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Facile Selective Detritylation of 5′-Primary Alcohols of Pyrimidine Nucleosides Using Tetra-*n*-butylammonium Peroxydisulfate

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ABSTRACT

Tetra-n-butylammonium peroxydisulfate has been found to be a good deprotecting reagent for removal of the trityl group: Treatment of 5′-O-dimethoxytrityl uridine or thymidine with tetra-n-butylammonium peroxydisulfate gave the corresponding dedimethoxytritylated nucleosides in excellent yields under neutral and mild conditions and without causing any side reactions such as cleavage of the glycosidic bond. © 1997 John Wiley & Sons, Inc. Heteroatom Chem 8*: 435–438, 1997*

INTRODUCTION

The protection of the 5′-hydroxy functions of nucleosides or nucleotides is important and is used in the preparation of various oligonucleotides. The trityl group and its derivatives have been used extensively to protect hydroxy groups in sugar, nucleoside, and steroid chemistry [1–5], since Khorana introduced the di-*p*-anisylphenylmethyl group for the protection of the 5′-hydroxy functions of 2′-deoxynucleosides [1].

Up to the present time, deprotection reactions of the trityl group have been carried out under acidic conditions by use of CCl_3COOH in CH_3NO_2-MeOH (95:5) [6], CF_3COOH in methylene chloride [7], BF_3OEt_2/MeOH in methylene chloride [8], formic acid in diethyl ether [8], or Lewis acids $ZnBr_2$ [9,10], $AlCl_3$, $ZnCl_2$, and $SnCl_4$ [9]. Dimethoxytrityl ethers are more rapidly cleaved than trityl, or monomethoxytrityl, ethers under acidic conditions [9]. However, the deprotections of dimethoxytrityl and other trityl ethers entail the problem of concomitant glycosidic C–N bond cleavage under acidic conditions.

Recently, we reported that tetra-*n*-butylammonium peroxydisulfate **2** is a good source of the tetra-*n*-butylammonium sulfate radical that has the ability to transform many functional groups [11–13]. We have now found that 5′-*O*-di-*p*-anisylphenylmethyl uridine or thymidine derivatives undergo reaction with tetra-*n*-butylammonium peroxydisulfate in acetonitrile under mild, neutral conditions to give the corresponding dedimethoxytritylated uridine or thymidine nucleosides in good yields.

RESULTS AND DISCUSSION

All of the known methods for detritylations require organic acids or Lewis acids. The present work proceeds smoothly under mild conditions without using any acids at 25–50°C without causing cleavage of glycosidic bonds. To our knowledge, it is the first example of such a selective dedimethoxytritylation in the absence of any acids. The reaction is shown in Scheme 1.

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday.

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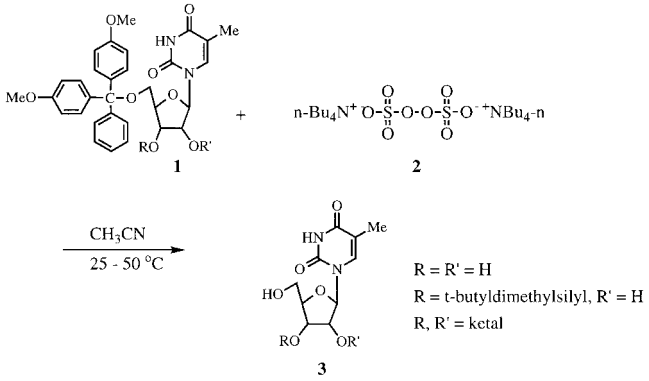
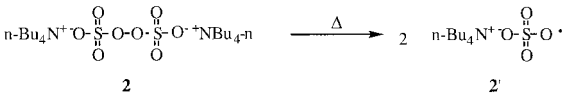


SCHEME 1

In detritylation, it is important to know how to avoid the cleavage of a glycosidic C–N bond of the nucleosides and how to detritylate selectively as against the behavior of other alcohol protectors. Since the present reaction is carried out under mild, neutral, and anhydrous conditions, glycosidic C–N bond cleavage does not occur, and other protecting groups, such as ketals that can easily be hydrolyzed in acidic conditions, survive under the reaction conditions. The results are summarized in Table 1.

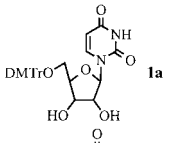
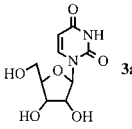
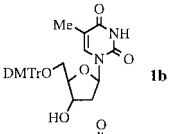
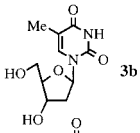
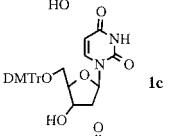
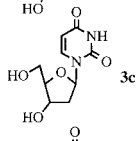
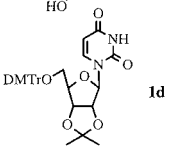
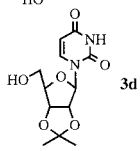
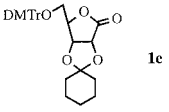
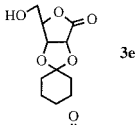
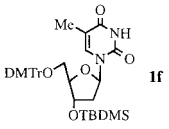
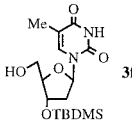
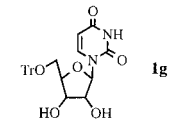
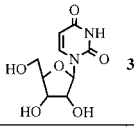
The isopropylidene ketal [14–17] and cyclohexylidene ketal [18] groups that are often used for the protection of alcohols were not affected during the removal of dimethoxytrityl groups (**1d** and **1e**). The *t*-butyldimethylsilyl group was also inert to tetra-*n*-butylammonium peroxydisulfate (**1f**).

The mechanism of this reaction is not clear. The reaction appears to involve a radical mechanism. This reaction does not proceed below 20°C. Homolysis of the peroxydisulfate **2** to the sulfate radical **2′** is known to occur only at higher temperatures:



The sulfate radical is well known to be able to capture one electron from a suitable aryl substrate to form an aryl cation radical [19–21]. A one-electron transfer from a phenyl ring of the trityl moiety to **2′** may form an aryl cation radical intermediate, which then undergoes a cleavage reaction of the C–O bond of the 5′-O ether to form the product **3.** Possibly consistent with this concept, treatment of **1a** with **2** gave di-*p*-anisyl ketone (20%) and *p*-anisylphenyl ketone (60%) as the major co-products of the reaction instead of di-*p*-anisylphenylmethanol.

TABLE 1

run	Substrates	Temp(°C)	Time(h)	Products	Yields(%)[a]
1[b]	 **1a**	25	70	 **3a**	76
		50	2		85
2	 **1b**	25	72	 **3b**	81
		50	2		90
3	 **1c**	50	2	 **3c**	88
4	 **1d**	50	2	 **3d**	93
5	 **1e**	50	2.5	 **3e**	91
6	 **1f**	50	1.5	 **3f**	93
7[c]	 **1g**	80	5	 **3a**	82

a. Isolated yields, b. DMTr : Dimethoxytrityl, c. Tr : Trityl

EXPERIMENTAL

^{1}H NMR spectra were measured by use of Bruker Fourier Transform AC 200 and AM 300 Spectrometers.

Tetra-n-butylammonium Peroxydisulfate **2**

A solution of tetra-*n*-butylammonium hydrogen sulfate (21.2 g, 64 mmol) and potassium persulfate (8.65 g, 32 mmol) in 140 mL of distilled water was stirred for 30 minutes at room temperature. After having been stirred for 30 minutes, the reaction mixture was extracted with 200 mL of methylene chloride three times. The methylene chloride layer was washed with 100 mL of water twice, dried over anhydrous magnesium sulfate, and filtered. The removal of methylene chloride through rotatory evaporation in vacuo gave 20 g of pure white solid (95%). ^{1}H NMR ($CDCl_3$) δ 0.7 (br, 12H), 1.4 (br, 16H), 3.2 (br, 8H); IR (NaCl) 2951, 2874, 1476, 1382, 1263,

1041, 676 cm^{-1}; mp 119°C (dec.); anal. found: C, 56.9; H, 10.8; N, 4.15. Requires: C, 56.7; H, 10.7; N, 4.14.

Dimethoxytrityl Ethers **1**

General Procedure. To a solution of 1 mmol of dimethoxytrityl chloride in dry pyridine was added 1 mmol of alcohol, and the mixture was kept at room temperature until the reaction was completed. Then, the reaction mixture was poured into ice water with vigorous stirring. The precipitates were collected by filtration, washed with ice water, and dried. The product was isolated by column chromatography (solvent: EtOAc/*n*-Hex = 2/1, v/v).

5′-O-(Dimethoxytrityl)uridine **1a.** ^{1}H NMR ($CDCl_3$) δ 3.48–3.54 (br, 2H), 3.63–3.67 (br, 2H), 3.73 (s, 6H), 4.13–4.16 (br, 1H), 4.32 (br, 1H), 4.40 (br, 1H), 5.32 (d, 1H), 5.88 (d, 1H), 6.81 (d, 4H), 7.17–7.38 (m, 9H), 7.99 (d, 1H), 10.4 (br, 1H).

5′-O-(Dimethoxytrityl)thymidine **1b.** ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 2.28–2.39 (br, 2H), 3.18 (br, 1H), 3.36–3.41 (m, 2H), 3.76 (s, 6H), 4.07 (br, 1H), 4.55 (br, 1H), 6.42 (t, 1H), 6.80 (d, 4H), 7.12–7.39 (m, 9H), 7.59 (s, 1H), 9.50 (s, 1H).

5′-O-(Dimethoxytrityl)-2′-deoxyuridine **1c.** ^{1}H NMR ($CDCl_3$) δ 2.18–2.47 (m, 2H), 3.40 (br, 2H), 3.74 (s, 6H), 4.04 (br, 1H), 4.52 (br, 1H), 5.37 (d, 1H), 6.30 (s, 6H), 6.80 (d, 4H), 7.14–7.37 (m, 9H), 7.76 (d, 1H), 9.79 (s, 1H).

5′-O-(Dimethoxytrityl)-2′,3′-isopropylidene Uridine **1d.** ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.54 (s, 3H), 3.41–3.42 (br, 2H), 3.73 (s, 6H), 4.27–4.32 (br, 1H), 4.82 (br, 2H), 5.39 (d, 1H), 5.92 (s, 1H), 6.79 (d, 4H), 7.12–7.37 (m, 9H), 7.56 (d, 1H), 9.83 (s, 1H).

5′-O-(Dimethoxytrityl)-2′,3′-hexylidene-D-ribonic-γ-lactone **1e.** ^{1}H NMR ($CDCl_3$) δ 1.37–1.65 (br, 10H), 3.05–3.11 (br, 1H), 3.65–3.67 (m, 1H), 3.75 (s, 1H), 4.45 (d, 1H), 4.59 (br, 1H), 4.99 (d, 1H), 6.72–6.86 (d, 4H), 7.04–7.38 (m, 9H).

3′-t-Butyldimethylsilyl-5′-O-(dimethoxytrityl)thymidine **1f.** ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H), 0.80 (s, 9H), 1.47 (s, 3H), 2.20–2.31 (m, 2H), 2.87 (d, 1H), 3.21–3.47 (m, 2H), 3.75 (s, 6H), 4.48–4.51 (br, 1H), 6.34 (t, 1H), 6.79 (d, 4H), 7.13–7.41 (m, 9H), 7.64 (s, 1H), 9.66 (s, 1H).

5′-O-trityl Uridine **1g.** ^{1}H NMR ($CDCl_3$) δ 3.44–3.56 (br, 2H), 3.62–3.66 (br, 2H), 4.15–4.18 (br, 1H), 4.37 (br, 1H), 4.43 (br, 1H), 5.33 (d, 1H), 5.87 (d, 1H), 7.17–7.42 (m, 15H), 8.02 (d, 1H), 10.5 (br, 1H).

The Reaction of Dimethoxytrityl Ethers with Tetra-n-butylammonium Peroxydisulfate

General Procedure. To a mixture of 1 mmol of the dimethoxytrityl ether and 2 mmol of tetra-*n*-butylammonium peroxydisulfate was added 2 mL of acetonitrile with vigorous stirring, and the reaction temperature was raised to 50°C. After the reaction had been completed, the reaction solvent was evaporated on a rotatory evaporator. The resulting residue was purified by silica gel column chromatography (solvent: methylene chloride / MeOH = 10/1, v/v) to give the deprotected product **3.**

Uridine **3a.** ^{1}H NMR (DMSO-d_6) δ 3.59 (q, 2H), 3.85 (m,1H), 3.97–4.05 (m, 2H), 5.10 (br, 2H), 5.39 (br, 1H), 5.67 (d, 1H), 5.79 (d, 1H), 7.90 (d, 1H).

Thymidine **3b.** ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3H), 2.02–2.08 (m, 2H), 3.53–3.57 (m, 2H), 3.73–3.74 (m, 1H), 5.02 (t, 1H), 5.21–5.23 (d, 1H), 6.11–6.18 (t, 1H), 7.68 (s, 1H), 11.4 (br, 1H).

2′-Deoxyuridine **3c.** ^{1}H NMR (DMSO-d_6) δ 2.02–2.15 (m, 2H), 3.54–3.59 (m, 2H), 3.78–3.79 (m, 1H), 4.21–4.25 (m, 1H), 5.02 (br, 1H), 5.26 (br, 1H), 5.64–5.67 (d, 1H), 7.86–7.88 (d, 1H), 11.5 (br, 1H).

2′,3′-Isopropylidene Uridine **3d.** ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.37 (s, 3H), 3.50–3.68 (m, 2H), 4.08 (dd, 2H), 4.68 (m, 2H), 5.46 (d, 1H), 5.63 (d, 1H), 7.47 (d, 1H), 10.5 (br, 1H).

2′,3′-Hexylidene-D-ribonic-γ-lactone **3e.** ^{1}H NMR ($CDCl_3$) δ 1.36–1.68 (br, 10H), 2.51 (t, 1H), 3.75–3.82 (m, 1H), 3.93–4.01 (m, 1H), 4.62 (s, 1H), 4.77 (dd, 2H).

3′-t-Butyldimethylsilyl Thymidine **3f.** ^{1}H NMR ($CDCl_3$ with one drop of DMSO-d_6) δ −0.32 (s, 6H), 0.47 (s, 9H), 1.46 (s, 3H), 1.71–1.77 (m, 2H), 2.94 (s, 1H), 3.28–3.34 (m, 2H), 3.66 (br, 1H), 4.05–4.06 (m, 1H), 5.86 (t, 1H), 7.30 (s, 1H), 10.49 (s, 1H).

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