

## Convenient and efficient synthesis of functionalized unsymmetrical alkynyl sulfides

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**Abstract:** We developed a simple and efficient method for the synthesis of functionalized unsymmetrical alkynyl sulfides under mild conditions in good yields. The designed method is based on the reaction of 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-disulfanyl derivatives with lithium acetylides. The developed method allows the preparation of unsymmetrical alkynyl sulfides bearing additional hydroxyl, carboxyl, or amino functionalities.

**Key words:** alkynyl sulfides, alkynes, lithium acetylides, phosphorodithioic acid, disulfanyl derivatives

### 1. Introduction

The development of practical and versatile methods for introduction of functional groups into molecules to modify their properties is one of the most important task of organic chemistry. The easy to perform reactions that do not require highly specialized synthetic skills have a particularly broad impact to other fields such as medicine, biology, or materials science. From this point of view, among all functional groups in organic chemistry, alkynes occupy a privileged position [1]. Although alkynes contain one of the simplest functional group, two carbon atoms connected with triple bond, the reactivity of that bond makes alkynes exceptionally useful in organic synthesis. They were applied in the stereoselective construction of the carbon backbone of complex natural products [2], bulk chemical synthesis based on acetylene gas [3] and in the variety of complexity-enhancing metal-catalyzed cyclization reactions to provide carbo- and heterocycles [4]. The electronic properties of alkynes have found also wide applications in preparation of organic materials and dyes [5]. Moreover, their [3+2] cycloaddition with azides is recognized as one of the best biorthogonal conjugation method to modify biomolecules and polymers [6]. In this context, the development of new synthetic methods to access alkynes and their derivatives efficiently under user-friendly conditions is highly desirable.

Driven by the exceptional reactivity of sulfur and its importance in biology, medicine, and materials science [7], recent research efforts targeted a series of thiol-based transformations including thiol alkylations and the thiol addition to alkenes and alkynes respectively [8]. Unlike the well-established S-Csp<sup>3</sup> bond forming reactions, existing methods to construct S-Csp bonds are rare in number and often lack generality or require harsh conditions.

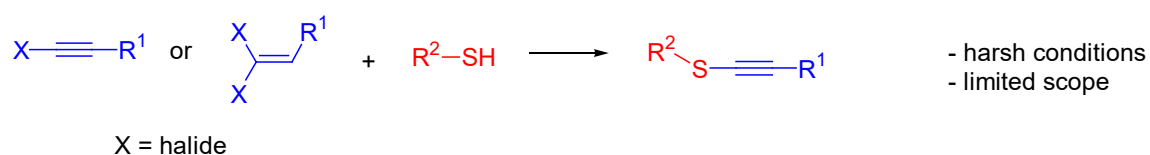
Alkynyl sulfides can be obtained by methods utilize transition-metal catalysts, such as the copper-catalyzed carbon sulfur coupling between terminal alkynes and disulfides [9], or as in the elegant study by Yamaguchi, the use of catalytic rhodium to achieve C-S bond formation by C-H and S-S bond metathesis (Scheme 1, A) [10]. Alternatively, a range of processes utilize alkenyl [11] or alkynyl [12] halides bearing leaving groups that undergo elimination under strongly basic conditions to furnish the desired alkynyl sulfides (Scheme 1, B). Consequently, the limited functional group tolerance exhibited by these methods is not surprising as they require harsh conditions, proceed via highly reactive intermediates, or involve the use of sensitive catalytic systems. Recently, Waser has developed a thiol-alkynylation procedure utilizing the hypervalent iodine alkyne transfer reagent TIPS-

ethynylbenziodoxolone (Scheme 1, C) [13]. Although the method is highly chemoselective as a vast array of functional groups are tolerated, the problems associated with preparation and stability hypervalent iodine alkyne transfer reagent are the major disadvantages of that transformation. Currently, the most common methods to form alkynyl sulfides require a prefunctionalization of the thiol (Scheme 1, D). These methods are generally based on nucleophilic substitutions between highly reactive lithium acetylide intermediates with pre-activated thiols or disulfide species [14]. The major drawback of that approach emerges from availability and long term stability of pre-activated thiols.

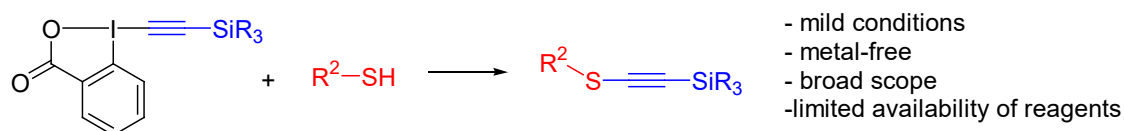
A. S-Csp bonds from transition metals promoted coupling of disulfides and alkynes



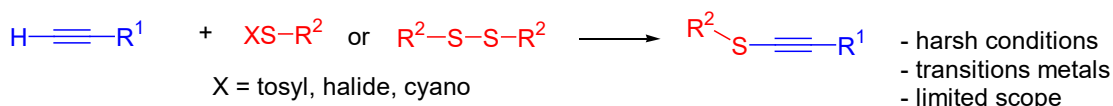
B. S-Csp bonds directly from thiols



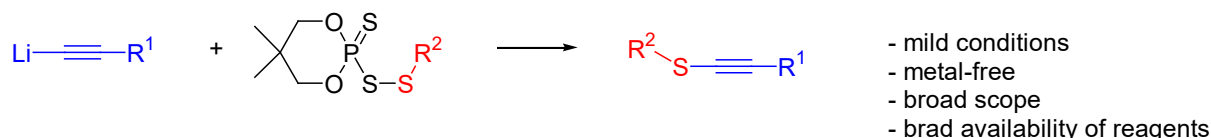
C. S-Csp bonds from thiols and hypervalent iodine alkynes



D. S-Csp bonds from pre-activated thiols



E. This work



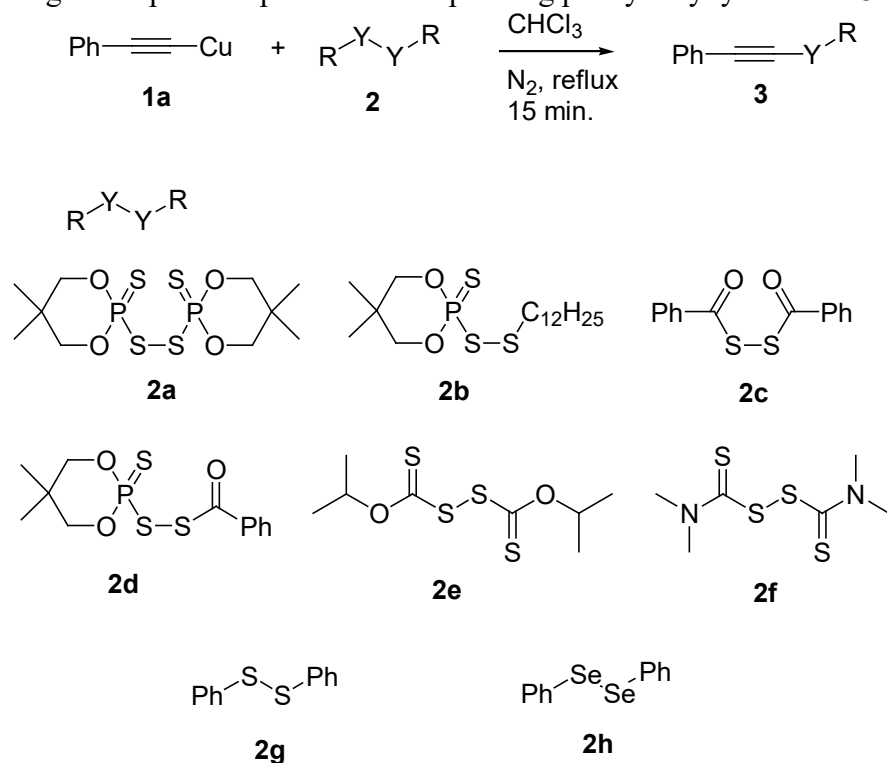
Scheme 1. Previously reported methods for the synthesis of alkynyl sulfides (A-D) and our new approach (E)

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyldisulfanes [15], alkyl-aryl disulfanes [16], ‘bioresistant’ disulfanes [17], the unsymmetrical disulfanes of L-cysteine and L-cystine [18], and diaryldisulfanes [19], based on the readily available electrophilic 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **2** [20]. These disulfanyl derivatives of phosphorodithioic acid were also convenient for the preparation of  $\alpha$ -sulfenylated carbonyl compounds [21], functionalized phosphorothioates [22], as well as symmetrical [23-24] and unsymmetrical [25-26] trisulfanes. All these transformations are based on the electrophilic properties of disulfanyl derivatives of phosphorodithioic acid **2**, so we expected that also

reaction with nucleophilic acetylides should provide corresponding alkynyl sulfides (Scheme 1, E). Furthermore, the development of a robust, efficient, and orthogonal alkynyl sulfides synthesis is particularly attractive to the field of material and polymer science as an alternative tool to the current array of thiol-functionalization reactions. In this context, we set out to investigate the feasibility of more convenient and experimentally practical method to gain access to alkynyl sulfides.

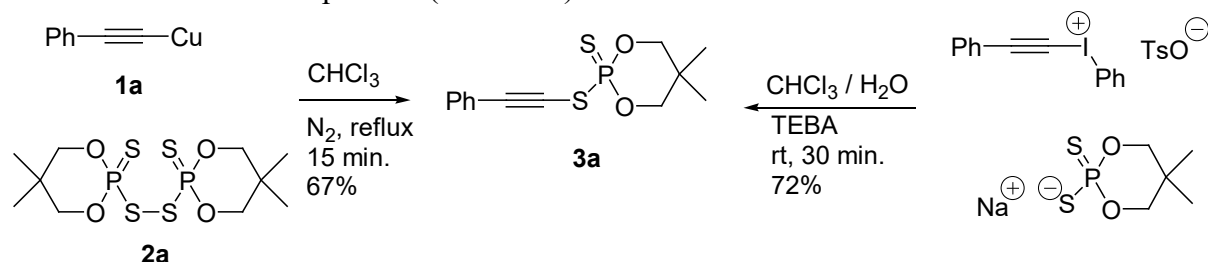
## 2. Results and discussion

The terminal alkynes can be easily converted into the 1-Cu(I) acetylides [27]. The presence of additional groups (as carbonyl, carboxyl or hydroxyl) did not disturb the formation of corresponding salts. Moreover, these compounds were stored in a bottle and no notable decomposition was observed within one year. We began our study with copper (I) phenylacetylide **1a** as starting substrate while screening different disulfanyl derivatives reagents capable to produce corresponding phenylethynyl sulfides **3** (Scheme 2).



Scheme 2. The reaction of copper (I) phenylacetylide **1a** with disulfanyl derivatives **2**.

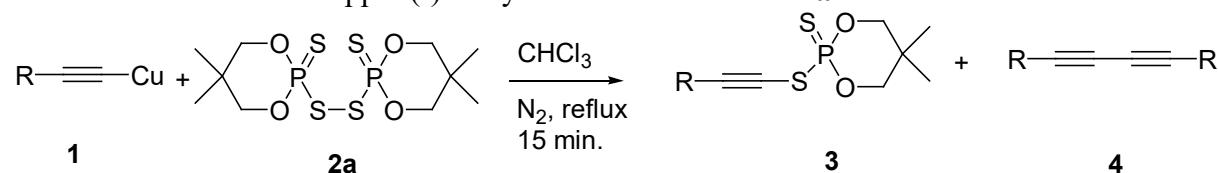
Unfortunately, in the most cases the reaction did not occur or provided complex mixture without formation of compound **3**. The only successful transformation was the reaction of copper (I) phenylacetylide with phosphorodithioic acid disulfane **2a** when the expected product **3a** was isolated in 67% yield. Additionally, we have accomplished the synthesis of **3a** by independent method based on the phenylethynylphenyliodonium tosylate [28] to confirm the structure of the final product (Scheme 3).



Scheme 3. The synthesis of 1-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)sulfanyl]-2-phenylacetylene **3a**

We examined the reactivity of functionalized copper acetylides **1** with disulfane **2a**. The results are summarized in the Table 1.

Table 1. Reaction of 1-Copper (I) acetylides **1** with disulfane **2a**<sup>a</sup>.



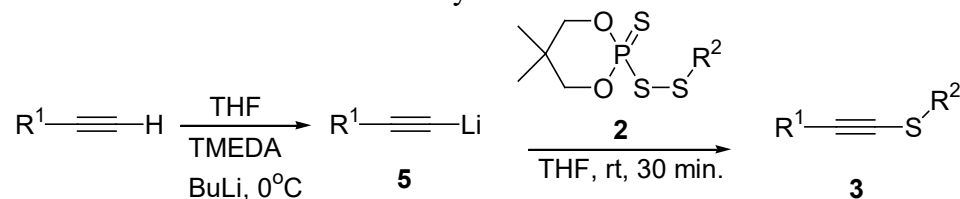
Entry	R	Yield <sup>b</sup> (%)	
		<b>3</b>	<b>4</b>
1	Ph- <b>1a</b>	67	30
2	PhCH <sub>2</sub> OCH <sub>2</sub> - <b>1b</b>	40	55
3	BocNH-CH <sub>2</sub> - <b>1c</b>	30	40

<sup>a</sup> Conditions: copper alkyne **1** (1.0 mmol), disulfane **2a** (1.0 mmol), 10.0 mL of chloroform, reflux 15 min. under N<sub>2</sub>. <sup>b</sup> Isolated yields.

As the data in Table 1 demonstrate, the yield of product **3** is moderate (30-67%) and the reaction is hampered by the formation of dimer **4** (30-55%). Although acetylides **1** are stable and readily available their application in the alkynyl sulfides synthesis, under developed conditions, seems to be limited by an oxidative coupling that produces bis-acetylenes **4**.

The reaction of electrophilic disulfanyl derivatives **2** and lithium acetylides **5** was expected to produce the corresponding alkynyl sulfides **3** with higher yield due to the limited formation of bis-acetylenes **4**. The results are summarized in Table 2.

Table 2. Reaction of Lithium Acetylides **5** with disulfanes **2**



	R <sup>1</sup> = -Ph <b>5a</b>	R <sup>1</sup> = -CH <sub>2</sub> OCH <sub>2</sub> Ph <b>5b</b>	R <sup>1</sup> = -CH <sub>2</sub> NHBoc <b>5c</b>
R <sup>2</sup> = (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) <b>2a</b>	(78) <b>3a</b>	(75) <b>3b</b>	(60) <b>3c</b>
R <sup>2</sup> = (CH <sub>2</sub> ) <sub>11</sub> -CH <sub>3</sub> <b>2b</b>	(99) <b>3d</b>	(83) <b>3e</b>	(57) <b>3f</b>
R <sup>2</sup> = (CH <sub>2</sub> ) <sub>11</sub> -OH <b>2i</b>	(63) <b>3g</b>	(55) <b>3h</b>	(50) <b>3i</b> <sup>c</sup>
R <sup>2</sup> = (CH <sub>2</sub> ) <sub>10</sub> -CO <sub>2</sub> H <b>2j</b>	(72) <b>3j</b>	(73) <b>3k</b>	(51) <b>3l</b> <sup>d</sup>
R <sup>2</sup> = 4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> - <b>2k</b>	(98) <b>3m</b>	(89) <b>3n</b>	(78) <b>3o</b>

<sup>a</sup> Conditions: Lithium acetylide **5** (1.0 mmol), TMEDA (1.0 mmol), disulfane **2** (1.1 mmol), 12 mL of THF, rt 30 min. under N<sub>2</sub>. <sup>b</sup> Isolated yields in parenthesis. <sup>c</sup> R<sup>2</sup> = (CH<sub>2</sub>)<sub>11</sub>-OTHP. <sup>d</sup> R<sup>2</sup> = (CH<sub>2</sub>)<sub>10</sub>-CO<sub>2</sub>Me

The lithium acetylides **5** were generated from the corresponding terminal alkynes and BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF to avoid the potential aggregation of lithium salts. In the case of disulfanes **2i** and **2j** with acidic protons (OH and CO<sub>2</sub>H respectively) the two fold excess of **5a** and **5b** was used. It was also possible to treat **2i** and **2j** with NaH before addition to solution of **5a** or **5b** in THF. Both methods provided appropriate alkynyl sulfides **3g**, **3h** and **3j**, **3k** with comparable yield respectively. However, the generation of **5c** from *N*-Boc propargylamine required the using of two equivalents of BuLi. Moreover, the corresponding alkynyl sulfides **3i** and **3l** were obtained when hydroxyl and carboxyl groups were protected in disulfanes **2i** and **2j** (THP or methyl ester respectively). The preparation of alkynyl sulfides **3** from disulfanyl derivatives **2** and lithium acetylides **5** is very convenient because both starting materials are stable and readily available. The transformation tolerates the presence of additional functional groups. However, the presence of acidic protons in the starting materials may require the using of larger quantity of base to avoid the protonation of acetylides anions.

## Conclusions

In summary, we developed an efficient and convenient method for the preparation of unsymmetrical alkynyl sulfides **3** directly from the readily available disulfanyl derivatives of phosphorodithioic acid **2** and functionalized alkynes in the presence of TMEDA and BuLi. A variety of functional groups is tolerated, including the hydroxyl, carboxyl, and protected amino, hydroxyl and carboxyl group. Reactions of lithium acetylides **5** with a variety of disulfanes **2** in the presence of TMEDA in THF at rt were generally complete within 30 minutes and gave unsymmetrical alkynyl sulfides **3** exclusively in good or very good yield after isolation. The simplicity and good yields render this method one of the most attractive approaches to the preparation of functionalized unsymmetrical alkynyl sulfides.

## A typical procedure for the preparation of alkynyl sulfides **3d** and representative analytical data

BuLi (2.5M, 0.44 mL, 1.1 mmol) was added to a solution of phenylacetylene (0.11 mL, 1.0 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (0.15 mL, 1.0 mmol) in anhydrous THF (10 mL) at 0 °C under N<sub>2</sub>. After 5 min, a solution of 1-[(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfanyl]dodecane **2b** (0.438 g, 1.1 mmol) in anhydrous THF (2 mL) was added. The mixture was stirred at r.t. for 30 min and evaporated under vacuum. The residue was purified by column chromatography (SiO<sub>2</sub>, petroleum ether, R<sub>f</sub>= 0.6) to give **3d** as a colorless oil; yield: 0.300 g (99%).

IR (ATR): 2900 (s), 2850 (s) (C-H), 2170 (w) (C≡C), 1600 (w), 1450 (w), 1370 (w), 750 (m), 700 (m) cm<sup>-1</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 0.89 (t, *J* = 7.0 Hz, 3H, CH<sub>3</sub>), 1.20-1.40 (m, 16H, CH<sub>2</sub>), 1.46 (qu, *J* = 7.0 Hz, 2H, CH<sub>2</sub>), 1.8 (qu, *J* = 7.4 Hz, 2H, CH<sub>2</sub>), 2.81 (t, *J* = 7.3 Hz, 2H, SCH<sub>2</sub>), 7.26-7.35 (m, 3H, Ar), 7.40-7.45 (m, 2H, Ar).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 131.4, 128.2, 127.9, 123.6, 92.8, 79.7, 35.8, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.1, 28.2, 22.7, 14.1; signals: 19 expected, 18 observed.

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