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Aqueous trifluoroacetic acid—an efficient reagent for exclusively cleaving the 5′-end of 3′,5′-TIPDS protected ribonucleosides†

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Abstract

The 5′-silyl ethers of 3′,5′-TIPDS protected nucleosides can be selectively cleaved in excellent yields (95–99%) by treatment with TFA–H_2O–THF (1:1:4) at 0°C.

Keywords: protection groups; hydrolysis; cleavage reactions; regiospecificity; nucleosides; nucleotides.

The selective protection and deprotection of hydroxyl groups has occupied a unique position on the stage of chemical synthesis.[1] Among numerous methods and reagents that have been developed for this purpose, silyl protecting agents are, without doubt, the most widely used agents for temporarily masking the hydroxyl function.[2] In 1979, Markiewicz introduced the bifunctional 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) group for the synchronous selective protection of the 3′- and 5′-hydroxy groups of the sugar moiety of nucleosides.[3] Since then, this elegant protection method has seen many applications in nucleoside and nucleotide chemistry,[4] general carbohydrate chemistry[5] and even in natural product synthesis.[6]

One particularly valuable feature of the TIPDS protecting group is its ability to be partially cleaved at the less stericly hindered site when hydrolyzed under acidic conditions,[3] a procedure which has significant utility in the synthesis of nucleosides, nucleotides and polysaccharides.[7] However, surprisingly few conditions, such as 0.2 M HCl in dioxane–H_2O (4:1),[3] 1 M HCl in dioxane,[8] and HF–pyridine complex[9] have been reported for achieving this goal over the last two decades. Since the cleavage of the 3′-end as well as full deprotection of TIPDS are often unavoidable under these conditions, yields of the expected 5′-desilylation products are only moderate.

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† Dedicated with respect and affection to Professor Harry Wasserman on the occasion of his 80th birthday.

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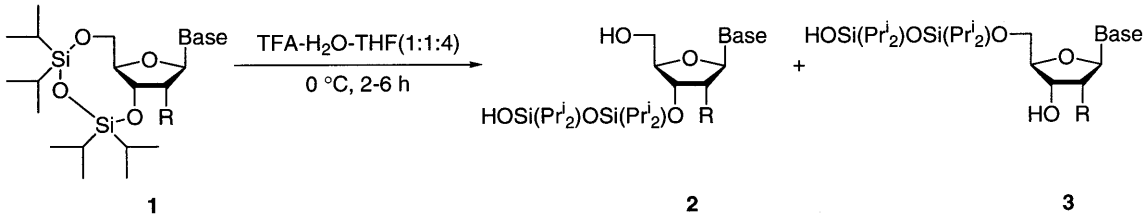
In a preceding communication, we demonstrated that TFA–H_2O–THF (1:1:4) was an efficient reagent for highly selective 5′-desilylation of multisilylated nucleosides.[10] For example, under these optimized conditions, 2′,3′,5′-tri-*O*-TBDMS nucleosides are quantitatively transformed into the 2′,3′-disilylated derivatives. We expected that such a deprotecting system can be usefully exploited for the partial cleavage of a 3′,5′-TIPDS protected nucleoside at its 5′-position. We now report that application of this mild reagent to 3′,5′-TIPDS protected ribonucleosides **1a**–**g** affords exclusively the corresponding 5′-desilylation products **2a**–**g** in excellent yields. No detectable 3′-desilylation product **3** was obtained (Scheme 1).



Scheme 1.

The general experimental procedure for the 5′-desilylation of 3′,5′-TIPDS protected ribonucleosides is as follows: To a stirred solution of 3′,5′-TIPDS ribonucleoside **1a**–**g** (200 mg) in THF (4 mL) was added aqueous TFA (2 mL, TFA:H_2O = 1:1) at 0°C. After stirring for 2–6 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 on silica gel (eluent: CH_2Cl_2:CH_3OH = 100:1 to 100:4) to provide the pure 5′-desilylated product **2a**–**g** as a white solid. The results are summarized in Table 1.

Table 1
Selective 5′-desilylation of 3′,5′-TIPDS protected nucleosides by TFA–H_2O–THF (1:1:4)

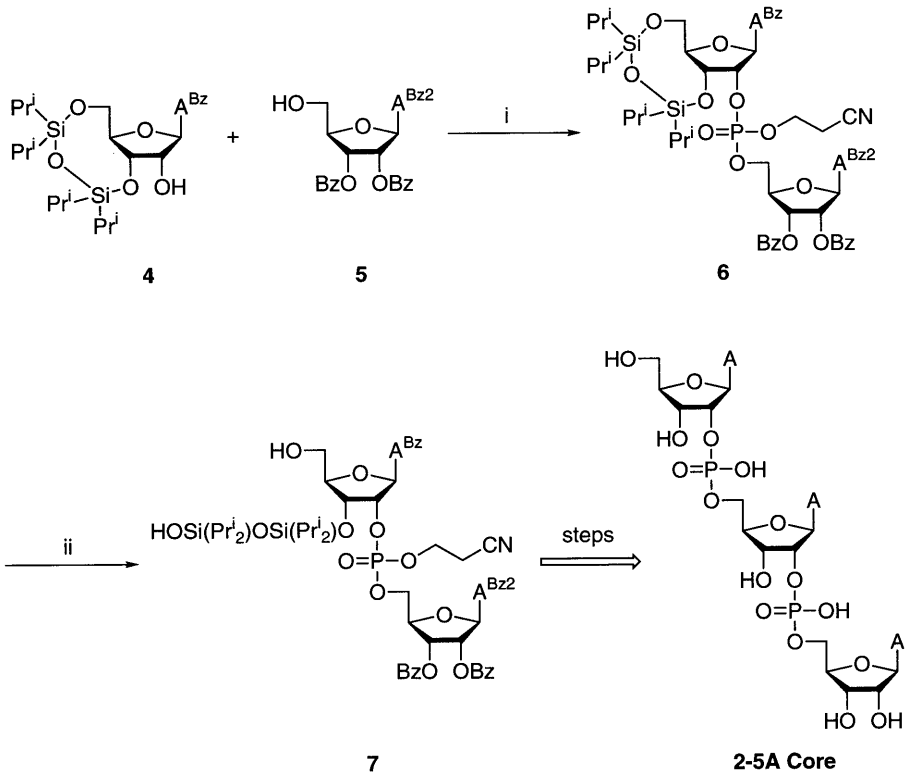
Entry	Substrate	Base[a]	R	Time (h)	Product (yield %[b])
1	**1a**	U^{Bz}	OBz	2	**2a** (98)
2	**1b**	U	OBz	3.5	**2b** (98)
3	**1c**	U	OTBDMS	4	**2c** (95)
4	**1d**	U	Ara-OTBDMS	4	**2d** (99)
5	**1e**	C^{Bz}	OTBDMS	6	**2e** (96)
6	**1f**	G^{Bz}	OTBDMS	4.5	**2f** (99)
7	**1g**	A^{Bz}	OTBDMS	4	**2g** (95)
8	**1h**	A^{Bz}	H	2	**2h** (86), **3h** (12)
9	**1i**	C^{Bz}	H	4	**2i** (74), **3i** (21)

[a] U^{Bz} = 3-*N*-benzoyluracil, U = uracil, C^{Bz} = 4-*N*-benzoylcytosine, G^{Bz} = 2-*N*-benzoylguanine, A^{Bz} = 6-*N*-benzoyladenine.

[b] Isolated yield characterized by ^1H, ^{13}C NMR and MS.

In terms of regioselectivity and efficiency, this mild deprotecting protocol is superior to conventional methods, where mineral acids such as HCl and HF are used. The combination of TFA, H_2O and THF was found to be critical for the success of selective desilylation. We eventually discovered that TFA–H_2O–THF (1:1:4) gives the most satisfactory results at 0°C. Furthermore, the two most commonly employed protecting group in nucleosides, namely the benzoyl group (used to protect both nucleoside base and 2′-hydroxyl), and the *tert*-butyldimethylsilyl (TBDMS) group (used to protect 2′-hydroxyl) were not affected under these hydrolysis conditions. It is noteworthy that substrates **1a**–**g** are also ideal models for multifunctional monosaccharides, in which the TIPDS group may co-exist with benzoyl and TBDMS groups.

In addition to using an organic acid (TFA) and choosing the right combination of TFA–H_2O–THF, the excellent selective cleavage could be explained further by the steric differences associated with 3′- and 5′-end silyl ethers, the primary 5′-ethers being less hindered than the secondary 3′-ethers. The bulky OTBDMS or OBz groups located on the 2′-position of nucleosides make the 3′-end silyl ethers' steric environment even more crowded. As a result, 3′-ethers are much more resistant to acidic hydrolysis than their 5′-counterparts. This explanation was confirmed by the reaction of TFA–H_2O–THF (1:1:4) with the 2-deoxyribonucleosides **1h**–**i** (entries 8–9). Because no functional group exists at the 2′-position, the steric differences between 3′-end and 5′-end silyl ethers are reduced in the **1h**–**i**, leading to relatively lower



Scheme 2. *Reagents and conditions:* (i) (a) **4**, 1*H*-tetrazole (1.2 equiv.), (iPr$_2$N)$_2$POCH$_2$CH$_2$CN (1.2 equiv.), CH_2Cl_2, rt, 7 h, (b) 1*H*-tetrazole (1.2 equiv.), **5** (1.2 equiv.), CH_2Cl_2, rt, 20 h, (c) I_2/THF/H_2O/pyridine, rt, 10 min, 64% overall yield. (ii) TFA–H_2O–THF (1:1:4), 0°C, 4.5 h, 99%

regioselectivity of partial cleavage of the 3′,5′-TIPDS group. However, the 5′-desilylation products **2h–i** are still the major ones and are easily separable by silica gel chromatography.

We also extended the use of this procedure to the selective desilylation of dinucleotide **6**, which is a key step in the synthesis of the known antiviral and anti-tumor agent 2–5A.[11] Dinucleotide **6** was synthesized using a one-pot protocol developed in this laboratory in 64% yield.[12] When **6** was treated with TFA–H_2O–THF (1:1:4) at 0°C for 4.5 h, dinucleotide **7** was obtained in nearly quantitative yield (Scheme 2).

In summary, we have demonstrated that an exclusive 5′-end cleavage of 3′,5′-TIPDS protected nucleosides can be achieved using TFA–H_2O–THF (1:1:4) as a mild deprotecting agent, and other commonly used nucleoside protecting groups such as TBDMS and benzoyl groups can survive under these conditions, thus providing a valuable alternative to conventional deprotecting methods.

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