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Removal of Cyclic Di-*t*-butylsilanediyl Protecting Groups Using Tributylamine Hydrofluoride (TBAHF) Reagent

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Cyclic di-*t*-butylsilanediyl protecting groups were rapidly and cleanly removed from 3',5'-cyclic silanediyl nucleosides by a mild and convenient reagent, tributylamine hydrofluoride in tetrahydrofuran.

Recently Trost[1)] and Corey[2)] introduced di-*t*-butylsilanediyl (DTBS) group as a bifunctional protecting group in organic synthesis. The bifunctional protecting groups are expected to be useful in selective transformation of polyhydroxy compounds.

We have already reported the formation of 3',5'-*O*-dialkylsilanediyl nucleosides, new silane-analogues of cyclic nucleotides, in the reaction of deoxyribonucleosides and dialkyldichlorosilane.[3)] DTBS groups introduced between the 3' and 5' positions of deoxyribonucleosides were more durable to acidic or basic treatment in 80% acetic acid or conc NH_3-MeOH than other bifunctional silyl protecting groups such as diisopropylsilanediyl[2)] and tetraisopropyldisiloxane-1,3-diyl (TIPDS) groups.[4)] This fact means DTBS group is promising as a protecting group in nucleic acid chemistry.

Diisopropylsilanediyl and TIPDS groups, as well as monofunctional silyl protecting groups, can be removed smoothly using tetrabutylammonium fluoride (TBAF) in THF. On the other hand, when DTBS derivatives were treated with TBAF in THF, longer time (10 h for DTBST, 1 M (1 M=1 mol dm^{-3}), rt, 20 equiv.) than expected for the removal of usual silyl groups was necessary to achieve a complete removal of DTBS group.

A close examination of the desilylation reaction of DTBS thymidine revealed that the removal proceeded in two stages and a di-*t*-butylhydroxysilyl (HODTBS) derivative was found in the second stage. Separately-prepared HODTBS thymidine showed better stability to TBAF reagent than ordinary silyl derivatives such as *t*-butyldimethylsilyl thymidine. This implies that HODTBS group is promising as the protecting group. The desilylation scheme is proposed as follows:

$$\begin{tikzcd}
\begin{array}{c}\text{Cyclic } (t\text{-}C_4H_9)_2SiT \\ \text{(DTBST)}\end{array} \arrow[r, "F^-"] & F(t\text{-}C_4H_9)_2SiT\ \text{(I)} \arrow[r, "F^-"] \arrow[d, "HO^-"'] & T \\
 & HO(t\text{-}C_4H_9)_2SiT\ \text{(II)} \arrow[ur, "F^-"'] &
\end{tikzcd}$$

It is well known that the fluoride ion of TBAF in THF is not solvated and has a high affinity with silicon and in the first stage of desilylation, a siloxane bond (Si-O) is rapidly cleaved by the attack of the fluoride ion on the silicon center with the concomitant formation of FDTBS deriv (I). Such naked fluoride ion is a strong base and it is also reported that the complete removal of water from TBAF in an aprotic solvent is virtually impossible.⁵⁾ When intermediate I (FDTBS deriv) reacts with fluoride ion, it results in the regeneration of thymidine, but with hydroxyl ion, which is activated by unsolvated fluoride ion, HODTBS deriv (II) is formed as a by-product. HODTBS group is cleaved slowly from the sterically hindered intermediate II to regenerate thymidine. This two stage degradation need not be considered for monofunctional silyl groups and bifunctional TIPDS group of which each silicon atom has only one cleavable silyl ether bond (Si-OC).

We examined another kind of desilylating agent, tributylamine hydrofluoride (TBAHF) in THF, of which the basicity was expected largely decreased. Because the nucleophilicity of fluoride of TBAHF was lower than that of TBAF, TBAHF reacted slowly with usual silyl protecting groups but very rapidly with cyclic DTBS group, cleanly regenerating thymidine without the formation of a HODTBS by-product (5 min for DTBST, 1 M, rt, 20 equiv.). 3',5'-Cyclic DTBS nucleosides contain 6-membered 1,3,2-dioxasilaheterocycle,⁶⁾ which is very reactive to nucleophilic attacks compared with the corresponding acyclic compound. The reaction of intermediate I with second fluoride ion is expected to be facilitated by the attachment of fluorine to silicon, resulting in smooth regeneration of thymidine.

A stock solution (1 M) of TBAHF was conveniently prepared by the addition of tributylamine and hydrofluoric acid (47%) in THF without desiccating the reagents (calculated formula : $[CH_3(CH_2)_3]_3NHF \cdot 1.25H_2O$) and could be stored stable and homogeneous in a polytetrafluoroethylene bottle. This reagent (1 M) also cleaves monofunctional silyl protecting groups effectively and mildly.

The simply and easily prepared TBAHF reagent is also a mild and convenient reagent when compared with the acidic reagent (hydrofluoric acid in acetonitrile) used by Corey and pyridinium hydrofluoride prepared from corrosive hydrogen fluoride-pyridine by Trost.

In conclusion, bifunctional DTBS groups in 3',5'-O-DTBS nucleosides could be smoothly removed using tributylamine hydrofluoride(TBAHF) without giving by-products, di-t-butylhydroxysilyl compounds, formed in the course of removal of protecting groups with tetrabutylammonium fluoride (TBAF). It was characteristic of DTBS group not of disilyl TIPDS group.

A combination of bifunctional DTBS group and a mild and convenient TBAHF reagent is useful in organic synthesis and analysis.

References
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