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Substituted 1,2-Thiazetidine 1,1-Dioxides. Synthesis and Properties of N-Alkylated and N-Acylated Derivatives of 1,2-Thiazetidine-3-acetic Acid 1,1-Dioxide

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Summary. 1,2-Thiazetidine-3-acetic acid 1,1-dioxide was *N*-alkylated using bromoacetates, and *N*-acylated using either acyl chlorides, protected amino acid fluorides, or *N*-protected amino acid *NCA*, which seemed to be the most universal method. Most of the obtained "β-sultam peptides" were sensitive against humidity, they hydrolyzed forming sulfonic acids, and reactions with amines resulted in sulfonamides. Reactions of *N*-acylated products showed that the sulfonyl group was faster attacked than the imide structure.

Keywords. 1,2-Thiazetidine 1,1-dioxide; β-Sultam; β-Sultam peptide.

Introduction

1,2-Thiazetidine 1,1-dioxide (β-sultam) is the sulfone analogue of the β-lactam ring. Its reactivity is depending on the substituents usually higher than that of the analogue β-lactam system. Therefore, it should be highly interesting to replace the β-lactam ring in special compounds by the β-sultam moiety, and to study properties and specific reactivity. We have described a number of β-lactam peptides showing inhibitor activity against the serine protease elastase and/or the cysteine protease papain [1, 2]. In continuation of this project, we synthesized derivatives of 1,2-thiazetidine-3-acetic acid 1,1-dioxide (β-sultam-3-acetic acid) at the C-terminus with esters of amino acids or dipeptides [3]. Here we report about reactions at the nitrogen atom of **1**, and about the properties of those structures obtained by combination of both reactions.

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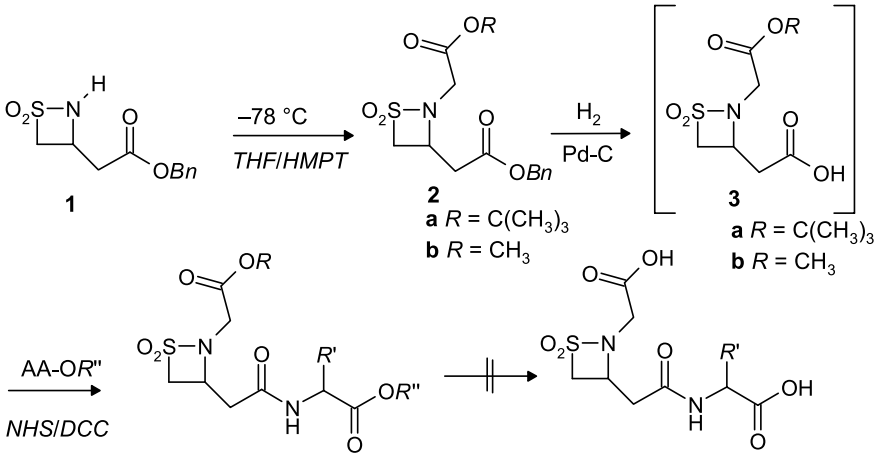
Results and Discussion

To explore the alkylation at the nitrogen atom of the β-sultam ring, we first studied the reaction between **1** and alkyl bromoacetates. The deprotonation was successful only with *Bu*Li. Using NaOH, KOH, or amines we observed always partial or complete ring opening. The alkylation finally was best done at $-78°C$ in *THF* in the presence of *HMPT* [4], whereby yields of up to 80% of **2a** or **2b** were isolated. Without *HMPT* the yields were completely unsatisfactory. After purification by CC, **2a** and **2b** were obtained as colourless viscous liquids, which had to be stored under N_2 at low temperature. By hydrogenolytic cleavage of the benzyl ester group at the *C*-terminus we obtained the carboxylic acids **3a** and **3b** as very unstable compounds. Therefore, they were immediately reacted with amino acid esters using the *NHS/DCC* methodology yielding the *N*-alkylated ''sultam peptides'' **4a**–**4e**. These compounds may be interpreted as peptide analogues with two protected *C*-terminals, as the substituent at the nitrogen can be seen as a built-in glycine. We tried different methods to obtain the free diacids, but all experiments failed completely until today. Probably, these diacids are much more sensitive than the acids **3**.

The structures of the diesters were confirmed by the characteristic C–H bands around $\bar{\nu} = 3020\,cm^{-1}$ of the protons in position 4 of the β-sultam ring [5], the SO_2 bands at $\bar{\nu} = 1320$ and $1150\,cm^{-1}$, and the bands of other functional groups in their IR spectra. The ^1H NMR spectra are characterized by the ABX system of the ring protons 3-H (A), 4-H_{trans} (B), and 4′-H_{cis} (X) with coupling constants, *e.g.* for **4b**, $J_{AB} = 6$, $J_{AX} = 8.25$, and $J_{BX} = 12.5$ Hz. The protons of the acetyl part at C-3 show a geminal coupling of $J = 15.8$ Hz, and couplings with 3-H of $J = 6$ and 7.5 Hz, while the coupling constant of the acetyl protons next to the nitrogen is 18 Hz. The protons of the fourth methylene group finally exhibit a clear doublet with $J = 6$ Hz. From these values one might deduce a pseudo equatorial orientation of the protons in the structure of **4b** (Fig. 1). It has to be noted that all



4
a $R = CH_3$ $R' = H$ $R'' = Bn$ **b** $R = C(CH_3)_3$ $R' = H$ $R'' = CH_3$
c $R = C(CH_3)_3$ $R' = Bn$ $R'' = CH_3$ **d** $R = CH_3$ $R' = Bn$ $R'' = CH_3$
e $R = C(CH_3)_3$ $R' = (CH_2)_3NHC(=NNO_2)NH_2$ $R'' = CH_3$

Scheme 1