

Communication

# Convenient Synthesis of Functionalized Unsymmetrical Vinyl Disulfides and Their Inverse Electron-Demand Hetero-Diels-Alder Reaction <sup>†</sup>

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<sup>†</sup> Dedicated to Professor Grzegorz Młostoń on the occasion of his 70th anniversary.

**Abstract:** The simple, convenient, and efficient methods for the preparation of unsymmetrical vinyl disulfides with additional functional groups under mild conditions with moderate to high yields were designed. The developed methods include the reaction of *S*-vinyl phosphorodithioate with thiotosylates or *S*-vinyl thiotosylate with thiols. The designed methods allow for the synthesis of unsymmetrical vinyl disulfides with additional functionalities such as hydroxy, carboxy, protected amino, or ester groups. Vinyl disulfides reacted with the generated transient *o*-iminothioquinones in an inverse electron-demand [4+2] cycloaddition to produce benzo[*b*][1,4]thiazine derivatives.

**Keywords:** alkenes; cycloaddition; hetero-Diels-Alder; thiosulfonates; vinyl disulfides



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## 1. Introduction

The disulfide bond is one of the most important structural functionalities which plays a crucial role affecting the stability, folding, and biological function of proteins and peptides. It also allows the maintenance of the cellular redox balance in cells. Although aforementioned biological properties are significant in life science, disulfides [1–3] are also important and versatile compounds due to their applications in material and food chemistry.

The unsymmetrical disulfides can be applied in the formation of self-assembled monolayers (SAMs) on gold or other metals [4–6]. Good quality SAMs can be produced both from thiols and disulfides [5]. However, the disulfides provide several practical advantages. They are more stable and significantly more resistant to oxidation. Moreover, in the case of disulfides, the problems associated with intra or intermolecular reactivity of the thiol group can be avoided [7]. The unsymmetrical disulfides give monolayers of well-defined surface compositions without phase separation [8]. When a mixture of two different thiols is used, in some cases, the elimination of cooperative effects associated with the co-adsorption of corresponding thiols cannot be avoided [9]. The surface composition modified by the unsymmetrical disulfides has been applied for double-stranded DNA–protein microarrays [10], DNA immobilization via intercalation [11], and studies on surface reactions on nanoparticles [9]. Unsymmetrical disulfides have been involved in the preparation of the electrostatic self-assembly of nanostructured materials [12,13] and chemosensors for biological applications [3].

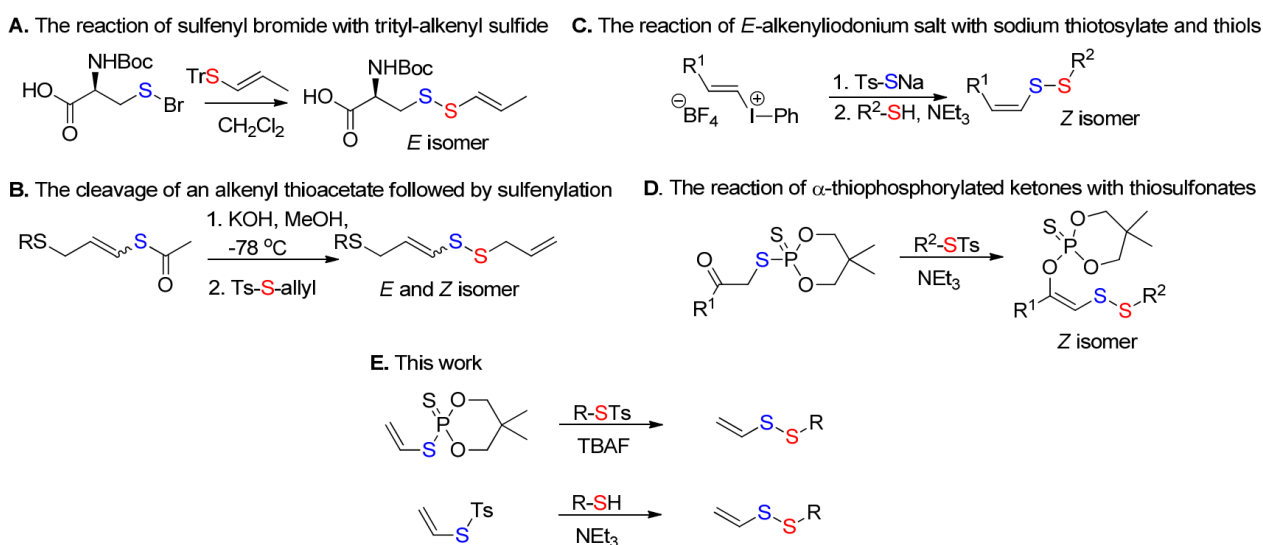
Moreover, the synthesis of unsymmetrical disulfides is an important step for the preparation of a variety of compounds involved in medicinal chemistry and advanced organic synthesis [14–17]. The developments in disulfide bond synthesis have been reviewed recently [18–22]. Although disulfides are very important in numerous fields, effective methods for the preparation of unsymmetrical disulfides are still rare. The most common synthesis of disulfide functionality is based on the nucleophilic substitution reaction of a sulfenyl derivative with a thiol or thiol derivative. The most frequently utilized electrophilic

sulfenyl derivatives are: sulfenyl chlorides [23,24], *S*-alkylsulfanylisothiouras [25,26], *S*-alkyl thiosulfates and *S*-aryl thiosulfates (Bunte salts) [27], benzotriazolyl sulfanes [28,29], benzothiazol-2-yl disulfides [30], (alkylsulfanyl)dialkylsulfonium salts [31,32], dithioperoxyesters [33], 2-pyridyl disulfides and derivatives [34,35], sulfonamides [36], *N*-alkyltetrazolyl disulfides [37], sulfenyl thiocyanates [38], sulfenyldimesylamines [39], thiosulfates [40] and thiosulfonates [41–43], 4-nitroarenesulfenylidene [44], thionitrites [45], thioimides [46], sulfenyl sulfanylsulfonamides [47–49], and thiophosphonium salts [50]. The disulfides can also be efficiently obtained by the reaction of a thiol with a sulfinylbenzimidazole [51], a disulfide exchange reaction promoted by rhodium catalyst [52,53], an electrochemical method [54], using tetrathiomolybdate in the presence of a symmetrical disulfide to promote a ring opening of an aziridine [55,56], or the application of diethyl azodicarboxylate (DEAD) [57] or a solid support [58] to promote a sequential coupling of two different thiols. The oxidation of a mixture of two different thiols to obtain an unsymmetrical disulfide has also been reported recently. The reactions can be accomplished by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) [59–61] or iridium (III) photoredox catalysis [62].

The 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives are readily available and can be applied for the synthesis of unsymmetrical disulfides with additional functional groups. The synthetic methodology based on the electrophilic disulfanyl derivatives allow one to obtain alkyl-aryl disulfides [63], dialkyl disulfides [64], “bioresistant” disulfides [65], unsymmetrical disulfides of L-cysteine and L-cystine [66], and diaryl disulfides [67]. The electrophilic properties of disulfanyl derivatives of phosphorodithioic acid can also be applied for the synthesis of  $\alpha$ -sulfenylated carbonyl compounds [68], phosphorothioates with additional functional groups [69], unsymmetrical alkynyl sulfides [70,71], and symmetrical [72,73] and unsymmetrical trisulfides [74,75].

Block and co-workers isolated ajoene as an *E/Z* isomers mixture in 1984 [76]. Ajoene was produced as a rearrangement product of allicin from freshly crushed garlic. The structure was established as an allyl sulfoxide containing a vinyl disulfide functionality. The presence of an unusual vinyl disulfide functionality was unexpected and other natural products with such functionality are rare. The activity of *Z*-ajoene as an anti-thrombotic agent [77] is higher than its *E*-isomer. Due to the higher biological activity of the *Z*-isomer, anticancer studies have focused primarily on this isomer [78,79].

Although unsymmetrical disulfides can be obtained by several different synthetic methods, the synthesis of unsymmetrical alkenyl disulfides can be accomplished by only four methods (Scheme 1A–D).



**Scheme 1.** Previously reported methods for the synthesis of alkenyl disulfides (A–D) and our new synthesis approach (E).

The first method involves the reaction of sulfenyl bromide with trityl-alkenyl sulfide [80] (Scheme 1A). The alkenyl disulfides can also be obtained by the low-temperature cleavage of an alkenyl thioacetate with hydroxide to give alkenethiolate and the subsequent sulfenylation reaction with corresponding *S*-alkyl *p*-toluenethiosulfonate. The appropriate vinyl disulfide was obtained with a high yield after column chromatography in the second method [81–83] (Scheme 1B). Unfortunately, the formation of the *E* isomer or a mixture of *Z/E* alkenyl disulfides for both methods (Scheme 1A,B) was observed. The synthesis of unsymmetrical *Z*-alkenyl disulfides with additional functional groups can be accomplished with readily available starting materials under mild conditions with moderate to high yields (Scheme 1C). The third method is diastereoselective and an exclusive formation of *Z*-isomer is observed. The developed method includes the reaction of *E*-alkenyliodonium salt with sodium thiosylate and thiols in the presence of a base [84]. The fourth method [85] is based on the base-promoted rearrangement of  $\alpha$ -thiophosphorylated ketones followed by thioalkylation with thiosylates (Scheme 1D).

There are a limited amount of synthetic methods available for the synthesis of alkenyl disulfides (Scheme 1). We were interested in the development of an experimentally practical and versatile method to access vinyl disulfides with additional functional groups. The designed method is based on the readily available *S*-vinyl phosphorodithioate and *S*-vinyl thiosulfonate (Scheme 1E).

The synthetic potential of vinyl disulfides can involve formation of complexes with metals, multicomponent reactions, Heck reaction, olefin metathesis, or the variety of cycloaddition reactions. Due to the poor availability of vinyl disulfides, aforementioned transformations has not been examined yet.

## 2. Materials and Methods

Preparation of thiosylates 1a–1e; 1k; 1m–1n; 1r was described previously [71,85]. All bromides were purchased from ProChimia (Sopot, Poland) and were used for synthesis of required thiosylates. Sodium 4-methylbenzenesulfonate was purchased from Merck and was used for preparation of sodium 4-methylbenzenesulfonothioate as described previously [85]. Vinyl magnesium bromide solution (1M) in THF (tetrahydrofuran) and tetrabutylammonium fluoride (TBAF) solution (1M) in THF were purchased from Merck. Tetrahydrofuran was pre-dried over KOH pellets and distilled. Subsequently, tetrahydrofuran (THF) was dried by heating under reflux over potassium in the presence of benzophenone as an indicator and distilled. Silica gel plates Supelco UV254 (St. Louis, MS, USA) were used for thin layer chromatography (TLC). A silica gel 60 (230–400 mesh, Merck, Darmstadt, Germany) was used for column chromatography. NMR spectra were recorded on Bruker 400 MHz spectrometers. The residual solvent peak was used as the internal reference ( $\text{CDCl}_3$ :  $\delta = 7.26$  ppm for  $^1\text{H}$ ,  $\delta = 77.0$  ppm for  $^{13}\text{C}$ ). Nicolet Is50 Fourier-transform infrared (FT-IR) spectrometer (Wien, Austria) was used to record the IR spectra by attenuated total reflectance (ATR) method. A Gallenkamp 7936B apparatus (Warwick, UK) was used to determine melting points.

### 2.1. Synthesis of 5,5-Dimethyl-2-thioxo-2-vinylsulfanyl-[1,3,2]dioxaphosphorinane

A stirred solution of 868 mg (2.2 mmol) bis-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-yl) disulfide in dry THF (3 mL) was cooled to  $-5$  °C under nitrogen, then vinylmagnesium bromide (2.0 mmol, 1M solution in THF, 2 mL) was added dropwise. After complete addition, the mixture was stirred for 15 min at rt, and the solvent was removed in vacuo. Crude product was purified by silica gel column chromatography (petroleum ether/DCM 4:1) to provide 296 mg of *S*-vinyl phosphorodithioate as a white powder with 66% yield.

Chromatography: PE/DCM 4/1 ( $R_f = 0.2$ ), Yield 0.296 g 66%, white solid, mp. 57.8–58.8 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.50 (dt,  $J = 16.6, 9.3$  Hz, 1 H), 5.79–5.63 (m, 2 H), 4.21 (dd,  $J = 10.8, 7.0$  Hz, 2 H), 4.02 (dtd,  $J = 11.2, 2.4, 1.2$  Hz, 2 H), 1.29 (s, 3H), 0.97 (s, 3 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  124.0 (d,  $J = 4.5$  Hz), 123.5 (d,  $J = 12.6$  Hz), 77.6 (d,  $J = 9.0$  Hz), 32.5 (d,  $J = 7.0$  Hz), 21.0 (d,  $J = 1.2$  Hz).

$^{31}\text{P}$  NMR (202 MHz,  $\text{CDCl}_3$ )  $\delta$  82.46.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_7\text{H}_{14}\text{O}_2\text{PS}_2$ : 225.0167; found: 225.0168.

## 2.2. A Typical Procedure for the Preparation of Vinyl Disulfides 2 from S-vinyl Thiotosylate and Representative Analytical Data

To a stirred, ice-cooled solution of S-vinyl thiotosylate 428 mg (2.0 mmol) and thiol 4 (1.0 mmol) in dry DCM (10 mL) under nitrogen,  $\text{NEt}_3$  (1.0 mmol, 140  $\mu\text{L}$ ) was added in one portion. The mixture was stirred at rt for 15 min. Then, the solvent was evaporated and the residue was purified by column chromatography ( $\text{SiO}_2$ ) to provide disulfide 2.

1-Vinylbisulfanyldodecane 2a.

Chromatography: Hexene ( $R_f = 0.6$ ), Yield 0.253 g, 97%, colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.41 (dd,  $J = 16.2, 9.6$  Hz, 1 H), 5.56 (d,  $J = 16.2$  Hz, 1 H), 5.36 (d,  $J = 9.6$  Hz, 1 H), 2.73 (t,  $J = 7.3$  Hz, 2 H), 1.74–1.64 (m, 2 H), 1.44–1.26 (m, 18 H), 0.91 (t,  $J = 6.9$  Hz, 3 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  133.8, 113.1, 38.3, 31.9, 29.6, 29.6, 29.6, 29.5, 29.3, 29.2, 29.1, 28.5, 22.7, 14.1.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{29}\text{S}_2$ : 261.1705; found: 261.1711.

11-Vinylbisulfanylundecanoic acid methyl ester 2c

Chromatography: Hexene/DCM 2/1 ( $R_f = 0.25$ ), Yield 0.256 g, 88%, colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.40 (dd,  $J = 16.2, 9.6$  Hz, 1 H), 5.55 (d,  $J = 16.3$  Hz, 1 H), 5.36 (d,  $J = 9.6$  Hz, 1 H), 3.69 (s, 3 H), 2.72 (t,  $J = 7.3$  Hz, 2 H), 2.32 (t,  $J = 7.5$  Hz, 2 H), 1.77–1.62 (m, 4 H), 1.48–1.20 (m, 12 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  174.3, 133.8, 113.1, 51.5, 38.2, 34.1, 29.4, 29.3, 29.2, 29.2, 29.1, 29.1, 28.5, 24.9.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{27}\text{O}_2\text{S}_2$ : 291.1447; found: 291.1452.

## 2.3. A Typical Procedure for the Preparation of benzo[b][1,4]thiazine disulfanyl derivatives 7 and Representative Analytical Data

To a solution of 2-N-sulfonylthiophthalimide 5.242 mg (0.5 mmol) and vinyl disulfide 2 (0.75 mmol) in dry  $\text{CHCl}_3$  (20 mL) under nitrogen, triethylamine (0.5 mmol, 70  $\mu\text{L}$ ) was added. Mixture was stirred under reflux for 17 h. Then, the solvent was evaporated and the residue was purified by column chromatography ( $\text{SiO}_2$ ) to provide 7.

3-(Dodec-1-ylbisulfanyl)-6,8-dimethoxy-4-(4-toluenesulfonyl)-3,4-dihydro-2H-benzo-[1,4]thiazine 7a

Chromatography: Hexane/DCM 2/1 ( $R_f = 0.32$ ), Yield 0.150 g, 50%, thick yellow oil

IR (ATR): 2922(w), 2851(w), 1578(w), 1455(w), 1434(w), 1308(s), 1284(w), 1228(w), 1185(w), 1060(w), 1039(w), 842(s), 829(s), 812(s), 705(w), 694(s), 644(s)  $\text{cm}^{-1}$

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 (d,  $J = 8.3$  Hz, 2 H), 7.21 (d,  $J = 8.1$  Hz, 2 H), 7.03 (d,  $J = 2.4$  Hz, 1 H), 6.37 (d,  $J = 2.4$  Hz, 1 H), 5.89 (t,  $J = 5.2$  Hz, 1 H), 3.83 (s, 3 H), 3.83 (s, 3 H), 3.15–2.85 (m, 2 H), 2.87–2.74 (m, 2 H), 2.40 (s, 3 H), 1.71–1.54 (m, 2 H), 1.44–1.21 (m, 18 H), 0.88 (t,  $J = 6.9$  Hz, 3 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.8, 156.0, 144.2, 135.9, 133.4, 129.6, 127.4, 109.2, 105.1, 97.4, 65.4, 56.1, 55.6, 39.2, 31.9, 29.7, 29.7, 29.5, 29.4, 22.7, 21.6, 14.1.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{29}\text{H}_{44}\text{NO}_4\text{S}_4$ : 598.2148; found: 598.2153.

Synthesis of starting materials, vinyl disulfides 2 and benzo[b][1,4]thiazine disulfanyl derivatives 7 with analytical data, copy of IR, and NMR spectra are in the Supplementary Materials.

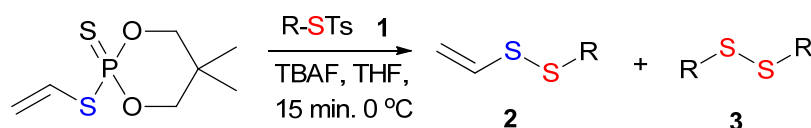
## 3. Results and Discussion

The corresponding S-vinyl phosphorodithioate was obtained by the reaction of bis-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl)disulfide with vinylmagnesium bromide in THF with 66% yield. We examined several methods to prepare S-vinyl thiotosylate.

The most effective reaction was the reaction of ditosylsulfide (1,3-di-*p*-toluene-trisulfane-1,1,3,3-tetraoxide) with vinylmagnesium bromide in THF at  $-78\text{ }^{\circ}\text{C}$  to produce the required *S*-vinyl thiosylate with 60% yield.

The first method developed for the preparation of unsymmetrical vinyl disulfides with additional functional groups included the reaction of *S*-vinyl phosphorodithioate with thiosylates **1** in the presence of tetrabutylammonium fluoride (TBAF) in THF at  $0\text{ }^{\circ}\text{C}$  for 15 min. We selected a variety of thiosylates **1a–r** to determine the limitations and scope of the designed transformation. Compound **1** contained alkyl and aryl groups with additional thioacetyl, ester, protected amino, nitro or carbon–carbon double-bond functionalities. The results are presented in Table 1.

**Table 1.** Synthesis of vinyl disulfides **2** from *S*-vinyl phosphorodithioate.

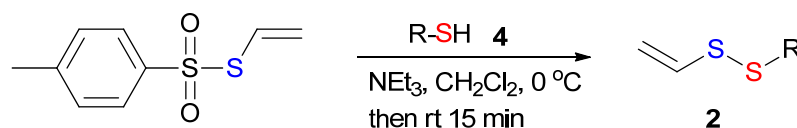


Entry <sup>1</sup>	R	Yield (%) <sup>2</sup>	Yield (%) <sup>2</sup>
1	$-\text{n-C}_{12}\text{H}_{25}$ <b>1a</b>	93 <b>2a</b>	-
2	$-(\text{CH}_2)_9\text{CH}=\text{CH}_2$ <b>1b</b>	82 <b>2b</b>	-
3	$-(\text{CH}_2)_{10}\text{COOMe}$ <b>1c</b>	73 <b>2c</b>	-
4	$-(\text{CH}_2)_{11}\text{OMe}$ <b>1d</b>	62 <b>2d</b>	-
5	$-(\text{CH}_2)_{11}\text{SAc}$ <b>1e</b>	85 <b>2e</b>	-
6	$-(\text{CH}_2)_2\text{NHBoc}$ <b>1f</b>	75 <b>2f</b>	-
7	$-(\text{CH}_2)_2\text{C}_6\text{H}_4-4-\text{CH}_3$ <b>1g</b>	76 <b>2g</b>	-
8	$-(\text{CH}_2)_2-3\text{-indyl}$ <b>1h</b>	75 <b>2h</b>	-
9	$-(\text{CH}_2)_2\text{C}_6\text{H}_4-4-\text{CF}_3$ <b>1i</b>	65 <b>2i</b>	-
10	$-(\text{CH}_2)_2\text{C}_6\text{H}_4-4-\text{F}$ <b>1j</b>	-	100 <b>3j</b>
11	$-\text{C}_6\text{H}_4-4-\text{CH}_3$ <b>1k</b>	-	100 <b>3k</b>
12	$-\text{CH}_2-2\text{-naphthyl}$ <b>1l</b>	-	80 <b>3l</b>
13	$-\text{CH}_2\text{C}_6\text{H}_4-4-\text{NO}_2$ <b>1m</b>	-	70 <b>3m</b>
14	$-\text{CH}_2\text{C}_6\text{H}_4-4-\text{OMe}$ <b>1n</b>	-	85 <b>3n</b>
15	$-\text{CH}_2\text{C}_6\text{H}_4-4-\text{CN}$ <b>1o</b>	-	75 <b>3o</b>
16	$-(\text{CH}_2)_2\text{C}_6\text{H}_4-4-\text{OMe}$ <b>1p</b>	-	86 <b>3p</b>
17	$-\text{CH}_2\text{Ph}$ <b>1r</b>	-	76 <b>3r</b>

<sup>1</sup> Reaction conditions: TBAF (1.1 mmol) was added to a solution of *S*-vinyl phosphorodithioate (1.0 mmol) and thiosylate **1** (1.0 mmol) in dry THF (5 mL) at  $0\text{ }^{\circ}\text{C}$ . A mixture was stirred for 15 min under a  $\text{N}_2$  atmosphere at  $0\text{ }^{\circ}\text{C}$ . <sup>2</sup> Isolated yields.

Although vinyl disulfides **2a–i** were obtained with high or very high yields of 62–93% (entries 1–9), other vinyl disulfides **2j–r** could not be obtained by the developed method. We noticed that thiosulfonate **1** could be converted to symmetrical disulfide **3** in the presence of TBAF when *S*-vinyl phosphorodithioate was not added. The success of the above method depended on the rate of the reaction of fluoride anion with *S*-vinyl phosphorodithioate and thiosylate. When the reaction of the fluoride anion with *S*-vinyl phosphorodithioate was faster than the reaction with thiosylate, the corresponding vinylthiolate anion was generated, and the subsequent reaction with thiosylate provided vinyl disulfide **2**. However, when the reaction of the fluoride anion with thiosylate was faster, symmetrical disulfide **3** was produced. As shown in Table 1, the developed method is efficient for alkyl thiosulfonates. In the case of aryl- or benzyl-type thiosulfonates, the corresponding symmetrical disulfides **3** were produced exclusively.

We developed another method for the synthesis of unsymmetrical vinyl disulfides to overcome the above limitations. The transformation comprises the reaction of *S*-vinyl thiosylate with thiols **4** in the presence of  $\text{NEt}_3$  at room temperature. The obtained results are presented in Table 2.

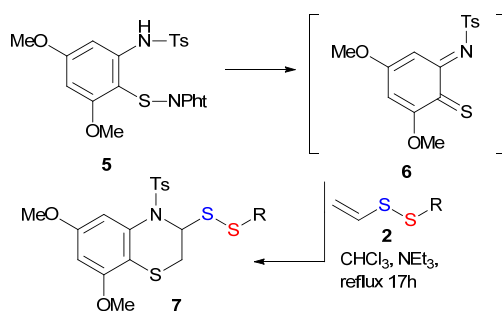
**Table 2.** Synthesis of vinyl disulfides **2** from *S*-vinyl thiosylate.

Entry <sup>1</sup>	R <sup>1</sup>	Yield (%) <sup>2</sup>
1	- <i>n</i> -C <sub>12</sub> H <sub>25</sub> <b>4a</b>	97 <b>2a</b>
2	-(CH <sub>2</sub> ) <sub>10</sub> COOMe <b>4c</b>	88 <b>2c</b>
3	-(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-F <b>4j</b>	90 <b>2j</b>
4	-C <sub>6</sub> H <sub>4</sub> -4-CH <sub>3</sub> <b>4k</b>	96 <b>2k</b>
5	-CH <sub>2</sub> -2-naphthyl <b>4l</b>	92 <b>2l</b>
6	-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-NO <sub>2</sub> <b>4m</b>	80 <b>2m</b>
7	-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-OMe <b>4n</b>	87 <b>2n</b>
8	-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-CN <b>4o</b>	89 <b>2o</b>
9	-CH <sub>2</sub> Ph <b>4r</b>	98 <b>2r</b>
10	-(CH <sub>2</sub> ) <sub>10</sub> COOH <b>4s</b>	84 <b>2s</b>
11	-(CH <sub>2</sub> ) <sub>11</sub> OH <b>4t</b>	91 <b>2t</b>

<sup>1</sup> Reaction conditions: NEt<sub>3</sub> (1.0 mmol) was added to a solution of *S*-vinyl thiosylate (2.0 mmol) and thiol **4** (1.0 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C. Then the mixture was stirred for 15 min under a N<sub>2</sub> atmosphere at room temperature. <sup>2</sup> Isolated yields.

As shown in Table 2, the corresponding functionalized unsymmetrical vinyl disulfides **2a–t** were obtained with very high yields of 80–98%. The developed method is effective for alkyl-vinyl disulfides **2a** and **2c** (entries 1,2) and for disulfides **2j–r**, which could not be obtained with *S*-vinyl phosphorodithioate (Table 1 entries 10–17). The developed method is more convenient and versatile. The method allows for a broad range of products to be accessed, and all starting materials are readily available.

Benzo[*b*][1,4]thiazine is a valuable heterocyclic system with promising and wide applications in medical chemistry [86,87]. We decided to explore the possibility of benzo[*b*][1,4]thiazine derivative synthesis with a disulfide functionality. The hetero-Diels–Alder reaction [88] is the most convenient approach for the synthesis of benzo[*b*][1,4]thiazine derivatives based on the generation of transient *o*-iminothioquinone **6** from 2-*N*-sulfonylthiophthalimides **5** and subsequent reaction with vinyl disulfides **2** in an inverse electron-demand [4+2] cycloaddition to produce compounds **7**. The preliminary results are summarized in Table 3.

**Table 3.** Synthesis of benzo[*b*][1,4]thiazine disulfanyl derivatives **7**.

Entry <sup>1</sup>	R	Yield (%) <sup>2</sup>	Recovered <b>2</b> (%) <sup>2</sup>
1	- <i>n</i> -C <sub>12</sub> H <sub>25</sub> <b>2a</b>	50 <b>7a</b>	35 <b>2a</b>
2	-(CH <sub>2</sub> ) <sub>10</sub> COOMe <b>2c</b>	30 <b>7c</b>	42 <b>2c</b>
3	-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-NO <sub>2</sub> <b>2m</b>	29 <b>7m</b>	46 <b>2m</b>
4	-CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -4-OMe <b>2n</b>	27 <b>7n</b>	44 <b>2n</b>
5	-CH <sub>2</sub> Ph <b>2r</b>	25 <b>7r</b>	52 <b>2r</b>

<sup>1</sup> Reaction conditions: A solution of 2-*N*-sulfonylthiophthalimides **5** (0.5 mmol), vinyl disulfide **2** (0.75 mmol) and NEt<sub>3</sub> (0.5 mmol) in dry CHCl<sub>3</sub> (20 mL) was refluxed for 17 h under N<sub>2</sub> atmosphere.

<sup>2</sup> Isolated yields.

Although the reaction conditions were not optimized, the corresponding benzo-*b*[1,4]thiazine disulfanyl derivatives **7** were obtained with moderate yields of 25–50%. Moreover, there is no alternative method that allows for the preparation of compounds **7a**, **7c**, **7m**, **7n**, **7r**. The recovered vinyl disulfides **2** demonstrated the possibility of improving the yield of product **7** by prolonging the reaction time or selecting a solvent with a higher boiling point. The optimal conditions, scope of starting materials and stereoselectivity of the hetero-Diels-Alder reaction are under investigation.

#### 4. Conclusions

In summary, we developed a convenient and experimentally practical method for preparing unsymmetrical vinyl disulfides with additional functional groups under mild conditions. The method is based on readily available starting materials. The applied mild reaction conditions tolerate a variety of additional functionalities, including esters, carboxy, carbon–carbon double bonds, and protected amino, nitro, cyano, and hydroxy groups. We demonstrated that functionalized unsymmetrical vinyl disulfides can be used in the inverse electron-demand [4+2] hetero-Diels–Alder reaction to produce benzo-*b*[1,4]thiazine disulfanyl derivatives.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/1996-1944/14/6/1342/s1>: Synthesis of starting materials, vinyl disulfides **2**, and benzo-*b*[1,4]thiazine disulfanyl derivatives **7** with analytical data, copy of IR, and NMR spectra.

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#### References

1. Kondo, K.; Mitsudo, T. Metal-Catalyzed Carbon–Sulfur Bond Formation. *Chem. Rev.* **2000**, *100*, 3205–3220. [CrossRef]
2. Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Elsevier BV: Amsterdam, The Netherlands, 1994.
3. Lee, M.H.; Yang, Z.; Lim, C.W.; Lee, Y.H.; Dongbang, S.; Kang, C.; Kim, J.S. Disulfide-Cleavage-Triggered Chemosensors and Their Biological Applications. *Chem. Rev.* **2013**, *113*, 5071–5109. [CrossRef]
4. Ulman, A. Formation and Structure of Self-Assembled Monolayers. *Chem. Rev.* **1996**, *96*, 1533–1554. [CrossRef]
5. Witt, D.; Klajn, R.; Barski, P.; Grzybowski, B. Applications, Properties and Synthesis of  $\omega$ -Functionalized *n*-Alkanethiols and Disulfides—The Building Blocks of Self-Assembled Monolayers. *Curr. Org. Chem.* **2004**, *8*, 1763–1797. [CrossRef]
6. Love, J.C.; Estroff, L.A.; Kriebel, J.K.; Nuzzo, R.G.; Whitesides, G.M. Self-Assembled Monolayers of Thiolates on Metals as a Form of Nanotechnology. *Chem. Rev.* **2005**, *105*, 1103–1170. [CrossRef]
7. Houseman, B.T.; Gawalt, E.S.; Mrksich, M. Maleimide-Functionalized Self-Assembled Monolayers for the Preparation of Peptide and Carbohydrate Biochips. *Langmuir* **2003**, *19*, 1522–1531. [CrossRef]
8. Chen, S.; Li, L.; Boozer, C.L.; Jiang, S. Controlled Chemical and Structural Properties of Mixed Self-Assembled Monolayers by Coadsorption of Symmetric and Asymmetric Disulfides on Au(111). *J. Phys. Chem. B* **2001**, *105*, 2975–2980. [CrossRef]
9. Shon, Y.S.; Mazzitelli, C.; Murray, R.W. Unsymmetrical Disulfides and Thiol Mixtures Produce Different Mixed Monolayer-Protected Gold Clusters. *Langmuir* **2001**, *17*, 7735–7741. [CrossRef]
10. O'Brien, J.C.; Stickney, J.T.; Porter, M.D. Preparation and Characterization of Self-Assembled Double-Stranded DNA (dsDNA) Microarrays for Protein:dsDNA Screening Using Atomic Force Microscopy. *Langmuir* **2000**, *16*, 9559–9567. [CrossRef]
11. Higashi, N.; Takahashi, M.; Niwa, M. Immobilization of DNA through Intercalation at Self-Assembled Monolayers on Gold. *Langmuir* **1999**, *15*, 111–115. [CrossRef]

12. Kalsin, A.M.; Fialkowski, M.; Paszewski, M.; Smoukov, S.K.; Bishop, K.J.M.; Grzybowski, B.A. Electrostatic Self-Assembly of Binary Nanoparticle Crystals with a Diamond-Like Lattice. *Science* **2006**, *312*, 420–424. [[CrossRef](#)]
13. Kalsin, A.K.; Smoukov, S.K.; Kowalczyk, B.; Klajn, R.; Grzybowski, B.A. Ionic-like Behavior of Oppositely Charged Na-nanoparticles. *J. Am. Chem. Soc.* **2006**, *128*, 15046–15047. [[CrossRef](#)]
14. Cremlyn, R.; An, J. *Introduction to Organosulfur Chemistry*; Wiley: New York, NY, USA, 1996.
15. Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press: Boca Raton, FL, USA, 2018.
16. Vrudhula, V.M.; MacMaster, J.F.; Li, Z.; Kerr, D.E.; Senter, P.D. Reductively activated disulfide prodrugs of paclitaxel. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3591–3594. [[CrossRef](#)]
17. Mu, Y.; Nodwell, M.; Pace, J.L.; Shaw, J.-P.; Judice, J. Vancomycin disulfide derivatives as antibacterial agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 735–738. [[CrossRef](#)]
18. Shcherbakova, I.; Pozharskii, A.F. *Comprehensive Organic Functional Group Transformations II*; Katritzky, A.R., Taylor, R., Ramsden, C., Eds.; Pergamon: Oxford, UK, 2004; Volume 2, pp. 177–187.
19. Sato, R.; Kimura, T. *Science of Synthesis*; Kambe, N., Drabowicz, J., Molander, G.A., Eds.; Thieme: Stuttgart, Germany; New York, NY, USA, 2007; Volume 39, pp. 573–588.
20. Witt, D. Recent Developments in Disulfide Bond Formation. *Synthesis* **2008**, 2491–2509. [[CrossRef](#)]
21. Mandal, B.; Basu, B. Recent advances in S–S bond formation. *RSC Adv.* **2014**, *4*, 13854–13881. [[CrossRef](#)]
22. Musiejuk, M.; Witt, D. Recent Developments in the Synthesis of Unsymmetrical Disulfanes (Disulfides). A Review. *Org. Prep. Proced. Int.* **2015**, *47*, 95–131. [[CrossRef](#)]
23. Harpp, D.N.; Friedlander, B.T.; Larsen, C.; Steliou, K.; Stockton, A. Organic sulfur chemistry. 29. Use of the trimethylsilyl group in synthesis. Preparation of sulfinates esters and unsymmetrical disulfides. *J. Org. Chem.* **1978**, *43*, 3481–3485. [[CrossRef](#)]
24. Brown, C.; Evans, G.R. The “thio-Arbuzov” reaction of sulfenates esters with sulfonyl chlorides: Fate of the thiosulfinate product. *Tetrahedron Lett.* **1996**, *37*, 9101–9104. [[CrossRef](#)]
25. Swan, J.M. Thiols, Disulphides and Thiosulphates: Some New Reactions and Possibilities in Peptide and Protein Chemistry. *Nat. Cell Biol.* **1957**, *180*, 643–645. [[CrossRef](#)]
26. Hiver, P.; Dicko, A.; Paquer, D. Medium effects in unsymmetrical disulfides compounds synthesis from bunte salts. *Tetrahedron Lett.* **1994**, *35*, 9569–9572. [[CrossRef](#)]
27. Sirakawa, K.; Aki, O.; Tsujikawa, T.; Tsuda, T. S-Alkylthioisothioureas. I. *Chem. Pharm. Bull.* **1970**, *18*, 235–242. [[CrossRef](#)]
28. Ternay, A.L.; Cook, C.; Brzezinska, E. The Synthesis of Unsymmetric and Symmetric Disulfides. *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *95*, 351–352. [[CrossRef](#)]
29. Ternay, A.L.; Brzezinska, E. Disulfides. 1. Syntheses Using 2,2'-Dithiobis(benzothiazole). *J. Org. Chem.* **1994**, *59*, 8239–8244.
30. Hunter, R.; Caira, M.; Stellenboom, N. Inexpensive, One-Pot Synthesis of Unsymmetrical Disulfides Using 1-Chlorobenzotriazole. *J. Org. Chem.* **2006**, *71*, 8268–8271. [[CrossRef](#)] [[PubMed](#)]
31. Leriverend, C.; Metzner, P. A New Mild Synthesis of Unsymmetrical Disulfides by Reaction of Dithioperoxyesters with Thiols. *Synthesis* **1994**, 1994, 761–762. [[CrossRef](#)]
32. Dai, Z.; Xiao, X.; Jiang, X. Nucleophilic disulfurating reagents for unsymmetrical disulfides construction via copper-catalyzed oxidative cross coupling. *Tetrahedron* **2017**, *73*, 3702–3706. [[CrossRef](#)]
33. Dubs, P.; Stuessi, R. Eine neue Methode zur Herstellung gemischter Disulfide. Vorläufige Mitteilung. *Helv. Chim. Acta* **1976**, *59*, 1307–1311. [[CrossRef](#)]
34. Barton, D.H.; Chen, C.; Wall, G.M. Synthesis of disulfides via sulfonylation of alkyl and arylthiopyridine n-oxides. *Tetrahedron* **1991**, *47*, 6127–6138. [[CrossRef](#)]
35. Barton, D.H.R.; Hesse, R.H.; O'Sullivan, A.C.; Pechet, M.M. A new procedure for the conversion of thiols into reactive sulfonylating agents. *J. Org. Chem.* **1991**, *56*, 6697–6702. [[CrossRef](#)]
36. Ohtani, M.; Narisada, N. Sulfur-sulfur bond formation reaction using bis(1-methyl-1H-tetrazol-5-yl) disulphide. *J. Org. Chem.* **1991**, *56*, 5475–5478. [[CrossRef](#)]
37. Bao, M.; Shimizu, M. N-Trifluoroacetyl arenesulfenamides, effective precursors for synthesis of unsymmetrical disulfides and sulfenamides. *Tetrahedron* **2003**, *59*, 9655–9659. [[CrossRef](#)]
38. Blaschette, A.; Naveke, M. Polysulfonylamides. Part 25. N-Sulfonyldimesylamines and (1-Sulfonyl-4-dimethylamino-pyridinium) Dimesylaminides. Synthesis of New Compounds and Application as Sulfonylation Reagents. *Chem. Ztg.* **1991**, *115*, 61–64.
39. Hiskey, R.G.; Ward, B.F. Sulfur-containing polypeptides. XII. Scope and limitations of the sulfonylthiocyanate method as a route to cystine peptides. *J. Org. Chem.* **1970**, *35*, 1118–1121. [[CrossRef](#)]
40. Benati, L.; Montevecchi, P.C.; Spagnolo, P. 4'-Nitroarenesulphenanilides: Their use in the synthesis of unsymmetrical di-sulphides. *Tetrahedron Lett.* **1986**, *27*, 1739–1742. [[CrossRef](#)]
41. Armitage, D.A.; Clark, M.J.; Tso, C.C. Synthesis of unsymmetrical disulphides. *J. Chem. Soc. Perkin Trans. 1* **1972**, *1*, 680–683. [[CrossRef](#)]
42. Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Del Duce, R.; Menichetti, S. Silicon in organosulphur chemistry. Part 2. Synthesis of unsymmetrical disulphides. *Tetrahedron Lett.* **1989**, *30*, 2995–2998. [[CrossRef](#)]
43. Rajca, A.; Wiessler, M. Synthesis of unsymmetrical disulfides with thiol-sulfonates immobilised on a polystyrene support. *Tetrahedron Lett.* **1990**, *31*, 6075–6076. [[CrossRef](#)]



44. Koval, I.V. Imination of Sulfur-containing Compounds: XXXV. New Preparation Method and Oxidative Benzenesulfonylimination of Unsymmetrical Disulfides. *Russ. J. Org. Chem.* **2002**, *38*, 232–234. [[CrossRef](#)]
45. Oae, S.; Kim, Y.H.; Fukushima, D.; Shinhama, K. New syntheses of thionitrites and their chemical reactivities. *J. Chem. Soc. Perkin Trans. 1* **1978**, *1*, 913–917. [[CrossRef](#)]
46. Brois, S.J.; Pilot, J.F.; Barnum, H.W. New synthetic concepts in organosulfur chemistry. I. New pathway to unsymmetrical disulfides. The thiol-induced fragmentation of sulfenyl thiocarbonates. *J. Am. Chem. Soc.* **1970**, *92*, 7629–7631. [[CrossRef](#)]
47. Boustang, K.S.; Sullivan, A.B. Chemistry of sulfur compounds-VI. A novel method for the preparation of disulfides. *Tetrahedron Lett.* **1970**, *11*, 3547–3549. [[CrossRef](#)]
48. Harpp, D.N.; Ash, D.K.; Back, T.G.; Gleason, J.G.; Orwig, B.A.; VanHorn, W.F.; Snyder, J.P. A new synthesis of unsymmetrical disulfides. *Tetrahedron Lett.* **1970**, *11*, 3551–3554. [[CrossRef](#)]
49. Klose, J.; Reese, C.B.; Song, Q. Preparation of 2-(2-cyanoethyl)sulfanyl-1H-isoindole-1,3-(2H)-dione and related sulfur-transfer agents. *Tetrahedron* **1997**, *53*, 14411–14416. [[CrossRef](#)]
50. Masui, M.; Mizuki, Y.; Sakai, K.; Ueda, C.; Ohmori, H. The reaction of Ph<sub>3</sub>P+SR with thiols: A simple, efficient synthesis of unsymmetrical disulphides. *J. Chem. Soc. Chem. Commun.* **1984**, 843–844. [[CrossRef](#)]
51. Graber, D.R.; Morge, R.A.; Sih, J.C. Reaction of 2-(alkylsulfinyl)-, 2-(arylsulfinyl)-, and 2-(aralkylsulfinyl)benzimidazoles with thiols: A convenient synthesis of unsymmetrical disulfides. *J. Org. Chem.* **1987**, *52*, 4620–4622. [[CrossRef](#)]
52. Arisawa, M.; Yamaguchi, M. Rhodium-Catalyzed Disulfide Exchange Reaction. *J. Am. Chem. Soc.* **2003**, *125*, 6624–6625. [[CrossRef](#)]
53. Tanaka, K.; Ajiki, K. Phosphine-free cationic rhodium(I) complex-catalyzed disulfide exchange reaction: Convenient synthesis of unsymmetrical disulfides. *Tetrahedron Lett.* **2004**, *45*, 5677–5679. [[CrossRef](#)]
54. Do, Q.T.; Elothmani, D.; Le Guillanton, G.; Simonet, J. A new electrochemical method of preparation of unsymmetrical di-sulfides. *Tetrahedron Lett.* **1997**, *38*, 3383–3384. [[CrossRef](#)]
55. Sureshkumar, D.; Ganesh, V.; Vidyarini, R.S.; Chandrasekaran, S. Direct Synthesis of Functionalized Unsymmetrical  $\beta$ -Sulfonamido Disulfides by Tetrathiomolybdate Mediated Aziridine Ring-Opening Reactions. *J. Org. Chem.* **2009**, *74*, 7958–7961. [[CrossRef](#)]
56. Sureshkumar, D.; Koutha, S.M.; Chandrasekaran, S. Chemistry of Tetrathiomolybdate: Aziridine Ring Opening Reactions and Facile Synthesis of Interesting Sulfur Heterocycles. *J. Am. Chem. Soc.* **2005**, *127*, 12760–12761. [[CrossRef](#)] [[PubMed](#)]
57. Mukaiyama, T.; Takahashi, K. A convenient method for the preparation of unsymmetrical disulfides by the use of diethyl azodicarboxylate. *Tetrahedron Lett.* **1968**, *9*, 5907–5908. [[CrossRef](#)]
58. Galande, A.K.; Spatola, A.F. Solid-Phase Synthesis of Disulfide Heterodimers of Peptides. *Org. Lett.* **2003**, *5*, 3431–3434. [[CrossRef](#)] [[PubMed](#)]
59. Vandavasi, J.K.; Hu, W.-P.; Chen, C.-Y.; Wang, J.-J. Efficient synthesis of unsymmetrical disulfides. *Tetrahedron* **2011**, *67*, 8895–8901. [[CrossRef](#)]
60. Smith, R.; Zeng, X.; Müller-Bunz, H.; Zhu, X. Synthesis of glycosyl disulfides containing an  $\alpha$ -glycosidic linkage. *Tetrahedron Lett.* **2013**, *54*, 5348–5350. [[CrossRef](#)]
61. Musiejuk, M.; Klucznik, T.; Rachon, J.; Witt, D. DDQ-mediated synthesis of functionalized unsymmetrical disulfanes. *RSC Adv.* **2015**, *5*, 31347–31351. [[CrossRef](#)]
62. Dethe, D.H.; Srivastava, A.; Dherange, B.D.; Kumar, B.V. Unsymmetrical Disulfide Synthesis through Photoredox Catalysis. *Adv. Synth. Catal.* **2018**, *360*, 3020–3025. [[CrossRef](#)]
63. Lach, S.; Demkowicz, S.; Witt, D. An efficient and convenient synthesis of unsymmetrical disulfides from thioacetates. *Tetrahedron Lett.* **2013**, *54*, 7021–7023. [[CrossRef](#)]
64. Antoniow, S.; Witt, D. A Novel and Efficient Synthesis of Unsymmetrical Disulfides. *Synthesis* **2007**, *3*, 363–366. [[CrossRef](#)]
65. Kowalczyk, J.; Barski, P.; Witt, D.; Grzybowski, B.A. Versatile and Efficient Synthesis of  $\omega$ -Functionalized Asymmetric Di-sulfides via Sulfenyl Bromide Adducts. *Langmuir* **2007**, *23*, 2318–2321. [[CrossRef](#)]
66. Szymelfejnik, M.; Demkowicz, S.; Rachon, J.; Witt, D. Functionalization of Cysteine Derivatives by Unsymmetrical Disulfide Bond Formation. *Synthesis* **2007**, *22*, 3528–3534.
67. Demkowicz, S.; Rachon, J.; Witt, D. A Versatile and Convenient Preparation of Unsymmetrical Diaryl Disulfides. *Synthesis* **2008**, *13*, 2033–2038.
68. Witt, D.; Okragla, E.; Demkowicz, S.; Rachón, J. A Convenient and Efficient  $\alpha$ -Sulfonylation of Carbonyl Compounds. *Synthesis* **2009**, *2009*, 1720–1724. [[CrossRef](#)]
69. Lach, S.; Witt, D. A New and Convenient Method for the Preparation of Functionalized Phosphorothioates. *Synthesis* **2011**, *2011*, 3975–3978. [[CrossRef](#)]
70. Dorozuk, J.; Musiejuk, M.; Demkowicz, S.; Rachon, J.; Witt, D. Convenient and efficient synthesis of functionalized unsymmetrical alkynyl sulfides, *RSC Adv.* **2016**, *6*, 105449–105453. *RSC Adv* **2016**, *6*, 105449–105453. [[CrossRef](#)]
71. Dorozuk, J.; Musiejuk, M.; Ponikiewski, L.; Witt, D. Convenient and Efficient Diastereoselective Preparation of Functionalized Z-Alkenyl Sulfides. *Eur. J. Org. Chem.* **2018**, *45*, 6333–6337. [[CrossRef](#)]
72. Kertmen, A.; Lach, S.; Rachon, J.; Witt, D. Novel and Efficient Methods for the Synthesis of Symmetrical Trisulfides. *Synthesis* **2009**, *9*, 1459–1462.
73. Lach, S.; Witt, D. TBAF Promoted Formation of Symmetrical Trisulfides. *Heteroat. Chem.* **2013**, *25*, 10–14. [[CrossRef](#)]
74. Lach, S.; Sliwka-Kaszynska, M.; Witt, D. Novel and Efficient Synthesis of Unsymmetrical Trisulfides. *Synlett* **2010**, *19*, 2857–2860.

75. Witt, D.; Lach, S. Efficient Synthesis of Functionalized Unsymmetrical Dialkyl Trisulfanes. *Synlett* **2013**, *24*, 1927–1930. [[CrossRef](#)]
76. Block, E.; Ahmad, S.; Jain, M.K.; Crecely, R.W.; Apitz-Castro, R.; Cruz, M.R. The chemistry of alkyl thiosulfate esters. 8. (E,Z)-Ajoene: A potent antithrombotic agent from garlic. *J. Am. Chem. Soc.* **1984**, *106*, 8295–8296. [[CrossRef](#)]
77. Block, E.; Ahmad, S.; Catalfamo, J.L.; Jain, M.K.; Apitz-Castro, R. The chemistry of alkyl thiosulfinate esters. 9. Antithrombotic organosulfur compounds from garlic: Structural, mechanistic, and synthetic studies. *J. Am. Chem. Soc.* **1986**, *108*, 7045–7055. [[CrossRef](#)]
78. Li, M.; Ciu, J.-R.; Ye, Y.; Min, J.-M.; Zhang, L.-H.; Wang, K.; Gares, M.; Cros, J.; Wright, M.; Leung-Tack, J. Antitumor activity of Z-ajoene, a natural compound purified from garlic: Antimitotic and microtubule-interaction properties. *Carcinog* **2002**, *23*, 573–579. [[CrossRef](#)] [[PubMed](#)]
79. Li, M.; Min, J.-M.; Cui, J.-R.; Zhang, L.-H.; Wang, K.; Valette, A.; Davrinche, C.; Wright, M.; Leung-Tack, J. Z-Ajoene Induces Apoptosis of HL-60 Cells: Involvement of Bcl-2 Cleavage. *Nutr. Cancer* **2002**, *42*, 241–247. [[CrossRef](#)] [[PubMed](#)]
80. Zhang, G.; Parkin, K.L. S-Alk(en)ylmercaptocysteine: Chemical Synthesis, Biological Activities, and Redox-Related Mechanism. *J. Agric. Food Chem.* **2013**, *61*, 1896–1903. [[CrossRef](#)]
81. Hunter, R.; Kaschula, C.H.; Parker, I.M.; Caira, M.R.; Richards, P.; Travis, S.; Taute, F.; Qwebani, T. Substituted ajoenes as novel anti-cancer agents. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5277–5279. [[CrossRef](#)] [[PubMed](#)]
82. Kaschula, C.H.; Hunter, R.; Stellenboom, N.; Caira, M.R.; Winks, S.; Ogunleye, T.; Richards, P.; Cotton, J.; Zilbeyaz, K.; Wang, Y.; et al. Structure–activity studies on the anti-proliferation activity of ajoene analogues in WHCO1 oesophageal cancer cells. *Eur. J. Med. Chem.* **2012**, *50*, 236–254. [[CrossRef](#)]
83. Silva, F.; Khokhar, S.S.; Williams, D.M.; Saunders, R.; Evans, G.J.S.; Graz, M.; Wirth, T. Short Total Synthesis of Ajoene. *Angew. Chem. Int. Ed.* **2018**, *57*, 12290–12293. [[CrossRef](#)]
84. Musiejuk, M.; Doroszk, J.; Witt, D. Convenient and efficient synthesis of functionalized unsymmetrical Z-alkenyl disulfanes. *RSC Adv.* **2018**, *8*, 9718–9722. [[CrossRef](#)]
85. Musiejuk, M.; Doroszk, J.; Jędrzejewski, B.; Nieto, G.O.; Navarro, M.M.; Witt, D. Diastereoselective Synthesis of Z-Alkenyl Disulfides from  $\alpha$ -Thiophosphorylated Ketones and Thiosulfonates. *Adv. Synth. Catal.* **2020**, *362*, 618–626. [[CrossRef](#)]
86. Rathore, B.S.; Kumar, M. Synthesis of 7-chloro-5-trifluoromethyl/7-fluoro/7-trifluoromethyl-4H-1,4-benzothiazines as antimicrobial agents. *Bioorg. Med. Chem.* **2006**, *14*, 5678–5682. [[CrossRef](#)] [[PubMed](#)]
87. Huang, W.; Yang, G.-F. Microwave-assisted, one-pot syntheses and fungicidal activity of polyfluorinated 2-benzylthiobenzothiazoles. *Bioorg. Med. Chem.* **2006**, *14*, 8280–8285. [[CrossRef](#)] [[PubMed](#)]
88. Vigliani, C.; Bonaccorsi, P.M.; Simone, L.; Nassini, L.; Menichetti, S. Copper-Mediated One-Pot Access to Benzo[b][1,4]thiazines from 2-N-Sulfonylaminoaryl Disulfides. *Eur. J. Org. Chem.* **2012**, *2012*, 1707–1711. [[CrossRef](#)]

