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New Reactions of Selenocarboxylates

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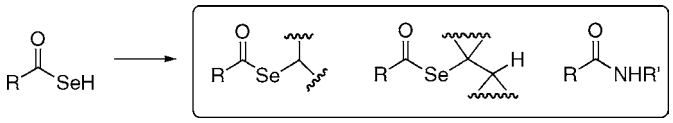
ABSTRACT

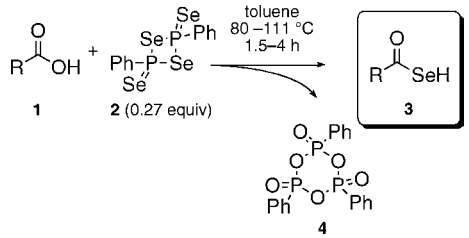


By treatment with Woollins' reagent in toluene solution, carboxylic acids are converted to selenocarboxylic acids. The latter react in situ to provide new products of acid- or base-promoted substitution, addition, and amidation.

Organoselenium compounds are important as reagents and intermediates in organic synthesis,[1−4] as heavy-atom versions of oligonucleotides[5,6] and proteins[7] for crystallographic study, as human metabolites,[8] as cancer-preventative agents[9,10] and other medicinals,[11,12] and as substrates for biomimetic studies.[13−15] Selenonucleophiles are even more reactive than the corresponding thio reagents,[16] and this is a property that can be exploited for the introduction of the selenium atom into organic structures. While hundreds of reactions of nucleophilic selenolate reagents RSe^- are known, far fewer reactions of the selenocarboxylate anion $RCOSe^-$ have been reported. These include Se-alkylation with simple alkyl halides,[17,18] Se-arsination with arylchloroarsines,[19] and O-silylation to give $RC(=Se)OSiR'_3$.[20] Undoubtedly, better synthetic use could be made of selenocarboxylic acids if they could be easily prepared under conditions where their ready conversion to the nonnucleophilic diacyldiselenides RCOSeSeCOR could be suppressed. We find that a heterogeneous suspension of Woollins' reagent,[21,22] $[PhP(=Se)Se]_2$, in toluene converts carboxylic acids to a solution of the corresponding selenocarboxylic acid, which may be used directly for a variety of new reactions of selenocarboxylates, including acid- or base-promoted substitution, addition, and amidation under mild conditions.

Woollins' reagent (**2**, Scheme 1) is a selenium analogue of Lawesson's reagent, $[ArP(=S)S]_2$ (Ar = *p*-methoxyphenyl); the latter has been used extensively for various thionation reactions.[23] The preparation of **2** entails treating

Scheme 1. Synthesis of Selenocarboxylic Acids



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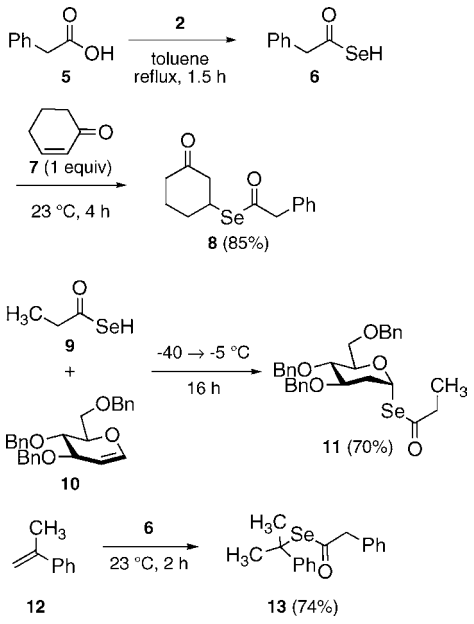
$(PhP)_5$ with 10 equiv of selenium powder in refluxing toluene. The resulting red solid is collected by filtration and stored in a desiccator at 23 °C. Reaction of **2** with amides to give selenoamides has been reported.[24,25] We observe that carboxylic acids **1** react with **2** in hot toluene solution over the course of several hours. During this period, **2** is consumed, as evidenced by the disappearance of the red solid and the appearance of a white solid coating the inside of the flask, presumably the byproduct 2,4,6-triphenyl-1,3,5-trioxa-2,4,6-triphosphinane-2,4,6-trioxide **4**.[24] The resulting yellow-orange toluene solution contains the selenocarboxylic acid **3**. The odor and toxicity issues normally associated with organophosphorus and organoselenium compounds are easily minimized by the standard precautions of working with gloves and in a good fume hood, and no special handling techniques are required.

Efficient reaction of **3** with various substrates can be effected by simply adding them to the toluene solution and then monitoring their disappearance by TLC. Treatment of phenylacetic acid **5** with **2** (Scheme 2) and then addition of

Scheme 2. Addition of Selenocarboxylates to Alkenes

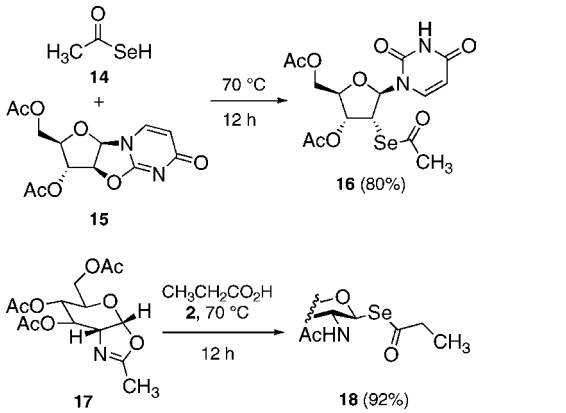


1 equiv of cyclohexenone **7** to the presumed selenocarboxylic acid **6** gave the product of Michael addition, selenolester **8**. Selenolesters such as **8** show diagnostic Se−*C*═O resonances at ∼200 ppm.[18] The yield of **8** was increased to quantitative by using excess **6**. The acidity of **6** is predicted to be greater than that of the corresponding carboxylic and thiocarboxylic acids;[26,27] hence, the reaction of **6** with **7** can be thought of as an acid-promoted conjugate addition of the seleno-carboxylate, $PhCH_2COSe^-$. This is to our knowledge the first example of addition of a selenocarboxylate to an alkene.

The efficiency of the selenocarboxylate addition to **7** prompted us to examine a more electron-rich alkene, tri-*O*-benzyl-D-glucal **10** (Scheme 2). Selenylation of propionic acid as for **5** led to a toluene solution of the presumed selenopropionic acid **9**, which was cooled to −40 °C and then treated with **10**. Completion of the reaction occurred over 16 h at −5 °C and led cleanly to a single adduct, the 2-deoxy-1-seleno-α-D-glucopyranose derivative **11** (H-1 at 6.31 ppm, dd, J = 4.6 and 1.2 Hz). This reaction is noteworthy for the stereoselectivity of the addition, which required no additional catalyst. Also notable is the noninterference by a Ferrier rearrangement,[28] which might have competed with glycal addition[29] under these conditions. Another electron-rich alkene, α-methylstyrene (**12**) was smoothly converted to selenolester **13** by simply stirring with **6**. Very few methods exist for the synthesis of tertiary selenols,[30] and reduction or hydrolysis of alkene adducts such as **13** ought to provide a straightforward route.

The pronounced acidity of selenocarboxylates was exploited in two acid-promoted heterocyclic ring-opening addition reactions (Scheme 3). Cyclo-uridine diacetate **15**

Scheme 3. Heterocyclic Ring-Opening Reactions



reacted[31] with the selenocarboxylic acid (**14**) prepared from acetic acid to give the 2′-seleno ribonucleoside **16**. Although

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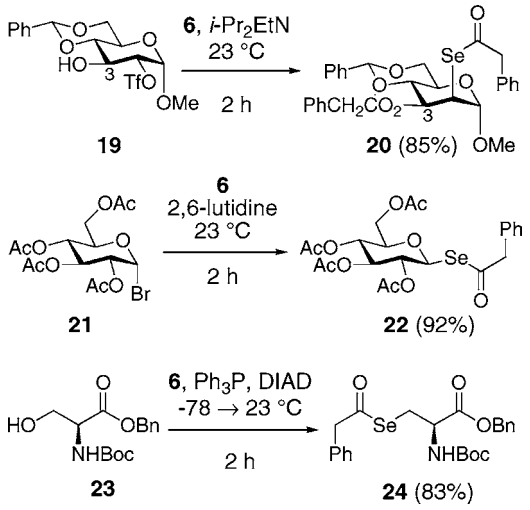
prolonged heating at 70 °C was required, **14** survived without significant side reactions to give the adduct in good yield. GlcNAc-oxazoline **17**, which is known to open under acidic conditions,[32] reacted in one pot with **2** and propionic acid to provide directly the 2-acetamido-2-deoxy-1-seleno-β-D-glucopyranose derivative **18**. The selenoacid **9** is thus formed in situ and then reacts with **17**, which is otherwise stable to **2** and to the starting carboxylic acid. Selenolesters such as **11**, **16**, and **18** might serve as precursors, by way of derivatization on Se, to various carbohydrate seleno-conjugates.[33−35]

Given the demonstrated nucleophilicity of anionic thiocarboxylates, the S_N2 reaction of selenocarboxylates ought to be an excellent way to introduce selenium into carbohydrate, peptidyl, and other frameworks. Indeed, the partially protected α-D-glucopyranoside 2-triflate[36] **19** reacted with **6** in the presence of diisopropylethylamine to give the 2-seleno-α-D-mannopyranoside derivative **20** (Scheme 4). Clean S_N2 reaction has occurred under mild conditions, significantly milder, in fact, than those required by the anion of thioacetic acid in the same displacement reaction.[36] The 3-hydroxy becomes acylated under the reaction conditions, possibly by way of base-promoted intramolecular Se-to-O acyl migration, followed by intermolecular Se-acylation by additional **6**.

Scheme 4. Alkylation of Selenocarboxylate Anions

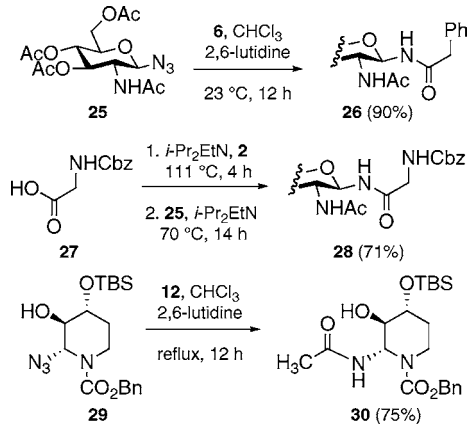


Acetobromo-α-D-glucose **21** reacted with selenocarboxylate **6** in the presence of 2,6-lutidine to give the product of S_N2 reaction at the anomeric center, 1-seleno-β-D-glucopyranose derivative **22** (Scheme 4). The absence of both eliminated product and the α-anomer attests to the mildness of the displacement conditions. Anomeric S_N2 displacements by other selenium nucleophiles have been previously reported.[33,35]

Mitsunobu reactions with thiocarboxylates as the nucleophile have been known for some time and are among the most dependable ways to introduce the protected thiol group,[37] and yet no selenocarboxylate example has appeared. Notably, however, *N*-*tert*-butoxycarbonylserine benzyl ester (**23**) underwent successful conversion to the selenocysteine derivative **24** in the presence of **6** (Scheme 4). To avoid addition of **6** to the diisopropyl azodicarboxylate, the complex of triphenylphosphine and DIAD was preformed in THF solution at −40 °C. The solution was cooled to −78 °C; the substrate **23** was added, and then the toluene solution of **6** was added by cannula at the same temperature.

The Williams amidation reaction of thiocarboxylic acids with azides provides amides under mildly basic conditions.[38] It is particularly useful in situations where the corresponding amine is configurationally or solvolytically unstable. Selenocarboxylic acids ought to undergo an analogous amidation; this was evaluated with the 2-acetamido-2-deoxy-β-D-glucopyranosyl azide[39] **25** as the substrate (Scheme 5). Generation of selenocarboxylic acid **6** as before, and then addition of **25** and 1.7 equiv of 2,6-lutidine, led to an amidation reaction at room temperature, and the *N*-glucopyranosyl amide product **26** was isolated in high yield following chromatography. Related *N*-glycosylamides have been shown to inhibit rabbit muscle glycogen phosphorylase *b*.[40] Inasmuch as the corresponding reaction of thiocarboxylates with glucopyranosyl azides requires heating at 60 °C,[41] the selenocarboxylate is probably more reactive in Williams amidation. A parallel observation of the greater reactivity

Scheme 5. Williams Amidations with Selenocarboxylates



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of selenophenolate (compared with thiophenolate) toward azides was recorded in 1990.[42]

A more stringent test of amidation uses the electron-poor carboxylic acid *N*-Cbz-glycine (**27**, Scheme 5). Conversion of **27** to its ammonium salt with Hünig's base, followed by selenylation with **2**, gave a toluene solution of the presumed selenocarboxylic acid. Heating with **25** (0.2 equiv based on **27**) in the presence of $CHCl_3$ and additional Hünig's base produced *N*-glycosyl-glycine derivative **28**.[43] The selenylation method is selective for the carboxylate in the presence of the carbamate protecting group and gives as an intermediate the first example of a protected α-amino selenocarboxylic acid.

Another challenge to amidation is provided by the hindered 2-azidopiperidine derivative **29** (Scheme 5), an intermediate in a projected synthesis of XylNAc-isofagamine. While **29** proved to be entirely unreactive toward an excess of thioacetic acid, it was effectively converted to the acetamide **30** by selenoacetic acid **12** at 70 °C.

In summary, selenocarboxylates generated in situ are versatile reagents for the introduction of selenium into organic structures and for amidation. They also ought to prove useful for applications where the nucleophilicity of the corresponding thiocarboxylic acid is insufficient.

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Supporting Information Available: Experimental details, spectral characterization, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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