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# An improved practical synthesis of protected $\alpha$ -amino selenocarboxylates and its application to the synthesis of *N*-( $\alpha$ -aminoacyl)sulfonamides

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### ABSTRACT

An improved practical synthetic method was developed for the preparation of selenocarboxylates of amino acids through the reaction of the corresponding activated esters with sodium hydrogen selenide in alcoholic or aqueous medium. The protected  $\alpha$ -amino selenocarboxylates reacted readily with sulfonyl azide to form *N*-( $\alpha$ -aminoacyl)sulfonamides in high yields. The commonly used protecting groups in amino acid and peptide chemistries are well tolerated under these reaction conditions. No protecting groups are needed for the side chains of Arg, Met, Ser, Tyr, and Typ.

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*N*-Acylsulfonamide is an important functional group in organic chemistry and is present in many biologically active molecules including drugs. It has also been used in solid phase synthesis as a linker to anchor to solid support and in chemoselective ligation and bioconjugation reactions.<sup>1,2</sup> *N*-Acylsulfonamide has a pK<sub>a</sub> around 4–5 and excellent stability to chemical and enzymatic hydrolyses, making it a suitable bioisostere for carboxylates<sup>3–5</sup> and phosphates<sup>6</sup> in drug design. *N*-Acylsulfonamide functionality has been incorporated into investigational drugs and therapeutic agents for Alzheimer's disease,<sup>7</sup> bacterial infection,<sup>8</sup> osteoporolysis,<sup>9</sup> and cancer.<sup>10</sup> For example, a small molecule ABT-737 with an *N*-acylsulfonamide motif was shown to be a potent inhibitor of Bcl-2/Bcl-xL interaction with BH3 domain only proteins<sup>11</sup> and is currently under clinical trials as a potential therapeutic agent for the treatment of cancer.<sup>10</sup>

*N*-Acylsulfonamides are most commonly prepared either from direct acylation of the parent sulfonamide with acid chloride or anhydride under basic conditions (e.g., trialkylamine, sodium hydroxide),<sup>12,13</sup> or from direct condensation of carboxylic acid in the presence of coupling reagents such as EDC and CDI.<sup>8,14,15</sup> Although these methods proved to be effective in many cases, they do require strong coupling/condensation conditions (acyl chloride, anhydride, CDI), strong basic conditions, and/or elevated reaction temperature. Furthermore, the yields are often low due to the incompatibility between the reaction conditions and the functional groups present.<sup>16</sup> Williams group recently reported a novel method for the preparation of *N*-acylsulfonamides utilizing amino thioacid/azide amidation reaction with excellent yields.<sup>17</sup> However, the procedure uses lithium trimethylsilyl thiolate that is not read-

ily available. In addition, the procedure requires anhydrous conditions that might limit its application as a general procedure for the synthesis of *N*-acylsulfonamides.

Although first prepared in 1980s,<sup>18–20</sup> selenocarboxylates have not been successfully applied to chemoselective amidation reaction until recently.<sup>21,22</sup> Similar to thio acids, selenocarboxylates can react with azido compounds forming amide bonds, but in a more efficient manner and under milder conditions. We recently reported this new selenocarboxylate/azide amidation reaction<sup>21,23</sup> and its application to the direct coupling of amino acids with azides.<sup>24</sup> We demonstrated that the selenocarboxylate/azide amidation was highly chemoselective and mild, and worked very efficiently for electron-deficient azides including aromatic azides substituted with an electron-withdrawing group. We wanted to explore the use of the selenocarboxylate/azide amidation in amino acid chemistry to obtain N-( $\alpha$ aminoacyl)sulfonamides. To do so, we needed to overcome the problem of the lack of efficient methods to prepare  $\alpha$ -amino selenocarboxylates that are prone to oxidation. Our goal, therefore, also included the development of a procedure that would meet the following criteria: mild reaction conditions, compatibility with common protecting groups used in peptide chemistry such as Fmoc, Boc, Cbz, and Trt; high yield of amidation, and ease of handling. Previously, we reported a one-pot selenocarboxylate/azide amidation procedure<sup>24</sup> starting directly from  $N^{\alpha}$ protected amino acids where the corresponding  $N^{\alpha}$ -protected amino selenocarboxylates were prepared in situ by the treatment of the mixed anhydrides of amino acids with LiAlHSeH<sup>25</sup> and subsequently reacted with azides to form the corresponding amides. However, the preparation of LiAlHSeH required strict anhydrous conditions and the reaction solvents were limited to THF and Et<sub>2</sub>O. We would prefer aqueous or alcoholic reaction



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conditions for selenocarboxylate/azide amidation, since the rate of selenocarboxylate/azide amidation increases with increasing solvent polarity. Herein, we report an improved route to prepare the  $N^{\alpha}$ -protected amino selenocarboxylates by the reaction of the activated ester of  $N^{\alpha}$ -protected amino acids with sodium hydrogen selenide (NaHSe) and its application in a one-pot procedure to prepare N-( $\alpha$ -aminoacyl)sulfonamides using the selenocarboxylate/azide amidation strategy.

In protic solvents, selenium was reported to react rapidly with sodium borohydride (NaBH<sub>4</sub>) to generate sodium hydrogen selenide (NaHSe) according to Eqs. 1 and  $2.^{26}$  The selenium present in such a solution is predominantly in the form of hydrogen selenide ions (HSe<sup>-</sup>, >99%) with <0.5% of selenide ions (Se<sup>2-</sup>). The obtained sodium hydrogen selenide could be used directly to prepare selenocarboxylates as its alcoholic or aqueous solution without further purification.

$$4NaBH_4 + 2Se + 7H_2O \rightarrow 2NaHSe + Na_2B_4O_7 + 14H_2 \tag{1}$$

$$NaBH_4 + Se + 3EtOH \rightarrow NaHSe + B(OEt)_3 + 3H_2$$
(2)

Commercially available N-hydroxysuccinimide (OSu) esters of  $N^{\alpha}$ -protected amino acid were first used for our model reactions. The active esters were mixed with a stoichiometric amount of NaHSe, freshly prepared as mentioned above in a mixed solvent of THF with water or 2-propanol, to generate the corresponding selenocarboxylates in situ. Aliphatic selenocarboxylates were generally thought to be less stable than aromatic selenocarboxylates; to our surprise, we were able to monitor the formation of  $N^{\alpha}$ -protected amino selenocarboxylates using LC-MS in ES<sup>-</sup> mode. As shown in a representative analysis in Figure 1, the major peak at 3.08 min in the UV trace (Fig. 1A) is Z-Gly-SeH, which has an observed m/z of the most abundant molecular ion [M–H]<sup>-</sup> at 271.9 shown in the extracted ion chromatogram (Fig. 1B). The isotopic pattern of the molecular ion is characteristic of selenium-containing compounds (Fig. 1C): selenium has six naturally occurring isotopes, five of which are stable, including <sup>74</sup>Se (0.89%), <sup>76</sup>Se (9.37%), <sup>77</sup>Se (7.63%), <sup>78</sup>Se (23.79%), and <sup>80</sup>Se (49.61%), along with the fission products <sup>79</sup>Se and <sup>82</sup>Se (8.73%) that are considered stable due to their very long halflives.<sup>27</sup> Thus, using LC-MS, we were able to observe that NaHSe reacted rapidly with  $N^{\alpha}$ -protected amino acid–OSu esters to produce the corresponding selenocarboxylates. Most of the reactions were generally complete within 0.5 h at 0 °C. However, for sterically hindered amino acid-OSu esters, such as that of isoleucine, valine, and threonine, the reactions were slower and required room temperature to reach completion.

After completion of selenocarboxylation as monitored by LC–MS, a solution of *p*-toluenesulfonyl azide in THF was added via syringe. The amount of protected  $\alpha$ -amino selenocarboxylates generated was slightly in excess (1.2 equiv) relative to the azide used. The reactions started immediately with the precipitation of gray selenium and the formation of nitrogen gas, and were complete within 2 h at room temperature to form the corresponding *N*-( $N^{\alpha}$ -protected aminoacyl)sulfonamides. As shown in Table 1, Z, Boc, Fmoc, and Trt protecting groups were all well tolerated under our conditions and excellent yields of *N*-( $N^{\alpha}$ -protected aminoacyl)sulfonamides were obtained. We also found that the hydroxy group of tyrosine and threonine did not need to be protected. No significant intermolecular esterification was observed under the present reaction conditions and the desired *N*-( $\alpha$ -aminoacyl)sulfonamides were obtained in excellent yields (Table 1, entries 2 and 3).

Furthermore, we prepared an aqueous solution of NaHSe according to Eq. 1 and reacted it with Z-Gly-OSu in 50% aqueous THF to produce Z-Gly-SeNa. Subsequent amidation with *p*-toluenesulfonyl azide afforded the desired *N*-(Z-glycyl)sulfonamide



**Figure 1.** LC–MS analysis of the reaction between Z-Gly-OSu and sodium hydrogen selenide. Shown are the UV trace at 280 nm (A); extracted ion chromatogram using 271.9, the most abundant molecular ion–H (B); and ES<sup>–</sup> mass spectrum of Z-Gly-SeH (C).

in 92% yield (Table 1, entry 1), indicating that the reaction could be carried out under aqueous conditions. When Fmoc-Ile-OSu was used to react with NaHSe, room temperature, instead of 0 °C, was required to complete the selenocarboxylation, suggesting the presence of steric hindrance of Ile side chain. However, once the Fmoc-Ile-SeNa was formed, it quickly reacted with *p*-toluenesulfonyl azide to provide *N*-(Fmoc-isoleucyl)sulfonamide in an excellent yield (Table 1, entry 4). This indicated that the steric hindrance of selenocarboxylates did not play a significant role in the step of amidation, which is consistent with our previous observation that the rate of selenocarboxylate/azide amidation primarily depends on the electronic properties of the azide.<sup>24</sup> Furthermore, the indole unit of tryptophan did not need protection and was well tolerated without affecting the yield of amidation reaction (Table 1, entry 6).

In summary, a convenient and high-yield synthesis of selenocarboxylates of amino acids was developed and applied to the synthesis of *N*-( $\alpha$ -aminoacyl)sulfonamides. This strategy can also be applied to the synthesis of other electron-deficient amides that are usually difficult to prepare via conventional amidation methods due to the poor nucleophilicity of the corresponding amines.

## Table 1

Synthesis of N-( $N^{\alpha}$ -protected aminoacyl)sulfonamides via selenocarboxylate/azide amidation<sup>a</sup>



<sup>a</sup> Conditions: NaHSe (1.2 equiv) and  $N^{\alpha}$ -protected amino acid–OSu (1.2 equiv) in THF/2–PrOH, 0 °C, then *p*-toluenesulfonyl azide(1.0 equiv).

 $^{\rm b}$  Isolated yield under standard conditions unless noted otherwise in c and d.

с

<sup>c</sup> NaHSe (1.2 equiv) and  $N^{\alpha}$ -protected amino acid-OSu (1.2 equiv) in THF/H<sub>2</sub>O, 0 °C, then *p*-toluenesulfonyl azide (1.0 equiv). <sup>d</sup> NaHSe (1.2 equiv) and  $N^{\alpha}$ -protected amino acid-OSu (1.2 equiv) in THF/2-PrOH, rt, then *p*-toluenesulfonyl azide (1.0 equiv).

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