One-pot synthesis of orthogonally protected dipeptide selenazoles employing N²-amino selenocarboxamides and α-bromomethyl ketones

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ABSTRACT

A simple and efficient protocol for the synthesis of selenazole containing dipeptidomimetics using N²-amino selenocarboxamides and α-bromomethyl ketones is described. All the compounds made were isolated in good yields and fully characterized.

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Selenium is an essential trace element for higher organisms and the enzymes which contain selenium such as glutathione peroxidase (GPX), 5-碘代-1-type-1 play an important role in human physiology. In recent years organoselenium derivatives have shown marked biological and enzyme inhibitory activities. Notably, selenazole derivatives are one of the significant groups of organoselenium compounds due to their pharmacological relevance and are of interest in the field of material science. Molecules containing this functional group possess strong inhibitory activity against inducible nitric oxide synthase. The prominent examples are selenazofurin, a potent known antiviral agent, 2-piperidinoselenazole and 4-phenyl-2-piperidinoselenazole, which exhibit superoxide anion-scavenging activity.

Selenocarboxamides are a class of reactive intermediates, similar to their oxygen and sulfur analogs. They are important precursors for the synthesis of biologically active heterocycles like 1,3-selenazoles and 1,3-selenazines. The reported methods for the synthesis of selenocarboxamides include the reaction of nitrile with hydrogen selenide (H₂Se), sodium hydrogen selenide (NaHSe), monoselenophosphate, and bis(trimethylsilyl)selenide. Geisler et al., reported an efficient protocol for the synthesis of selenocarboxamides from the corresponding nitriles using phosphorous pentaselenide (P₂Se₅). P₂Se₅ is a more reliable reagent because of its ease of preparation, less toxic than NaSeH or H₂Se, and moreover the ability of P₂Se₅ circumvents the addition of NEt₃/pyridine and borontrifluoride diethyletherate. This prompted us to opt for P₂Se₅ toward the synthesis of selenocarboxamides from the corresponding N²-protected amino nitriles (Fig. 1).

Recently our group has reported the synthesis of selenoxopeptides, N²-protected amino alkyl isoselenocyanate, selenoureia, selenohydantoin, selenocarbamate, and selenazole containing peptidomimetics. The utility of both carboxamides, as well as thiocarboxamide derived from N²-protected amino acids as building blocks for the construction of oxazole/thiazole peptidomimetics has been well documented. In continuation of our interest on organoselenium compounds, herein we report the one-pot synthesis of orthogonally protected selenazole dipeptidomimetics employing N²-Fmoc/Boc/Z protected amino selenocarboxamides and α-bromomethyl ketone which involves the following retrosynthetic pathway (Fig. 2).

Initially, the preparation of N²-protected amino nitrite was undertaken. N²-Protected amino acid was converted to the corresponding carboxamide via its mixed anhydride and then treated with aqueous ammonia. The resulting amide was subjected with
trifluoroacetic anhydride (TFAA)/pyridine (py) at 0 °C in THF to obtain the nitrile (Scheme 1). Later, elemental Se was heated with red phosphorus under electric Bunsen burner till the mixture became glassy black purple solid indicating the formation of P$_2$Se$_5$. Then it was cooled to rt and powdered thoroughly.

In the next step, the synthesis of $N^a$-protected amino selenocarboxamide 2 was carried out (Scheme 1). In a typical procedure Fmoc-Leu-$\psi$[CN] (1.0 equiv) 1b was dissolved in EtOH and freshly prepared P$_2$Se$_5$ (2.0 equiv) was added. The reaction mixture was heated to reflux and then a few drops of water were added to generate H$_2$Se, which reacts with nitrile 1b for the formation of the corresponding selenocarboxamide 2b. After completion of the reaction, the reaction mixture was filtered and washed with EtOH to obtain Fmoc-Leu-[$\psi$(C(=Se)NH$_2$) 2b. The crude residue was purified by column chromatography and the isolated pure compound 2b was characterized by Mass, $^{1}H$, $^{13}C$ and $^{77}Se$ NMR spectroscopy. The $^{77}Se$ NMR shows a characteristic single peak at around $\delta$ 529.9 for the selenocarbonyl group. The adoptability and efficacy of the protocol were further demonstrated by synthesizing a series of $N^a$-Fmoc/Boc/Cbz selenocarboxamides 2 from the corresponding nitriles 1 (Table 1).

Heterocyclic amino acids such as oxazoles and thiazoles are substructures comprising numerous macrolactam natural products having biological activities including cytotoxicity, $\beta$-glycoprotein pump inhibition, and metal binding properties. Oxazole containing amino acids are suitable building blocks for the preparation of model systems with well defined secondary structures. Peptides containing thiazole subunits are characterized by reduction of multi drug resistance of certain types of lymphoblasts, antifungal, antibacterial, antimicrobial, and antitubercular activities. The structure of fascinating selenazole resembles with oxazole/thiazole. Different protocols have been reported for the synthesis of selenazo-oles by using selenoamide or selenourea as the starting material. Selenoureas are inconvenient due to their high cost and low stability to air and light. In particular Zhang et al., have synthesized selenazole containing cyclic peptides (QZ59Se-SSS and QZ59Se-RRR) for crystallization with $\beta$-glycoprotein (pgp) but this protocol is limited to the preparation of Boc-amino selenocarboxamides. Thus, the limited applicability with the available literature prompted us to prepare orthogonally protected dipeptide selenazole from the corresponding $N^a$-amino selenocarboxamides.

In the next part of our study, the synthesis of $N^a$-urethane orthogonally protected selenazole linked dipeptidomimetics was carried out (Scheme 2). In a typical procedure, Fmoc-Leu-$\psi$[C(=Se)NH$_2$] 2b was refluxed with Boc-Phe-[$\psi$(O)CH$_2$Br] 3b in acetone to obtain selenazole linked dipeptidomimetic 4b. The reaction was found to be complete within 30 min, as observed by TLC analysis. It was also evident by the disappearance of bromomethyl ketone peak at around 1735 cm$^{-1}$ in the IR spectrum. The isolated crude selenazole dipeptidomimetic 4b was purified through column chromatography (hexane/EtOAc 9:1%) and characterized by NMR and mass spectrometry. The generality of
the protocol was demonstrated for the synthesis of a series of orthogonally protected dipeptide selenazoles (Table 2). Using chiral HPLC, the racemization study of the prepared diastereomeric dipeptide selenazoles \(4d\) and \(4d'\) were analyzed. They showed peaks at \(R_t = 13.53\) min (\(4d\)) and \(R_t = 18.42\) min (\(4d'\)), respectively. Also intentionally prepared equimolar mixture of \(4d\) and \(4d'\) showed distinct peaks at \(R_t = 13.62\) and \(R_t = 18.60\) min. These observations inferred that the present protocol was free from racemization.

In conclusion we have developed a simple protocol for the synthesis of selenazole linked \(N^\alpha\)-orthogonally protected dipeptidomimetics by the condensation of \(N^\alpha\)-amino selenocarboxamides with \(\alpha\)-bromomethyl ketones. Various \(N^\alpha\)-protected selenocarboxamides have also been synthesized.
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Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.085.

References and notes
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1.38–1.41 (m, 2H), 1.50–1.53 (m, 2H), 2.85 (t, 2H, \(J = 4.8\) Hz), 3.72 (t, 1H, \(J = 4.2\) Hz), 5.18 (s, 2H), 6.88 (br, 1H), 7.10 (br, 1H), 7.12–7.16 (m, 5H), 9.56 (br s, 1H), 9.92 (br s, 1H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): 21.9, 27.9, 31.2, 33.5, 40.8, 50.3, 66.1, 78.5, 127.2, 127.6, 129.8, 140.9, 151.9, 153.3, 197.1; \(^{77}\)Se NMR (75 MHz, CDCl\(_3\)): \(\delta 517.1\); HRMS (m/z) calcd for: C\(_{19}\)H\(_{29}\)N\(_3\)O\(_4\)SeNa 466.1221; found: 466.0982 [M+Na]+.

Compound 2i: \(^1H\) NMR (300 MHz, DMSO-d\(_6\)): \(\delta 2.72 (d, 2H, J = 6.6\) Hz), 3.61 (s, 2H), 3.81 (t, 1H, \(J = 3.8\) Hz), 5.37 (s, 2H), 7.05 (br, 1H), 7.12–7.19 (m, 10H), 9.88 (br s, 1H), 10.07 (br s, 1H); \(^{13}C\) NMR (75 MHz, DMSO-d\(_6\)): 35.5, 39.5, 53.2, 65.9, 127.2, 127.6, 127.9, 128.2, 128.6, 128.8, 137.2, 141.3, 152.2, 196.7; \(^{77}\)Se NMR (75 MHz, DMSO-d\(_6\)): \(\delta 497.8\); HRMS (m/z) calcd for: C\(_{18}\)H\(_{20}\)N\(_2\)O\(_2\)SeNa 431.0308; found: 431.0314 [M+Na]⁺.

Compound 4a: \(^1H\) NMR (300 MHz, CDCl\(_3\)): \(\delta 0.95 (d, 6H, J = 6.2\) Hz), 1.17 (d, 6H, \(J = 6.4\) Hz), 1.38 (s, 9H), 1.52–1.57 (m, 2H), 1.71–1.74 (m, 1H), 2.33–2.37 (m, 1H), 3.25 (d, 1H, \(J = 6.8\) Hz), 4.21 (t, 1H, \(J = 5.2\) Hz), 5.15 (s, 1H), 5.31 (s, 2H), 5.75 (br, 1H), 6.62 (br, 1H), 7.15–7.19 (m, 5H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): 17.8, 21.2, 24.5, 29.3, 32.7, 41.4, 49.8, 56.9, 65.7, 81.1, 114.5, 127.1, 127.6, 128.5, 141.4, 149.8, 155.7, 156.5, 174.5; \(^{77}\)Se NMR (75 MHz, CDCl\(_3\)): \(\delta 656.3\); HRMS (m/z) calcd for: C\(_{25}\)H\(_{37}\)N\(_3\)O\(_4\)SeNa 546.1847; found: 546.1884 [M+Na]⁺.

Compound 4b: \(^1H\) NMR (300 MHz, CDCl\(_3\)): \(\delta 1.10 (d, 6H, J = 7.4\) Hz), 1.35 (s, 9H), 1.67–1.93 (m, 3H), 2.63 (d, 2H, \(J = 5.6\) Hz), 3.41 (t, 1H, \(J = 4.8\) Hz), 4.16 (t, 1H, \(J = 5.2\) Hz), 4.41 (t, 1H, \(J = 7.0\) Hz), 4.68 (d, 2H, \(J = 7.0\) Hz), 5.17 (s, 1H), 6.15 (br, 1H), 6.92 (br, 1H), 7.13–7.78 (m, 13H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): 23.5, 24.7, 25.1, 35.2, 38.7 41.1, 47.4, 55.2, 67.7, 80.4, 115.9, 126.1, 126.6, 127.7, 128.1, 128.5, 128.7, 129.2, 138.8, 141.5, 143.2, 151.5, 156.3, 157.2, 175.4; \(^{77}\)Se NMR (75 MHz, CDCl\(_3\)): \(\delta 681.7\); HRMS (m/z) calcd for: C\(_{36}\)H\(_{41}\)N\(_3\)O\(_4\)SeNa 682.2160; found: 682.2195 [M+Na]⁺.

Compound 4e: \(^1H\) NMR (300 MHz, CDCl\(_3\)): \(\delta 1.34 (d, 3H, J = 7.2\) Hz), 2.51 (d, 2H, \(J = 6.8\) Hz), 3.85 (t, 1H, \(J = 4.6\) Hz), 4.32 (t, 1H, \(J = 6.2\) Hz), 4.42–4.47 (m, 1H), 4.78 (d, 2H, \(J = 6.2\) Hz), 5.12 (s, 1H), 5.28 (s, 2H), 6.31 (br, 1H), 6.52 (br, 1H), 7.15–7.71 (m, 18H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): 17.6, 15.4, 45.1, 47.3, 54.0, 65.7, 68.2, 110.9, 126.4, 126.8, 127.3, 127.6, 127.8, 128.3, 128.5, 128.7, 128.9, 129.2, 139.2, 140.8, 141.5, 143.2, 152.1, 156.2, 157.5, 171.8; \(^{77}\)Se NMR (75 MHz, CDCl\(_3\)): \(\delta 681.1\); HRMS (m/z) calcd for: C\(_{36}\)H\(_{33}\)N\(_3\)O\(_4\)SeNa 674.1534; found: 674.1527 [M+Na]⁺.