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Meyer-Schuster-type Rearrangement for the Synthesis of α-Selanyl-α,β-Unsaturated Thioesters

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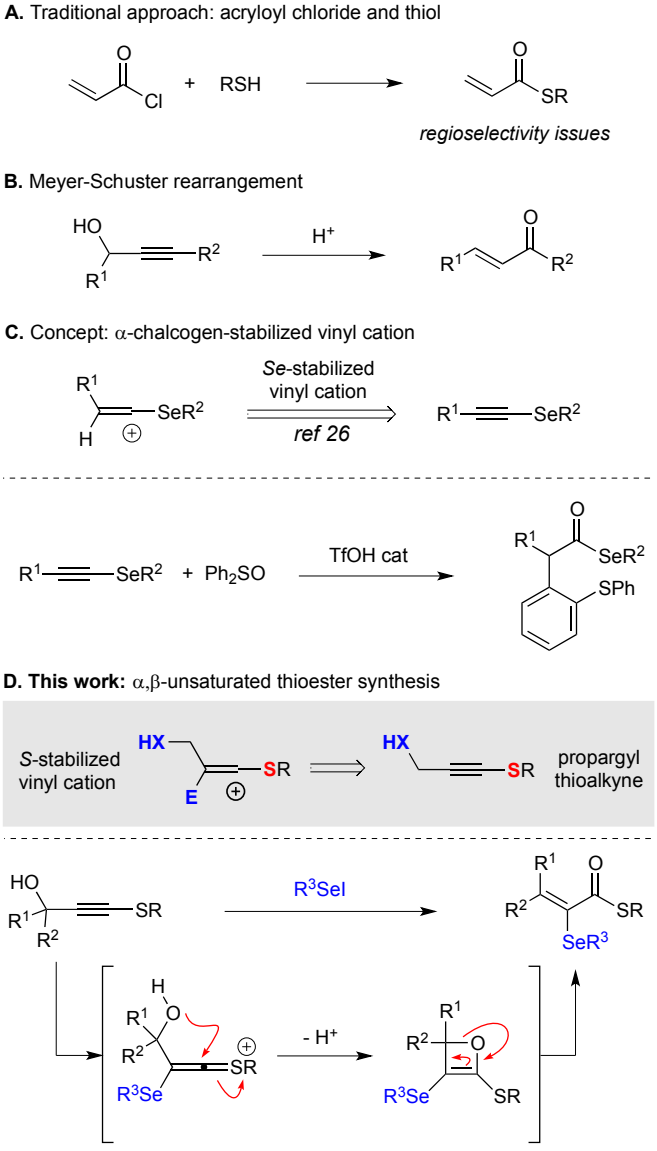
A new approach to prepare α-selanyl-α,β-unsaturated thioesters from propargylthioalkynes and an electrophilic selenium species is reported. Pivotal is the intermediacy of a sulfur-stabilized vinyl cation, which is captured intramolecularly and ultimately enables 37 examples of the target compounds to be prepared in good yields. Computational studies shed light on the nature of intermediates in this transformation.

α,β-Unsaturated thioesters are a class of significant molecules and their importance is highlighted by their use in several areas, such as polymer chemistry,[1] enoyl-CoA carboxylase/reductases substrate in enzymatic catalysis,[2] and as an intermediate for the synthesis of commercially important fragrances phenoxanol and hydroxycitronellal.[3] Indeed, this functional group is a useful synthetic building block, being a common substrate for 1,4-additions,[4] asymmetric conjugate additions,[5] α-trifluoromethylations,[6] Diels-Alder cycloadditions,[7] hydrogenations,[8] intramolecular rearrangements,[9] and decarbonylative reactions.[10] The vast majority of the methods available for their synthesis typically involves the use of acryloyl chlorides and thiols, a route that commonly presents issues related to the handling of unstable acryloyl chlorides and competing thiol 1,4-addition side reactions (Scheme 1A).[11] Other methodologies are based on the use of carbonyl compounds[12] or epoxides[13] and thioacetylenes, catalyzed by Lewis acid. Conversion of carboxylic acids into thioesters,[14] ruthenium catalyzed rearrangement of propargyl sulfoxides,[15] thiol 1,4-addition to alkylidene Meldrum's acid derivatives,[16] Horner[17] and Wittig[18] olefinations of thiophosphonates, aldol reaction promoted by $TiCl_4$,[19] thermal decomposition of α-sulfinyl-thioesters,[20] thiocarbonylation of acetylenes with thiols and carbon monoxide[21] and thioesterification of aldehydes with disulfides catalyzed by *N*-heterocyclic carbenes[22] have also been reported. Despite of the available methods, α,β-unsaturated thioesters are on several occasions not easy to synthesize, presenting regioselectivity problems and formation of difficult separation mixtures, leaving its general synthesis still a challenge to synthetic chemists.



Scheme 1. Key precedents and this work

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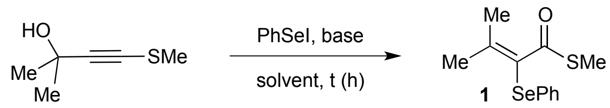
One elegant method for the synthesis of α,β-unsaturated compounds is the Meyer-Schuster rearrangement of propargyl acetylenes to the corresponding enones (Scheme 1B).[23,24]

Recently, our research group has been studying the potential use of heteroatom-substituted alkynes atoms in the stabilization of vinyl cations and their reactivity towards a number of different reactions.[25] In particular, we have reported the use of selenoalkynes for the synthesis of α-arylated selenol esters in a redox-neutral oxyarylation (Scheme 1C).[26] In continuation of our studies, we hypothesized that the concept of vinyl cation stabilization could be extended to propargyl thioalkynes, which would be suitable substrates for electrophilic activation.[27] Therefore, an ensuing sulfur-stabilized vinyl cation would result from the reaction of the alkyne with an appropriate soft selenium electrophile (*e.g.* PhSeX). This intermediate might then be intercepted by an intramolecular nucleophilic attack of oxygen, leading to the formation of an oxetene ring, which would then decompose, delivering the final α-selanyl-α,β-unsaturated thioesters in a Meyer-Schuster-type rearrangement (Scheme 1D). Besides the above-mentioned utility of α,β-unsaturated thioesters organic selenium compounds, including vinyl selenides, have found widespread application in several areas of science, including organic synthesis, material sciences, and pharmacology.[28] Therefore, mild methods that are able to deliver functionalized alkenes bearing an organoselenium moiety are desirable.

Reducing our plan to practice, we started our studies by reacting the propargyl thioalkyne with an *in situ* generated selenium electrophile. The results are summarized in Table 1. The first attempt was performed in the absence of base, using 2 equiv. of PhSeI (generated *in situ* by the reaction of 1 equiv Ph_2Se_2 with 1 equiv I_2) as the electrophilic selenium source, and led to the formation of the desired α-selanyl-α,β-unsaturated thioester **1** in 39% yield (entry 1). Subsequently, the influence of the use of base in the reaction was verified. Carrying out the experiment with 2 equiv. of Cs_2CO_3 resulted in product **1** in 64% yield. Additional studies have revealed that NaH is also a suitable base for promoting the reaction (entry 3). A decrease in the amount of Cs_2CO_3 to 1.2 equivalents resulted in a slight increase in the yield (entry 4, 70%). A solvent screening was performed and the best yield was obtained using dichloromethane (entries 4–8). Increasing the temperature to 40 °C led to a drop in the yield to 44% (entry 9). Longer reaction times proved beneficial to the reaction and an increase in the yield was observed by keeping the reaction for 16 h (entry 10). Finally, we have found that changing the stoichiometry from 2 to 4 equiv. of PhSeI led to an increase in the yield of **1** (entries 10-12, 75 to 88% yield). It is worth pointing out that the excess of the selenium compound is recovered at the end of the reaction as Ph_2Se_2 and reused. Importantly, the PhSeI electrophile is conveniently generated *in situ* by the reaction of Ph_2Se_2 with I_2, and after 30 minutes, potassium persulfate is added to reduce any remaining molecular iodine and suppress the formation of iodinated side-products. After establishing the optimal conditions for the α,β-unsaturated thioester synthesis **1**, we proceeded to examine the reaction scope in respect of the propargylic thioalkynes (Scheme 2). A number of thioacetylenes with different substitution patterns have been studied. Variations at the R[3] attached to the sulfur atom have shown that linear alkyl chains of different sizes (**1** = methyl; **2** = *n*-butyl and **3** = octyl), branched alkyl chain (**4**), benzyl (**5**) and aromatic groups bearing electron-donating (**6**–**9**) and electron-withdrawing groups (**10**-**14**) groups have been well tolerated under the reaction conditions. It's worth pointing out that compound **7**, bearing a bulky *iso*-propyl group at the *ortho* position was obtained in 84% isolated yield.

Table 1. Optimization of the reaction conditions[a]



#	$(PhSe)_2$ (equiv)	I_2 (equiv)	Base (equiv)	Solvent, t (h)	Yield (%)[b]
1	1.0	1.0	-	CH_2Cl_2, 3	39
2	1.0	1.0	Cs_2CO_3 (2.0)	CH_2Cl_2, 3	64
3	1.0	1.0	NaH (2.0)	CH_2Cl_2, 3	61
4	1.0	1.0	Cs_2CO_3 (1.2)	CH_2Cl_2, 3	70
5	1.0	1.0	Cs_2CO_3 (1.2)	THF, 3	NR
6	1.0	1.0	Cs_2CO_3 (1.2)	DCE, 3	67
7	1.0	1.0	Cs_2CO_3 (1.2)	$PhCH_3$, 24	40
8	1.0	1.0	Cs_2CO_3 (1.2)	CH_2Cl_2/THF, 3	29
9	1.0	1.0	Cs_2CO_3 (1.2)	CH_2Cl_2, 3	44[c]
10	1.0	1.0	Cs_2CO_3 (1.2)	CH_2Cl_2, 16	75[d]
11	1.5	1.5	Cs_2CO_3 (1.2)	CH_2Cl_2, 16	80[d]
12	2.0	2.0	Cs_2CO_3 (1.2)	CH_2Cl_2, 16	88[e]

[a]Reaction was performed using 0.25 mmol of thioalkyne, at 25 °C. PhSeI was generated *in situ* by the reaction of $(PhSe)_2$ with I_2, and after 30 min, $Na_2S_2O_3$ was added to reduce the unreacted I_2 [b]Yields determined by ^1H-NMR using mesitylene as internal standard. [c] reaction performed at 40 °C. [d]18% of unreacted starting material. [e]Starting material was fully consumed after 16 h.

In addition, variations at the R[1] and R[2] groups were also examined. When R[1] and R[2] = ethyl, the corresponding thioester **15** was obtained in 73% yield. Cyclic moieties have also been well tolerated and the corresponding products bearing 5-, 6- and 7-membered rings (**16**-**19**) have been obtained in good yields. Unfortunately, when unsubstituted propargyl thioacetylene was used, product **20** was not observed, despite full consumption of the starting thioalkyne. In order to study the selectivity of the reaction, compounds bearing different R[1] and R[2] substituents have been evaluated. In these cases, albeit products **21**, **22** and **23** have been isolated in good yields, unfortunately 1:1 *E/Z* mixtures of have been obtained. Importantly, the reaction is amenable to scale-up and when the reaction was performed on a 3 mmol scale only a small decrease in the isolated yield for product **3** was observed (82% on 0.25 mmol to 74% on a 3 mmol scale).

Aiming to study the versatility in the synthesis of α,β-unsaturated thioesters, we then turned our attention to the scope of the reaction with respect to the substitution pattern on selenium (Scheme 3). When R[4] group is *n*-butyl, the corresponding products **24**-**27** were isolated in good yields, for different substitution at the remaining positions of the molecule. An electrophilic Se species bearing a benzyl group was also tested, delivering product **28** in 74% yield. Diverse arylseleno derivatives are competent activators and both electron-donating and electron-withdrawing groups are suitable substituents (**29**-**38**). For example, products bearing *p*-Cl (**29** and **30**), *m*-CF_3 (**31**), *o*-Me (**32**-**33**), *p*-Me (**34**), 2-naphthyl (**35**), 1-naphthyl (**36**) and *p*-Ph (**37**) were successfully obtained. Finally, the reaction is also amenable to the use of a sulfur electrophile and product **38** was isolated in 80% yield, highlighting the versatility of the method for the synthesis of α,β-unsaturated thioesters with different chalcogen atoms at the alpha position.

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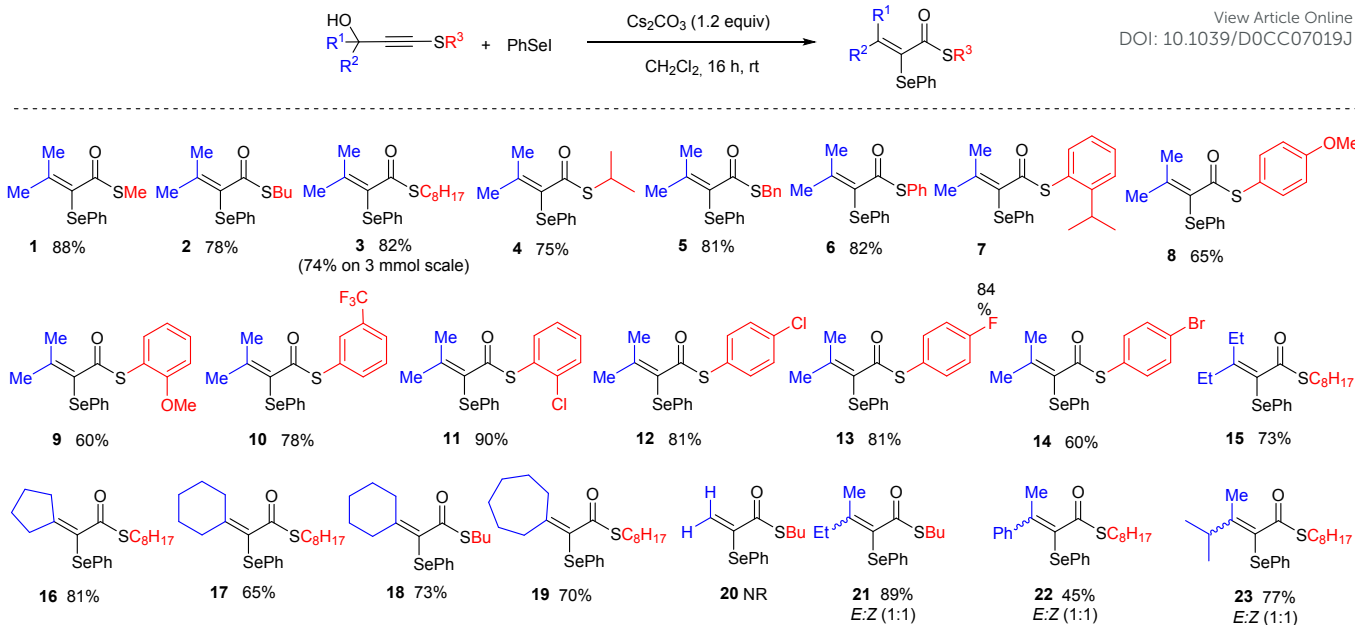
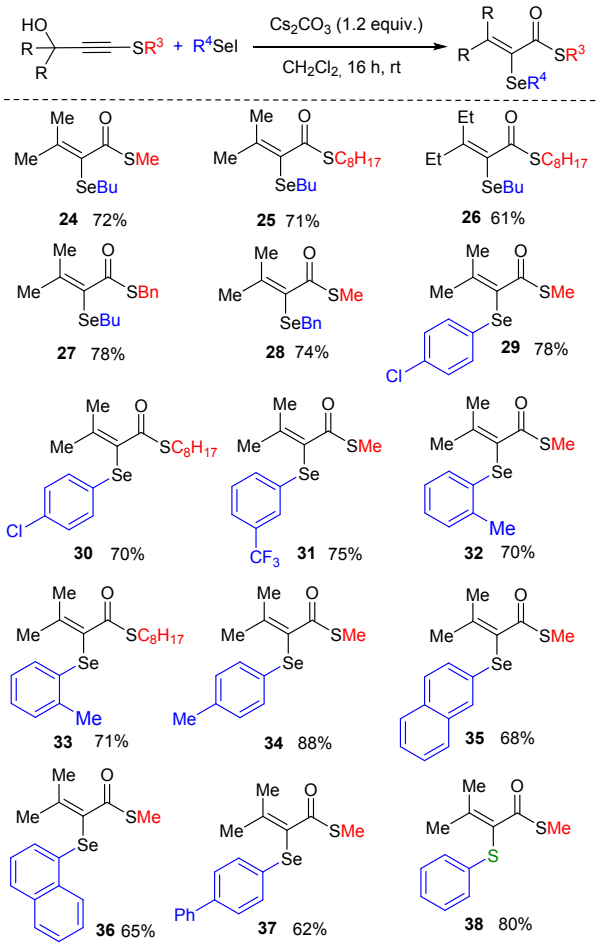


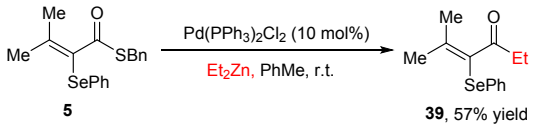
Scheme 2. Scope of thioacetylenes



Scheme 3. Scope of diselenides

In order to get additional information on the reaction pathway, quantum chemical calculations have been performed (Figure 1). The first step **A**→**B** is the S_N2 type attack of phenylselenyl iodide on the alkyne with the formation of a ketenethionium intermediate **B**. The next stage is the cyclisation of **B** to generate the oxetene intermediate **C.** The oxetene ring-opens via cleavage of the **C**-**O** bond forming the intermediate **D**. This step, **C**→**D**, is highly exergonic (ΔG(**C**→**D**) = -27.4 kcal mol^{-1}) and thus it compensates the endergonic formation of intermediate **B** (ΔG(**A**→**B**) = +15.2 kcal mol^{-1} at the first stage of the reaction pathway. Finally, **D** is deprotonated by the base, yielding the final product. The whole process is both thermodynamically (ΔG(**A**→**D**) = -17.2 kcal mol^{-1}) and kinetically favorable (the highest transition state $TS_{B\text{-}C}$ is only 17.8 kcal mol^{-1} less stable energetically compared to the sum of the reactants **A**). Therefore, the computed mechanism suggests that the reaction can readily proceed at room temperature, in accordance with the experimental evidence.

Finally, as an application, we have performed a derivatization of the thioester products by a Fukuyama coupling reaction[29] with Et_2Zn, smoothly delivering the corresponding ketone in moderate yield (Scheme 4).



Scheme 4. Derivatization of the product

In summary, we have presented a new methodology for the synthesis of a broad range of α-selanyl-α,β-unsaturated thioesters by a Meyer-Schuster-type rearrangement of propargylic thioalkynes and selenium electrophilic species. The reaction proceeds through the initial activation of the thioalkyne with a soft selenium electrophile, leading to a sulfur-stabilized vinyl cation, which undergoes an intramolecular attack, forming an oxetene intermediate, which in turn, decomposes to the final product. Support for the mechanism was obtained from quantum chemical calculations underlining the kinetic and thermodynamic favored nature of the process.

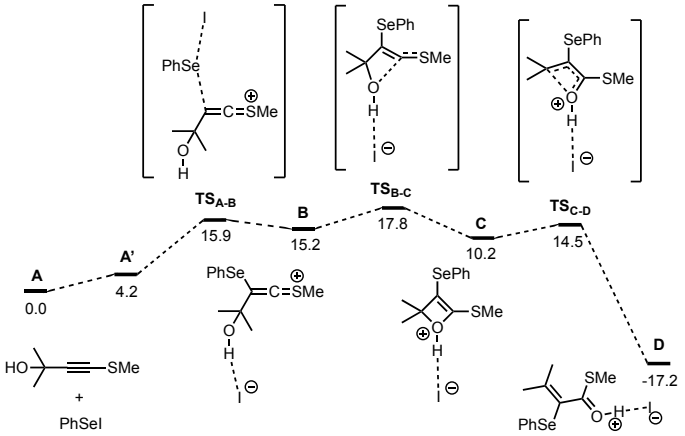


Figure 1. Computed relative free energy profile (DLPNO-CCSD(T)/def2-TZVP//B3LYP-D3/def2-SVP, $\Delta G_{298,DCM}$, kcal mol^{-1}) for the conversion of the reactants **A** (taken as a reference 0.0 kcal mol^{-1}) to the final intermediate **D**.

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Conflicts of interest

There are no conflicts to declare.

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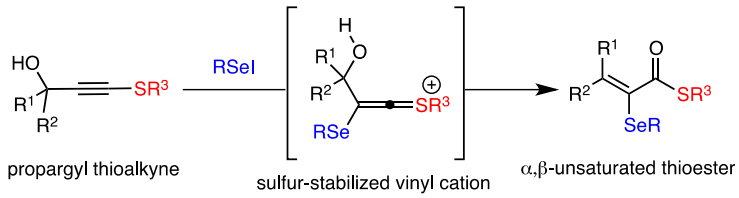

- > 30 examples
- activation with soft Se electrophile
- tetrasubstituted double bond
- computational studies