, 2H), 10.02 (br s, 1H); ^{13}C NMR (75 MHz) 13.7 (q), 23.6 (t), 24.5 (t), 33.0 (t), 52.6 (d), 60.7 (t), 83.4 (d), 115.2 (d), 126.8 (d), 129.3 (d), 131.2 (d), 134.80 (d), 138.8 (s), 162.9 (s), 165.0 (s), 166.3 (s); LRMS (EI) m/z 367 (M^+, 6), 300 (M^+ − Im, 100). Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.82; H, 6.79; N 11.29.

(*Z*)-3-Cyclohexylamino-1-(1*H*-1-imidazolyl)-2-penten-1-one (2j). MPLC (EtOAc) gave a yellow oil (43%, method A; 68%, method B): ^{1}H NMR (250 MHz) 1.24 (t, J = 7.6, 3H), 1.20−1.95 (m, 10H), 2.40 (q, J = 7.6, 2H), 3.45 (m, 1H), 5.04 (s, 1H), 7.05 (d, J = 1.6, 1H), 7.42 (d, J = 1.6, 1H), 8.12 (s, 1H), 10.15 (br d, 1H); ^{13}C NMR (100 MHz) 12.8 (t), 24.4 (t), 25.1 (t), 25.6 (t), 34.0 (q), 51.7 (d), 80.1 (d), 115.7 (d), 129.6 (d), 135.2 (d), 163.7 (s), 170.8 (s); IR (KBr) 3243, 1630, 1590, 1110. HRMS calcd for $C_{14}H_{21}N_3O$: 247.1684. Found: 247.1686. Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.99; H, 8.56; N, 16.99. Found: C, 68.40; H, 8.62; N, 17.28.

(*Z*)-3-Cyclohexylamino-1-(1*H*-1-imidazolyl)-2-methyl-2-buten-1-one (2j′). MPLC (EtOAc) gave a yellow oil (30%, method A): ^{1}H NMR (250 MHz) 1.38−1.80 (m, 10H), 1.91 (s, 3H), 2.14 (s, 3H), 3.50 (m, 1H), 7.03 (d, J = 1.6, 1H), 7.21 (d, J = 1.6, 1H), 7.89 (s, 1H), 10.80 (br s, 1H); ^{13}C NMR (100 MHz) 15.4 (t), 16.3 (t), 24.3 (q), 25.2 (t), 33.6 (q), 52.4 (d), 88.1 (s), 117.8 (d), 128.4 (d), 136.6 (d), 165.9 (s), 166.8 (s). HRMS calcd for $C_{14}H_{21}N_3O$: 247.1684. Found: 247.1685. Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.99; H, 8.56; N, 16.99. Found: C, 67.81; H, 8.41; N, 16.81.

(*Z*)-3-Anilino-1-(1*H*-1-imidazolyl)-3-phenyl-2-propen-1-one (2k). Recrystallization (*n*-hexane−chloroform (3:1)) gave a yellow solid (84%): mp 146−148 °C; ^{1}H NMR (300 MHz) 5.48 (s, 1H), 6.80−7.45 (m, 11H), 7.50 (d, J = 1.6, 1H), 8.60 (s, 1H), 11.51 (br s, 1H); ^{13}C NMR (75 MHz) 87.8 (d), 115.8 (d), 123.4 (d), 124.3 (d), 128.1 (d), 128.6 (d), 128.7 (d), 130.2 (d), 134.8 (s), 138.5 (s), 163.8 (s), 164.3 (s); IR (KBr) 3200, 1670, 1630, 1600; LRMS (EI) m/z 289 (M^+, 8), 222 (M^+ − Im, 100). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.33; H, 5.01; N, 14.31.

(*Z*)-1-(1*H*-1-Imidazolyl)-3-(4-methylanilino)-3-phenyl-2-propen-1-one (2l). Recrystallization (*n*-hexane−chloroform (3:1)) gave a yellow solid (75%): mp 137−139 °C; ^{1}H NMR (250 MHz) 2.20 (s, 3H), 5.47 (s, 1H), 6.75 (d, J = 8.6, 2H), 7.00 (d, J = 8.6, 2H), 7.16−7.65 (m, 7H), 8.30 (s, 1H), 11.50 (br s, 1H); ^{13}C NMR (62.8 MHz) 20.1 (q), 88.5 (d), 116.8 (d), 123.6 (d), 128.6 (d), 129.6 (d), 130.8 (d), 130.9 (d), 131.5 (d), 135.2 (d), 136.6 (s), 137.9 (s), 138.8 (s), 164.1 (s), 165.3 (s); LRMS (EI) m/z 303 (M^+, 3), 236 (M^+ − Im, 100). Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.24; H, 5.61; N, 13.86. Found: C, 75.01; H, 5.47; N, 13.73.

(*Z*)-1-(1*H*-1-Imidazolyl)-3-phenyl-3-[(*Z*)-1-propenylamino]2-propen-1-one (2m). Flash chromatography (*n*-hexanes−ether (1:6)) recrystallization (ether) gave a white solid (88%): mp 141−143 °C; ^{1}H NMR (300 MHz) 1.82 (d, J = 7.1, 3H), 4.82 (m, 1H), 5.31 (s, 1H), 6.23 (m, 1H), 7.14 (d, J = 1.6, 1H), 7.58 (m, 6H), 8.21 (s, 1H), 11.80 (br d, 1H); ^{13}C NMR (75 MHz) 11.0 (q), 85.7 (d), 107.9 (d), 116.5 (d), 125.0 (d), 128.0 (d), 128.8 (d), 130.1 (d), 130.3 (d), 133.9 (s), 135.4 (d), 163.2 (s), 163.6 (s); LRMS (EI) m/z 253 (M^+, 18), 186 (M^+ − Im, 100). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.12; H, 5.96; N, 16.61.

2-(2-Azolanyliden)-1-(1*H*-1-imidazolyl)-1-ethanone (2n). Recrystallization (*n*-hexanes−EtOH (3:1)) gave a yellow solid (68%): mp 149−151 °C;^{1}H NMR (250 MHz) 2.06 (m, 2H), 2.72 (t, J = 3.7, 2H), 3.64 (t, J = 3.7, 2H), 5.16 (s, 1H), 7.02 (d, J = 1.6, 1H), 7.40 (d, J = 1.6, 1H), 8.09 (s, 1H), 9.13 (br s, 1H); ^{13}C NMR (100 MHz) 21.3 (t), 33.1 (t), 47.9 (t), 77.3 (d), 115.8 (d), 129.8 (d), 135.4 (d), 163.6 (s), 171.2 (s). HRMS calcd for $C_9H_{11}N_3O$: 177.0902. Found: 177.0901. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.69; H, 6.21; N, 23.83.

(±)-(*Z*)-1-(1*H*-1-Imidazolyl)-4-methyl-3-(1-phenylethylamino)2-penten-1-one (2o). Flash chromatography (EtOAc) on silica gel gave a yellow oil (59%): ^{1}H NMR (250 MHz) 0.92 (d, J = 7.2, 3H), 1.25 (d, J = 7.2, 3H), 1.65 (d, J = 7.2, 3H), 2.79 (m, 1H), 4.85 (m, 1H), 5.15 (s, 1H), 7.10−7.40 (m, 5H), 7.14 (d, J = 1.6, 1H), 7.50 (d, J = 1.6, 1H), 8.13 (s, 1H), 10.65 (br d, 1H); ^{13}C NMR (62.8 MHz) 21.4 (q), 22.6 (q), 25.6 (d), 30.1 (q), 53.4 (d), 78.7 (d), 116.3 (d), 126.0 (d), 128.3 (d), 129.7 (d), 129.7 (d), 135.60 (d), 144.5 (s), 163.3 (s), 177.2 (s); IR (KBr) 3140, 1629, 1586, 1128. HRMS calcd for $C_{17}H_{21}N_3O$: 283.1684. Found: 283.1679. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.86. Found: C, 72.02; H, 7.55; N, 14.80.

(±)-(*Z*)-1-(1*H*-1-Imidazolyl)-3-phenyl-3-(1-phenylethylamino)-2-propen-1-one (2p). MPLC (*n*-hexanes−EtOAc (3:1)) on silica gel gave a yellow oil (69%): ^{1}H NMR (250 MHz) 1.60 (d, J = 7.2, 3H), 4.61 (m, 1H), 5.20 (s, 1H), 7.00 (d, J = 1.6, 1H), 7.10−7.52 (m, 11H), 8.15 (s, 1H), 10.45 (br s, 1H); ^{13}C NMR (62.8 MHz) 24.3 (q), 54.2 (d), 84.5 (d), 115.6 (d), 125.3 (d), 127.2 (d), 127.2 (d), 128.4 (d), 128.6 (d), 129.8 (d), 129.8 (d), 134.8 (s), 135.3 (d), 143.3 (s), 163.5 (s), 168.2 (s). HRMS calcd for $C_{20}H_{19}N_3O$: 317.1528. Found: 317.1525. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 76.16; H, 5.85; N, 13.40.

(*R*)-(*Z*)-1-(1*H*-1-Imidazolyl)-4-methyl-3-(1-phenylethylamino)2-penten-1-one (2q). Flash chromatography (*n*-hexanes−EtOAc (1:2)) on silica gel gave a white solid (58%): mp 96−98 °C; $[\alpha]^{25}_D$ −533.2° (*c* 0.01, $CHCl_3$); ^{1}H NMR (250 MHz) 0.83 (d, J = 6.9, 3H), 1.15 (d, J = 6.9, 3H), 1.55 (d, J = 6.9, 3H), 2.66 (m, 1H), 4.77 (m, 1H), 5.07 (s, 1H), 6.99 (d, J = 1.6, 1H), 7.19−7.29 (m, 5H), 7.39 (d, J = 1.6, 1H), 8.09 (s, 1H), 10.55 (br d, 1H); ^{13}C NMR (62.8 MHz) 20.8 (q), 22.0 (q), 24.9 (q), 29.4 (d), 52.7 (d), 78.2 (d), 115.7 (d), 125.3 (d), 127.5 (d), 129.0 (d), 129.9 (d), 135.3 (d), 143.8 (s), 164.5 (s), 176.6 (s). HRMS calcd for $C_{17}H_{21}N_3O$: 283.1684. Found: 283.1678. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.86. Found: C, 71.88; H, 7.36; N, 14.58.

(*S*)-(*Z*)-1-(1*H*-1-Imidazolyl)-4-methyl-3-(1-phenylethylamino)2-penten-1-one (2r). Flash chromatography (*n*-hexanes−EtOAc (1:3)) on silica gel gave a yellow solid (61%): mp 96−98 °C; $[\alpha]^{25}_D$ +595.6° (*c* 0.015, $CHCl_3$); ^{1}H NMR (250 MHz) 0.83 (d, J = 6.8, 3H), 1.15 (d, J = 6.9, 3H), 1.55 (d, J = 6.9, 3H), 2.66 (m, 1H), 4.77 (m, 1H), 5.07 (s, 1H), 6.99 (d, J = 1.6, 1H), 7.17−7.32 (m, 5H), 7.39 (d, J = 1.6, 1H), 8.09 (s, 1H), 10.53 (br d, 1H); ^{13}C NMR (62.8 MHz) 20.7 (q), 21.9 (q), 24.8 (q), 29.3 (d), 52.6 (d), 78.1 (d), 115.6 (d), 125.2 (d), 127.5 (d), 128.9 (d), 129.8 (d), 135.2 (d), 143.8 (s), 164.4 (s), 176.56 (s). HRMS calcd for $C_{17}H_{21}N_3O$: 283.1684. Found: 283.1684. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.86. Found: C, 71.87; H, 7.56; N, 14.61.

***N*-Substituted *β*-Enamino Esters and Thioesters (4). General Procedure. Method C.** To a stirred solution of *β*-enamino carbonyl imidazole derivative **2** (10.0 mmol) in 20 mL of dried THF was added an excess of alcohol or thiol (10.0−30.0 mmol) in the presence of sodium alkoxide or RS^-. The reaction mixture was stirred at reflux under argon atmosphere. The reaction was monitored by TLC. After 6−24 h, the resulting mixture was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After filtration, the solvents were removed under reduced pressure to furnish the crude product **4** (X = O, S). Purification was carried out as indicated in each case.

Method D. "One Pot". To a stirred solution of *N*,*N*′-carbonyldiimidazole (2.2 g, 14 mmol) in THF (15 mL) was

added boron trifluoride (1.72 mL, 14 mmol) in THF (5 mL) at room temperature. The resulting solution was stirred at room temperature for 30 min. Ketimine **1** (12.7 mmol) in THF (15 mL) was added dropwise to the imidazole solution. The resulting mixture was stirred at reflux for 24 h. Then a solution of the desired alcohol (12.7−38.1 mmol) in THF (10 mL) was added slowly. The reaction mixture was stirred for 24−48 h. When TLC analyses showed the disappearance of the β-enamino carbonyl imidazole **2**, the reaction was quenched by addition of 3 N NaOH. The aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under vacuum to afford β-enamino esters derivatives **4**.

Method E. *n*-Butyllithium (2.5 M in hexane, 8.0 mL, 20 mmol) was added to a solution of freshly distilled diisopropylamine (2.6 mL, 20 mmol) in 10 mL of THF at 0 °C. After being stirred for 10 min, ketimine **1** (10.0 mmol) in THF (15 mL) was added. The solution stirred 30 min at 0 °C and then cooled at −78 °C. Alkoxy carbonyl imidazole **5** (13.0 mmol) in 5 mL of THF was added and allowed to stir for 1 h at −78 °C. The solution was allowed to warm to room temperature. When TLC analysis showed the disappearance of the starting material, the reaction was quenched by addition of saturated ammonium chloride solution. The aqueous layer was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine, then dried (Na_2SO_4), and evaporated under vacuum to furnish the crude product **4**. The purification was carried out as indicated in each case.

Method F. A solution of boron trifluoride (5.0 mmol, 0.6 mL) in 5 mL of THF was added to a solution of alcoxy carbonyl imidazole **5** (5.0 mmol) in 15 mL of THF at room temperature for 30 min. Ketimine **1** (4.5 mmol) in 10 mL of THF was added dropwise. The solution was heated at reflux for 24 h under argon atmosphere. The reaction mixture was poured onto saturated ammonium chloride solution. Work up of the reaction followed the procedure described in Method E.

***tert*-Butyl (*Z*)-3-Butylamino-4-methyl-2-pentenoate (4a).** Flash chromatography (*n*-hexanes−EtOAc (9:1)) on silica gel gave a yellow oil (75%): ^{1}H NMR (400 MHz) 0.68 (t, J = 7.2, 3H), 0.86 (d, J = 6.8, 6H), 1.13 (m, 2H), 1.20 (s, 9H), 1.31 (m, 2H), 2.40 (m, 1H), 2.95 (q, J = 6.4, 2H), 4.14 (s, 1H), 8.31 (br s, 1H); ^{13}C NMR (100 MHz) 13.3 (q), 19.6 (t), 20.9 (q), 28.0 (d), 28.2 (q), 32.3 (t), 41.4 (t), 76.3 (s), 78.4 (d), 170.4 (s), 171.0 (s). HRMS calcd for $C_{14}H_{27}NO_2$: 241.2041. Found: 241.2041. Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.67; H, 11.27; N, 5.80. Found: C, 69.19; H, 11.09; N, 5.91.

Methyl (*Z*)-3-Butylamino-4-methyl-2-pentenoate (4b). Flash chromatography (*n*-hexanes−EtOAc (9:1)) on silica gel gave a yellow oil (88%): ^{1}H NMR (400 MHz) 0.91 (t, J = 7.4, 3H), 1.06 (d, J = 7.2, 6H), 1.30 (m, 2H), 1.56 (m, 2H), 2.65 (m, 1H), 3.14 (q, J = 6.5, 2H), 3.53 (s, 3H), 4.41 (s, 1H), 8.31 (br s, 1H); ^{13}C NMR (100 MHz) 13.3 (q), 19.6 (t), 20.9 (q), 28.1 (d), 32.2 (t), 41.4 (t), 49.2 (q), 76.4 (d), 171.2 (s), 171.3 (s). HRMS calcd for $C_{11}H_{21}NO_2$: 199.1572. Found: 199.1571. Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.30; H, 10.62; N, 7.03. Found: C, 66.19; H, 10.69; N, 7.13.

2,2,2-Trifluoroethyl (*Z*)-Butylamino-4-methyl-2-pentenoate (4c). MPLC (*n*-hexanes−EtOAc (15:1)) on silica gel gave a colorless oil (65%): ^{1}H NMR (400 MHz) 0.95 (t, J = 7.2, 3H), 1.23 (d, J = 6.9, 6H), 1.46 (m, 2H), 1.58 (m, 2H), 2.68 (m, 1H), 3.22 (q, J = 6.4, 2H), 4.41 (q, J = 8.8, 2H), 4.55 (s, 1H), 8.65 (br t, 1H); ^{13}C NMR (100 MHz) 13.6 (q), 19.9 (t), 21.1 (q), 28.7 (d), 32.4 (t), 41.9 (t), 58.5 (q, J_{C-C-F} = 34.9), 75.2 (d), 123.7 (s, J_{C-F} = 276.1), 158.8 (s), 173.6 (s). HRMS calcd for $C_{12}H_{20}NO_2F_3$: 267.1446. Found: 267.1436. Anal. Calcd for $C_{12}H_{20}NO_2F_3$: C, 55.17; H, 7.66; N, 5.36. Found: C, 54.79; H, 7.49; N, 5.33.

(*S*)-1-Ethyloxycarbonylethyl (*Z*)-3-Butylamino-4-methyl-2-pentenoate (4d). MPLC (*n*-hexanes−EtOAc (8:1)) on silica gel gave a yellow oil (85%): $[\alpha]^{25}_D$ −59.78° (*c* 0.0136, CH_2Cl_2); ^{1}H NMR (250 MHz) 0.90 (t, J = 7.2, 3H), 1.12 (d, J = 6.8, 6H), 1.28 (t, J = 7.2, 3H), 1.50 (d, J = 7.0, 3H), 1.48 (m, 2H), 1.57 (m, 2H), 2.65 (m, 1H), 3.20 (q, J = 6.4, 2H), 4.22 (m, 2H), 4.59 (s, 1H), 5.04 (q, J = 7.0, 1H), 8.63 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.6 (q), 13.9 (q), 17.1 (q), 19.8 (t), 21.0 (d), 21.1 (q), 28.5 (d), 32.3 (t), 41.8 (t), 60.8 (t), 66.7 (d), 75.9 (d), 170.0 (s), 172.1 (s), 172.7 (s). HRMS calcd for $C_{15}H_{27}NO_4$: 285.1940. Found: 285.1941. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.66; H, 9.75; N, 4.98.

Benzyl (*Z*)-3-Butylamino-4-methyl-2-pentenethioate (4e). Flash chromatography (*n*-hexanes−EtOAc (20:1)) on silica gel gave a yellow oil (78%): ^{1}H NMR (250 MHz) 0.92 (t, J = 7.2, 3H), 1.06 (d, J = 6.8, 6H), 1.37 (m, 2H), 1.52 (m, 2H), 2.59 (m, 1H), 3.17 (q, J = 6.5, 2H), 4.05 (s, 2H), 4.90 (s, 1H), 7.13−7.30 (m, 5H), 9.47 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.4 (q), 19.6 (t), 20.2 (q), 28.4 (t), 32.0 (t), 32.1 (d), 41.6 (t), 88.0 (d), 126.2 (d), 128.0 (d), 128.4 (d), 139.0 (s), 169.4 (s), 185.1 (s). HRMS calcd for $C_{17}H_{25}NOS$: 291.1657. Found: 291.1661. Anal. Calcd for $C_{17}H_{25}NOS$: C, 70.06; H, 8.65; N, 4.81; S, 14.60. Found: C, 69.87; H, 8.54; N, 4.90; S, 14.53.

Allyl (*Z*)-3-Butylamino-4-methyl-2-pentenethioate (4f). Flash chromatography (*n*-hexanes−EtOAc (20:1)) on silica gel gave a yellow oil (86%): ^{1}H NMR (250 MHz) 0.84 (t, J = 7.2, 3H), 1.04 (d, J = 6.8, 6H), 1.29 (m, 2H), 1.50 (m, 2H), 2.58 (m, 1H), 3.14 (q, J = 6.4, 2H), 3.43 (dd, J = 6.8 and 0.9, 2H), 4.86 (s, 1H), 4.98 (dd, J = 10.7 and 1.5, 1H), 5.15 (dd, J = 16.8 and 1.4, 1H), 5.80 (m, 1H), 9.41 (br s, 1H); ^{13}C NMR (62.8 MHz) 13.1 (q), 19.3 (t), 20.5 (q), 27.7 (t), 30.1 (t), 31.8 (d), 41.3 (t), 87.8 (d), 115.5 (t), 134.5 (d), 168.9 (s), 184.8 (s). HRMS calcd for $C_{13}H_{23}NOS$: 214.1500. Found: 241.1496. Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80; S, 14.94. Found: C, 64.79; H, 9.48; N, 5.73; S, 14.75.

***tert*-Butyl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4g).** MPLC (*n*-hexanes−EtOAc (10:1)) on silica gel gave a yellow oil (68%): ^{1}H NMR (250 MHz) 0.76 (t, J = 7.2, 3H), 1.23 (m, 2H), 1.45 (m, 2H), 1.50 (s, 9H), 2.95 (q, J = 6.4, 2H), 4.41 (s, 1H), 7.28 (m, 5H), 8.32 (br s, 1H); ^{13}C NMR (62.8 MHz) 14.0 (q), 20.1 (t), 28.9 (q), 33.4 (t), 44.5 (t), 78.5 (s), 87.0 (d), 128.1 (d), 128.4 (d), 129.1 (d), 137.3 (s), 164.5 (s), 171.1 (s); IR (KBr) 3276, 3056, 1645, 1609, 1593, 1141. HRMS calcd for $C_{17}H_{25}NO_2$: 275.1885. Found: 275.1874. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.35; H, 9.23; N, 5.30.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4h). Flash chromatography (*n*-hexanes−EtOAc (10:1)) on silica gel gave a yellow oil (80%): $[\alpha]^{25}_D$ −3.9° (*c* 0.0025, CH_2Cl_2); ^{1}H NMR (250 MHz) 0.70 (t, J = 7.2, 3H), 0.74 (d, J = 7.0, 3H), 0.78 (d, J = 7.0, 3H), 0.86 (d, J = 7.0, 3H), 0.96−1.97 (m, 9H), 1.35 (m, 2H), 1.50 (m, 2H), 2.92 (q, J = 6.4, 2H), 4.46 (s, 1H), 4.62 (dt, J = 10.7, 4.3, 1H), 7.15−7.27 (m, 5H), 8.47 (br t, 1H); ^{13}C NMR (62.8 MHz) 13.6 (q), 16.5 (q), 19.7 (t), 20.7 (q), 22.0 (q), 23.5 (t), 26.1 (d), 31.3 (d), 32.9 (t), 34.3 (t), 41.4 (t), 44.2 (t), 47.1 (d), 71.8 (d), 85.2 (d), 127.67 (d), 128.4 (d), 128.9 (d), 136.3 (s), 164.6 (s), 170.0 (s). HRMS calcd for $C_{23}H_{35}NO_2$: 357.2668. Found: 357.2667. Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.31; H, 9.80; N, 3.92. Found: C, 77.73; H, 10.00; N, 3.98.

1-Adamantyl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4i). MPLC (*n*-hexanes−EtOAc (20:1)) on silica gel gave a pale green oil (50%): ^{1}H NMR (250 MHz) 0.82 (t, J = 7.2, 3H), 1.31 (m, 2H), 1.45 (m, 2H), 1.64−2.17 (m, 15H), 3.05 (q, J = 6.4, 2H), 4.48 (s, 1H), 7.31−7.38 (m, 5H), 8.45 (br t, 1H); ^{13}C NMR (62.8 MHz) 13.9 (q), 20.0 (t), 31.0 (d), 33.4 (t), 36.6 (t), 42.1 (t), 44.5 (t), 78.6 (s), 87.0 (d), 128.0 (d), 128.3 (d), 129.0 (d), 136.8 (s), 164.6 (s), 170.5 (s); IR (KBr) 3274, 3055, 1686, 1640, 1609, 1173. HRMS calcd for $C_{23}H_{31}NO_2$: 353.2354. Found: 353.2354. Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.18; H, 8.78; N, 3.96. Found: C, 78.53; H, 8.91; N, 3.93.

(2*S*)-5-Oxo-2-azolanyl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4j). Flash chromatography (*n*-hexanes−EtOAc (1:3)) on silica gel gave a yellow solid (75%): $[\alpha]^{25}_D$ −3.18° (*c* 0.0017, $CHCl_3$); mp 70−72 °C; ^{1}H NMR (250 MHz) 0.77 (t, J = 7.2, 3H), 1.23 (m, 2H), 1.39 (m, 2H), 1.81 (m, 1H), 2.21 (m, 1H), 2.30 (m, 2H), 3.00 (q, J = 6.4, 2H), 3.85 (m, 2H), 4.13 (m, 1H), 4.47 (s, 1H), 5.96 (br s, 1H), 7.20−7.35 (m, 5H), 8.50 (br t, 1H); ^{13}C NMR (62.8 MHz) 13.6 (q), 19.7 (t), 23.3 (t), 29.6 (t), 32.9 (t), 44.3 (t), 53.4 (d), 65.4 (t), 83.4 (d), 127.7 (d), 128.35 (d), 129.2 (d), 135.9 (s), 165.9 (s), 169.8 (s), 177.9 (s). HRMS calcd for $C_{18}H_{24}N_2O_3$: 316.1786. Found: 316.1783. Anal.

Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.19; H, 7.53; N, 8.72.

(2*E*)-3,7-Dimethyl-2,6-octadienyl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4k). MPLC (*n*-hexanes−EtOAc (10:1)) on silica gel gave a yellow oil (80%): ^{1}H NMR (250 MHz) 0.83 (t, J = 7.2, 3H), 1.31 (m, 2H), 1.46 (m, 2H), 1.59 (s, 3H), 1.67 (s, 3H), 1.71 (s, 3H), 2.00−2.07 (m, 4H), 3.05 (q, J = 6.4, 2H), 4.59 (s, 1H), 4.63 (d, J = 7.0, 2H), 5.11 (br t, 1H), 5.40 (br t, 1H), 7.34−7.39 (m, 5H), 8.45 (br t, 1H); ^{13}C NMR (62.8 MHz) 13.6 (q), 16.4 (q), 17.6 (q), 19.7 (t), 25.6 (q), 26.3 (t), 33.0 (t), 39.6 (t), 44.2 (t), 59.7 (t), 84.7 (d), 119.3 (d), 123.8 (d), 127.7 (d), 128.2 (d), 128.99 (d), 131.6 (s), 136.3 (s), 140.9 (s), 164.5 (s), 170.4 (s); IR (KBr) 3279, 3055, 1645, 1609, 1593, 1167, 1145. HRMS calcd for $C_{23}H_{33}NO_2$: 355.2511. Found: 355.2506. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.42; H, 9.10; N, 3.81.

1,2:5,6-Di-*O*-isopropilyden-α-D-glucofuranos-3-*O*-yl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4l). Flash chromatography (*n*-hexanes−EtOAc (2:1)) on silica gel gave a yellow oil (82%): $[\alpha]^{25}_D$ −18.55° (*c* 0.0076, CH_2Cl_2); ^{1}H NMR (250 MHz) 0.84 (t, J = 7.2, 3H), 1.28 (m, 2H), 1.29 (s, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.48 (m, 2H), 1.52 (s, 3H), 3.08 (q, J = 6.4, 2H), 4.05 (d, J = 5.4, 2H), 4.32 (m, 2H), 4.54 (s, 1H), 4.58 (d, J = 3.7, 1H), 5.24 (d, J = 2.8, 1H), 5.87 (d, J = 3.7, 1H), 7.37 (m, 5H), 8.75 (br t, 1H); ^{13}C NMR (62.8 MHz) 13.5 (q), 19.6 (t), 25.2 (q), 26.1 (q), 26.6 (q), 32.8 (t), 44.2 (t), 66.4 (t), 72.7 (d), 74.6 (d), 79.56 (d), 83.5 (d), 83.6 (d), 104.9 (d), 108.8 (s), 111.8 (s), 127.5 (d), 128.3 (d), 129.2 (d), 135.8 (s), 165.9 (s), 168.7 (s). HRMS calcd for $C_{25}H_{35}NO_7$: 461.2413. Found: 461.2413. Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64; N, 3.03. Found: C, 65.45; H, 7.49; N, 2.89.

5α-Cholestan-3-*β*-yl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4m). Flash chromatography (*n*-hexane−EtOAc (15:1)) on silica gel gave a yellow oil (74%): $[\alpha]^{25}_D$ +13.6° (*c* 0.01, CH_2Cl_2); ^{1}H NMR (250 MHz) 0.65 (s, 3H), 0.72 (s, 3H), 0.85 (d, J = 6.4, 3H), 0.65−2.06 (m, 42H), 3.03 (q, J = 6.4, 2H), 4.52 (s, 1H), 7.35 (m, 5H), 8.56 (br t, 1H); ^{13}C NMR (62.8 MHz) 12.0 (t), 12.2 (q), 13.6 (q), 18.6 (q), 19.7 (s), 21.2 (t), 22.5 (d), 22.8 (d), 23.8 (t), 24.2 (t), 27.9 (d), 27.9 (t), 28.2 (t), 28.6 (t), 32.0 (t), 33.0 (t), 34.5 (t), 35.4 (q), 35.7 (d), 36.1 (t), 36.9 (t), 40.0 (t), 42.5 (s), 44.2 (t), 44.8 (d), 54.2 (d), 56.2 (d), 56.4 (d), 71.7 (d), 85.4 (d), 127.7 (d), 128.1 (d), 128.9 (d), 136.4 (s), 164.8 (s), 170.0 (s). HRMS calcd for $C_{40}H_{63}NO_2$: 589.4858. Found: 589.4848. Anal. Calcd for $C_{40}H_{63}NO_2$: C, 81.49; H, 10.69; N, 2.37. Found: C, 81.58; H, 10.60; N, 2.42.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (*Z*)-3-Butylamino-3-phenyl-2-propenoate (4n). Flash chromatography (*n*-hexanes−EtOAc (5:1)) on silica gel gave a yellow oil (71%): $[\alpha]^{25}_D$ +44.6° (*c* 0.012, $CHCl_3$); ^{1}H NMR (250 MHz) 0.78 (t, J = 7.2, 3H), 0.81 (m, 3H), 0.80−0.95 (m, 4H), 1.23 (s, 3H), 1.29 (s, 3H), 1.36−1.21 (m, 6H), 1.37−1.45 (m, 2H), 2.96 (q, J = 6.4, 2H), 4.14 (s, 1H), 4.74 (dt, J = 7.5, 4.2, 1H), 7.02−7.33 (m, 10H), 8.43 (br t, 1H); ^{13}C NMR (62.8 MHz) 13.7 (q), 19.8 (t), 21.8 (d), 25.0 (q), 27.0 (t), 28.2 (q), 31.3 (d), 33.0 (t), 34.6 (t), 40.1 (t), 42.3 (t), 44.3 (t), 50.8 (d), 72.6 (d), 85.7 (d), 124.8 (d), 125.5 (d), 127.7 (d), 128.1 (d), 128.9 (d), 136.3 (s), 151.4 (s), 164.5 (s), 169.5 (s). HRMS calcd for $C_{29}H_{39}NO_2$: 433.2980. Found: 433.3004. Anal. Calcd for $C_{29}H_{39}NO_2$: C, 80.33; H, 9.06; N, 3.23. Found: C, 80.01; H, 8.79; N, 3.19.

***tert*-Butyl (*Z*)-3-Cyclohexylamino-3-phenyl-2-propenoate (4o).** Recrystallization (cyclohexane−chloroform) gave a white solid (58%): mp 118−120 °C; ^{1}H NMR (400 MHz) 1.00−1.80 (m, 10H), 1.49 (s, 9H), 3.00 (m, 1H), 4.46 (s, 1H), 7.35 (m, 5H), 8.40 (br d, 1H); ^{13}C NMR (100 MHz) 24.8 (t), 25.3 (t), 28.7 (q), 34.6 (t), 52.6 (d), 78.2 (s), 87.4 (d), 127.7 (d), 128.2 (d), 128.8 (d), 137.0 (s), 163.5 (s); 170.2 (s). HRMS calcd for $C_{19}H_{27}NO_2$: 301.2041. Found: 301.2046. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.97; H, 9.21; N, 4.81.

***tert*-Butyl (*Z*)-3-Cyclohexylamino-3-phenyl-2-propenethioate (4p).** Flash chromatography (*n*-hexanes−EtOAc (20:1)) on silica gel gave a yellow solid (70%): mp 124−126 °C;^{1}H NMR (250 MHz) 1.01−1.73 (m, 10H), 1.45 (s, 9H), 3.02 (m, 1H), 4.81 (s, 1H), 7.20−7.34 (m, 5H), 9.20 (br d, 1H); ^{13}C NMR (62.8 MHz) 24.7 (t), 25.2 (t), 30.6 (q), 34.5 (t), 46.7 (s), 52.9 (d), 95.8 (d), 127.6 (d), 128.3 (d), 129.1 (d), 136.1 (s), 161.0 (s), 189.0 (s). HRMS calcd for $C_{19}H_{27}NOS$: 317.1813. Found: 317.1813. Anal. Calcd for $C_{19}H_{27}NOS$: C, 71.88; H, 8.57; N, 4.41; S, 10.10. Found: C, 71.57; H, 8.69; N, 4.53; S, 9.98.

Methyl (*Z*)-3-Anilino-3-phenyl-2-propenoate (4q). Recrystallization (*n*-hexane) gave an orange solid (94%): mp 84−86 °C; ^{1}H NMR (300 MHz) 3.81 (s, 3H), 5.00 (s, 1H), 6.70−7.12 (m, 5H), 7.39 (m, 5H), 10.30 (br s, 1H); ^{13}C NMR (75 MHz) 50.5 (q), 90.6 (d), 122.1 (d), 122.9 (d), 128.1 (d), 128.3 (d), 128.5 (d), 129.3 (d), 135.8 (s), 140.2 (s), 159.1 (s), 170.3 (s); LRMS (EI) *m*/*z* 253 (M^+, 73), 193 (100). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.67; H, 5.81; N, 5.33.

Isopropyl (*Z*)-3-Anilino-3-phenyl-2-propenoate (4r). Flash chromatography (*n*-hexanes−ether (3:1)) on silica gel gave a yellow solid (71%): mp 82−84 °C; ^{1}H NMR (300 MHz) 1.32 (d, J = 7.2, 6H), 5.00 (s, 1H), 5.15 (m, 1H), 6.65−7.10 (m, 5H), 7.32 (m, 5H), 10.38 (br s, 1H); ^{13}C NMR (75 MHz) 22.0 (q), 66.2 (d), 91.7 (d), 121.9 (d), 122.7 (d), 128.0 (d), 128.2 (d), 128.4 (d), 129.2 (d), 135.9 (s), 140.3 (s), 158.7 (s), 169.5 (s); LRMS (EI) *m*/*z* 281 (M^+, 50), 194 (100). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.04; H, 6.81; N, 5.20.

***tert*-Butyl (*Z*)-3-Anilino-3-phenyl-2-propenoate (4s).** Flash chromatography (*n*-hexanes−ether (5:1)) on silica gel gave a yellow oil (75%): ^{1}H NMR (300 MHz) 1.55 (s, 9H), 4.98 (s, 1H), 6.62−7.01 (m, 5H), 7.30 (m, 5H), 10.25 (br s, 1H); ^{13}C NMR (75 MHz) 28.4 (q), 79.2 (s), 93.1 (d), 121.9 (d), 122.5 (d), 128.0 (d), 128.2 (d), 128.4 (d), 129.1 (d), 136.0 (s), 140.5 (s), 158.1 (s), 169.9 (s); LRMS (EI) *m*/*z* 295 (M^+, 21), 193 (100). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.88; H, 6.93; N, 4.79.

Benzyl (*Z*)-3-Anilino-3-phenyl-2-propenoate (4t). Flash chromatography (*n*-hexanes−ether (1:2)) on silica gel gave a yellow solid (84%): mp 70−72 °C; ^{1}H NMR (300 MHz) 5.10 (s, 1H), 5.23 (s, 2H), 6.72−7.45 (m, 15H), 10.30 (br s, 1H); ^{13}C NMR (75 MHz) 64.9 (t), 90.1 (d), 122.2 (d), 127.8 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.5 (d), 129.4 (d), 137.1 (s), 138.0 (s), 140.1 (s), 159.9 (s), 170.0 (s). HRMS calcd for $C_{22}H_{19}NO_2$: 329.1415. Found: 329.1408. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.20; H, 5.88; N, 4.63.

Methyl 2-(2-Azolanyliden)acetate (4u). Flash chromatography (*n*-hexanes−EtOAc (3:1)) on silica gel gave a white solid (50%): mp 95−97 °C; ^{1}H NMR (250 MHz) 2.15 (m, 2H), 2.74 (t, J = 7.7, 2H), 3.68 (t, J = 6.6, 2H), 3.79 (s, 3H), 4.68 (s, 1H), 8.10 (br s, 1H); ^{13}C NMR (62.8 MHz) 21.6 (t), 31.8 (t), 46.7 (q), 49.4 (t), 75.6 (d), 166.1 (s), 170.4 (s). HRMS calcd for $C_7H_{11}NO_2$: 141.0789. Found: 141.0788. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.87; H, 7.74; N, 9.87.

Allyl (*Z*)-3-Phenyl-3-(1-phenylethylamino)-2-propenoate (4v). Flash chromatography (*n*-hexanes−EtOAc (9:1)) on silica gel gave an orange oil (76%): ^{1}H NMR (300 MHz) 1.50 (d, J = 7.2, 3H), 4.43 (m, 1H), 4.70 (m, 2H), 4.71 (s, 1H), 5.22 (dq, J = 10.4, 1.4, 1H), 5.31 (dq, J = 17.2, 1.5, 1H), 6.00 (m, 1H), 7.10−7.40 (m, 10H), 8.92 (br d, 1H); ^{13}C NMR (75 MHz) 24.3 (q), 53.6 (d), 63.3 (t), 86.1 (d), 116.9 (t), 125.3 (d), 126.6 (d), 127.4 (d), 127.9 (d), 128.2 (d), 128.9 (d), 133.1 (d), 136.0 (s), 144.5 (s), 164.3 (s), 169.6 (s); IR (KBr) 3280, 1657, 1613, 1594, 1479; LRMS (EI) *m*/*z* 307 (M^+, 15), 105 (100). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.71; H, 6.68; N, 4.41.

***tert*-Butyl (*Z*)-4,4-Dimethyl-3-(1-phenylethylamino)-2-pentenoate (4w).** Flash chromatography (*n*-hexanes−EtOAc (10:1)) on silica gel gave a yellow oil (75%):^{1}H NMR (250 MHz) 1.45 (d, J = 6.9, 3H), 1.51 (s, 9H), 4.40 (m, 1H), 4.56 (s, 1H), 7.06−7.30 (m, 10H), 8.79 (br d, 1H); ^{13}C NMR (62.8 MHz) 24.5 (q), 28.6 (q), 53.7 (d), 78.4 (s), 88.9 (d), 125.7 (d), 126.7 (d), 127.7 (d), 128.0 (d), 128.3 (d), 128.8 (d), 136.6 (s), 145.0 (s), 163.5 (s), 170.1 (s). HRMS calcd for $C_{21}H_{25}NO_2$: 323.1885. Found: 323.1880. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 74.79; H, 9.50; N, 4.39.

(*R*)-Methyl (*Z*)-4-Methyl-3-(1-phenylethylamino)-2-pentenoate (4x). Flash chromatography (*n*-hexanes−EtOAc (4:1)) on silica gel gave a yellow oil (68%): $[\alpha]^{25}_D$ −420.0° (*c* 0.00705, $CHCl_3$); ^{1}H NMR (250 MHz) 0.74 (d, J = 6.8, 3H),

1.07 (d, $J = 6.8$, 3H), 1.47 (d, $J = 6.8$, 3H), 2.45 (m, 1H), 3.61 (s, 3H), 4.50 (s, 1H), 4.68 (m, 1H), 7.16−7.29 (m, 5H), 9.08 (br d, 1H); ^{13}C NMR (62.8 MHz) 20.8 (q), 22.5 (q), 25.2 (q), 28.9 (d), 50.0 (d), 52.0 (q), 78.3 (d), 125.4 (d), 127.0 (d), 128.7 (d), 145.3 (s), 171.7 (s), 171.7 (s). HRMS calcd for $C_{15}H_{21}NO_2$: 247.1572. Found: 247.1572. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.39; H, 8.77; N, 5.67.

(*R*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (*Z*)-4-Methyl-3-(1-phenylethylamino)-2-pentenoate (4y). Flash chromatography (*n*-hexanes−EtOAc (10:1)) on silica gel gave a yellow oil (75%): $[\alpha]^{25}_D$ −357.0° (*c* 0.010, $CHCl_3$); ^{1}H NMR (250 MHz) 0.72 (d, $J = 6.8$, 6H), 0.85(d, $J = 6.8$, 6H), 1.05 (d, $J = 6.8$, 3H), 1.45 (d, $J = 6.8$, 3H), 0.67−1.93 (m, 10H), 2.43 (m, 1H), 4.44 (s, 1H), 4.57 (dt, $J = 10.7$, 4.2, 1H), 7.15−7.29 (m, 5H), 9.06 (br d, 1H); ^{13}C NMR (62.8 MHz) 16.5 (q), 20.8 (q), 22.1 (d), 22.5 (q), 23.6 (t), 25.3 (q), 26.1 (t), 28.9 (d), 31.5 (q), 34.5 (d), 41.6 (t), 47.3 (q), 52.0 (d), 71.8 (d), 79.4 (d), 125.4 (d), 127.0 (d), 128.7 (d), 145.5 (s), 171.1 (s), 171.4 (s). HRMS calcd for $C_{24}H_{37}NO_2$: 371.2824. Found: 371.2828. Anal. Calcd for $C_{24}H_{37}NO_2$: C, 77.84; H, 9.73; N, 3.78. Found: C, 78.30; H, 9.70; N, 3.89.

(*S*)-Ethyl (*Z*)-4-Methyl-3-(1-phenylethylamino)-2-pentenoate (4z). Flash chromatography (*n*-hexanes−EtOAc (4:1)) on silica gel gave a yellow oil (64%): $[\alpha]^{25}_D$ +43.8° (*c* 0.017, $CHCl_3$); ^{1}H NMR (250 MHz) 0.73 (d, $J = 6.8$, 3H), 1.06 (d, $J = 6.8$, 3H), 1.20 (t, $J = 7.0$, 3H), 1.45 (d, $J = 6.8$, 3H), 2.44 (m, 1H), 4.06 (q, $J = 7.0$, 2H), 4.47 (s, 1H), 4.62 (m, 1H), 7.15−7.28 (m, 5H), 9.06 (br d, 1H); ^{13}C NMR (62.8 MHz) 14.6 (q), 20.8 (q), 22.4 (q), 25.1 (t), 28.8 (q), 51.9 (d), 58.3 (d), 78.7 (d), 125.3 (d), 126.9 (d), 128.6 (d), 145.3 (s), 171.4 (s), 171.7 (s). HRMS calcd for $C_{16}H_{23}NO_2$: 261.1729. Found: 261.1736. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.29; H, 8.69; N, 5.51.

X-ray Analysis of (*Z*)-3-Cyclohexylamino-1-(1*H*-1-imidazolyl)-3-phenyl-2-propen-1-one (2h). $C_{18}N_3OH_{21}$, $M = 294.4$, pale yellow prismatic crystal, orthorhombic *Pmnb*, $a = 9.143(1)$ Å, $b = 10.798(1)$ Å, $c = 17.171(1)$ Å, $V = 1695.2(3)$ Å^3, $Z = 4$, $F(000) = 628$, Mo Kα radiation ($\lambda = 0.7107$ Å), $\mu = 0.73$ cm^{-1}, $D_c = 1.15$ g cm^{-3}, Enraf-Nonius CAD4 diffractometer: 1590 independent reflections, 801 observed with $I > 2\sigma(I)$. Solution by direct methods with the program SIR92,[43] non-hydrogen atoms anisotropically refined using the XRAY76 system,[44] hydrogen atoms placed at calculated positions and included as fixed contributors with a common isotropic temperature factor, 121 refined parameters. In the final stages an empirical weighting scheme was chosen as to give no trends in ΔF vs $\langle \omega \Delta^2 F \rangle$ and vs $\langle \sin \theta/\lambda \rangle$ using the program PESOS,[45] $R = 0.065$, $R_w = 0.069$, geometrical calculations with PARST.[46]

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Supporting Information Available: General procedure, spectroscopical (^{1}H and ^{13}C NMR and HRMS) and analytical data for products **6**, tables of atomic coordinates, bond angles and distances, anisotropic thermal parameters (Tables 3−7) for **2h**, and optimized structures at the HF/6-31G* level for complexes **3A** and **3B** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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