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KETENE METHYL TRIALKYLSILYL ACETALS AS EFFECTIVE SILYLATING AGENTS FOR ALCOHOLS, CARBOXYLIC ACIDS, MERCAPTANS, AND AMIDES

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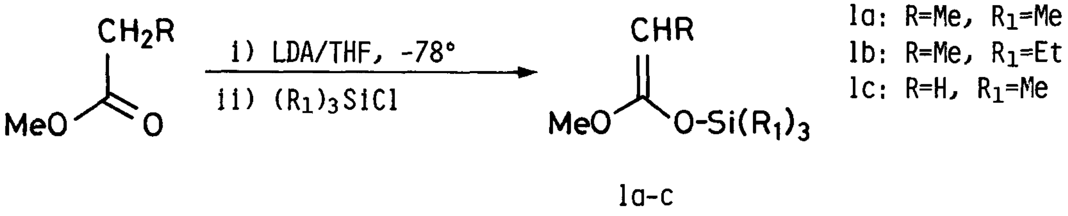
Summary: Silyl-proton exchange reactions with ketene methyl trialkylsilyl acetals proceeded rapidly and quantitatively under mild conditions. The preparative silylation of alcohols, carboxylic acids, mercaptans, and amides is described.

The silylation of organic compounds has been recognized as an important part of organic chemistry and biochemistry, because of the protection of functional groups (ease of recovery of the parent compounds) and of increasing thermal stability, solubility in non-polar solvent and reactivity toward attacking reagents, either at the site of newly introduced silyl substituent or in adjacent positions of the molecule[1]. Silylation of the hydrogen-bonded materials such as alcohols, carboxylic acids, mercaptans, and amides has been reported using chlorosilanes[2], silylamines[3], silylamides[4], silylacetates[5], and silyl ethers[6]. However, these methods have some disadvantages: i) Strong base, acid, or catalyst is usually required in the reactions, ii) A large amount of by-product such as inorganic salt or HCl-amine salt is produced with the moisture-sensitive silyl ethers, esters, or amides, and iii) Product yields are not always very high.

We now report here unique silylating agents, ketene methyl trialkylsilyl acetals (1a,b), which circumvent these disadvantages[7]. The reagents provide the most direct, mild, and effective silylation of alcohols, carboxylic acids, mercaptans, and amides in the absence of base, acid, or catalyst, and allow easy isolation of pure products in almost quantitative yields.

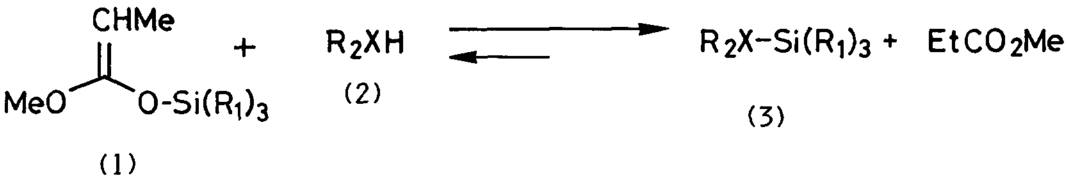
Preparation of ketene methyl trialkylsilyl acetals (1a-c)

Among several methods for preparation of ketene silyl acetals[8], the modification of Ainsworth's method[8a] is desirable for the preparative purpose. Thus, lithio methyl propionate generated from methyl propionate with lithium diisopropyl amide (LDA) was allowed to react with trialkylsilyl chloride to give reasonable yields of the ketene methyl trialkylsilyl acetals (1a-c) as judged by tlc. However, attempts to separate the acetals from diisopropyl amine by distillation of the mixture and also by extraction of the amine with cold aqueous acetic acid failed[9]. Consequently, the pure O-silyl ketene acetal could be obtained by filtering off the resulted quaternary salt of the amine with CH_3I in pentane followed by distillation. The following procedures for the preparation of ketene methyl trimethylsilyl acetal (1a) from methyl propionate is representative: An equimolar amount of n-butyllithium (150 ml of 0.15 M solution in hexane, 225 mmole) was added dropwise with stirring to a solution of diisopropyl amine (22.5 g, 225 mmole) in THF (150 ml) at 0° under argon. Stirring was continued for 15 min under the same conditions and the flask was cooled in a dry ice-acetone bath. Methyl propionate (19.8 g, 225 mmole) was added dropwise, and the mixture was stirred for additional 30 min to complete the formation of lithio methyl propionate. Trimethylsilyl chloride (29.2 g, 270 mmole) was added dropwise with stirring at -78° over 10 min and the mixture was stirred for 3 hrs under the same conditions. CH_3I (42 ml, 675 mmole) and then pentane (100 ml) were added to the mixture. The mixture was kept in a refrigerator overnight and the resulted LiCl and quaternary salt were removed off by filtration. The filtrate was concentrated <u>in vacuo</u> to produce a liquid, which was distilled to give the ketene methyl trimethylsilyl acetal (1a)[10] in 57% yield [bp. 46.3-46.5°/23 mmHg, $\nu_{max}^{CCl_4}$ 1680 cm^{-1}, δ (CCl_4) ppm: 0.20 (s, 9H, $Si(CH_3)_3$), 1.42 (d, 3H, =CH-C$\underline{H}_3$), 3.45 (s, 3H, OCH_3), and 3.56 (q, 1H, =C$\underline{H}$-CH_3)]. Similarly, ketene methyl triethylsilyl acetal (1b) (R=CH_3, R =C_2H_5, bp. 46.3-47°/0.14 mmHg) was prepared in moderate yield.



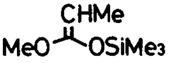
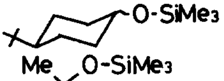
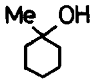
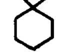
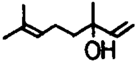
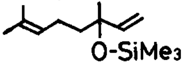
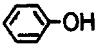
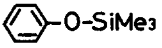
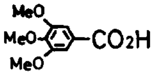
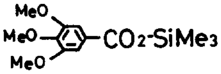
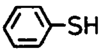
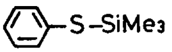
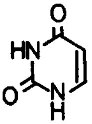
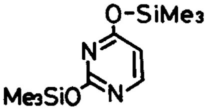
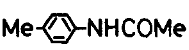
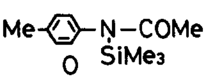
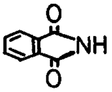
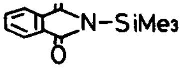
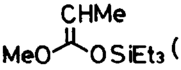
<u>Silylation of alcohols, carboxylic acids, mercaptans, and amides</u>

Silyl-proton transfer between (1) and acceptor molecules (2) is in an equilibrium as shown in the equation. In the case of the reaction with "good" acceptor such as alcohol, carboxylic acid, mercaptan, or amide, the rapidly established equilibrium lies far on the product side, so the silylation proceeds



completely in a short period with the elimination of methyl propionate. In this reaction, only volatile methyl propionate (bp. 79.7°) is accompanied with the desired silylated compound (3) as a by-product. The general procedure of silylation is as follows: A dry flask equipped with a septum inlet, magnetic

Table Conversion of alcohols, carboxylic acids, mercaptans, and amides into silyl ethers, ester, and amides

Entry	Ketene acetals (1)	R_2XH (2)	Product (3)*	Reaction Conditions	Isolated Yields(%)**
1	 $MeOC(=CHMe)OSiMe_3$ (1a)	$C_6H_5CH_2CH_2OH$	$C_6H_5CH_2CH_2O\text{-}SiMe_3$	in CH_3CN 50 min at 50°	95
2				in CH_2Cl_2 30 min at 50°	99
3				in CH_2Cl_2 50 min at 50°	87***
4				in CH_2Cl_2 40 min at 50°	83***
5				in CH_2Cl_2 5 min at 25°	99
6		$C_6H_5CH_2CO_2H$	$C_6H_5CH_2CO_2\text{-}SiMe_3$	in CH_2Cl_2 5 min at 15°	99
7				in CH_3CN 40 min at 25°	99
8		$C_6H_5CH_2SH$	$C_6H_5CH_2S\text{-}SiMe_3$	in CH_2Cl_2 50 min at 50°	97
9				in CH_2Cl_2 5 min at 25°	97
10				in CH_3CN 1.5 hrs at 55°	95****
11				in CH_3CN 10 min at 50°	95****
12				in CH_3CN 10 min at 50°	99****
13	 $MeOC(=CHMe)OSiEt_3$ (1b)	$C_6H_5CH_2CH_2OH$	$C_6H_5CH_2CH_2O\text{-}SiEt_3$	in CH_2Cl_2 2.5 hrs at 50°	92

* The Structures were confirmed by nmr and ir spectral data.

** Purity was checked by tlc, nmr, and ir data.

*** Addition of a catalytic amount of p-TsOH in the mixture accelerated the reaction.

**** The compound is very unstable to moisture.

bar and nujor bubbler was maintained under a constant pressure of argon. The flask was charged with alcohol, carboxylic acid, mercaptan, or amide (2) (5 mmole) in CH_2Cl_2 or CH_3CN (3 ml). To the stirred solution, the acetal (1) (5-20 mmole) was added dropwise by syringe. After stirring for a requisite period at 15-55°, the reaction mixture was concentrated in vacuo to give almost pure silylated product (3), in many cases, which was purified by micro-distillation. A variety of alcohols, carboxylic acids, mercaptans, and amides have been explored. The results are listed in the Table. It is worth noting that tertiary alcohols (entry 3 and 4) as well as other hydrogen-bonding materials (both non-aromatic and aromatic compounds) readily afford the corresponding silyl ethers under these mild conditions.

To date, the ketene silyl acetal has been used as an enol equivalent, which reacts with a variety of electrophiles[8d], but this is the first synthetic use as a silylating agent.

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9 The acetal (1a) has been reported by Ainsworth[8a], but none of the purification procedure, physical data were provided.

10 The corresponding O-silyl ketene acetal (1c) is expected to be a better silylating agent than 1a, but, in this case, considerable ratio of C-silyl acetal is produced besides the desired 1c, and they could not be separated by distillation each other because of azeotropic mixture[8b]. The stereochemistry of 1a was assigned as an E-isomer by the inspection of NMR data.

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