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# Synthesis of new α-amino- acids containing the isoxazole moiety

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**Abstract**

Methodology for preparing a series of novel α-amino-acids and their derivatives containing an isoxazole ring as a substituent is presented. The synthesis starts from a readily available L-serine derivative from which, depending on the synthetic strategy, it is possible to obtain isoxazol-3-yl or isoxazol-5-yl amino-acid precursors.



*Keywords: Amino acids and derivatives, Cycloadditions, Isoxazoles*

Demand for "unnatural" amino-acids is increasing in connection with the design and synthesis of drug candidates and for use as chiral starting materials for a variety of synthetic applications. In consequence, one of the main objectives of modern organic chemistry [1] is the development of synthetic methodologies for the preparation of new α-amino-acids in enantiomerically pure form, through both asymmetric synthesis [2] and modification of natural amino-acids [3].

Recently, ibotenic acid, a constituent of the fly agaric mushroom, *Amanita muscaria*, was regarded as a conformationally restricted analogue of glutamic acid [4]. Following our interest in the synthesis of constrained heterocycle-containing amino acids [5], we decided to prepare a series of unnatural α-amino acids containing heterocyclic moieties as possible analogues of natural amino-acids.

We now report the syntheses of new α-amino-acid derivatives containing isoxazol-3-yl or isoxazol-5-yl substituents.

Our strategy is based on the possibility of building the amino-acid functionality from L-serine through the corresponding aldehyde **1**, well known as Garner's aldehyde. This seemed to be suitable as the chiral starting material for both isomeric isoxazole derivatives. The aldehyde **1** was converted through a modified Corey-Fuchs procedure into the dibromo-alkene **2** which was isolated in a 87% yield. This intermediate was then transformed (71% yield) into (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine **3** by reaction with 2 equiv. of BuLi at -78°C [6] (Scheme 1). The alkyne **3** was reacted with a nitrile oxide

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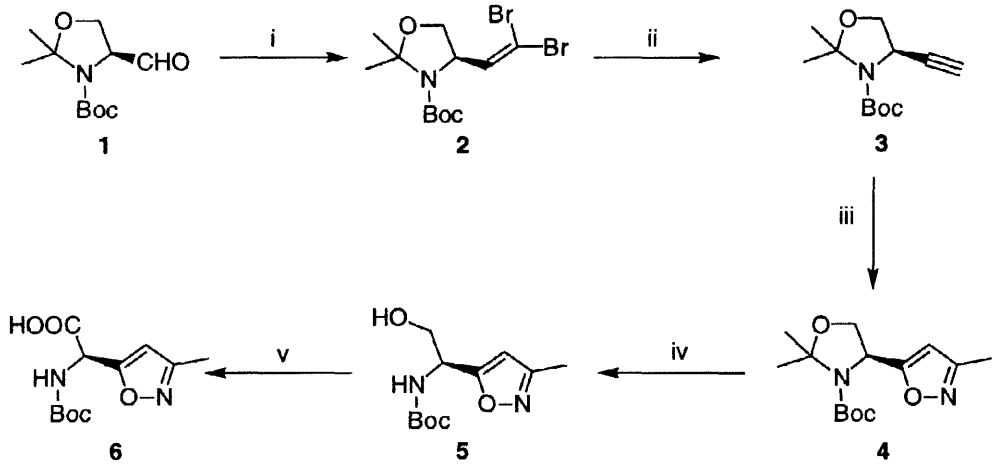
generated *in situ* from nitroethane precursor [7] to afford (*S*)-3-methyl-5-(2,2-dimethyl-3-*tert*-butoxycarbonyloxazolidin-4-yl)isoxazole **4** in good yield (50%).

Scheme 1




i) $PPh_3$, $CBr_4$, $Et_3N$, $CH_2Cl_2$, -60°C. ii) 2BuLi, THF, -78°C ↔ -15°C. iii) PhNCO, $EtNO_2$, $Et_3N$, benzene. iv) PTSA, MeOH, rt. v) Jones' reagent, 0°C.

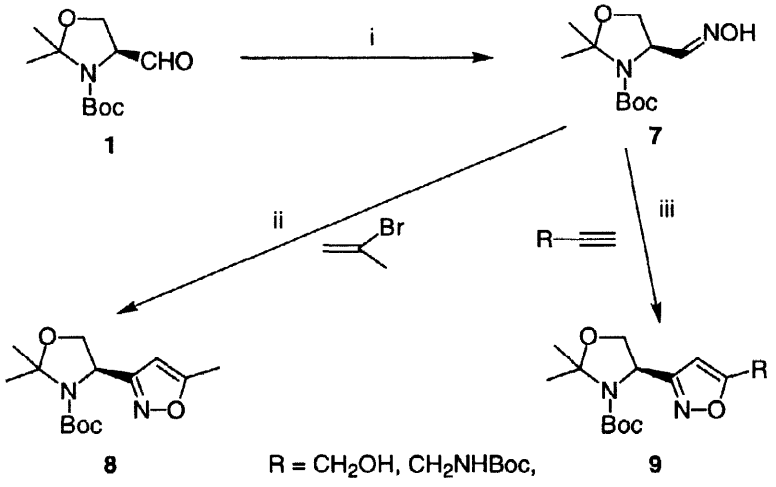
In order to obtain the target compound **6**, cleavage of the oxazolidine ring must be performed without affecting the *N*-Boc protection: this reaction was tested with various reagents. The best reaction conditions were found using *p*-toluenesulfonic acid (PTSA) in dry methanol at room temperature and even under these conditions the reaction occurs with low conversion after 24 h (25%). However, the unreacted oxazolidine **4** can be recovered almost quantitatively and recycled. Subsequent oxidation using Jones's conditions afforded (*R*)-2-*N*-*tert*-butoxycarbonylamino-2-(3-methylisoxazol-5-yl) acetic acid in 93% yield.

Molecules with rigid frameworks containing α-amino-acid moieties are attractive synthetic targets since they can be used as conformationally restricted modules in the design of new peptidomimetic structures with biological activity. In this context, amino alcohols of type **5** or derivatives such as **4** are of interest as unnatural (not coded) amino-acid precursors, taking into account the presence of the isoxazole ring, which allows the possibility of introducing other functionalities in the basic structure of the molecule. However, this procedure suffers from the limitation of the poor availability of nitro compounds.

Therefore we have undertaken the synthesis of amino-acid derivatives containing an isoxazol-3-yl substituent utilizing a more straightforward method. Thus, the preparation of compounds **8** and **9** was conducted according to Scheme 2 starting from the same intermediate **1**. The aldehyde **1** was treated with hydroxylamine in pyridine to give the oxime **7** in quantitative yield; this was converted to the chloro-oxime by treatment with *N*-chlorosuccinimide (NCS). Generation of the corresponding nitrile oxide with Et3N and subsequent reaction with 2-bromopropene in the presence of excess Et3N afforded (*S*)-5-methyl-3-(2,2-dimethyl-3-*tert*-butoxycarbonyloxazolidin-4-yl)isoxazole **8** in good yields (58%). As 2-bromopropene can be regarded as a synthetic equivalent of propyne, we tested the method using acetylenic derivatives so extending the procedure to the synthesis of more

complex amino-acid precursors. The use of functionalized acetylenes, such as trimethylsilylacetylene, *N-tert*-butoxycarbonyl propargylamine, propargyl alcohol and 3,3-diethoxy-1-propyne led to the desired products **9** in good yields (up to 90%) and high regioselectivity using very mild conditions.

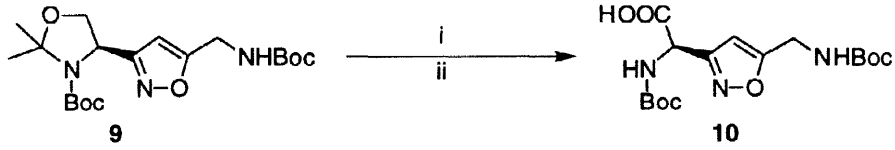
Scheme 2




i) $NH_2OH$, pyridine, rt. ii) NCS, $(CH_2Cl)_2$, $3Et_3N$, -5°C. iii) NCS, $(CH_2Cl)_2$, $3Et_3N$, -5°C.

Although we had previously succeeded in the cleavage of the oxazolidine ring, a sample of **9** (R = $CH_2NHBoc$) was treated with PTSA in dry methanol at room temperature to give the amino-alcohol (22%) and then oxidized using Jones's conditions to furnish (55%) (*R*)-2-*N-tert*-butoxycarbonylamino-2-(5-*N-tert*-butoxycarbonylaminomethylisoxazol-3-yl) acetic acid **10** (Scheme 3).

Scheme 3

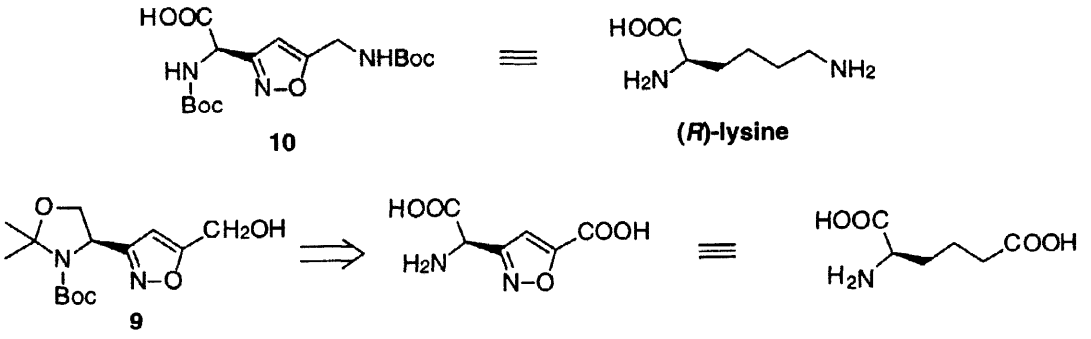



i) PTSA, MeOH, rt. ii) Jones reagent, 0°C.

In summary, a methodology for the preparation of structurally different new optically active α-amino-acids [8] has been developed using a chiral starting material: it is worth pointing out that compound **10** has to be compared to (*R*)-lysine while compounds **9** [R = $CH_2OH$, $CH(OEt)_2$] can be regarded as precursors of (*R*)-glutamic acid homologues (Scheme 4).

Future efforts will focus on further refinements of the methodology on the preparation of amino acids having different heterocyclic structures to study their potential application in the design of peptidomimetics with defined and predictable conformations.

Scheme 4

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## References and notes

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[8] All new compounds were fully characterized by $^{1}H$ and $^{13}C$ NMR analysis and gave satisfactory elemental analysis. Although the synthetic sequences adopted were known to be stereospecific, the amino alcohols recovered were found to be enantiomerically pure ($^{1}H$ NMR analysis, 300 MHz in the presence of $Eufod_3$). Compound **10** was found to be >95% e.e. by chiral GC (Chirasil-L-Val column), after converting to the corresponding methyl ester.