COMMUNICATION

Synthesis of racemic 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid as a new constrained γ-amino dicarboxylic acid bypassing alkyl 3-aza-2-oxobicyclo[3.1.0]hexane-1-carboxylates

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To the memory of professor Živadin Bugarčić

Abstract: The first synthesis of racemic 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid was developed involving sequential iodocarbocyclization, azidation, saponification and reduction of dimethyl 2-allylmalonate. The developed synthetic pathway avoids reactions such as ring opening of the cyclopropane ring toward acyclic δ-amino carboxylic acid derivatives or lactamisation toward bicyclic methyl 3-aza-2-oxobicyclo[3.1.0]hexane-1-carboxylates which occur in alternative synthetic strategies.

Introduction

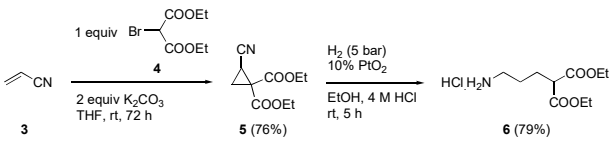
The synthesis of 2-(aminomethyl)cyclopropane-1-carboxylic acid derivatives has received significant interest because these functionalized cyclopropanecarboxylic acids are biologically and synthetically important γ-amino carboxylic acid derivatives.[1] *Cis*- and *trans*-2-(aminomethyl)cyclopropane-1-carboxylic acid are bioactive as analogues of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).[2] *Trans*-2-(aminomethyl)cyclopropane-1-carboxylic acid units have been incorporated in γ-peptides with stabilized parallel sheet structures.[3] However, the corresponding 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid derivatives **1** (Figure 1) have received far less attention. Only a few syntheses of the corresponding heterocyclic 3-aza-2-oxobicyclo[3.1.0]hexane-1-carboxylic acid derivatives **2** (Figure 1) have been reported,[4] en route to the synthesis of tetracyclic spiroindolines,[5] conformationally constrained α-amino acid derivatives,[6] 3,4-methano-β-proline,[7] a conformationally constrained β-amino acid, γ-lactam derivatives[4b] and several *Lycopodium* alkaloids.[8] Therefore, we envisioned that the unknown 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid would be of significant interest, and herein, the development of a synthetic pathway to this cyclopropyl γ-amino dicarboxylic acid is reported.

1 **2**

Figure 1. 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid and 3-aza-2-oxobicyclo[3.1.0]hexane-1-carboxylic acid derivatives.

Results and Discussion

Initially, the reduction of diethyl 2-cyanocyclopropane-dicarboxylate **5** was investigated as a direct route to 2-(aminomethyl)cyclopropanedicarboxylic acid derivatives **1**. Diethyl 2-cyanocyclopropanedicarboxylate **5** was prepared via Michael-induced ring closure reaction of diethyl bromomalonate and acrylonitrile in the presence of potassium carbonate in THF according to a literature procedure (Scheme 1).[9] Unfortunately, all attempts to selectively reduce the cyclopropanecarbonitrile **5** to the corresponding diethyl 2-(aminomethyl)cyclopropane-dicarboxylate failed. For example, treatment of cyclopropane-carbonitrile **5** with BH_3 in THF at room temperature gave no reaction, while PtO_2-catalyzed hydrogenation in EtOH in the presence of 4 M HCl (aq.) at room temperature for 5 h resulted in reduction and ring opening to δ-amino diester **6** in 79% yield. It is interesting to mention that the corresponding trifluoroacetate salt of the δ-amino diester **6** has been used for the synthesis of a δ-dicarboxybutylphosphoramidate conjugate of 2'-deoxycytidine-5'-monophosphate, acting as a substrate for DNA polymerization by HIV-1 reverse transcriptase.[10] The non-natural δ-dicarboxylic amino acid moiety was chosen as a pyrophosphate mimic in which the bidentate chelating malonate dianion could result in coordination of a magnesium cation within the polymerization site. Moreover, a 5'-phosphorylated dinucleotide bearing the bis-negatively charged δ-dicarboxylic amino acid side chain was proven to be a potent inhibitor of hepatitis C virus (HCV) NS5B polymerase.[11] Reduction of cyclopropane **5** with $NaBH_4$-$NiCl_2$ in MeOH at room temperature led to the formation of unidentifiable reaction products.



3 **5** (76%) **6** (79%)

Scheme 1. Synthesis of diethyl 2-cyanocyclopropanedicarboxylate **5** and reduction to the δ-amino diester **6**.

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