O-Silylated Ketene Acetal Chemistry[1]; A Mild and Efficient t-Butyldimethylsilylating Agent

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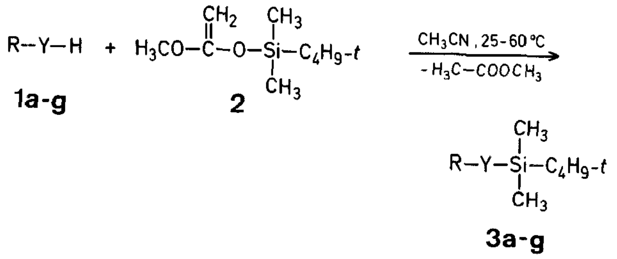
In synthetic organic chemistry, the sterically hindered t-butyldimethylsilyl (TBDMS) group is extremely useful for the protection of hydroxy functions[2–8]. The established procedures for the preparation of TBDMS ethers involve the reaction of an alcohol with (a) t-butyldimethylchlorosilane (TBDCS) in the presence of imidazole in dimethylformamide[2–5], (b) TBDMS perchlorate in the presence of pyridine in acetonitrile[6], (c) TBDCS in the presence of 4-dimethylaminopyridine and triethylamine in dimethylformamide or dichloromethane[7], and (d) TBDCS in the presence of lithium sulfide in acetonitrile[8]. These methods, however, still have some disadvantages. The reaction by method (a) often involves forceful conditions and the yields are not always satisfactory. The perchlorate in method (b) should be handled with great care because of its thermal instability and shock sensitivity, and methods (a–c) should be carried out in basic media. All methods (a–d) need an aqueous work-up and the crude products always contain t-butyldimethylsilanol among other impurities.

In our recent communication[9], we have reported on the extremely useful silylating agents, ketene methyl trialkylsilyl acetals, which provide a ready silylation of H-acidic materials in the absence of base, and allow easy isolation of pure products without aqueous work-up in almost quantitative yields. As an extension of that work, we have explored a new approach to perform t-butyldimethylsilylation of such H-acidic materials **1a–g** using ketene methyl t-butyldimethylsilyl acetal (**2**)[1]. The method was found to be quite useful for the silyl/proton exchange reactions of alcohols, carboxylic acids, mercaptans, phenols, or imides, **1**, particularly for water-sensitive compounds[10].



$$R{-}Y{-}H + H_3CO{-}C(=CH_2){-}O{-}Si(CH_3)_2{-}C_4H_9\text{-}t \xrightarrow[-\,H_3C{-}COOCH_3]{CH_3CN,\ 25\text{-}60\,^{\circ}C} R{-}Y{-}Si(CH_3)_2{-}C_4H_9\text{-}t$$

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Table. *t*-Butyldimethylsilylated Derivatives **3a–g**

Product No.	R—Y—	Reaction conditions Equiv of **2**/ temperature/time	Yield [%][a]	m.p. [°C] (solvent) or b.p. [°C]/ torr[b]	Molecular formula[c] or Lit. b.p./torr	I.R. ($CHCl_3$)[d] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[e] δ [ppm]
3a	$C_6H_5CH_2$—O—	1.2/25 °C/1 h[f]	93 (84)	111.5–112.0°/11.5	58–60°/0.2[8]	1250	0.08 (s, 6H); 0.94 (s, 9H); 4.7 (s, 2H); 7.25 (s, 5H)
3b	*c*-C_6H_{11}—O—	1.5/60 °C/1.5 h[f]	94 (80)	95.0–96.0°/12	57–58°/0.4[8]	1250	0.05 (s, 6H); 0.88 (s, 9H); 1.0–2.0 (m, 10H); 3.4–3.8 (m, 1H)
3c	$C_6H_5CH_2CH_2$—CO—O—	1.0/25 °C/15 min	100 (83)	158.5–159.0°/20	$C_{15}H_{24}O_2Si$ (264.4)	1250; 1700	0.23 (s, 6H); 0.90 (s, 9H); 2.5–3.0 (m, 4H); 7.23 (s, 5H)
3d	C_6H_5—CO—O—	1.0/25 °C/<5 min	92 (80)	126–126.5°/12	$C_{13}H_{20}O_2Si$ (236.4)	1295; 1685	0.37 (s, 6H); 1.01 (s, 9H); 7.3–7.6 (m, 3H); 7.9–8.1 (m, 2H)
3e	C_6H_5—S—	1.0/25 °C/<5 min	92 (72)	120.5–121.5°/12	$C_{12}H_{20}SSi$ (224.4)	1245	0.16 (s, 6H); 0.97 (s, 9H); 7.0–7.5 (m, 5H)
3f	C_6H_5—O—	1.0/0 °C/<5 min	91 (84)	98.5–99.5°/14	$C_{12}H_{20}OSi$ (208.4)	1260	0.14 (s, 6H); 0.94 (s, 9H); 6.6–7.4 (m, 5H)
3g	phthalimidyl	1.0/60 °C/15 min	99 (77)	115.5–117° (CH_3CN)	$C_{14}H_{19}NO_2Si$ (261.4)	1300; 1650	0.52 (s, 6H); 1.00 (s, 9H); 7.6–7.8 (m, 4H)

[a] Yields of isolated products (%) were based on the substrate and the purity of the products (≧95%) was determined by G.L.C. Yields of distilled or recrystallized products are given in parentheses.

[b] Uncorrected boiling points and melting point are given.

[c] The microanalyses of the new compounds were in satisfactory agreement with the calculated values (C, ±0.30; H, ±0.24).

[d] All I.R. spectra were measured with a Hitachi EPI-G2 spectrometer.

[e] All ^{1}H-N.M.R. spectra were measured with a Hitachi R-20A spectrometer with tetramethylsilane as an internal standard.

[f] A catalytic amount of *p*-toluenesulfonic acid was added.

The silylation of the compounds **1a–g** is generally carried out by employing 1.0–1.5 equivalent amounts of the reagent **2** and the substrate **1** in acetonitrile, in a few cases, containing a catalytic amount of *p*-toluenesulfonic acid, and proceeds completely at low temperature within a short period to give the desired silyl/proton exchanged product **3** accompanied by the volatile methyl acetate as the only side product. The structures of **3a–g** were proved by microanalyses, mass, I.R.-, and ^{1}H-N.M.R. spectral data. The results are summarized in the Table. To our knowledge, this is the first example of *t*-butyldimethylsilylation of carboxylic acids, mercaptans, phenols, and imides.

The present method is superior to those reported previously for the *t*-butyldimethylsilylation of hydroxy functions because of the ready availability and stability of the reagent, the mild reaction conditions, the ease of performance and work-up, and the high yields of the product.

Ketene Methyl *t*-Butyldimethylsilyl Acetal (2):

The ketene acetal **2** is obtained according to the reported methods[11,12] and distilled at 76–76.5 °C/24 torr to give a colorless liquid; yield: 72%.

$C_9H_{20}O_2Si$	calc.	C 57.40	H 10.70
(188.3)	found	57.02	10.71

I.R. (CCl_4): ν = 1645 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ = 0.14 [s, 6H, $(H_3C)_2Si$]; 0.93 (s, 9H, *t*-C_4H_9); 2.95 (d, 1H, *J* = 3 Hz, —CH=); 3.10 (d, 1H, *J* = 3 Hz, —CH=); 3.49 ppm (s, 3H, OCH_3).

t-Butyldimethylsilylation of 1a–g; General Procedure:

To a solution of the substrate **1** (5 mmol) in dry acetonitrile (5 ml), the acetal **2** (5–7.5 mmol) is added dropwise from a syringe under argon. In the case of alcohols (**1a** or **1b**), a catalytic amount of *p*-toluenesulfonic acid (0.035–0.2 mmol) is added before addition of **2**. After stirring of the reaction mixture for the requisite period at 25–60 °C, it is concentrated in vacuo to give the almost pure *t*-butyldimethylsilylated compound **3**. In the case of alcohols, an equivalent amount of triethylamine (0.035–0.2 mmol) is added to the solution prior to concentration of the reaction mixture. Pure samples are obtained by recrystallization or distillation under the conditions listed in the Table.

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