



3rd International Electronic Conference on Medicinal Chemistry

1-30 November 2017

chaired by Dr. Jean Jacques Vanden Eynde

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A synthetic entry to amino acid derivatives through Davidson-like Heterocyclization

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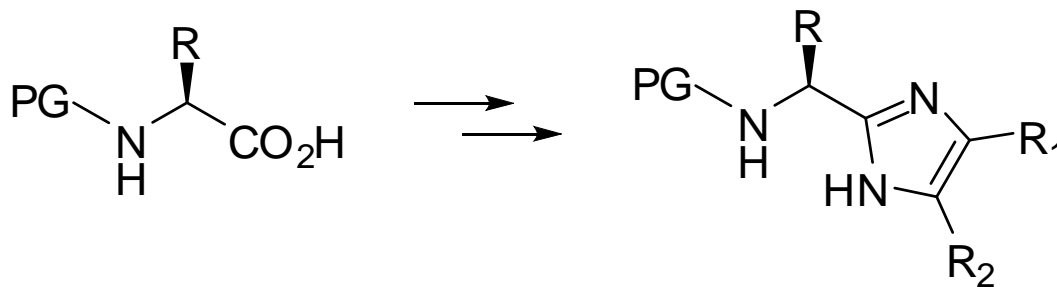
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A synthetic entry to amino acid derivatives through Davidson-like Heterocyclization



Abstract:

The modification of amino acids leads to valuable building blocks for the synthesis of bioactive compounds. By keeping the amino group protected, the carboxylic acid functionality can be converted in two steps to an imidazole moiety via a Davidson-like heterocyclization. This reaction allows for a combinatorial approach, in which two positions at the heterocycle can be modified. Herein, we report on the synthesis of such imidazole derivatives by using N-protected cyclohexylalanine as the starting material, which was subjected to Davidson-like heterocyclization. By using different α -haloketones, two points of diversity were examined, position 4 and 5, respectively. The building blocks can serve as the starting point for the synthesis of bioactive peptides to be provided to pharmacological studies.

Keywords: Davidson cyclization; amino acids; imidazoles



Introduction

Davidson's original synthesis comprises the cyclization of α -acyloxyketones with ammonium acetate in acetic acid to yield 2,4,5-trisubstituted oxazoles [1]. The reaction can be performed similarly upon heating in unpolar solvents to produce imidazole derivatives [2-9]. Such imidazole heterocycles appear in a variety of bioactive compounds and in important biological molecules, such as derivatives of histidine and of the related hormone histamine. The Davidson-like synthesis allows to easily access imidazoles also with amino acids as the starting material. In this study, it was intended to expand the repertoire of imidazole-containing compounds derived from a N-protected amino acid as potential building blocks to obtain new lead structures for drug discovery.

[1] Davidson et al. *J. Org. Chem.* **1937**, 2, 319-327.



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Introduction

Davidson-like imidazole syntheses have been successfully utilized for the preparation of sphingosine-1-phosphate analogues [2], antimalarial imidazolopiperazines [3, 4] and tetrahydro- β -carboline-type somatostatin antagonists [5]. The Davidson imidazole synthesis was also applied to generate linker structures in antiplasmodial 7-chloro-4-aminoquinoline derivatives [6] and to assemble dimeric inhibitors of the hepatitis C virus non-structural protein 5A (NS5A), i.e. daclatasvir and its derivatives [7, 8] The method was furthermore utilized to generate azole peptide mimetics [9].

[2] Clemens et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3568-3572.

[3] Meister et al. *Science* **2011**, *334*, 1372-1377.

[4] Nagle et al. *J. Med. Chem.* **2012**, *55*, 4244-4273.

[5] Poitout et al. *J. Med. Chem.* **2001**, *44*, 2990-3000.

[6] Casagrande et al. *Bioorg. Med. Chem.* **2012**, *20*, 5965-5979.

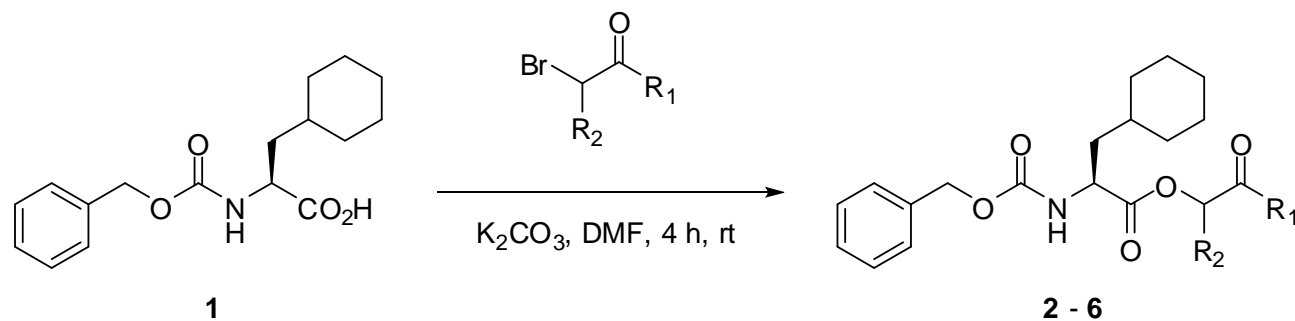
[7] Sun et al. *Nature* **2015**, *527*, 245-248.

[8] Bana et al. *Bioorg. Med. Chem.* **2017**, <https://doi.org/10.1016/j.bmc.2016.12.046>.

[9] Gordon et al. *Tetrahedron Lett.* **1993**, *34*, 1901-1904.



Results and discussion: Preparation of α -acyloxyketones

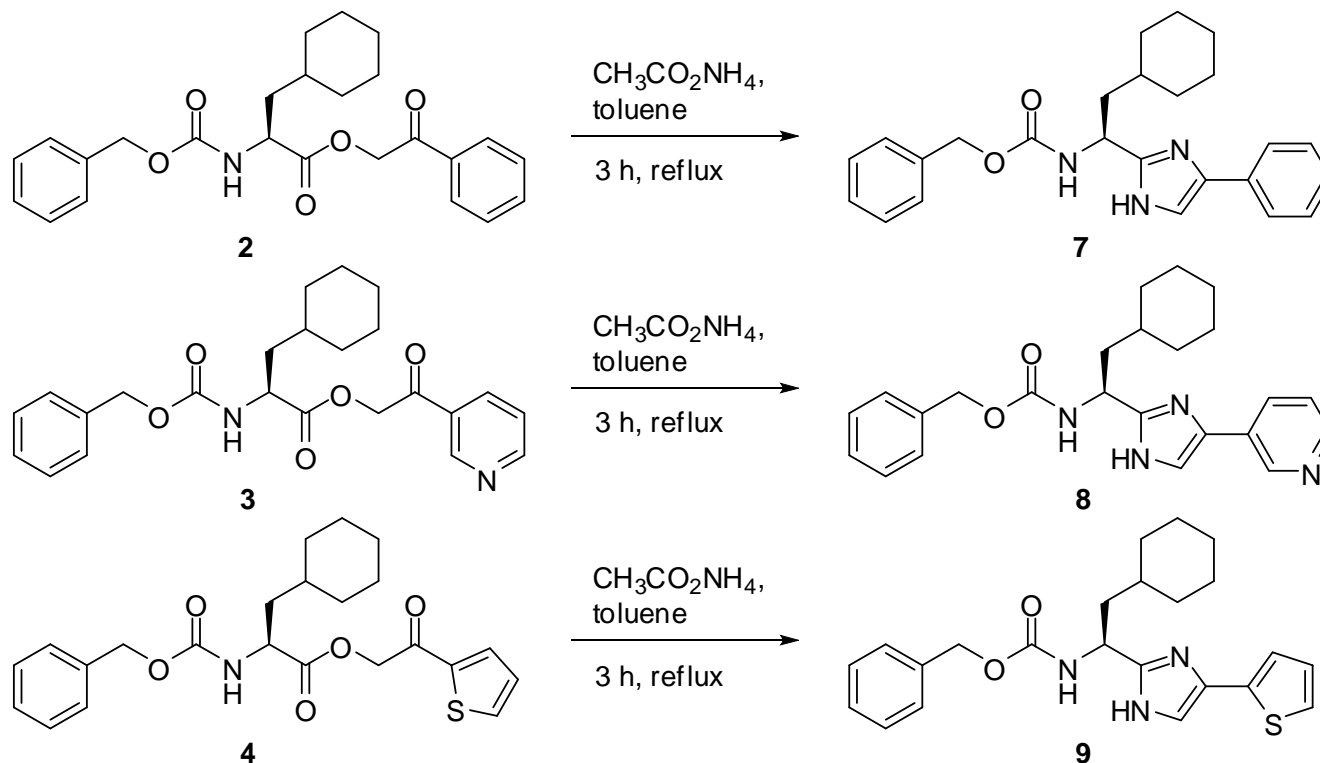


- 2** $\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{H}$
- 3** $\text{R}_1 = 3\text{-pyridyl}$, $\text{R}_2 = \text{H}$
- 4** $\text{R}_1 = 2\text{-thienyl}$, $\text{R}_2 = \text{H}$
- 5** $\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{CH}_3$
- 6** $\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{C}_6\text{H}_5$

Compounds **2 – 6** were obtained in yields ranging from 72% to 82% after column chromatography in a purity over 95% based on LC/MS analysis.



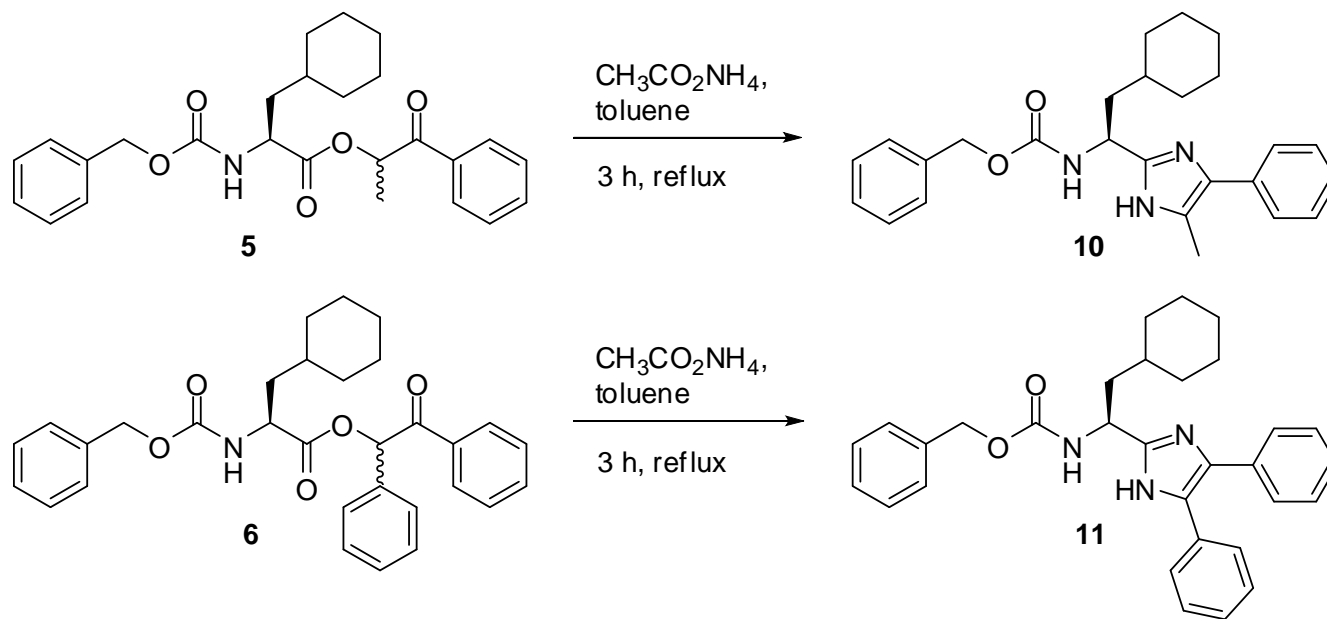
Results and discussion: Variations at position 4



Compounds **7** – **9** were obtained in yields ranging from 66% to 92% after column chromatography in a purity over 95% based on LC/MS analysis.



Results and discussion: Variations at position 5



Compounds **10** and **11** were obtained in 61% and 21% yield after column chromatography in a purity of 95% and 98% based on LC/MS analysis, respectively.



Results and discussion

Initially, we prepared the precursors for the Davidson-type cyclodehydration, i.e. cyclohexylalanine-derived, N-protected amino acid esters (compounds **2** - **6**). These esters were then subjected to the cyclization reaction upon treatment over 3 hours with ammonium acetate in boiling toluene. In the course of this reaction, the imidazole formation is assumed to occur through the formation of an imine, which subsequently attacks the carbonyl carbon of the ester, leading to an O- to N-acyl migration. The second ammonia molecule is then incorporated and a second imine is formed, which effects the final cyclocondensation. The structures of the final products **7-11** were confirmed by LC/MS and NMR analysis.



Conclusions

The reactions described herein were performed to convert the polar carboxylic acid group of a model amino acid to a rather non-polar, substituted imidazole core. However, the deprotection of the parent amino acid will release the terminal NH_2 group capable to undergo a variety of subsequent transformations. Thus, such chiral, amino acid-derived imidazoles can be considered as valuable building blocks to generate more complex peptidomimetic compounds. Besides the opportunity to subject different amino acids to this heterocyclization, structural diversity can be introduced due to different substituents at position 4 and 5 of the newly formed imidazole ring.



Acknowledgments

The authors would like to acknowledge financial support by the DFG Forschergruppe under grant number FOR2372.



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