Research Article

Journal of PeptideScience

Received: 3 April 2010 Revised: 14 June 2010 Accepted: 15 June 2010 Published online in Wiley Online Library: 16 September 2010

(wileyonlinelibrary.com) DOI 10.1002/psc.1276

Isoselenocyanates derived from amino acid esters: an expedient synthesis and application to the assembly of selenoureidopeptidomimetics, unsymmetrical Selenoureas and selenohydantoins‡

Hosahalli P. Hemantha and Vommina V. Sureshbabu*

An important class of organoselenium compounds-α-isoselenocyanato esters 4 hasbeen prepared by a reaction of α-isocyano esters with elemental selenium powder. The reaction issimple, rapid and all the isoselenocyanates havebeen isolated as stable ones after chromatographic purification. These *hitherto* unreported classes of molecules would be useful building blocks for the preparation of variety of selenium containing peptidomimetics. In this study, the utility of the title molecules in the preparation of selenoureidopeptidomimetics 6, unsymmetrical selenoureas 8 and selenohydantoins 10 isdemonstrated. Copyright © 2010 European Peptide Society and John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article

Keywords: organoselenium compounds; isoselenocyanato esters; unsymmetrical selenoureas; selenoureidopeptidomimetics; selenohydantoins

Introduction

Our studies on the synthesis of peptidomimetics led to some useful intermediates such as isocyanates derived from Fmoc-N^{α}-amino [1]/peptide acids [2], which were employed for the synthesis of *N*-(1-Fmoc-amino alkyl)formamides [3], chiral *N*-Fmoc-β-amino alkyl isonitriles [4] and ureidopeptidomimetics [2]. Recently, we have also reported N^{β}-urethane (Fmoc/Boc/Z) protected amino alkyl isothiocyanates and demonstrated their utility in the preparation of thioureidopeptidomimetics [5,6]. With continued interest in this area, our attention is now drawn towards the preparation of α-isoselenocyanato esters/amides (Figure 1), *hitherto* unreported classes of building blocks useful for the assembly of selenium containing peptidomimetics [7,8]. Various types of N-terminal modifications of amino/peptide acid esters have been reported in the literature leading to the generation of important class of peptidomimetic precursors. Nowick *et al*., reported [9] the synthesis of enantiomerically pure α-isocyanato esters, which are useful precursors to several classes of peptidomimetics [10–12]. However, isothiocyanate derivatives of amino acids (Figure 1) were initially prepared by the treatment of amino acid esters with carbon disulphide in THF in the presence of triethylamine (TEA) *via* dithiocarbamate intermediates followed by their decomposition [13]. The use of thiophosgene under modified Schotten–Baumann conditions was also reported to afford isothiocyanato peptide esters [12]. With this background, we became interested to explore another amine terminal modification of amino acids leading to the generation of yet another class of intermediates – isoselenocyanato esters (Figure 1).

Isoselenocyanates, such as their oxygen and sulfur analogs, are reactive organoselenium compounds [14,15]. They are, in general, generated when required and transformed further into the desired target molecules, are somewhat unstable and decompose over a period of time at ambient temperatures. These key intermediates have marked applications in organic synthesis, including carbohydrate chemistry [16,17]. Isoselenocyanates are precursors for a number of Se-heterocycles such as selenazoles, selenazepanes [17]. Although isoselenocyanates **4** derived from proteinogenic amino acids is yet to be accomplished (Scheme 1), it is well established that selenium compounds play significant role in both chemistry as well as biology of peptides and proteins. Among the important selenium compounds known in amino acid chemistry [18], two prominent ones are: selenocysteine, being considered as the 21st amino acid [19,20], often used in native chemical ligation [21] and the corresponding selenopeptides. In the present communication, we report isoselenocyanates derived from amino acid esters/amides and demonstrate their utility as building blocks in the synthesis of selenoureidopeptidomimetics and selenohydantoins.

* *Correspondence to: Vommina V. Sureshbabu, Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr B. R. Ambedkar Veedhi, Bangalore-560 001, India. E-mail: hariccb@hotmail.com; sureshbabuvommina@rediffmail.com*

Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr B. R. Ambedkar Veedhi, Bangalore-560 001, India

‡ *Dedicated to Prof. K. M. Sivanandaiah on his 75th birth anniversary.*

Journal of PeptideScience

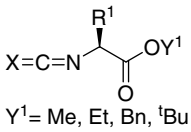
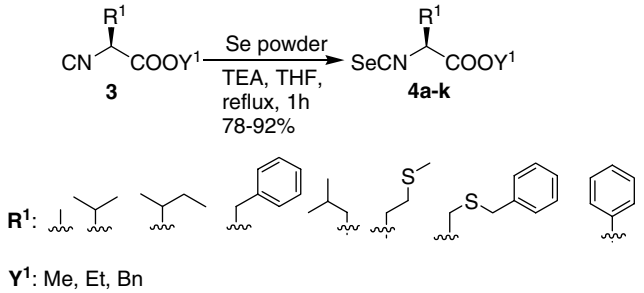


Figure 1. α-Isocyanato (X═O)/α-isothiocyanato (X═S)/α-isoselenocyanato (X═Se) esters derived from amino acids.



Scheme 1. Conversion of isonitriles into isoselenocyanates **4**.

Results and Discussion

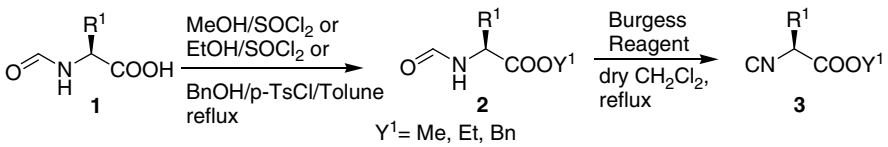
Synthesis of α-Isoselenocyanato Esters SeC-Xaa-OY 4

In the beginning of this study we had proposed a reaction for the straightforward synthesis of isoselenocyanato esters starting from appropriate α-amino acid esters by treating with either carbon diselenide [22] or selenophosgene [23]. But, the execution of this reaction appeared impractical owing to the cost and the availability of the reagents. Alternatively, a reaction of isonitriles with elemental selenium is also known to furnish isoselenocyanates [24–26]. Although several other methods have been investigated for the synthesis of isoselenocyanates [27–29], we had to adopt a practically feasible protocol applicable to amino acid chemistry. Among all the procedures, the one involving isonitrile and selenium powder has emerged as classical protocol for general use [17,30] because this approach gives isoselenocyanates in satisfactory to good quantities. Elemental selenium is easy to handle, commercially available and less expensive than other selenating agents. Above all, isonitriles [31–40] derived from *N*-formyl (For group) protected α-amino acid esters **2** [41] are already known compounds employed as C-protected derivatives in peptide science. Hence, we chose α-isocyano amino acid esters **3** (isonitriles derived from amino acid esters) as precursors to isoselenocyanates to accomplish our studies (Scheme 2).

N-For-amino acids **1** were made and transformed to the corresponding methyl, ethyl or benzyl esters **2** [42,43]. The next step is the preparation of isonitriles which is the key aspect from the point of maintaining the enantiomeric purity. Ivar Ugi has pioneered the chemistry of isocyanides, including those derived from α-amino acid esters [34]. Because of the exhaustive works from the groups of Ugi and others, isonitriles have gained tremendous synthetic interest especially in multi-component reaction (MCR)s which have been developed into vital tools for combinatorial synthesis of drug candidates [34–40]. In particular, the α-isocyano esters obtained by the dehydration of corresponding For-amino esters have registered wide utility especially in MCRs for generating peptidic structures. For the dehydration of For-Xaa-esters into isocyano esters, Ugi has employed reagents such as Phosgene or its derivatives in the presence of a base or oxomethylenebis-(3H$^+$-imidazolium)bis(methanesulphonate) [35]. Danishefsky's group recently investigated the aspect of retaining enantiomeric purity during dehydration of For-amino esters employing triphosgene and a base at low temperatures [31]. It is reasonable that a mild protocol involving neutral or slightly acidic reaction medium is advantageous. The strong dehydrating conditions employing excess base at higher temperature need to be completely circumvented. McCarthy, *et al*., [44] employed Burgess reagent, a well known dehydrating agent for the conversion of several types of formamides into isonitriles, including a few amino acid derived ones. Sureshbabu *et al*., recently employed Burgess reagent for the synthesis of chiral *N*-Fmoc-β-aminoalkyl isonitriles [4]. In view of these two feasibilities, we selected two isonitriles, C-Ala-OMe **3a** and C-Phe-OMe **3b** as model compounds to prepare. Thus, two separate experiments were carried out starting from For-Ala-OMe **2a** and For-Phe-OMe **2b**. Both the conditions: (a) Burgess reagent at 50 °C in dry CH_2Cl_2 for 1.5 h and (b) triphosgene (0.35 eq.)/*N*-methyl morpholine (NMM; 2 eq.) at −78 to −30 °C for about 30 min were run separately on these two model compounds. The optical rotation values and the yield of the four products obtained from these experiments are summarized in the Table 1. The former route has been found to give higher yield, consequently, all the other isonitriles in this study were made employing Burgess reagent. Two unnatural amino acids α-aminoisobutyric acid (Aib) [45] and gabapentin (Gpn) [46], well known to be useful in *de novo* design of peptides, were also selected during these studies. The formyl compounds For-Aib-OMe and For-Gpn-OEt were prepared using established procedures. They were then dehydrated to the isonitriles C-Aib-OMe **3l** and C-Gpn-OEt **3m** as described above.

The key step of this study is the conversion of isocyano ester **3** to the corresponding isoselenocyanato derivatives **4**. In order to investigate an appropriate condition for this conversion, preliminary experiments were conducted using the isonitrile C-Ala-OMe **3a**. To a solution of isonitrile **3a** in THF, elemental selenium powder was added and the resulting suspension was refluxed in the presence of TEA. Quantitative conversion of the starting material was observed in about an hour as adjudged by TLC.

The isoselenocyanate **4a** was isolated by a simple work up and the crude compound was isolated analytically pure by column chromatography in 92% yield. Either at lower temperature or under the influence of ultrasound, this conversion was not satisfactory (Table 2). The isoselenocyanate retains a prominent brown patch on the TLC plate, which is a characteristic feature of most of the selenated compounds. Further, the protocol was extended successfully to prepare a series of isoselenocyanate derivates from



Scheme 2. Synthesis of isonitrile derivatives of amino acid esters **3**.

Table 1. Synthesis of isocyano esters **3a** and **3b** under different conditions

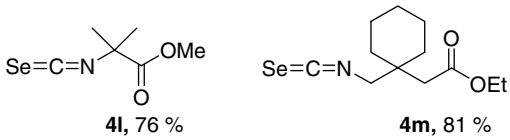
Entry	Method	$[\alpha]^{25}_D$ (c 1, $CHCl_3$) (% yield) C-Ala-OMe	C-Phe-OMe
1	Burgess reagent, dry CH_2Cl_2, reflux; 1.5 h	−42.1 (95)	−52.6 (92)
2	Triphosgene/NMM −78to −40 °C, 30 min	−43.8 (72)	−50.2 (80)

Table 2. Synthesis of SeC-Ala-OMe **4a** under various conditions

Sl. No	Condition	Temp (°C)	Time (min)	Yield (%)
1	Thermal	65	60	92
2	Thermal	50	95	57
3	Ultrasound	30	120	20
4	Ultrasound	40	120	53
5	Ultrasound	50	90	78

other amino acid esters (methyl/ethyl/benzyl) as well. All the α-isoselenocyanates **4b–k** were obtained in good yield (78–92%; Table 3). Isonitrile derivatives of two unnatural amino acids Aib and Gpn were also converted to the corresponding isoselenocyanates **4l** and **4m** (Figure 2) in 76 and 81% yields respectively. The IR spectrum of these isoselenocyanates contain a sharp peak at around 2248 cm^{-1} corresponding to the stretching frequency of C═Se bond of NCSe. The ^{13}C NMR of the isoselenocyanates possesses a characteristic signal at δ 133 corresponding to isoselenocyanate carbon, whereas the ^{77}Se NMR had a signal at δ −349.

These isoselenocyanates showed appreciable stability. At low temperature they can be stored for about two weeks without any noticeable degradation of the product. For example, there was no change in the ^1H NMR and IR spectra of SeC-Val-OMe **4c** recorded after storing for two weeks.



4l, 76 % **4m**, 81 %

Figure 2. Isoselenocyanates of Aib **4l** and Gpn **4m**.

α-Isoselenocyanato Carboxamides 5a–f

The protocol was then extended to prepare few isoselenocyanato carboxamides also. Unlike esters and α-isocyano carboxamides are stable solids and odorless but retain the isocyanide reactivity in isocyanide based multicomponent reactions (IMCRs) [47,48]. Four complementary protocols are available to access this important starting material [48,49]. To implement our other objective in making α-isoselenocyanato carboxamides **5** (Figure 3), six known α-isocyano carboxamides were made employing known procedure.

Briefly, For-amino acids were coupled with the desired amines under standard peptide coupling conditions (DCC/HOBt) followed by the dehydration of the For group into isocyano moiety employing Burgess reagent. They were isolated in good yield and high enantiomeric purity. Further, it was found that their conversion to the desired isoselenocyanates **5** under the present conditions was simple and straightforward. Thus, all the products formed **5a–f** were isolated easily with an overall yield of 68–76%.

Selenoureidopeptidomimetics 6

A simple, straightforward and useful approach to selenium analogs of ureas is the reaction of isoselenocyanates with an amine. There are several other routes reported in the literature for the preparation of selenoureas but their general applicability is yet to be fully demonstrated [50]. In order to illustrate the scope of isoselenocyanates **4** and **5**, the synthesis of selenoureidopeptidomimetics **6** was undertaken (Scheme 3). It was found that the reaction of isoselenocyanates **4** with amino acid esters **7** at room temperature proceeded rapidly and complete starting material was generally consumed within 60 min. All the selenoureas **6** were obtained in 67–71% yield after column chromatographic purification and were fully characterized. In these experiments, the hydrochloride salts of amino acid esters were neutralized using activated zinc [51] prior to their addition

Table 3. List of amino acid ester derived α-isoselenocyanates **4**

Entry	Comp. No.	Se═C═N-Xaa-COOY Xaa	Y	Yield (%)	HRMS Obsrd. (Calcd.)	$[\alpha]^{25}_D$ (c 1, $CHCl_3$)
1	**4a**	CH_3	CH_3	92	215.9554 (215.9540)	−27.5
2	**4b**	$CH_2C_6H_5$	CH_3	88	291.9860 (291.9853)	−74.2
3	**4c**	$CH(CH_3)_2$	CH_3	90	243.9855 (243.9855)	−44.0
4	**4d**	$CH(CH_3)CH_2CH_3$	CH_3	84	258.0017 (258.0009)	−19.6
5	**4e**	$CH_2CH_2SCH_3$	CH_3	80	275.9563 (275.9573)	−32.2
6	**4f**	H	CH_2CH_3	79	215.9556 (215.9540)	–
7	**4g**	C_6H_5	CH_3	82	277.9683 (277.9696)	−10.2
8	**4h**	$CH_2SCH_2C_6H_5$	CH_2CH_3	78	351.9875 (351.9885)	−11.6
9	**4i**	CH_3	$CH_2C_6H_5$	89	291.9867 (291.9853)	−67.5
10	**4j**	$CH(CH_3)_2$	$CH_2C_6H_5$	87	320.0155 (320.0166)	−80.0
11	**4k**	$CH_2CH(CH_3)_2$	$CH_2C_6H_5$	80	334.0330 (334.0320)	−70.2

Journal of PeptideScience

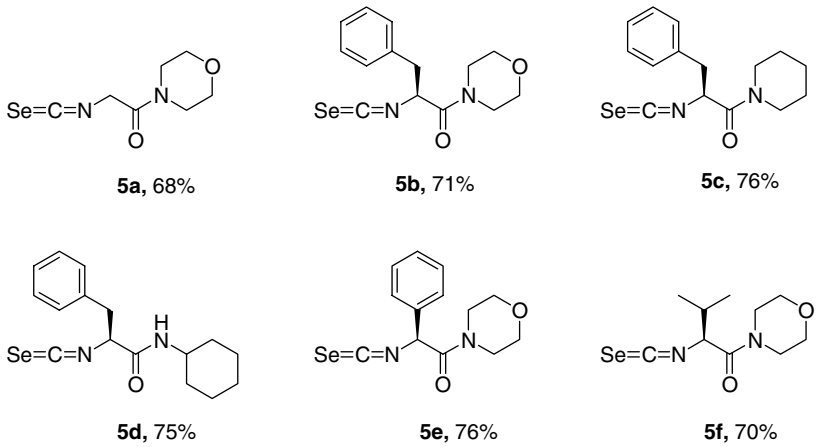
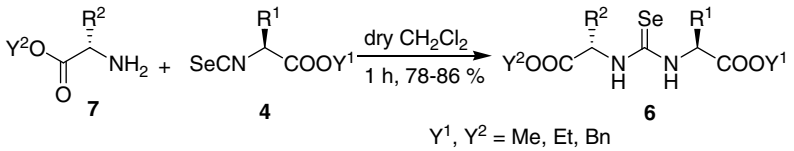


Figure 3. α-Isoselenocyanato carboxamides **5a–f**.



Scheme 3. Synthesis of selenoureidopeptides **6**.

into the reaction mixture. However, when benzyl esters were employed for coupling, as in the case of Phe (in **6a**), the corresponding *p*-toluene sulphonic acid salt was neutralized using an equimolar quantity of NMM. No additional base was necessary for carrying out the coupling of isoselenocyanates with amino acid esters. The ^{13}C NMR of selenoureas showed a signal at δ 182 corresponding to the selenocarbonyl carbon. Furthermore, ^{77}Se NMR spectra possess peaks around δ 230–300, which also confirms the selenocarbonyl carbon. Under the same conditions, isoselenocyanate derived from Gpn, **4k** also reacted very fast to give the expected urea **6b** (Table 4).

Unsymmetrical Selenoureas 8

In recent years, organic catalysts are being explored for various kinds of studies in asymmetric synthesis [52]. Thioureas to a larger extent and ureas in specific case studies have been developed as very useful catalysts [53]. Among the unsymmetrically substituted ureas being designed and developed, amino/peptide acid [54] or sugar moiety [55] is selected as one of the substituents in many catalysts where the other substituent is an aromatic moiety. There are already a couple of reports describing the utility of selenoureas as catalysts as well [56]. In view of these recent advancements in organic synthesis, we extended this study to prepare several unsymmetrical selenoureas also (Scheme 4). Thus, the isoselenocyanates **4** were allowed to react with various amines such as aniline, *p*-bromoaniline and cyclohexylamine to obtain the designed ureas **8a–e**, which were purified and characterized (Table 4).

Test for Racemization

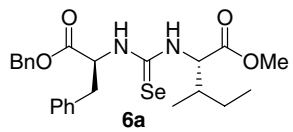
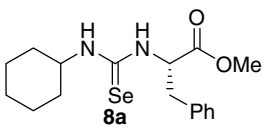
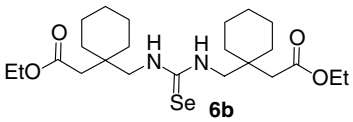
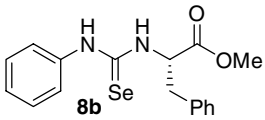
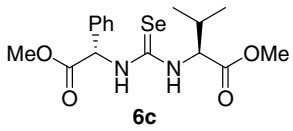
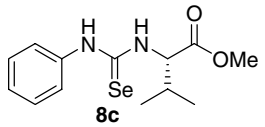
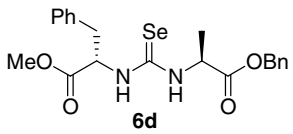
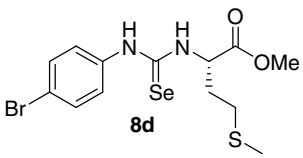
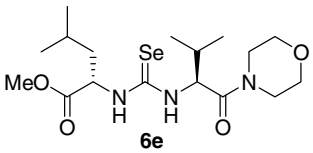
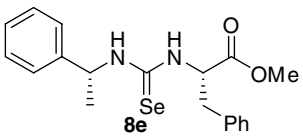
The chemistry of amino acids can involve epimerization during the reactions at amino as well as carboxy functions. Any study involving these substrates should be accompanied by a test for examining the extent of racemization or otherwise. During the assembly of ureidopeptidomimetics, ^{1}H NMR analysis of the urea adducts made using enantiomer(s)/racemate of 1-phenylethylamine was considered to establish enantiomeric purity of the products [9]. In this regard, (*S*, 3*R*)**8e** was taken as specimen example. Its epimer (*S*, 3*S*)**8e** and racemate (*S*, 3*R*, *S*)**8e** were prepared by coupling (*S*)-methyl 2-isoselenocyanato-3-phenylpropanoate **4b** with (*S*) and (*R*/*S*)-1-phenylethylamine, respectively (Figure 4). Each epimer (*S*, 3*R*)**8e** and (*S*, 3*S*)**8e** had a single distinct methyl group doublet in their ^{1}H NMR spectrum. The recorded values for these two isomers are: δ 1.47 and 1.49 and 1.49 and 1.51. respectively. Further, the δ values for methyl group's resonance of (*S*, 3*R*, *S*)**8e** are 1.46, 1.47 and 1.48, 1.51, which revealed the presence of two epimers. Similar studies were also made on selenourea adducts prepared by coupling (*R*) and (*S*)-1-phenylethylamine with SeC-Phg-OMe **4g** separately. In this case also, the ^{1}H NMR spectrum showed distinct doublets at δ 1.50 and 1.52 and 1.52 and 1.53 respectively for (*S*, 3*R*)**8f** and (*S*, 3*S*)**8f** selenoureido epimers. These results demonstrate the optical purity of SeC-Phe-OMe **4b** as well as SeC-Phg-OMe **4g** prepared by the present protocol at levels detectable by ^{1}H NMR.

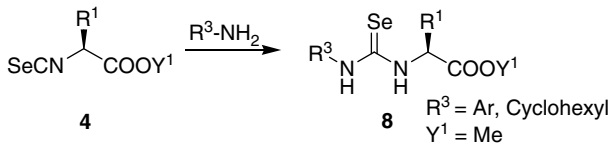
Synthesis of Hydantoins 10a–h

Hydantoins are an important class of biologically active molecules [57]. Both chemistry and biology of thiohydantoins are also known [58]. Ishihara *et al*., [59] demonstrated the preparation of selenohydantoins derived from Val, Ala, Gly, Met, Leu and Phe by treating the phenyl isoselenocyanate with amino acid esters at reflux. As a final part of this study, the isoselenocyanates **4** are employed as starting compounds for the synthesis of a few selenohydantoins. They were allowed to react with an amine (aniline in four case studies, cyclohexylamine, *m*-toluidine, 3-chloroaniline and 3-bromoaniline in one example each) in THF at reflux for 3–4 h (Scheme 5).

It was found to be a smooth reaction, complete in about 4 h. After a simple workup, the selenohydantoins **10a–h** were

Table 4. List of selenoureido derivatives **6** and **8**

Entry	Selenoureidopeptidomimetics **6**		Unsymmetrical selenoureas **8**	
	Compound	Yield (%)	Compound	Yield (%)
1	 **6a**	71	 **8a**	76
2	 **6b**	78	 **8b**	75
3	 **6c**	67	 **8c**	82
4	 **6d**	70	 **8d**	70
5	 **6e**	55	 **8e**	72



Scheme 4. Preparation of selenoureas **8**.

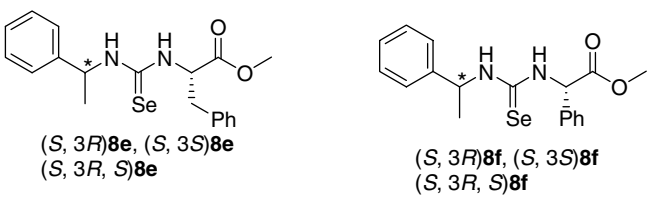


Figure 4. *R, S, R/S*-phenylethylamine coupled selenourea derivatives **8**.

obtained as pure compounds in 74–92% yields. The ^{77}Se NMR of **10g** had a sharp signal at δ 229.46 confirming the presence of C═Se bond of selenoureido group. Characteristic peaks in IR, ^{1}H and ^{13}C NMR along with high resolution mass spectroscopy (HRMS) data confirmed their structures.

Conclusions

A new class of isoselenocyanates derived from amino acid esters/amides is described by a reaction of corresponding isonitriles with elemental selenium. They have been isolated, characterized and their utility in assembling selenoureidopeptidomimetics and selenohydantoins is also demonstrated. In view of the known utility of organoselenium compounds in biological studies, we suspect that selenoureidopeptides also may have unrealized potential with respect to drug design. They may appear as attractive entities useful in asymmetric synthesis and in biological studies. In spite of the demonstration of this type of studies in sugar chemistry, it was not applied in peptide science. A word of caution in this regard is 'toxicity' which needs to be dealt with at an appropriate time. In addition, it seems reasonable that other bioactive compounds in this class would be discovered whether screening efforts in this area are thoroughly investigated. The 'alphabets' of isoselenocyanate monomers may find applications in combinatorial chemistry.

Experimental

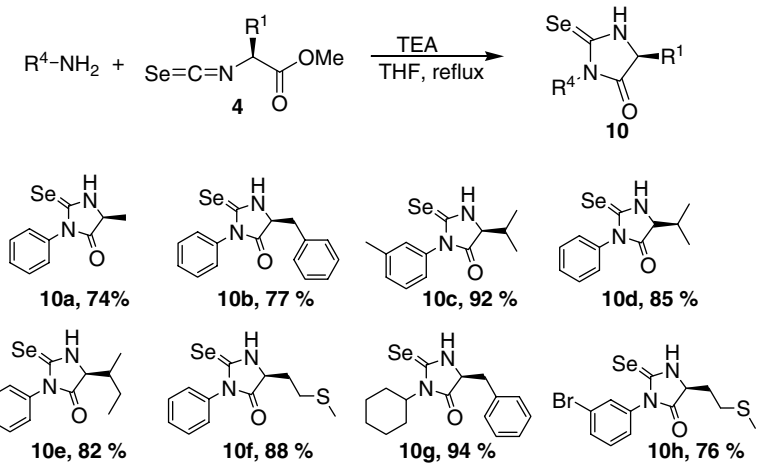
General Procedure for the Preparation of α-Isocyano Esters 3

A solution of For-amino acid ester **2** (1 mmol) in dry CH_2Cl_2 (8 ml) was refluxed for 1.5 h, along with Burgess reagent (0.24 g, 1 mmol). After the completion of reaction (TLC analysis), it was diluted with CH_2Cl_2 (10 ml) and the organic phase was washed with aq. citric acid (5%, 10 ml), water and brine. Evaporation of the solvent under vacuum afforded the α-isocyano ester **3** in excellent yield and high purity which was taken for next step as such.

General Procedure for the Preparation of α-Isoselenocyanato Esters 4

The isonitrile **3** (1 mmol) was dissolved in THF (10 ml), to which were added triethyl amine (97 µl; 0.7 mmol), Se black powder

Journal of PeptideScience



Scheme 5. Synthesis of selenohydantoins 10.

(94 mg; 1.2 mmol) and the reaction mixture was refluxed for 60–75 min. After the completion of the reaction, it was passed through a pad of celite and the filtrate was concentrated. The residue was dissolved in ethyl acetate (15 ml) and the organic layer was washed with water (10 ml × 2) and brine (10 ml). The organic layer was concentrated by rotary evaporation under reduced pressure and the crude residue was purified by column chromatography (silica gel, 100–200 mesh, 10% ethyl acetate in hexane) to afford pure isoselenocyanates **4**.

General Procedure for the Preparation of Selenoureido Compounds 6 and 8

To a solution of isoselenocyanate **4** or **5** (1.5 mmol) in dry CH_2Cl_2 (10 ml) at room temperature was added a solution of amino acid ester (1.8 mmol, obtained by neutralizing the corresponding salt; treating with either commercial zinc dust [45] in case of hydrochloride salts or using an equimolar quantity of NMM in the case of *p*-toluenesulfonic acid salts) or aliphatic/aromatic amine (1.6 mmol) and the reaction mixture was stirred at the same temperature for an hour. After the completion of reaction (TLC), it was diluted with CH_2Cl_2 (10 ml) and washed with citric acid solution (10%, 10 ml), water (10 ml) and brine (10 ml). After the evaporation of the solvent under reduced pressure, the crude product was purified using column chromatography (silica gel, 100–200 mesh, 15–20% ethyl acetate in hexane) to isolate the analytically pure selenoureas in good yields.

General Procedure for the Synthesis of Selenohydantoin 10

To a solution of isoselenocyanato methyl ester **4** (1 mmol) and an amine (1.2 mmol) in THF (8 ml) was added TEA (410 µl; 3.0 mmol) and it was refluxed for 3 h. After completion of the reaction, it was concentrated and the residue was dissolved in ethyl acetate (15 ml). The organic phase was washed with citric acid solution (10 ml, 10%), water and brine. After drying over anhydrous sodium sulfate, the crude compound was purified through column chromatography (silica gel 100–200 mesh, 15% EtOAc in hexane) to afford the corresponding selenohydantoin as colorless crystalline solid.

Spectral Characterization Data of Representative Compounds

(*S*)-Methyl 2-Isoselenocyanato-3-Phenylpropanoate 4b

Colorless gum; yield: 88%; R_f 0.78 (*n*-hexane-EtOAc 4:1); IR (film) υ_{max} = 2148, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.26–7.42 (m, 5H), 4.64 (m, 1H), 3.83 (s, 3H), 3.22 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.7, 135.1, 131.4, 129.9, 129.4, 128.3, 61.6,53.9, 39.9; ^{77}Se NMR ($CDCl_3$, 400 MHz) δ = −348.872; HRMS (*m/z*) Calculated for $C_{11}H_{11}NO_2Se$+Na: 291.9853; Observed: 291.9860.

(*S*)-2-Isoselenocyanato-3-Phenyl-1-(Piperidin-1-Yl)Propan-1-One 5c

Gum; yield: 76%; R_f 0.50 (*n*-hexane/EtOAc 4:1); IR (film) υ_{max} = 2150, 1758 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.14–7.39 (m, 5H), 4.16–4.20 (m, 2H), 4.04–4.08 (m, 2H), 1.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 129.8, 129.2, 128.9, 127.9, 126.9, 69.4, 54.1, 53.3, 39.9, 24.6, 21.1, 20.9; ^{77}Se NMR ($CDCl_3$, 400 MHz): δ = −376.761; HRMS (*m/z*) Calculated for $C_{15}H_{18}N_2OSe$+Na: 345.0482; Observed: 345.0480.

EtO-Gpn-CSe-Gpn-OEt 6b

Colorless gum; yield: 78%; R_f 0.40 (*n*-hexane/EtOAc 4:1); IR (film) υ_{max} = 1756, 1545 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (br, 1H), 6.73 (br, 1H), 4.08 (q, J = 5.1 Hz, 4H), 3.69–3.80 (m, 4H), 2.32 (s, 4H), 1.39 (br, 20 H), 1.21 (t, J = 5.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 180.1, 173.0, 67.9, 60.7, 53.5, 37.5, 33.9, 25.8, 21.4, 14.2; ^{77}Se NMR ($CDCl_3$, 400 MHz): δ = 184.82; HRMS (*m/z*) Calculated for $C_{23}H_{40}N_2O_4Se$+Na: 511.2051; Observed: 511.2043.

(*S*)-Methyl 2(3-Cyclohexylselenoureido)-3-Phenylpropanoate 8a

Gum; yield: 76%; R_f 0.40 (*n*-hexane/EtOAc 4:1); IR (film) υ_{max} = 1728, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.27 (br, 2H), 7.23–7.41 (m, 5H), 4.50 (m, 1H), 4.07 (s, 3H), 3.25 (d, J = 5.7 Hz, 2H), 2.94 (m, 1H), 1.92–2.25 (m, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.6, 172.6, 134.0, 129.3, 128.9, 127.7, 60.7, 57.3, 36.9, 28.5, 28.0, 25.8, 24.9; HRMS (*m/z*) Calculated for $C_{17}H_{24}N_2O_2Se$+Na: 391.0901, Observed: 391.0908.

(*S*)-5-Isopropyl-2-Selenoxo-3-*M*-Tolylimidazolidin-4-One 10c

Crystalline solid; yield: 92%; m.p.: 148 °C; R_f 0.45 (*n*-hexane/EtOAc 5 : 1); IR (KBr) $\upsilon_{max} = 1750, 1524\ cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.98$ (br, 1H), 7.00–7.34 (m, 4H), 3.94 (d, $J = 3.3$ Hz, 1H), 2.34 (s, 3H), 2.21 (m, 1H), 0.96–1.08 (dd, $J = 5.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 185.6, 173.2, 139.9, 133.6, 130.9, 129.5, 129.4, 125.9, 66.7, 31.4, 21.9, 19.4, 16.8$; HRMS (*m/z*) Calculated for $C_{13}H_{16}N_2OSe + Na$: 319.0326; Observed: 319.0330.

Acknowledgements

We thank the Council of Scientific and Industrial Research (grant No. 01(2323)/09/EMR-II) and Department of Science and Technology (Grant No. SR/S1/OC-26/2008), Government of India for financial support. We also thank the Departments of Inorganic & Physical Chemistry, Organic Chemistry, Sophisticated Instrument Facility, I.I.Sc., Bangalore for recording NMR and mass spectra. We would like to thank Professor Fred Naider, CUNY, New York, USA for useful discussion. We also acknowledge Dr K. Natarajan of Hical Ltd., Bangalore, India for a free sample of Gpn.

Supporting information

Supporting information may be found in the online version of this article.

References

1 Patil BS, Vasanthakumar GR, Sureshbabu VV. Isocyanates of N^{α}-[(9-Fluorenylmethyl) oxy]carbonyl amino acids: synthesis, isolation, characterization, and application to the efficient synthesis of urea peptidomimetics. *J. Org. Chem.* 2003; **68**: 7274–7280.
2 Sureshbabu VV, Patil BS, Venkataramanarao R. Preparation, isolation, and characterization of N^{α}-Fmoc-peptide isocyanates: solution synthesis of oligo-α-peptidyl ureas. *J. Org. Chem* 2006; **71**: 7697–7705.
3 Sudarshan NS, Narendra N, Hemantha HP, Sureshbabu VV. An efficient conversion of the carboxylic group of *N*-Fmoc α-amino acids/peptide acids into *N*-formamides employing isocyanates as key intermediates. *J. Org. Chem* 2007; **72**: 9804–9807.
4 Sureshbabu VV, Narendra N, Nagendra G. Chiral *N*-Fmoc-β-amino alkyl isonitriles derived from amino acids: first synthesis and application in 1-substituted tetrazole synthesis. *J. Org. Chem.* 2009; **74**: 153–157.
5 Sureshbabu VV, Naik SA, Hemantha HP, Narendra N, Das U, Row TNG. *N*-Urethane-protected amino alkyl isothiocyanates: synthesis, isolation, characterization, and application to the synthesis of thioureidopeptides. *J. Org. Chem.* 2009; **74**: 5260–5266.
6 Guichard G. *Pseudo-peptides in Drug Discovery*. Nielsen, PE (ed.). WILEY-VCH: Weinheim, 2004; 33–120.
7 *Synthesis of Peptides and Peptidomimetics (Houben-Weyl)*. Goodman, M., Felix, A. Moroder L. and Toniolo C. (eds.). Georg Thieme Verlag: Stuttgart, Germany, 2003; Vol. E22c and references cited therein.
8 Lam PY, Jadhav PK, Eyermann CJ, Hodge CN, Ru Y, Bacheler LT, Meek JL, Otto MJ, Rayner MM, Wong YN, Chang CH, Weber PC, Jackson DA, Sharpe TR, Erickson-Viitanen S. An unnatural biopolymer. *Science* 1994; **263**: 380–384.
9 Nowick JS, Powell NA, Nguyen TM, Noronha G. An improved method for the synthesis of enantiomerically pure amino acid ester isocyanates. *J. Org. Chem.* 1992; **57**: 7364–7366.
10 Soth MJ, Nowick JS. A peptide/oligourea/azapeptide hybrid that adopts a hairpin turn. *J. Org. Chem.* 1999; **64**: 276–281.
11 Nowick JS, Holmes DL, Mackin G, Noronha G, Shaka AJ, Smith EM. An artificial β-sheet comprising a molecular scaffold, a β-strand mimic and a peptide strand. *J. Am. Chem. Soc.* 1996; **118**: 2764–2765.
12 Nowick JS, Holmes DL, Noronha G, Smith EM, Nguyen TM, Huang SL. Synthesis of peptide isocyanates and isothiocyanates. *J. Org. Chem.* 1996; **61**: 3929–3934.
13 Munch H, Hansen JS, Pittelkow M, Christensen JB, Boas U. A new efficient synthesis of isothiocyanates from amines using di-*tert*-butyl dicarbonate. *Tetrahedron Lett.* 2008; **49**: 3117–3119.
14 Nogueira CW, Zeni G, Rocha JBT. Organoselenium and organotellurium compounds: Toxicology and pharmacology. *Chem. Rev.* 2004; **104**: 6255–6285.
15 Mugesh G, du Mont WW, Sies H. Chemistry of biologically important synthetic organoselenium compounds. *Chem. Rev.* 2001; **101**: 2125–2179.
16 Sommen GL, Linden A, Heimgartner H. Selenium-containing heterocycles from isoselenocyanates: synthesis of 1,3-selenazolidine and perhydro-1,3-selenazine derivatives. *Eur. J. Org. Chem.* 2005; 3128–3137.
17 Lopez O, Maza S, Ulgar V, Maya I, Fernandez-Bolanos JG. Synthesis of sugar-derived isoselenocyanates, selenoureas and selenazoles. *Tetrahedron* 2009; **65**: 2556–2566.
18 Muttenthaler M, Alewood PF. Selenopeptide chemistry. *J. Pept. Sci.* 2008; **14**: 1223–1239.
19 Combs GF, Lu J. *Selenium: Its Molecular Biology and Role in Human Health*. Hatfield (ed.). Kluwer: New York, 2001; 205–218.
20 Wessjohann LA, Schneider A. Synthesis of selenocysteine and its derivatives with an emphasis on selenenylsulfide (-Se-S-) formation. *Chem. Biodiver.* 2008; **5**: 375–388.
21 Hondal RJ, Nilsson BL, Raines RT. Selenocystein in native chemical ligation and expressed protein ligation. *J. Am. Chem. Soc.* 2001; **123**: 5140–5141.
22 Marquart JR, Belford RL. Gas chromatographic determination and purification of carbon diselenide. *Anal. Chem.* 1978; **50**: 656–657.
23 Butler IS. Transition-metal thiocarbonyls and selenocarbonyls. *Acc. Chem. Res.* 1977; **10**: 359–365.
24 Boccanfuso AM, Griffin DW, Dunlap RB, Odom JD. *Bioorg. Chem.* 1989; **17**: 231–239.
25 Sonoda N, Yamamoto G, Tsutsumi S. Synthesis of aliphatic isoselenocyanates by the reaction of aliphatic isocyanides with selenium in the presence of triethylamine. *Bull. Chem. Soc. Jpn.* 1972; **45**: 2937–2938.
26 Franklin WJ, Werer RL. Alkyl isoselenocyanates and related compounds. *Tetrahedron Lett.* 1965; **6**: 3003–3008.
27 Banert K, Toth C. Synthesis and reactions of vinyl isoselenocyanates. *Angew Chem. Int. Ed. Engl.* 1995; **34**: 1627–1629.
28 Burger H, Goetze U. Trimethylsilyl isoselenocyanat. *J. Organomet. Chem.* 1967; **10**: 380–382.
29 Koketsu M, Suzuki N, Ishihara H. Preparation of isoselenocyanate and synthesis of carbodiimide by oxidation of selenourea. *J. Org. Chem.* 1999; **64**: 6473–6475.
30 Barton DHR, Parekh SI, Tajbakhsh M, Theodorakis EA, Tse CL. A convenient and high yielding procedure for the preparation of isoselenocyanates. Synthesis and reactivity of *O*-alkylselenocarbamates. *Tetrahedron* 1994; **50**: 639–654.
31 Zhu J, Wu X, Danishefsky SJ. On the preparation of enantiomerically pure isonitriles from amino acid esters and peptides. *Tetrahedron Lett.* 2009; **50**: 577–579.
32 Zhdanko AG, Nenajdenko VG. Nonracemizable isocyanoacetates for multicomponent reactions. *J. Org. Chem.* 2009; **74**: 884–887.
33 *Multicomponent Reactions*. Zhu J. and Bienayme H. (eds.). WILEY-VCH, Verlag GmbH: Germany, 2005.
34 Domling A, Ugi I. Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* 2000; **39**: 3168–3210..
35 Giesemann G, Ugi I. Synthesis of chiral α-isocyano esters and other base-sensitive isocyanides with oxomethylenebis(3H$^+$-imidazolium) bis(methanesulphonate), a versatile dehydrating reagent. *J. Chem. Res.* 1982; 79.
36 Lindhorst T, Bock H, Ugi I. A new class of convertible isocyanides in the Ugi four-component reaction. *Tetrahedron* 1999; **55**: 7411–7420.
37 Domling A, Ugi I. The seven-component reaction. *Angew. Chem. Int. Ed.* 1993; **32**: 563–564.
38 Ugi I. From isocyanides via four-component condensations to antibiotic syntheses. *Angew. Chem. Int. Ed* 1982; **21**: 810–819.
39 Lehnhoff S, Goebel M, Karl RM, Klosel R, Ugi I. *Angew. Chem. Int. Ed.* 1995; **34**: 1104–1107.
40 Obrecht R, Ugi I. Isocyanide synthesis with phosphoryl chloride and diisopropylamine. *Synthesis* 1985; **4**: 400–402.
41 Chorev M. The partial retro-inverso modification: a road traveled together. *Peptide Sci. (Biopolymers)* 2005; **80**: 67–84.

Journal of PeptideScience

42 Yamazaki T, Benedetti E, Kent D, Goodman M. Conformational requirements for sweet-tasting peptides and peptidomimetics. *Angew. Chem. Int. Ed.* 1994; **33**: 1437–1451.
43 Vasanthakumar GR, Patil BS, Sureshbabu VV. Microwave assisted facile synthesis of amino acid benzyl ester *p*-toluenesulfonate and hydrochloride salts. *Lett. Pept. Sci.* 2002; **9**: 207–209.
44 Creedon SM, Crowley HK, McCarthy DG. Dehydration of formamides using the Burgess reagent: a new route to isocyanides. *J. Chem. Soc., Perkin Trans. 1* 1998; 1015–1017.
45 Venkataraman J, Shankaramma SC, Balaram P. Design of folded peptides. *Chem. Rev.* 2001; **101**: 3131–3152.
46 Aravinda S, Ananda K, Chatterjee S, Shamala N, Balaram P. Hybrid peptide design. Hydrogen bonded conformations in peptides containing the stereochemically constrained γ-amino acid residue, gabapentin. *J. Am. Chem. Soc.* 2007; **129**: 4039–4048.
47 Fayol A, Zhu J. Synthesis of polysubstituted 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines by a novel multicomponent reaction. *Org. Lett.* 2004; **6**: 115–118.
48 Domling A, Beck B, Fuchs T, Yazbak A. Parallel synthesis of arrays of amino acid-derived isocyanoamides useful as starting materials in IMCR. *J. Comb. Chem.* 2006; **8**: 872–880.
49 Fayol A, Housseman C, Sun X, Janvier P, Bienayme H, Zhu J. Synthesis of α-isocyano-alkyl(aryl) acetamides and their use in the multicomponent synthesis of 5-aminooxazole, pyrrolo[3,4-b]pyridin-5-one and 4,5,6,7-tetrahydrofuro[2,3-c]pyridine. *Synthesis* 2005; 161–165.
50 Koketsu M, Fukuta Y, Ishihara H. Reaction of *N*,*N*-dimethylselenocarbamoyl chloride with neucleophiles. Preparation of diselenocarbamates, selenothiocarbamates, and selenoureas. *J. Org. Chem.* 2002; **67**: 1008–1011.
51 Ananda K, Sureshbabu VV. Deprotonation of hydrochloride salts of amino acid esters and peptide esters using commercial zinc dust. *J. Pept. Res.* 2001; **57**: 223–226.
52 *Enantioselective Organocatalysis*. Dalko PI. (ed.). WILEY-VCH, Verlag: Germany, 2007.
53 Doyle AG, Jacobsen EN. Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev* 2007; **107**: 5713–5743.
54 Zou W, Ibrahem I, Dziedzic P, Sunden H, Cordova A. Small peptides as modular catalysts for the direct asymmetric aldol reaction: ancient peptides with aldolase enzyme activity. *Chem. Commun.* 2005; 4946–4948.
55 Wang C, Zhou Z, Tang C. Novel bifunctional chiral thiourea catalyzed highly enantioselective aza-Henry reaction. *Org. Lett.* 2008; **10**: 1707–1710.
56 Koketsu M, Ishihara H. Thiourea and selenourea and their applications. *Curr. Org. Synth* 2006; **3**: 439–455.
57 Brouillete WJ, Jestkov VP, Brown ML, Akthar MS, Delorey TM, Brown GB. Bicyclic hydantoins with a bridgehead nitrogen. Comparison of anticonvulsant activities with binding to the neuronal voltage-dependent sodium channel. *J. Med. Chem.* 1994; **37**: 3289–3293.
58 Blanco-Ania D, Hermkens PHH, Sliedregt LAJM, Scheeren HW, Rutjes FPLT. Synthesis of hydantoins and thiohydantoins spiro-fused to pyrrolidines: drug like molecules based on the 2-aylethyl amine scaffold. *J. Comb. Chem.* 2009; **11**: 527–538.
59 Koketsu M, Takahashi A, Ishihara H. A facile preparation of selenohydantoins using isoselenocyanato. *J. Heterocycl. Chem.* 2007; **44**: 79–81.

