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Synthesis of vinyl thioethers and bis-thioethenes from calcium carbide and disulfides

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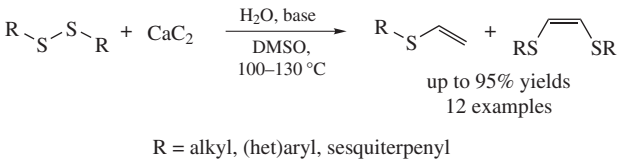
Bis-thioethenes and vinyl thioethers were obtained from the reaction of disulfides and calcium carbide in good to high yields using a simple synthetic procedure and common laboratory setup. The tolerance of the reaction was investigated by the examples of aliphatic, aromatic, heteroaromatic and sesquiterpenic substrates.

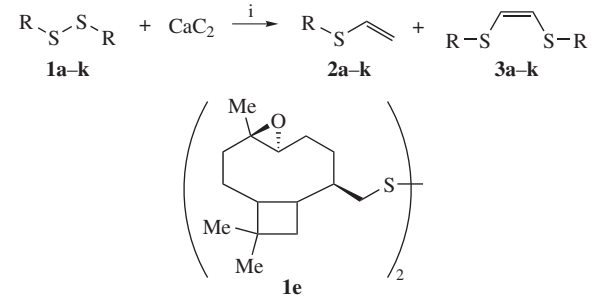


Nucleophilic addition to triple C≡C bond is a key tool to the broad scope of organic compounds and materials.[1] Gaseous acetylene is not widely used in common laboratory technique because of safety and equipment requirements.[2] These limitations motivate searching for its substitute with two *sp* hybridized carbon atoms. Calcium carbide has enormous potential in insertion, addition and click-like reactions.[3] Moreover, it is inexpensive and industrially available.

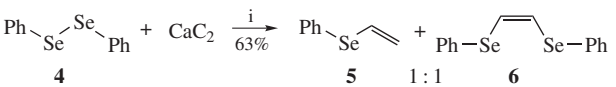
Recently, we have developed a new access to vinyl sulfides through calcium carbide and thiols.[4] Vinyl sulfides can undergo cycloaddition,[5] Heck reaction,[6] hydrosilylation,[7] diimide reduction[8] and asymmetric oxidation.[9] They are also promising precursors to functionalized monomers.[10] Sulfur-containing polymers are used in optoelectronics because of high refractive index.[11] Thioether-containing styrene derivatives were tested in combinatorial screening and biomedical diagnostics,[12] synthesis of gold nanocomposites,[13] and catalysis.[14]

Previously described synthetic procedures for vinyl sulfides require metal catalysts,[15] special synthetic protocols[16] or the use of toxic thiols.[4] Herein, we present an original access to vinyl sulfides through addition of organic disulfides to acetylene generated *in situ* from calcium carbide. Thus, toxic thiols can be replaced with the corresponding disulfides. Disulfides **1** are more suitable for common laboratory practice due to better stability in air and absence of nasty smell. The reaction was carried out in DMSO in the presence of potassium hydroxide and stoichiometric amounts of water on heating in a sealed vessel, no organometal catalyst having been used (DMSO was chosen as a medium since gaseous acetylene is well soluble in it and would evaporate slowly from the solutions[4]). Surprisingly, the reaction afforded, along with expected vinyl thioethers, some bis(1,2-organyl thio)ethenes. Both products were isolated in good total yields after simple isolation procedure (Scheme 1).†

The reaction started also in DMF and mixtures of DMSO and DMF with dioxane, while nonpolar solvents were not suitable. The process required the action of bases, *e.g.*, KOH, which



	R	Total isolated yield (%)	**2** : **3** ratio
a	*n*-dodecyl	93	1 : 0
b	*n*-hexyl	90	1 : 3
c	Bu	60	0 : 1
d	cyclohexyl	64	1 : 1
e	4,5-epoxycaryophyll-9-ylmethyl	95	1 : 1
f	Ph	93	1 : 0
g	4-MeC_6H_4	69	1 : 0
h	4-ClC_6H_4	60	1 : 0
i	4-FC_6H_4	64	1 : 0
j	3-MeC_6H_4	84	1 : 3
k	2-pyridyl	92	1 : 0



Scheme 1 *Reagents and conditions*: i, H_2O, base, DMSO, 100 °C, 3 h. KF (69 mg, 1.2 mmol, 130 °C) or CsF (90 mg, 0.6 mmol) were used as an additive in the cases of **1e** and **4**, respectively.

† *Synthesis of vinyl sulfides*. Potassium hydroxide (67 mg, 1.5 mmol), disulfide **1** (0.4 mmol) and DMSO (1.5 ml) were placed into 8 ml pressure vessel, and the mixture was stirred at room temperature for 20 min. Freshly powdered calcium carbide (256 mg, 4 mmol) and water (144 μl, 8 mmol) were added, the vessel was immediately sealed and heated to 100 °C for 3 h. The mixture was allowed to cool to room temperature and extracted with hexane (3×20 ml). Then, new portions of calcium carbide and water were added into the reaction tube which was sealed and heated again. This operation was repeated twice, and, totally, the product was extracted three times. All hexane extracts were combined and washed with 10% aq. KOH (2×10 ml), brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography on neutralized silica gel (hexane or/and diethyl ether–hexane as the eluents). For further purification, if necessary, the products were bulb-to-bulb distilled *in vacuo* and kept cold under argon. In the case of volatile products, pentane was used for extraction instead of hexane.

For characteristics of the products, see Online Supplementary Materials.

would cleave S–S bond. The thus formed nucleophile adds at triple bond, which leads to vinyl sulfide. On the other hand, acetylene insertion into S–S bond of the disulfide is not impossible. The rates of two reactions depend on the nature of an initial substrate. The vinylation reaction mechanism is known,[17] but the mechanism of insertion reaction is not completely clear. We also found an optimal reactant ratio of $CaC_2 : H_2O : KOH$: disulfide being 4 : 8 : 1.2 : 0.4. Generally, the addition is preferable in the case of excess of calcium carbide. Deficiency of calcium carbide causes incomplete conversion, and some amounts of the starting disulfide remain unchanged. At higher temperatures, destruction of formed vinyl thioethers and bis-thioethenes does occur. To investigate the scope of the reaction, we tested aliphatic, cycloaliphatic, aromatic, heteroaromatic and sesquiterpenoid disulfides‡ (see Scheme 1), with the product composition having been dependent on the nature of the disulfide.

Interestingly, the elongation of aliphatic chain length leads to growth of the vinyl sulfide (products **2a**–**c**) fraction. In the case of diphenyl disulfide **1f** and its *para*-substituted analogues **1g**–**i**, as well as di(2-pyridyl) disulfide **1k**, the vinylated products **2f**–**i**,**k** are exclusively formed. Meantime, with secondary cycloaliphatic (**1d**), sterically hindered terpenoid (**1e**) and *meta*-substituted aromatic (**1j**) disulfides mainly insertion products **3d**,**e**,**j** were obtained; the same phenomenon took place with diphenyl diselenide **4** (see Scheme 1). We also developed the triple vinylation procedure. After the first cycle, the product is extracted, new portions of calcium carbide and water are added, and the reaction is run again. This procedure allows one to raise the product yields by 10–30%.

The structure of compound **3e** was proved with X-ray diffraction analysis (Figure 1).§ According to X-ray analysis data, its double bond has *Z*-configuration.

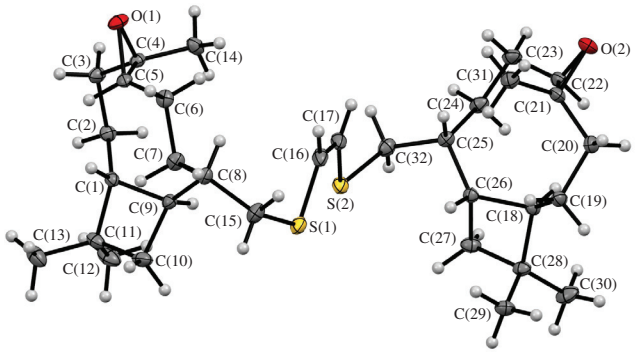


Figure 1 The model of crystal structure of compound **3e**.

‡ Disulfides were commercially available or synthesized from the corresponding thiols. The caryophyllane-containing disulfide **1e** was obtained as described.[18]

§ *X-ray diffraction analysis of* **3e**. A suitable crystal of $C_{32}H_{52}O_2S_2$ **3e** was mounted on an Xcalibur EOS diffractometer. The crystal was kept at 100.0(3) K during data collection. Using Olex2,[19] the structure was solved with the ShelXS[20] structure solution program using Direct Methods and refined with the ShelXL[21] refinement package using Least Squares minimization.

Crystal data for **3e**. $C_{32}H_{52}O_2S_2$, M =532.85, monoclinic, space group $P2_1$ (no. 4), a = 11.8086(3), b = 8.9786(2) and c = 14.7740(4) Å, β = = 98.854(3)°, V = 1547.75(7) Å^3, Z = 2, T = 100.0(3) K, μ(MoKα) = 0.198 mm^{-1}, d_{calc} = 1.143 g cm^{-3}, 19755 reflections were measured (5.326° ⩽ 2θ ⩽ 54.996°), 7132 unique (R_{int} = 0.0271, R_σ = 0.0351) which were used in all calculations, the final R_1 = 0.0343 [$I > 2\sigma(I)$] and wR_2 = = 0.0794 (all data). GOF on F^2 = 1.037; largest diff. peak/hole 0.30/ –0.16 eÅ^{-3}; flack parameter is 0.01(2), peak/hole 2.553/–2.876 eÅ^{-3}.

CCDC 1502546 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Caryophyllane molecular core is known for its biological activity.[22] In particular, being a minor component of essential oils, caryophyllene confers high antiviral properties against herpes viruses of various strains including those resistant to acyclovir,[23] and influenza virus on animal model.[24] Based on these results, we tested caryophyllane derivatives obtained herein for their ability to suppress influenza virus. Cytotoxic and antiviral properties of compounds **2e** and **3e** were tested in MDCK cells against influenza virus A/Puerto Rico/8/34 (H1N1).¶ The compounds under investigation possessed close cytotoxicity. The highest virus-inhibiting activity was demonstrated by **3e** (CC_{50} = 17 μM, IC_{50} = 2 μM, SI = 9). Importantly, the corresponding vinyl thioether **2e** revealed similar toxicity (CC_{50} = 6 μM, IC_{50} = 7 μM, SI = 1) but lack of virus-directed selectivity. This suggests symmetric bis-thioethene **3e** based on caryophyllane scaffold may be further optimized for enhancing antiviral properties. No data on anti-influenza activity of pure caryophyllene *in vitro* are available. For comparison, the values of CC_{50}, IC_{50} and SI for β-caryophyllene against herpes virus type 1 were found to be 35 μg ml^{-1}, 0.25 μg ml^{-1} and 140, respectively.

In conclusion, calcium carbide was successfully employed in new access to vinyl thioethers and bis-1,2-thioethenes. The synthetic procedure is simple and does not require special laboratory equipment. We replaced toxic and easily oxidized thiols with stable disulfides. Cytotoxicity and antiviral activity of selected substrates were estimated.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.09.015.

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