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Preparation of 2,5,7-Trithiabicyclo[2.2.1]heptane from 1,2-Bis-triisopropylsilanylsulfanyl Alkenes

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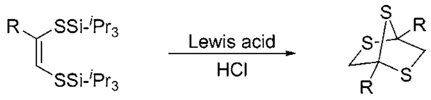
ABSTRACT



1 2

The chemical behavior of 1,2-bis-triisopropylsilanylsulfanyl alkenes 1 is relatively unexplored, and the weak sulfur–silicon bonds give rise to various transformations. Under acidic conditions (HCl) and in the presence of a Lewis acid at room temperature the bicyclic adduct 2 is obtained in good yield. The structure was confirmed by X-ray crystal analysis with R = benzyl.

We have recently shown that substituted 1,3-dithiol-2-ones are readily accessible in good yields from the reaction of **1** with either chlorothiolformate−TBAF[1] or phosgene−$ZnCl_2$.[2] While working on the latter case we also discovered that a mixture of $ZnCl_2$ and HCl led to the formation of an unexpected product if no trapping agent was added. For example, when we combined compound **4**, solid $ZnCl_2$ (0.5 equiv), and concentrated HCl in dichloromethane (0.2 M) for 4 h, we isolated 71% of a white solid from the reaction mixture, whose structure was determined to be 1,4-dibenzyl-2,5,7-trithiabicyclo[2.2.1]heptane, **5**. This was confirmed by X-ray crystal analysis (Figure 1). The starting material for this reaction was readily prepared from a palladium cross-coupling reaction between an alkyne and bis-triisopropylsilyl disulfide **3**.[1] More specifically, treatment of **3** with 3-phenyl-1-propyne and tetrakistriphenylphosphine palladium(0) in refluxing benzene furnished 86% isolated yield of compound **4** (Scheme 1).

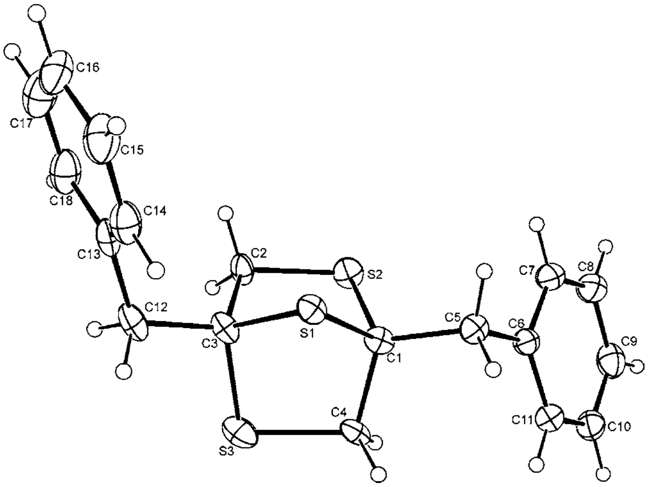


Figure 1. X-ray crystal structure of 1,4-dibenzyl-2,5,7-trithiabicyclo[2.2.1]heptane, **5**.

This type of core is not well-known, and only two molecules of this type have been reported in the literature.

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(1) Gareau, Y.; Tremblay, M.; Gauvreau, D.; Juteau, H. *Tetrahedron* **2001**, *57*, 5739.

(2) Gareau, Y.; Juteau, H. *Phosphorus Sulfur Silicon Relat. Elem.* **2003**, *178*, 5739.

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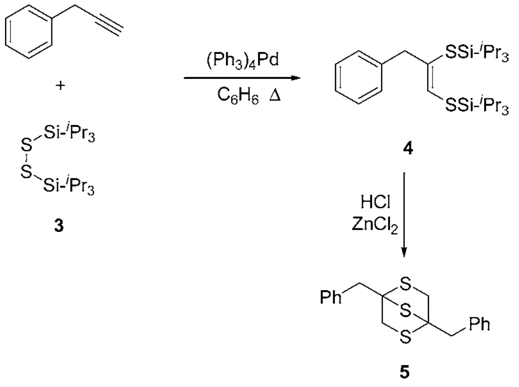
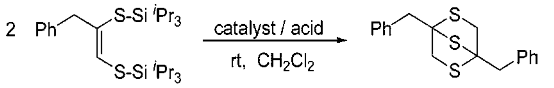
Scheme 1. Preparation of 1,4-Dibenzyl-2,5,7-trithiabicyclo[2.2.1]heptane from 3-Phenyl-1-propyne



They are prepared from the condensation of an α-haloketone and an α-halothioketone with HCl.[3] Until now, this method was the only route to reach these derivatives

For the reaction to proceed efficiently both reagents are required. To demonstrate this, a DCM solution of compound **4** was stirred with 1 N HCl (1.0 M ether) and with $ZnCl_2$ separately at room temperature for 24 h. No deprotection or product formation was observed in both cases. We then started to investigate other Lewis acids, and the results are summarized in Table 1.

Table 1. Preparation of 1,4-Dibenzyl-2,5,7-trithiabicyclo[2.2.1]heptane under Various Lewis Acid Conditions



	catalyst	acid	M	yield (%)	time (h)
1	$ZnCl_2$	HCl	0.2	71	4
2	$Zn(OTf)_2$	HCl	0.2	82	2
3	$Zn(OTf)_2$	HCl	1.0	78	1
4	$Sc(OTf)_3$	HCl	0.2	75	8
5	$In(OTf)_3$	HCl	0.2	82	24
6	$Zn(OAc)_2$	HCl	0.2	47	4
7	$Cu(OTf)_2$	HCl	0.2	<10	1
8	$Mg(OTf)_2$	HCl	0.2	nr	24
9	$Zn(OTf)_2$	HOAc	0.2	*a*	24

[a] Not isolated.

Substitution of $ZnCl_2$ by $Zn(OTf)_2$ improved the yield to 82% and also reduced the reaction time required by half (entry 2). Furthermore, the reaction time could be reduced to 1 h at higher concentration (1.0 M) with the same Lewis acid (entry 3). Two other catalysts that also gave good results were $Sc(OTf)_3$ (entry 4) and $In(OTf)_3$ (entry 5). The first one was somewhat less reactive compared to zinc and required a longer period to go to completion with basically no change on the yield. A similar pattern was observed in the case of $In(OTf)_3$. This catalyst was the slowest of all with a reaction time of 24 h. Nonetheless, we obtained an excellent isolated yield of **5**. On the other hand copper-based catalysts such as $Cu(OTf)_2$ (entry 7) gave poor results. We mainly observed rapid decomposition of the starting material as soon as the catalyst was added. The only catalyst studied that did not work was $Mg(OTf)_2$. In this case no reaction or decomposition occurred.

Clearly, the strength of the Lewis acid has some importance in the reaction outcome. This was best appreciated by comparing three catalysts in the same class, such as $Zn(OTf)_2$, $ZnCl_2$, and $Zn(OAc)_2$. The most acidic catalyst gave the best results in the shortest period of time (entry 2). This was followed by $ZnCl_2$ with 71% in 4 h (entry 5), and the less acidic catalyst $Zn(OAc)_2$ gave the lowest yield with 47% also in 4 h (entry 6).

So far we have always used HCl 1.0 N in ether as the proton source, but the choice of the acid proved to be important. A weak proton supplier such as acetic acid slowed the rate of reaction to a great extent. After 24 h the starting material was totally consumed but only a small amount of product was detected by proton NMR (entry 9).

A series of 1,2 bis-triisopropylsilanylsulfanyl alkenes were prepared and submitted to the conditions of entry 2. The results of this study are reported in Table 2. The reaction proceeded very well with no functionalities attached to the molecule. For example, with R = *tert*-butyl or *p*-tolyl the yield went up to 86% (entry 2) and to 89% (entry 5), respectively. Many functional groups were well tolerated under the reaction conditions, and moderate to high yields of the desired product were produced. Those included acetate (entry 3), methylester (entry 6), imide (entry 7), and terminal alcohol (entry 4). The cyclohexenyl group (entry 8) was more problematic. In fact we only observed decomposition probably coming from polymerization assisted by the conjugated double bond.

Next we investigated a similar substrate that contained only one triisopropylsilanylsulfanyl group to see how it would behave under the same conditions. Compound **6** was easily prepared from *tert*-butylacetylene, triisopropylsilyl mercaptan, and AIBN in refluxing benzene.[4] Accordingly, treatment of **6** with 50 mol % $Zn(OTf)_2$ and 3 equiv of HCl afforded the trithiane adduct **9** in 59% isolated yield, whose structure was confirmed by X-ray crystal analysis. Trithiane formations are well-known to be the result of a trimerization of thioaldehydes formed during the reaction between aldehydes and H_2S in the presence of HCl.[5] To get a thioaldehyde that will provide **9**, a deprotection step assisted by $Zn(OTf)_2$–

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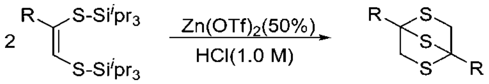
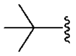
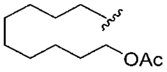
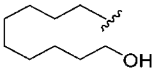
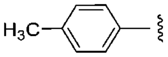
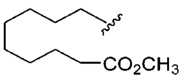
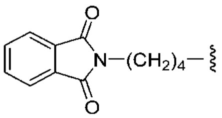
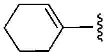
(3) (a) Shagun, L. G.; Papernaya, L. K.; Voronkov, M. G.; Dabizha, O. N.; Sarapulova, G. I.; Timokhina, L. V. *Russ. J. Org. Chem.* **1970**, *35*, 354. (b) Voronkov, M. G.; Shagun, L. G.; Dorofeev, I. A.; Usova, T. L. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *120*, 341. (c) Shagun, L. G.; Dorofeev, I. A.; Kozyreva, O. B.; Usova, T. L.; Voronkov, M. G. *Russ. J. Org. Chem.* **1995**, *31*, 733. (d) O'Connell, A. M. *Acta Crystallogr.* **1967**, *23*, 623. (e) Usov, V. A.; Shagun, L. G.; Belskii, V. K.; Usova, T. L. *Sulfur Lett.* **1992**, *14*, 145. Two more complex molecules were reported with very low yields. (f) Thaler, K. G.; Wurst, K.; Sladky, F. *Inorg. Chim. Acta* **2000**, *304*, 184. (g) Kato, H.; Tani, K. *Heterocycles* **1987**, *26*, 1313.

(4) Beauchemin, A.; Gareau, Y. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, *139*, 187.

(5) Douglass, I. B.; Hyro, W. R. *J. Am. Chem. Soc.* **1951**, *73*, 3507.

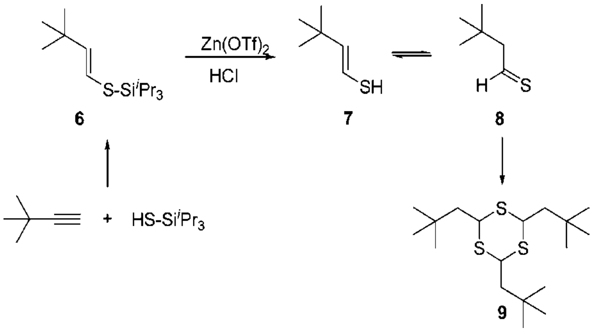
Table 2. Formation of 1,4-Substituted 2,5,7-Trithiabicyclo[2.2.1]heptane



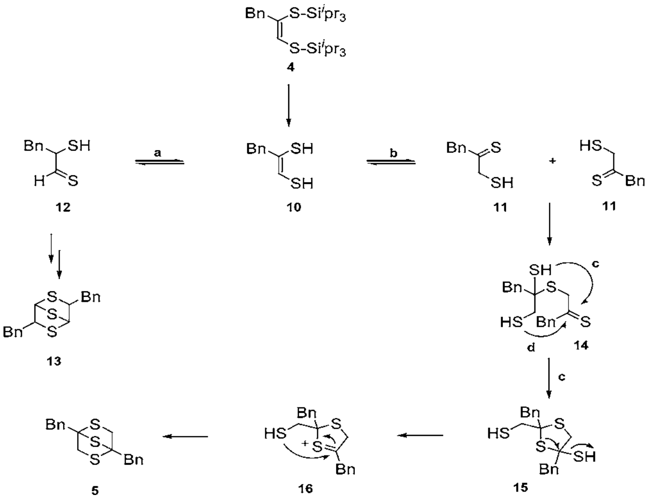
entry	R	yield
1-	benzyl	82%
2-		86%
3-	 OAc	62%
4-	 OH	60%
5-		89%
6-		83%
7-		78%
8-		decomposition

HCl must take place first (Scheme 2). This would lead to the vinyl mercaptan **7** in equilibrium with the thioaldehyde tautomer **8**, which can trimerize to the trithiane **9**. In this example, one can replace HCl by TFA successfully, and the desired product was obtained in 51% after 24 h. On the other hand, HOAc was much less efficient over the same period of time, suggesting that the role of the catalyst involves the removal of the silyl groups assisted by a strong proton source.

Scheme 2. Formation of Trithiane **9** from Mono-triisopropylsilanysulfanyl Alkene **6**



Scheme 3. Proposed Mechanism for the Formation of 1,4-Dibenzyl-2,5,7-trithiabicyclo[2.2.1]heptane



If we apply the same pattern of deprotection to compound **4**, then the formation of **5** can be rationalized according to Scheme 3. The first step is a protiodesilylation of both TIPS groups by Zn(OTf)$_2$−HCl to generate the intermediate **10**. From here, two distinct tautomeric forms could be present in various ratios. We can either go with path **a** or **b**. If we pursue path **b**, the more thermodynamically stable thioketone **11** could condense on a second molecule to produce **14**, which can now intramolecularly cyclize via one of the two thiols. Kinetically, the formation of a five-membered ring via route **c** should be favored, and this would provide the intermediate **15**. After ring closure with the terminal thiol on the thionium, the bicyclic desired adduct is generated. Route **d** would also give the same end result via a six-membered ring. A similar approach applied to tautomer **12** would have generated 3,6-dibenzyl-2,5,7-trithiabicyclo-[2.2.1]heptane **13**, which was not observed.

In conclusion we have shown that 1,2-bis-triisopropylsilanylsulfanyl alkenes are converted efficiently to 2,5,7-trithiabicyclo[2.2.1]heptane by the combination of HCl with various Lewis acid. Our study on the strength of both Lewis and Brönsted acids suggests that the initial deprotection step of triisopropylsilylsulfanyl is achieved by Zn(OTf)$_2$ and HCl prior to condensation.

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

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