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Asymmetric synthesis of nitrogen heterocycles by reaction of chiral β-enaminocarbonyl substrates with acrylate derivatives

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Abstract—We have studied the reactivity of β-enaminoesters **1** (R^2 = OMe) or β-enaminoketone **1** (R^2 = Me), derived from (*S*)-phenylglycinol, with activated acrylate derivatives. Substrates **1** (R^1 = Me) afforded by aza-annulation oxazololactams **2** and 3,4-dihydro-2-pyridones **3**. In the same conditions β-enaminoesters 1 (R^1 = H) furnish *N*-acylated oxazolidines **4**. © 2002 Published by Elsevier Science Ltd.

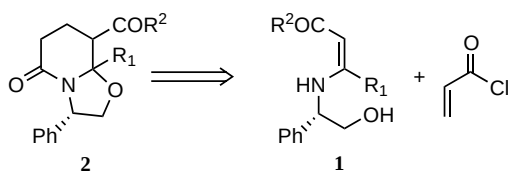
The aza-annulation of enamines[1] or β-enaminocarbonyl compounds with acrylate derivatives, originally studied by Hickmott,[2] is a convenient, efficient and now well-known route for the synthesis of δ-lactams. The aza-annulation is believed to proceed via an initial 1,4-addition of the β-enaminoester to an α,β-unsaturated acid derivative followed by an intramolecular *N*-acylation. Several research groups have used successfully this aza-annulation procedure in the synthesis of various nitrogen heterocycles.[3] Recently the aza-annulation was applied to solid-phase synthesis.[4]

To our knowledge, the aza-annulation of β-enaminocarbonyl compounds bearing an internal nucleophile as an hydroxyl function has not been yet described. Here we wish to present our first results concerning this topic. Our initial objective was the preparation of oxazololactams **2**. Meyers reported that similar chiral non-racemic bicyclic lactams derived from homochiral β-amino alcohols are versatile building blocks for the enantioselective synthesis of pyrrolidines and piperidines derivatives.[5] In these syntheses, the bicyclic ring system is usually generated by cyclocondensation of δ-oxoacid derivatives with β-amino alcohols. Formally bicyclolactams such as compound **2**, which contain an electron-withdrawing group on the C5 position of the lactam ring, could be obtained by treatment of β-enaminocarbonyl compounds **1** with acryloyl chloride (Scheme 1).

The formation of the oxazolidine ring might arise from internal nucleophilic trapping of an iminium intermediate formed during the aza-annulation process.

Condensation of (*S*)-phenylglycinol with methyl propiolate or methyl acetoacetate and 2,4-pentanedione afforded β-enaminoesters **1** (R^1 = H or Me, R^2 = OMe) and β-enaminoketone **1** (R^1 = Me, R^2 = Me) respectively, which were used in the next step without purification. The aza-annulation reactions were performed by adding 1 equiv. of acryloyl chloride derivatives to β-enaminocarbonyl compounds **1** in THF at 0°C. The reaction mixtures were then treated with an aqueous saturated sodium bicarbonate solution and extracted twice with dichloromethane. The results are presented in Table 1.

Three types of heterocycles (**2**–**4**) were formed and were fully characterized. The R^1 group in compounds **1** has a dramatic effect on the selectivity of the reaction. Products **2** and **3** arise from an aza-annulation process when R^1 = Me (entries 1–5); whereas oxazolidines **4** stem from competitive *N*-acylation when the β-position was not substituted (entries 6, 7).[6] In these experiments no product resulting from aza-annulation could be detected. The *cis*-*N*-acyloxazolidines **4** resulting were obtained with d.e. >90%.[7]



2 **1**

Scheme 1.

Keywords: β-enaminoesters; oxazolactams; 3,4-dihydro-2-pyridones; oxazolidines; aza-annulation.

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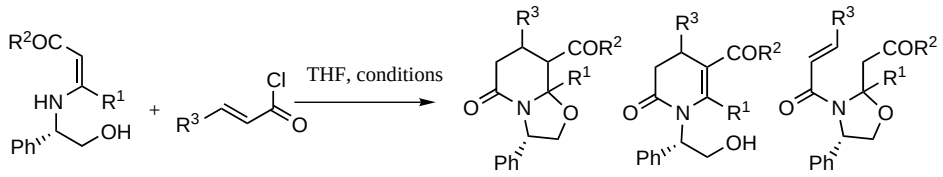
Table 1. Aza-annulation of β-enaminocarbonyl compounds **1**



Entry	R^1	R^2	R^3	Conditions	Ratio **2**+**3**/**4**[c]	Ratio **2**/**3**[c]	Yield (%)
1	Me	OMe	H	0°C/3 h	>95/5	83/17	70[a]
2	Me	OMe	H	0°C/3 h–rt/72 h	>95/5	>95/5	85[a]
3	Me	OMe	H	0°C/1 min	>95/5	52/48	ND
4	Me	OMe	Me	0°C/3 h–rt/72 h	50/50	>95/5	ND
5	Me	Me	H	0°C/3 h	>95/5	>95/5	91[a]
6	H	OMe	H	0°C/3 h	<5/95	–	38[b]
7	H	OMe	Me	0°C/3 h	<5/95	–	21[b]

[a] Combined yields of the two oxazolactam diastereomers **2**.
[b] Yield of isolated oxazolidines **4**.
[c] Ratios determined by ^{1}H NMR analysis of the crude mixture. ND: not determined.

Generally, the reaction of enamines, which exist in an equilibrium mixture with imine tautomers, with α,β-unsaturated acid chlorides, provides the annulation in low yield due to the formation of the uncyclized enamide derived from the competitive *N*-acylation. In contrast, with β-enaminocarbonyl compounds in which the amine function exists only as the enamine tautomer such as in substrates **1**, the annulation process is more easy.[8] Stille et al. have investigated the selectivity of this reaction in the presence of various acidic reagents to increase the yield of the annulated product.[9] Thus, compounds **1** bearing a hydrogen on the β-position (R^1 = H) react exclusively like imines by *N*-acylation. The methyl group enhances the electron density on the α-carbon and hence favors the annulation process. When the Michael acceptor is β-substituted (entry 4) the ratio **2**+**3**/**4** falls down and *N*-acyloxazolidine **4** was also formed. The low yield in oxazolidine **4** (entries 6, 7) is due to competitive formation of dihydropyridine **5** (yields = 30 and 38%, respectively) resulting from the trimerization of the starting β-enaminoester (Scheme 2).

Oxazololactams **2** were in all cases (entries 1–5) formed as a mixture of two diastereomers with a low diastereomeric excess (0–10%) and separated by chromatography on silica gel. The stereochemical assignment of the two oxazololactams **2a**, **2b** and oxazolidines **4** (entries 6, 7) was inferred by NMR spectroscopy (NOE experiments, Fig. 1).[10]

The ratios **2**/**3** (entries 1–3) suggest that the mechanism of formation of oxazololactams **2** involves the formation of an intermediate 3,4-dihydro-2-pyridone **3**.

Nevertheless, a relatively high proportion of oxazolactams **2** was detected when the reaction was quenched just after addition of acryloyl chloride (entry 3). This result suggests that a second mechanistic pathway is involved in the formation of oxazolactams **2**. This might be a fast internal trapping of an iminium intermediate formed after the 1,4-addition of enaminoester **1** to acryloyl derivatives. Noteworthy, β-enaminoketone **1** (R^1 = Me, R^2 = Me) is transformed after 3 h nearly quantitatively into two bicyclolactam diastereomers **2** (entry 5).[11]

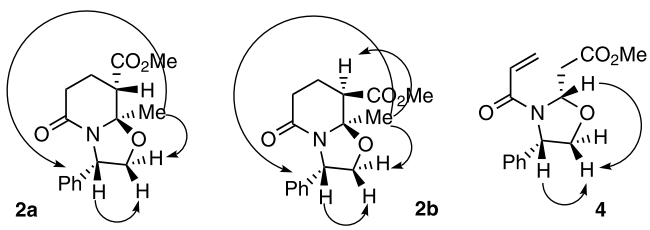
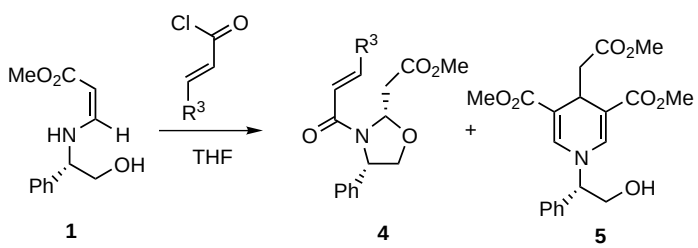


Figure 1.



Scheme 2.

In summary, we have found an easy and efficient route to oxazolactams **2** in two steps from (*S*)-phenylglycinol. We are currently investigating the stereochemical aspect of this bis-cyclization in order to enhance the stereoselectivity of the process. Moreover, we have shown that the regioselectivity of the reaction (i.e. aza-annulation versus *N*-acylation) is strongly dependent on the substitution of the β-carbonyl position.

The use of oxazolactams **2** as chiral templates in asymmetric synthesis should allow a rapid access to polysubstituted chiral non racemic piperidines. In this context, our first objective is the preparation of enantiopure derivatives of nipecotinic acid.[12]

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10. Spectral analysis of the major diastereomer **2a**: ^{1}H NMR (250 MHz, $CDCl_3$): 1.47 (s, 3H), 2.12–2.24 (m, 2H), 2.49 (m, 1H), 2.65 (m, 1H), 2.76 (dd, $J=8.5$ and 9 Hz, 1H), 3.78 (s, 3H), 3.99 (dd, $J=7.8$ and 9.2 Hz), 4.55 (dd, $J=8.2$ and 9 Hz), 5.24 (t, $J=8$ Hz), 7.19–7.36 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 20.3, 20.5, 29.8, 50.1, 52.4, 58.7, 70.2, 93.9, 125.5, 127.4, 128.7, 139.2, 168.4, 171.4. Mp: 115°C. $[\alpha]_D^{20}$: +137 (*c* 0.68, $CHCl_3$). Anal. calcd for $C_{15}H_{19}NO_4$; C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.78; N, 4.77%. IR ($CHCl_3$) 1734, 1655, 1395, 1218, 1165 cm^{-1}.
11. The two diastereomers **2** ($R^2=Me$) have the same absolute configurations as bicyclolactams **2a** and **2b**.
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