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A novel synthesis of amino-1,2-oxazinones as a versatile synthon for β-amino acid derivatives

Okiko Miyata, Megumi Namba, Masafumi Ueda and Takeaki Naito*
Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan.
E-mail: taknaito@kobepharma-u.ac.jp; Fax: +81-78-441-7556; Tel: +81-78-441-7554

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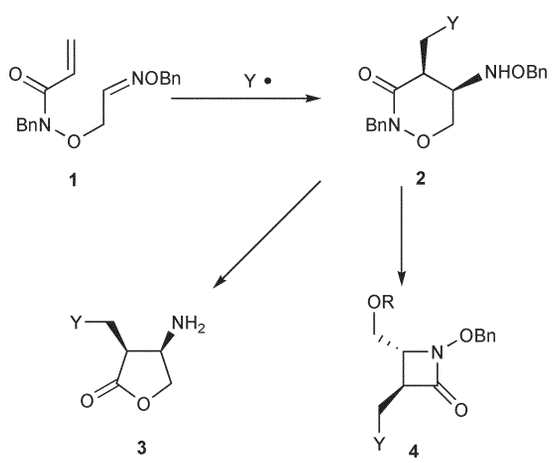
The radical addition–cyclisation of α,β-unsaturated hydroxamates containing an oxime ether provides a novel method for the stereoselective synthesis of amino-1,2-oxazinones. Its synthetic utility is demonstrated by a stereoselective synthesis of β-amino acid derivatives, such as α-alkyl-β-amino-γ-lactone and α,β-disubstituted β-lactam.

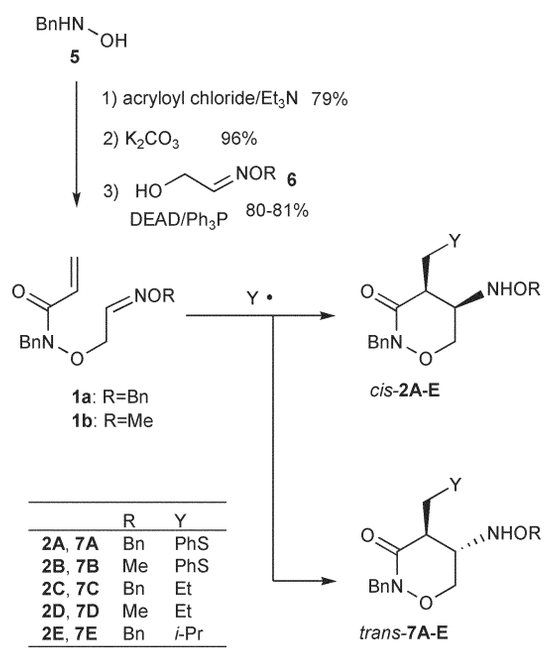
The development of new and improved methods for the synthesis of β-amino acids[1] is of considerable current interest, because β-amino acids possess unique biological activities as key components of bioactive materials. For this purpose, a number of synthetic methods for β-amino acids have been developed.[1] In this paper, we report a practical synthesis of β-amino acid derivatives **3** and **4** *via* amino-1,2-oxazinones **2** as key and common intermediates. The 1,2-oxazinones **2** are readily prepared by the radical addition–cyclisation of α,β-unsaturated hydroxamates **1** containing an oxime ether (Scheme 1).



Scheme 1

The main application of 1,2-oxazine derivatives has been as common intermediates in divergent syntheses.[2] There have been two general methods for synthesising 1,2-oxazines derivatives.[3] One is [4 + 2]-cycloaddition[4] of nitrosoalkenes with alkenes and the other is the recently-developed ring-closing metathesis[5] of dienes tethered by hydroxylamines. The 1,2-oxazines, prepared by these methods, were converted into amino sugars, piperidine and indolizidine alkaloids, proline analogs, and precursors to macrolides *via* reductive N–O bond cleavage.[6] However, both [4 + 2]-cycloaddition and the ring-closing metathesis do not allow the short synthesis of 4-amino-1,2-oxazin-3-ones[7] which are indispensable in the preparation of β-amino acids. Therefore, these methods are not suitable for the synthesis of β-amino acids using 1,2-oxazines as a precursor. The main feature of our method is that we can synthesise β-amino acid derivatives by ring opening of amino-1,2-oxazinones which are prepared readily by radical addition–cyclisation employing sulfanyl and carbon radicals.[8]

We first investigated the sulfanyl radical addition–cyclisation of α,β-unsaturated hydroxamates **1** containing an oxime ether functionality. The hydroxamates **1** were prepared by acylation of *N*-benzylhydroxyamine **5**, partial hydrolysis of the resulting diacylated compound and Mitsunobu reaction with the hydroxyl oxime ether **6**. (Scheme 2, Table 1). Sulfanyl radical addition–cyclisation of hydroxamate **1a** having *O*-benzyloxime ether in the presence of thiophenol (1 eq.) and AIBN (0.5 eq.) proceeded smoothly at 80 °C to give a *ca.* 3 : 1 separable mixture of the amino-1,2-oxazinones **2A** and **7A** in good yield (entry 1). Similarly, the hydroxamate **1b** with *O*-methyloxime ether gave *cis*-**2B** and *trans*-**7B** in 76% combined yield (entry 2).



	R	Y
2A, **7A**	Bn	PhS
2B, **7B**	Me	PhS
2C, **7C**	Bn	Et
2D, **7D**	Me	Et
2E, **7E**	Bn	*i*-Pr

Scheme 2

We next examined the ethyl radical addition–cyclisation of **1a**,**b**. Triethylborane was used as an ethyl radical source. When hydroxamate **1a** was treated with triethylborane (5 eq.) at room temperature, a 3.5 : 1 mixture of *cis*-**2C** and *trans*-**5C** was obtained in 71% combined yield (entry 3). The ethyl radical addition–cyclisation of **1a** proceeded smoothly even at −78 °C to give *cis*-**2C** with high stereoselectivity (entry 5).

When hydroxamate **1b** was used as a substrate, the cyclic hydroxamates **2D** and **7D** were also obtained in favour of the former (entry 8). Finally, we examined isopropyl radical addition–cyclisation of **1a** which was carried out in the presence of triethylborane and isopropyl iodide. The reaction using triethylborane (5 eq.) and isopropyl iodide (5 eq.) at room temperature gave the isopropylated products **2E** and **7E** in combined 70% yield in addition to ethylated oxazines **2C** and **7C** (12%) as minor products (entry 9). In order to decrease the formation of the side products **2C** and **7C**, we employed 15

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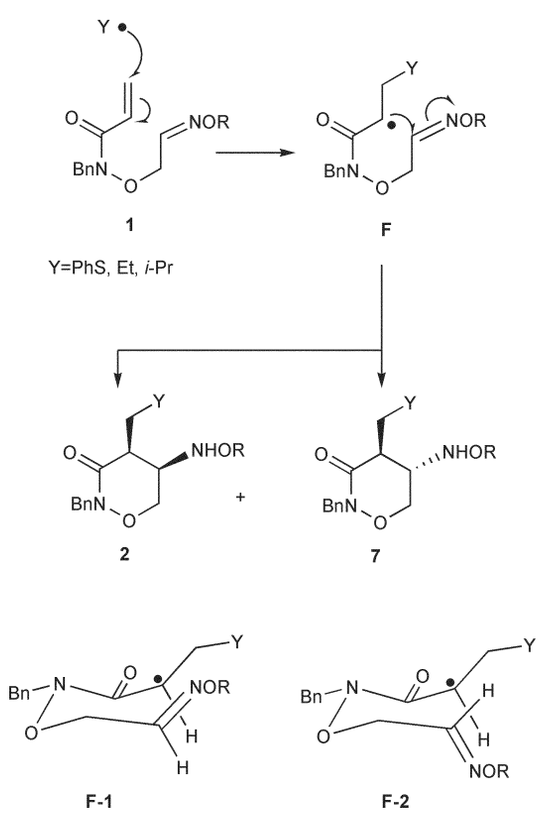
Table 1 Radical addition–cyclisation of hydroxamates

Entry	Substrate	R	Y	Conditions	Solvent	*T* (°C)	Yield (%)	*cis*-**2** : *trans*-**7**
1	**1a**	Bn	PhS	PhSH (1 eq.); AIBN (0.5 eq.)	benzene	80	80	71 : 29
2	**1b**	Me	PhS	PhSH (1 eq.); AIBN (0.5 eq.)	benzene	80	76	71 : 29
3	**1a**	Bn	Et	Et_3B (5 eq.)	toluene	rt	71	78 : 22
4	**1a**	Bn	Et	Et_3B (5 eq.)	toluene	0	84	80 : 20
5	**1a**	Bn	Et	Et_3B (5 eq.)	toluene	−78	79	91 : 9
6	**1b**	Me	Et	Et_3B (5 eq.)	toluene	rt	71	68 : 32
7	**1b**	Me	Et	Et_3B (5 eq.)	toluene	0	81	79 : 21
8	**1b**	Me	Et	Et_3B (5 eq.)	toluene	−78	72	89 : 11
9[a]	**1a**	Bn	i-Pr	Et_3B (5 eq.); i-PrI (5 eq.)	toluene	rt	70	77 : 23
10[a]	**1a**	Bn	i-Pr	Et_3B (3 eq.); i-PrI (15 eq.)	toluene	rt	66	76 : 24
11[a]	**1a**	Bn	i-Pr	Et_3B (3 eq.); i-PrI (15 eq.)	toluene	0	64	78 : 22
12[a]	**1a**	Bn	i-Pr	Et_3B (3 eq.); i-PrI (15 eq.)	toluene	−78	65	88 : 12

[a] The ethylated products **2C** and **7C** were also obtained; 12% (entry 9), 6% (entry 10), 4% (entry 11), 9% (entry 12).

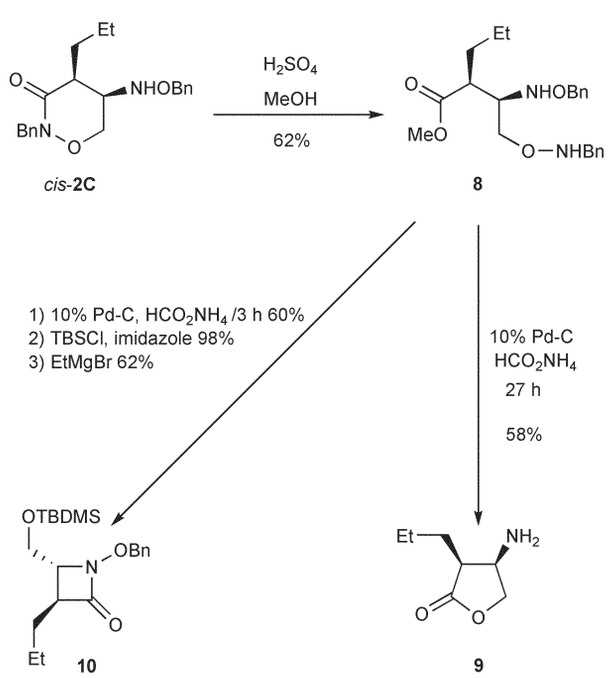
equivalents of isopropyl iodide and 3 equivalents of triethylborane and obtained only 6% yield of undesired products **2C** and **7C** (entry 10). When the reaction was carried out at −78 °C, the stereoselectivity was further improved (entry 12).

The radical addition–cyclisation can be summarised as follows. Addition of sulfanyl and alkyl radicals to the alkene and subsequent cyclisation onto the oxime ether proceeded regioselectively to give the substituted 1,2-oxazinones with an alkoxyamino group. Therefore, the cyclisation of intermediate **F** takes place exclusively in a 6-*exo*-*trig* manner. The fact that *cis*-1,2-oxazinones **2A**–**E** were formed in preference to the *trans*-isomer **7A**–**E** and a high degree of stereocontrol was observed in the alkyl radical reaction at −78 °C would be explained as follows. According to Beckwith's hypothesis,[9] the radical **F-1** leading to the formation of *cis*-**2** would be more stable than the radical **F-2**, the intermediate for *trans*-**7**, due to the effects of orbital symmetry in **F-1** (Scheme 3). Generally the cyclisation of the 6-heptenyl radical is known to proceed about 40 times slower than that of the corresponding hexenyl radical.[10] It is important to note that the radical addition–cyclisation of hydroxamate **1** having an oxime ether proceeded smoothly to form the six-membered ring in good yield.



Scheme 3

We next investigated the conversion of *cis*-amino-1,2-oxazinone **2C** into unnatural β-amino acid derivatives (Scheme 4). β-Amino acids are emerging as an interesting class of compounds for medicinal chemists.[1] The most well known and medicinally important class of nonpeptidic β-amino acids are found in β-lactams. We chose β-lactam **10** and β-amino-γ-lactone **9** as synthetic targets. Methanolysis of *cis*-**2C** in the presence of sulfuric acid gave acyclic amino ester **8** in moderate yield. On the other hand, the attempted reductive cleavage of N–O bond in amino-1,2-oxazine **2C** by hydrogenolysis (10% Pd–C/HCO_2NH_4, 20% $Pd(OH)_2$–C/H_2, Na–Hg) was unsuccessful. The reductive cleavage of the N–O bond of **8** with 10% Pd–C proceeded in the presence of ammonium formate for 27 h to give the desired *cis*-β-amino-α-*n*-propyl-γ-lactone **9**.[11] One of the *cis*-β-amino-α-alkyl-γ-lactones is a synthetic precursor of (2*S*,3*S*,4*E*,6*E*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda)[12] which is a component of nodularine[13] and microcystin[11] produced by some genera of cyanobacteria.



Scheme 4

Finally, we converted the amino ester **8** into β-lactam **10**. β-Lactams with a β-hydroxylmethyl group are synthons for various antibiotics, β-lactamase inhibitors and human leukocyte elastase inhibitors including β-lactams.[1,14] The treatment of **8** with 10% Pd–C in the presence of ammonium formate for 3 h followed by silylation of the resulting hydroxyl ester gave the

silyloxy ester which was subjected to cyclisation using the Breckpot reaction[15] to give the desired β-lactam **10**.

In conclusion, we have developed for the first time radical addition–cyclisation of α,β-unsaturated hydroxamates containing an oxime ether for the synthesis of amino-1,2-oxazinones. Furthermore, our novel method would provide a practical synthesis of unnatural β-amino acid derivatives that could be subjected to biological evaluation.

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