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## Reactions of glycidyl derivatives with ambident nucleophiles; part 2: amino acid derivatives

Gerald Dyker\*<sup>1</sup>, Andreas Thöne<sup>1</sup> and Gerald Henkel<sup>2</sup>

Address: <sup>1</sup>Dept. of Chemistry & Biochemistry, Ruhr-University Bochum, Universitätsstrasse 150, D-44780 Bochum, Germany and <sup>2</sup>Dept. of Chemistry, Paderborn University, 33098 Paderborn, Germany

Email: Gerald Dyker\* - gerald.dyker@rub.de; Andreas Thöne - gerald.dyker@rub.de; Gerald Henkel - hohhenkel@uni-paderborn.de  
\* Corresponding author

Published: 27 September 2007

Received: 24 August 2007

Beilstein Journal of Organic Chemistry 2007, 3:28 doi:10.1186/1840-5397-3-28

Accepted: 27 September 2007

This article is available from: <http://bjoc.beilstein-journals.org/content/3/1/28>

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### Abstract

A three-step procedure for the synthesis of multifunctionalized heterocycles from a pyroglutamic acid derivative, glycidyl components and anilines by nucleophilic substitution and cobalt catalysis is presented.

### Introduction

Recently we investigated the formation of 5- and 6-membered heterocycles from ethyl acetoacetate and glycidyl derivatives such as epichlorohydrin. [1] We found that the selectivity of this reaction was strongly influenced by the solvent and by the base applied, and especially by the nature of the leaving group at the glycidyl derivative. Despite the preparative potential of analogous cyclization reactions with other ambident nucleophiles, reports on this subject are surprisingly rare. [2]

For instance, amino acids and their derivatives **1** should be suitable as ambident nucleophiles. In principle the reaction with glycidyl derivatives **2** should lead to morpholinones **3** as depicted in Scheme 1, a class of heterocycles that are interesting as a crucial moiety of drugs for the treatment of various inflammatory and other diseases. [3-5]

### Results and Discussion

A high selectivity for the formation of one of the regioisomers **3a** and **3b** is anticipated, depending on the initial nucleophilic substitution either by the carboxylic acid or by the amino functionality, in both cases at a terminal carbon atom of **2**.



**Scheme 1:** Planned construction for morpholinones **3** from amino acid and glycidyl derivatives **1** and **2**. R<sup>1</sup>, R<sup>2</sup> = H, Alkyl, Aryl; R<sup>2</sup> = H, Acyl; X = leaving group: Cl, Br, I, p-OTf.

All attempts to achieve a one-step cyclization according to Scheme 1 starting from glycine or from phenylglycine seemed to fail under various reaction conditions (for instance one equiv. of NaOH, K<sub>2</sub>CO<sub>3</sub> or triethylamine in water), regularly giving rise to solid, presumably oligomeric material, insoluble even in DMSO.

We therefore tested the stepwise, controlled synthesis of products of type **3a** with glycidyl esters of N-acyl [6] and N-tosyl glycine and phenylglycine as isolated key intermediates: under basic reaction conditions (NaH, *sec*-BuLi or LDA in THF, or potassium carbonate in DMF) these glyci-

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## Reactions Of Glycidyl Derivatives With Ambident:

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In a digital era where connections and knowledge reign supreme, the enchanting power of language has become much more apparent than ever. Its ability to stir emotions, provoke thought, and instigate transformation is truly remarkable. This extraordinary book, aptly titled "**Reactions Of Glycidyl Derivatives With Ambident**," compiled by a highly acclaimed author, immerses readers in a captivating exploration of the significance of language and its profound effect on our existence. Throughout this critique, we shall delve into the book's central themes, evaluate its unique writing style, and assess its overall influence on its readership.

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