

Regio- and stereoselective synthesis of vinyl sulfides via PhSeBr-catalyzed hydrothiolation of alkynes

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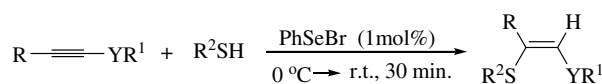
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Abstract—We present here a simple and mild method of hydrothiolation of internal and terminal alkynes under PhSeBr-catalyzed reaction in the absence of solvent at room temperature. The reaction tolerates a wide variety of substituents on thiol, and provides the corresponding product in good yield and selectivity.

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Many different classes of organochalcogen compounds have been prepared and studied to date. In this way, vinylic sulfides play an important role in the synthesis of organochalcogen compounds, especially in the development of many convenient methods for the stereoselective preparation of functionalized alkenes. Although various methods are mentioned for the preparation of vinylic sulfides, the more useful procedures have centered on the thiol addition to terminal or internal alkynes and transition-metal-catalyzed hydrothiolation.¹ In addition to their utility in the field of organic chemistry, toxicological, and pharmacological aspects of organochalcogen compounds have also been recently reviewed.² Our continuing interest in the synthesis³ and application⁴ of vinylic chalcogenides in organic synthesis prompted us to develop a new method for a convenient and efficient preparation of vinylic sulfides via PhSeBr-catalyzed hydrothiolation of terminal and internal alkynes in a very short reaction time, at a room temperature and under solvent-free conditions (Scheme 1).

Since our initial studies have focused on the development of an optimum set of reaction conditions, we have initially chosen alkynyl methyl sulfide **1a** and benzenethiol as standard starting materials. In this way, the benzenethiol (1.1 mmol) was added at 0 °C to a solution of compound **1a** (1 mmol) and PhSeBr (1 mol %). The



1a- R = C₈H₁₇, YR¹ = SMe; **1b**- R = C₆H₅, YR¹ = SMe; **1c**- R = C₈H₁₇, YR¹ = SPh;
1d- R = C₈H₁₇, YR¹ = SeMe; **1e**- R = Ph, YR¹ = TeBu

Scheme 1.

results of the reactions with the variation in the temperature, time, and the presence or absence of solvents are summarized in Table 1.

In this procedure, the reaction carried out in solvents such as THF and CH₂Cl₂ afforded moderate yields even after heating the reaction mixture for a long period (Table 1, entries 2–5). Gratifyingly, the absence of solvent resulted in the vinyl sulfide product in 75% yield (Table 1, entry 1). It is important to note that when the amount of catalyst is reduced from 10 to 1 mol % an increase in the yield was observed (Table 1, entries 1 and 7–9), while the increase to 1 equiv did not improve the yields (Table 1, entry 6), in fact traces of product was obtained, probably due to the direct electrophilic addition of PhSeBr to alkynes to give side products.⁵ As shown in Table 1, other catalysts such as PhSeCl, ICl and I₂ gave the product in moderate yield (Table 1, entries 11–13).

The analysis of the optimized reactions demonstrated that the optimal condition for this procedure was the addition of PhSeBr (1 mol %) to a solution of alkynyl

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Table 1. Optimization of the reaction conditions

Entry	Catalysts (mol %)	Solvent	Yield ^a (%)
1	PhSeBr (10)	—	75
2	PhSeBr (10)	CH ₂ Cl ₂	56 ^b
3	PhSeBr (10)	THF	69 ^b
4	PhSeBr (10)	THF	56 ^b
5	PhSeBr (10)	THF	51 ^c
6	PhSeBr (1 equiv)	—	Traces
7	PhSeBr (5)	—	66
8	PhSeBr (3)	—	67
9	PhSeBr (1)	—	77
10	PhSeBr (1)	—	74 ^d
11	PhSeCl (1)	—	60
12	ICl (1)	—	50
13	I ₂ (1)	—	35
14	—	—	45

^a Yields are given for isolated products.

^b The reaction was performed with 2 mL of solvent and heating at 50 °C.

^c 20 mL of THF.

^d 2 equiv of benzenethiol was used.

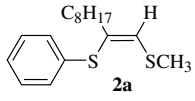
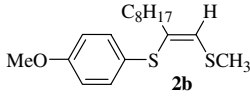
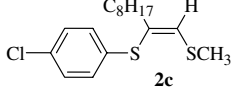
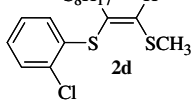
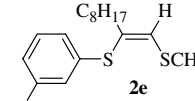
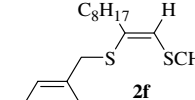
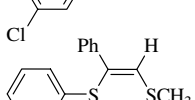
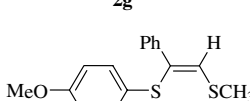
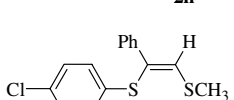
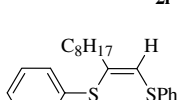
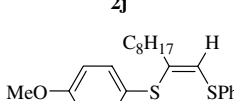
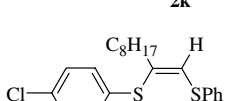
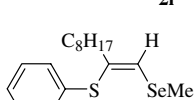
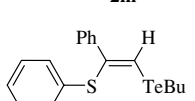
methyl sulfide **1a** (1 mmol) and benzenethiol (1.1 mmol) at 0 °C. After the addition, the reaction mixture was stirred for 1 h at room temperature. This reaction condition was systematically applied to other substrates to demonstrate the efficiency of this method, and the results are summarized in Table 2.⁶

Inspection of Table 2 shows that the reaction worked well for a variety of thiols and functionalized alkynes. A detailed analysis of the results revealed that the reaction is not sensitive to the electronic nature of functional groups present in the thiols (Table 2, entries 1–6). Either electron donating or electron withdrawing groups were applied leading to corresponding vinyl sulfide in good yield. Concerning the structure of thiols, we found some limitations in this methodology, for example, no reaction was observed with thiols bearing an alkyl group.

We also investigated the influence of substituent at the alkynes, where alkyl and aryl groups were compared. Satisfactorily, all alkynes tested were effective, although moderate yields were observed in the aryl alkynes (Table 2, entries 7–9). We have also performed a series of reactions to test whether unsymmetrical internal alkynes bearing a heteroatom such as Se, Te, and Sn would react in the same fashion with thiols (Table 2, entries 13 and 14). As a result, the internal selenoalkyne **1d** did not react under our standard condition; however changing the amount of PhSeBr from 1 to 10 mol % the desired product was obtained in moderate yield (Table 2, entry 13). The hydrothiolation did not proceed satisfactorily with unsymmetrical internal alkynes bearing a tellurium group **1e** bonded directly at the triple bond. In these cases we observed only traces of products.

On the other hand, the reaction of thiol with alkynes bearing an organotin group **1f** gave a mixture of *E* and *Z* vinylic compounds. Based on these results and with the knowledge that the carbon–tin bond exhibits an easier heterolytic cleavage towards nucleophilic reagents than the carbon–sulfur and carbon–selenium

Table 2. Hydrothiolation of functionalized alkynes

Entry	Thiol	Product	Yield ^a (%)
1	PhSH		77
2	<i>p</i> -OMePhSH		75
3	<i>p</i> -ClPhSH		52
4	<i>o</i> -ClPhSH		83
5	<i>m</i> -ClPhSH		74
6	ClPhCH ₂ SH		55
7	PhSH		70
8	OMePhSH		58
9	<i>p</i> -ClPhSH		30
10	PhSH		62
11	<i>p</i> -OMePhSH		51
12	<i>p</i> -ClPhSH		65
13	PhSH		40 ^b
14	PhSH		Trace

^a Yields are given for isolated products.

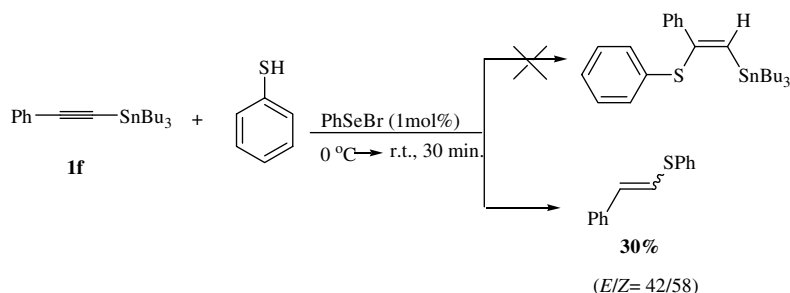
^b Reaction performed in presence of PhSeBr (10 mol%).

Table 3. Hydrothiolation of terminal and internal alkynes

Entry	Alkyne	Product	Yield (%)
1			50
2			NR
3			NR
4			NR
5			62 (E/Z = 90/10)
6			76 (E/Z = 25/75)
7			70 (E/Z = 17/83)
8			55

triple bonds, due to the large volume and greater ionic character of the tin atom and the easy polarization of the bonds, we assumed that the terminal alkyne was formed as an intermediate, which reacts with thiol to give the mixture of isomers (Scheme 2).

Next we decided to expand the scope of this methodology to include simple terminal and internal alkynes. As shown in Table 3, all the propargyl alcohols were found not effective, even the protected one. However, the use of 3-phenylprop-2-yn-1-ol gave the desired product in low yield (Table 3, entry 1). We also observed that the regioselectivity control was governed by the effective participation of the hydroxyl group from alkynol. In addition, only one isomer was obtained with alkynes containing hydroxyl group (Table 3, entry 1). Conversely, alkynes with no hydroxyl group gave a mixture of isomers (Table 3, entries 5–7).

**Scheme 2.**

Analysis of the ^1H and ^{13}C NMR spectra showed that all vinylic sulfides prepared presented data in full agreement with their assigned structures. The regio- and stereochemistries of trisubstituted vinylic sulfides were determined by NOE and NOESY experiments (for more details see Supporting data). The analysis of spectra showed that the hydrothiolation proceeds by the addition of thiol in an anti-fashion stereoselectively affording the corresponding Z vinylic sulfide.

In summary, we have developed a new application of PhSeBr in a highly selective catalyzed reaction of benzenethiols to terminal and internal alkynes to give vinylic sulfides. The importance of the chemistry described here lies in the established new synthetic method to prepare vinylic sulfides in a short reaction time, mild reaction conditions (room temperature) in the absence of base, solvent, and transition metals.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.076.

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6. *Typical procedure for the preparation of the vinyl sulfides:* To a Schlenk 10 mL tube under argon atmosphere containing PhSeBr (0.023 g, 1 mol %) was added alkynyl methyl sulfide **1a** (0.184 g, 1 mmol). After stirring the mixture at 0 °C, benzenethiol (0.121 g, 1.1 mmol) was added. The reaction

mixture was stirred at room temperature for 30 min. After this time the reaction mixture was treated with CH₂Cl₂ and concentrated under vacuum. The residue was purified by flash chromatography and eluted with hexane to afford the addition product **2a** (0.226 g, 77%) as a yellow oil.

Selected spectral and analytical data for 1-methylthio-2-phenylthiodeca-1-ene (2a): Yield: 0.226 g (77%). ¹H NMR: (CDCl₃, 200 MHz) δ (ppm): 7.33–7.12 (m, 5H), 6.31 (s, 1H), 2.31 (s, 3H), 2.18 (t, *J* = 7.05 Hz, 2H), 1.50 (t, *J* = 7.05 Hz, 2H), 1.21 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H). ¹³C NMR: (CDCl₃, 50 MHz), δ (ppm): 134.18, 133.27, 130.23, 129.68, 128.70, 126.16, 37.19, 31.72, 29.17, 29.10, 28.72, 28.44, 22.54, 17.01, 14.00. MS (EI, 70 eV) *m/z* (relative intensity): 294 (100), 185 (82), 170 (32), 155 (35), 140 (39), 125 (33), 109 (40), 88 (15), 77 (43), 29 (12). HRMS Calcd for C₁₇H₂₆S₂: 294.1475. Found: 294.1479.