O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium Tetrafluoroborate (TBTU): A New Reagent for the Cleavage of Tetrahydropyranyl, Silyl and 4,4'-Dimethoxytrityl Ethers

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Abstract: A new reagent for the cleavage of tetrahydropyranyl, silyl and 4,4'-dimethoxytrityl ethers is described.

Key words: Cleavage, THP, DMT, TBTU

The utility of various protecting groups[1] for the protection of hydroxyl function has been enhanced by the availability of diverse methods for their introduction and removal. Among these, tetrahydropyranyl and *tert*-butyldimethylsilyl groups have been exploited widely in organic synthesis and nucleoside synthetic chemistry. On the other hand, the 4,4'-dimethoxytrityl (DMT) protecting group has been used extensively for the protection of 5'-hydroxyl groups of nucleoside units during oligonucleotide synthesis. Moreover, the facile selective removal of tetrahydropyranyl (THP) and *tert*-butyldimethylsilyl (TBDMS) ethers render them attractive in complex carbohydrate synthesis.

A host of reagents are known for the removal of THP[2-13] and TBDMS[10,14-24] protecting groups. In contrast to THP and TBDMS ethers, DMT ethers are removed only with a handful of reagents.[25-28] We report here a new reagent, *O*-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) which efficiently removes THP, TBDMS and DMT ethers.

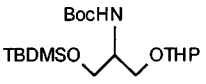
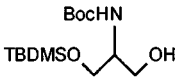
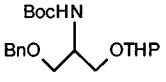
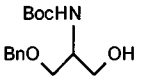
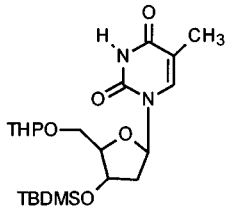
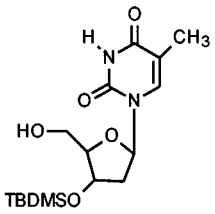
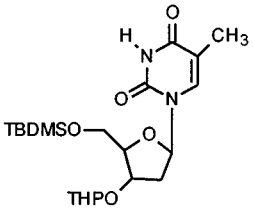
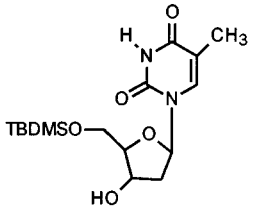
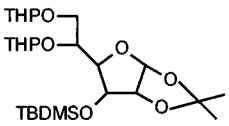
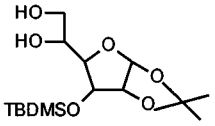
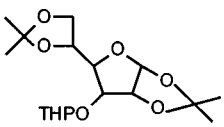
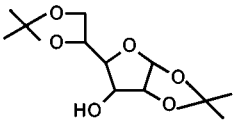
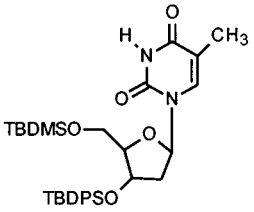
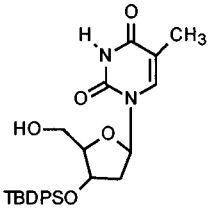
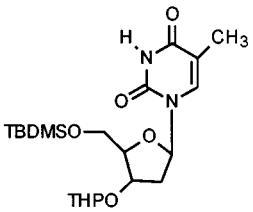
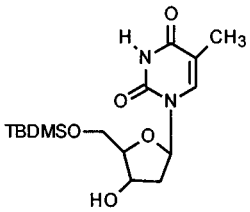
TBTU is a coupling reagent that was developed by Knorr *et al*[29] in 1989. This reagent has been used in peptide coupling reactions with minimum racemization. However, when we used this reagent in a coupling reaction where THP ether was present, we discovered that the THP group was removed quantitatively. This led us to investigate the possibility of utilizing TBTU as an effective reagent for the cleavage of THP ethers. To verify our finding, we reacted the readily available 1-*O*-tetrahydropyranyl-2-(N^{α}-*tert*-butyloxycarbonyl)amino-3-*O*-(*tert*-butyldimethylsilyl)-propane-1,3-diol (entry 1) with 1 equivalent of TBTU in CH_3CN/water mixture. After 12 h of stirring at room temperature, complete removal of THP ether was observed in 90% yield. When the same reaction was tried at 75 °C, the THP group cleaved selectively in 0.25 h. However, heating of the same reaction mixture for 3 h removed not only the THP group but also the TBDMS ether in 75% yield. To test the versatility of the reagent, we synthesized various THP ethers having TBDMS, Bn, Bz, Boc and isopropylidene protecting groups, and studied their cleavage with TBTU. The results are summarized in Table 1.

The deprotection was found to be very selective for the THP ether in the presence of TBDMS ether. As expected, reaction of the substrate (entry 2) with TBTU cleaved the THP group without affecting the benzyl protecting group. Next, we examined the removal of THP group in a sterically hindered environment. Treatment of substrate (entry 3) with TBTU gave the desired product in 93% yield. Moreover, when THP is secondary and TBDMS ether is primary (entry 4), the THP group was removed in 0.5 h selectively. The same trend was noticed in the case of entries 5 and 6. Most remarkably, the THP group was removed in the presence of isopropylidene functionality (entries 5 and 6). We have also observed the selective removal of TBDMS ethers in the presence of *tert*-butyldiphenylsilyl (TBDPS) ethers. TBTU cleaved TBDMS ether selectively in less than 2.5 h (entries 7 & 8). In contrast, the TBDPS group took more than 12 h to remove (data not shown). These results indicate that TBTU can readily differentiate not only THP over TBDMS but also TBDMS over TBDPS derivatives.

During the cleavage of THP ethers, we noticed that TBTU is an effective reagent for the deprotection of DMT ethers too. Thus, when the substrate (Table 2; entry 1) was treated with 1 equivalent of TBTU, the DMT group was removed to give 3'-*O*-*tert*-butyldimethylsilyl-2'-deoxy-β-D-*erythro*-pentofuranosylthymine in 93% yield. To illustrate the utility of TBTU for the deprotection of DMT group, we prepared different substrates having primary and secondary DMT groups and studied their cleavage (see Table 2). In all cases the deprotection reaction went to completion quickly and the products were obtained in high yields. From Table 2 it is clear that DMT groups are cleaved selectively in the presence of TBDMS, isopropylidene and benzyl ethers. Remarkably, even if the DMT ether is secondary and the TBDMS is primary, we did get selectivity (Table 2; entry 2). Furthermore, the DMT group is more readily cleaved than isopropylidene groups (entry 6). However, if the reaction time of entry 5 (Table 2) is extended beyond 0.25 h, the isopropylidene groups are also cleaved.

All the deprotection reactions were found to proceed smoothly in an acetonitrile-water mixture. In contrast, when the reaction was examined in neat acetonitrile, the reactions were sluggish, only producing 50% of the desired cleavage product even under reflux for 16 h. Preliminary investigation suggests that acetonitrile/water (7:3) is the best choice for deprotection reactions with TBTU. In

Table 1 Deprotection of THP and TBDMS Ethers with TBTU

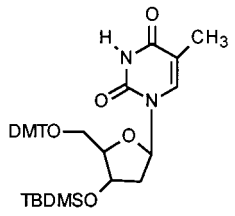
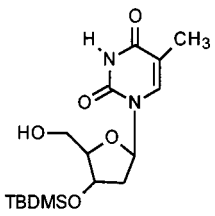
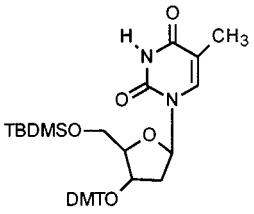
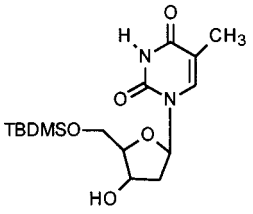
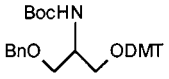
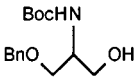
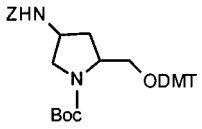
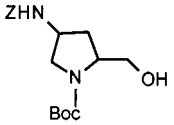
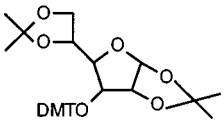
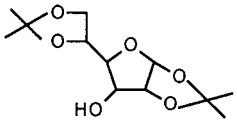
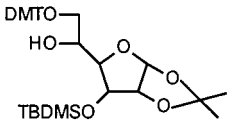
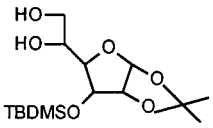
Entry	Substrate	Product[a]	t/h	Yield(%)
1			0.25[b] 12[c]	83 90
2			0.5[b]	95
3			0.5[b]	93
4			0.5[b]	87
5			0.5[b]	91
6			0.5[b]	91
7			1[b]	92
8			2.5[b]	92

[a]All products were identified by ^{1}H NMR and elemental analysis. [b]The reaction was carried at 75° C.
[c]The reaction was carried at room temperature. Bz = Benzoyl, Bn = Benzyl and Boc = *tert*-Butyloxycarbonyl.

other solvents like THF, CH_3OH and CH_2Cl_2, the deprotection does not work well.

We believe that the mechanism of this selective hydrolysis involves the generation of H_3O^+in the reaction medium. BF_4^- that is present in TBTU acts as a source of fluoride ion and Lewis acid (i.e., BF_3). The BF_3 on contact with water decomposes further producing hydrofluoric acid and boric acid.[30] The production of HF and boric acid may be responsible for the deprotection of THP, TBDMS and DMT ethers. In addition, the cleavage of *tert*-butyldimethylsilyl ethers can be rationalized by the donation of fluoride ion from BF_4^- to silicon, directly producing silyl fluoride and OBF_3^-. The OBF_3^- species are further hydrolyzed with water resulting in the formation of the desired alcohol.

Table 2 Deprotection of 4,4'-Dimethoxytrityl Ethers with TBTU

Entry	Substrate	Product[a]	t/h	Yield(%)
1			0.25[c]	93
2			0.25[c]	85
3			2[b]	95
4			0.5[c]	94
5			0.25[c]	85
6			0.15[c]	88

[a]All products were identified by ^{1}H NMR and elemental analysis. [b]The reaction was carried at room temperature. [c]The reaction was carried at 75° C. Bz = Benzoyl, Bn = Benzyl and Boc = *tert*-Butyloxycarbonyl.

In conclusion, we have shown that TBTU is useful for the deprotection of tetrahydropyranyl, silyl ethers, and 4,4'-dimethoxytrityl groups. This reagent allows the removal of THP ether in the presence of TBDMS group as well as the selective cleavage of DMT functionality over TBDMS ether. This selectivity is of use in a variety of synthetic schemes.

General Procedure for Deprotection reactions: To a stirred solution of the substrate (0.15 mmol) in acetonitrile/water (7:3; 10 ml) was added *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetra-fluoroborate (TBTU; 50 mg, 0.15 mmol). The reaction mixture was placed in a preheated oil bath at 75 °C and stirred at that temperature. The reaction was monitored by tlc. After the reaction was complete, the reaction mixture was immediately cooled, quenched with 5% sodium bicarbonate solution (5 ml) and evaporated to dryness. The residue was extracted with suitable solvent, and the organic extract was washed with brine, dried and evaporated. The crude material was crystallized in a suitable solvent or purified by flash chromatography to give the pure product. The product that obtained was identical with an authentic sample by tlc, ^{1}H NMR and C, H, N analysis.

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