Facile and highly selective 5′-desilylation of multisilylated nucleosides

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Efficient methods for selective 5′-desilylation of multi-silylated nucleosides are described.

Since its introduction by Stork and Hudrlik,[1] and Corey and Venkateswarlu,[2] the *tert*-butyldimethylsilyl (TBDMS) group has become the most popular and useful hydroxy protecting group in chemical synthesis.[3,4] One of the greatest challenges in this field is the selective deprotection of primary TBDMS groups in the presence of their secondary counterparts, a procedure which has considerable utility for synthetic chemists.[5]

During a recent oligonucleotide study, we needed to synthesize 2′,3′-di-*O*-TBDMS protected nucleosides, which can be prepared *via* the selective 5′-desilylation of the corresponding 2′,3′,5′-trisilylated derivatives. Because of the strong affinity of fluoride ions for silicon and lack of primary/secondary silyl preference, fluoride ion based reagents such as tetrabutyl-ammonium fluoride (TBAF) were not useful. Selective cleavage of primary TBDMS ethers using Lewis acids such as zinc bromide and lithium bromide/18-crown-6 suffers from longer reaction times, higher temperature, low yields and complicated procedures.[6–9]

It is well known that primary silyloxy groups are cleaved under acidic conditions more easily than secondary ones.[5] Ogilvie and co-workers demonstrated that selective 5′-desilylation can be accomplished using 80% aqueous acetic acid with yields up to 75%.[10,11] However, our attempts to partially deprotect *N*[6]-benzoyl-2′,3′,5′-tri-*O*-TBDMS adenosine **1a** with 80% acetic acid resulted in either no reaction (rt, 10 h) or complete deprotection (100 °C, 3 h). When **1a** was treated with acetic acid–H_2O–THF (13:7:3) at rt for 30 h, 2′,5′- and 3′,5′-didesilylation as well as the cleavage of the glycosidic linkage were observed. The poor selectivity of this procedure indicates that aqueous acetic acid is not an ideal reagent for selective 5′-desilylation. Robins *et al*. reported that selective deprotection of the 5′-OH of 2′,5′-di-*O*-TBDMS-3′-keto adenosine was achieved by reaction with aqueous trifluoroacetic acid (TFA).[12] During our preliminary study using aqueous acetic acid we observed that the addition of THF improves the selectivity toward primary silyl ethers. We therefore attempted to modify Robins' method by adding THF as a co-solvent. After extensive investigation of the various combinations of TFA, H_2O and THF, we finally discovered that TFA–H_2O–THF (1:1:4) gives the most satisfactory results at 0 °C. Under these optimized conditions, 2′,3′,5′-tri-*O*-TBDMS nucleosides are quantitatively transformed into the expected 2′,3′-disilylated derivatives and excellent yields of pure products are obtained (Scheme 1, Table 1). The use of THF as co-solvent affords the following benefits: (i) increase of solubility of nucleoside substrates and hence acceleration of the reaction rate; (ii)

Table 1 Selective 5′-desilylation of multisilylated nucleosides by TFA–H_2O–THF (1:1:4)
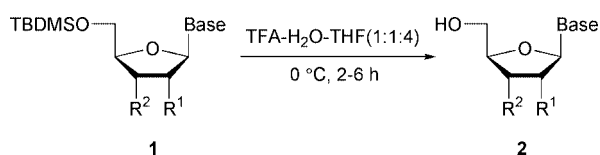
Entry	Base[a]	R[1]	R[2]	Time/h	Yield (%)[b]
1	A[Bz]	OTBDMS	OTBDMS	2	93
2	A	OTBDMS	OTBDMS	3	93
3	G[Bz]	OTBDMS	OTBDMS	3	95
4	G	OTBDMS	OTBDMS	3	96
5	C[Bz]	OTBDMS	OTBDMS	6	90
6	C	OTBDMS	OTBDMS	6	99
7	U	OTBDMS	OTBDMS	6	96
8	A[Bz]	OTBDMS	OH	2	92
9	A[Bz]	OH	OTBDMS	2	86
10	U	OTBDMS	OH	2	87
11	U	OH	OTBDMS	2	81
12	A[Bz]	H	OTBDMS	2	73
13	C	H	OTBDMS	2	85

[a] A[Bz] = *N*[6]-Benzoyladenine, A = adenine, G[Bz] = *N*[2]-benzoylguanine, G = guanine, C[Bz] = *N*[4]-benzoylcytosine, C = cytosine, U = uracil.
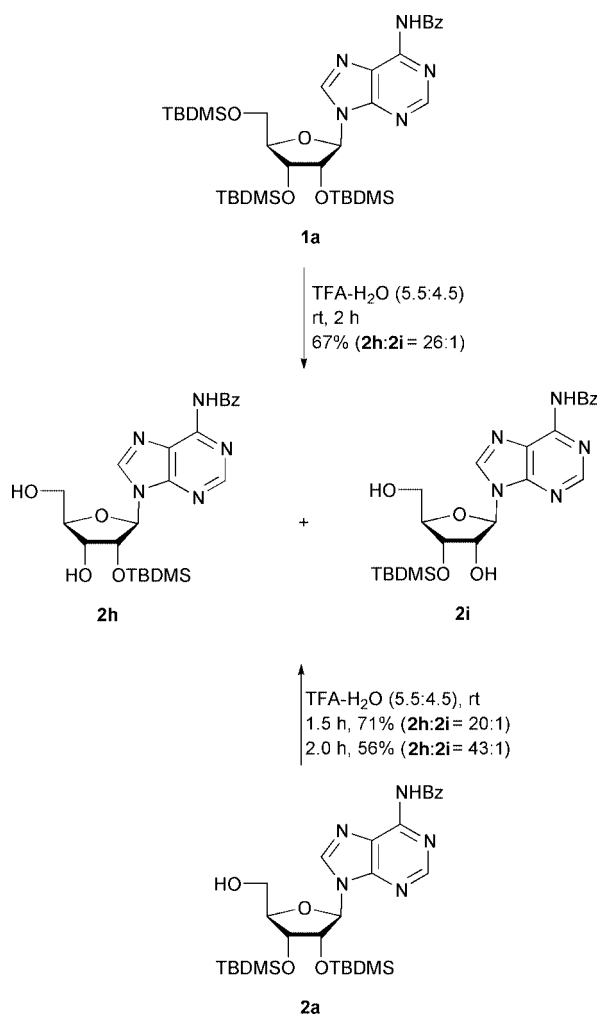[b] Isolated yield characterized by ^{1}H NMR, ^{13}C NMR and MS.

significantly improved selectivity of 5′-desilylation even when the reaction is carried out at rt; (iii) complete absence of depyrimidination and depurination, which are common side-reactions of the acidic hydrolysis of nucleosides.

Greene and Wuts attributed the rationale for Robins' selective desilylation to the reduced basicity of 2′-*O*-TBDMS due to the presence of a 3′-carbonyl group.[4] In our case, since there is no such electron-withdrawing group in the substrates, we reasoned that steric rather than electronic effects may dominate the selectivity of desilylation. The explanation is further supported by simple modeling in which Geistiger–Hückel charges are calculated indicating that 2′-, 3′- and 5′-*O*-TBDMS groups have almost the same charge on their oxygen atoms. On the other hand, the steric environments of these TBDMS groups are quite different. For example, 5′-*O*-TBDMS groups of tri-silylated nucleosides (**1a–g**) are obviously much less hindered than the 2′- and 3′-*O*-TBDMS groups, leading to excellent selectivity in favor of the removal of the 5′-*O*-TBDMS group (entries 1–7). These steric effects are somewhat reduced for disilylated ribonucleosides and deoxynucleosides in which 2′- or 3′-positions have smaller OH (entry 1 *vs*. entries 8–9, entry 7 *vs*. entries 10–11) or H (entries 12–13) moieties, leading to slightly poorer desilylation selectivity and yield.

We also assumed that the 2′-*O*-TBDMS group of 2′,3′,5′-trisilylated or 2′,3′-disilylated nucleosides should be more resistant to acidic hydrolysis than the 3′-*O*-TBDMS group due to the adjacent base of the nucleoside. This assumption was confirmed by treatment of **1a** (Scheme 2) with TFA–H_2O (5.5:4.5) at rt for 2 h which effected removal of the 5′-*O*-TBDMS and 3′-*O*-TBDMS groups to give *N*[6]-benzoyl-2′-*O*-TBDMS adenosine (**2h**) as the major product. Under these conditions, a similar result is obtained starting from **2a**. Extending the reaction time increases the ratio of the desired products (determined by HPLC), but the overall yield is decreased because of didesilylation and depurination.
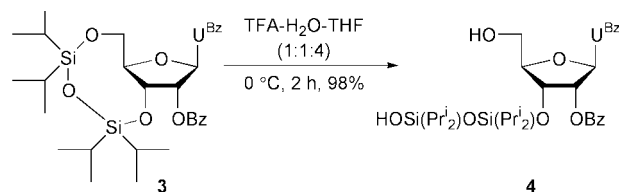

Scheme 1

TBDMSO—Base   TFA-H_2O-THF(1:1:4)   HO—Base
0 °C, 2-6 h
R[2] R[1]   R[2] R[1]
1   **2**

Scheme 2

Scheme 3

an efficient way to synthesize the 2′,3′-disilyl, 2′-monosilyl and 3′-monosilyl nucleosides, which are important building blocks for oligonucleotide synthesis. This method can also be applied to the 5′-end partial cleavage of a TIPDS protected nucleoside and to the best of our knowledge, this is the first example of partial cleavage of the TIPDS group by aqueous TFA. Given the very mild conditions, high regioselectivity and quantitative yield, this procedure provides a practical solution for the synthesis of various protected nucleosides. Further investigations of this methodology in our laboratory are currently underway.

Experimental

Typical procedure for the 5′-desilylation of 2′,3′,5′-tri-O-TBDMS nucleosides (entry 7 of Table 1): to a stirred solution of 2′,3′,5′-tri-O-TBDMS uridine (200 mg) in THF (4 ml) was added aqueous TFA (2 ml, TFA–H_2O = 1:1) at 0 °C. After stirring for 6 h at 0 °C, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and diluted with ethyl acetate (80 ml). After separation, the organic phase was washed with H_2O (10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The residue was subjected to flash chromatography (hexane–Et_2O = 2:1 then Et_2O) to provide 155 mg (96%) of 2′,3′-disilylated product as a white solid.

Acknowledgements

Since Markiewicz developed the 1,1,3,3-tetraisopropyl-disiloxane-1,3-diyl (TIPDS) group for the simultaneous protection of the 3′- and 5′-hydroxy groups of nucleosides,[13] this method has found widespread applications, particularly in carbohydrate and nucleotide chemistry.[3,4] One useful feature of the TIPDS protecting group is that it can be partially cleaved at the 5′-position of 3′,5′-TIPDS protected ribofuranoses using 0.2 M HCl in dioxane–H_2O (4:1)[13] or 1 M HCl in dioxane.[14] However, the cleavage of the 3′-end as well as full deprotection are often unavoidable under these conditions, so that the yields of expected 3′-silylation products are only moderate.[15–17] Markiewicz also mentions that the selectivity of this cleavage can be enhanced when electron-withdrawing groups are present in the 2′-position of nucleosides.[18]

In view of our successful 5′-desilylation of multisilylated nucleosides described above and in order to extend the scope of this procedure, the partial cleavage of TIPDS protected nucleoside 3 was tested using TFA–H_2O–THF (1:1:4) which was optimal for the O-TBDMS analogs. After stirring at 0 °C for 2 h, the expected product 4 was obtained in excellent yield (98%) (Scheme 3). Once again, selectivity is more likely to be the result of steric differences associated with 3′- and 5′-ethers rather than electronic effects. According to our calculations, the charges of the 3′- and 5′-oxygen atoms are almost equal, and replacing the benzoyl ester group at the 2′-position with other groups such as hydroxy and phosphate does not change the electron density.

In conclusion, we have demonstrated here a highly selective 5′-desilylation of multisilylated nucleosides using TFA–H_2O–THF (1:1:4) as a mild deprotection agent. Since the syntheses of 2′,3′,5′-tri-O-TBDMS nucleosides and 2′,5′- and 3′,5′-di-O-TBDMS nucleosides are well established, this method affords

References

1 G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, 1968, **90**, 4462.
2 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
3 P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 1994.
4 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Chemistry*, 3rd edn., John Wiley & Sons, New York, 1999.
5 T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031.
6 F. Seela, J. Ott and B. V. L. Potter, *J. Am. Chem. Soc.*, 1983, **105**, 5879.
7 F. Seela, E. Hiβmann and J. Ott, *Liebigs Ann. Chem.*, 1983, 1169.
8 M. J. Damha and K. K. Ogilvie, *J. Org. Chem.*, 1988, **53**, 3710.
9 M. Tandon and T. P. Begley, *Synth. Commun.*, 1997, **27**, 2953.
10 K. K. Ogilvie, A. L. Schifman and C. L. Penney, *Can. J. Chem.*, 1979, **57**, 2230.
11 K. K. Ogilvie, S. L. Beaucage, A. L. Schifman, N. Y. Theriault and K. L. Sadana, *Can. J. Chem.*, 1978, **56**, 2768.
12 M. J. Robins, V. Samano and M. D. Johnson, *J. Org. Chem.*, 1990, **55**, 410.
13 W. T. Markiewicz, *J. Chem. Res. (S)*, 1979, 24.
14 M. Pfister and W. Pfleiderer, *Nucleosides Nucleotides*, 1987, **6**, 505.
15 X. X. Zhou, A. Nyilas, G. Remaud and J. Chattopadhyaya, *Tetrahedron*, 1987, **43**, 4685.
16 X. X. Zhou, G. Remaud and J. Chattopadhyaya, *Tetrahedron*, 1988, **44**, 6471.
17 M. Pfister, H. Schirmeister, M. Mohr, S. Farkas, K.-P. Stengele, T. Reiner, M. Dunkel, S. Gokhale, R. Charubala and W. Pfleiderer, *Helv. Chim. Acta*, 1995, **78**, 1705.
18 W. T. Markiewicz, *Bull. Pol. Acad. Sci., Chem.*, 1984, **32**, 463.