

Promising system to reduce epimerization: stereoselective synthesis of α -amino compounds via cyclic α -amido radicals

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Abstract

Development of new system which could minimize the epimerization of the α -center at the α -amido radical stage is presented. To study the behaviour of this system, stereoselective synthesis of α -amino compounds via generating α -amido radicals of this system was attempted.

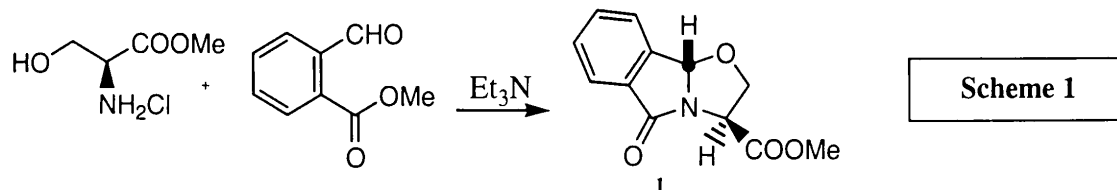
The system was prepared by condensation of *L*-serin methyl ester with methyl phthalaldehyde in the presence of triethyl amine. The desired system (tricyclic lactam) was formed in 70% yield and only as the *exo* isomer. This is the thermodynamically more stable "bowl-like" conformation. The α -alkylated derivative of this tricyclic lactam was prepared via enolate alkylation. The α -alkylated compound was formed in 30% yield and only as the *endo* isomer. This *endo* alkylation could be the result of the attack of alkyl group preferentially from concave face of the "bowl-like" tricyclic lactam. Then methyl esters of tricyclic lactams were directly converted into selenoesters, the radical precursors and radical reactions were carried out via generating α -amido radicals under standard radical reaction conditions. The radical reductions α -unsubstituted system with Bu_3SnH and Bu_3SnD gave reduced and deuterated products respectively in good yield with higher selectivity favouring *exo*-isomer while similar reactions with α -substituted system produced reduced and deuterated products also with higher selectivity but favouring *endo*-isomer. These higher selectivities for the radical reactions could be attributed to the stereoelectronic effect of novel tricyclic system used. The difference of the selectivities between α -substituted and α -unsubstituted stage could be rationalized by considering pyramidalization of the tertiary radical center in the transition state of the α -substituted stage.

Introduction

In the past most of the focus of the synthesis of biologically relevant compounds has been done using of ionic procedure¹. Since recently, chemists have paid much attention on the use of radical procedure for the synthesis of biologically important compounds, as over last thirty-five years a detailed picture of the reactivity, selectivity and the stability of the many types of organic radicals has emerged. It has been well realized that the high degree of control of regio- and stereochemistry could be achieved in the radical reaction process as in the case of ionic process and the radical reactions can be accomplished with good chemical yields. Moreover the reaction conditions and reagents used in radical procedure are milder, convenient and more compatible with the functional groups present in the molecule and with the stability of the compounds involved.

α -Amido radicals are interesting reactive intermediates which have been used in the synthesis of *N*-containing biologically important compounds such as amino acids, aminoalcohols and alkaloids etc.². The major problem faced in these syntheses is racemization of the product due to the epimerization of the α -center at the α -amido radical stage. Our objective was to find a new system which can involve in the synthesis of *N*-containing compounds via α -amido radicals with avoiding epimerization at the α -center. Consequently we intended to synthesis α -amino compounds from amino acids with high stereoselectivity.

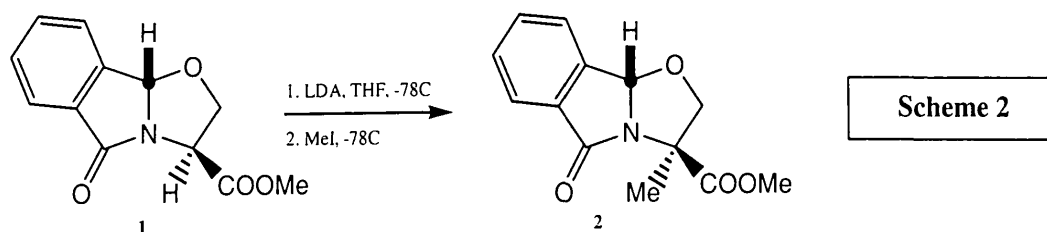
Experimental results



Scheme 1

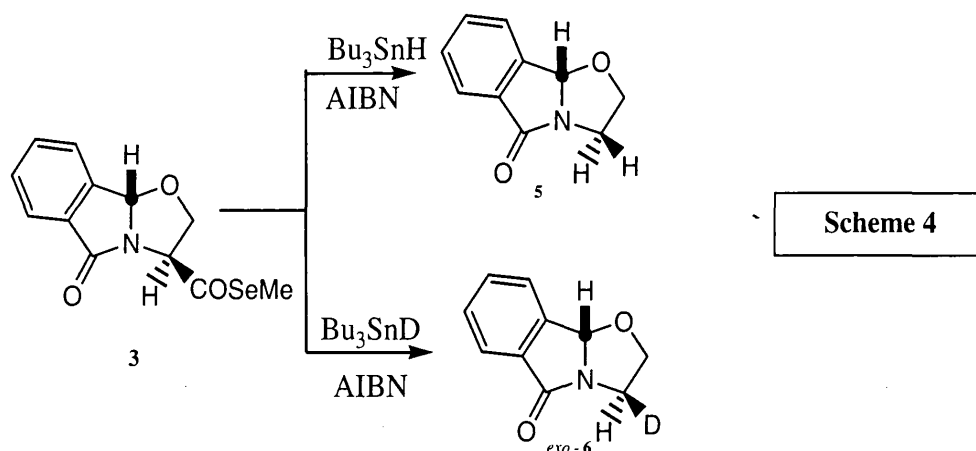
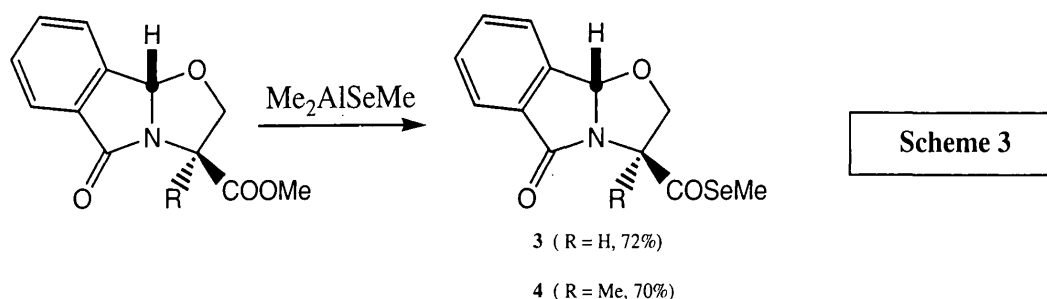
Easily available amino acids were used as starting compounds for the synthesis. The intended system was easily prepared by condensation *L*-serin methyl ester with methyl phthalaldehyde in the presence of

triethyl amine under Dean-Stark condition³ (Scheme 1). The desired tricyclic lactam (**1**) was formed in 70% yield and only as the *exo*-isomer.



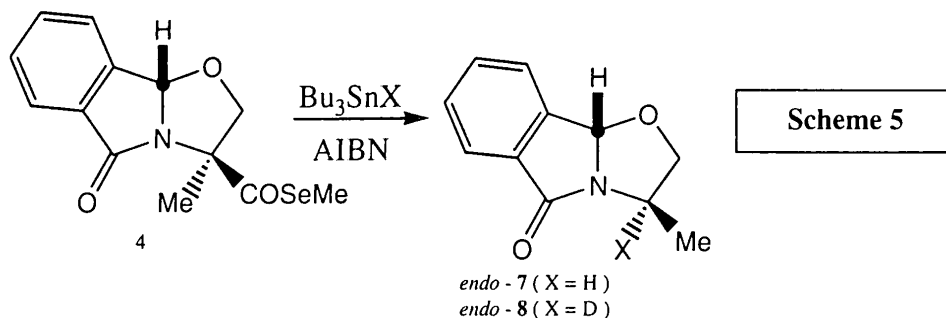
α -Methylated derivative of tricyclic system was prepared via generation of enolate with LDA followed by treating with methyl iodide at -78°C (Scheme 2). This reaction was totally selective and only *endo* methylated product (**2**) was formed in 30% yield.

Then radical reactions were carried out with these tricyclic systems. Here, we used selenoester procedure⁴ to generate α -amido radicals. The corresponding selenoesters were prepared by direct conversion of methyl esters into selenoesters as in the scheme 3.



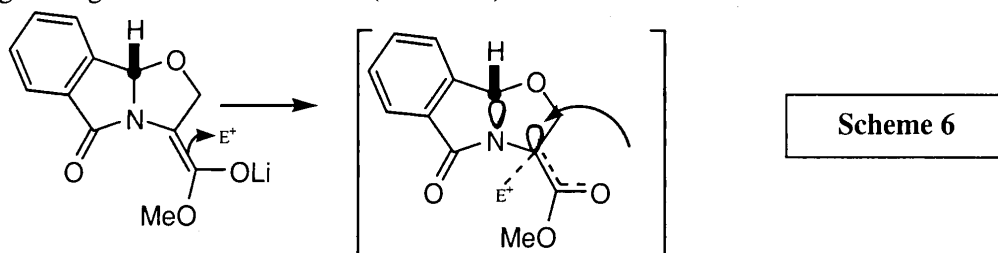
Radical reduction of the selenoester **3** with Bu_3SnH gave reduced product (**5**) in 65% yield while the reduction with Bu_3SnD produced deuterated product (**6**) in 75% yield and as a 58:42 mixture of isomer with favouring *exo* isomer (Scheme 4).

Radical reduction of α -methylated tricyclic lactam (**4**) with Bu_3SnH and Bu_3SnD gave reduced product (**7**) and deuterated product (**8**) as 79:21 and 81:19 mixtures of isomers respectively with favouring *endo* isomer (Scheme 5).

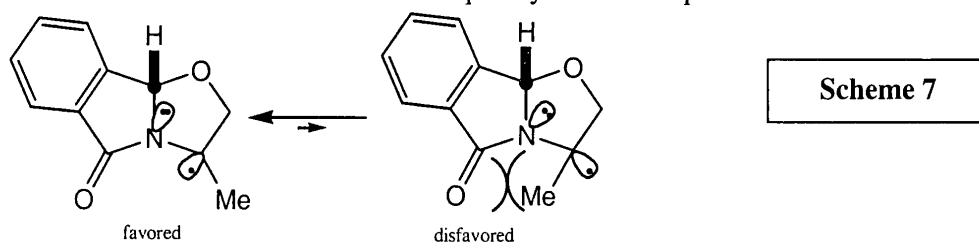


Results and discussion

The condensation reaction between *L*-serin methylester and methylphthalaldehyde was totally selective and only the *exo*-tricyclic lactam (**1**) was formed. According to the literature³, the *exo* product adopt a bowl-like shape with the bulky substituent lying on the outer face. This the thermodynamically more stable conformation. The *endo* alkylation of tricyclic system (**1**) could be rationalized with considering many factors of the system. One possible explanation is bowl-like conformation of the tricyclic lactam could lead the alkylation from concave face (*endo*). Other possible explanation could be given by considering Cieplak effect⁵. As proposed by Cieplak, this effect occurs during σ bond forming reaction between electrophile and electro negative carbon and involves stabilization of the developing σ^* orbitals by a neighboring electron - rich σ bond (Scheme 6).



Some selectivity for the radical reactions lead to synthesis of α -amino compounds via α -amido radical has been achieved with our tricyclic system derived from amino acid. Stereoelectronic effect of the system might play the role for these stereochemical outcomes. The difference between *exo* and *endo* selectivities in the reduction process of α -unsubstituted and α -substituted tricyclic lactams could be the result from partial pyramidalization of the tertiary radical center in the transition state of α -substituted tricyclic lactam as shown in scheme 7. Consequently more *endo* product is formed in α -substituted stage.



Conclusion

The tricyclic system derived from *L*-serin is a good alternative to avoid epimerization of the α -center during α -amido radical stage. This radical method could be applied for the synthesis of wide range of *N*-containing biologically important compounds using available amino acids.

References

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