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RESEARCH ARTICLE

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Click Reaction of Selenols with Isocyanates: Rapid Access to Selenocarbamates as Peroxide-switchable Reservoir of Thiol-peroxidase-like Catalysts

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Abstract. Selenols react with isocyanates under mild catalyst-free conditions to generate selenocarbamates in good yield and with high selectivity over potentially competing nucleophilic additions. The methodology enables the incorporation of a wide variety of functional groups providing rapid access to a broad array of densely functionalised selenocarbamates. In the presence of competing heteroatom-centered nucleophiles, isocyanates selectively couple with selenols. Selenocarbamates exhibited remarkable thiol-peroxidase-like properties, enabling the reduction of hydrogen peroxide at the expense of thiols, which are converted into the corresponding disulfides. A series of control experiments suggested that the catalytic mechanism proceeds through an unprecedented path, involving a H_2O_2-promoted transcarbamoylation reaction leading to a thiocarbamate with concomitant releasing of catalytically active selenolate anions. Readily undergoing peroxide-driven thiol-selenol exchange, selenocarbamates behave as equivalents of selenolate anions with good thiol-peroxidase-like activity.

Keywords: Selenocarbamates; Selenols; Isocyanates; Antioxidants; Glutathione peroxidase-like catalysts

Introduction

Selenocarbamates have considerable synthetic potential because of the facile homolytic cleavage of their weak carbon-selenium bond. In this regard, selenocarbamates have recently emerged as unconventional alternative reagents for the generation of *N*-acyl radicals. As such, radical cleavage of selenocarbamates has been exploited as a versatile tool in organic synthesis.[1-3] For example, Ishihara and co-workers constructed the azabicyclo[3.3.1]nonane core of (-)-haliclonin A through an elegant stereoselective tandem radical reaction of a key selenocarbamate precursor with allyltributylstannane.[4]

Selenocarbamates undergo palladium-catalysed insertion of isocyanides into the carbon-selenium bond providing amino-2-oxoethannimidoselenoates.[5] The palladium-catalysed reaction of selenocarbamates with alkynes was exploited for the regio- and stereo-selective synthesis of β-selenoacrylamides. An intramolecular version of such selenocarbamoylation was efficiently extended to *N*-alkynyl-substituted selenocarbamates to access conjugated α-alkylidene lactams.[6] A related Pd(0)-catalysed selenocarbamoylation of allenes enabled the regioselective formation of functionalised allyl selenides[7] and allylseleno-substituted α,β-unsaturated lactams.[8] *N*-Allenyl selenocarbamates also undergo palladium-catalysed decarbonylative rearrangement providing access to 3-seleno-1-azadienes.[9]

On the other hand, the unique biological properties of selenium-containing organic compounds continue to attract the interest of medicinal chemists and has led to disclose a wide array of biologically active selenium-based derivatives. For example, Ebselen, which arguably represents one of the most deeply investigated selenium-containing heterocycles, have been very recently found to exhibit a promising biological activitiy against the main protease M^{pro} of SARS-CoV-2.[10] In this context, selenocarbamates also exhibited interesting antiviral activity.[11]

However, in spite of their wide application, only a few methodologies have been reported for the preparation of selenocarbamates. These approaches generally rely on the reactivity of isocyanates with selenium-centered nucleophiles such as selenocarboxylic acids[12] or selenolates, generated by means of reductive cleavage of diselenides with $Zn/AlCl_3$.[13] *N*-Alkyl-*Se*-alkylselenocarbamates can be prepared from isocyanates and haloalkanes by using LiAlHSeH as the selenating reagent.[14] Other methods involve the reaction of amines and carbon monoxide with elemental selenium, followed by treatment with alkyl halides,[15] the reduction of diselenides with lithium triethylborohydride followed by the reaction with diethyl carbamoyl chloride,[16] as well as the reductive cleavage and subsequent

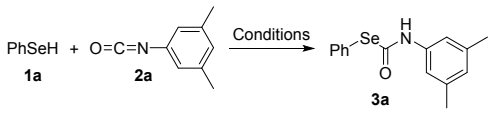
alkylation of bis(*N*,*N*-dimethylcarbamoyl)diselenide.[17] The reaction of *N*-tosylamines with triphosgene and benzeneselenol in the presence of pyridine have also been exploited for the synthesis of selenocarbamates.[18] Recently, a synthetic route relying on the oxidative C-Se coupling of *N*,*N*-disubstituted formamides and diselenides under tert-butyl hydroperoxide conditions has also been developed.[19]

Most of the reported methodologies rely on multistep procedures which often employ unstable selenylating reagents and require strictly controlled reaction conditions. The use of strong reducing agents, acids or bases significantly limits the functional group tolerance and the scope of the existing procedures. In order to address these limitations, we envisaged the possibility to employ selenols and isocyanates as convenient starting materials to develop a mild protocol for the synthesis of selenocarbamates. We recently reported a convenient approach towards stable aliphatic and aromatic selenols,[20] which reacted efficiently with a wide number of eletrophiles providing access to a plethora of functionalised organoselenium compounds.[21] Owing to their exquisite electrophilic character,[22] isocyanates would couple with selenols under mild conditions. Hereby, we report the synthesis of a diverse range of selenocarbamates with remarkable thiol-peroxidase-like properties through the catalyst-free click coupling of selenols with isocyanates. To our knowledge, these systems exhibited higher catalytic activity than most of the reported Se-containing catalysts, including ebselen and diphenyl diselenide. Our studies elucidated that catalytic mechanism proceeds through an unprecedented path involving a peroxide-driven transcarbamoylation which makes selenocarbamates a new class of highly effective peroxides-switchable antioxidants.

Results and Discussion

We commenced our investigations by studying the reaction of benzeneselenol **1a** with 3,5-dimethylphenylisocyanate **2a** in different solvents. Results of this screening are reported in the Table 1. Pleasingly, the coupling of **1a** with **2a** occurred smoothly, enabling the formation of the corresponding selenocarbamate **3a** with moderate to good conversion values in most of the evaluated solvents. Interestingly, higher conversions were generally achieved upon using polar non protic solvents such as acetonitrile and DMSO (Table 1, entries 5 and 6). Particularly, using acetonitrile as the solvent, the selenol-isocyanate coupling was found to be fast and highly selective, leading to **3a** with excellent yield. On the other hand, dichloromethane and methanol (Table 1, entries 2 and 7) proved to be poor solvents in promoting the desired transformation. Intriguingly, no reaction was observed in dichloromethane and unreacted **2a** was almost quantitatively recovered. Conversely, as expected, methanol reacted with isocyanate **2a** leading to the corresponding methyl-substituted carbamate, which was isolated as the main product alongside with a minor amount of **3a** (ca. 10%). Notably, excellent conversion was also observed under solvent-free conditions, although a longer time was required in order to achieve complete consumption of the starting material (Table 1, entry 8). The effect of catalysts was also evaluated. Both aluminium trioxide and triethylamine, employed in toluene and dichloromethane respectively, led to improved conversion values and enhanced selenocarbamate formation rates with respect to reactions performed in the same solvents under catalyst-free conditions (Table 1, entries 9 and 10 *vs* entries 1 and 2).

Table 1. Optimisation of the synthesis of selenocarbamates.



Entry	Conditions	Conversion (%)[a]	Yield (%)	Polarity Index[b]
1	PhMe, r.t., 4 h	76	68	2.3
2	CH_2Cl_2, r.t., 4 h	<10	n.d.	3.7
3	THF, r.t., 4 h	68	57	4.2
4	Acetone, r.t., 4 h	77	70	5.4
5	MeCN, r.t., 10 min	>96	89	6.2
6	DMSO, r.t., 2 h	>96	75	6.5
7	MeOH, r.t., 2 h	n.d.	n.d.	6.6
8	*neat*, r.t., 12 h	>96	90	
9	PhMe/Al_2O_3, r.t., 1 h	88	81	
10	CH_2Cl_2/Et_3N, r.t., 4 h	52	33	

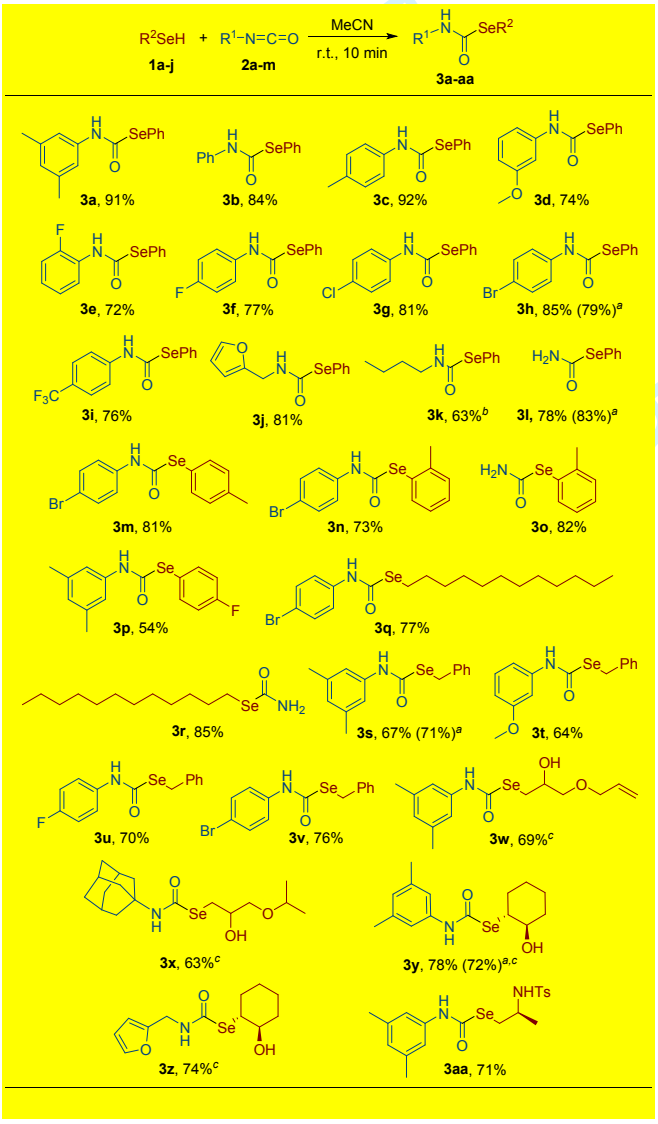
Increasing polarity

a) Determined by ^{1}H NMR spectroscopy. b) According Snyder.[23]

Having established two set of optimal conditions for the successful selenol-isoselenocyanate coupling, we next turned our attention to evaluating the scope of the two reaction partners. Employing benzeneselenol **1a** as a standard substrate, the scope of isocyanates was explored and found to be wide, encompassing a variety of electron-rich and electron-deficient aromatic derivatives (Scheme 1). Electron-rich aryl isocyanates bearing alkyl and alkoxy substituents worked well, providing access to *N*-aryl-selenocarbamates **3a,c,d** in good yields. In the case of electron-poor aryl substrates, selenocarbamates bearing fluoro (**3e,f**), chloro (**3g**), bromo (**3h**), and trifluoromethyl (**3i**) moieties were smoothly achieved from the corresponding isocyanates. Additionally, carbamoselenoate **3j**, bearing the furan moiety, was prepared in 81% yield upon reaction of furfuryl isocyanate with benzeneselenol. The reaction was also amenable to aliphatic isocyanates and could be successfully applied to the synthesis of *N*-butyl-selenocarbamate **3k**. Notably, *N*-trimethylsilyl isocyanate **2l** was also effective and led to the

corresponding 1-(phenylselanil)formamide **3l** upon coupling with **1a** and protodesilylation reaction occurring at the nitrogen atom; to our knowledge, this is the first example of selenocarbamate bearing the unsubstituted carbamoyl moiety.

Next, we set out to investigate the scope of the reaction with respect to the selenol partner. Thus, different selenols were used in the reaction with isocyanates **2** under the optimised conditions. Both *p*-tolueneselenol **1b** and *o*-tolueneselenol **1c** reacted efficiently with **2h** (R^1 = 4-Br-C_6H_4) providing selenocarbamates **3m** and **3n** in good yield. The *Se*-*o*-tolyl carbamoselenoate **3o**, bearing the unsubstituted carbamoyl group, was also easily achieved from *o*-tolueneselenol and *N*-trimethylsilyl isocyanate **2l**. Furthermore, selenylation reaction of **2a** with 4-fluorobenzeneselenol **1d** provided **3p**, albeit in rather low yield (Scheme 1).



Scheme 1. The scope of the coupling of selenols **1** with isocyanates **2** under catalyst-free conditions. All yields refer to isolated pure material. [a]Yields in parenthesis refer to reactions performed under neat conditions. [b]10% of diphenyl diselenide was detected. [c]Racemic.

The reaction was also found to be amenable to alkyl- and benzyl-selenols, enabling the synthesis of a variety of *Se*-alkyl and *Se*-benzyl-substituted carbamoselenoates. Dodecaneselenol **1e** was successfully employed, giving the corresponding *N*-aryl- and *N*-unsubstituted selenocarbamates **3q,r**. Benzyl selenol **1f** was reacted with a variety of *N*-substituted isocyanates which were readily converted into *Se*-benzyl carbamoselenoates **3s-v** (Scheme 1). To further demonstrate the utility of this catalyst-free click methodology, alkyl selenols bearing valuable functional groups were also employed. Through our simple approach, primary (**1g,h**) and secondary (**1i**) β-hydroxy-selenols could be easily and selectively functionalised at the selenol moiety, enabling the synthesis of β-hydroxy-selenocarbamates **3w-z**, bearing the 3,5-dimethylphenyl substituent, the furan group, and the sterically demanding adamantyl moiety, in good yield. *N*-tosyl β-amino-selenol **1k** was also efficiently used, providing access to the corresponding L-alanine-derived selenocarbamate **3aa** (Scheme 1).[24]

The structure of selenocarbamate **3h** was confirmed by single-crystal X-ray crystallography (Figure 1). A strong intermolecular H-bond involving the oxygen and the hydrogen of the carbamoyl group is evident in PARST analysis. Furthermore, the C(O)···Se intermolecular distance (3.374 A) is suggestive of intermolecular chalcogen bonding interactions (Figure S5).[25]

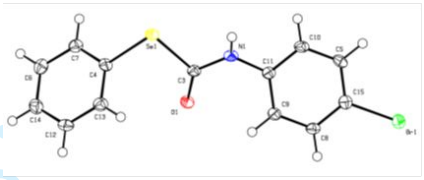


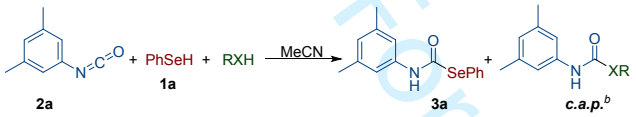
Figure 1. Molecular structure of **3h** and selected distances: C4-Se1 = 1.915(3) A; Se1-C3 = 1.959(3) A; C3-O1 = 1.211(4) A; N1-C3 = 1.345(4) A; N1-C11 = 1.412(5) A.

Given the fast and selective coupling of isocyanates with selenols here described, we were intrigued by the investigation of the reactivity of selenols in the presence of competing chalcogen-centered nucleophiles. Thus, an equimolar mixture of benzeneselenol and benzenethiol in acetonitrile was treated with isocyanate **2a** (1.0 equiv.). Surprisingly, the selenocarbamate **3a** was selectively formed while benzenethiol remained unreacted and no traces of thiocarbamate were detected (Table 2, entry 1). The exquisite selenophilicity of isocyanates in addition reactions was confirmed upon using different thiols (*p*-thiocresol and 1-pentanethiol: Table 2, entries 2, 3) as competing nucleophiles. Similar results in terms of selectivity were also observed in the presence of related O- and N-centered nucleophiles such as phenol and aniline (Table 2, entries 4, 5). These results suggest that the specificity of the selenol-

isocyanate coupling could be exploited for the development of isocyanate-based probes for the selective detection or the sensoring of selenols.

Owing to the high reactivity of the selenium-carbon bond of selenocarbamates, which can be easily cleaved both *via* radical and ionic pathway, we envisaged the possibility to employ such compounds as unconventional glutathione peroxidase (GPx)-like catalytic antioxidants. Indeed, the thiol-mediated ionic cleavage of the carbon-selenium bond of selenocarbamates would release a selenolate anion which, similarly to the selenocysteine-derived selenolate involved in the catalytic cycle of GPx, is expected to catalyse the reduction of hydroperoxides at the expense of a thiol cofactor.

Table 2. Competition experiments: reaction of benzeneselenol **1a** with isocyanate **2a** in the presence of competing nucleophiles.[a].



2a **1a** **3a** ***c.a.p.***[b]

Entry	X	R	Yield (%)[c]	3a:*c.a.p.*[c]
1	S	Ph	92	>98:2
2	S	*p*-Me-C_6H_4	94	>98:2
3	S	*n*-Pentyl	91	>98:2
4	O	Ph	87	>98:2
5	NH	Ph	88	>98:2

[a] Reaction conditions: **2a** (0.73 mmol), PhSeH (0.80 mmol), RXH (0.80 mmol), acetonitrile (1 mL), r.t., 10 min. [b] ***c.a.p.***: competitive addition product. [c] Determined by ^{1}H NMR spectroscopy.

In order to verify this hypothesis, *N*-3,5-dimethylphenyl-substituted selenocarbamate **3a** was used as catalyst in the oxidation of dithiothreitol (DTT^{red}) with hydrogen peroxide according to Iwaoka's method.[26] The progress of the reaction, performed in CD_3OD, was followed by ^{1}H NMR spectroscopy. Pleasingly, complete oxidation of DTT^{red} was observed within 2 minutes from the addition of H_2O_2. Such a short time, generally unusual for organoselenium-based thiol-peroxidase-like catalysts, highlights the excellent activity of compound **3a**. On the basis of these results, the catalytic properties of a series of differently *Se*- and *N*-substituted selenocarbamates was investigated. Results of this study are reported in Table S1 and in Figure 2 (see ESI for details). Compounds **3a** and **3c**, bearing a phenylseleno moiety and electron-rich *N*-aryl substituents, were showed to be the most effective catalysts within the studied series (T_{50} < 60 sec). On the other hand, the presence of an electron-poor *N*-4-fluorophenyl substituent brought about a significant reduction of the thiol-peroxidase-like properties (**3f**, T_{50} = 2845±126 sec). Selenocarbamate **3h**, bearing a 4-bromophenyl group onto the nitrogen atom, exhibited a higher catalytic activity with respect to the related fluoro-substituted analogue and led to complete DTT^{red} oxidation within 20 minutes from the addition of H_2O_2 (T_{50} = 368±21 sec). Intriguingly, the *N*-unsubstituted carbamoyl derivative **3l** behaved as a poor catalyst with respect to its *N*-aryl-substituted analogues (T_{50} > 3600 sec).

The nature of the group bond to the selenium atom also affected significantly the thiol-peroxidase-like catalytic properties of **3**.

Compounds **3m** and **3n**, bearing an electron-donating substituent respectively at the *para*- and at the *ortho*- position of the *Se*-aryl ring, exhibited lower catalytic activity (T_{50} > 3600 sec) with respect to the related *Se*-phenyl-substituted analogue **3h** (T_{50} = 368±21 sec). Notably, steric effects were demonstrated to play only a marginal role on the on the catalytic performances of **3m** and **3n**, which displayed comparable thiol-peroxidase-like properties. On the other hand, the presence of the electron-poor *Se*-4-fluorophenyl substituent (**3p**) led to an improved catalytic activity with respect to the related derivative **3a**, bearing the *Se*-phenyl substituent.[27]

The catalytic activity of *Se*-alkyl-substituted carbamates **3q,w** resulted dramatically decreased when compared with that of related *Se*-phenyl-substituted derivatives. This behaviour might be ascribed to the higher basicity – and therefore poor leaving group ability – of alkylselenolates with respect to arylselenolates. The presence of a rather poor leaving group engenders *Se*-alkyl-carbamoselenoates less sensitive to the trans-carbamoylation reaction with thiols (*vide infra*).[24]

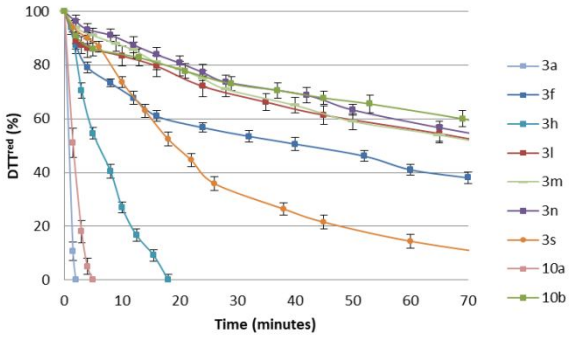
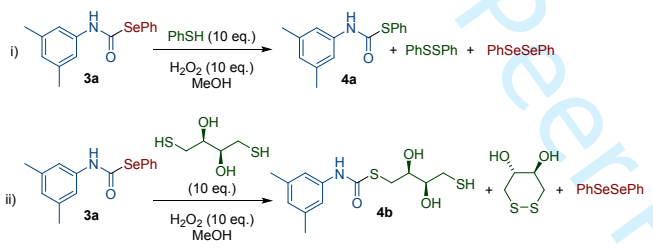


Figure 2. Oxidation of DTT^{red} with H_2O_2 in the presence of catalytic amounts of selenocarbamates **3** or selenolesters **10** (10 mol %). Reaction conditions: $[DTT^{red}]_0$=0.14 M, $[H_2O_2]_0$=0.16 M, [catalyst]=0.014 M, CD_3OD (1.1 mL). In the control experiment the reaction was run with no catalyst. The mean ± SD values of three separate experiments are reported.

To glean insights into the catalytic mechanism of the selenocarbamate-mediated oxidation of thiols, a series of control experiments and NMR investigations were carried out. We postulated that the first step of the mechanism involves the thiol-mediated cleavage of the carbon-selenium bond of **3** releasing a

thiocarbamate and a selenol or a selenolate anion. These latter entities are expected to react with H_2O_2 providing the active selenium-based oxidant species involved in the thiol-disulfide conversion. Our hypothesis was confirmed by the isolation of thiocarbamates **4a** and **4b** arising from the reaction of **3a** with thiophenol and dithiothreitol, respectively, in the presence of H_2O_2 (Scheme 2). Notably, when a solution of **3a** in methanol or acetonitrile was treated with PhSH or DTT in absence of H_2O_2, the thiol-selenol exchange occurred very slowly and only trace amounts (<10%) of **4a** and **4b** were detected after 12 h. The H_2O_2-mediated oxidation of the selenol or selenolate reasonably represents the driving force of the transcarbamoylation reaction. Indeed, in the presence of H_2O_2, diphenyl disulfide or DTT^{ox} and diphenyl diselenide were the sole reaction products formed along with **4a**,**b**. The formation of both **4a**,**b** and diphenyl diselenide is suggestive of a thiol-selenol exchange occurring at the carbamoyl carbon. Such a reaction would lead to a selenol or a selenolate anion. Both theoretical and experimental data suggest that selenolate anions undergo oxidation faster than the parent selenols.[28]



Scheme 2. Reaction of **3a** with thiols in the presence of H_2O_2 affording thiocarbamates **4**, disulfides, and diphenyl diselenide. Reaction time: 10 min. In control experiments performed in absence of H_2O_2, *c.a.* 90% of **3a** remained unreacted.Figure Caption.

Envisaging the cleavage of the carbon-selenium bond of **3** as the rate-determining step of the process, and considering the excellent catalytic performances of the selenocarbamate **3a**, we postulated that a selenolate, instead of a selenol, should be involved in the oxidation mechanism. To confirm this hypothesis, the catalytic properties of benzeneselenol and sodium benzeneselenolate, easily generated upon treatment of benzeneselenol with a stoichiometric amount of NaOH, were investigated and compared. Surprisingly, benzeneselenol exhibited poor catalytic activity and only 30% of DTT^{red} was converted into DTT^{ox} after 30 minutes from the addition of H_2O_2. On the other hand, complete DTT^{red} oxidation was achieved within 2 minutes when sodium benzeneselenolate was employed as the catalyst (Figure 3). To the best of our knowledge, this is the first study where the thiol-peroxidase-like activity of a selenol and a related selenolate anion is experimentally compared. Noticeably, when a slight excess of hydrogen peroxide (1.2 equiv. with respect to DTT) was used, sodium benzeneselenolate was converted into diphenyl diselenide at the end of the catalytic cycle (Figure 3, spectra *I* and *II vs* spectrum *III*).

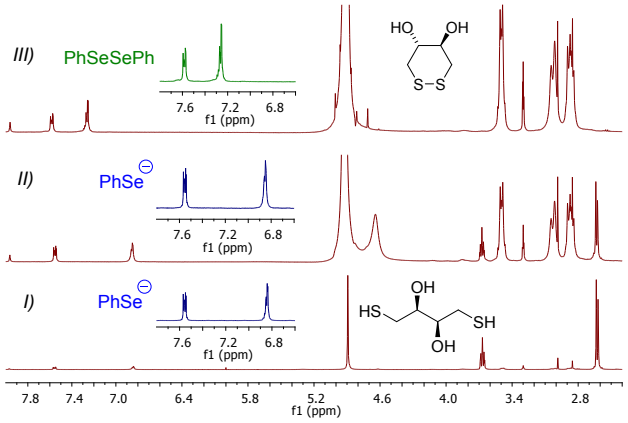
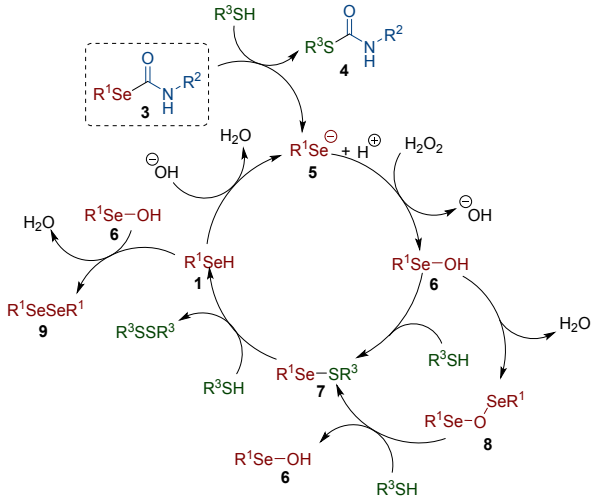


Figure 3. Series of ^1H NMR spectra obtained in the oxidation of DTT^{red} (0.15 mmol) with H_2O_2 (0.18 mmol) in the presence of 10% of sodium benzeneselenolate. *I*) ^1H NMR spectrum acquired before the addition of H_2O_2; *II*) ^1H NMR spectrum acquired after 90 seconds from the addition of H_2O_2. *III*) ^1H NMR spectrum acquired after 120 seconds from the addition of H_2O_2.

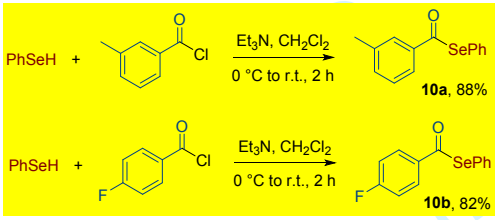
On the basis of results of our experiments and literature-reported data, we propose the catalytic mechanism outlined in Scheme 3. The first step reasonably involves a thiol-selenol exchange reaction occurring at the carbamoyl carbon and leading to a thiocarbamate **4** and a selenolate anion **5**, which readily undergoes oxidation to provide the corresponding selenenic acid **6**. The oxidation of the leaving selenolate reasonably drives the equilibrium of the transcarbamoylation reaction towards **4**. The selenenic acid **6** is then converted into the selenenyl sulfide **7** upon reaction with a thiol. Compound **7** can also be formed through an alternative pathway foreseeing the conversion of the selenenic acid into the anhydride **8**, which undergoes nucleophilic reaction with a thiol to give **7** and selenenic acid **6**. The thiophilic attack of a thiol onto the sulfur atom of **7** affords a disulfide and converts the selenenyl sulfide into the selenol **1**, whose deprotonation provides the selelenolate **5** to restart the catalytic cycle.

After complete consumption of the thiol substrate, the selenenic acid **6** reacts rapidly with selenol **1** to yield the corresponding diselenide **9** (Scheme 3 and Figure 3, *vide infra*).

Having disclosed that reactivity of the Se-C(O) bond is key for the thiol-peroxidase-like activity of selenocarbamates, we sought to compare their activity with those of selected related selenolesters. Compounds **10a**,**b**, structurally similar to **3a** and **3f**, easily prepared from the corresponding acyl chlorides and benzeneselenol,[29] were chosen as model compounds (Scheme 4).



Scheme 3. Proposed catalytic mechanism for the thiol-peroxidase-like activity of selenocarbamates.



Scheme 4. Synthesis of selenolesters **10a**,**b**.

Remarkedly, while **10a** catalysed efficiently the oxidation of DTT^{red} to DTT^{ox} (T_{50} = 90 ± 18 sec), the 4-fluorophenyl-substituted derivative **10b** exhibited a significantly lower catalytic activity (T_{50} > 3600 sec). These results are in line with the activity of selenocarbamates **3a** and **3f**, bearing respectively the 3,5-dimethylphenyl- and the 4-fluorophenyl- group, and suggest a catalytic mechanism that plausibly proceeds through a transesterification key step.

Conclusion

In summary, we have reported a direct approach to selenocarbamates through the catalyst-free coupling of selenols with isocyanates. Given the mild reaction conditions, the broad functional group tolerance and the readily availability of selenols and isocyanates, the protocol here described can be applied to the synthesis of a wide range of functionalised selenocarbamates. Owing to the high selenophilicity of isocyanates, selenocarbamates were also selectively formed in the presence of different heteroatom-centered competing nucleophiles.

The thiol-peroxidase-like catalytic properties of the so obtained selenocarbamates were investigated. The results of our study suggest that the catalytic mechanism proceeds through a peroxide-driven transcarbamoylation reaction engendering thiocarbamates and selenolate anions. The latter, readily released in the presence of the oxidant, catalyse the thiol-disulfide conversion with the concomitant reduction of hydrogen peroxide to water. Thus, owing to the reactivity of the selenium-carbon bond, selenocarbamates behave as equivalents of selenolate anions and can be considered as precatalysts capable of generating the catalytic species upon peroxide-mediated activation. Considering the broad scope of the methodology and the reactivity of selenocarbamates here described, we believe that the results of this study could find application for the preparation and the development of novel selenocarbamate-based synthetically and biologically valuable molecules.

Experimental Section

General Information

All commercial materials were purchased from Merck - Sigma-Aldrich and used as received, without further purification. Solvents were dried using a solvent purification system (Pure-Solv™). Flash column chromatography purifications were performed with Silica gel 60 (230-400 mesh). Thin layer chromatography was performed with TLC plates Silica gel 60 F254, which was visualised under UV light, or by staining with an ethanolic acid solution of *p*-anisaldehyde followed by heating. High resolution mass spectra (HRMS) were recorded by Electrospray Ionization (ESI). GC-MS was performed on a Varian CP 3800/Saturn 2200 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Varian Mercury 400 and Bruker 400 Ultrashield spectrometers operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. ^{77}Se NMR spectra were recorded using a Bruker 400 Ultrashield spectrometer, operating at 76 MHz. NMR signals were referenced to nondeuterated residual solvent signals (7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C). Diphenyl diselenide $(PhSe)_2$ was used as an external reference for ^{77}Se NMR (δ = 461 ppm). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. ^{1}H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, ap d = apparent doublet, m = multiplet, dd = doublet of doublet, bs = broad singlet, bd = broad doublet, ecc.), coupling constant (J) or line separation (ls), and assignment. Where reported, NMR assignments are made according to spin systems, using, where appropriate, 2D NMR experiments (COSY, HSQC, HMBC) to assist the assignment.

β-Hydroxy- and β-amino-selenols **(1g-j)** were synthesised from the corresponding epoxides and aziridines following a reported procedure.[20a] Aryl-selenols **1a-d**, dodecane-1-selenol **1e**, and phenylmethaneselenol **1f** were prepared through a reported procedure from the corresponding diselenides upon reduction with $NaBH_4$ followed by treatment with citric acid.[20b]

The catalytic thiol-peroxidase-like properties were determined following the oxidation of dithiothreitol (DTT^{red}) according Iwaoka's method.[26] The progress of the reaction was monitored by ^{1}H NMR spectroscopy. CD_3OD was used as the solvent. Hydrogen peroxide was freshly standardized prior to use.

Synthesis of Selenocarbamates 3

General Procedure. To a stirred solution of selenol **1a-j** (1.0 mmol, 1.1 equiv.) in anhydrous acetonitrile (1 mL) at room temperature under a nitrogen atmosphere, isocyanate **2a-m** (0.91 mmol, 1.0 equiv.) was added. After stirring for 10 minutes the solvent was removed under vacuum and the crude material purified by precipitation or subjected to flash column chromatography (petroleum ether/Ethyl acetate) to afford selenocarbamates **3a-aa**.

CCDC-2078950 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Detailed experimental procedures, products characterization, crystallographic details, and copy of NMR spectra of new products are reported in the Supplementary Material.

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References

[1] G. Rousseau, F. Robert, Y. Landais, *Chem. Eur. J.* **2009**, *15*, 11160-11173.

[2] G. E. Keck, M. C. Grier, *Synlett*, **1999**, *10*, 1657-1659.

[3] A. G. M. Barrett, H. Kwon, E. Wallace, *J. Chem. Soc. Chem. Commun*. **1993**, 1760-1761.

[4] K. Komine, Y. Urayama, T. Hosaka, Y. Yamashita, H. Fukuda, S. Hatakeyama, J. Ishihara, *Org. Lett*. **2020**, *22*, 5046-5050.

[5] D. Shiro, S.-i. Fujiwara, S. Tsuda, T. Iwasaki, H. Kuniyasu, N. Kambe, *Chem. Lett*. **2015**, *44*, 465-467.

[6] M. Toyofuku, S.-i. Fujiwara, T. Shin-ike, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc*. **2005**, *127*, 9706-9707.

[7] M. Toyofuku, E. Murase, S.-i. Fujiwara, T. Shin-ike, H. Kuniyasu, N. Kambe, *Org. Lett*. **2008**, *10*, 3957-3960.

[8] M. Toyofuku, E. Murase, H. Nagai, S. Fujiwara, T. Shin-ike, H. Kuniyasu, N. Kambe, *Eur. J. Org. Chem*. **2009**, 3141-3144.

[9] D. Shiro, H. Nagai, S.-i. Fujiwara, S. Tsuda, T. Iwasaki, H. Kuniyasu, N. Kambe, *Het. Chem.* **2014**, *25*, 518-524.

[10] Z. Jin, X. Du, Y. Xu, Y. Deng, M. Liu, Y. Zhao, B. Zhang, X. Li, L. Zhang, C. Peng, Y. Duan, J. Yu, L. Wang, K. Yang, F. Liu, R. Jiang, X. Yang, T. You, X. Liu, X. Yang, F. Bai, H. Liu, X. Liu, L. W. Guddat, W. Xu, G. Xiao, C. Qin, Z. Shi, H. Jiang, Z. Rao, H. Yang, *Nature*, **2020**, *582*, 289-293.

[11] a) H. Takahashi, A. Nishina, R.-h. Fukumoto, H. Kimura, M. Koketsu, H. Ishihara, *Eur. J. Pharm. Sci*. **2005**, *24*, 291-295; b) Y. N. Klimochkin, I. K. Moiseev, O. V. Abramov, G. V. Vladyko, L. V. Korobchenko, E. I. Boreko, *Pharm. Chem. J*. **1991**, *25*, 489-490.

[12] H. Kageyama, K. Tani, S. Kato, T. Kanda, *Heteroatom Chem*. **2001**, *12*, 250-258.

[13] B. Movassagh, M. Moradi, *Chin. Chem. Lett*. **2013**, *24*, 192-194.

[14] M. Koketsu, M. Ishida, N. Takakura, H. Ishihara, *J. Org. Chem*. **2002**, *67*, 486-490.

[15] S.-i., Fujiwara, K. Okada, Y. Shikano, Y. Shimizu, T. Shin-ike, J. Terao, N. Kambe, N. Sonoda, *J. Org. Chem*. **2007**, *72*, 273-276.

[16] W. A. Reinerth, J. M. Tour, *J. Org. Chem*. **1998**, *63*, 2397-2400.

[17] S. Kazuaki, O. Seiji, N. Hidenori, M. Akiko, K. Miho, M. Akiko, S. Takahiro, K. Hisashi, I. Yukiko, G. Yaling, A. Shigenobu, T. Yuji. Bull. *Chem. Soc. Jpn*. **2005**, *78,* 899-905.

[18] J.H. Rigby, D.M. Danca, J.H. Horner, *Tetrahedron Lett*. **1998**, *39*, 8413-8416.

[19] P. Singh, A. Batra, P. Singh, A. Kaur, K. N. Singh, *Eur. J. Org. Chem*. **2013**, 7688-7692.

[20] a) D. Tanini, C. Tiberi, C. Gellini, P. R. Salvi, A. Capperucci, *Adv. Synth. Catal*. **2018**, *360*, 3367-3375; b) A. Angeli, D. Tanini, A. Nocentini, A. Capperucci, M. Ferraroni, P. Gratteri, C. T. Supuran, *Chem. Commun*. **2019**, *55*, 648–651.

[21] a) D. Tanini, V. D'Esopo, D. Tatini, M. Ambrosi, P. Lo Nostro, A. Capperucci, *Chem. Eur. J*. **2020**, *26*, 2719-2725; b) D. Tanini, S. Scarpelli, E. Ermini, A. Capperucci, *Adv. Synth. Catal*. **2019**, *361*, 2337-2346; c) D. Tanini, B. Lupori, G. Malevolti, M. Ambrosi, P. Lo Nostro, A. Capperucci, *Chem. Commun*. **2019**, *55*, 5705-5708.

[22] S. Ozaki, *Chem. Rev*. **1972**, *72*, 457-496.

[23] L.R. Snyder, *J. Chromatogr*. **1974**, *92*, 233-240.

[24] *Se*-Aryl-selenocarbamates proved to be less stable than *Se*-alkyl-substituted analogues and significantly decomposed when we attempted to purify them on silica gel. For this reason, while *Se*-alkyl-carbamoselenoates were purified by column chromatography on silica gel, *Se*-aryl-substituted derivatives were purified by precipitation. The lower stability of *Se*-aryl-carbamoselenoates (*i.e.* higher reactivity of the selenium-carbon bond) makes these substrates more prone to undergo transcarbamoylation reactions and also accounts for their excellent thiol-peroxidase-like catalytic properties.

[25] K. T. Mahmudov, M. N. Kopylovich, M. F. C. G. da Silva, A. J. L. Pombeiro, *Dalton Trans*. **2017**, *46*, 10121-10138.

[26] a) A. Capperucci, M. Coronnello, F. Salvini, D. Tanini, S. Dei, E. Teodori, L. Giovannelli, *Bioorg. Chem*. **2021**, *110*, 104812; b) D. Tanini, V. D'Esopo, D. Chen, G. Barchielli, A. Capperucci, Phosphorus, Sulfur Silicon Relat. Elem., 2017, 192, 166-168; c) D. Tanini, A. Grechi, L. Ricci, S. Dei, E. Teodori, A. Capperucci, *New J. Chem*. **2018**, *42*, 6077-6083; d) M. Iwaoka, F. Kumakura, *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 1009-1017; e) F. Kumakura, B. Mishra, K. I. Priyadarsini, M. Iwaoka, *Eur. J. Org. Chem*., **2010**, 440-445.

[27] Complete DTT oxidation was observed within 2 min when using 10 mol % of **3a** or **3p**. No significant differences were observed and, in both cases, $T_{50} < 60$

sec. However, DTT oxidation proceeded significantly faster upon using 5 mol % of **3p** instead of 5 mol % of **3a**.

[28] a) H. J. Reich, R. J. Hondal, *ACS Chem. Biol*. **2016**, *11*, 821−841; b) B. Cardey, M. Enescu, *ChemPhysChem* **2005**, *6*, 1175-1180; c) T. G. Back, B. P. Dyck, *J. Am. Chem. Soc*. **1997**, *119*, 2079-2083.

[29] A. Angeli, F. Carta, S. Donnini, A. Capperucci, M. Ferraroni, D. Tanini, C. T. Supuran, Chem. Commun. **2020**, *56*, 4444-4447.