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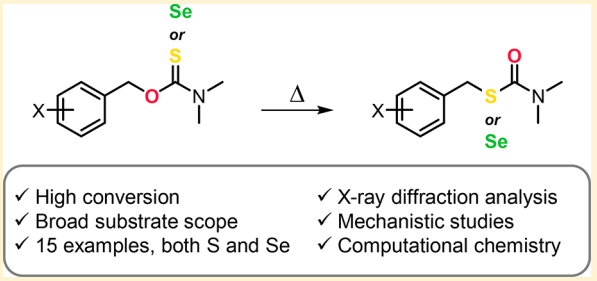
Benzylic Thio and Seleno Newman−Kwart Rearrangements

Kristina Eriksen, Anne Ulfkjær, Theis I. Sølling, and Michael Pittelkow*

Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

Supporting Information

ABSTRACT: The thermally induced $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ migration reactions facilitate the rearrangement of *O*-benzyl thio- and selenocarbamates [$BnOC(=X)NMe_2$] (X = S or Se) into their corresponding *S*-benzyl thio- and *Se*-benzyl selenocarbamates [$BnXC(=O)NMe_2$] (X = S or Se). A series of substituted *O*-benzyl thio- and selenocarbamates were synthesized and rearranged in good yields of 33−88%. The reaction rates are higher for substrates with electron-donating groups in the 2 or 4 position of the aromatic ring, but the rearrangement also proceeds with electron-withdrawing substituents. The rearrangement follows first-order reaction kinetics and proceeds via a tight ion pair intermediate consisting of the benzylic carbocation and the thio- or selenocarbamate moiety. Computational studies support these findings.



INTRODUCTION

Thiols and selenols play important parts in a range of chemistry, biochemistry, and materials applications.[1−6] Their uses as ligands in inorganic chemistry and as components in supramolecular assemblies are two central examples.[7−9] The subtle interplay between the thiol/disulfide and the selenol/diselenide through oxidation/reduction reactions is a defining trait of the chemical properties of these functional groups.[10−13] Prominently, both the thiol and selenol are parts of chiral amino acids as cysteine and selenocysteine, respectively. Selenocysteine is known as the 21st amino acid,[14] and the role of selenocysteine (selenol) and selenocystine (diselenide) in protein function and structure is becoming increasingly recognized, as is the role of the more common cysteine/cysteine system.[12,14,15] The presence of selenocysteine is known to influence the catalytic properties of enzymes and can provide a means of altering the structural properties of the protein as compared to those of the corresponding proteins containing cysteine.[12,13,16] Native chemical ligation with selenocysteine is also known to be highly effective,[17−19] and selenols/diselenides are also efficient in catalyzing the disulfide exchange reaction.[8]

The thiol functionality can efficiently be introduced via the Newman−Kwart rearrangement that facilitates the conversion from phenol to thiophenol via the thermal $O_{Ar} \rightarrow S_{Ar}$ rearrangement of aromatic thiocarbamates (Scheme 1, top).[20,21] However, the widespread use of selenols is hampered by their limited synthetic availability. We have initiated a research program focused on identifying new reactions that make selenols, and also thiols, readily available. Recently, we described how the conversion of a phenol into the corresponding selenophenol can be performed effectively by expanding the Newman−Kwart rearrangement from using *O*-aryl thiocarbamate substrates to *O*-aryl selenocarbamate substrates.[22] The rearrangement yields *Se*-aryl selenocarbamates that can then conveniently be hydrolyzed to the arylselenols using an aqueous base (Scheme 1, top). Attempts to introduce aliphatic versions of the Newman−Kwart rearrangement have been hampered by competitive reaction pathways, especially elimination pathways yielding alkenes instead.[23,24] One example describing a derived benzylic version of the original Newman−Kwart rearrangement has been published. Here, the conversion of *O*-(*o*-azidobenzyl) thiocarbamates into *S*-(*o*-azidobenzyl) thiocarbamate was found to

Scheme 1. Original Newman−Kwart Rearrangements (top) and the Two New Benzylic Newman−Kwart Rearrangements Presented Here (bottom)

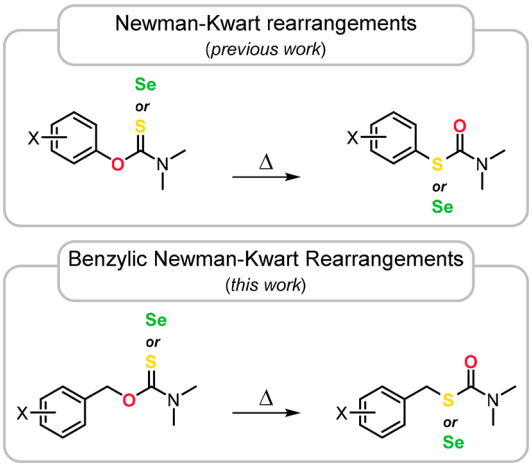


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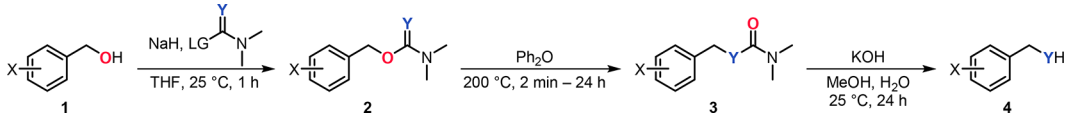
Table 1. Overview of Synthesised *O*-Benzyl Thio- and Selenocarbamates 2 and Their Conversion to the Corresponding *S*-Benzyl Thiocarbamates and *Se*-Benzyl Selenocarbamates 3[a]



compound	X	Y	isolated yield of **2** (%)	isolated yield of **3** (%)	conversion of **2** after 10 h[f] (%)
a	2-OMe	S	97	48	100[h]
b	3-OMe	S	94	59	35
c	4-OMe	S	96	70	100[h]
d	4-OMe[b]	S	98	60	100[h]
e	4-OEt	S	82	54	100[h]
f	4-OEt[b]	S	91	62	100[h]
g	4-Me	S	87	41	75
h	4-H	S	92	33	66
i	*rac*-4-H[c]	S	96	–[d]	–[d]
j	(*R*)-4-H[c]	S	98	–[d]	–[d]
k	4-Cl	S	99	51	45
l	4-Br	S	90	59	55
m	4-CO_2CH_3	S	83	67	40
n	4-NO_2	S	52	–	trace
o	4-OMe	Se	93	88[e]	100[e]
p	4-H	Se	93	54	100[h]
q	*rac*-4-H[c]	Se	97	–[d]	–[d]
r	4-Br	Se	89	61	100[h]
s[g]	4-Cl	Se	–	–	–
t[g]	4-NO_2	Se	–	–	–

[a]The notation LGC(=Y)NMe_2 corresponds to the reagents *N*,*N*-dimethylthiocarbamoyl chloride (used for **2a**–**2n**) or *S*-phenyl *N*,*N*-dimethylthioselenocarbamate (used for **2o**–**2t**). [b]The carmabate group is the ethyl derivative, *N*,*N*-diethylthiocarbamate. [c]The benzylic position is methylated; i.e., the phenol used is 1-phenylethan-1-ol. [d]No rearrangement occurs; instead, an elimination reaction takes place. [e]The rearrangement was performed at 150 °C. [f]Monitored by ^{1}H NMR spectroscopy; see the Supporting Information for further information. [g]The compound is not synthesized and used for only computational studies. [h]The reaction is complete before 10 h.

proceed as a [1,3]-shift via an uncoupled concerted mechanism.[25] Computational studies suggested that the benzylic rearrangement is activated by electron-donating groups substituted on the aromatic ring and thereby exhibits the opposite pattern, compared to that of the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements.

In this contribution, we describe the use of benzylic substrates for the Newman–Kwart rearrangement using both *O*-benzyl thiocarbamates and *O*-benzyl selenocarbamates to yield the corresponding *S*-benzyl thiocarbamates and *Se*-benzyl selenocarbamates (Scheme 1, bottom). A fundamental change in mechanism is inevitable when changing the phenyl group in the original Newman–Kwart rearrangement to a benzyl group. Instead of a nucleophilic attack on an sp^2-hybridized carbon atom, the rearrangement is now initiated via an sp^3-hybridized carbon atom. We present general reaction conditions for both types of conversions and discuss the reaction mechanism based on reaction scope, kinetics, and computational studies. The reaction mechanism involves a solvated ion pair, and the reaction rate is favored by substituents on the aromatic ring of the benzyl group that aid in the stabilization of the benzylic carbocation and is thus favored by electron-donating substituents on the aromatic ring.

RESULTS AND DISCUSSION

Synthesis of the Carbamates. The starting material for the thiol version of the benzylic Newman–Kwart rearrangement, the *O*-benzyl thiocarbamates, was prepared by reaction of *N*,*N*-dimethylthiocarbamoyl chloride with the desired benzyl alcohol in the presence of sodium hydride in THF giving the products in good yields of 82–99% (Table 1, step 1). The *O*-benzyl selenocarbamate equivalents were more arduous to synthesize because the seleno analogue of *N*,*N*-dimethylthiocarbamoyl chloride, *N*,*N*-dimethylselenocarbamoyl chloride, is sensitive to both air and moisture.[26] This makes it unpractical to handle, and we therefore explored *S*-phenyl *N*,*N*-dimethylthioselenocarbamate as a shelf stable alternative.[26,27] This reacts readily with the benzyl alcohols upon addition of sodium hydride in THF to form the *O*-benzyl selenocarbamates in excellent yields ranging from 89 to 93% (Table 1, step 1). All compounds were characterized by ^{1}H, ^{13}C, and ^{77}Se NMR spectroscopy (when appropriate) together with a high-resolution mass spectrometry analysis, and the details are presented in the Experimental Section.

With the *O*-benzyl thiocarbamates in hand, we were ready to investigate whether the various substrates were prone to rearrange to the corresponding *S*-benzyl thiocarbamates (Table 1, step 2). The migration reaction was initially tested in 1-methylpyrrolidin-2-one (NMP), a solvent often used for Newman–Kwart rearrangements,[28,29] as well as *N*,*N*-dimethylformamide (DMF) and diphenyl ether, where diphenyl ether was found to be superior. After the optimal solvent had been found, the reaction temperature was investigated next. When *O*-(4-methylbenzyl) *N*,*N*-dimethylthiocarbamate (**2g**) was heated to 150 °C in diphenyl ether for 2 days, no reaction occurred and no notable decomposition was observed. When the temperature was increased to 175 °C, some conversion was seen after 2 days but unfortunately together with a non-

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negligible amount of unwanted byproducts. Finally, when the temperature was increased to 200 °C, complete conversion was observed within 1 day, thus showing the importance of a high reaction temperature in overcoming the reaction barrier. The desired product **3g** was, however, isolated in an only 41% yield, showing how rearrangement and degradation are competing reactions. Most other substrates gave better yields.

The unambiguous proof of the successful benzylic Newman−Kwart rearrangement came by single-crystal X-ray crystallography, which showed how the oxygen and sulfur atoms are exchanged during the rearrangement of **2k** into **3k** (Figure 1a,b).[30]

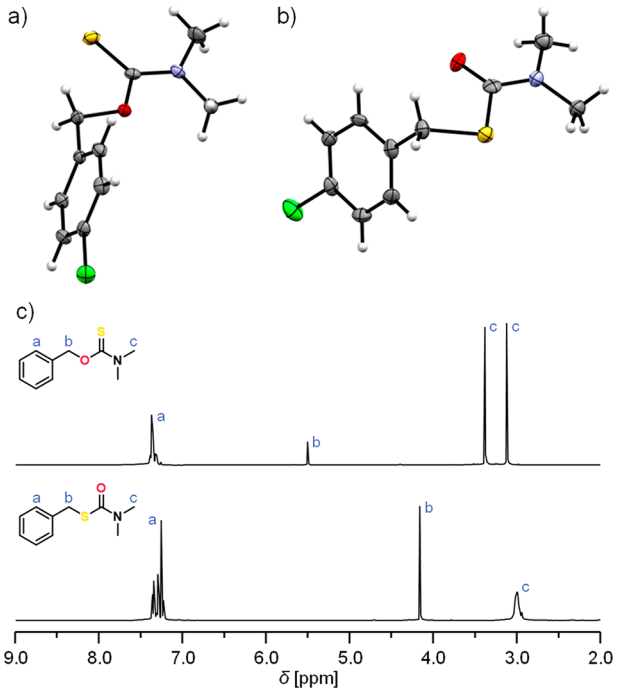

Figure 1. Analytical data supporting the $O_{Bn} \rightarrow S_{Bn}$ rearrangement by showing (a) the single-crystal X-ray structure of **2k**, (b) the single-crystal X-ray structure of **3k** (S, yellow; O, red; N, blue; Cl, green; C, gray; H, white), and (c) ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2h** and **3h**. Assignment of the signals is based on the labeling shown on the structures.

The progress of the rearrangement can be monitored easily by ^{1}H NMR spectroscopy as shown in Figure 1c where the ^{1}H NMR spectra of *O*-benzyl *N*,*N*-dimethylthiocarbamate (**2h**) and the corresponding rearranged **3h** are shown. Focusing on the signals corresponding to the *N*,*N*-dimethylamino group (H_c), we discovered how the two well-resolved singlets in the reactant merge into one broad singlet in the product. This is a result of a changed energy barrier for the internal rotation about the C−N thiocarbamate bond going from reactant to product. In **2h**, the rotational energy barrier is sufficiently high to allow slow exchange on the NMR time scale, thus showing two distinctive peaks for the *N*,*N*-dimethylamino group, whereas the barrier in **3h** is lower, giving rise to a merger of the two peaks as the domain of fast exchange is entered. The peak corresponding to the benzylic protons (H_b) moves 1.34 ppm upfield during the rearrangement, showing how the electron density decreases on the benzylic center as oxygen is exchanged for sulfur. Similar trends are observed in the corresponding ^{13}C NMR spectra (see the Supporting Information).

The benzylic Newman−Kwart rearrangement shows great tolerance toward a wide range of functional groups ranging from methoxy, through alkyl and halogens, to ester-substituted *O*-benzyl thiocarbamates (Table 1, step 2). Performing the rearrangement with electron-donating groups increases the reaction time. For example, the conversions of ethers **2c**−**2f** were complete within 2 h at 200 °C, while halogens **2k** and **2l** required 24 h for complete conversion. The rearrangement also allows substituents at the 2, 3, and 4 positions of the aromatic unit (**2a**−**2c**, respectively), and extending the *N*,*N*-dimethylamino group to an *N*,*N*-diethylamino group is also feasible (**2d** and **2f**). The rearrangement is also possible when the electron-withdrawing nitro group is placed in the *para* position (**2s**). However, the reaction time is, not surprisingly, very long, and the rearrangement was only 50% complete after heating to 200 °C for 3 days.

In addition, the racemic and enantiomerically pure *O*-(1-phenylethyl) *N*,*N*-dimethylthiocarbamate (**2i** and **2j**, respectively) were tested to determine if they were feasible for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement. It was envisaged that the products of these could give insight into the stereochemical aspect of the reaction mechanism with respect to whether we would obtain an inversion of the configuration or a racemic mixture of the rearranged product. Analysis of the reaction mixture did not show the desired rearranged product but instead complete and clean conversion to styrene (Figure 2 and the Supporting Information). The presence of a beta proton in similar *O*-benzyl thiocarbamates is known to facilitate elimination over rearrangement through a Chugaev-like elimination.[23]

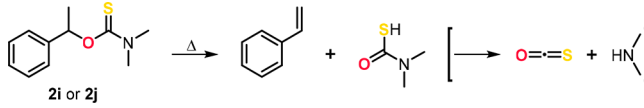

Figure 2. Heating *O*-(1-phenylethyl) *N*,*N*-dimethylthiocarbamate does not give the rearranged product but instead styrene and *N*,*N*-dimethylthiocarbamic acid, where the latter compounds react further to form carbonyl sulfide and *N*,*N*-dimethylamine.

After the successful rearrangement of the *O*-benzyl thiocarbamates, we investigated whether the selenium analogues would be just as efficient. The first substrate examined was the *O*-(4-methoxybenzyl) *N*,*N*-dimethylselenocarbamate (**2o**), which was found to rearrange within only 5 min when heated to 200 °C. Via comparison of this with the sulfur analogue **2c** for 2 h, heating was necessary to obtain the same conversion. This observation, showing how the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement proceeds significantly faster than the $O_{Bn} \rightarrow S_{Bn}$ rearrangement, is also known for the aryl versions of the Newman−Kwart rearrangement.[22] The *O*-benzyl *N*,*N*-dimethylselenocarbamate (**2p**) and bromo derivative **2r** also smoothly underwent rearrangement and again with reaction times substantially shorter than those of their sulfur analogues (Table 1, step 2).

A single crystal suitable for X-ray crystallography of rearranged product **3p** was obtained, proving the connectivity in the product (Figure 3a).[31] Consulting the ^{1}H NMR spectra of the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement of substrate **2p** into **3p**, we observed trends similar to those for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement (Figure 1c vs Figure 3b). As the rearrangement proceeds, the signals corresponding to the *N*,*N*-dimethylamino

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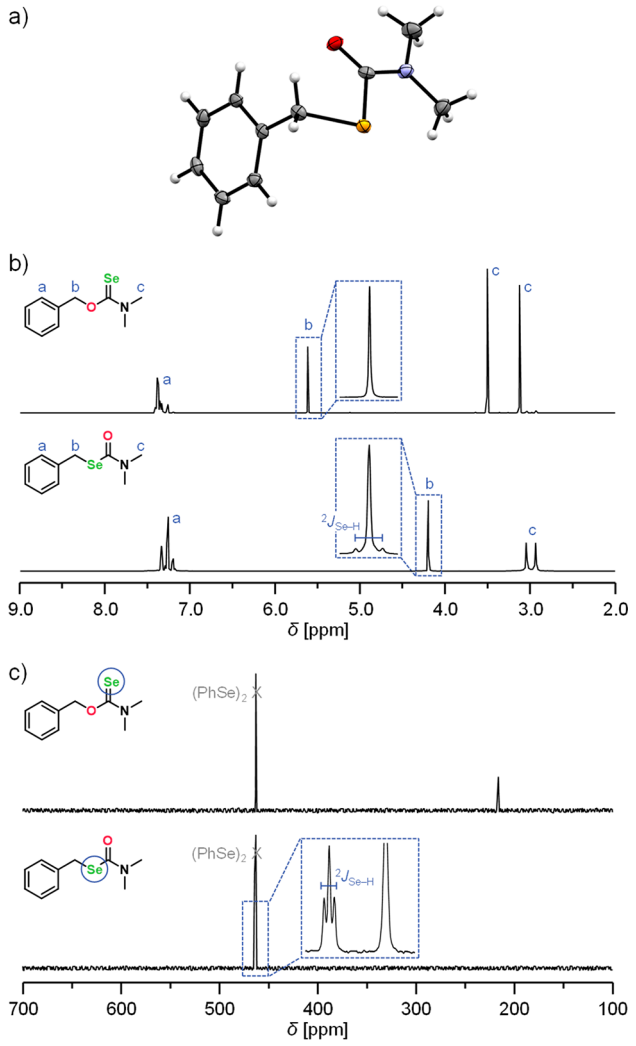

Figure 3. Analytical data supporting the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement by showing (a) the single-crystal X-ray structure of **3p** (Se, orange; O, red; N, blue; C, gray; H, white), (b) ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2p** and **3p**, and (c) ^{77}Se NMR spectra [57 MHz, $CDCl_3$ with a saturated solution of $(PhSe)_2$ in $CDCl_3$ as an external standard, 25 °C] of **2p** and **3p**. The spectra show an enlargement of selected ^{77}Se- and ^{1}H-coupled signals, and the assignment of the signals is based on the labeling shown on the structures.

group (H_c) change from being two well-separated singlets in **2p** to approaching each other forming two closely connected broad singlets in **3p**. In comparison, the H_c protons in the sulfur analogue merged completely. This agrees with the reported observation that the rotational barrier increases from amides through thioamides to selenoamides.[32,33] Again, the benzylic proton H_b shifts substantially upfield during the rearrangement, but in addition to increasing the shielding of the H_b protons, the selenium atom also causes the signal to split into a triplet (Figure 3b). Selenium has six naturally occurring isotopes; only ^{77}Se (7.58%) is NMR active, having a nuclear spin quantum number (I) of $^{1}/_{2}$. Therefore, it is possible in the ^{1}H NMR spectrum of rearranged product **3p** to observe a $^{2}J_{Se-H}$ spin−spin coupling between the H_b protons and the selenium atom with a strength of 11 Hz, which is in agreement with the literature.[34] In comparison, no coupling is observed in **2p** as the $^{4}J_{Se-H}$ coupling is too small to observe. Similar observations can be made in the corresponding ^{13}C NMR spectra (see the Supporting Information).

The $^{2}J_{Se-H}$ spin−spin coupling can also be observed in the corresponding ^{77}Se NMR spectrum (Figure 3c). Non-rearranged **2p** shows a singlet, as expected, at 216 ppm, while the signal for rearranged **3p** appears as a triplet at 464 ppm with an equivalent $^{2}J_{Se-H}$ spin−spin coupling of 11 Hz between the H_b protons and the selenium atom (Figure 3c). Besides the spin−spin coupling, the ^{77}Se NMR spectrum also provides information about the chemical environment of the selenium atom within the molecule.[34] As the rearrangement occurs, the signal for the selenium atom shifts remarkably 248 ppm downfield, demonstrating a changed environment for the selenium atom that corresponds well with the change in connectivity within the molecule due to the rearrangement.

The $O_{Bn} \rightarrow Se_{Bn}$ rearrangement was also investigated for the *rac*-*O*-(1-phenylethyl) *N*,*N*-dimethylselenocarbamate (**2q**), but again, the presence of beta protons favored a very efficient Chugaev-like elimination,[23] thus affording styrene (Figure 2 and the Supporting Information).

Hydrolysis of the rearranged products provides access to the corresponding benzyl thiols or selenols (Table 1, step 3). As representative examples, both 4-methoxy-substituted *S*-benzyl thiocarbamates and *Se*-benzyl selenocarbamates **3c** and **3o** were treated with potassium hydroxide in a methanol/water mixture, thus giving hydrolyzed products **4c** and **4o**, respectively, in quantitative yield. Benzyl selenol **4o** was isolated as the diselenide, 1,2-bis(4-methoxyphenyl)diselane, because of the rapid oxidation of the selenol functionality.

Mechanistic Studies. To gain insight into the course of the reaction, the kinetics for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement of *O*-(4-methoxybenzyl) *N*,*N*-dimethylthiocarbamate (**2c**) was studied in detail and compared with previously reported results from the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements. The conversion from **2c** into **3c** follows clearly first-order reaction kinetics, which is similar to the aryl version of the rearrangement. Via measurement of the conversion at different temperatures, the activation parameters were derived. The enthalpy of activation ($\Delta H^{\ddagger}$) was calculated to 35.7 kcal/mol, while the entropy of activation ($\Delta S^{\ddagger}$) was 1.45 cal mol^{-1} K^{-1} (see the Supporting Information). The $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements have both been reported to proceed in a unimolecular concerted manner via a four-membered cyclic transition state, which is why it would be reasonable to believe that the benzylic version would follow the same route.[22,35] However, the activation parameters obtained from those studies differ substantially from those obtained in this study, thus contradicting the mechanistic proposal [$\Delta H^{\ddagger}(O_{Ar} \rightarrow S_{Ar})$ = 28.8 kcal/mol, $\Delta S^{\ddagger}(O_{Ar} \rightarrow S_{Ar})$ = −10.0 cal mol^{-1} K^{-1}, $\Delta H^{\ddagger}(O_{Ar} \rightarrow Se_{Ar})$ = 26.7 kcal/mol, and $\Delta S^{\ddagger}(O_{Ar} \rightarrow Se_{Ar})$ = −11.9 cal mol^{-1} K^{-1}; all values obtained for the 4-nitro-substituted derivative].[22,35] The $\Delta H^{\ddagger}$ value of the $O_{Bn} \rightarrow S_{Bn}$ rearrangement is increased greatly compared to those of both aryl rearrangements, indicating that the C−O bond breaking in the reactant is more important for the benzylic rearrangement than for the aryl rearrangements. Also, the $\Delta S^{\ddagger}$ value changes significantly. The large negative values obtained in the aryl rearrangements correspond well to the strained four-membered cyclic transition state. In comparison, the $\Delta S^{\ddagger}(O_{Bn} \rightarrow S_{Bn})$ value is small and positive, indicating that the transition state is not very constrained structurally. The positive $\Delta S^{\ddagger}$ value points toward a dissociative mechanism, where bond breaking has occurred to a greater extent than has

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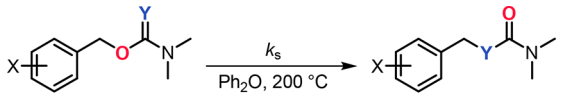
bond formation in the transition state, with the extreme case being the S_N1 reaction mechanism. Via comparison of the $\Delta S^{\ddagger}$ values, the $O_{Bn} \rightarrow S_{Bn}$ rearrangement possesses less S_N2 character than the aryl version does but has not quite reached the limiting domain of the S_N1 mechanism.

To clarify the influence of the substituents on the aromatic ring upon the reaction rate of the benzylic rearrangement, the kinetics was studied on the different substrates (Table 2 and the Supporting Information). The $O_{Bn} \rightarrow S_{Bn}$ reaction rate shows a strong dependence on the nature of the substituent. Substrates with an electron-donating group attached, i.e., the ether group in **2c** and **2f**, accelerate the reaction by more than 1 order of magnitude compared to that with unsubstituted compound **2h**. Conversely, the rate constant decreases even more when electron-withdrawing substituents are attached to the aromatic unit, like ester **2m**; however, the reaction still proceeds. The reaction rate is also influenced by the position of the substituent on the aromatic ring where the 2 and 4 positions are favored over the 3 position (**2a** and **2c** vs **2b**).

Table 2. Overview of the Obtained Rate Constants (k_s) for the Rearrangement of Substituted *O*-Benzyl Thio- and Selenocarbamates into Their Corresponding *S*-Benzyl Thiocarbamates and *Se*-Benzyl Selenocarbamates in Diphenyl Ether (0.4 M) at 200 °C[a]



2 3

compound	X	Y	k_s (s^{-1})
a	2-OMe	S	8.38×10^{-5}
b	3-OMe	S	1.53×10^{-5}
c	4-OMe	S	5.03×10^{-4}
f	4-OEt[b]	S	2.97×10^{-4}
g	4-Me	S	3.65×10^{-5}
h	4-H	S	3.59×10^{-5}
k	4-Cl	S	2.89×10^{-5}
l	4-Br	S	2.49×10^{-5}
m	4-CO_2CH_3	S	1.42×10^{-5}
o	4-OMe	Se	9.25×10^{-3}[c]
p	4-H	Se	8.51×10^{-4}[c,d]

[a]The values were obtained via ^{1}H NMR spectroscopy analysis unless otherwise stated. [b]The carmabate group is the ethyl derivative, *N*,*N*-diethylthiocarbamate. [c]Determined by LC–MS analysis. [d]Performed at a substrate concentration of 20 mM.

The substrates for the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement have already been shown to proceed at lower reaction temperatures and have reaction rates faster than those of the corresponding $O_{Bn} \rightarrow S_{Bn}$ rearrangements. This is also proven quantitatively, and the reaction rates of the seleno analogues are found to be ~2 orders of magnitude larger than those of the equivalent sulfur analogues, both following first-order reaction kinetics (Table 2). Again, electron-donating groups accelerate the rearrangement compared to that with the unsubstituted analogue (**2o** vs **2p**). The electron demand in the $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ rearrangements is thus found to be completely opposite compared to that in the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Ar} \rightarrow Se_{Ar}$ rearrangements. Here, electron-withdrawing substituents increase the rate significantly, while electron-donating substituents deter the rearrangement from proceeding.[22,28]

To elucidate the reaction mechanism, a linear free energy relationship study of the $O_{Bn} \rightarrow S_{Bn}$ rearrangement was performed. Ordinary Hammett plots were constructed from the obtained rate constants of the substrates in Table 2 and the tabulated substituent constants σ, σ^+, and σ^- (see the Supporting Information).[36] Unfortunately, none of these gave linear correlations. The plot against the σ^+ substituent constant presented the best, but still not optimal, correlation, in agreement with the observation that electron-donating substituents increase the reaction rate. The $O_{Ar} \rightarrow S_{Ar}$ rearrangement has previously been analyzed successfully with the Yukawa–Tsuno equation, which is why we also applied this analytical method to the $O_{Bn} \rightarrow S_{Bn}$ rearrangement (see the Supporting Information).[37−40] For a particular substituent, the σ value is generally considered constant; however, for compounds in which the transition state bears a nearly full charge, this no longer applies and the Hammett equation becomes invalid. The Yukawa–Tsuno equation manages to account for the enhanced resonance effects that are present in such reactions with high electron demand. A good linear relationship was obtained with this modified version of the Hammett equation, and a value of −0.44 was obtained for the Hammett reaction constant (ρ); the Yukawa–Tsuno constant, the enhanced resonance parameter (r), equals 5.40 (Figure 4).

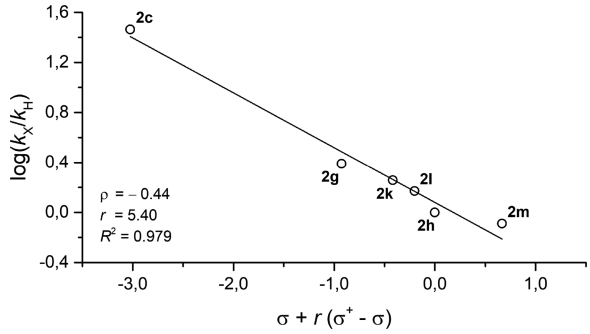


Figure 4. Yukawa–Tsuno plot used to descibe the $O_{Bn} \rightarrow S_{Bn}$ rearrangement in diphenyl ether at 200 °C. The parameters obtained are as follows: ρ = −0.44, and r = 5.40.

The obtained negative ρ value indicates that the reaction rate is favored by electron-donating substituents on the aromatic ring, due to an accumulation of positive charge in the transition state structure, which is in accordance with the observed reaction rates (Table 2). The greater the magnitude of ρ, the more sensitive the rearrangement is to the nature of the substituents. However, the comparison should always be relative to other related systems. A ρ value of +1.92 was obtained for the $O_{Ar} \rightarrow S_{Ar}$ rearrangement (using σ^- values).[40] According to this, the reaction mechanisms of the $O_{Ar} \rightarrow S_{Ar}$ and $O_{Bn} \rightarrow S_{Bn}$ rearrangements are not equivalent as the electron demand in the transition state in the benzylic version is the complete opposite of the aryl version.

The enhanced resonance parameter r is a measure of the influence of resonance on the reaction. Positive values show that the reaction is more sensitive to resonance effects than the standard, unsubstituted reaction, while negative values are less sensitive.[41] As stated, the r value for the $O_{Bn} \rightarrow S_{Bn}$ rearrangement is 5.40, and in comparison, the $O_{Ar} \rightarrow S_{Ar}$ rearrangement has an r value of 1.6 (using σ^- values).[40] This is in agreement with the proposal that the mechanism of the $O_{Bn} \rightarrow S_{Bn}$ rearrangement possesses more S_N1 character, i.e., retains

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more ionic character, than does the $O_{Ar} \rightarrow S_{Ar}$ rearrangement and is thereby more stabilized by resonance than the aryl version in which only partial charges in the transition state structure are present.

The benzylic Newman−Kwart rearrangement was further investigated by a crossover experiment to examine whether the rearrangement is inter- or intramolecular. The two similar, but distinguishable, reactants, *O*-(4-methoxybenzyl) *N*,*N*-dimethylthiocarbamate (**2c**) and its ethyl analogue, **2f**, possess similar reaction rates (Table 2) and were thus chosen for further investigation. Performing the crossover experiment at high concentrations (1.0 M, diphenyl ether, 200 °C), we found non-crossover rearranged products **3c** and **3f** formed with comparable rates together with a minor fraction of crossover products **3d** and **3e** as observed by ^{13}C NMR spectroscopy and MS analysis (Figure 5 and the Supporting Information). Thus,

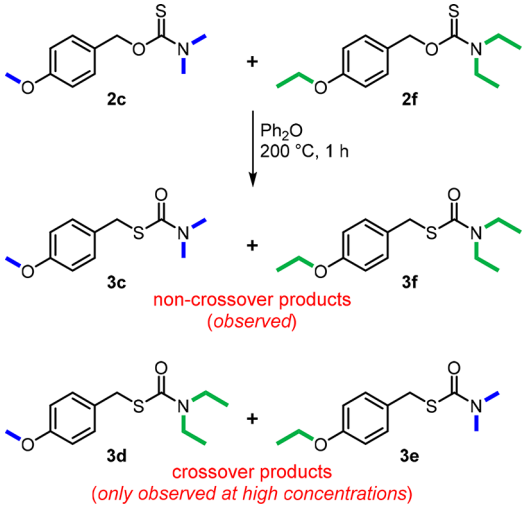

Figure 5. Crossover experiment between **2c** and **2f** indicating that the benzylic Newman−Kwart rearrangement proceeds via an ionic mechanism.

under the conditions presented here, the rearrangement proceeds via an ionic reaction mechanism in which the substrates rearrange mainly intramolecularly but also to a lesser degree intermolecularly. However, a 10-fold decrease in concentration (0.1 M, diphenyl ether, 200 °C) gave only products **3c** and **3f**, and none of the crossover products were observed. This indicates that even though the rearrangement follows an ionic reaction mechanism, the low-concentration crossover experiments show that the rearrangement has not reached the pure domain of an S_N1 mechanism. Instead, it proceeds via a tight ion pair intermediate consisting of the benzylic carbocation and the thiocarbamate moiety.

Computational Studies. A theoretical study was sought to gain further insight into the reaction mechanism of the rearrangement. The study included both *O*-benzyl thio- and selenocarbamates substituted with electron-donating (**2c** and **2o**), neutral (**2h** and **2p**), halogen (**2k** and **2s**), and electron-withdrawing groups (**2n** and **2t**) on the aromatic unit. The fourth-generation composite method termed G4MP2 was used as the level of theory with the GAUSSIAN09 suite of programs.[42,43] G4MP2 is approximating large basis set CCSD(T) single-point calculations on a B3LYP/6-31G(2df,p) geometry and is incorporating a so-called higher-level correction that is derived by a fit to the experimental values in the G3/05 test set with 454 experimental entries. The average absolute derivation from the experimental test set values is 1.04 kcal/mol.[44]

A potential energy diagram has been constructed to visualize the mechanism showing the reactant, transition state, and product for the $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ conversion of **2h** into **3h** and **2p** into **3p**, respectively (Figure 6 and the

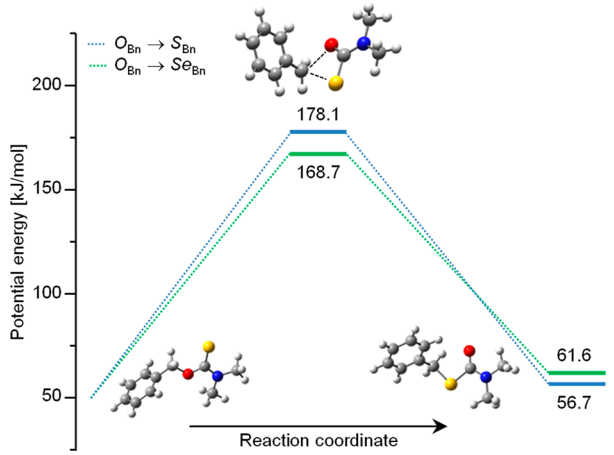

Figure 6. Schematic potential energy profile comparing the $O_{Bn} \rightarrow S_{Bn}$ conversion (**2h** into **3h**; G4MP2-calculated structures are shown) and $O_{Bn} \rightarrow Se_{Bn}$ conversion (**2p** into **3p**). The energies are given in kilojoules per mole, and the reactants for both reactions are set at 0 kJ/mol with an offset at 50 kJ/mol.

Supporting Information). The local minima on the potential energy surfaces were characterized by real vibrational frequencies, while the transition states were characterized by one imaginary frequency corresponding to a molecular displacement along the reaction coordinate. The nature of the transition state structures was investigated by an intrinsic reaction coordinate (IRC) calculation that verified the transition states to connect the reactants and the products without intermediates.[45,46] An optimization of the end points of the IRC was compared to that of the optimized reactants and products and found to be similar, indicating that the transition state structures are reliable. According to the IRC, the mechanism contains one transition state and no intermediates.

On the basis of the optimized structures, activation energies ($\Delta E^{\ddagger}$) and reaction energies (ΔE°), including zero-point vibrational energies, were calculated. The $O_{Bn} \rightarrow S_{Bn}$ rearrangement of substrate **2h** into **3h** gives a $\Delta E^{\ddagger}$ value of 178.1 kJ/mol and a ΔE° of 56.7 kJ/mol, while the corresponding $O_{Bn} \rightarrow Se_{Bn}$ rearrangement of **2p** into **3p** gives values of 168.7 and 61.6 kJ/mol for $\Delta E^{\ddagger}$ and ΔE°, respectively (Figure 6). These values show, in agreement with the experimental work, how the $O_{Bn} \rightarrow Se_{Bn}$ rearrangement proceeds with a lower activation barrier, and thus a higher reaction rate, compared to that of the $O_{Bn} \rightarrow S_{Bn}$ rearrangement. The $\Delta E^{\ddagger}$ values of the benzylic rearrangements are comparable in size to the corresponding aryl versions, which have been calculated to be 159 kJ/mol for the $O_{Ar} \rightarrow S_{Ar}$ rearrangement [B3LYP/6-31+G(d,p) level of theory][47] and 142 kJ/mol for the $O_{Ar} \rightarrow Se_{Ar}$ rearrangement [MP2/6-31G(d) level of theory].[22]

Comparing the energies for all examined substrates, we found that the activation energy for the rearrangement

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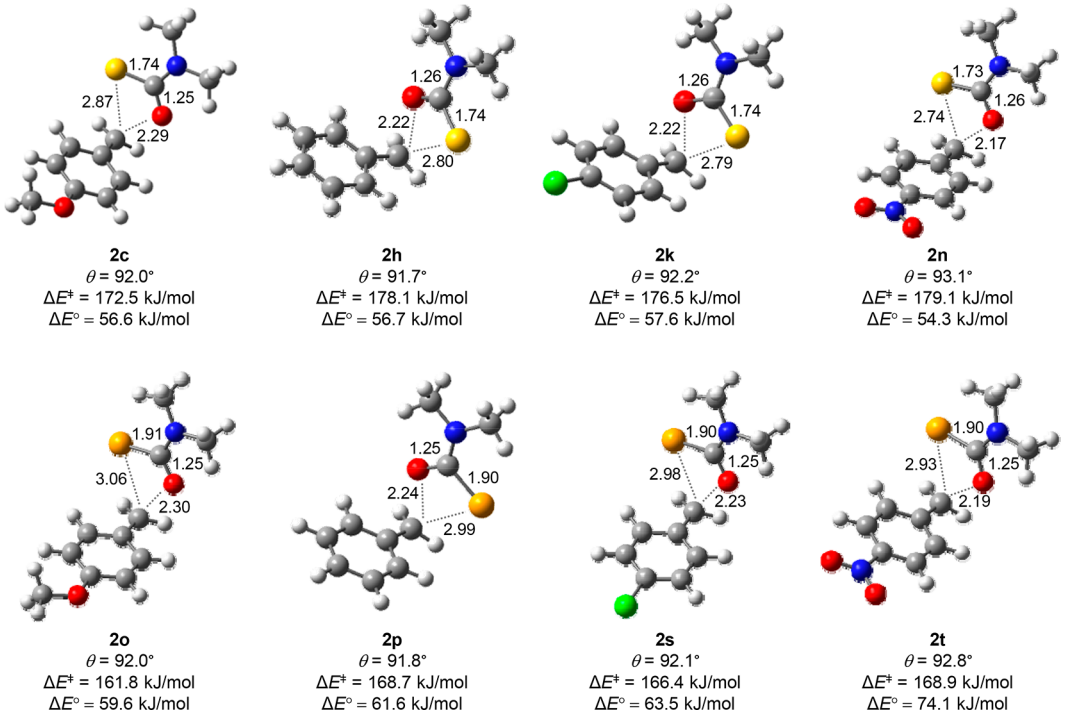

Figure 7. G4MP2-optimized transition state structures for the $O_{Bn} \rightarrow S_{Bn}$ conversion (top) and $O_{Bn} \rightarrow Se_{Bn}$ conversion (bottom). Selected bond lengths are shown in angstroms on the structure, while the dihedral angle (θ), the activation energy ($\Delta E^{\ddagger}$), and the reaction energy (ΔE°) are given below for each structure (S, yellow; Se, orange; O, red; N, blue; Cl, green; C, gray; H, white).

generally decreases with electron-donating groups attached on the aromatic unit and vice versa for electron-withdrawing groups (Figure 7). This is in accordance with the experimental results. The activation barrier is, however, decreased only 6−7 kJ/mol, altering the substituent from an electron-withdrawing one to an electron-donating one (**2c** vs **2n** or **2o** vs **2t**). This makes it possible to rearrange a wider collection of derivatives with different electron demands, a possibility that is not feasible for the aryl rearrangements. These results are also confirmed experimentally.

Examination of the geometry of the various substituted transition states gives access to more knowledge of the reaction mechanism for the rearrangement. All eight transition state structures possess two planar units, one consisting of the benzylic carbocation and one comprising the thio- or selenocarbamate moiety. The two elements are placed perpendicular to each other in all cases, as seen by the measured dihedral angle (θ) given for each structure (Figure 7). Analysis of the bond length distances between the two units gives an indication of whether the structures are connected covalently or through ionic interactions. The average C−O, C−S, and C−Se distances were found to be 2.2, 2.8, and 3.0 Å, respectively. These values are all larger than the values for a corresponding covalent bond (C−O, 1.4 Å; C−S, 1.8 Å; C−Se, 2.0 Å),[13] thus indicating an ionic interaction. The measured distances are, however, still relatively close to the covalent bond lengths, supporting the proposal of a tight ion pair intermediate consisting of the benzylic carbocation and the thio- or selenocarbamate moiety. Also, the changes in the geometry of the transition states as a function of the different substituents have been examined (Figure 7). As shown here, the C−O and C−S/Se distances between the two ionic species increase when an electron-donating group (**2c** and **2o**) is introduced and similarly decrease upon substitution with an electron-withdrawing substituent (**2n** and **2t**). The chlorine atom in **2k** and **2s** can both donate a lone pair to the aromatic ring that is also electronegative and thus withdraw electron density inductively. These two opposing effects is the reason why a difference in the bond lengths between the chlorine (**2k** and **2s**) and unsubstituted (**2h** and **2p**) substrates is not observed.

These computational studies of the benzylic Newman−Kwart rearrangement further support a tight ion pair intermediate consisting of the benzylic carbocation and the thio- or selenocarbamate moiety. The electron-donating substituents can stabilize the benzylic carbocation to a greater degree than the electron-withdrawing derivatives, thus giving rise to a more ionic intermediate, envisaged through longer bond lengths and thus lower activation energies.

CONCLUSION

In this paper, we present a systematic and in-depth study of the $O_{Bn} \rightarrow S_{Bn}$ and $O_{Bn} \rightarrow Se_{Bn}$ Newman−Kwart rearrangements. Synthetic procedures are presented together with thorough mechanistic studies as well as a theoretical elucidation of the reaction mechanism. The values obtained from computational chemistry support the experimental results that the rearrangement proceeds via an ionic reaction mechanism. The rate-determining step is the bond breaking of the $C_{benzylic}$−O bond in the reactant, thus forming a tight ion pair intermediate consisting of a benzylic carbocation and a thio- or selenocarbamate moiety. Ion pair formation is feasible because of the benzylic stabilization of charge. This mechanism supports the trend that electron-donating groups increase the rate of the rearrangement and the electron demand is thereby the opposite of that of the original aryl version of the Newman−Kwart rearrangement.

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EXPERIMENTAL SECTION

General Methods. All chemicals, unless otherwise stated, were purchased from commercial suppliers and used as received. Solvents were HPLC grade and used as received except THF, which was tapped from a Solvent Purification System (Innovative Technology, Inc.), and diphenyl ether, which was distilled prior to use. All reactions involving selenium were performed under an anhydrous nitrogen atmosphere.

Analytical thin layer chromatography (TLC) was performed on Merck DC-Alufolien SiO_2 60 F_{254} 0.2 mm thick precoated TLC plates and visualized under UV light (254 nm). Column chromatography and dry column vacuum chromatography were performed using SiO_2 from ROCC (SI 1721, 60 Å, 40−63 μm, and SI 1722, 60 Å, 15−40 μm). Melting points were determined on a Büchi melting point apparatus and are uncorrected.

^1H and ^{13}C NMR spectra were recorded at 500 and 126 MHz, respectively, on a Bruker Ultrashield Plus 500 spectrometer using a residual nondeuterated solvent as the internal standard. ^{77}Se NMR spectra were recorded on a Bruker spectrometer operating at 57 MHz using a saturated solution of diphenyl diselenide (δ 463) in $CDCl_3$ at 20 °C in a sealed tube as an external standard. All chemical shifts (δ) are in parts per million, and coupling constants (J) are expressed in hertz. The following abbreviations are used for convenience in reporting the multiplicity for NMR resonances: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The NMR data were processed using MestReNova version 10.0.2. Assignment of all ^1H and ^{13}C resonances was achieved using standard 2D NMR techniques such as $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC, and $^1H-^{13}C$ HMBC.

Standard HPLC analyses were performed on a Dionex UltiMate 3000 system coupled to an UltiMate 3000 diode array UV/vis detector. Separations were achieved using a Dionex Acclaim RSLC 120 C18 2.2 μm, 120 Å, 2.1 mm × 50 mm column maintained at 40 °C. The mobile phase solution was prepared with 0.1% HCOOH in the solvents. The water used as the eluent was purified with a Millipore system. LC−MS was performed on a Bruker MicrOTOF-QII system with an ESI source with a nebulizer of 1.2 bar, a dry gas of 8.0 L min^{-1}, a dry temperature of 200 °C, a capillary voltage of −4500 V, an end plate offset of −500 V, funnel 1 RF 200.0 Vpp, an ISCID energy of 0.0 eV, funnel 2 RF 200.0 Vpp, hexapole RF 100.0 Vpp, a quadrupole ion energy of 5.0 eV, a low mass of m/z 100.00, a collision energy of 8.0 eV, collision RF 100.0 Vpp, a transfer time of 80.0 μs, and a prepulse storage time of 1.0 μs. LC−HRMS samples were calibrated by an automated prerun internal mass scale calibration of the individual samples by injecting a sodium formate solution, consisting of 10 mM $NaOH_{(aq)}$ in a 1:1 (v/v) i-PrOH/H_2O mixture (with 1% HCOOH). Subsequent calibration was performed on the basis of the calibrator ions. The LC−MS data were processed using DataAnalysis version 4.0 SP5. For Se-containing ions in the mass spectrum, only the main selenium isotope (^{80}Se) is quoted.

Elemental analyses were performed by the microanalytical service of the Department of Chemistry of the University of Copenhagen on a CE Instrument, Flash 1112 series EA instrument.

Experimental Procedures for the *O*-Benzyl Thio- and Selenocarbamates. *General Procedure.* The desired alcohol (1.0 equiv) and sodium hydride (60% in mineral oil, 1.2 equiv for S substrates and 2.2 equiv for Se substrates) were added to anhydrous, degassed THF under a nitrogen atmosphere. The reaction mixture was cooled by a water bath and stirred for 10 min. *N,N*-Dimethylthiocarbamoyl chloride (1.0 equiv, used for S substrates) or *S*-phenyl *N,N*-dimethylthioselenocarbamate[27] (1.0 equiv, used for Se substrates) was added *in situ*, and the reaction mixture was stirred for a further 1 h at 25 °C. The mixture was concentrated *in vacuo* before CH_2Cl_2 was added, and the solution was filtered through a plug of Celite and concentrated *in vacuo*. If needed, the product was purified by column chromatography.

*O-(2-Methoxybenzyl) N,N-Dimethylthiocarbamate (**2a**).* 2-Methoxybenzyl alcohol (559 mg, 4.05 mmol) and NaH (60% in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a white powder (884 mg, 3.92 mmol, 97%): mp 37−38 °C; ^1H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.34−7.31 (m, 2H), 7.04−7.02 (m, 1H), 6.97−6.94 (m, 1H), 5.41 (s, 2H), 3.81 (s, 3H), 3.29 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C) δ 187.0, 156.9, 129.4, 128.8, 123.9, 120.2, 110.8, 67.8, 55.4, 42.3, 37.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{16}NO_2S$ 226.0896, found 226.0898.

*O-(3-Methoxybenzyl) N,N-Dimethylthiocarbamate (**2b**).* 3-Methoxybenzyl alcohol (559 mg, 4.05 mmol) and NaH (60% in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a light yellow oil (857 mg, 3.80 mmol, 94%): ^1H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.29 (t, J = 8.2 Hz, 1H), 6.99−6.94 (m, 2H), 6.90 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 5.42 (s, 2H), 3.75 (s, 3H), 3.29 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C) δ 186.9, 159.3, 137.8, 129.5, 119.7, 113.3, 113.2, 71.7, 55.0, 42.4, 37.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{16}NO_2S$ 226.0896, found 226.0900.

*O-(4-Methoxybenzyl) N,N-Dimethylthiocarbamate (**2c**).* 4-Methoxybenzyl alcohol (559 mg, 4.05 mmol) and NaH (60% in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a yellow oil (875 mg, 3.88 mmol, 96%): ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.32 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 5.43 (s, 2H), 3.80 (s, 3H), 3.37 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 188.1, 159.7, 130.0, 128.3, 114.0, 72.9, 55.3, 42.8, 37.9; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{15}NNaO_2S$ 248.0716, found 248.0723.

*O-(4-Methoxybenzyl) N,N-Diethylthiocarbamate (**2d**).* 4-Methoxybenzyl alcohol (455 mg, 3.29 mmol) and NaH (60% in mineral oil, 158 mg, 3.95 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-diethylthiocarbamoyl chloride (500 mg, 3.29 mmol) following the general procedure. The product was isolated as a yellow oil (818 mg, 3.23 mmol, 98%): ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.32 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.44 (s, 2H), 3.84 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.45 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 187.2, 159.7, 130.0, 128.5, 114.0, 72.6, 55.4, 47.9, 43.5, 13.5, 12.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{19}NNaO_2S$ 276.1029, found 276.1019.

*O-(4-Ethoxybenzyl) N,N-Dimethylthiocarbamate (**2e**).* 4-Ethoxybenzyl alcohol (616 mg, 4.05 mmol) and NaH (60% in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.05 mmol) following the general procedure. The product was isolated as a yellow oil (794 mg, 3.32 mmol, 82%): ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.31 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.43 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.38 (s, 3H), 3.10 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 188.2, 159.1, 130.1, 128.2, 114.6, 73.1, 63.6, 42.9, 38.0, 15.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{12}H_{17}NNaO_2S$ 262.0872, found 262.0873.

*O-(4-Ethoxybenzyl) N,N-Diethylthiocarbamate (**2f**).* 4-Ethoxybenzyl alcohol (502 mg, 3.30 mmol) and NaH (60% in mineral oil, 158 mg, 3.96 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-diethylthiocarbamoyl chloride (408 mg, 3.30 mmol) following the general procedure. The product was isolated as white crystals (802 mg, 3.00 mmol, 91%): mp 44−46 °C; ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.31 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.43 (s, 2H), 4.04 (q, J = 7.0 Hz, 2H), 3.84 (q, J = 7.1 Hz, 2H), 3.45 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 187.3, 159.1, 130.0, 128.3, 114.6, 72.7, 63.6, 47.9, 43.5, 15.0, 13.5, 12.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{14}H_{21}NNaO_2S$ 290.1185, found 290.1189.

*O-(4-Methylbenzyl) N,N-Dimethylthiocarbamate (**2g**).* 4-Methylbenzyl alcohol (494 mg, 4.04 mmol) and NaH (60% in mineral oil, 194 mg, 4.85 mmol) in anhydrous THF (25 mL) were reacted with

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N,N-dimethylthiocarbamoyl chloride (500 mg, 4.04 mmol) following the general procedure. The product was isolated as light yellow needles (737 mg, 3.52 mmol, 87%): mp 33−35 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.29 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.40 (s, 2H), 3.28 (s, 3H), 3.08 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C) δ 186.9, 137.3, 133.2, 128.9, 127.9, 71.9, 42.3, 37.4, 20.7; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{15}NNaOS$ 232.0767, found 232.0762.

*O-Benzyl N,N-Dimethylthiocarbamate (**2h**).* Benzyl alcohol (438 mg, 4.05 mmol) and NaH (60% in mineral oil, 194 mg, 4.86 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (501 mg, 4.05 mmol) following the general procedure. The product was isolated as a yellow oil (727 mg, 3.72 mmol, 92%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.42−7.28 (m, 5H), 5.50 (s, 2H), 3.38 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 188.0, 136.2, 128.5, 128.1, 128.0, 72.9, 42.8, 37.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{14}NOS$ 196.0791, found 196.0795.

*rac-O-(1-Phenylethyl) N,N-Dimethylthiocarbamate (**2i**).* 1-Phenylethan-1-ol (494 mg, 4.04 mmol) and NaH (60% in mineral oil, 194 mg, 4.85 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.04 mmol) following the general procedure. The product was isolated as a light yellow oil (813 mg, 3.88 mmol, 96%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.40−7.25 (m, 5H), 6.55 (q, J = 6.6 Hz, 1H), 3.35 (s, 3H), 3.15 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 187.3, 141.8, 128.4, 127.7, 126.2, 78.9, 42.6, 37.8, 22.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{16}NOS$ 210.0947, found 210.9050.

*(R)-O-(1-Phenylethyl) N,N-Dimethylthiocarbamate (**2j**).* (*R*)-1-Phenylethan-1-ol (494 mg, 4.04 mmol) and NaH (60% in mineral oil, 194 mg, 4.85 mmol) in anhydrous THF (25 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (500 mg, 4.04 mmol) following the general procedure. The product was isolated as a light yellow oil (830 mg, 3.97 mmol, 98%): ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.43−7.34 (m, 4H), 7.37−7.25 (m, 1H), 6.40 (q, J = 6.6 Hz, 1H), 3.26 (s, 3H), 3.16 (s, 3H), 1.54 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C) δ 186.1, 141.8, 128.4, 127.6, 125.9, 78.1, 42.2, 37.5, 22.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{15}NNaOS$ 232.0767, found 232.0767. Elemental analysis (%) calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.50; H, 7.67; N, 5.64.

*O-(4-Chlorobenzyl) N,N-Dimethylthiocarbamate (**2k**).* 4-Chlorobenzyl alcohol (1.00 g, 7.01 mmol) and NaH (60% in mineral oil, 337 mg, 8.42 mmol) in anhydrous THF (50 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (867 mg, 7.01 mmol) following the general procedure. The product was isolated as white crystals (1.59 g, 6.92 mmol, 99%): mp 36−37 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.37−7.29 (m, 4H), 5.48 (s, 2H), 3.39 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 188.0, 134.9, 134.2, 129.6, 128.9, 72.1, 43.1, 38.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{13}ClNOS$ 230.0401, found 230.0400.

*O-(4-Bromobenzyl) N,N-Dimethylthiocarbamate (**2l**).* 4-Bromobenzyl alcohol (1.00 g, 5.35 mmol) and NaH (60% in mineral oil, 257 mg, 6.42 mmol) in anhydrous THF (50 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (661 mg, 5.35 mmol) following the general procedure. The product was isolated as dark yellow crystals (1.31 g, 4.79 mmol, 90%): mp 54−55 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.49 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.46 (s, 2H), 3.39 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 188.0, 135.4, 131.8, 129.9, 122.3, 72.1, 43.1, 38.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{13}BrNOS$ 273.9896, found 273.9898. Elemental analysis (%) calcd for $C_{10}H_{12}BrNOS$: C, 43.81; H, 4.41; N, 5.11. Found: C, 43.98; H, 4.40; N, 5.11.

*O-(4-Carbomethoxybenzyl) N,N-Dimethylthiocarbamate (**2m**).* 4-Carbomethoxybenzyl alcohol (1.00 g, 6.02 mmol) and NaH (60% in mineral oil, 289 mg, 7.22 mmol) in anhydrous THF (50 mL) were reacted with *N,N*-dimethylthiocarbamoyl chloride (744 mg, 6.02 mmol) following the general procedure. The product was isolated as a light yellow solid (1.27 g, 5.01 mmol, 83%): mp 67−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.04 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 5.57 (s, 2H), 3.92 (s, 3H), 3.40 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 188.0, 166.9, 141.5, 130.0, 130.0, 127.6, 72.2, 52.3, 43.2, 38.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{12}H_{15}NNaO_3S$ 276.0665, found 276.0673.

*O-(4-Nitrobenzyl) N,N-Dimethylthiocarbamate (**2n**).* 4-Nitrobenzyl alcohol (501 mg, 3.27 mmol) was dissolved in anhydrous, degassed THF (50 mL) under a nitrogen atmosphere. The reaction mixture was cooled with a water bath, potassium *tert*-butoxide (441 mg, 3.93 mmol) added slowly *in situ*, and the mixture subsequently stirred for 15 min. The reaction mixture turned brown/yellow after being stirred for 15 min; *N,N*-dimethylthiocarbamoyl chloride (404 mg, 3.27 mmol) was added *in situ*, and the reaction mixture was stirred for a further 18 h at 25 °C. The mixture was concentrated *in vacuo* before CH_2Cl_2 was added, and the solution was filtered through a plug of Celite and concentrated *in vacuo*. The reaction mixture was purified by column chromatography (ethyl acetate/heptane, 2% gradient). The product was isolated as yellow needles (409 mg, 1.70 mmol, 52%): mp 32−34 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.23 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 5.64 (s, 2H), 3.41 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 187.7, 147.8, 143.8, 128.3, 124.0, 71.2, 43.3, 38.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{12}N_2O_3S$ 241.06569, found 241.06555.

*O-(4-Methoxybenzyl) N,N-Dimethylselenocarbamate (**2o**).* 4-Methoxybenzyl alcohol (283 mg, 2.05 mmol) and NaH (60% in mineral oil, 180 mg, 4.51 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a light yellow oil (518 mg, 1.90 mmol, 93%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.33 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.53 (s, 2H), 3.79 (s, 3H), 3.47 (s, 3H), 3.07 (s, 3H);[48] ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 190.5 (d, J_{C-Se} = 235 Hz), 159.8, 130.1, 127.8, 114.0, 76.5, 55.3, 45.3, 38.2; ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 216.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{11}H_{15}NNaO_2Se$ 296.0160, found 296.0165.

*O-Benzyl N,N-Dimethylselenocarbamate (**2p**).* Benzyl alcohol (221 mg, 2.05 mmol) and NaH (60% in mineral oil, 180 mg, 4.50 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a light yellow oil (461 mg, 1.90 mmol, 93%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.42−7.31 (m, 5H), 5.61 (s, 2H), 3.50 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 190.7 (d, J_{C-Se} = 236 Hz), 135.8, 128.7, 128.4, 128.2, 76.6, 45.4, 38.3; ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 216.1; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{14}NOSe$ 244.0235, found 244.0231.

*rac-O-(1-Phenylethyl) N,N-Dimethylselenocarbamate (**2q**).* 1-Phenylethan-1-ol (250 mg, 2.05 mmol) and NaH (60% in mineral oil, 180 mg, 4.50 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a yellow oil (508 mg, 1.98 mmol, 97%): ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.43−7.27 (m, 5H), 6.58 (q, J = 6.6 Hz, 1H), 3.37 (s, 3H), 3.16 (s, 3H), 1.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C) δ 188.3 (d, J_{C-Se} = 235 Hz), 141.3, 128.4, 127.7, 126.0, 81.7, 44.6, 37.8, 22.4; ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 220.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{16}NOSe$ 258.0392, found 258.0374.

*O-(4-Bromobenzyl) N,N-Dimethylselenocarbamate (**2r**).* 4-Bromobenzyl alcohol (383 mg, 2.05 mmol) and NaH (60% in mineral oil, 180 mg, 4.50 mmol) in anhydrous THF (25 mL) were reacted with *S*-phenyl *N,N*-dimethylthioselenocarbamate (500 mg, 2.05 mmol) following the general procedure. The product was isolated as a yellow oil (585 mg, 1.82 mmol, 89%): ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.58 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.55 (s, 2H), 3.40 (s, 3H), 3.12 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 25 °C) δ 189.2 (d, J_{C-Se} = 236 Hz), 135.4, 131.4, 130.0, 121.3, 74.3, 44.9, 37.9; ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 219.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{13}BrNOSe$ 321.9337, found 321.9341.

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Experimental Procedures for the *S*-Benzyl Thiocarbamates and *Se*-Benzyl Selenocarbamates. *S-(2-Methoxybenzyl) N,N-Dimethylthiocarbamate (**3a**).* *O*-(2-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (132 mg, 586 μmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 4 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (63.4 mg, 281 μmol, 48%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.40 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.5, 1.8 Hz, 1H), 6.89 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 2.98 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 168.6, 157.5, 130.8, 128.7, 126.8, 120.7, 110.6, 55.7, 36.8 (2 × C), 29.7; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}NO_2S$ 226.0896, found 226.0900.

*S-(3-Methoxybenzyl) N,N-Dimethylthiocarbamate (**3b**).* *O*-(3-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (210 mg, 932 μmol) was dissolved in Ph_2O (1 mL) and heated to 200 °C for 20 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (124 mg, 550 μmol, 59%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.21 (t, *J* = 7.9 Hz, 1H), 6.94 (dt, *J* = 7.9, 1.1 Hz, 1H), 6.91 (t, *J* = 2.3 Hz, 1H), 6.78 (ddd, *J* = 7.9, 2.3, 1.1 Hz, 1H), 4.14 (s, 2H), 3.80 (s, 3H), 3.00 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 167.9, 159.8, 140.0, 129.7, 121.4, 114.5, 112.9, 55.4, 36.9 (2 × C), 35.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}NO_2S$ 226.0896, found 226.0895.

*S-(4-Methoxybenzyl) N,N-Dimethylthiocarbamate (**3c**).* *O*-(4-Methoxybenzyl) *N*,*N*-dimethylthiocarbamate (100 mg, 444 μmol) was dissolved in Ph_2O (5 mL) and heated to 200 °C for 2 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (70.0 mg, 311 μmol, 70%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.11 (s, 2H), 3.78 (s, 3H), 3.00 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 168.1, 158.9, 130.5, 130.2, 114.1, 55.4, 36.8 (2 × C), 34.5; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}NO_2S$ 226.0896, found 226.0893.

*S-(4-Methoxybenzyl) N,N-Diethylthiocarbamate (**3d**).* *O*-(4-Methoxybenzyl) *N*,*N*-diethylthiocarbamate (107 mg, 422 μmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 2 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow oil (64.1 mg, 253 μmol, 60%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.11 (s, 2H), 3.78 (s, 3H), 3.37 (m, 4H), 1.16 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 167.0, 158.8, 130.4, 130.2, 114.1, 55.4, 42.3, 42.1, 34.2, 13.8, 13.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{20}NO_2S$ 254.1209, found 254.1211.

*S-(4-Ethoxybenzyl) N,N-Dimethylthiocarbamate (**3e**).* *O*-(4-Ethoxybenzyl) *N*,*N*-dimethylthiocarbamate (168 mg, 702 μmol) was dissolved in Ph_2O (1 mL) and heated to 200 °C for 2 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow oil (90.0 mg, 376 μmol, 54%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.11 (s, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 2.98 (bs, 6H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 168.2, 158.2, 130.3, 130.2, 114.7, 63.6, 36.8 (2 × C), 34.5, 15.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{18}NO_2S$ 240.1053, found 240.1052.

*S-(4-Ethoxybenzyl) N,N-Diethylthiocarbamate (**3f**).* *O*-(4-Ethoxybenzyl) *N*,*N*-diethylthiocarbamate (78.8 mg, 295 μmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 2 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow oil (49.0 mg, 183 μmol, 62%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.11 (s, 2H), 4.01 (q, *J* = 7.0 Hz, 2H), 3.37 (m, 4H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.16 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 167.0, 158.2, 130.2, 130.2, 114.7, 63.6, 42.3, 42.0, 34.3, 15.0, 13.8, 13.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{22}NO_2S$ 268.1366, found 268.1365.

*S-(4-Methylbenzyl) N,N-Dimethylthiocarbamate (**3g**).* *O*-(4-Methylbenzyl) *N*,*N*-dimethylthiocarbamate (144 mg, 688 μmol) was dissolved in Ph_2O (3 mL) and heated to 200 °C for 19 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (59.0 mg, 282 μmol, 41%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.24 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 4.12 (s, 2H), 2.99 (bs, 6H), 2.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 168.1, 136.9, 135.4, 129.4, 129.0, 36.8 (2 × C), 34.7, 21.3; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{16}NOS$ 210.0947, found 210.0951.

*S-Benzyl N,N-Dimethylthiocarbamate (**3h**).* *O*-Benzyl *N*,*N*-dimethylthiocarbamate (133 mg, 681 μmol) was dissolved in Ph_2O (1 mL) and heated to 200 °C for 22 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (44.0 mg, 225 μmol, 33%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.38−7.27 (m, 4H), 7.25−7.21 (m, 1H), 4.16 (s, 2H), 3.00 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 168.0, 138.5, 129.1, 128.7, 127.2, 36.9 (2 × C), 35.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}NOS$ 196.0791, found 196.0788.

*S-(4-Chlorobenzyl) N,N-Dimethylthiocarbamate (**3k**).* *O*-(4-Chlorobenzyl) *N*,*N*-dimethylthiocarbamate (232 mg, 1.01 mmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 22 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as an orange solid (119 mg, 518 μmol, 51%): mp 40−41 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.32−7.23 (m, 4H), 4.11 (s, 2H), 2.99 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 167.6, 137.3, 133.0, 130.4, 128.8, 36.9 (2 × C), 34.2; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{13}ClNOS$ 230.0401, found 230.0410.

*S-(4-Bromobenzyl) N,N-Dimethylthiocarbamate (**3l**).* *O*-(4-Bromobenzyl) *N*,*N*-dimethylthiocarbamate (324 mg, 1.18 mmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 23 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a light yellow solid (190 mg, 693 μmol, 59%): mp 37−38 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.09 (s, 2H), 2.99 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 167.6, 137.9, 131.7, 130.8, 121.1, 36.9 (2 × C), 34.3; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{13}BrNOS$ 273.9896, found 273.9888.

*S-(4-Carbomethoxybenzyl) N,N-Dimethylthiocarbamate (**3m**).* *O*-(4-Carbomethoxybenzyl) *N*,*N*-dimethylthiocarbamate (176 mg, 695 μmol) was dissolved in Ph_2O (0.5 mL) and heated to 200 °C for 23 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (118 mg, 466 μmol, 67%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 4.18 (s, 2H), 3.90 (s, 3H), 3.01 (bs, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 167.4, 167.0, 144.1, 130.0, 129.4, 129.1, 52.2, 36.9 (2 × C), 34.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{16}NO_3S$ 254.0845, found 254.0855.

*S-(4-Methoxybenzyl) N,N-Dimethylselenocarbamate (**3o**).* *O*-(4-Methoxybenzyl) *N*,*N*-dimethylselenocarbamate (204 mg, 749 μmol) was dissolved in Ph_2O (0.5 mL) and heated to 150 °C for 2.5 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after column chromatography (SiO_2, heptane to CH_2Cl_2) as a yellow oil (179 mg, 659 μmol, 88%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 4.16 [s (d, $^2J_{H-Se}$ = 11.5 Hz), 2H], 3.78 (s, 3H), 3.04 (bs, 3H), 2.93 (bs, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 165.3 (d, J_{C-Se} = 127 Hz), 158.5, 131.5, 130.0, 114.0, 55.3, 37.3, 36.7, 30.0 (d, J_{C-Se} = 58.1 Hz); ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 464.4 (t, $^2J_{Se-H}$ = 11.5 Hz); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{15}NNaO_2Se$ 296.0160, found 296.0157.

*S-Benzyl N,N-Dimethylselenocarbamate (**3p**).* *O*-Benzyl *N*,*N*-dimethylselenocarbamate (200 mg, 826 μmol) was dissolved in Ph_2O

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(10 mL) and heated to 200 °C for 6 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after dry column vacuum chromatography (SiO_2, heptane to ethyl acetate with a 4% gradient) as a white solid (108 mg, 446 μmol, 54%): mp 55−56 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.37−7.17 (m, 5H), 4.20 [s (d, $^2J_{H-Se}$ = 11.4 Hz), 2H], 3.04 (bs, 3H), 2.94 (bs, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 165.3 (d, J_{C-Se} = 126 Hz), 139.7, 129.1, 128.7, 127.0, 37.4, 36.9, 30.6 (d, J_{C-Se} = 58.7 Hz); ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 464.3 (t, $^2J_{Se-H}$ = 11.4 Hz); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{14}NOSe$ 244.0235, found 244.0237.

*S-(4-Bromobenzyl) N,N-Dimethylselenocarbamate (**3r**).* *O*-(4-Bromobenzyl) *N,N*-dimethylselenocarbamate (200 mg, 623 μmol) was dissolved in Ph_2O (10 mL) and heated to 200 °C for 4 h. The reaction mixture was cooled to 25 °C, and the title compound was isolated after dry column vacuum chromatography (SiO_2, heptane to ethyl acetate with a 4% gradient) as a yellow oil (122 mg, 380 μmol, 61%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.38 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.11 [s (d, $^2J_{H-Se}$ = 12.4 Hz), 2H], 3.03 (bs, 3H), 2.91 (bs, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 164.7 (d, J_{C-Se} = 125 Hz), 139.0, 131.7, 130.8, 120.7, 37.3, 36.9, 29.7 (d, J_{C-Se} = 59.5 Hz); ^{77}Se NMR (57 MHz, $CDCl_3$, 25 °C) δ 472.8 (t, $^2J_{Se-H}$ = 12.4 Hz); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{13}BrNOSe$ 321.9337, found 321.9336.

Experimental Procedures for the Benzyl Thiol and Benzyl Selenol. *4-Methoxybenzenethiol (**4c**).* A solution of *S*-(4-methoxybenzyl) *N,N*-dimethylthiocarbamate (53.0 mg, 235 μmol) in 1.75 M KOH in a degassed (N_2, 30 min) MeOH/H_2O mixture [2:1 (v/v), 10 mL] was stirred for 21 h at 25 °C. The mixture was cooled to 0 °C before concentrated $HCl_{(aq)}$ (3 mL) was added. A white precipitate was formed, which was isolated by centrifugation and washed extensively with water to give the product as white crystals (36.0 mg, 233 μmol, 99%): ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.17 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 3.59 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 159.2, 130.7, 129.6, 114.0, 55.4, 42.9. The analytical data are in accordance with the literature.[49]

*1,2-Bis(4-methoxyphenyl)diselane (**4o**).* A solution of *Se*-(4-methoxybenzyl) *N,N*-dimethylselenocarbamate (70.5 mg, 259 μmol) in 1.75 M KOH in a degassed (N_2, 30 min) MeOH/H_2O mixture [2:1 (v/v), 15 mL] was stirred for 21 h at 25 °C. The mixture was cooled to 0 °C before concentrated $HCl_{(aq)}$ (5 mL) was added. A light yellow precipitate was formed, which was isolated by centrifugation and washed extensively with water to give the oxidized product, the diselenide, as a light yellow solid (51.0 mg, 127 μmol, 98%): ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.16 (d, J = 8.6 Hz, 4H), 6.83 (d, J = 8.6 Hz, 4H), 3.84 [s (d, $^2J_{Se-H}$ = 7.1 Hz), 4H], 3.79 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 158.9, 131.3, 130.3 (d, J_{Se-C} = 16.0 Hz), 114.0, 55.4, 32.4. The analytical data are in accordance with the literature.[50]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01468.

Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Spectral characterization data together with details from the attempted stereochemical analysis, kinetic studies, linear free energy relationship studies, crossover studies, X-ray crystallography, and computational studies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pittel@chem.ku.dk.

ORCID

Michael Pittelkow: 0000-0002-3371-9500

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Wirth, T. *Organoselenium Chemistry: Synthesis and Reactions*; Wiley, 2012.
(2) Xu, H.; Cao, W.; Zhang, X. Selenium-Containing Polymers: Promising Biomaterials for Controlled Release and Enzyme Mimics. *Acc. Chem. Res.* **2013**, *46*, 1647−1658.
(3) Cao, W.; Zhang, X.; Miao, X.; Yang, Z.; Xu, H. γ-Ray-responsive supramolecular hydrogel based on a diselenide-containing polymer and a peptide. *Angew. Chem., Int. Ed.* **2013**, *52*, 6233−7.
(4) Boyd, R. Selenium stories. *Nat. Chem.* **2011**, *3*, 570−570.
(5) Arnér, E. S. J. In *Selenium*; Hatfield, D. L., Berry, M. J., Gladyshev, V. N., Eds.; Springer: New York, 2012; pp 1−19.
(6) Reich, H. J.; Hondal, R. J. Why Nature Chose Selenium. *ACS Chem. Biol.* **2016**, *11*, 821−841.
(7) Chandrashekar, T. K.; Venkatraman, S.; Prabhuraja, V.; Misra, R.; Baskar, V. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 845−872.
(8) Rasmussen, B.; Sørensen, A.; Gotfredsen, H.; Pittelkow, M. Dynamic combinatorial chemistry with diselenides and disulfides in water. *Chem. Commun.* **2014**, *50*, 3716−3718.
(9) Petrukhina, M. A.; Henck, C.; Li, B.; Block, E.; Jin, J.; Zhang, S.-Z.; Clerac, R. Spirocyclic Sulfur and Selenium Ligands as Molecular Rigid Rods in Coordination of Transition Metal Centers. *Inorg. Chem.* **2005**, *44*, 77−84.
(10) Jacob, C.; Giles, G. I.; Giles, N. M.; Sies, H. Sulfur and Selenium: The Role of Oxidation State in Protein Structure and Function. *Angew. Chem., Int. Ed.* **2003**, *42*, 4742−4758.
(11) Moroder, L. Isosteric replacement of sulfur with other chalcogens in peptides and proteins. *J. Pept. Sci.* **2005**, *11*, 187−214.
(12) Muttenthaler, M.; Alewood, P. F. Selenopeptide chemistry. *J. Pept. Sci.* **2008**, *14*, 1223−1239.
(13) Beld, J.; Woycechowsky, K. J.; Hilvert, D. In *Oxidative Folding of Peptides and Proteins*; The Royal Society of Chemistry, 2009; pp 253−273.
(14) Stadtman, T. C. Selenocysteine. *Annu. Rev. Biochem.* **1996**, *65*, 83−100.
(15) Johansson, L.; Gafvelin, G.; Arnér, E. S. J. Selenocysteine in proteins—properties and biotechnological use *Biochim. Biophys. Acta. Biochim. Biophys. Acta, Gen. Subj.* **2005**, *1726*, 1−13.
(16) Muttenthaler, M.; Alewood, P. F. In *Oxidative Folding of Peptides and Proteins*; The Royal Society of Chemistry, 2009; pp 396−418.
(17) Durek, T.; Alewood, P. F. Preformed selenoesters enable rapid native chemical ligation at intractable sites. *Angew. Chem., Int. Ed.* **2011**, *50*, 12042−5.
(18) McGrath, N. A.; Raines, R. T. Chemoselectivity in Chemical Biology: Acyl Transfer Reactions with Sulfur and Selenium. *Acc. Chem. Res.* **2011**, *44*, 752−761.
(19) Townsend, S. D.; Tan, Z.; Dong, S.; Shang, S.; Brailsford, J. A.; Danishefsky, S. J. Advances in proline ligation. *J. Am. Chem. Soc.* **2012**, *134*, 3912−6.
(20) Newman, M. S.; Karnes, H. A. The Conversion of Phenols to Thiophenols via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31*, 3980−3984.
(21) Kwart, H.; Evans, E. R. The Vapor Phase Rearrangement of Thioncarbonates and Thioncarbamates. *J. Org. Chem.* **1966**, *31*, 410−413.
(22) Sørensen, A.; Rasmussen, B.; Agarwal, S.; Schau-Magnussen, M.; Sølling, T. I.; Pittelkow, M. Conversion of Phenols into

DOI: 10.1021/acs.joc.8b01468
J. Org. Chem. 2018, 83, 10786−10797

Selenophenols: Seleno Newman−Kwart Rearrangement. *Angew. Chem., Int. Ed.* **2013**, *52*, 12346−12349.
(23) Newman, M. S.; Hetzel, F. W. Preparation of olefins by pyrolysis of O-alkyldimethythiocarbamates. *J. Org. Chem.* **1969**, *34*, 3604−3606.
(24) Taguchi, T.; Nakao, M. Thermal rearrangement of xanthates to dithiolcarbonates—I. *Tetrahedron* **1962**, *18*, 245−255.
(25) Alajarin, M.; Marin-Luna, M.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A. Benzylic Newman−Kwart rearrangement of *O*-azidobenzyl thiocarbamates triggered by phosphines: pseudopericyclic [1,3] shifts via uncoupled concerted mechanisms. *Tetrahedron* **2009**, *65*, 2579−2590.
(26) Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. Reaction of Lithium Aluminum Hydride with Elemental Selenium: Its Application as a Selenating Reagent into Organic Molecules. *J. Am. Chem. Soc.* **2001**, *123*, 8408−8409.
(27) Koketsu, M.; Fukuta, Y.; Ishihara, H. Reaction of *N,N*-Dimethylselenocarbamoyl Chloride with Nucleophiles. Preparation of Diselenocarbamates, Selenothiocarbamates, and Selenoureas. *J. Org. Chem.* **2002**, *67*, 1008−1011.
(28) Moseley, J. D.; Sankey, R. F.; Tang, O. N.; Gilday, J. P. The Newman-Kwart rearrangement re-evaluated by microwave synthesis. *Tetrahedron* **2006**, *62*, 4685−4689.
(29) Lloyd-Jones, G. C.; Moseley, J. D.; Renny, J. S. Mechanism and Application of the Newman-Kwart O→S Rearrangement of O-Aryl Thiocarbamates. *Synthesis* **2008**, *2008*, 661−689.
(30) CCDC 1847961 (**2k**) and CCDC 1847970 (**3k**) contain the supplementary crystallographic data for these structures. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(31) CCDC 1847971 (**3p**) contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(32) Svanholm, U. ^{1}H NMR spectroscopy of selenosemicarbazides and related compounds. *Ann. N. Y. Acad. Sci.* **1972**, *192*, 124−131.
(33) Sørensen, A.; Rasmussen, B.; Pittelkow, M. ^{77}Se NMR Spectroscopy As a Sensitive Probe for Hammett σ Constants. *J. Org. Chem.* **2015**, *80*, 3852−3857.
(34) Duddeck, H. *Chemical Shifts and Coupling Constants for Selenium-77*; Gupta, R. R., Lechner, M. D., Eds.; Springer, 2004; pp 1−15.
(35) Gilday, J. P.; Lenden, P.; Moseley, J. D.; Cox, B. G. The Newman−Kwart Rearrangement: A Microwave Kinetic Study. *J. Org. Chem.* **2008**, *73*, 3130−3134.
(36) Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **1991**, *91*, 165−195.
(37) Tsuno, Y.; Ibata, T.; Yukawa, Y. Resonance Effect in Hammett Relationship. I. The Substituent Effect in the Acid Catalyzed Decompositions of ω-Diazoacetophenones in Acetic Acid. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 960−965.
(38) Yukawa, Y.; Tsuno, Y. Resonance Effect in Hammett Relationship. II. Sigma Constants in Electrophilic Reactions and their Intercorrelation. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 965−971.
(39) Yukawa, Y.; Tsuno, Y. Resonance Effect in Hammett Relationship. III. The Modified Hammett Relationship for Electrophilic Reactions. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 971−981.
(40) Miyazaki, K. The thermal rearrangement of thionocarbamates to thiolcarbamates. *Tetrahedron Lett.* **1968**, *9*, 2793−2798.
(41) Anslyn, E. V.; Dougherty, D. A. In *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; pp 421−488.
(42) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. Gaussian-4 theory using reduced order perturbation theory. *J. Chem. Phys.* **2007**, *127*, 124105.
(43) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 09*, revision A.02 and D.01; Gaussian, Inc.: Wallingford, CT, 2009.
(44) Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. Gaussian-4 theory. *J. Chem. Phys.* **2007**, *126*, 084108.
(45) Gonzalez, C.; Schlegel, H. B. An improved algorithm for reaction path following. *J. Chem. Phys.* **1989**, *90*, 2154−2161.
(46) Gonzalez, C.; Schlegel, H. B. Reaction path following in mass-weighted internal coordinates. *J. Phys. Chem.* **1990**, *94*, 5523−5527.
(47) Jacobsen, H.; Donahue, J. P. Expanding the scope of the Newman−Kwart rearrangement — A computational assessment. *Can. J. Chem.* **2006**, *84*, 1567−1574.
(48) The ^{1}H NMR spectrum of the pure compound contains 10% rearranged product, showing how this substrate rearranges spontaneously.
(49) Yin, Y.; Zhou, H.; Liu, X.; Chen, H.; Wu, F.; Zhang, H.; Tao, R.; Cheng, F.; Feng, Y. A metal-free and recyclable synthesis of benzothiazoles using thiourea as a sulfur surrogate. *Tetrahedron Lett.* **2015**, *56*, 1709−1712.
(50) Panduranga, V.; Prabhu, G.; Panguluri, N. R.; Sureshbabu, V. V. Alternative Protocol for the Synthesis of Symmetrical Dibenzyl Diselenides and Disulfides. *Synthesis* **2016**, *48*, 1711−1718.

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J. Org. Chem. 2018, 83, 10786−10797