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Straightforward synthesis of fluorinated amino acids by Michael addition of ethyl bromodifluoroacetate to α,β-unsaturated α-amino acid derivatives

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ABSTRACT

Copper-mediated Michael addition of ethyl bromodifluoroacetate to *N*-protected α,β-unsaturated α-amino acid esters was applied for straightforward synthesis of γ,γ-difluorinated analogues of glutamic acid (compound **1**) and glutamine (compound **10**). Moreover, a proline-based, sterically constrained analog of γ,γ-difluoroglutamic acid (compound **24**) was prepared.

1. Introduction

Fluorinated α-amino acids as well as their derivatives represent an important class of organofluorine compounds, which found multiple application in drug discovery [1,2], peptide chemistry [3] and as PET-imaging agents [4].

Numerous synthetic approaches to diverse fluorinated amino acids were developed [5]. On the other hand, for many promising fluorine containing amino acids there is still a lack of efficient synthetic protocols in the literature. Especially the preparation of α-amino acids featuring a CF_2-moiety is still methodologically underdeveloped. For instance, amino acid **1**, a promising analogue of glutamic acid [6], was first synthesized by Taguchi et al. using a Michael addition of difluoroketene silyl acetal to a dehydroalanine derivative [7]. Later other approaches towards compound **1** (as racemate or in enantiopure form) were published. Authors used various methods to introduce fluorine including desulfurization-fluorination [8], electrophilic fluorination [9] and different multistep methods [6,10]. Despite of different advantages of the mentioned methods, they can scarcely be used for the multigram synthesis of target compound **1** because of costly starting materials, scalability problems etc.

In order to develop a more convenient method to prepare compound **1** and analogs, we considered the copper-mediated Michael addition of ethyl bromodifluoroacetate to α,β-dehydro α-amino acid derivatives as an alternative synthetic pathway (Scheme 1).

Ethyl bromodifluoroacetate is a readily available versatile organofluorine building block, which was extensively used in various coupling/addition reactions with different C = C-double bonds and aromatic systems under various conditions [11]. Michael addition of ethyl bromodifluoroacetate to C = C-double bond of different substrates was first described by Kumadaki et al. [12] and was later applied by other groups [13]. Surprisingly, addition to α,β-unsaturated α-amino acid derivatives is not described in the literature yet [14]. A methodologically similar approach was realized by Yajima et al. [15], who reacted ethyl iododifluoroacetate with phthalimide protected dehydro alaninate **2a**. However, this reaction is intractable case of Michael addition via photoinduced radical process (Scheme 2) [16].

2. Results and discussion

We investigated the Michael addition of ethyl bromodifluoroacetate toward *N*-phthalimidyl dehydroalanine methyl ester (**2b**). The latter was previously used in our group for halofluorination reactions [17]. The Michael addition proceeded smoothly under Kumadaki's conditions

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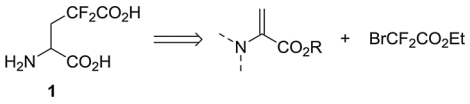
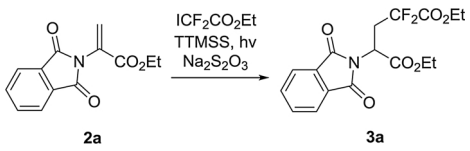
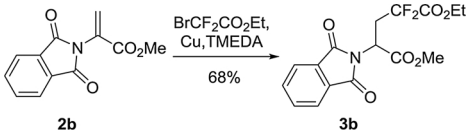


Scheme 1. Retrosynthesis of γ,γ-difluoroglutamic acid **1** by Michael addition of ethyl bromodifluoroacetate to *N*-protected α,β-dehydro alanine derivatives.



Scheme 2. Yajima's synthesis of compound **3a** by a photoinduced radical addition using tris(trimethylsilyl)silane (TTMSS) as a hydrogen donor [15].



Scheme 3. Michael addition of ethyl bromodifluoroacetate to dehydroalanine ester **2b**.

(6 equiv Cu, TMEDA, THF, 7 h reflux) giving the corresponding product **3b** in 68% isolated yield (Scheme 3).

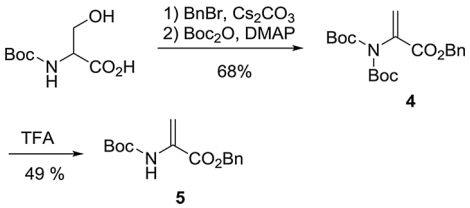
The *N*-phthalimido group is not a convenient protective group in amino acid synthesis. Frequently, the harsh deprotection conditions are accompanied by side-processes. Therefore, we prepared *N*-Boc-dehydroalanine benzyl ester (**5**) starting from *N*-Boc-serine via the *N,N*-di-Boc-derivative **4** (Scheme 4) according to an approach previously applied for similar compounds [18].

Surprisingly, the treatment of the mono-Boc-protected compound **5** with ethyl bromodifluoroacetate did not result in any product formation under Kumadaki's conditions, presumably because of instability of **5** under the reaction conditions. In contrast, the Michael addition proceeded smoothly with the *N,N*-di-Boc protected compound **4** giving product **6** in 75% yield (Scheme 5). This reaction was easily scaled up for the synthesis of 142 g of product **6** (71% yield) using 1.5 equiv. of ethyl bromodifluoroacetate and 3 equiv. of copper. The product contains the mono-Boc-protected amino acid ester as a minor impurity but can be used for the subsequent step without purification.

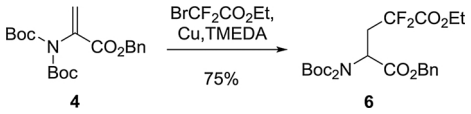
We have also carried out the reaction with sulfonamide derivative of dehydroalanine - compound **7** [17]. In this case a complex product mixture was formed. Only traces of expected product **8** [19] were observed by ESI-MS and NMR. The pure compound could not be isolated (Scheme 6).

The mechanism of formation of compounds **3b** and **6** is probably the same as the previously proposed for the reaction with other Michael acceptors [12c,13c]. Thus the initially formed organocopper complex **A** can further react with one more Cu equivalent giving the stabilized TMEDA intermediate **B**, which participates in Michael addition to the C = C-double bond (Scheme 7).

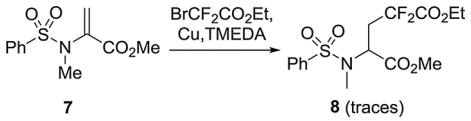
Synthetic approach to compound **6** is simple, cheap and robust that makes it especially valuable for further application of CF_2-containing functionalized compounds especially CF_2-containing α-amino acids.



Scheme 4. Synthesis of *N*-protected dehydroalanine benzyl esters **4** and **5**.



Scheme 5. Michael addition of ethyl bromodifluoroacetate to compound **4**.



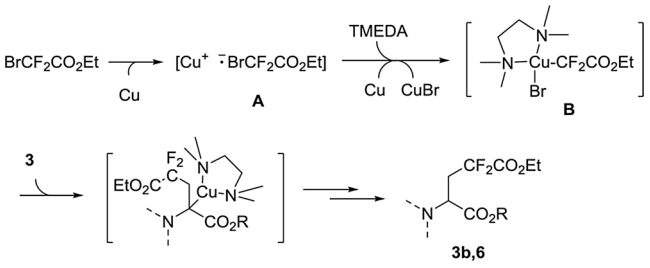
Scheme 6. Michael addition of ethyl bromodifluoroethylacetate to compound **7**.

Bearing orthogonal protective groups, compound **6** is a convenient derivative of γ,γ-difluoroglutamic acid (**1**) for synthesis of difluoro analogues of natural amino acids and their derivatives. Thus, hydrogenolysis of the benzyl ester **6** followed by Boc-deprotection using 6 N hydrochloric acid led to amino acid **1** (as hydrochloride) in 86% yield (Scheme 8).

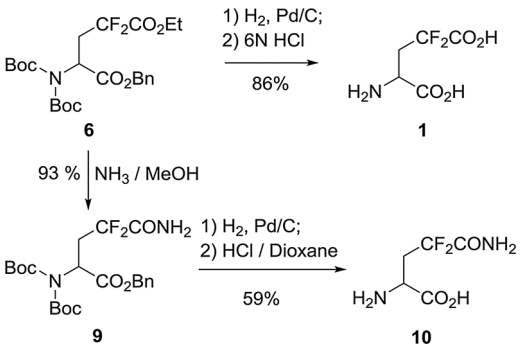
On the other hand, the reaction of compound **6** with ammonia in methanol at room temperature gave amide **9** by selective amidation of the more reactive difluoroacetate moiety [20]. This compound was easily transformed to γ,γ-difluoroglutamine **10** [20,21] by hydrogenolysis and subsequent HCl-mediated Boc-deprotection.

Compound **6** is also a convenient starting material for the synthesis of mono-Boc-protected derivatives of amino acids **1** and **10**. Thus, treatment of compound **6** with LiBr [22] led to mono-Boc-deprotection giving compound **11** (Scheme 9). The following hydrogenolysis led to monoester **12** [21], which on treatment with ammonia in methanol afforded the *N*-Boc-protected γ,γ-difluoroglutamine **13** [20,21].

The smooth addition of ethyl bromodifluoroacetate across the C = C-double bond of di-Boc-protected amino acid ester **5** in good yield led us to carry out reactions with other α,β-unsaturated α-amino acid derivatives. We prepared hitherto unknown dehydro α-aminobutyric acid derivative **14** as well as compounds **15–19** [17,23,24] (Fig. 1) according to literature procedures. Unfortunately, all our attempts to react bromodifluoroacetate with these compounds using Kumadaki's



Scheme 7. Mechanism of formation of compounds **3b** or **6**.



Scheme 8. Synthesis of amino acids **9** and **10** from compound **6**.