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Novel Coupling Reactions of Dithioacetals with Organocuprate Reagents. Propargylic Dithioacetal as an Allene−1,3-Zwitterion Synthon

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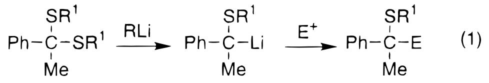
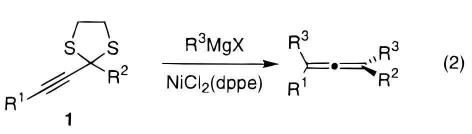
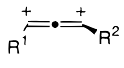
The carbon−sulfur bond is known to be ambiphilic toward nucleophiles because the electronegativities for carbon and sulfur atoms are similar. Accordingly, different kinds of reagents or conditions may alter the selectivity of the reaction. It is well documented that the nickel-catalyzed cross-coupling reactions of organosulfur compounds with Grignard reagents provide a useful entry to convert a carbon−sulfur bond into a carbon−carbon bond.[1,2] The carbon−sulfur bond in these reactions can be considered as a carbocation synthon. On the other hand, the production of a carbanionic leaving group from the corresponding thioether is rare unless a stabilized anionic species is produced. For example, the reaction of an (α-thioalkoxy)carbonyl compound with methyl mercaptide affords the corresponding desulfurized product.[3] More recently, treatment of benzylic dithioacetals with organolithium reagents has led to the formation of the corresponding carbanions (eq 1).[4]



$$\text{Ph}-\overset{\text{SR}^1}{\underset{\text{Me}}{\text{C}}}-\text{SR}^1 \xrightarrow{\text{RLi}} \text{Ph}-\overset{\text{SR}^1}{\underset{\text{Me}}{\text{C}}}-\text{Li} \xrightarrow{\text{E}^+} \text{Ph}-\overset{\text{SR}^1}{\underset{\text{Me}}{\text{C}}}-\text{E} \quad (1)$$

Whereas propargylic acetals react readily with organocopper reagents to give the corresponding ring-opening products,[5] the corresponding reaction with sulfur analogs has not been explored. We recently reported that the propargylic dithioacetal **1** can serve as an allene-1,3-dication synthon **2** upon treatment with the Grignard reagent in the presence of a nickel catalyst (eq 2).[2,6] In this regard, the displacement of the two carbon−sulfur bonds by two carbon−carbon bonds can be achieved in one pot. However, the reaction would be more versatile if the two carbon−sulfur bonds in **1** could be substituted by different moieties. In this paper, we report an unprecedented organocopper-induced C−S bond-cleavage reaction of propargylic dithioacetals leading to the corresponding thioethers **3** or **4**. The combination of this process with the nickel-catalyzed cross coupling reaction results in the sequential transformation of **1** into substituted allenes **5** or **6** (eqs 3−5).





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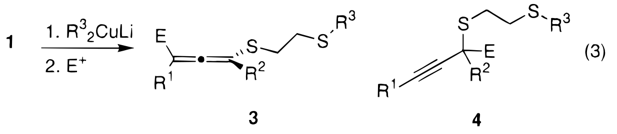
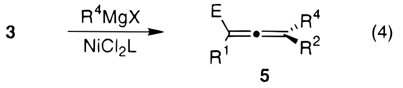
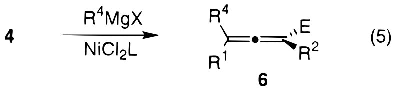
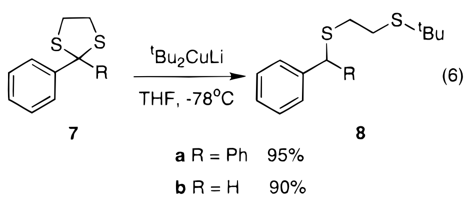


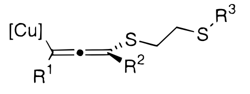




In the beginning of this work, we tested the reactivity of benzylic dithioacetals **7** toward organocopper reagents, Thus, each of **7a** and **7b** was treated with 0.6 equiv of ^{t}Bu$_2$CuLi at −78 °C for 30 min followed by quenching with MeOH to give **8a** and **8b** in 95 and 90% yields, respectively (eq 6). These promising preliminary results demonstrated the first examples of ring-opening reactions of dithiolanes with organocopper reagents.



An extension of this procedure to the reaction of **1a** with the same copper reagent at −78 °C followed by quenching with MeOH at −78 °C gave the corresponding allenyl thioether **3a** in 88% yield. When D_2O was employed to scavenge the reaction, deuterium incorporation at allenyl carbon (C_3) was observed (Table 1, entry 2). On the other hand, when 3 equiv of MeI and 2 equiv of HMPA[7] were introduced at −78 °C instead of adding D_2O, methylation at the propargylic carbon occured to give **4a** (Table 1, entry 7). Representative results are summarized in Table 1. Apparently, allenyl/propargyl organocopper intermediates **9** or **10** are involved in these reactions. It is noteworthy that neither **3** nor **4** reacted further with the organocopper reagent under these conditions.



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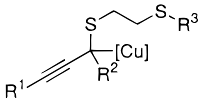

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As can be seen from Table 1, a number of allenyl/parpogylic thioethers **3**/**4** can be easily obtained from the reactions of **1** with organocopper reagents. Sequential

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(1) For reviews, see: (a) Naso, F. *Pure Appl. Chem.* **1988**, *60*, 79. (b) Fiandanese, V. *Pure Appl. Chem.* **1990**, *62*, 1987. (c) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89.

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(3) For example, see: Gassman, P. G.; Gilbert, D. P.; Luh, T.-Y. *J. Org. Chem.* **1977**, *42*, 1340.

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(7) HMPA was essential for the alkylation with MeI or allyl bromide under these conditions (Table 1, entries 7 and 8). The yield was otherwise much lower. (Cf. Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; Chapter 4.)

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Table 1. Reaction of 1 with $R^3{}_2CuLi$ Followed by Treatment with Electrophile (E^+)

entry	substrate	R^1	R^2	R^3	E	product (% yield)
1	**1a**	Ph	Me	^{t}Bu	H	**3a** (88)
2				^{t}Bu	D	**3b** (81)
3	**1b**	Ph	Ph	^{t}Bu	H	**3c** (95)
4				^{n}Bu	H	**3d** (93)
5	**1c**	Bu	Me	^{t}Bu	H	**3e** (82)
6	**1d**	TMS	Me	^{t}Bu	H	**4c** (94)
7	**1a**	Ph	Me	^{t}Bu	Me	**4a** (81)
8				^{t}Bu	$CH_2{=}CHCH_2$	**4b** (80)[a]

[a] Crude yield. The product was used directly for the next reaction.

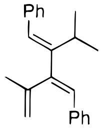
Table 2. $NiCl_2$(dppf)-Catalyzed Cross-Coupling Reactions of 2 or 6 with Grignard Reagents

entry	substrate	R^4MgX	product (% yield)
9	**3a**	MeMgI	**5a** (81)
10	**3e**	PhMgBr	**5b** (67)
11	**3c**	^{i}PrMgBr[a]	**5c** (50)
12	**4a**	$TMSCH_2MgCl$	**6a** (72)
13	**4b**	^{n}BuMgBr	**6b** (62)
14	**4c**	PhMgBr	**6c** (67)
15	**3a**	MeMgI[a]	**11** (52)

[a] $NiCl_2$(dppe) was employed as the catalyst.

treatment of these thioethers with the Grignard reagent in the presence of 5 mol% of $NiCl_2$(dppf) resulted in a convenient synthesis of substituted allenes **5**/**6**. Table 2 summarizes representative examples. As expected,[8] reduction of the C−S bond in **3c** was observed when ^{i}-PrMgBr was employed (Table 2, entry 11).

When $NiCl_2$(dppe) was employed as the catalyst in the coupling reaction of **3a**, the corresponding dimeric product **11** was obtained in 52% yield (Table 2, entry 15). The stereochemistry of **11** was determined by the NOE experiments. Dimerization of **5a** was also achieved in 59% yield upon treatment with MeMgI in the presence of $NiCl_2$(dppe).



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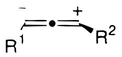

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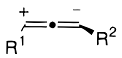

12b

In summary, we have demonstrated for the first time the use of propargylic dithioacetals as allene−1,3-zwitterion synthons **12**. By employing this procedure, di-, tri-, as well as tetra-substituted allenes are thus synthesized conveniently.

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Supporting Information Available: NMR spectra for **3a**−**e**, **4a,c**, **5b**, and **6a**−**c**, **8a,b**, and **11** (14 pages).

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