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Synthesis and Utilization of a Novel Glycine Derived Chiral Precursor, Based on a Recyclable L-Prolinol Auxiliary, for the Enantioselective Preparation of α- Amino acids and their N-methyl Derivatives

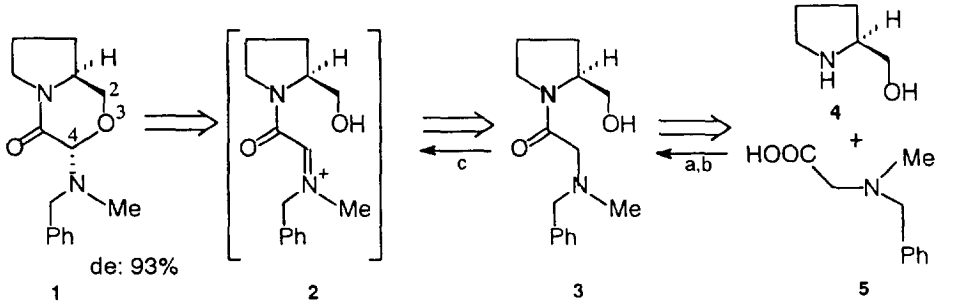
Ganesh Pandey*, P. Yella Reddy and Parthasarathi Das

Division of Organic Chemistry Synthesis
National Chemical Laboratory
Pune-411 008 , INDIA
FAX : 0212-335153

Abstract: α-Amino Acids and their N-Methyl derivatives are synthesised in fairly high optically purity employing a new glycine derived template based on a recyclable L-Prolinol chiral auxiliary.

Due to the central role played by α-amino acids in chemistry and biology, the development of versatile and new methodology for the synthesis of natural and non-natural amino acids in optically active form has emerged as an important and challenging synthetic endeavor for organic chemists.[1]. Similarly, the preparation of N-methyl-L-amino acids has also been attracting considerable attention recently[2] owing to their use as building blocks for many peptides and depsipeptides antibiotics[3]. Among the various methodologies reported for α-amino acid synthesis, alkylation of several glycine derived chiral templates has served as an important approach[4]. However, the problem associated with the cleavage of the auxiliary ring system, recovery of chiral information and the difficulty in extending these strategies for the synthesis of N-methyl amino acids led us to explore an alternative strategy. In this context, we have designed substrate **1** as an ideal precursor for the synthesis of various α-amino acids as well as their N-methyl derivatives. The designing of **1** was done by considering its unique structural features; a reactive α-amino ether moiety highly suitable for stereoselective nucleophilic alkylation reaction, easy hydrolysability of the resultant amide (**6**)

Scheme-I



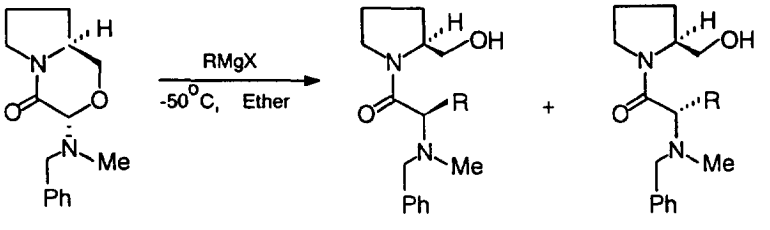
a) *N*-Hydroxy succinimide, DCC, DMAP, DCM (80%) b) DMAP, THF (68%) c) hν, DCN, MV^{++}, CH_3CN, 8h (73%)

to procure corresponding α-amino acids and to recover prolinol chiral auxiliary, and the opportunity of

manipulating amine functionality to incorporate different substituents. We wish to disclose our preliminary success in this communication.

The synthesis of **1** was envisioned through an intramolecular photosensitised electron transfer (PET) cyclization strategy of an *in situ* generated iminium cation, an approach well established from our group[5], as shown retrosynthetically in **Scheme - 1.** The details of the synthetic sequences leading to **1** is also depicted in the same scheme. The photocyclisaton of **3** was essentially achieved by following the standard PET irradiation procedure as reported by us earlier[5]. Photolysis of the mixtures of **3** (2 g, 7.69 mmole), 1,4-dicyanonaphthalene (DCN) (0.32 g, 1.79 mmole), and methyl viologen (MV^{++}) (0.08 g, 0.311 mmole) in dry CH_3CN for 8 h followed by usual workup and chromatographic purification gave **1** (73%yield) as a mixture of diastereomers (de = 93%). The formation of **1** as the only product in this photoreaction may be explained by considering the regioselective *in situ* generation of iminium cation (**2**), by selective deprotonation followed by electron loss from the more acidic methylene group of the glycine moiety, from the PET generated amine radical cation. The primary deprotonation site, which determines the iminium cation regioselectivity[5], from the unsymmetrically substituted *tert*-amine radical cations have been shown[5,6] to depend mainly upon the kinetic acidity of the - C-H group α- to the nitrogen atom. The diastereomeric ratio of **1** (13.3:1) was established by

Scheme-II



1 **6a** (major) **6b** (minor)

Table-I

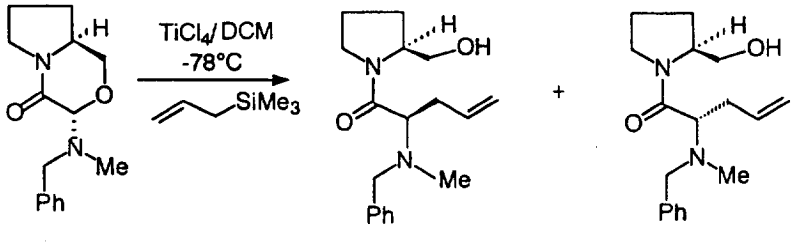
Entry	R	6a/6b[a]	Yield (%)[b]	Configuration of α-amino acids(esters)[c]
i	CH_2Ph	5.1:1	76	(S)
ii	Me	3.6:1	72	(S)
iii	$CH(Me)_2$	3.2:1	68	(S)
iv	Ph	2.8:1	70	(S)

a: Diastereomeric ratio measured by the area ratio of N-Me peaks from ^1H NMR and confirmed by HPLC. b: Isolated yields, c:Absolute configuration with respect to authentic samples.

HPLC analysis. The stereochemistry of the major isomer, purified by careful chromatography[7], was determined by comparing the relatively high field ^{13}C NMR and ^{1}H NMR chemical shifts values for C-4 and H-4, respectively, with minor isomer[8] which was further confirmed by no NOE between H-4 and H-1. The preference for the formation of major diastereomer (**1**) may be interpreted by assuming the back side attack of OH moiety of prolinol to a preferred energy minimised transition state encompassing iminium cation where amine group remains at the equatorial position in order to produce less energetic *trans* bicyclic ring system.

The high reactivity profile of the α-amino ether chiral center (masked iminium cation equivalent) of **1** gave us an opportunity to exploit it for stereoselective nucleophilic alkylation reactions[9]. Nucleophilic ring opening of **1** (**Scheme-II**), achieved by the addition of separately prepared Grignard reagent (4 equivalent) to a stirred solution of **1** (0.5 g, 1.93 mmole) in dry ether at -50^{0} C for 4 h and allowing the stirring to continue for another 20 h, followed by usual workup and purification gave corresponding amides (**6**) in very good yields (70-76%). The details of the ring opened products with the diastereomeric ratios are listed in the **Table-I**. These products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectral data. The diastereomeric ratios of **6a/6b** were determined by measuring the area ratio of N-methyl peaks in ^{1}H NMR spectra and were further confirmed by analyzing them by HPLC. The hydrolysis of **6**, either boiling with 6 N HCl (8-10 h.) or in methanol saturated with HCl in sealed tube (16 h) followed by usual workup, basification and purification, gave corresponding α-amino acids or ester[10] (60 - 70%), respectively, and L-prolinol (96%). The absolute configuration of the α-amino acids or esters thus obtained were determined by comparing their optical rotations with the authentic samples prepared independently from the commercially available α-amino acids. Debenzylation by hydrogenation over 10% Pd-charcoal gave corresponding N-methyl α-amino acids.

Scheme-III



1 **7a** **7b**

Free amino acids or esters may also be obtained by the N-demethylation of debenzylated product using known procedure[11].

In order to explore an alternative approach for the alkylation reaction, Lewis acid mediated alkylation[12,13] of **1** was also carried out. The addition of $TiCl_4$ (0.546 g, 2.88 mmole) to a stirred solution of **1** (0.5 g, 1.93 mmole) in dry DCM at -78°C followed by the addition of allyl trimethyl silane (0.32 g, 2.8

mmole) gave **7a** and **7b** (90% yield) in 9:1 ratio . The absolute stereochemistry of alkylated products (**7a and 7b**) as shown in **Scheme -III**, was determined by comparing the optical rotation of the corresponding α-amino acid ester, obtained after usual hydrolysis reaction in methanolic HCl, with an authentic sample prepared independently from L-Methionine[14].

In summary, we have developed a new glycine derived chiral template, based on a recyclable chiral L-prolinol auxiliary, for the synthesis of α-amino acids and their corresponding N-methyl derivatives in fairly good optical purity. Further study is in progress.

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