

Silyl methallylsulfonates: efficient and powerful agents for the chemoselective silylation of alcohols, polyols, phenols and carboxylic acids†

Xiaogen Huang, Cotinica Craita, Loay Awad and Pierre Vogel*

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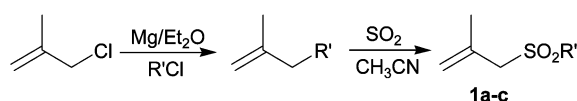
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Alcohols, phenols and carboxylic acids are silylated with very good yields in the presence of silyl methallylsulfonates under non-basic conditions and with the formation of volatile co-products.

Silylation of alcohols, polyols and phenols¹ is one of the most commonly used methods for their protection.² Silylation is a classic way to produce volatile derivatives of polyols, as required for their vapour phase chromatography/mass spectrometric analysis.³ Classical methods of alcohol and phenol silylation involve trialkylsilyl halides⁴ or triflates⁵ in the presence of a stoichiometric amount of a tertiary amine. Other methods employ silazanes,⁶ hexamethyldisilazane,⁷ hydrosilanes,⁸ disilanes,⁹ alkylsilanes,¹⁰ methallylsilanes,¹¹ trimethylsilyl azide,¹² or silylphosphines¹³ in the presence of a suitable catalyst. Because of the co-production of salts or other side-products (catalyst, *etc.*) all these methods necessitate a work-up with, sometimes, a delicate purification step. Quite often, sterically hindered alcohols react only sluggishly. In 1976, Kuwajima and co-workers showed that the silylation of alcohols, aldehydes and ketones can be carried out with ethyl trimethylsilyl acetate in the presence of a catalytic amount of tetrabutylammonium fluoride and without solvent. Apart from tetrabutylammonium salts, the side product is ethyl acetate which is readily eliminated by evaporation.¹⁴

We are presenting here trialkylsilyl methallylsulfonates (Scheme 1) as a new class of silylating agents that react with functionalized, aliphatic, homoallylic, benzylic, phenolic, acidic and sterically hindered hydroxyl groups. Neither base, nor catalyst are required. The co-products are fully volatile (SO₂ and isobutene) thus reducing the work-up of the silyl ethers to solvent evaporation.

Recently we have shown that allyl and 2-substituted allyl (trimethyl)silanes undergo ene reactions with sulfur dioxide and produce the corresponding β,γ -unsaturated silyl sulfonates.¹⁵ For instance, **1a** was obtained by reaction of trimethyl-(2-methallyl)-silane with an excess of SO₂ in CH₃CN at –40 °C and in the presence of 0.2 equiv. of TMSOTf. We now report (Table 1) that



Scheme 1 Ene-reaction of SO₂ with methallylsilanes.

† Electronic supplementary information (ESI) available: experimental section. See <http://www.rsc.org/suppdata/cc/b417894g/>
*pierre.vogel@epfl.ch

1b and **1c** can be prepared by reaction of SO₂ with triethyl- and (*tert*-butyl)dimethyl(2-methallyl)silane, respectively.¹⁶

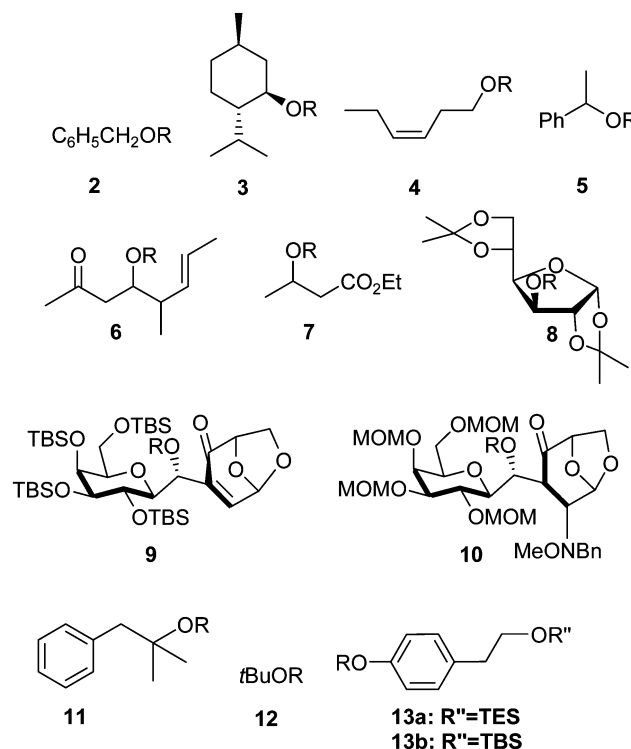
The outcome of silylation reactions of a variety of substrates (Scheme 2), using the reagents **1a–c**, are presented in Table 2. In the presence of one equivalent of **1a–c**, primary and secondary alcohols were silylated completely in less than 5 min in CD₂Cl₂ or CDCl₃ at 20 °C. The reactions were accompanied by fast evolution of SO₂ gas. Acetonitrile and tetrahydrofuran can also be used as solvent.

Compounds with fragile structures, sensitive to acids or bases, survived under our silylation conditions (see *e.g.* **6**,¹⁷ **7**, **8**). The

Table 1 Synthesis of silyl methallylsulfonates **1a–c**

R'(1)	Yield (%)	Temperature
TMS-(1a) ^a	54	–40 °C
TES-(1b)	50	–30 °C
TBS-(1c)	40	–20 °C

^a Obtained as well at 20 °C, in sealed tubes without Lewis acid.



Scheme 2 Variety of hydroxyl groups for silylation reaction (R = H).

Table 2 Silylation of alcohols and phenols; a: R = TMS, b: R = TES, c: R = TBS

Entry	Alcohol	Silyl ether ^a	Entry	Alcohol	Silyl ether ^a
1	2	2a 2b	7	8	8a
2	3	3a 3b 3c^b	8	9	9b^c
3	4	4c	9	10	10b^d
4	5	5b	10	11	11b 11c^e
5	6	6b	11	12	12a 12b 12c^f
6	7	7a 7b	12	13	13ab^g 13bc^h

^a At 20 °C, in CD₂Cl₂ or CDCl₃, with 1.1 equiv. of **1a–c**, obtained with 100% ¹H-NMR yield, in 5 min. ^b 15 min, 1.4 equiv. of **1c**. ^c 89% isolated yield. ^d 92% isolated yield. ^e In 7 h with 1.5 equiv. of **1c**. ^f In 10 h with 1.5 equiv. of **1c**. ^g In THF-*d*₈. ^h In THF-*d*₈, 3 h.

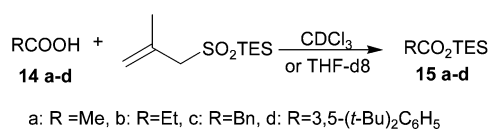
silylation of tertiary alcohols with **1c** was much slower, most probably because of steric hindrance. Nevertheless, the use of a slight excess of reagent led to complete silylation. The excess of reagent **1c** can be destroyed into volatile compounds by adding MeOH at the end of the reaction.

The usefulness of our new silylating reagents is demonstrated once more in the case of unreactive, sterically hindered alcohols **9**¹⁸ and **10**.¹⁹ The semi-protected C-linked disaccharide precursor **9** possesses a secondary alcohol moiety that refused to be silylated to the triethylsilyl ether applying known techniques [e.g.: Et₃SiOTf/lutidine/CH₂Cl₂, 2 days or Et₃SiOTf/pyridine/4-(Me₂N)-pyridine, 2 days]. Heating led to product decomposition. We found that the desired silyl ether can be formed at 25 °C using silylating agent **1b** in CH₂Cl₂. Protection of alcohol **10** as its silyl ether using classical conditions is low yielding because of concurrent β-elimination. With **1b**, the alcohol reacts smoothly forming the corresponding silyl ether with good yield and without the formation of other products.

Triethylsilyl esters are obtained in quantitative yields by treatment of the carboxylic acids **14a–d** with our silylating reagent **1b** (1.1 equiv.), in a few minutes at 20 °C (Scheme 3).

We explored also the ability of our reagents **1a–c** to discriminate between different kinds of hydroxyl groups (primary, secondary, tertiary and phenolic) present in the same substrates. As expected on the basis of steric factors, the reactivity sequence is primary > secondary > tertiary alcohols. In the case of diols **16**, **17** and **18**, exclusive silylation of the primary alcohols was observed using one equivalent of **1b,c**. The greater acidity of phenols *versus* alcohols does not make the former function more reactive than the latter.

Kinetic studies on the reaction *tert*-BuOH(D) + **1c** in CDCl₃ (¹H-NMR, 298 K), showed a first order rate law in *tert*-BuOH(D) (1.5 equiv.) and *k*_H/*k*_D = 1.0 ± 0.05. All silylations with **1a–c** were inhibited by Et₃N (0.05, 0.5, 1.0 equiv.). A few experiments have

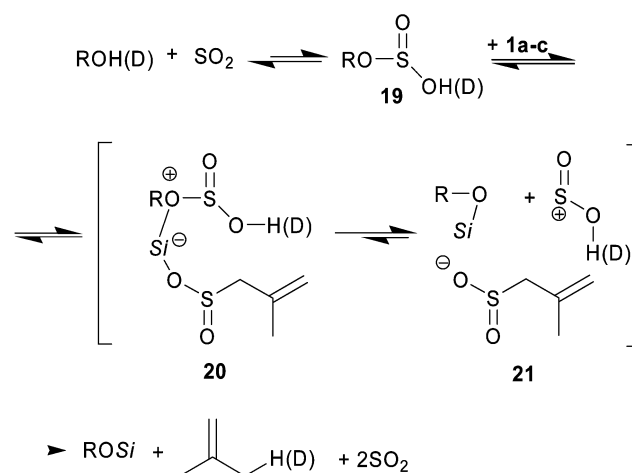
**Scheme 3** Silylation of carboxylic acids.

been done in order to establish which component of the reaction mixture interacts with triethylamine and, thus, slows down the reaction. Firstly, we examined whether the amine generates complexes with the reagents. In the presence of Et₃N (0.05, 0.5, 1.0 equiv.) no formation of complexes of type **1a–c**:Et₃N could be detected by ¹H-NMR. Moreover, no traces of acids (TMSOTf was used to catalyse the synthesis of **1a–c**) were detected by ¹⁹F-NMR; this excludes the acid catalysis in our silylation reaction. We proposed that triethylamine complexes SO₂, which is formed once the silylation takes place. As we shall see a small amount of SO₂ is necessary to catalyze the reaction. This hypothesis was confirmed by the next experiment. Reaction **18** + **1b** → **18b**, which requires usually 0.5 h for initiation, was accelerated on adding at 25 °C a diluted solution of SO₂ in CDCl₃ (Table 3, entry 3).

All these observations are consistent with the mechanism proposed in Scheme 4 in which SO₂ promotes the silylation. Thus, silyl group transfer from **1a–c** to alcohols is slower than

Table 3 Selective silylation of diols with 1 equiv. of **1b** and **1c**

Diol	Product	Conditions
		CD ₂ Cl ₂ , 20 °C, 5 min
		THF- <i>d</i> ₈ , or CD ₃ CN, 20 °C, 5 min
		For OTBS: CDCl ₃ , 20 °C, 4 h For OTES: CDCl ₃ , 20 °C, 2.5 h

**Scheme 4** Possible mechanism of silylation.

from hydrogenosulfites **19** equilibrating with the alcohols and sulfur dioxide. The silyl group transfer might imply the formation of adduct **20** in the rate determining step and it is not assisted significantly by proton transfer. Alternatively, the rate determining step could be the formation of intermediates **21**. In this hypothesis, the silyl group transfer is assisted by the O–S bond breaking of the hydrogenosulfite, but not by proton transfer.

In conclusion we have developed a new method for alcohol, phenol and carboxylic acid silylation which does not require base, or other catalysts, and which generates only volatile co-products reducing the work-up to simple solvent evaporation.

Xiaogen Huang, Cotinica Craita, Loay Awad and Pierre Vogel*

Laboratoire de Glycochimie et de Synthèse Asymétrique, Ecole Polytechnique Fédérale de Lausanne, (EPFL), BCH, CH-1015, Lausanne, Suisse. E-mail: pierre.vogel@epfl.ch; Fax: (+41)216939375; Tel: (+41)216939370

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