Synthetic Methods

DOI: 10.1002/anie.201303773

Conversion of Phenols into Selenophenols: Seleno Newman–Kwart Rearrangement**

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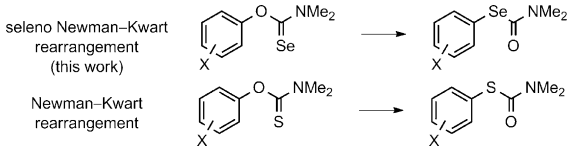
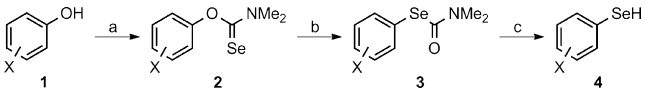
Diselenides and selenols play important roles in a range of chemistry, biochemistry, and materials chemistry applications.[1,2] The widespread use of aryl selenols in catalysis,[3] as ligands in inorganic chemistry,[4] and supramolecular chemistry[5] is hampered by their limited synthetic availability. Diselenides perform important roles in proteins where they are typically present in the form of selenocysteine,[6] the seleno analogue of cysteine.[7] The presence of selenocysteines influences the catalytic properties of enzymes and their presence provides a means to alter the structural properties of the proteins as compared to proteins containing cysteines.[6] Selenocysteines can engage in native chemical ligation[8] and diselenides/selenols also catalyze the disulfide exchange reaction.[9]

The conversion of a phenol into the corresponding selenophenol is a transformation for which no method has been developed to date.[1,2] The known synthetic protocols for the preparation of selenophenols are typically based on harsh chemical transformations such as Grignard-type chemistry,[10] nucleophilic-aromatic-type substitutions,[11] or Sandmeyer-type chemistry.[12] The reaction conditions required make it challenging to prepare complex structures containing selenols, and new procedures that compliment these protocols are desirable.

We report herein the first thermally induced $O_{Ar}\rightarrow Se_{Ar}$ migration reaction by the rearrangement of a range of substituted *O*-aryl selenocarbamates [ArOC(Se)NMe_2] into the corresponding *Se*-aryl selenocarbamates [ArSeC(O)NMe_2] (Scheme 1, top). The reaction can be viewed as a seleno analogue of the $O_{Ar}\rightarrow S_{Ar}$ rearrangement, which is known as the Newman–Kwart rearrangement (Scheme 1, bottom).[13] The rearrangement protocol enables the preparation of arylselenols from the corresponding phenols in three convenient steps (Scheme 2). The reaction mechanism of the rearrangement reaction is unique in organoselenium chemistry, and the rearrangement protocol allows the preparation of arylselenols containing a wide variety of functional groups.



Scheme 1. The seleno Newman–Kwart rearrangement (top) and the original Newman–Kwart rearrangement (bottom).



Scheme 2. Synthesis of arylselenols (isolated as diselenides) from phenols via the seleno Newman–Kwart rearrangement. a) 1. *N*-(dichloromethylene)-*N*-methylmethanaminium chloride (1 equiv), phenol **1** (2 equiv), CH_2Cl_2, 1 hour, reflux; 2. Se (1.5 equiv), $NaBH_4$ (1.8 equiv), *i*PrOH, 1 hour, 25 °C; 3. dropwise addition of (1) into (2), 25 °C, 1 hour. b) Neat or solvent. c) KOH, MeOH, H_2O, 24 hours, 25 °C (isolated as diselenide).

The *O*-aryl selenocarbamates (**2**; Scheme 2) were prepared in moderate yields ranging from 12–71 % by using a procedure similar to that developed by Ishihara and coworkers for the preparation of *S*-aryl selenocarbamates [ArSC(Se)NMe_2].[14] Elemental Se was reduced with $NaBH_4$ in *i*PrOH and added to a mixture of *N*-(dichloromethylene)-*N*-methylmethanaminium chloride and the desired phenol in CH_2Cl_2. It was found that the formation of *O*-aryl selenocarbamates was sensitive to the choice of solvent, base, temperature, concentration, and the stoichiometry of the reagents.

The reduction of Se with $NaBH_4$ was faster in H_2O, MeOH, and EtOH (minutes) than in *i*PrOH (an hour), but the use of *i*PrOH prevented the formation of *O*-alkyl selenocarbamates under the reaction conditions. The use of two equivalents of the phenol gave higher yields than the use of one, but the addition of excess phenol also gave rise to the formation of minor amounts of diarylcarbonates and *O*-arylcarbonates (after hydrolysis). The use of CH_2Cl_2 was superior to $CHCl_3$ and THF as the solvent, and the reactions proceeded more smoothly without the use of additional base (Et_3N or NaH).

The first substrates for the rearrangement reaction were the 4-nitro-*O*-aryl selenocarbamate (**2c**) and 4-nitro-2-methylester-*O*-aryl selenocarbamate (**2m**). These compounds were found to rearrange when the melting points of the pure compounds were measured (Figure 1a). Recovery of the melted compound and subsequent TLC analysis showed complete conversion of **2m** into **3m** after less than 20 minutes at 130 °C and the outcome of the reaction was unambiguously

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[**] We acknowledge financial support from the Danish Research council (FNU) for a Steno Fellowship (M.P.) and the Lundbeck Foundation for a Young Group Leader Fellowship (M.P.). We thank Dr. S. R. Beeren for valuable discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201303773.

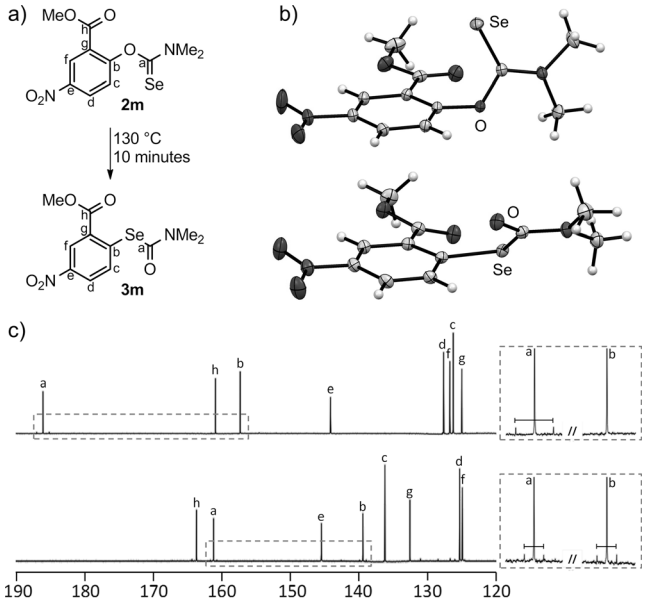
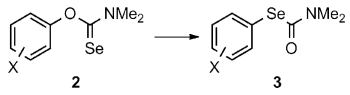


Figure 1. a) Rearrangement reaction for **2m** into **3m**. b) Single-crystal X-ray structures of **2m** and **3m**.[15] c) Low-field region of the ^{13}C NMR spectra (125 MHz, $CDCl_3$, 298 K) of **2m** and **3m** together with an enlargement of selected ^{77}Se,^{13}C-coupled signals.

Table 1: Conditions, conversion, and yields for the seleno Newman–Kwart rearrangement.



2 **3**

Substrate	X	*T* [°C]	Conversion[a]
2a	*o*-NO_2	160[b,c,d]	quant. (89%)
2b	*m*-NO_2	200[d]	quant. (58%)
2c	*p*-NO_2	130[b,c]	quant. (90%)
2d	*p*-CN	130[b,c,d]	quant. (95%)
2e	*p*-CO_2CH_3	180[d]	quant. (88%)
2f	*p*-Br	200[d]	(60%)
2g	*p*-F	200[d]	(trace)[e]
2h	*p*-H	200[d]	(55%)
2i	*p*-CH_3	210[d]	33% (n/a)[e]
2j	*o*-OCH_3	210[d]	no reaction
2k	*m*-OCH_3	210[d]	no reaction
2l	*p*-OCH_3	210[b,c,d]	no reaction
2m	*p*-NO_2-*o*-CO_2CH_3	130[b,c]	quant. (97%)

[a] Estimated by GC/MS, LC/MS, or TLC analysis. Yield of isolated product given within parentheses. [b] Heated neat in a dry flask. [c] Heated in anhydrous DMA. [d] Heated in anhydrous Ph_2O. [e] Decomposition and rearrangement are competing reactions.

confirmed by single-crystal X-ray crystallography (Figure 1b).[15] The clean conversion of the rearrangement reaction was also confirmed using NMR spectroscopy (Figure 1c). Selenium has several isotopes and ^{77}Se is NMR active (spin $^1/_2$).[16] ^1J couplings, resulting from the coupling of the ^{13}C nuclei to the ^{77}Se nuclei, were observed in the ^{13}C NMR spectra. In the aromatic region of the ^{13}C NMR spectrum of **2m** only carbon *a* couples to ^{77}Se, while in **3m** both carbons *a* and *b* couple to ^{77}Se. This ^{13}C NMR experiment confirms the connection of the Se atom to the aromatic core. Additional NMR experiments (^1H, COSY, HSQC, and HMBC) established the regiochemical outcome of the rearrangement reaction.

The $O_{Ar}\rightarrow Se_{Ar}$ rearrangement of the *O*-aryl selenocarbamates **2** into *Se*-aryl carbamates **3** is mediated by heat. The rearrangement proceeds faster and at lower temperature with electron-deficient aromatic substrates, such as 4-nitro- and 4-cyano-*O*-aryl selenocarbamate, as compared to electron-rich substrates such as 4-methyl-*O*-aryl selenocarbamate (Table 1). This trend is analogous to the Newman–Kwart rearrangement ($O_{Ar}\rightarrow S_{Ar}$).[13]

Similar to the $O_{Ar}\rightarrow S_{Ar}$ rearrangement, the $O_{Ar}\rightarrow Se_{Ar}$ rearrangement proceeds smoothly in a variety of solvents. However, it is important that the reactions are performed in anhydrous solvents, otherwise the carbamates hydrolyze, and the hydrolysis reactions are particularly effective at elevated temperatures where the rearrangement takes place. The 2- and 4-nitro-substituted substrates rearrange at 130°C neat and in solution, but when less activated substrates are used higher temperatures are required. We have found that Ph_2O and *N*,*N*-dimethylacetamide (DMA) are good solvents for the rearrangement reaction. The two solvents are high boiling and if dried carefully before use they enable the rearrangement without hydrolysis. Hydrolysis of the rearranged products leads to the formation of arylselenols, which are isolated as the diselenides because of the rapid oxidation of the selenophenols. Controlled hydrolysis of **3m** to yield the diselenide of **4m** (see Scheme 2; X = *p*-NO_2-*o*-CO_2CH_3) proceeded quantitatively with KOH in MeOH/H_2O (2:1).

The $O_{Ar}\rightarrow S_{Ar}$ Newman–Kwart rearrangement has been reported to proceed in a unimolecular manner via a four-membered transition state.[17] In the transition state of the reaction the sulfur atom interacts with the *ipso*-carbon atom and electron density is transferred to the aromatic ring. This explanation is in agreement with the observation that substrates with electron-withdrawing substituents placed in the *ortho* and/or *para* positions proceed with a lower energy barrier of activation than the unsubstituted substrates and substrates with electron-donating substituents. A similar trend is observed in the $O_{Ar}\rightarrow Se_{Ar}$ rearrangement. Furthermore, the $O_{Ar}\rightarrow Se_{Ar}$ rearrangement reaction also proceeds at significantly lower temperatures than does the $O_{Ar}\rightarrow S_{Ar}$ rearrangement when the same phenols are used. To gain insight to the course of the reaction the kinetics for the rearrangement of 4-nitro–*O*-aryl selenocarbamate (**2c**) was studied and compared with previously reported results obtained with 4-nitro-*O*-arylthiocarbamate.[18] It was found that both the $O_{Ar}\rightarrow S_{Ar}$ and the experimental $O_{Ar}\rightarrow Se_{Ar}$ rearrangement proceeds with first-order kinetics and a comparison of the kinetic parameters are presented in Figure 2. Here it is shown how the $O_{Ar}\rightarrow Se_{Ar}$ proceeds significantly faster than the $O_{Ar}\rightarrow S_{Ar}$ rearrangement.

Further insight into the reaction mechanism of the rearrangement was sought by means of a computational study using ab initio molecular orbital calculations at the G2 level of theory.[19–22] The study was performed on three representative *O*-aryl selenocarbamates (**2c**, **2h**, and **2l**) and all three substrates revealed a cyclic four-membered ring transition state where the oxygen atom, the selenium atom,

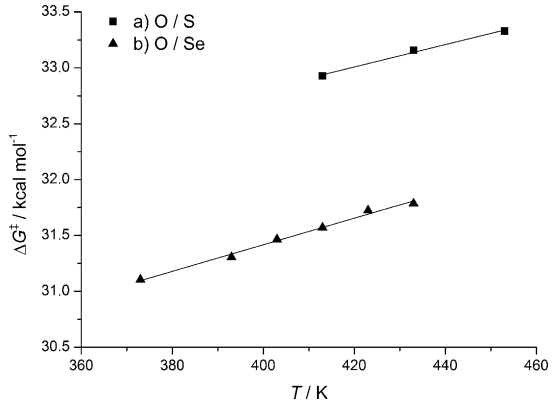


Figure 2. Gibbs free energy of activation ($\Delta G^{\ddagger}$) as a function of the temperature (T) for a) the Newman–Kwart rearrangement of the 4-NO_2 derivative in DMA (0.44 M)[17] and b) the seleno Newman–Kwart rearrangement of the 4-NO_2 derivative **2c** in DMA (0.02 M).

and the carbonyl carbon atom form a ring together with the *ipso*-carbon atom, and it is perpendicular to the aromatic ring (Figure 3).[23] By comparing the activation energy of the rearrangement reaction of structures in Figure 3 it again transpired that electron-deficient aromatic compounds (**2c**)

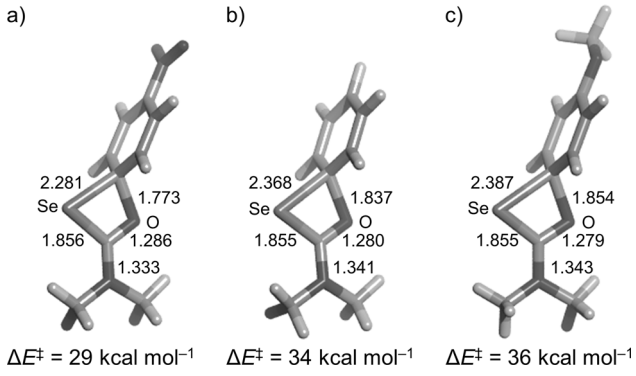


Figure 3. Calculated transition-state structures (MP2/6-3G(d)) and the corresponding activation energy ($\Delta E^{\ddagger}$) for the $O_{Ar}\rightarrow Se_{Ar}$ rearrangement of a) **2c**, b) **2h**, and c) **2l**.

have a lower energy barrier for the rearrangement than do electron-rich compounds (**2h** and **2l**). Analogous calculations on the $O_{Ar}\rightarrow S_{Ar}$ rearrangement show, as expected,[24] a similar cyclic four membered ring transition state. By comparing the energies for the transition states of the $O_{Ar}\rightarrow S_{Ar}$ rearrangement with the one from the $O_{Ar}\rightarrow Se_{Ar}$ rearrangement, it was again confirmed that the $O_{Ar}\rightarrow Se_{Ar}$ rearrangement has the lower energy barrier (see the Supporting Information).

To summarize, we have described the discovery of the first *O*-aryl selenocarbamate to *Se*-aryl carbamate rearrangement reaction. This reaction enables the convenient synthesis of arylselenols in three steps from the corresponding phenols.

Received: May 2, 2013
Revised: July 30, 2013
Published online: September 17, 2013

Keywords: density functional calculations · kinetics · rearrangement · selenium · X-ray crystallography

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