Tetrahedron 73 (2017) 6085–6091

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Application of bis-2-(trimethylsilyl)ethyl diselenide to the synthesis of selenium-containing amino acid derivatives

Tsubasa Yonezawa [a], Masahito Yamaguchi [a], Masayuki Ninomiya [a, b], Mamoru Koketsu [a, b, *]

[a] Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan
[b] Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

ARTICLE INFO

Article history:
Received 1 August 2017
Received in revised form
30 August 2017
Accepted 4 September 2017
Available online 7 September 2017

Keywords:
Selenation
Bis-2-(trimethylsilyl)ethyl diselenide
Selenium-containing amino acid
Selenocysteine
Selenoglutathione

ABSTRACT

Selenium-containing amino acids play a pivotal role as biomaterials for the synthesis of *Se*-dependent enzymes and repair proteins. Especially, selenocysteine and selenoglutathione are prominently involved in fundamental biological processes. In this study, a series of selenocysteine (Sec) and selenoglutathione (GSeH) derivatives were synthesized via 2-(trimethylsilyl)ethylselenation as a key step. Our findings suggested the relevance and application of a 2-(trimethylsilyl)ethylselenyl group to the *Se*-containing amino acid synthesis.

1. Introduction

Since the element selenium was firstly discovered from copper pyrites by the Swedish chemist Jöns Jacob Berzelius in 1817,[1] it had been predicted as a dangerous component causing livestock poisoning for over a century. In 1950s, Schwarz et al., reported its ability to serve interchangeably with vitamin E in the prevention of vascular or muscular signs.[2] Subsequently, it was reported that the glutathione peroxidase (GPx) having *Se* in its catalytic center spares vitamin E by *Se*.[3] Owing to the discoveries of several *Se*-dependent GPx forms,[4–7] other selenoenzymes (iodothyronine deiodinases,[8–10] thioredoxin reductases,[11,12] and selenophosphate synthetase[7,13]), and specific selenoproteins (SelH, SelI, SelK, SelN, SelM, SelO, SelP, SelR, SelS, SelT, SelV, SelW, and Sep15),[13–16] the selenium is now recognized to be nutritionally essential for humans.

Selenocysteine (Sec) is often referred to as the 21st amino acid found in 25 human selenoenzymes and selenoproteins. The GPxs catalyze the reduction of harmful hydroperoxides through the catalytic triad formation of the Sec residue at the active site with tryptophan and glutamine.[16] The key role of Sec in the overall catalytic process is believed to arise from the powerful nucleophilicity of *Se*. In general, selenoproteins are involved in a variety of fundamental functions, most notably redox homeostasis.[17] With the exception of plasma selenoprotein P, selenoproteins contain a single Sec residue, which is incorporated by the co-translational modification of transfer RNA-bound serine at certain loci coded by specific uracil-guanine-adenine codons.[18,19]

Organoselenium chemistry has attracted a great deal of attention due to the unique chemical behavior and potent pharmacological efficacy of *Se*-containing compounds. Our efforts have been directed to searching the possibilities of bis-2-(trimethylsilyl)ethyl (TSE) diselenide as a selenating agent in the synthesis of *Se*-containing biomolecules including sugars,[20,21] β-lactams,[22,23] and nucleosides.[24,25] Within the scope of our ongoing program, we would like to report the application of bis-TSE diselenide to the *Se*-containing amino acid synthesis, particularly Sec and selenoglutathione (GSeH) analogues.

2. Results and discussion

For preparation of Sec derivatives, there are two general types of synthetic approaches: (1) those employing a Sec selenolate anion that attacks alkyl halides (RX), and (2) those using a substituted

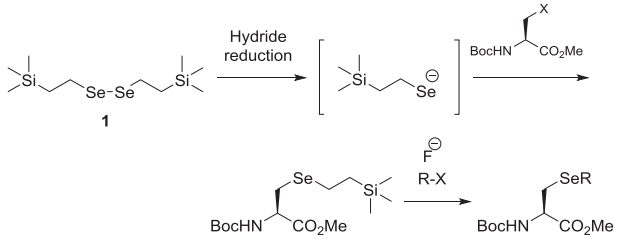
* Corresponding author. Department of Chemistry and Biomolecular Science, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan.
E-mail address: koketsu@gifu-u.ac.jp (M. Koketsu).

http://dx.doi.org/10.1016/j.tet.2017.09.004
0040-4020/

selenolate anion (RSe^-) that attacks β-halo alanine, *O*-tosyl serine, or serine-β-lactone, to form RSec. (1) One of the approaches utilizes selenocystine (dimeric Sec) as a precursor to possible building of structures.[26–28] By reference to a previous report,[29] Koide et al., prepared *Se*-4-methoxybenzylselenocysteine through *in situ* formation of a Sec selenolate anion by reduction of selenocystine with $NaBH_4$ and reaction with 4-methoxybenzyl chloride.[30] (2) In the other, the substituted diselenide or selenol are needed to prepare with respect to each functionality. Gieselman et al., reported the synthetic procedure which involved nucleophilic displacement of the *O*-tosyl moiety of L-serine derivatives by a 4-methoxybenzyl selenolate anion generated from 4-methoxybenzyl diselenide.[31] In this study, we therefore planned to use bis-2-(trimethylsilyl) ethyl (TSE) diselenide (TSE-Se-Se-TSE, **1**) as a selenating reagent which has two latent sites of reactivity. As outlined in Scheme 1, the initial step commences with *in situ* generation of a TSE selenolate anion (TSE-Se^-) from bis-TSE diselenide (**1**) by hydride reduction. This anion attacks to β-halo alanine, resulting in introduction of TSE selenyl moiety onto amino acid skeleton. Second step involves *Se*-alkylation with alkyl halides using high specificity and affinity between Si and F. Our approach never goes through selenocystine or even offers to prepare the suitable diselenide or selenol.

Bis-TSE diselenide (**1**) was prepared as published previously; following treatment of elemental selenium with sodium borohydride ($NaBH_4$), alkylation of the activated selenium with 2-(bromoethyl)trimethyl silane provided the desired selenating reagent (**1**) in 73% yield.[22,24] Under the Appel conditions,[32] *N*-[*tert*-butoxycarbonyl (Boc)]-3-iodo-L-alanine methyl ester (**2**) was prepared in 84% yield starting from *N*-Boc-L-serine methyl ester (Scheme 2). It is noteworthy that treatment of **2** with bis-TSE diselenide (**1**, 1.2 equiv.) in the presence of $NaBH_4$ (1.2 equiv.) and EtOH (3.0 equiv.) in DMF for 1 h proceeded swimmingly to afford the requisite *Se*-TSE-selenocysteine (**3**) in 89% yield. The characteristic ^{77}Se NMR signal for the TSE selenyl group appeared at 177.8 ppm.[24] Subsequently, we attempted *Se*-methylation of **3** by means of iodomethane (MeI, 5.0 equiv.) and tetrabutylammonium fluoride (TBAF, 3.0 equiv.) at room temperature for 24 h, however, the reaction yielded an unexpected α-methylated compound as a major product. It was deemed that the basicity of TBAF was the cause of α-methylation. In order to suppress of the bothersome side effect of TBAF, AcOH was selected. Addition of AcOH (3.0 equiv.) brought the role switching of TBAF in the reaction progress, leading to facilitation of *Se*-methylation (**4a**, 43% yield). The ^{77}Se NMR signal arising from **3** significantly sifted to the higher magnetic side of 45.6 ppm in **4a**.

Having successfully established *Se*-methylation of **3**, we next probed the generality of this protocol with a variety of electrophiles. Results are summarized in Table 1. Although reactions with MeI and EtI furnished the corresponding *Se*-alkylated products (**4a**, 43% and **4b**, 48%, Entries 1 and 2), **3** did not react with *i*-PrI at all (Entry 3). Compared to these results, treatment with allyl and propargyl bromides offered easy access to the products in good yields (**4d**, 81% and **4e**, 78%, Entries 4 and 5). With 2-bromoethyl methyl ether and bromoacetonitrile, the yields were decreased considerably (Entries 6 and 7). In the category of benzyl bromides bearing various functional groups on the benzene ring, treatment with benzyl and *p*-methylbenzyl bromides gave *Se*-benzylated products (**4h** and **4i**) in 86% and 73% yields, respectively (Entries 8 and 9). With *o*-, *m*-, and *p*-nitro substituted benzyl bromides, the yields were affected by substitution patterns (Entries 10–12). In contrast, chloro-substituted positions have little influence on the reaction progress (Entries 13–15). When α-haloacyl reagents were used, the reactions worked well (Entries 16–19). To further explore the scope of our synthetic strategy, we tried nucleophilic aromatic substitution and acylation. Although the reactivity of **3** with nitrofluorobenzenes was low, the *Se*-arylated product (**4t**) was obtained in 13% yield only by the reaction with *o*-nitrofluorobenzene (Entry 20). The *Se*-benzoylation was unsuccessful (Entry 22), and the instability of the produced acyl selenide could explain it as a result of its hydrolysis.



Scheme 1. Synthetic strategy for the synthesis of alkylselenocysteine derivatives.

Selenoglutathione (GSeH) appears to supply benefits by acting as a redox tripeptide substrate comprising glutamic acid (Glu), selenocysteine (Sec), and glycine (Gly).[33,34] In light of the above results, we shifted our focus to synthesize GSeH analogues from **3** as the starting point. Due to their structural complexity, their chemical synthesis is challenging. For conjugation of Gly with Sec, the methyl ester (**3**) was converted to the free carboxylate (**5**) under basic conditions (Scheme 3). Without further purification by silica gel column chromatography, Gly methyl ester was inserted into **5** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), and *N*,*N*-diisopropylethylamine (DIPEA), giving **6** in 60% yield with maintenance of the TSE selenyl moiety. Under slightly modified conditions of Table 1, *Se*-methylation and *Se*-benzylation actually succeeded in 60% for **7a** and 68% for **7b**. Acidic Boc-deprotection gave **8**, which was coupled with *N*-Boc-glutamic acid *tert*-butyl ester, to provide the tripeptide analogues (**9a**, 91% and **9b**, 85%). The final step was deprotection of the both amino and carboxylate functionalities which was effected in the same fashion, affording the targeted GSeH derivatives (**10a**, 74% and **10b**, 75% over two steps). The multistep sequence from **3** depicted in Scheme 3 allowed to construct the alkylselenyl Glu-Sec-Gly frameworks in overall yields of 21% for **10a** and 34% for **10b**.

3. Conclusion

We have demonstrated a concise route for the preparation of Sec analogues by tuning the selenation step. Given the convenient methodology presented herein was easily applicable to the GSeH synthesis, it may be suited for the incorporation of alkylselenyl moieties into peptide scaffolds. Our findings highlight the great utility and versatility of a 2-(trimethylsilyl)ethylselenyl group. We believe that these results will contribute to the better understanding of physiological roles of selenopeptide-containing biomacromolecules.

4. Experimental section

4.1. General

All solvents and reagents were purchased from the suppliers and used without further purification. IR spectra were recorded on a JASCO FT/IR-460 Plus spectrophotometer. Optical rotations were measured with a JASCO P-2300. MS spectra were obtained using the Waters UPLC-MS system (Aquity UPLC XevoQTof). NMR spectra were recorded with JEOL JNM-ECS 400 and JNM-ECA 600 spectrometers with tetramethylsilane as an internal standard. ^{77}Se chemical sifts were expressed in δ values deshielded with respect to neat Me_2Se. Silica gel column chromatography (CC) was performed on silica gel N-60 (40–50 μm). Thin-layer chromatography (TLC) spots on plates pre-coated with silica gel 60 F_{254} were