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Synthesis of β-Amino Acids Based on Oxidative Cleavage of Dihydropyridone Derivatives

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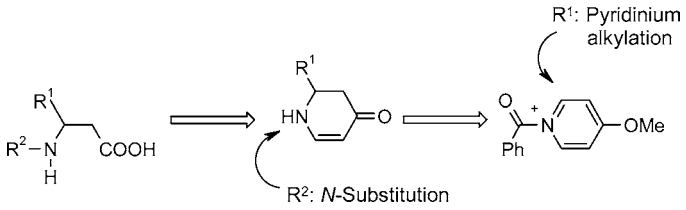
ABSTRACT



A new method for the synthesis of β-amino acids based on 2,3-dihydropyridones as starting materials is presented. Conversions of 2,3-dihydropyridones with $NaIO_4$ and subsequently with base gave the corresponding β-amino acids in a one-pot procedure. The reactions have been monitored by ^1H NMR indicating that the β-amino acids were formed in quantitative yields mostly. This method appears to be of broad scope, as 2-substituted 2,3-dihydropyridones are easily accessible via *N*-acyliminium ions generated from 4-methoxypyridine.

In recent years, β-amino acid derivatives gained much attention[1] by being key components of a variety of bioactive molecules such as the antitumor agent taxol,[2a] the antifungal jasplakinolide,[2b] the enzyme inhibitor bestatin,[2c] and many others.[1] Furthermore, β-amino acid derivatives are of high interest as precursors for peptidomimetics[3] and β-lactams.[4] In addition, they may also display useful biological activities as free amino acids.[5]

In the context of a study aimed at the development of new GABA uptake inhibitors, we realized that there is still a lack of general methods for the stereoselective construction of highly substituted and functionalized β-amino acid derivatives. We became aware of 4-methoxypyridine as a putative building block of high versatility for the synthesis of this type of compound (see Scheme 1).

Transformation reactions of 4-methoxypyridine to dihydropyridones bearing substituents at the ring nitrogen as well as in positions 2 and 3 of the heterocycle are well established. *N*-Acyliminium ion chemistry gives access to 2,3-dihydropyridones **3** possessing a substituent at the 2-position. Subsequently, a broad array of different substituents ranging from aliphatic[6a,b] and aromatic residues[6a,b] to heteroatomic groups[6c−f] may be introduced at the 3-position via the corresponding enolate of the *N*-acyl-2,3-dihydropyridone. This may be accomplished in a diastereoselective fashion when a substituent in the 2-position of 2,3-dihydropyridone **3** is present.[6] Finally, substitution reactions at the ring

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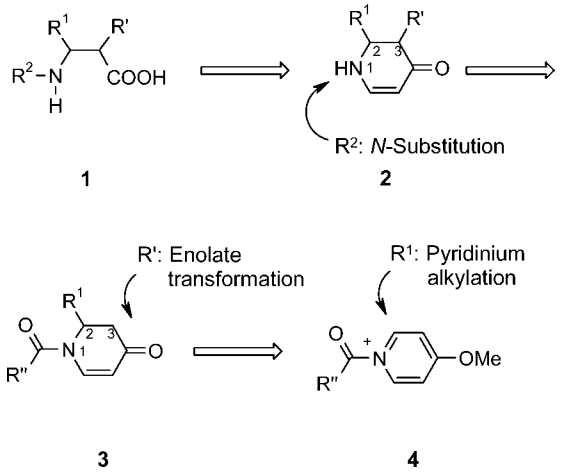
Scheme 1. Synthetic Strategy



nitrogen via the corresponding anion of the N-unprotected dihydropyridone (e.g., **2**) leading to N-substituted dihydropyridones[7] are also well-known. Thus, when aiming at the synthesis of β-amino acids, the oxidative breakdown of the substituted 2,3-dihydropyridone ring represents the crucial step to be established. Successful oxidative transformation would pave the way to various series of β-amino acids, in which substituents either in the β-position or in α- and β-positions are present, and to compounds bearing additional N-substituents as well.

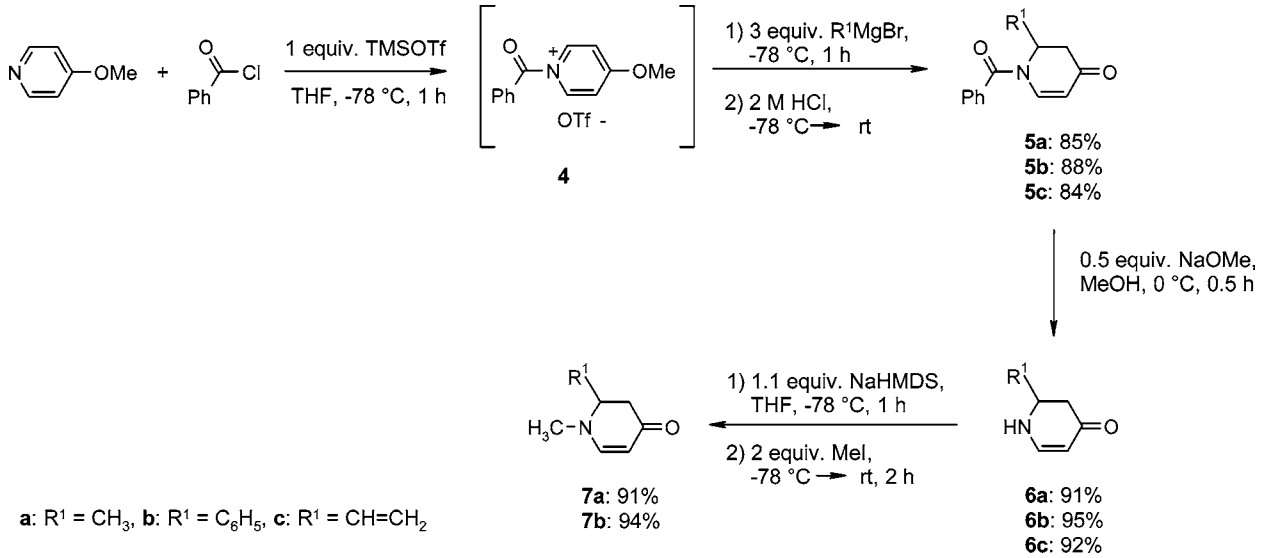
Besides, an asymmetric synthesis of β-amino acids could follow the same line, as the set up of the first stereocenter in the 2-position of the 2,3-dihydropyridone ring may be efficiently accomplished in a stereoselective manner by utilizing well-established chiral *N*-acyliminium ion chemistry featuring *N*-acyl groups as chiral auxiliaries.[8] In this paper, we describe the successful implementation of this plan for the synthesis of β-mono- and N,β-disubstituted β-amino acids **1**.

The synthesis of racemic dihydropyridones **5a**−**c** was accomplished according to standard procedures by trapping reactions of *N*-acylpyridinium salt **4**[9] with appropriate nucleophiles providing the required compounds in yields of 84−88%. To remove the benzoyl group, **5a**−**c** were treated with 3.5 equiv of NaOMe at room temperature,[8a,b,10] yielding dihydropyridones **6a**−**c** in 82−86%. We observed that this reaction could be clearly improved when only catalytic amounts of NaOMe (0.5 equiv) were employed and the temperature was lowered to 0 °C, leading to compounds **6a**−**c** in almost quantitative yields (91−95%). Finally, deprotonation of **6a**,**b** with NaHMDS and subsequent treatment with MeI afforded compounds **7a**,**b** as precursors for N-substituted β-amino acids (**7a**, 91%; **7b**, 94%).

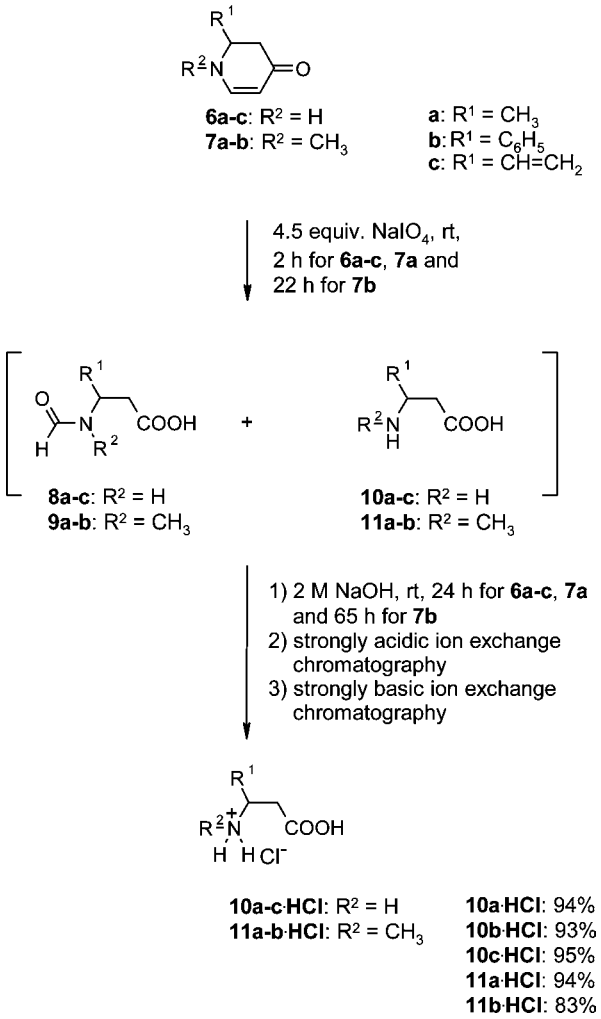
Initial attempts focused on the oxidation of the *N*-acyl-protected dihydropyridones **5a**−**c**. However, all oxidizing agents employed, $KMnO_4$, $KMnO_4/NaIO_4$, $RuCl_3/NaIO_4$, $OsO_4/NaIO_4$, and $NaIO_4$, required harsh reaction conditions and led to mixtures of products providing the desired *N*-acyl-protected amino acid even after extensive optimization studies only in low to moderate yields. The best result were obtained using $NaIO_4$ as a single oxidant. As $NaIO_4$ does not interfere with free amines, it seemed quite promising to undertake oxidative cleavage reactions of the N-unprotected dihydropyridones **6a**−**c** or **7a**,**b** with this reagent.

Thus, when the N-unprotected dihydropyridone **6b** was treated with $NaIO_4$, the starting material was rapidly consumed, even at room temperature, and following workup, the amino acid **10b**·HCl was obtained in a yield of 51%. However, in addition, the *N*-formyl amino acid **8b** was also isolated in 28% yield. Monitoring the reaction by ^{1}H NMR spectroscopy revealed that **8b** and the amino acid **10b** were the only products formed and that the ratio of these two products (**8b**/**10b**) did not change significantly during the course of the reaction. Therefore, the *N*-formyl derivative **8b** and the free β-amino acid **10b** might be formed by two competing reaction pathways and not by a stepwise process

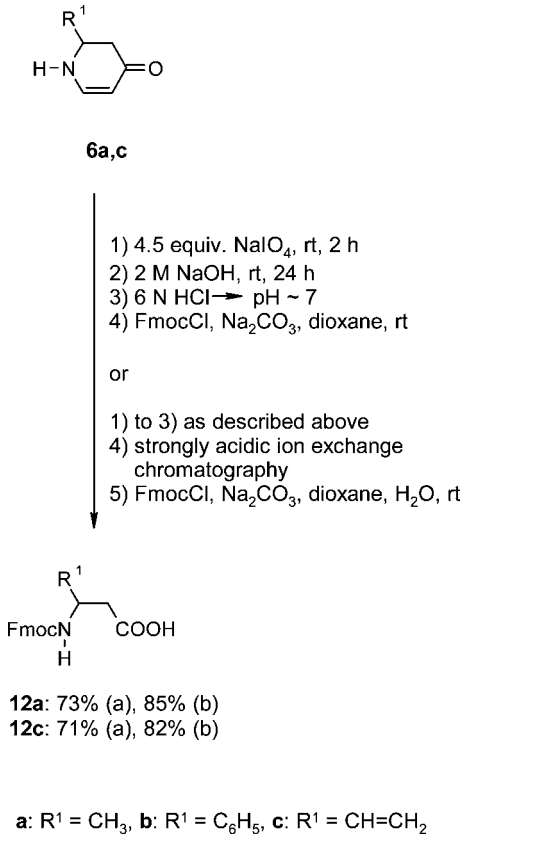
Scheme 2. Synthesis of the Amino Acid Precursors **6** and **7**[a]



Scheme 3. Transformation of Dihydropyridones to β-amino Acids[a]



Scheme 4. Synthesis of the *N*-Fmoc-Protected Amino Acids **12**[a]



where the *N*-formyl derivative **8b** represents a precursor of **10b**. Consequently, we tried to solve this problem by simply subjecting the crude reaction mixture resulting from the oxidation process to an alkaline hydrolysis, as this should transform the *N*-formyl derivative **8b** into the desired compound **10b**, thus leaving only the latter as the final compound. Indeed, when the crude product consisting of **8b** and **10b** was treated with NaOH at room temperature for 24 h the reaction product became uniform, with the free amino acid **10b** being the only product detectable by ^{1}H NMR spectroscopy.

Fortunately, the above-mentioned procedure worked well also for the oxidative degradation of dihydropyridones **6a**,**c** and **7a**,**b**. For the oxidation of **6a**,**c** and **7a** with $NaIO_4$, in each case a clean reaction product was obtained. According to the ^{1}H NMR spectra of the crude reaction mixtures in addition to the free amino acids **10a**,**c** and **11a**, only a second product had been formed in each case. The latter are likely to be the *N*-formyl derivatives **8a**,**c** and **9a**, as their ^{1}H NMR data corresponded well with those of the *N*-formyl amino acid **8b**, though these compounds were not isolated and further characterized. However, in line with this assumption, these compounds disappeared when the reaction mixtures were treated with sodium hydroxide, and the amino acids **10a**,**c** and **11a** remained as single products.

To convert the sterically more demanding dihydropyridone **7b** to the amino acid **11b**, the reaction time for the oxidative cleavage and the subsequent saponification had to be increased from 2 to 22 h and from 24 to 65 h, respectively. Thereby, the starting material had been completely consumed. However, in addition to the desired β-amino acid **11b**, this time small amounts of unidentified side products were also present in the crude product obtained after the alkaline hydrolysis.

Notably, N-substituents as present in compounds **7a** and **7b** do not hamper the oxidation reaction, though their presence may significantly slow the reaction rate, which is likely a result of steric hindrance, as indicated by the long reaction time necessary for the conversion of **7b** (22 h for **7b** as compared to 2 h for **7a**). Moreover, the amino function of the dihydropyridone ring may also be part of a benzylic

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or an allylic system, and as such commonly highly susceptible to oxidative degradation, without interfering with the $NaIO_4$ oxidation, which is best demonstrated by the clean conversion of **6b** and **6c** into **10b** and **10c**, respectively. Thus, this method should be of broad applicability and prove to be useful even for the synthesis of β-amino acids with functional groups sensitive to oxidizing agents.

To remove inorganic salts resulting from the oxidation reaction, the crude reaction mixtures were purified by anion and subsequent cation exchange chromatography providing the free amino acid hydrochlorides **10a**−**c**·HCl and **11a**,**b**·HCl in almost quantitative yields (83−95%, see Scheme 3).

Alternatively, the amino acids may also be isolated as *N*-Fmoc derivatives, as demonstrated for **10a** and **10c**. Direct treatment of the crude reaction mixtures resulting from the oxidation of **6a** and **6c** with FmocCl afforded the desired Fmoc-protected amino acids **12a** and **12c** in 73 and 71% yield, respectively (see Scheme 4). However, under these conditions the reaction mixtures became highly viscous, which, besides hampering the isolation procedure, might have had a negative impact on the reaction. When the crude reaction mixtures were first purified by cation exchange chromatography to remove inorganic salts present in high amount, this problem vanished and the Fmoc-protected amino acids **12a** and **12c** were obtained in even better yields (**12a**, 85%; **12c**, 82%).

In summary, a mild and efficient method for the preparation of β-amino acids based on the oxidative cleavage of suitably substituted dihydropyridones, e.g., **6a**−**c** and 7**a**,**b**, has been developed. Further applications exploiting the scope of this new reaction for the synthesis of highly functionalized β-amino acids are in progress.

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Supporting Information Available: Experimental details and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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