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New chiral 4-substituted 2-cyanoethyl-oxazolines: Synthesis and assessment of some biological activities

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ABSTRACT

This paper describes the synthesis of new enantiomerically pure 2-cyanoethyl-oxazolines in one step starting from a wide range of amino alcohols and 4-ethoxy-4-iminobutanenitrile with high to good yields (73–96%) via an appropriate procedure which can be used for a selective synthesis of mono-oxazolines. A simple operation as well as a practical separation is additional eco-friendly attributes of this method. All the synthesized compounds were identified and characterized with their physicochemical features and their spectral data (^{1}H NMR, ^{13}C NMR and TOFMS ES$^+$). Among the prepared mono-oxazolines, the mono-oxazoline **(3a)** [3-[(4S)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl] propanenitrile] was tested to detect some biological activities. This compound was studied *in vitro* given the various types of pharmacological properties characterizing these compounds such as antioxidant, antimicrobial and analgesic activities. The antioxidant activity and mechanism of **(3a)** were identified using various *in vitro* antioxidant assays including 1,1-diphenyl-2-picryl-hydrazyl (DPPH$^\cdot$), and superoxide anion radicals ($O_2^{\cdot-}$) scavenging activity. In addition, compared to Quercetin, the tested synthetic product reveals a relatively-strong antiradical activity towards the DPPH (activity percentage of 81.22%) free radicals and significantly decreased the reactive oxygen species such as ($O_2^{\cdot-}$) formation evaluated by the non-enzymatic (nitroblue tetrazolium/riboflavine) and the enzymatic (xanthine/xanthine oxidase) systems. Related activity values were, respectively, 66% and 60.30%. The oxazoline **(3a)** showed a high ability to reduce the $O_2^{\cdot-}$ generation and proved to be a very potent radical scavenger. On the other hand, the analgesic property of the 3[(4S)-benzyl-4,5-dihydro-1,3-oxazol-2-yl] propanenitrile **(3a)** was demonstrated. The subcutaneous administration of **(3a)** produced a significant reduction in the number of abdominal constrictions amounting to 73.81% in the acetic acid writhing test in mice. In addition to these advances, the oxazoline **(3a)** has been investigated as an antimicrobial agent. Our results showed that this molecule exhibited various levels of antibacterial effect against all the tested bacterial strains.

1. Introduction

Literature reveals that nitrogen containing heterocyclic molecules constitutes the largest portion of chemical entities which are part of many natural products, fine chemicals, biologically-active pharmaceuticals and agrochemicals playing a vital role in enhancing the quality of life.

Among a large variety of nitrogen-containing heterocyclic compounds, the 2-oxazolines have impregnated numerous sub-disciplines in the field of synthetic organic chemistry over 100 years since their discovery [1]. This versatile heterocycles has served as a protecting group, a coordinating ligand, and an activating moiety, often exhibiting all of these characteristics in a single transformation. The well-defined reactivity of chiral

Abbreviations: ASL, lysine acetylsalicylate; COX, cyclooxygenases; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; DPPH, 1,1-diphenyl-2-picrylhydrazyl radical; EDTA, ethylenediaminetetraacetic acid; EtOH, ethanol; HIV-1, *Human immunodeficiency virus*; ^{1}H NMR, proton nuclear magnetic resonance; IC_{50}, concentration inhibiting a biological response by 50%; Me_3SiCl, trimethylsilylchloride; MICs, Minimum Inhibitory Concentrations; MBCs, Minimum Bactericidal Concentrations; NBT, nitroblue tetrazolium; NSADs, n-steroidal anti-inflammatory drugs; PGE, prostaglandin E; TLC, thin layer chromatography; TOFMS ES$^+$, time-of-flight mass spectrometry; $Zn(OAc)_2$, zinc acetate.

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oxazolines has given rise to numerous highly-efficient strategies for an asymmetric synthesis including their use as ligands in an asymmetric catalysis.

Various properties have imposed their use in a multitude of dissimilar applications: as monomers in polymer production, as moderators in analytical processes, and as conformationally rigid peptide mimics in medicinal chemistry. Even natural systems have chosen to incorporate 2-oxazolines into their chemical arsenal, as evidenced by the rapidly growing number of identified natural products and their attendant pharmacological properties (Fig. 1). This could be explained also by the various applications of these products in the synthesis of different therapeutic and biologically-active compounds [2] such as antidiabetic, antihypertensive, antidepressive, antihypercholesterolemic, anticancer, anti HIV-1, antitumor and antialzheimer agents [3]. Thanks to their structural relationship with procaine, 2-oxazolines derivatives are expected to have local anaesthetic properties [4]. In addition to these serious matters, some 2-oxazoline derivatives act as enzyme inhibitors [5,6]. Furthermore, the 2-oxazoline moieties are often found in various bioactive natural compounds and designed medicinal agents, such as the Brasilibactin A [7]. These compounds exist as the key fragment in numerous marine organisms, such as epi-oxazoline halipeptin D [8].

On the other hand, 2-oxazolines are considered an important class of heterocycles and are versatile intermediates in synthetic organic chemistry [9,10]. Moreover, chiral oxazolines have been widely used in asymmetric synthesis both as building blocks [11], protecting groups for amino alcohols [12] and as auxiliaries, metal entrapment ligands and ligands [13]. In this setting, a number of methods have been developed for the preparation of 2-oxazolines from carboxylic acids [14], carboxylic esters [15], nitriles [16], aldehydes [17], hydroxyamides [18] and olefins [19]. In spite of the potential utility of aforementioned routes for the synthesis of oxazoline derivatives, many of these procedures have demonstrated various drawbacks including strong acidic conditions, long reaction times, tedious work-up, low yields, use of expensive, toxic or non-reusable catalysts, high temperatures, harsh reaction conditions and use of toxic solvents such as CCl_4, hexachloroethane or chlorobenzene and/or co-occurrence of several side reactions. In some cases, more than one step is required for the synthesis of these heterocycles. Therefore, to avoid these limitations, there is still a need to search for an efficient method with regard to toxicity, solubility and reaction time.

In the present work, we describe the synthesis in one step of some new chiral 4-substituted 2-cyanoethyl-oxazolines using α-amino alcohols and the monohydrochloride of an iminoether as starting materials. The results indicate that the present protocol is potentially applicable for the chemoselective conversion of α-amino alcohols to their corresponding 2-oxazolines in the presence of iminoether. It is well known that the oxazolines' derivatives have different biological activities. Based on the literature, we have assessed their pharmacological properties such as antioxidant, antimicrobial and analgesic activities.

2. Materials and methods

2.1. Analytical methods

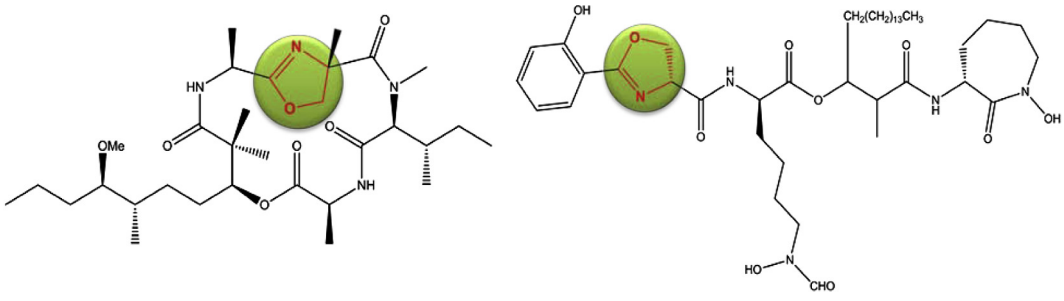
All reactions were monitored on thin-layer chromatographic (TLC) Merck 60 F-254 silica-gel plates (0.25 mm layer thickness). Column chromatography was performed on silica gel (70–230 mesh) using dichloromethane and methanol mixture as eluents. Melting points were determined on an Electrothermal 9002 apparatus and were uncorrected. The optical rotations were measured by an Atago Polax-2L polarimeter. NMR spectra were recorded on a Bruker AC 300 spectrometer [300 MHz (^{1}H) and 75 MHz (^{13}C)]. All chemical shifts were reported as δ values (ppm) relative to internal tetramethylsilane. Time-of-flight mass spectroscopy (TOFMS ES$^+$) was carried out on Micromass, UK and Manchester. Ultraviolet (UV) detector (Jasco 2075) and a data system processor was used (Clarity Lite) to confirm the presence of the targeted products. Detection was performed at 254 nm and 365 nm.

2.2. Chemicals

(S)-2-Amino-3-methylbutanoic acid (L-valine), S-(+)-α-amino-phenylacetic acid ((L)-(+)-(α)-phenylglycine), (S)-2-amino-3-phenylpropanoic acid (L-phenylalanine), (S)-2-Amino-4-methyl-pentanoic acid (L-leucine), (S)-2-Aminopropanoic acid (L-alanine), (S)-2-amino-3-(1H-indol-3-yl)propanoic acid (L-tryptophan), succinonitrile and trimethylsilylchloride were purchased from Sigma–Aldrich. The (R)-2-amino-1-butanol **c** was purchased from Sigma–Aldrich while the α-amino alcohols **a**, **b**, **d**, **e**, **f**, **g** and **e** were obtained by the reduction of the corresponding amino acids using the method developed by Meyers [20]. 1,1-Diphenyl-2-picrylhydrazyl radical (DPPH), ethylenediaminetetraacetic acid (EDTA), potassium phosphate buffer, α-tocopherol, nitro blue tetrazolium (NBT) and riboflavin were purchased from Aldrich (St. Louis, MO). All the other chemicals and solvents used in this work were of an analytical quality and purchased from commercial spots.

2.3. Preparation of the synthetic compounds (general procedure)

The synthesis of the 4-ethoxy-4-iminobutanenitrile monohydrochloride **(2)** was performed according to the modified method described by Ben Ammar et al. [21]. The synthesis of 3-[4-benzyl-4,5-dihydro-1,3-oxazol-2-yl] propanenitrile (**3a**–**g**) was synthesized as described by Meyers [22] (Scheme 1). The structures



Epi-oxazoline halipeptin D Brasilibactin A

Fig. 1. Examples of several biologically-active and pharmacological oxazolines.