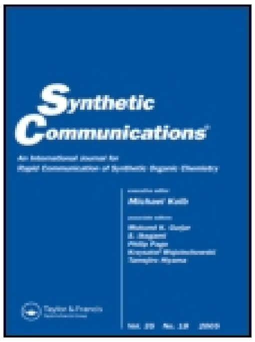

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G. Negrón , F. Vásquezy , G. Calderón , R. Cruz , R. Gaviño & G. Islas

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EFFICIENT DESILYLATION OF SOME NUCLEOSIDE DERIVATIVES WITH POTASSIUM *tert*-BUTOXIDE IN DIMETHYLFORMAMIDE

G. Negrón*, F. Vásquez y G. Calderón

Area de Química Aplicada, Universidad Autónoma Metropolitana-Azcapotzalco, Av. San Pablo No. 180, C. P. 02200, México, D.F., México.

R. Cruz*, R. Gaviño and G. Islas

Instituto de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, 04510, México D.F., México.

Abstract

A new method for deprotecting silyl ethers of nucleosides has been established by using potassium *tert*-butoxide in dimethylformamide at room temperature.

Protection and deprotection of hydroxyl groups as silyl ethers have become one the most popular procedures used in carbohydrate and nucleoside chemistry.[1] The *tert*-butyldimethylsilyl(TBDMS) and the *tert*-butyldiphenylsilyl (TBDPS) ethers are among the most useful protective groups.[2]

The lability of silyl groups towards acids, bases, and fluorine ions can be specifically tuned by varying the substituents on silicon atom *tert*-Butyldimethylsilyl ethers can be cleaved with, for example, tetrabutylammonium fluoride (TBAF), while the cleavage of the more stable *tert*-Butyldiphenylsilyl requires solutions of HF in pyridine, acetonitrile, or even water. However, strong acids and/or TBAF often cause difficulties in the work up and purification of products.[3] Recently combination of water and DMSO,[4] K_2CO_3 in ethanol-water[5] a complex

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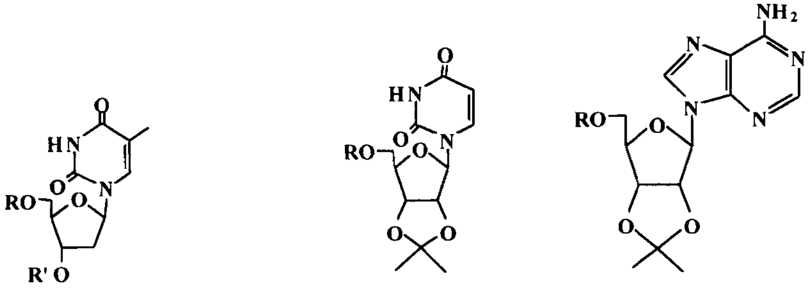

1: R=R' = H
1a: R=TBDMS, R'=H
1b: R=TBDPS, R'=H
1c: R=(Ph)$_3$C, R'=TBDMS
1d: R=(Ph)$_3$C, R'=TBDPS
1e: R=R'=TBDMS
1f: R=R'=TBDPS
1g: R=TBDMS, R'=TBDPS

2: R=H
2a: R=TBDMS
2b: R=TBDPS

3: R=H
3a: R=TBDMS
3b: R=TBDPS

Scheme 1

generated from TBAF and BF$_3$.Et$_2$O,[6] clay in aqueous methanol[7]and sodium sulphide in ethanol[8] have also been used for desilylation.

We herein report, a new method for deprotecting of a variety of nucleoside silyl ethers, it is performed in a mild basic medium, and does not require an aqueous work up.

Removal of the TBDMS and TBDPS groups of **1a-g**, **2a-b**, **3a-b** was accomplished by treatment with potassium *tert*-butoxide in DMF at room temperature to give the thymidine **1**, 2',3'-O-isopropylideneuridine **2** and 2',3'-O-isopropylideneadenosine **3** respectively, scheme **1**.

Silyl groups can be removed from the 5' and 3'-position (**1a-g**, **2a-b**, **3a-b**) with base. However the *t*BuMe$_2$Si are more sensitive to base hydrolysis than the *t*BuPh$_2$Si. For example with 3 equiv. of *tert*-BuOK in DMF at room temperature **1a** is 92% converted to **1** while under the same conditions **1b** was 79% converted to **1**. Compound **2a** was 98% converted to **2** and compound **2b** was only 62% converted to **2** after 0.75 h under the same conditions, indicating that the *t*BuPh$_2$Si is more stable than the *t*BuMe$_2$Si. Experiments with 3',5'-O-silylthymidine (**1e-g**) gave **1** without clear preference for the 5' deprotection, table **1.**

Table 1. Cleavage of Silyl Ethers to Alcohols

Substrate	*t*BuOK (equiv)	**Time** (h)	**Product**	**Yield** (%)[a]
1a	3	24.0	**1**	92
1b	3	2.00	**1**	79
1c	2	1.00	**1**	93
1d	3	1.50	**1**	71
1e	4	1.00	**1**	98
1f	4	1.00	**1**	89
1g	4	1.50	**1**	93
2a	2	0.50	**2**	98
2b	3	0.50	**2**	74
3a	3	0.75	**3**	83
3b	3	0.50	**3**	71

[a]Yield of isolated product

In summary, the mild reaction conditions, non aqueous wok-up required and the goal yields obtained made the present procedure an attractive alternative to cleave silyl ethers.

Experimental

The ^{1}H spectra were recorded in $CDCl_3$ and CD_3OD at 300 MHz on a Varian UNITY-300 S spectrometer and the chemical shift data are reported in parts per million (δ) with tetramethylsilane as internal standard, coupling constants in hertz. Infrared (IR) spectra were recorded on a Nicolet 5-SX FT IR spectrophotometer. Low-resolution mass spectra were determinated with Hewlet-Packard 5985B GC/MS. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX102A mass spectrometer. Thin layer chromatography (TLC) was performed using Merck 60 F254 plates and the spots were detected under UV light (254 nm). Column chromatography was performed using Kieselgel 60, 230-400 mesh ASTM type 9385.

General procedure for desilylating *tert*-butyldimethylsilyl-ether and *tert*-butyldiphenylsilylether. Mixtures of 100 mg of the appropriate substrate, *t*BuOK, and DMF (20 ml) was stirred for indicated periods at room temperature (Table 1). Mixtures were filtered and washed with a 10% $MeOH/CH_2Cl_2$. Combined filtrates were concentrated under reduced pressure, and the product was purified by flash-chromatography on silica gel ($MeOH/CH_2Cl_2$). By products were not isolated or characterized. ^1H NMR, IR spectra and physical on these know compounds were identical with those measured with commercial samples. Protected starting materials have been classically prepared by stirring the nucleoside and the appropriate silyl chloride in DMF and in presence of an excess of imidazole.[9] and were fully characterized by IR, ^1H NMR and mass spectral analysis.

DATA FOR:

1a

Colorless solid,[10] mp 198-199 °C. IR ($CHCl_3$) 3559, 1716, 1677, 1473, 1262, 1124, 841, 782 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.091 (s, 3H, CH_3SiO),0.096 (s, 3H, CH_3SiO), 0.90 (s, 9H, $(CH_3)_3CSi$), 1.89 (d, 3H, J=0.60, 5-CH_3), 2.08 (ddd, 1H, J=5.7, 8.1, 13.5, H-2'), 2.35 (ddd, 1H, 2.7, 5.7, 13.5, H-2"), 3.83 (dd, 1H, J=2.7, 11.4, 5'-H), 3.89 (dd, 1H, J=2.7, 11.4, 5"-H), 4.03 (dt, 1H, J=2.7, 5.7, 4'-H), 4.43 (dt, 1H, J=2.7, 2.7, 3'-H), 6.34 (dd, 1H, J=5.7, 8.1, 1'-H), 7.47 (q, 1H, J=0.60, 6-H), 8.70 (m, 1H, NH). MS: (EI) m/z 357 (M^++1), 281, 145, 81 (100%), 73.

1b

Colorless solid,[11] mp 164-165 °C. IR ($CHCl_3$) 3454, 1703, 1479, 1433, 1281, 1117, 1065, 762, 709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H, $(CH_3)_3CSi$), 1.60 (d, 3H, J=0.65, 5-CH_3), 2.16 (ddd, 1H, J=2.4, 8.2, 13.8, H-2'), 2.43 (ddd, 1H, 2.4, 5.7, 13.8, H-2"), 3.84 (dd, 1H, J=2.8, 11.7, 5'-H), 3.95 (dd, 1H, J=2.8, 11.7, 5"-H), 4.03 (dt, 1H, J=2.4, 2.8, 4'-H), 4.55 (dt, 1H, J=2.4, 2.4, 3'-H), 6.41 (dd, 1H, J=5.7, 8.2, 1'-H), 7.38 (m, 6H, $(Ph)_2SiO$), 7.42 (q, 1H, J=0.65, 6-H), 7.65 (dd, 4H, 4.6, 8.0, $(Ph)_2SiO$), 9.67 (m, NH). MS: (EI) m/z 481 (M^++1), 405 (100%), 199, 81.

1c

Colorless solid, mp 65-66 °C. IR ($CHCl_3$) 3190, 1703, 1479, 1111, 841, 788, 703 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.054 (s, 6H, $(CH_3)_2SiO$), 0.90 (s, 9H, $(CH_3)_3CSi$), 1.52 (d, 3H, J=0.60, 5-CH_3), 2.30 (ddd, 1H, J=2.7, 6.6, 12.6, H-2'), 3.33 (ddd, 1H, 2.7, 6.6, 12.6, H-2"), 3.41 (dd, 1H, J=3.6, 10.8, 5'-H), 3.49 (dd, 1H, J=3.6, 10.8, 5"-H), 3.95 (dt, 1H, J=2.4, 3.6, 4'-H), 4.60 (dt, 1H, J=2.4, 2.7, 3'-H), 6.29 (dd, 1H, J=6.6, 6.6, 1'-H), 7.30 (m, 9H, $(Ph)_3C$), 7.45 (m, 7H, $(Ph)_3C$, 6-H), 7.73 (m, 1H, NH). MS: (CI) m/z 599 (M^++1), 243, 231, 167 (100%), 127. HRMS (FAB) m/z calcd for $C_{35}H_{42}O_5N_2Si$ (M^++1) 599.2941, found 599.2947.

1d

Colorless solid, mp 62-63 °C. IR ($CHCl_3$) 3408, 1690, 1466, 1281, 1177, 749, 709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.016(s, 9H, $(CH_3)_3CSi$), 1.56 (d, 3H, J=0.60, 5-

CH3), 2.03 (ddd, 1H, J=2.7, 5.7, 10.1, H-2'), 2.38 (ddd, 1H, 2.7, 8.1, 10.1, H-2"), 2.89 (dd, 6.0, 10.5, 5'-H), 3.19 (dd, 1H, J=6.0, 10.5, 5"-H), 4.03 (dt, 1H, J=2.4, 2.7, 4'-H), 4.52 (dt, 1H, J=2.4, 6.0, 3'-H), 6.44 (dd, 1H, J=5.7, 8.1, 1'-H), 7.1-7.7 (m, 26H, (Ph)3C, (Ph)2SiO, 6-H), 7.99 (m, 1H, NH). MS: (CI) m/z 723 (M^+1), 243 (100%), 199, 165, 135. HRMS (FAB) m/z calcd for $C_{45}H_{46}O_5N_2Si$ (M^++1) 723.3554, found 723.3239.

1e

Colorless solid,[10] mp 140-141 °C. IR (CHCl3) 3730, 1697, 1479, 1262, 1111, 841, 775 cm^{-1}. ^{1}H NMR (CDCl3) δ 0.058 (s, 3H, CH3SiO),0.065 (s, 3H, CH3SiO), 0.095 (s, 6H, (CH3)2SiO), 0.87 (s, 9H, (CH3)3CSi), 0.91 (s, 9H, (CH3)3CSi), 1.89 (d, 3H, J=0.60, 5-CH3), 1.98 (ddd, 1H, J=2.7, 7.8, 12.9, H-2'), 2.21 (ddd, 1H, 2.7, 5.7, 12.9, H-2"), 3.73 (dd, 1H, J=6.0, 11.7, 5'-H), 3.84 (dd, 1H, J=6.0, 11.7, 5"-H), 3.90 (dt, 1H, J=2.4, 2.7, 4'-H), 4.39 (dt, 1H, J=2.4, 6.0, 3'-H), 6.30 (dd, 1H, J=5.7, 7.8, 1'-H), 7.43 (q, 1H, J=0.60, 6-H), 8.07 (m, 1H, NH). MS: (CI) m/z 471 (M^++1) (100%), 155, 145, 127, 81.

1f

Colorless solid,[12] mp 65-66 °C. IR (CHCl3) 3192, 1703, 1466, 1433, 1281, 1117, 748, 709 cm^{-1}. ^{1}H NMR (CDCl3) δ 0.927 (s, 9H, (CH3)3CSi), 1.073 (s, 9H, (CH3)3CSi) 1.49 (d, 3H, J=0.60, 5-CH3), 1.94 (ddd, 1H, J=2.7, 9.0, 13.2, H-2'), 2.32 (ddd, 1H, 2.7, 5.7, 13.2, H-2"), 3.31 (dd, 1H, J=5.7, 11.4, 5'-H), 3.73 (dd, 1H, J=5.7, 11.4, 5"-H), 3.98 (dt, 1H, J=2.4, 2.7, 4'-H), 4.54 (dt, 1H, J=2.4, 5.7, 3'-H), 6.49 (dd, 1H, J=5.7, 9.0, 1'-H), 7.4 (m, 21H, (Ph)2SiO, (Ph)2SiO, 6-H), 8.57 (m, NH). MS: (FAB) m/z 719 (M^++1), 269, 197, 135 (100%).

1g

Colorless solid, mp 50-51 °C. IR (CHCl3) 3191, 1703, 1473, 1433, 1268, 1104, 834, 709 cm^{-1}.^{1}H NMR (CDCl3) δ -0.13 (s, 3H, CH3SiO), -0.09 (s, 3H, CH3SiO), 0.76 (s, 9H, (CH3)3CSi), 1.06 (s, 9H, (CH3)3CSi) 1.84 (d, 3H, J=1.0, 5-CH3), 1.80 (ddd, 1H, J=6.3, 9.0, 12.9, H-2'), 2.29 (ddd, 1H, 5.4, 6.3, 12.9, H-2"), 3.13 (dd, 1H, J=2.4, 11.4, 5'-H), 3.61 (dd, 1H, J=2.4, 11.4, 5"-H), 3.97 (dt, 1H, J=5.4, 6.3, 4'-H), 4.32 (dt, 1H, J=2.4, 5.4, 3'-H), 6.45 (dd, 1H, J=5.4, 9.0, 1'-H), 7.38 (m, 7H, (Ph)2SiO, 6-H), 7.61 (m, 4H, (Ph)2SiO) 8.44 (m, NH). MS: (EI) m/z 595 $(M+1)^+$, 537, 281 (100%), 197, 135, 89, 73. HRMS (FAB) m/z calcd for $C_{32}H_{46}O_5N_2Si_2$ (M^++1) 595.3024, found 595.3024.

2a

Colorless solid,[13] mp 136-137 °C. IR (CHCl3) 3427, 1703, 1459, 1387, 1117, 1091, 709 cm^{-1}. ^{1}H NMR (CDCl3) δ 0.111 (s, 3H, CH3SiO), 0.115 (s, 3H,

CH_3SiO), 0.925 (s, 9H, $(CH_3)_3CSi$), 1.36 (s, 3H, CH_3C), 1.53 (s, 3H, CH_3C) 3.81 (dd, 1H, J=2.4, 11.4, 5'-H), 3.92 (dd, 1H, J=2.4, 11.4, 5"-H), 4.31 (dt, 1H, J=2.4, 2.7, 4'-H), 4.69 (dd, 1H, J=2.7, 6.0, 3'-H), 4.78 (dd, 1H, J=2.7, 6.0, H-2'), 5.66 (d, 1H, J=8.1, H-5), 6.95 (d, 1H, J=2.7, H-1'), 7.78 (d, 1H, J=8.1, 6-H), 9.1 (m, 1H, NH). MS: (EI) m/z 399 $(M+1)^+$, 341 (100%), 171, 137 (100%), 75, 73. HRMS (FAB) m/z calcd for $C_{28}H_{34}O_6N_2Si$ (M^++1) 523.2264, found 523.2265.

2b

Colorless solid, mp 67-68 °C. IR ($CHCl_3$) 3191, 1697, 1473, 1387, 1091, 828, 709 cm^{-1}. ^1H NMR (CD_3OD) δ 1.06 (s, 9H, $(CH_3)_3CSi$), 1.33 (s, 3H, CH_3C), 1.53 (s, 3H, CH_3C) 3.86 (dd, 1H, J=5.1, 11.4, 5'-H), 3.96 (dd, 1H, J=5.1, 11.4, 5"-H), 4.23 (dt, 1H, J=3.9, 5.1, 4'-H), 4.79 (dd, 1H, J=3.9, 6.3, 3'-H), 4.90 (dd, 1H, J=2.9, 6.3, H-2'), 5.44 (d, 1H, J=8.1, H-5), 5.82 (d, 1H, J=2.9), 7.41 (m, 6H, Ph), 7.64 (m, 5H, Ph, 6-H). MS: (CI) m/z 523 $(M+1)^+$ (100%), 445, 387. HRMS (FAB) m/z calcd for $C_{28}H_{34}O_6N_2Si$ (M^++1) 523.2264, found 523.2265.

3a

Colorless solid, mp 125-126 °C. IR ($CHCl_3$) 3329, 3177, 1650, 1598, 1479, 1381, 1296, 1091, 841, 788 cm^{-1}.^1H NMR ($CDCl_3$) δ -0.029 (s, 3H, CH_3SiO), -0.024 (s, 3H, CH_3SiO), 0.80 (s, 9H, $(CH_3)_3CSi$), 1.36 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C) 3.71 (dd, 1H, J=4.2, 11.4, 5'-H), 3.82 (dd, 1H, J=4.2, 11.4, 5"-H), 4.36 (dt, 1H, J=2.7, 4.2, 4'-H), 4.91 (dd, 1H, J=2.7, 6.3, 3'-H), 5.25 (dd, 1H, J=2.4, 6.3, H-2'), 6.12 (d, 1H, J=2.4, H-1'), 7.99 (s, 1H, H-2), 8.32 (s, 1H, H-8). MS: (FAB) m/z 422 $(M+1)^+$, 364, 218 (100%). HRMS (FAB) m/z calcd for $C_{19}H_{31}O_4N_5Si$ (M^++1) 422.2224, found 422.2225.

3b

Colorless solid, mp 45-46 °C. IR ($CHCl_3$) 3329, 3177, 1651, 1604, 1479, 1433, 1380, 1261, 1117, 1091, 709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (s, 9H, $(CH_3)_3CSi$), 1.35 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C) 3.73 (dd, 1H, J=4.2, 11.1, 5'-H), 3.86 (dd, 1H, J=4.2, 11.1, 5"-H), 4.37 (dt, 1H, J=3.0, 4.2, 4'-H), 4.94 (dd, 1H, J=3.0, 6.3, 3'-H), 5.29 (dd, 1H, J=2.4, 6.3, H-2'), 6.08 (d, 1H, J=2.4, H-1'), 7.31 (s, 1H, H-2), 7.31 (m, 6h, Ph), 7.56 (m, 4H, Ph), 7.93 (s, 1H, H-8). MS: (FAB) m/z 546 (M^++1), 418, 218 (100%). HRMS (FAB) m/z calcd for $C_{29}H_{35}O_4N_5O_4N_5Si$ (M+1) 546.2537, found 546.2544.

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