

Organic & Supramolecular Chemistry

 β -Lactam-Synthon Interceded Diastereoselective Synthesis of 2-Azido- γ -amino Alcohols with Subsequent Transformations to Functionally Enriched HeterocyclesAmandeep Singh,^[a] Bharvi Sharma,^[a] Divya Sachdeva,^[a] Vishu Mehra,^[b] Pardeep Singh,^[c] and Vipin Kumar^{*[a]}

The present manuscript explicates Boron-dimethylsulfide-promoted diastereoselective synthesis of 2-azido- γ -amino alcohols using β -lactam synthon protocol along with its utilization in the formation of diversely functionalized heterocycles having biological relevance. The developed protocol has the potential to surpass the typical drawbacks of conventional protocols.

Introduction

Amino alcohol fragment is a common structural core in natural products and an important synthetic intermediate in the preparation of wide range of biologically active amino acids and chiral auxiliaries.^[1] Compounds containing β -amino alcohol exhibit a broad spectrum of biological activities,^[2] for example Hapalosin and Swainsonine act as potential anticancer agents.^[3] Piperazine based β -amino alcohols are well known for their applications such as positive inotropic agents, increasing myocardial contractivity and in the treatment of congestive heart failure.^[4] β -amino alcohols have been thoroughly studied, and synthetic approaches to access such molecules by chemical and biocatalytic ways are abundant.^[5] On the other hand, compounds containing γ -amino alcohol are widely used for the treatment of psychiatric and metabolic disorders.^[6] γ -amino alcohols are also considered as efficient chelating agents applicable in asymmetric synthesis.^[7] Despite the potential importance of γ -amino alcohols, comparatively few methods for their preparations have been reported. Classical methods for the synthesis of γ -amino alcohols involved the reduction of isoxazoles, isoxazolines, β -amino carbonyl compounds or enamines,^[8] and reductive amination of β -hydroxy ketones via Schiff bases.^[9] The above reported synthetic protocols are far from ideal and suffered from significant drawbacks such as

the use of expensive or air sensitive reagents, extended reaction times, the requirement for prolonged work-up procedures and poor toleration by sensitive substituents.

β -lactam antibiotics are generally recognized as cornerstone of human health care due to the unparalleled clinical efficacy and safety.^[10] Besides the importance as key structural component of β -lactam antibiotics, this four-membered ring system has been attracting considerable interest in organic synthesis as a versatile synthetic intermediate^[11] and provide efficient access to variety of non-protein amino acids, functionalized piperazines, 1,4-diazepanes, quinolones, isoquinolones, isoquinolines, enantiopuresuccinimides, oligopeptides, peptidomimetics and biologically relevant heterocycles, such as indolizidines, paclitaxel, docetaxel, taxoids, cryptophycins, lan-kacidins.^[12]

In continuation with our recent exposure to the prospective of β -lactam synthon approach for the synthesis of novel heterocyclic compounds,^[13] and in view of the lack of convenient approaches for the synthesis of C-2 functionalized γ -amino alcohol, the present manuscript describes boron-dimethyl sulphide-promoted the single-pot diastereoselective synthesis of γ -amino alcohol with subsequent transformations to functionally decorated heterocycles having biological relevance *viz* azetidines, oxazinanes and fused triazoles.

Results and Discussion

Recent reports from our lab have shown the methoxide-promoted ring amidolysis of 3-azido-azetidin-2-ones resulting in equimolar diastereomeric mixture of β -aminoesters, which were subsequently used for the synthesis of functionalized imidazolines without prior separation due to very closed Rf values.^[14] In order to circumvent the problem of enolization and to introduce the selectivity, it was considered worthwhile to explore the selective reduction of 3-azido-azetidin-2-ones using boron-dimethylsulfide. Thus, the treatment of **1** with $\text{BH}_3(\text{CH}_3)_2\text{S}$, afforded diastereoselective access to 2-azido- γ -amino alcohols. The synthetic approach included an initial synthesis of racemic *cis*-3-azido-2-azetidinones **1** via Staudinger reaction of 1-azadiene with azidoketene, generated in situ from azido acetic acid and *p*-toluene sulphonyl chloride in the presence of triethylamine. The *cis* stereochemistry was assigned to compound **1** on the basis of observed coupling constant $J=5.2$ Hz between H-1 and H-2. *N*-phenyl-substituted azetidine-2-one, **1a**

[a] A. Singh, B. Sharma, D. Sachdeva, Dr. V. Kumar
Department of Chemistry, Guru Nanak Dev University, Amritsar-143005,
Punjab, India
E-mail: vipan_org@yahoo.com

[b] Dr. V. Mehra
Department of Chemistry, Hindu college, Amritsar, 143001.

[c] Dr. P. Singh
Department of Chemistry, Umea University, 90187 Umea, Sweden

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