

Synthesis and Properties of 1-Methylthiopropargylammonium Salts and Their Use as Key Precursors to Sulfur-Containing Ene-diynes

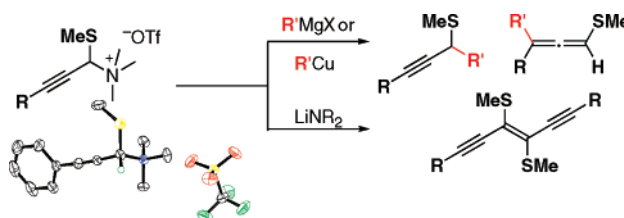
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Received October 12, 2007

ABSTRACT



1-Methylthiopropargylammonium salts were synthesized in a highly efficient manner by reaction of alkynyl *S,N*-acetals with methyl triflate. Reactions of the 1-methylthiopropargylammonium salts with Grignard reagents gave propargyl sulfides or allenyl sulfides, whereas the reaction with organocopper reagents led to exclusive formation of allenyl sulfides regardless of the nature of substituents on the acetylenic carbon. The salts undergo self-dimerization reactions when treated with organolithium and lithium amide bases.

Quaternary ammonium salts are among the most ubiquitous and important classes of organic compounds.¹ Numerous propargylammonium salts have been prepared and utilized as key reactants in synthetic chemistry.² Although the introduction of heteroatom-containing functional groups at the propargylic positions of these substances is expected to provide new and interesting classes of compounds, to the best of our knowledge, no reports describing these substances

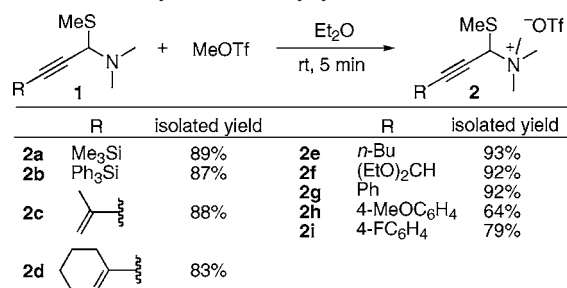
have appeared thus far. During the course of studies of the synthesis and properties of chalcogenoamides,³ we found that relatively stable alkynyl *S,N*-acetals are formed in reactions of thioiminium salts with lithium acetylides.^{3a} Below, we describe the results of recent efforts which show that methylation of alkynyl *S,N*-acetals results in formation of 1-methylthiopropargylammonium salts. In addition, findings made in studies of the chemical and physical properties of these substances and their use as key precursors of sulfur-containing enediynes are reported.

In initial investigations, electrophilic methylation reactions of alkynyl *S,N*-acetals by using a variety of reagents were examined. We observed that reactions promoted by methyl trifluoromethanesulfonate (MeOTf) give good yields of 1-methylthiopropargylammonium salts **2** within 5 min (Scheme 1).⁴ All reactions lead to products in which the nitrogen atom

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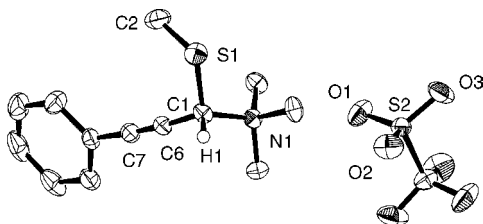
(2) For recent examples of propargylammonium salts, see: (a) Honda, K.; Yasui, H.; Inoue, S. *Synlett* **2003**, 2380–2382. (b) Gevorgyan, A. R.; Chukhadzhan, E. O.; Chukhadzhan, E. O.; Panosyan, G. A. *Chem. Heterocycl. Com.* **2004**, *40*, 177–182. (c) Ryu, E.-H.; Zhao, Y. *Org. Lett.* **2005**, *7*, 1035–1037. (d) Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejovic, E.; Frost, T. M.; Michlich, B.; Frey, W.; Bats, J. W. *Chem. Eur. J.* **2006**, *12*, 5806–5814. (e) Ikeda, M.; Hasegawa, T.; Numata, M.; Sugikawa, K.; Sakurai, K.; Fujiki, M.; Shinkai, S. *J. Am. Chem. Soc.* **2007**, *129*, 3979–3988.

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Scheme 1. Methylation of Alkynyl *S,N*-Acetals **1** with MeOTf

of the starting *S,N*-acetals **1** is methylated. Substituents at the alkynyl carbon of **1**, such as alkyl, aryl, alkenyl, and silyl, do not affect the yields or stabilities of the salts. Purification of **2** is achieved simply by washing with solvents. Elemental analyses of **2a,b,d,g–i**, obtained in this manner, indicate high levels of purity.

X-ray structural analyses of the 1-methylthiopropargylammonium salts (Figure 1) confirm their structures and show

**Figure 1.** Molecular structure of **2g**. Selected intraatomic distances (Å) and angles (deg): S1–C1, 1.805(3); N1–C1, 1.561(3); C1–C6, 1.459(3); C6–C7, 1.190(3); S1–C1–N1, 112.7; C1–S1–C2, 105.6(1), C2–S1–C1–C6, –25.3(2).

that the methyl group in the methylthio moiety and trimethylamino group adopt an almost *anti* conformation with respect to the C–S single bond. In addition, no apparent interaction exists between ammonium cation and triflate anion groups. Finally, the length of the N1–C1 bond in **2g** was found to be 1.56 Å, which is longer than the length of ordinary N–C single bonds (1.47 Å).

The reactivity of the salts **2** toward carbon nucleophiles was examined. The results of reactions with Grignard and organocopper reagents are shown in Table 1. In all cases, substitution reactions with these carbon nucleophiles proceed with elimination of trimethylamine to give propargyl sulfides **3** and/or allenyl sulfides **4**.⁶ For example, reaction of **2a** with

(4) Methylation of propargylamines with MeI is known to give propargylammonium salts,⁵ but alkynyl *S,N*-acetals **1** were inert toward MeI at room temperature and the reaction in refluxing THF results in the formation of complex product mixtures.

(5) (a) Nussbaumer, P.; Leitner, I.; Mraz, K.; Stütz, A. *J. Med. Chem.* **1995**, 38, 1831–1836. (b) Turgunov, E.; Sadikov, M. K.; Nurnakhmedova, T.; Sirlibaev, T. S. *Russ. J. Org. Chem.* **1999**, 35, 1131–1134. (c) Quash, G.; Fournet, G.; Chantepie, J.; Gore, J.; Ardiet, C.; Ardail, D.; Michal, Y.; Reichert, U. *Biochem. Pharm.* **2002**, 64, 1279–1292.

Table 1. Reaction of 1-Methylthiopropargylammonium Salts **2** with Grignard or Organocopper Reagents^a

entry	2	R	R'-M	product	yield ^b
1	2a	Me ₃ Si	PhMg ^c	3a/4a = 84/16	99% (52%)
2	2g	Ph	EtMg ^c	4b	86% (46%)
3			<i>t</i> -BuMg ^d	4c	83% (57%)
4	2a	Me ₃ Si	Bu ₂ Mg ^e	4d	81% (78%)
5	2d			4e	72% (51%)
6	2f	(EtO) ₂ CH		4f	80% (55%)

^a The details of the reaction conditions are included in the Supporting Information. ^b NMR yields. The isolated yields are shown in parentheses.

^c M = MgBr. ^d M = MgCl. ^e M = CuLi·LiI.

PhMgBr gives predominantly propargyl sulfide **3a** along with allenyl sulfide **4a** as a minor product (entry 1). In contrast, reactions of **2g** with Grignard reagents proceed selectively by addition to the alkynyl carbon atom to yield allenyl sulfides **4** (entries 2 and 3). More interestingly, reactions of organocopper reagents with **2** take place exclusively at the alkynyl carbon atom regardless of the substituents present at the alkynyl position (entries 4–6).

The reaction of the salts **2** with lithium reagents was also probed (Table 2).

Table 2. Reaction of 1-Methylthiopropargylammonium Salts **2** with Lithium Reagents^a

entry	2	R	lithium reagent	conditions	product	yield ^b (major:minor) ^c
1	2a	Me ₃ Si	<i>n</i> -BuLi ^d	–20 °C, 1 h then rt, 3 h	5a	79% (75:25)
2	2a	Me ₃ Si	LDA	–55 °C, 45 min then rt, 10 min	5a	90% (75:25)
3	2b	Ph ₃ Si	LDA	–45 °C, 45 min then rt, 10 min	5b	63% (85:15)
4	2c		LHMDS	–45 °C, 15 min then rt, 1 h	5c	40% (68:32)
5	2d		LHMDS	–45 °C, 15 min then rt, 1 h	5d	77% (69:31)
6	2e	<i>n</i> -Bu	LHMDS	–45 °C, 15 min then rt, 1 h	5e	60% (78:22)
7	2g	C ₆ H ₅		–78 °C, 15 min then 0 °C, 1 h	5g	16% (62:38)
8	2i	4-FC ₆ H ₄		–78 °C, 15 min then 0 °C, 1 h	5i	28% (59:41)

^a The details of the reaction conditions are included in the Supporting Information. ^b Isolated yield. ^c Major and minor products correspond to *E* and *Z* isomers of **5**, but it has not been determined which are major products.

^d *n*-BuLi (1 equiv) was used.

At first, we believed that lithium reagents would deprotonate **2** and promote Stevens rearrangements.⁷ However, reaction of **2a** with BuLi gives the enediyne **5a**⁸ (entry 1), in which the starting salt has formally undergone self-

dimerization accompanied by elimination of the proton and trimethylamine from the propargylic carbon. This process can also be performed by using LDA as the base (entry 2). By choosing appropriate bases, it is possible to carry out dimerization reactions of a variety of ammonium salts, having aliphatic, alkenyl, and aromatic groups at the alkynyl carbon (entries 4–8). The stability of the enediyne products is pronouncedly impacted by the nature of substituents at the alkynyl carbon. Those with aromatic groups at this position (e.g., **5g** and **5i**) are labile and gradually decompose even at low temperature.

Reaction of the Ph_3Si -containing salt **2b** under these conditions gives enediyne **5b** as a crystalline solid (entry 3). The molecular structure of **5b**, successfully determined by using X-ray crystallographic analysis (Figure 2), contains

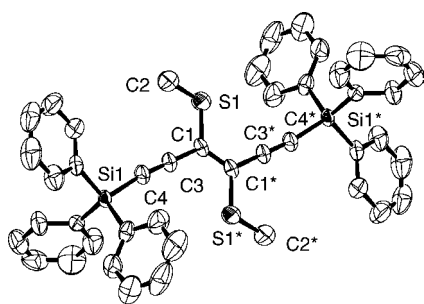
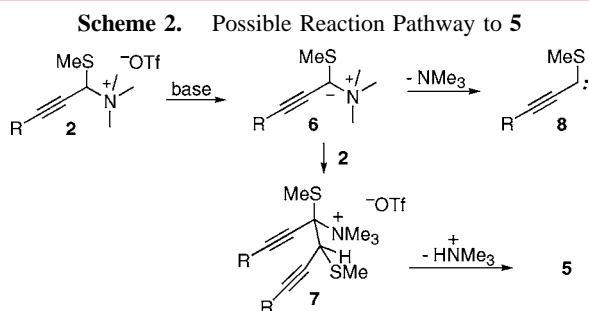


Figure 2. Molecular structure of **5b**. Selected intraatomic distances (Å) and angles (deg): C1–C1*, 1.353(3); C1–C3, 1.421(2); C3–C4, 1.205(2); C1–S1, 1.762(2); S1–C1–C1*, 119.9(1); S1–C1–C3, 118.8(1); C1–S1–C2, 102.9(9); C2–S1–C1–C3, 26.1(2); Si1–C4–C3–C1, –116; S1–C1–C1*–S1*, 180.8.

two silylethynyl groups oriented in the same plane and two methylthio groups with a trans disposition.

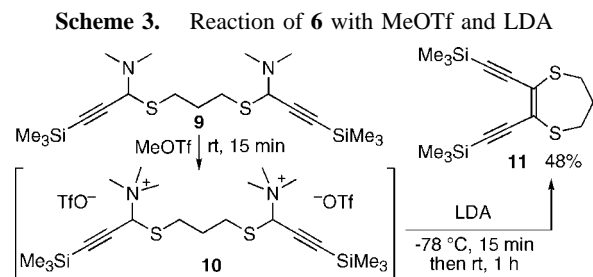
In this dimerization reaction, deprotonation from **2** may initially take place to generate zwitterionic intermediates **6** (Scheme 2). Then, **6** reacts with another molecule of **2**,



followed by the elimination of trimethylammonium, to give **5**.⁹ Alternatively, the carbene intermediates **8**, which have been known to be trapped with styrene to give cyclopropanes,¹² are generated from **6** and may undergo dimerization

to give **5**. However, the present reaction in the presence of styrene did not give cyclopropanes. Therefore, the reaction via carbene intermediates **8** is less plausible.

Finally, an intramolecular counterpart of the dimerization reaction of the methylthiopropargylammonium salts was explored (Scheme 3). The *S,N*-acetal **9** was methylated with



MeOTf to generate the ammonium salt **10**. Addition of LDA to a solution of **10** results in formation **11**, which to our knowledge is the first example of a sulfur-containing cyclic enediyne¹³ and can be a candidate for photochemical Bergman cyclization.¹⁴

In summary, the studies described above have led to the first synthesis of novel 1-methylthiopropargylammonium salts. Preparation of these salts is achieved by selective MeOTf-promoted electrophilic *N*-methylation reactions of alkynyl *S,N*-acetals. Reactions of the salts with a variety of carbon nucleophiles take place to form propargyl and allenyl sulfides. Importantly, lithium amides react in an unprecedented manner with these salts to generate enediynes. Further studies are underway probing the scope and applica-

(6) For recent examples of alkyl propargylsulfides and alkyl allenyl sulfides, see: (a) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172–15173. (b) Huang, X.; Xiong, Z.-C. *Tetrahedron Lett.* **2003**, *44*, 5913–5915. (c) Tsutsumi, K.; Fujimoto, K.; Yabukami, T.; Kawase, T.; Morimoto, T.; Kakiuchi, K. *Eur. J. Org. Chem.* **2004**, 504–510. (d) Shavrin, K. N.; Gvozdev, V. D.; Pinus, I. Y.; Dotsenko, I. P.; Nefedov, O. M. *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 2546–2553.

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(9) Additionally, carbon-centered radicals stabilized by alkynyl, thio and amino groups may be generated from **6** and undergo coupling reaction to give **5**.¹⁰ For the reaction of cyclic oxonium ylides, the formation of homodimers is reported, and the radical coupling process has been proposed.¹¹

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tions of reactions of heteroatom-containing cationic species and cyclic enediynes.¹⁵

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (No. 19020020,

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“Advanced Molecular Transformations of Carbon Resources”) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL7024923