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A Convenient Procedure for the Deprotection of Silylated Nucleosides and Nucleotides Using Triethylamine Trihydrofluoride

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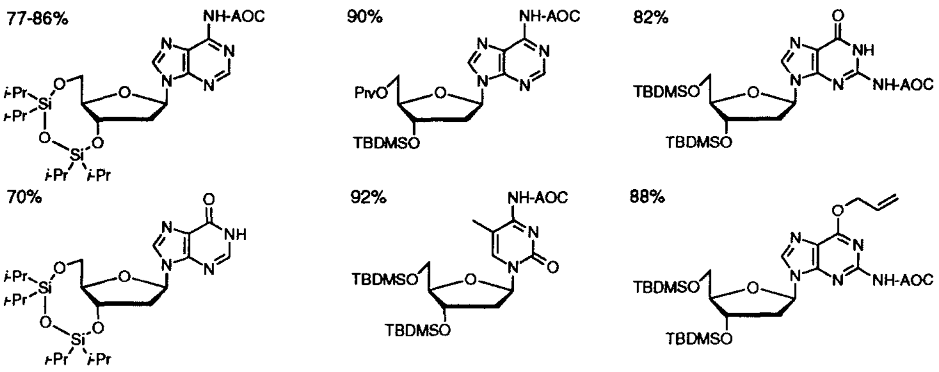
Abstract: *A new procedure for the deprotection of nucleosides and nucleotides bearing silyl protecting groups has been developed based on the commercially-available reagent triethylamine trihydrofluoride.*

In the conversion of the available ribonucleosides and deoxyribonucleosides to derivatives suitably protected and activated for solid-phase nucleic acid synthesis, distinction between the different alcohol functionalities and an amino group is required. Reagents commonly used include silyl ethers and the Markiewicz disiloxane.[1] A variety of reagents have been used to remove silyl protecting groups after they serve their purpose including, in nucleoside/tides, ammonium fluoride and tetrabutylammonium fluoride.[2] Experience in our laboratory has shown that each of these has disadvantages. Aqueous workup procedures can be incompatible with the high-yield isolation of many nucleotides/sides, and it is often difficult to separate products from residues of tetrabutylammonium fluoride. Consequently, we have investigated other fluoride sources for the removal of silyl groups on nucleic acid precursors. We report in this Letter that triethylamine trihydrofluoride is a particularly convenient reagent for the removal of silyl protecting groups from nucleosides and nucleotides.

$$\mathrm{ROSiR_3} \xrightarrow[\mathrm{THF}]{\mathrm{Et_3N{\bullet}3HF}} \mathrm{ROH}$$

Triethylamine trihydrofluoride is a commercially-available (current Aldrich price, $56/mole of fluoride) hygroscopic, free-flowing liquid that has previously been used in complex fluorinating agents[3] and for nucleophilic displacements in carbohydrate chemistry.[4] The deprotection of silyl cyanohydrins has also been recorded.[5] For the deprotection of nucleosides (A, G, I, and MeC; Table 1) and nucleotides (A, G, and MeC; Table 2) bearing disiloxane, *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl groups, we use dry THF as solvent and an excess (4-10 equiv) of the fluoride reagent. After a reaction time of 8-16h, workup is accomplished by evaporation and chromatography. Excess triethylamine was added before workup in some cases, but products of depurination were not observed even in its absence despite the seemingly acidic nature of the reagent. It is also harmless to pivaloyl, allyl, dimethoxybenzoin, and cyanoethyl protection.

Table 1



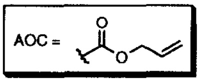
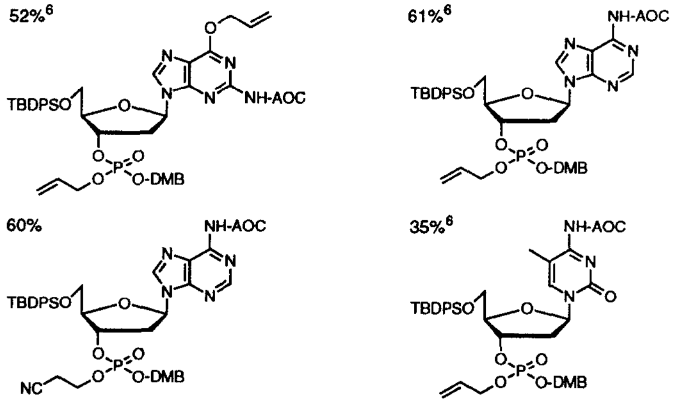


Table 2



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References & Notes.

1. Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817-845. Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can J. Chem.* **1978**, *56*, 2768-2780. Markiewicz , W. T.; Wiewiorowski, M. *Nucleic Acids Res. Spec. Publ.* **1978**, *4*, 185.
2. Recent references: Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177-80. Crisp, G. T.; Flynn, B. T. *J. Org. Chem.* **1993**, *58*, 6614. Jenny, T. F.; Benner, S. A. *Helv. Chim. Acta* **1993**, *76*, 826. Payne, A. N.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. I*, **1992**, 2633. Wu, T.; Ogilvie, K. K.; Perreault, J.-P.; Cedergren, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 8531-8533.
3. Haufe, G.; Alvernhe, G.; Anker, D.; Laurent, A.; Saluzzo, C. *J. Org. Chem.* **1992**, *57*, 714-19. Meurs, J. H. H.; Eilenberg, W. *Tetrahedron* **1991**, *47*, 705-14. Giudicelli, M. B.; Picq D.; Veyron, B.; *Tetrahedron Lett.* **1990**, *31*, 6527-30. Brigaud, T.; Laurent, E. *Tetrahedron Lett.* **1990**, *31*, 2287-90. Saluzzo, C.; Alvernhe, G.; Anker, D.; Haufe, G. *Tetrahedron Lett.* **1990**, *31*, 2127-30. Franz, R. *J. Fluorine Chem.* **1980**, *15*, 423-34.
4. Picq, D.; Anker, D. *Carbohydr. Res.* **1987**, *166*, 309-13. Miethchen, R ; Kolp, G. *J. Fluorine Chem.* **1993** , *60*, 49-55. Baer, H. H.; Mateo, F. H.; Siemsen, L. *Carbohydr. Res.* **1989**, *187*, 67-92.
5. Hünig, S.; Wehner, G. *Synthesis* **1975**, 391-39. Fischer, K.; Hünig, S. *J. Org. Chem.* **1987**, *52*, 564-9.
6. Includes coupling of the 3'-phosphoramidite to 3',5'-dimethoxybenzoin (DMB-OH) and oxidation.

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