

Notes

Detritylation of Ethers Using Iodine–Alcohol Reagents: An Acid-Catalyzed Reaction

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Trityl (Tr) and dimethoxytrityl (DMTr) ethers are common protecting groups in both carbohydrate and nucleoside chemistry.¹ These protecting groups are typically removed under strong protic or Lewis acid conditions, including formic acid,² TFA,³ ZnBr₂,⁴ or AlClEt₂.⁵ Sensitive substrates, however, frequently undergo acid-catalyzed deglycosylations when subjected to strong protic acids,⁶ and Lewis acid detritylation methods (using ZnBr₂ in CH₃NO₂) require anhydrous conditions for optimal product yields.⁷ Trityl groups are also used to protect thiols by forming *S*-trityl thioether derivatives.

In contrast to trityl ethers, *S*-trityl thioether protecting groups are commonly removed from cysteine residues using methanolic solutions of iodine,⁸ where the oxidizing power of iodine concurrently forms disulfide linkages. To the best of our knowledge, no reports exist on the use of this reagent system for the removal of trityl ethers, although recent reports indicate that acetone,⁹ *p*-methoxybenzyl,¹⁰ and *tert*-butyldimethylsilyl¹¹ protecting groups are removed using solutions of iodine in methanol.

Our work shows that 1% (w/v) solutions of iodine in methanol readily remove trityl and dimethoxytrityl ether groups selectively and in good yield (Scheme 1). The trityl groups are converted to trityl methyl ether and triphenylmethane (60% and 30%, respectively) as shown by GC/MS, although triphenylmethanol (10%) is also formed if the methanol is wet (eq 1). Glycosidic linkages



were shown to be tolerant to these conditions. Both trityl

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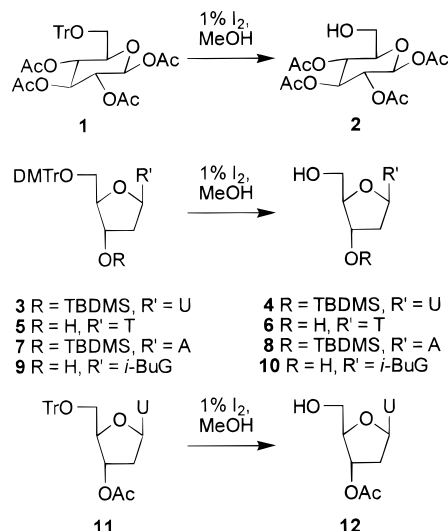
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Scheme 1^a

^a U = uridine; T = thymidine; A = adenosine; *i*-BuG = N²-isobutyrylguanosine.

and dimethoxytrityl groups are selectively removed in the presence of acetate and *tert*-butyldimethylsilyl ether protecting groups at 40 °C. Reflux temperatures promote competitive deprotection of both trityl and TBDMS ethers. The more acid-sensitive (and labile) dimethoxytrityl group is removed more rapidly and at lower temperature than the trityl group.

Two modes of action have been proposed for reactivity of the iodine–methanol system: (1) electrophilic attack of iodine on sulfur⁸ or oxygen⁹ or (2) acid-catalyzed cleavage.^{10,11} Iodine oxidizes methanol to produce small amounts of a variety of products, including methyl iodide, carbon monoxide, and HI.^{12,13} Although the iodine–methanol system produces a complex reaction mixture, we suspected that traces of acids produced by oxidation of methanol by iodine were the main agents responsible for trityl ether cleavage. Iodine can oxidize other primary and secondary alcohols to produce HI. This is supported by the observation that detritylation of **1** was shown to be complete within 6 h in methanol, ethanol, and 2-propanol, as monitored by TLC. The reaction was sluggish in non-oxidizable *tert*-butyl alcohol, requiring 140 h for completion.¹⁴ However, when an equal volume of methanol was added to the *tert*-butyl alcohol, the reaction was completed in 6 h, the same time required to detritylate **1** in methanol alone. Detritylation of **1** did not proceed using a 1% (w/v) solution of iodine in CCl₄, even after 2 weeks at reflux. These results suggest oxidative production of acid as a key factor for trityl ether removal.

The cleavage of *S*-trityl thioethers using iodine in methanol proceeds equally well under acidic, basic, or

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Table 1. Effects of Added Base on Detritylation of **1**

base	mmol base/mmol I ₂	reactn temp (°C)	reactn time (h)
BaCO ₃	0.1	67	116
NaHCO ₃	0.2	67	92
NaF	0.2	67	98
NaOAc	0.2	67	16
DBU	0.1	67	12

neutral conditions.⁸ If electrophilic attack by iodine causes detritylation, trityl ether removal should proceed under basic conditions. However, if acids are responsible for ether cleavage, detritylation should be inhibited by addition of bases. When small amounts of insoluble bases, such as barium carbonate, sodium bicarbonate, or sodium fluoride, were added to the reaction mixture, the detritylation reaction was severely retarded. Table 1 shows the times required for removal of the trityl group, as determined by the disappearance of the starting material using TLC. The insoluble bases were effective because they sequester traces of acid out of solution, rendering them ineffective. After prolonged reaction times, the oxidation of methanol eventually produced enough acid to neutralize the added bases, thus allowing the detritylation reaction to commence. Soluble bases such as DBU were not as effective in stopping the reaction. In contrast to its sulfur counterpart, the deprotection of trityl ethers using solutions of iodine in alcohol is most probably catalyzed by traces of HI (or other acids) and not by direct attack of an electrophilic iodine species on the ether.

Experimental Section

General Remarks. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Chromatography was performed using silica gel (230–400 mesh, EM-9385) purchased from EM Science. Thin-layer chromatography was performed using silica gel plates (EM-5715) purchased from EM Science. Commercial reagents were purchased from Aldrich Chemical Co. and were used without further purification except as noted. Compounds **1**,¹⁵ **3**,¹⁶ **5**,¹⁷ and **7**¹⁸ were synthesized using literature methods. All compounds were characterized by ¹H and ¹³C NMR spectroscopy.

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General Procedure. A typical procedure for detritylation is given by the reaction of **1**. Into a solution of I₂ (20 mg, 0.079 mmol) in methanol (2 mL) was dissolved **1** (0.100 g, 0.17 mmol). The solution was heated to 60 °C, and TLC (ether/petroleum ether, 2:1) was used to monitor the reaction. Upon completion, the solvent was removed on the rotary evaporator, and the resulting residue was dissolved in ethyl acetate (5 mL), washed with 10% sodium thiosulfate (2 mL), followed by water (2 mL), and dried using sodium sulfate. The ethyl acetate extract was concentrated, and the residue was purified by flash chromatography (45 g of SiO₂, ether/petroleum ether, 2:1) to give **2** (50 mg, 84%): mp 128–130 °C (lit.¹⁵ mp 128–129 °C). Melting point data for the detritylation products follow.

4. **3** (149 mg, 0.19 mmol) gave **4** (67.5 mg, 85%) using the standard procedure followed by recrystallization from EtOH/H₂O: mp 198–200 °C (lit.¹⁹ mp 160–170 °C); ¹H NMR (CDCl₃) δ 8.35 (bs, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 6.16 (t, *J* = 6.6 Hz, 1H), 5.74 (d, *J* = 8.1 Hz, 1H), 4.48 (m, 1H), 3.93 (m, 2H), 3.76 (dd, *J* = 3.4, 12.4 Hz, 1H) 2.29 (m, 2H), 1.62 (bs, 1H), 0.89 (s, 9H), 0.09 (s, 6H); ¹³C NMR δ 164.0, 150.7, 141.6, 103.0, 88.2, 87.2, 72.0, 62.4, 41.5, 26.3, 18.6, –4.8, –5.5; EIMS *m/z*²⁰ 343, 285, 231, 187, 173, 155, 147, 139, 117, 101, 81, 75; HRMS *m/z* (M + 1)⁺ 343.1663 (calcd 343.1689).

6. **5** (61.0 mg) gave **6** (19.7 mg, 82%) using the standard procedure: mp 186–187 °C (lit.²¹ mp 187–189 °C).

8. **7** (123 mg, 0.23 mmol) gave **8** (54.1 mg, 80%) using the standard procedure: mp 213–215 °C (lit.²² mp 216–217 °C).

10. **9** (100 mg, 0.16 mmol) gave **10** (45.9 mg, 87%) using the standard procedure: mp darkens > 300 °C (lit.²¹ mp darkens > 300 °C).

12. **11** (135 mg, 0.33 mmol) gave **12** (66.8 mg, 90%) using the standard procedure followed by recrystallization from EtOH/H₂O: mp 174–175 °C (lit.¹⁷ mp 188 °C, recrystallized from cyclohexane/acetone/EtOH); ¹H NMR (CDCl₃) δ 8.49 (bs, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 6.28 (dd, *J* = 6.1, 8.0 Hz, 1H), 5.77 (d, *J* = 8.2 Hz, 1H), 5.35 (m, 1H), 4.12 (m, 1H), 3.94 (m, 2H), 3.51 (bs, 1H), 2.48–2.37 (m, 2H), 2.11 (s, 3H); ¹³C NMR δ 170.5, 163.5, 150.5, 139.9, 102.7, 84.7, 84.1, 74.7, 63.5, 38.3, 21.0; HRMS *m/z* (M + 1)⁺ 270.0843 (calcd 270.0852).

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