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Syntheses of Heterocyclic Amino Acid Derivatives *via* Nitrile Oxide Cycloadditions with β,γ-Unsaturated-α-Amino Acid Compounds

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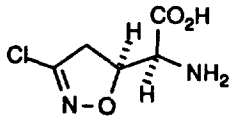
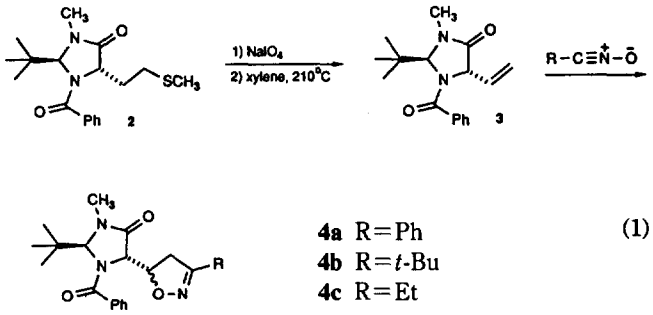
A novel antitumor antibiotic, (α*S*, 5*S*)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (**1**, AT-125, Acivicin), isolated from fermentation broths of *Streptomyces sviceus*[1], displayed significant activity against a number of tumors in experimental animals[2]. The biological activity of this unusal amino acid and its novel structure have elicited our interest in the synthesis of the related amino acid derivatives possessing 2-isoxazoline rings. We report here the preliminary results of our synthetic efforts.



1 : AT-125(Acivicin)

To synthesize our desired products by cycloadditive approach, we needed to prepare the β,γ-unsaturated-α-amino acid derivatives as chial dipolarophiles. The β,γ-unsaturated-α-amino acids are a class of compounds that possess antibiotic and enzyme inhibitory activity[3]. (2*S*, 5*S*)-Imidazolidinone **2**[4] was prepared from L-methionine in 5 steps (42% overall yield) by a modification of the Seebach's method[5]. Oxidation of **2** by $NaIO_4$ (96%), followed by thermal elimlination of the resulting sulfoxide (88%) provided the desired β,γ-unsaturated-α-amino acid derivative **3**. Dipolar cycloadditions of various nitrile oxides (R=Ph, *t*-Bu, Et) with **3** afforded the corresponding cycloadducts **4a-c** (Eq. 1).

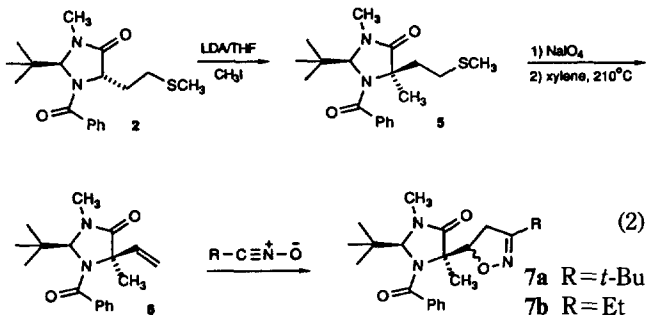


4a R=Ph
4b R=*t*-Bu
4c R=Et (1)

In the case of benzonitrile oxide cycloaddition, a mixture of two diastereomers was obtained. The major diastereomer (**4am**) and minor one of the above cycloaddition were isolated in 56% and 2% yield, respectively. The major cycloadducts of 2,2-dimethylpropionitrile oxide and propionitrile oxide were isolated in 63% and 50% yield, respectively.

These amino acid derivatives possessing 2-isoxazoline rings underwent the pyramidal nitrogen inversion[6]. This dynamic equilibrium was detected by recording ^{1}H-NMR spectra of **4am** at room temperature and 70℃. The ^{1}H-NMR spectrum taken at 70℃ showed the coalescence phenomenon due to the rapid equilibrium between two invertomers[7]. The absolute stereochemistry of the newly generated stereogenic center in the major products of **4a-c** was tentatively assigned as *R* by examining molecular models of **3** and **4a-c**.

L-Vinylalanine derivative **6** was prepared from **2** in 3 steps. Stereoselective methylation[8] of **2** provided **5** in 70% yield. Sequential $NaIO_4$ oxidation (95%) and sulfoxide elimination (93%) afforded the chiral dipolarophile **6**. 2,2-Dimethylpropionitrile oxide and propionitrile oxide cycloadditions with **6** gave the diastereomeric mixtures (60 : 40 in both cases) of cycloadducts **7a-b** in 72% and 52% yield, respectively (Eq. 2).



7a R=*t*-Bu
7b R=Et (2)

The heterocyclic amino acid derivatives **4a-c** and **7a-b** have been easily prepared by nitrile oxide cycloadditions and these compounds have some antiviral activity[9]. Thus, the asymmetric cycloadditive approach[10] to β,γ-unsaturated α-amino acids may provide a general entry for biofunctional heterocyclic amino acid derivatives.

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