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Sequential One-pot Reactions of Thioformates with Lithium Silylacetylides, Arylmagnesium Halides, and Electrophiles Leading to Formation of Propargyl Sulfides

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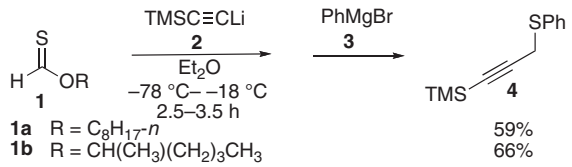
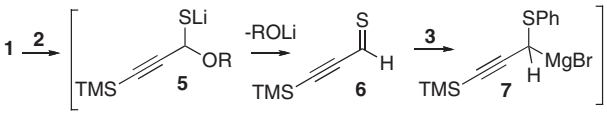
One-pot reactions of thioformates with lithium silylacetylides, arylmagnesium halides, and electrophiles that produce propargyl (2-propynyl) sulfides are described. The pathway for this process begins with addition of lithium (trimethylsilyl)acetylide to the thioformate C=S carbon. This step is followed by addition of the arylmagnesium halide to the sulfur atom of the C=S group in the in situ generated propynethial. The intermediacy of the propynethial in this process was confirmed by trapping through a Diels–Alder reaction with cyclopentadiene.

Addition reactions of organolithium and Grignard reagents to carbonyl compounds are among the most traditional, well-established processes in synthetic organic chemistry.[1] Studies using thiocarbonyl compounds as substrates in these addition reactions[2] have uncovered the striking feature that organolithium and Grignard reagents add to these reagents at both carbon and sulfur of the C=S moiety, depending on the substitution patterns. For example, phenyllithium undergoes thiophilic addition to thiobenzophenone[3] and (2,4,6-tri-*t*-butyl)thiobenzaldehyde,[4] whereas addition of Grignard reagents to thioaldehydes takes place at both carbon and sulfur in the C=S group.[4] In recent studies that were guided by the aim to develop sequential one-pot reactions,[5] we uncovered an addition reaction in which two different organometallic reagents add successively to thioiminium salts derived from thioamides[6] and to thioformamides directly.[7] In these transformations, the organometallic reagents selectively add to the carbon atom of the thiocarbonyl group. In more recent investigations aimed at applying this process to thioformate substrates, we observed that both the thiocarbonyl carbon and sulfur serve as electrophilic centers when two different organometallic reagents are used. Below, we describe the results of this effort, which have led to the development of a novel sequential reaction between thioformates, lithium silylacetylide, arylmagnesium halides, and electrophiles that leads to the production of propargyl sulfides.

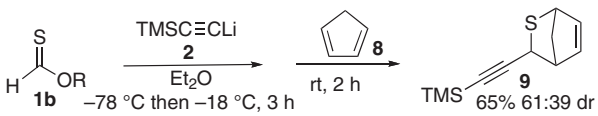
In initial studies, thioformates **1**[8] were subjected to sequential addition reactions with lithium (trimethylsilyl)acetylide (**2**) and phenylmagnesium bromide (**3**) since these combinations have led to better results in the reaction of thioamides.[6] Aqueous workup of the reaction mixtures gave rise to the propargyl sulfide **4**[9] (Scheme 1) in yields that were only slightly influenced by the alkoxy group in **1**. The highest yield of **4** was obtained when **1b** was used as the substrate.[10] Inspection of the product of these reactions shows that lithium acetylide **2** was introduced at the C=S carbon in **1** whereas the Grignard reagent added to the sulfur atom. Among the lithium acetylides tested, only the one derived from (trimethylsilyl)acetylene led to efficient formation of products. Since the silyl group at the terminal position of the products can be used to affect carbon–



Scheme 1.



Scheme 2.



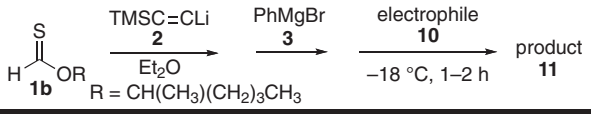
Scheme 3.

carbon bond forming reactions, the process described above is potentially applicable to the preparation of a variety of derivatives of the sulfide **4**.

A plausible mechanistic pathway for this process, given in Scheme 2, involves initial nucleophilic addition of **2** to the C=S carbon in **1** to form lithium hemithioacetals **5**. Elimination of ROLi from **5** then generates the propynethial **6**, which reacts with phenylmagnesium bromide at sulfur to form propargylmagnesium bromide **7**. Finally, aqueous workup produces the propargyl sulfide **4**. Evidence for the existence of intermediate thioaldehyde **6** in this pathway was gained by addition of excess cyclopentadiene **8** to the mixture formed by reaction of **1b** and **2**. This process leads to formation of adduct **9**, derived by the Diels–Alder reaction between **6** and **8**, in a manner similar to known cycloaddition reactions of thioaldehydes[11] (Scheme 3).

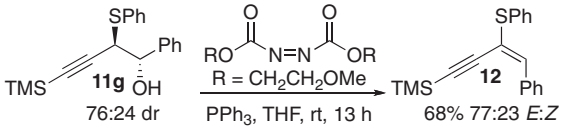
We envisioned that the in situ generated propargylic Grignard reagent **7** could be used as a novel nucleophile in reactions with a variety of electrophilic reagents. The results of studies probing reactions of **7** with alkyl halides, trimethylsilyl chloride, and carbonyl compounds are shown in Table 1. In all cases, sequential reactions took place to yield the corresponding propargyl sulfides. For example, addition of methyl (**10a**) and propyl iodide (**10b**) to mixtures containing **7**, formed by reaction of **1b**, **2**, and **3**, at −18 °C leads to formation of the respective alkylation products **11a** and **11b** (Entries 1 and 2). Trimethylsilyl chloride also participates in a reaction that affords **11c** (Entry 3). Allylation of in situ generated **7** also occurs upon treatment with the allylic halide **10d** to give 4-phenylsulfanyl-1,5-enyne **11d** (Entry 4). Also, reactions of aldehydes **10e**–**10g** with in situ

Table 1. Sequential one-pot reaction of thioformate, lithium silylacetylide, phenylmagnesium bromide, and electrophiles[a]



Entry	Electrophile **10**	Product **11**	Yield/%[b,c]
1	**10a** MeI	**11a** R = Me	66
2	**10b** *n*-PrI	**11b** R = Pr-*n*	61
3	**10c** TMSCl	**11c** R = TMS	60
4	**10d**	**11d**	62
5	**10e**	**11e**[d]	59 (77:23)
6	**10f**	**11f**[d]	65 (83:17)
7	**10g**	**11g**[d]	51 (76:24)
8	**10h**	**11h**	59

[a]Thioformate **1b** (1.0 mmol) was reacted with lithium acetylide **2** (1.5 equiv), phenylmagnesium bromide (**3**) (3.3 equiv), and electrophiles **10** (3.0 equiv). [b]Isolated yields. [c]The ratio of diastereomers is in parentheses. [d]The structure of the major products is shown.



Scheme 4.

generated **7** lead to formation of homopropargyl alcohols **11e**–**11g** in similar diastereomeric ratios (76:24 to 83:17, respectively, Entries 5–7). Reaction of **7** with acetone **10h** also proceeds in a regioselective manner to generate **11h** (Entry 8) rather than an allene-containing product. The latter observation contrasts with those made in studies of reactions of propargyl Grignard reagents without PhS groups with ketones, in which allenes are formed as by-products.[12]

Propargyl sulfides, although rarely studied thus far, are of interest not only in terms of biological applications[13] but also as key synthetic intermediates[14] for the preparation of allenylamines and cyclic ethers. In an exploration of further uses of these substances, transformation of the propargyl sulfide **11g** to enynes was probed. The reaction of **11g** under Mitsunobu conditions[15] leads to production of enyne **12**, which retains a phenylsulfanyl group (Scheme 4).

In summary, the studies described above have led to the development of a new sequential one-pot reaction. In this process, lithium (trimethylsilyl)acetylide, and Grignard reagents sequentially add to thioformates to generate propargylmagnesium bromide intermediates, which react with a variety of electrophiles to form a range of propargyl sulfides in high yields.[16] Moreover, the existence of a propynethial as an intermediate in this reaction was demonstrated by using a Diels–Alder trapping process. Overall, in this methodology two different organometallic reagents add to the thiocarbonyl group of thioformates. Interestingly, the first addition takes place selectively at the carbon of the C=S group, whereas the latter reagent adds again selectively to the sulfur atom of the thioaldehyde intermediate. Further applications of sequential reactions using thiocarbonyl compounds with a variety of organometallic regents are currently being investigated.

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