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Selenium-Epoxy 'Click' Reaction and Se-Alkylation—Efficient Access to Organo-Selenium and Selenonium Compounds

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Abstract: This work establishes the 'click' nature of the base-catalyzed oxirane ring opening reaction by the selenolate nucleophile. The 'click'-generated ß-hydroxy selenide can be alkylated to afford cationic selenium species. Hemolytic studies suggest that selenonium cations do not lyse red blood cells even at high concentrations. Overall, these results indicate the future applicability of the developed organo-selenium chemistry in the preparation of a new class of cationic materials based on the seleno-ether motif.

Keywords: 'click' chemistry; oxirane ring opening reaction; organo-selenium; organo-selenonium

1. Introduction

Selenium was discovered in early 1800 [1,2]. The chemistry of organo-selenium nucleophiles, however, only began in 1973 with Sharpless and Lauers' report on the preparation of phenylselenolate and its application in converting epoxides into allylic alcohols [3]. Since then a wide range of reactions based on nucleophilic selenium reagents have been developed for use in organic synthesis [1,2]. Inspired by Sharpless' selenium reagent and the growing interest in organoselenium materials [4], we began to examine the full scope of the ring opening reaction of epoxides by the selenolates in context of 'click' chemistry—another area of research pioneered by Sharpless [5]. 'Click' chemistry entails modular and wide in scope reactions that can be carried out under simple experimental conditions and produce quantitative yields and inoffensive byproducts [6]. This philosophy has been quickly adapted in the arena of materials science and application of 'click' reactions has revolutionized the way functional soft materials are being created [7–12]. The copper catalyzed azide-alkyne cycloaddition reaction has been at the forefront of this revolution since its advent in 2002 [6]. However, other potential 'click' processes originally identified by Sharpless, such as thiol and amine-based ring opening of the epoxide group, are also making a considerable impact in the protective-group-free synthesis of reactive and functionalizable polymers [13], hydrogels [14] and patterned surfaces [15]. The addition of selenium to this list would enhance the repertoire of nucleophilic ring opening 'click' reactions. Simple and efficient access to the ß-hydroxy selenide motif would also help in evaluating its applicability in terms of creating new bio-relevant materials.

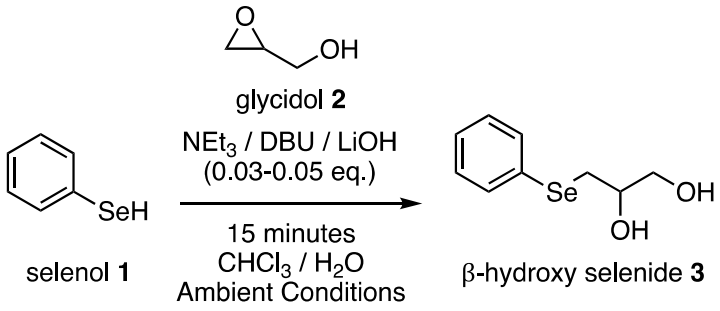
In examining previous studies, it becomes clear that the most successful method to access ß-hydroxy selenides relies on stoichiometric amounts of metal-hydrides (e.g., $LiAlH_4$, NaH, $LiBEt_3H$, Na/NH_3, Bu_3SnH, $NaBH_4$) or reducing agents such as zinc metal to create selenolate from diselenide precursors [16–20]. Often, selenolate is used in excess, reaction times range in hours at elevated temperatures (>50 °C), the isolated yields are moderate to high (<90%) and inert conditions are required. A strong reducing atmosphere also compromises functional group tolerance in such reactions. These attributes do not satisfy the 'click' chemistry criteria.

Since selenols possess a relatively low pK_a (5.2) [21], we hypothesized that simple organic and inorganic bases such as triethylamine (TEA), diazabicycloundecene (DBU) or lithium hydroxide (LiOH) may catalyze selenolate formation under mild conditions and may lead to the development of simple protocols in epoxide ring opening reactions. Herein, we show that indeed small amounts (0.01–0.05 eq./SeH) of the aforementioned bases in an organic or aqueous medium can catalyze regio-selective formation of ß-hydroxy selenides in >95% yield in 15 min of reaction time under ambient conditions. Due to a mild and fast nature, the reaction tolerates a variety of electrophiles and nucleophiles in the system. The selenium atom in the formed ß-hydroxy selenides can be quantitatively transformed into selenonium-based cationic species with full compatibility towards mammalian red blood cells. Overall, these results indicate that the base-catalyzed selenium-epoxy reaction meets the requirements of a 'click' reaction. The strength of this chemistry is also the reactivity of the 'click'-generated motif that allows for further installation of an alkyl group and cationization of the structure.

2. Results

2.1. Selenol Nucleophile in Organic Medium

Initially, commercially available benzene selenol (**1**) and glycidol (**2**) were chosen as the precursors (Scheme 1) [22–25]. The reaction was performed under ambient conditions in chloroform and the crude reaction mixture was analyzed with the help of ^{1}H-NMR spectroscopy (Figure 1, Figures S1–S3). Ambient conditions were chosen to fulfill one of the criteria of 'click' chemistry, which entails the reactions to be tolerant of moisture and oxygen. A 1:1 stoichiometry between the reactants was employed. From the ^{1}H-NMR data, it became clear that prolonging the reaction (from 15 min to 30 min) did not improve the yield of the product **3** significantly (Table 1). Instead, the nature and the amount of the catalyst influenced the reaction in a more profound way. The relatively stronger bases, DBU and LiOH, led to 94 and 97% ring opening reaction within 15 min of reaction time with 0.03 eq./SeH (4.76 mol%) loading. In all cases, diselenide **4** (PhSeSePh) was produced as the side product. It appears that stronger catalysts and short reaction times are required to facilitate a fast ring opening reaction and to hinder the formation of diselenide through oxidative dimerization of selenol reactant under ambient conditions.



Scheme 1. Base-catalyzed epoxide ring opening reaction with selenol nucleophile.

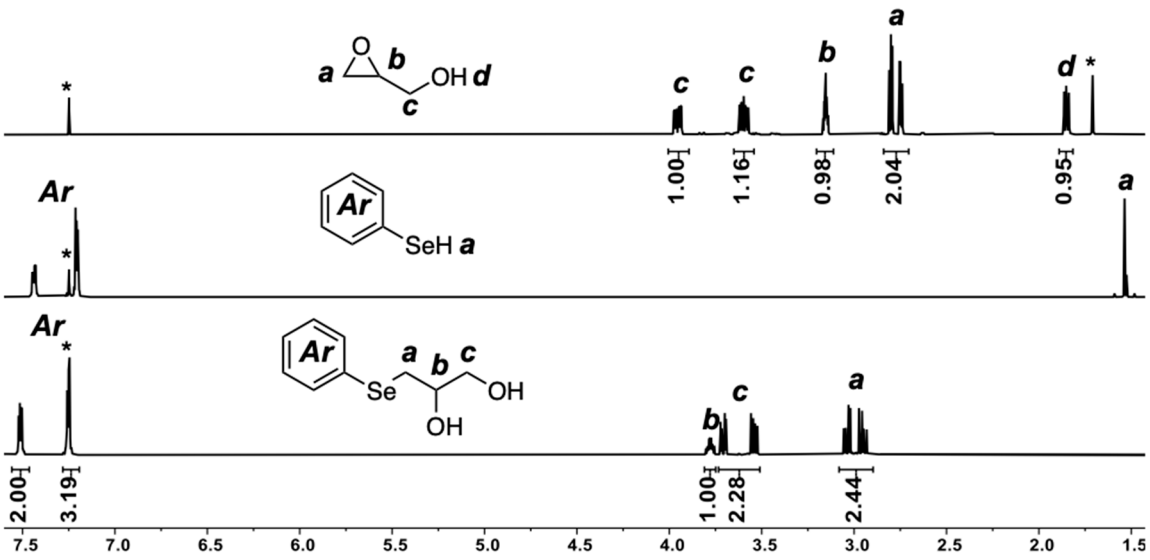


Figure 1. ^{1}H-NMR of the reactants and the reaction mixture (bottom) in deuterated chloroform ($CDCl_3$).

Table 1. Ring opening reaction in chloroform.

Entry	Solvent	Selenol (1)	Epoxide (2)	Catalyst	Catalyst (mol%)	Catalyst (eq./SeH)	Time (min)	Ring Opening (%)
1	$CHCl_3$	1	1	TEA	0.99	0.01	15	75
2	$CHCl_3$	1	1	TEA	0.99	0.01	30	77
3	$CHCl_3$	1	1	TEA	2.91	0.03	15	81
4	$CHCl_3$	1	1	TEA	2.91	0.03	30	83
5	$CHCl_3$	1	1	TEA	4.76	0.05	15	87
6	$CHCl_3$	1	1	TEA	4.76	0.05	30	87
7	$CHCl_3$	1	1	DBU	0.99	0.01	15	88
8	$CHCl_3$	1	1	DBU	0.99	0.01	30	89
9	$CHCl_3$	1	1	DBU	2.91	0.03	15	89
10	$CHCl_3$	1	1	DBU	2.91	0.03	30	90
11	$CHCl_3$	1	1	DBU	4.76	0.05	15	94
12	$CHCl_3$	1	1	DBU	4.76	0.05	30	94
13	$CHCl_3$	1	1	LiOH	0.99	0.01	15	94
14	$CHCl_3$	1	1	LiOH	0.99	0.01	30	94
15	$CHCl_3$	1	1	LiOH	2.91	0.03	15	95
16	$CHCl_3$	1	1	LiOH	2.91	0.03	30	96
17	$CHCl_3$	1	1	LiOH	4.76	0.05	15	97
18	$CHCl_3$	1	1	LiOH	4.76	0.05	30	97
19	$CHCl_3$	1.1	1	TEA	3.19	0.03	15	91
20	$CHCl_3$	1.1	1	DBU	3.19	0.03	15	>99
21	$CHCl_3$	1.1	1	LiOH	3.19	0.03	15	>99

2.2. Selenol Nucleophile in Water

Water is clearly a better reaction medium than chloroform (Table 2, Figures S4–S6) [26,27]. The best results were obtained with the help of LiOH that produces near quantitative ring opening reaction even when used in 0.99 mol% (0.01 eq./SeH) loading. DBU required 2.91 mol% (0.03 eq./SeH) to achieve similar results. Interestingly, TEA also led to near full conversion with 2.91 mol% loading.

Table 2. Ring opening reaction in water.

Entry	Solvent	Selenol (1)	Epoxide (2)	Catalyst	Catalyst (mol%)	Catalyst (eq./SeH)	Time (min)	Ring Opening (%)
1	H_2O	1	1	TEA	0.99	0.01	15	94
2	H_2O	1	1	TEA	0.99	0.01	30	95
3	H_2O	1	1	TEA	2.91	0.03	15	>99
4	H_2O	1	1	TEA	2.91	0.03	30	>99
5	H_2O	1	1	TEA	4.76	0.05	15	>99
6	H_2O	1	1	TEA	4.76	0.05	30	>99
7	H_2O	1	1	DBU	0.99	0.01	15	94
8	H_2O	1	1	DBU	0.99	0.01	30	95
9	H_2O	1	1	DBU	2.91	0.03	15	>99
10	H_2O	1	1	DBU	2.91	0.03	30	>99
11	H_2O	1	1	DBU	4.76	0.05	15	>99
12	H_2O	1	1	DBU	4.76	0.05	30	>99
13	H_2O	1	1	LiOH	0.99	0.01	15	>99
14	H_2O	1	1	LiOH	0.99	0.01	30	>99
15	H_2O	1	1	LiOH	2.91	0.03	15	>99
16	H_2O	1	1	LiOH	2.91	0.03	30	>99
17	H_2O	1	1	LiOH	4.76	0.05	15	>99
18	H_2O	1	1	LiOH	4.76	0.05	30	>99
19	H_2O	1.1	1	TEA	3.19	0.03	15	>99
20	H_2O	1.1	1	DBU	3.19	0.03	15	>99
21	H_2O	1.1	1	LiOH	3.19	0.03	15	>99

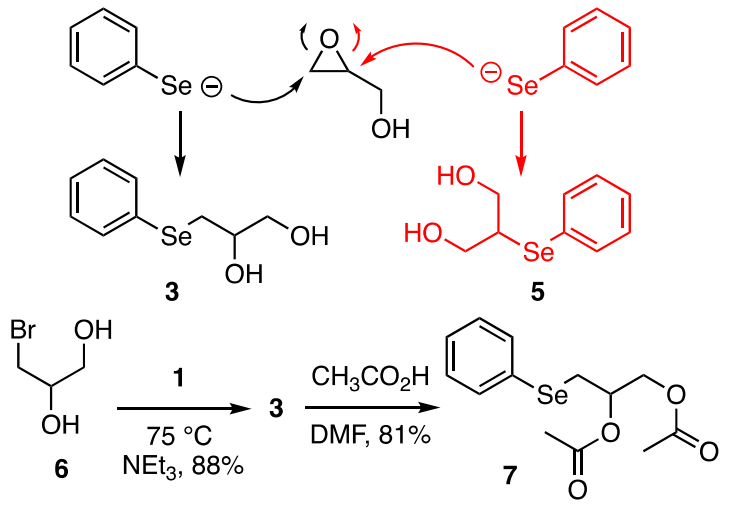
2.3. Non-Stoichiometric System

In general, the reaction performs very well in water (>99%) under stoichiometric conditions. In an organic medium, however, it is relatively sluggish (75%–97%). Therefore, a slight excess of selenol (1.1 eq./epoxide) was employed to further push the reaction in an organic medium. These results indicated that even in the case of TEA in chloroform, a reaction that typically underperformed, conversions exceeding 90% could be obtained with stoichiometry imbalance (Figures S7 and S8). In all other catalysts/solvent combinations, a quantitative ring opening reaction was observed (Tables S1 and S2).

2.4. Regio-Chemistry

Depending upon electronic and steric situation as well as reaction conditions, two isomers can form upon ring opening reaction (Scheme 2) [28]. Compound **3** is formed when the nucleophile attacks the least substituted carbon atom. Conversely, **5** is formed if the new bond is established between the nucleophile and the most substituted carbon atom.

To examine whether the present reaction led to the formation of one or more regio-isomers, **3** was synthesized from a different synthetic route. In this scheme, a commercially available compound **6** with the known structure was allowed to react to benzene selenol through selenium-halide reaction. The proton resonances from the compounds prepared by the selenium-epoxy and selenium-halide reactions were identical (Figure 2). In addition, no extra signals could be observed from the isomer **5**. The ^{1}H-NMRs were recorded in deuterated dimethylsulfoxide (DMSO-d_6), which allows for observing the hydroxyl protons too and indicate that one hydroxyl group is located adjacent to a tertiary carbon atom and the other to a secondary carbon atom. Hence, a doublet and a triplet arise and the doublet is downfield shifted due to its vicinity to the selenium atom. In isomer **5**, the hydroxyl groups are both secondary and would only produce one (triplet) signal for the hydroxyl group. The signal assignment was further confirmed by esterification with acetic acid (**7**), which produces two different types of acetyl groups and the signals from the hydroxyl groups disappear upon acetylation. From these experiments, it can be concluded that regio-isomer **3** forms exclusively under basic conditions. The carbon (Figures S9 and S10) and selenium NMRs discussed later further reinforces this notion.



Scheme 2. The regio-isomers **3** and **5** that can form upon ring opening reaction. The bottom shows an alternative synthesis of **3** through the alkylation route.

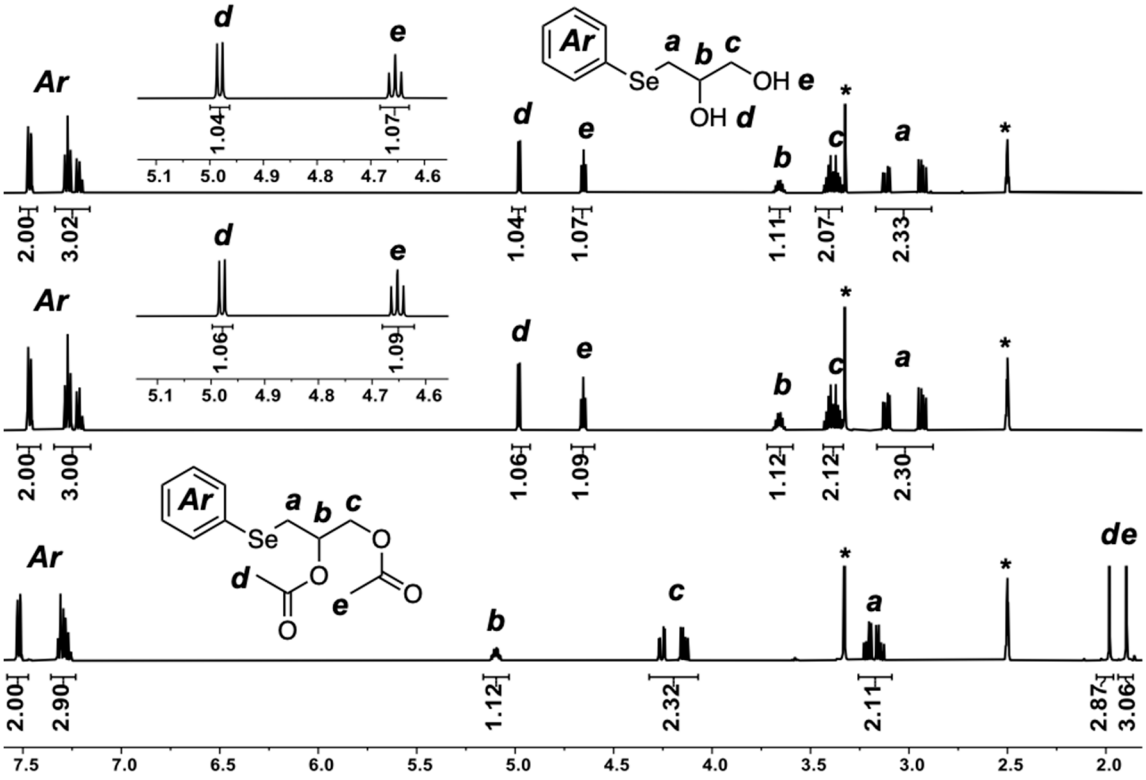
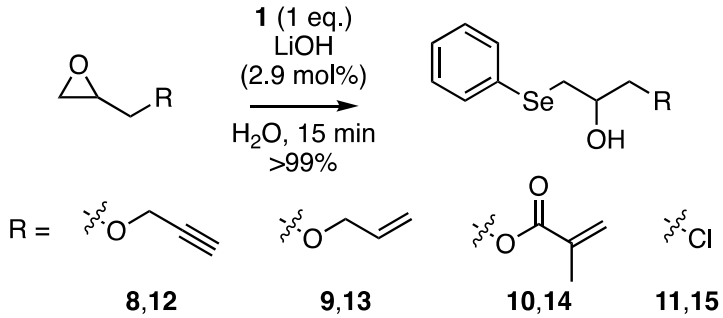


Figure 2. Crude ^{1}H-NMRs of **3** produced by ring opening reaction (**top**) and alkylation reaction (**middle**) and after acetylation (**bottom**) in deuterated dimethylsulfoxide (DMSO-d_6).

2.5. Chemo-Selectivity

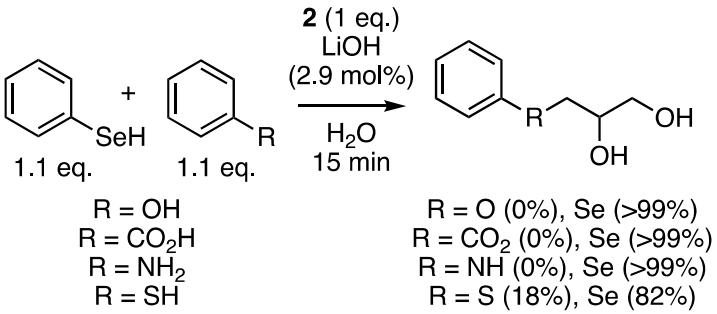
The mild and fast reaction indicated that the selenium-epoxy reaction might tolerate other functional groups. For this, initially, epoxides **8** and **9** carrying terminal acetylene and allyl groups were chosen (Scheme 3). These groups can be involved in azide-alkyne and thiol-ene/yne 'click' reactions [29–33], respectively. In these cases, complete preservation of the acetylene and allyl moieties were observed (Figures S11–S14). Encouraged by this, epoxide **10** with a more reactive methacrylate group was chosen. In this case as well, the methacrylate was not involved in a Michael-type of addition

reaction with benzeneselenolate (Figures S15 and S16) [34]. A further increase in the reactivity of the second electrophilic site in the molecule was sought with the help of an alkyl halide (**11**). Surprisingly, even in this case, no substitution reaction was observed (Figures S17 and S18). These results indicated that the selenium-epoxy reaction tolerated a number of other electrophilic sites in the system and only the ring-opened products **12–15** were obtained.



Scheme 3. Ring opening reaction in the presence of other electrophiles in the system.

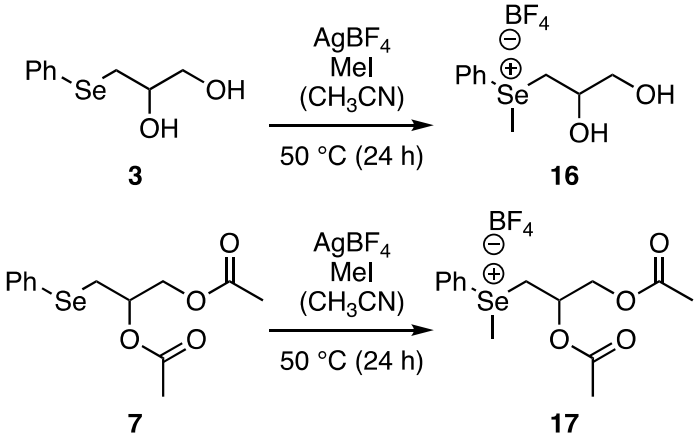
To examine tolerance for other nucleophilic sites in the system, competing reactions were performed (Scheme 4, Figures S19–S22). Initially, phenol, benzoic acid and aniline were employed in a 1:1 ratio with selenol **1**. Although these nucleophiles are known to open the epoxide ring, they fail due to a faster ring opening reaction with the selenolate nucleophile. This led us to employ thiophenol as the nucleophile. It is one of the best nucleophiles that organic chemistry can offer. As expected, it can compete with selenol and 18% thio-ether can form under LiOH catalysis. In this case, therefore, milder systems employing DBU and TEA were also explored and led to 16 and 11% thio-ether formation, respectively.



Scheme 4. Ring opening reaction in the presence of other nucleophiles in the system.

2.6. Selenium Alkylation

Methylation of the selenium atom in **3** and **7** could be achieved with the help of $AgBF_4$ as a catalyst and methyl iodide as an alkylating agent in acetonitrile at 50 °C for 24 h (Scheme 5, Figures S23–S26) [35]. This reaction proceeds cleanly and requires just precipitation for isolation of the cationic products **16** and **17**. Interestingly, the addition of a substituent on selenium adds one more stereogenic center to the molecule and the ^{1}H- and ^{13}C-NMR becomes relatively complex due to the formation of four diastereomers (Figure 3).



Scheme 5. Alkylation of seleno-ethers to access selenonium cations.

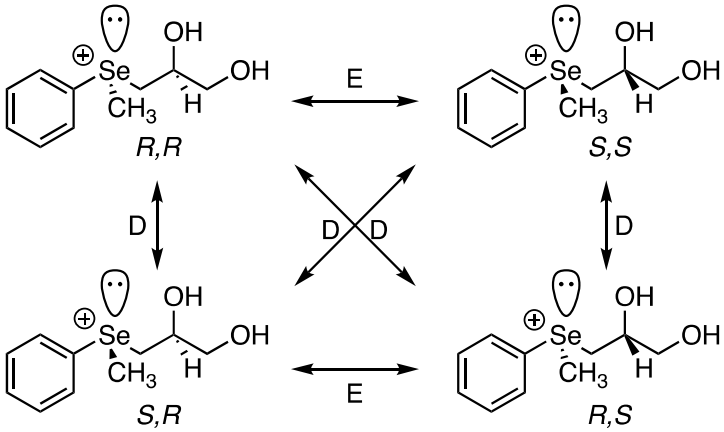


Figure 3. Formation of diastereomers upon Se-alkylation (E = enantiomer, D = diastereomer).

2.7. Selenium NMR

Among six natural isotopes, ^{77}Se with spin quantum number $l = \frac{1}{2}$ is active in nuclear magnetic resonance spectroscopy. A common reference, however, is not established in the field. Historically, a number of compounds have been used as standards [36]. A practical standard is diphenyldiselenide (**4**) with a chemical shift of δ = 463 ppm. This standard allows for fathoming the chemical shifts of other selenium compounds (Figure 4 and Figures S27–S30). As can be seen in Figure 4, selenium in **3** resonates at 262 ppm. The single signal once again confirms one regio-isomer. Upon esterification of this compound into **7**, a downfield shift in the selenium is observed by 10 ppm due to the electron withdrawing nature of the carbonyl groups. In compounds **16** and **17** in which the selenium atom becomes a cation and electron poor, a downfield shift of >100 ppm is observed. Interestingly, as expected from the ^{1}H and ^{13}C-NMRs, two signals for two diastereomers were observed in the case of **17**. However, **16** only exhibited one broad signal, perhaps due to an overlap of the two expected signals.

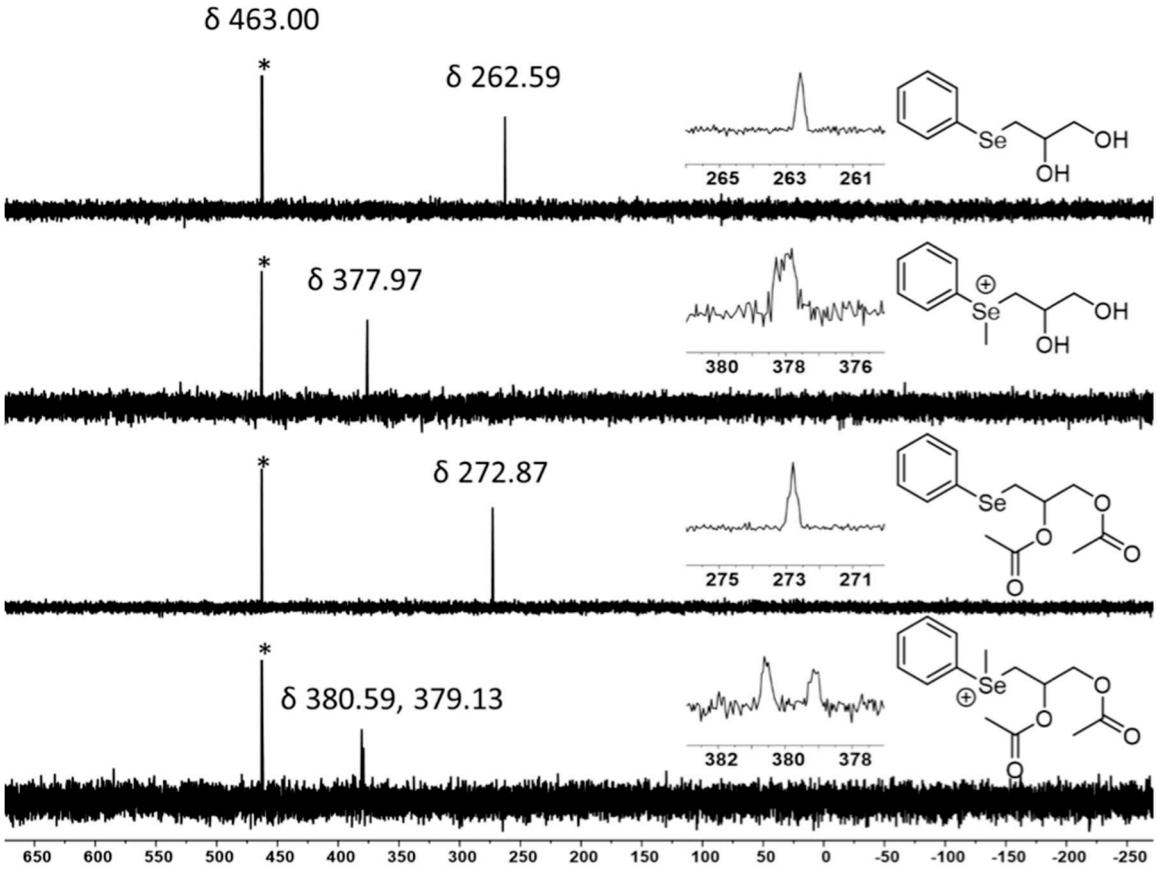


Figure 4. ^{77}Se-NMR of **3**, **7** and **16–17.**

2.8. Hemolysis

A hemolysis assay was performed to evaluate the lytic activity of **16** and **17** using sheep red blood cells (RBCs). In this study, the released hemoglobin was detected with the help of a microplate reader at the wavelength of 540 nm and compared to control systems. The negative control was phosphate buffered saline (PBS) in which the RBCs do not rupture due to the isotonic effect and a net zero movement of molecules across the cell membrane [37]. The positive control is represented by deionized (DI) water in which cells rupture fully due to a hypotonic effect and movement of pure water into the RBCs through osmosis. In the case of **16** and **17**, however, no hemolysis was observed even at a concentration of 1000 µg/mL (Figure 5). This indicates that selenonium cations **16** and **17** have no toxic effects on the mammalian cell membranes.

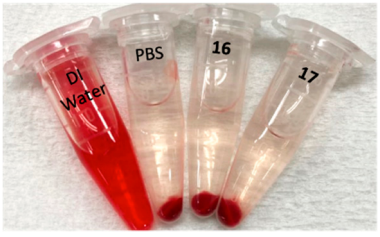


Figure 5. Digital picture showing the release of hemoglobin from red blood cells in DI water and complete orthogonality with PBS, **16** and **17.**

3. Conclusions

In summary, by tweaking the nature of the base-catalyst and reaction medium, high (>95%) yields of ß-hydroxy selenides can be obtained in a 15 min of reaction time under ambient conditions. The reaction

is regio-selective and tolerates many electrophilic and nucleophilic sites in the system. A post-synthesis alkylation of the 'click'-generated seleno-ether linkage furnishes selenonium-based cationic structures with hemocompatibility. Overall, the presented chemistry is anticipated to become a practical synthetic tool in accessing selenium-based materials of ever increasing demand in biological applications.

Supplementary Materials: The synthesis and characterization details are available online at http://www.mdpi.com/2624-8549/2/4/54/s1.

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Conflicts of Interest: The authors declare no conflict of interest.

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