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TRIFLUOROMETHYLPHOSPHINYL BIS-TRIAZOLIDES IN THE SYNTHESIS OF TRIFLUOROMETHYLPHOSPHONATE ANALOGUES OF NUCLEOTIDES

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Abstract. *The bis-triazolide of trifluoromethylphosphinic acid is prepared from trifluoromethylphosphorous dibromide, CF_3PBr_2, and reacted* in situ *with alcohols. The resulting triazolomonoesters are efficiently hydrolysed and oxidised to give trifluoromethylphosphonate monoesters, as shown for the nucleotide analogues adenosine 5'-O-trifluoromethylphosphonate and 2'-O-deoxythymidine 3'-O-trifluoromethylphosphonate, novel nucleotside esters having a trifluoromethylphosphoryl function.*

Phosphonates have been widely used as analogues of biologically important phosphate esters.[1] In particular, alkylphosphonate esters of nucleosides are generally more stable to nucleases and exhibit higher cell permeability.[2] The advantages of α-CF_2 and α-CFH groups in phosphonates have been linked to their isosteric and isopolar character as replacements for neutral oxygen[3] and Bergstrom has recently made useful advances with difluoromethylphosphonate analogues of dinucleoside phosphates.[4] We are seeking currently to employ trifluoromethylphosphonate esters, $CF_3P(O)(OR)_2$, as non-ionic analogues of phosphates as they have the maximum isopolar character of any phosphonate in relation to phosphate diesters. Such nucleotide analogues are anticipated to be more labile to hydrolysis and might well be hydrolysed with P-C cleavage to give phosphate diesters after passage across the cell membrane. In a parallel study,[5] we have made some progress using (*N,N*-diethylamino)trifluoromethylphosphorous bromide[6] to generate nucleoside phosphonamidites. However, hydrolysis of the trifluoromethylphosphonamidates derived by oxidation unexpectedly results in P-O cleavage in addition to the desired P-N cleavage. In the present work we describe the successful synthesis of 3'-deoxythymidyl and 5'-adenosyl esters of trifluoromethylphosphonic acid.

Classically, Haszeldine[7] made CF_3P compounds from a bomb reaction involving red phosphorus, iodotrifluoromethane, and iodine, which gives mixtures of $(CF_3)_3P$, $(CF_3)_2PI$, CF_3PI_2, and other species in rather poor yield. Burton has prepared $CF_3P(O)(OEt)_2$ from CF_3I and $(Et_3O)P$ by a photochemical reaction.[8] More recently, Ruppert described the reaction between trifluoromethyl bromide, hexaethylphosphorous triamide, and phosphorus trichloride in diethyl carbonate, which gives tetraethyl trifluoromethylphosphorous diamide, $CF_3P(NEt_2)_2$.[6] He further transformed this product (1) into the monobromide $CF_3P(NEt_2)Br$ (2), in which the bromine can be replaced by alcoholysis to give trifluoromethylphosphorous (III) monoester mono-

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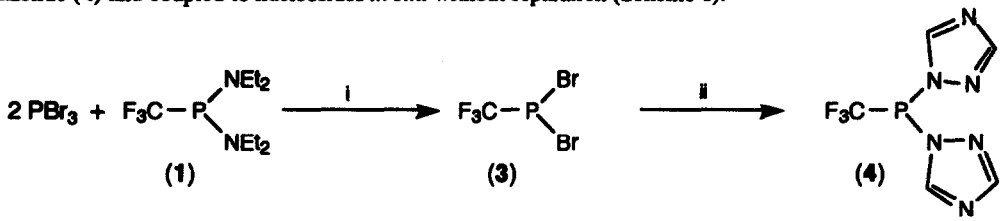
This paper is dedicated to Professor Fritz Eckstein on the occasion of his 60th Birthday

amides, $CF_3P(NEt_2)OR$. Here we report[9] the use of CF_3PBr_2 (3), readily prepared[6] from (2), in the synthesis of trifluoromethylphosphonate esters of nucleosides, $CF_3P(O)(OR)OH$.

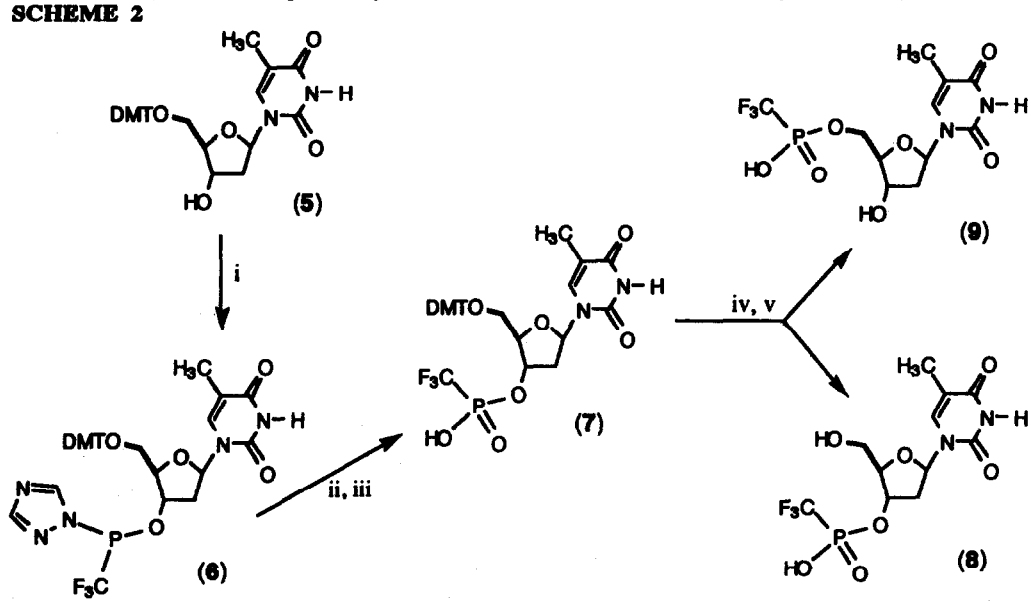
Trifluoromethylphosphorous dibromide, CF_3PBr_2 (3), is accessible with difficulty from the exchange reaction between CF_3PI_2 and AgBr.[10] We have therefore prepared CF_3PBr_2 (3) conveniently and in improved yield (50%) through the reaction of $CF_3P(NEt_2)_2$ (1) with excess PBr_3, based on the work of Ruppert.[6] The trifluoromethylphosphorous dibromide (3) can then be converted into the trifluoromethylphosphorous bis-triazolide (4) and coupled to nucleosides *in situ* without separation (Scheme 1).



SCHEME 1 Reagents: i, 150-170°C; ii, 1-H-triazole / Et_3N

In a typical experiment triazole (1.1 g, 16 mmol) and triethylamine (2.5 ml, 17.8 mmol) were dissolved in dry dioxane (50 ml) and cooled with ice until solid dioxane appeared. Trifluoromethylphosphorous dibromide, CF_3PBr_2 (2.08 g, 8 mmol), dissolved in dry dioxane (50 ml), was then added under nitrogen over 30 min and the reaction stirred at room temperature for 2 h. The precipitate of triethylammonium bromide was filtered off under nitrogen to give a solution of trifluoromethylphosphorous bis-triazolide (4) in dioxane. 5'-*O*-Dimethoxytrityl thymidine[11] (5) (1.1 g, 2 mmol) dissolved in dioxane (100 ml) was then added dropwise to a solution of (4) (2.0 mmol) in dioxane (50 ml). After this addition, the reaction mixture was stirred at room temperature overnight to complete the formation of the monotriazolide intermediate (6) (Scheme 2). Hydrolysis of the triazolide (6) was accomplished by the addition of water and was immediately followed by oxidation with

SCHEME 2

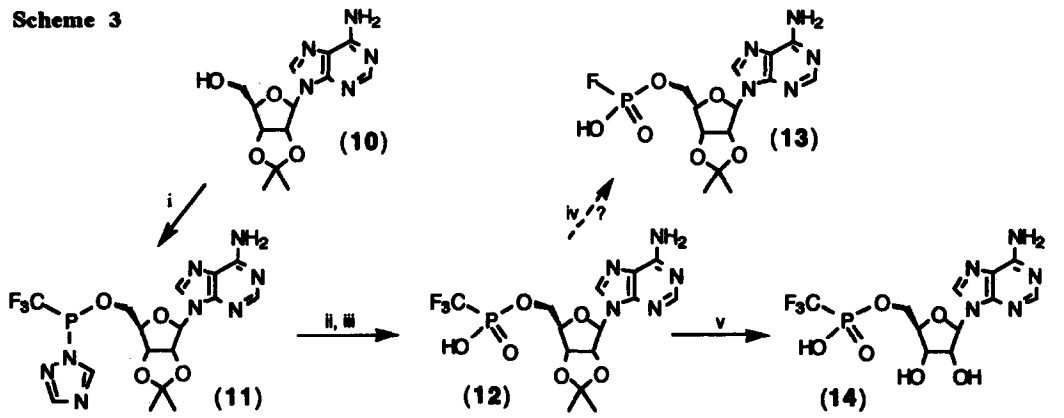


Reagents: i, $F_3CP(C_2H_2N_3)_2$; ii, H_2O; iii, *t*-BuOOH; iv, 80% AcOH; v, separation.

tert-butylhydroperoxide[12] to convert the intermediate H-phosphinate into the trifluoromethylphosphonate (**7**). The protective 5'-dimethoxytrityl group was removed by treatment with 80% HOAc at room temperature overnight (Scheme 2). The crude product was then neutralised to pH 8.8 and twice chromatographed on DEAE Sephadex A-25 using a triethylammonium bicarbonate gradient to give the 2'-deoxythymidin-3'-yl trifluoromethylphosphonate esters as triethylammonium salts, seen by ^{31}P NMR (101.25 MHz) as a mixture of two esters each showing a quartet peak at δ_P -4.40 ppm (J_{PF} 108.3 Hz) and δ_P -3.35 ppm (J_{PF} 107.5 Hz) respt. This mixture was finally purified by semipreparative C-18 reverse phase chromatography using acetonitrile (6 %) in ammonium bicarbonate (0.1 M). The first component eluted was (**8**) (51 % yield from (**5**)) while the second proved to be 2'-deoxythymidine 5'-*O*-trifluoromethylphosphonate (**9**) (33 % yield from (**5**)) as shown by analysis of the proton-coupled ^{31}P NMR signal.[13] Compounds (**8**) and (**9**) were individually characterized by FAB-MS, by ^{1}H and ^{19}F NMR, and by proton-coupled and -decoupled ^{31}P NMR. [This apparent migration of the trifluoromethylphosphoryl residue from the 3'- to the 5'-oxygen is unexpected but appears to be genuine since it was not possible to detect either 3'-*O*-dimethoxytrityl-2'-deoxythymidine or free 2'-deoxythymidine in the starting material (**5**).]

Application of the same methodology to 2',3'-*O*-isopropylideneadenosine (**10**) provided the triazolyl-trifluoromethylphosphonite (**11**) which on hydrolysis and oxidation[12] with *t*-BuOOH gave the desired 2',3'-*O*-isopropylideneadenosine 5'-trifluoromethylphosphonate (**12**) in 52% yield. Unexpectedly, our attempts to remove the protecting group using 80% acetic acid led to recovery of unchanged (**12**) admixed with a trace amount of a byproduct (2.6 %), which was separated and characterised as the phosphorofluoridate (**13**) (Scheme 3). [While this minor formation of (**13**) formally involves the loss of difluorocarbene from (**12**), such a process seems very improbable under the conditions employed and other possibilities are under exploration]. However, the hydrolysis of (**12**) using 10% AcOH at 95 °C for 1.5 h[14] provided the desired analogue of AMP (**14**) in 95 % yield.

Scheme 3



Reagents: i, $CF_3P(C_2H_2N_3)_2$; ii, H_2O; iii, *t*-BuOOH; iv, 80% AcOH; v, 10% AcOH.

Finally, we note that the monotriazolide P(III) species (**6**) and (**11**) generated in this work are close relatives of the intermediates used in P(III) oligonucleotide synthesis while reagent (**4**) or its bis-tetrazolide congener might well in future be developed for the synthesis of deoxyoligonucleotides, especially enabling the introduction of a trifluoromethylphosphonate residue at a specified position.

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REFERENCES

1. Engel R. *Chem. Rev.*, 1977, **77**, 349.
2. Agris, C.H., Blake, K.R., Miller, P.S., Reddy, M.P., and Ts'o, P.O.P., *Biochemistry*, 1986, **25**, 6268; Markus-Sekura, C.J., Woerner, A.M., Shinozuka, K., Zon, G., and Quinnan, G.V., *Nucleic Acids Res.*, 1987, **15**, 5749; Noble, S.A, Fisher, E.F., and Caruthers, M.H., *Nucleic Acids Res.*, 1984, **12**, 3387.
3. Blackburn G.M., *Chemistry Industry (London)*, 1981, 134; Blackburn, G.M., Eckstein F, Kent D.E., and Perrée T.M., *Nucleosides Nucleotides*, 1985, **4**, 165; Blackburn, G.M., Guo, M.J., Langston, S.P., and Taylor, G.E.,*Tetrahedron Lett.*, 1990, **31**, 5637; Blackburn, G.M. and Langston, S.P., *Tetrahedron Lett.*, 1991, **32**, 6425.
4. Bergstrom, D.E. and Shum, P.W., *J. Org. Chem.*, 1988, **53**, 3953.
5. Blackburn, G.M., Gough, N.J., and Guo, M-J., unpublished results.
6. Volbach, W. and Ruppert, I., *Tetrahedron Lett.*, 1983, **24**, 5509.
7. Bennett, F.W., Emeléus, H.J., and Haszeldine, R.N., *J. Chem. Soc.*, 1953, 1565.
8. Burton, D.J. and Flynn, R.M., *Synthesis*, 1979, 615.
9. Guo, M.J., and Blackburn, G.M., Abstracts 33rd IUPAC Congress, Budapest, 1991.
10. Burg, A.B. and Griffiths, J.E., *J. Amer. Chem. Soc.*, 1960, **82**, 3514.
11. Weimann, G., Schaller, H., Lerch, X., and Khorana, H.G., *J. Amer. Chem. Soc.*, 1963, **85**, 3823.
12. Engels, J. and Jäger, A., *Angew. Chem. Int. Ed.*, 1982, **21**, 912.
13. Spectral data. *2'-Deoxythymidine 3'-O-trifluoromethylphosphonate* (**8**). ^{31}P NMR (D_2O) δ_P -4.40 ppm, (q, J_{PF} 108.8 Hz; H-coupled dq, $^3J_{PH}$ 7.7 Hz); ^{19}F NMR (D_2O) δ_F -73.37 ppm (d, J_{PF} 108.9 Hz); ^{1}H NMR (D_2O) δ_H 7.6 (s, 1H, H-6), 6.26 (t, 1H, H-1'), 4.15 (q, 1H, H-4'), 3.80 (ABX, 2H, H-5',H-5"), 2.45 (m, 2H, H-2',H-2"), (H-3' was overlapped by solvent); +ve FAB-MS m/z 375 (M + H^+), 392 (M + NH_4^+); Calcd for $C_{11}H_{14}F_3N_2O_7P$ m/z 374; mono ammonium salt m/z 391.

2'-Deoxythymidine 5'-O-trifluoromethylphosphonate (**9**). ^{31}P NMR (D_2O) δ_P -3.66 ppm, (q, $^2J_{PF}$ 107.8 Hz; H-coupled, q,t,d, $^3J_{PH}$ 5.4 Hz, $^4J_{PH}$ 2.3 Hz); ^{19}F NMR (D_2O) δ_F -72.75 ppm (d, J_{PF} 108.2 Hz);^{1}H NMR (D_2O) δ_H 7.65 (s, 1H, H-6), 6.32 (t, 1H, H-1'), 4.55 (m, 1H, H-3'), 4.25 (m, 2H, H-5',H-5"), 4.15 (m, 1H, H-4'), 2.30 (m, 2H, H-2',H-2"), +ve FAB-MS m/z 397 (M + Na^+), 392 (M + NH_4^+), 375 (M + H^+); Calcd for $C_{11}H_{14}F_3N_2O_7P$ m/z 374; mono sodium salt 396, mono ammonium salt 391.

2',3'-O-Isopropylideneadenosine 5'-O-trifluoromethylphosphonate (**12**). ^{31}P NMR (D_2O) δ_P -3.76 ppm (q, $^2J_{PF}$ 108.3 Hz; H-coupled, m); ^{19}F NMR (D_2O) δ_F -72.90 (d, J_{PF} 108.2 Hz); ^{1}H NMR (D_2O) δ_H 8.22 (s, 1H), 8.12 (s, 1H), 6.20 (d, 1H), 5.38 (dd, 1H), 5.12 (dd, 1H), 4.60 (m, 1H), 4.18 (m, 2H), 1.68 (s, 3H), 1.38 (s, 3H); +ve FAB-MS m/z 440 (M + H^+), 462 (M + Na^+); Calcd for $C_{14}H_{17}F_3N_5O_6P$ m/z 439.

2,3-O-Isopropylideneadenosine 5'-O-fluorophosphate (**13**). ^{31}P NMR (D_2O) δ_P -6.23 (d, $^1J_{PF}$ 933.1 Hz; H-coupled; d,t,d, $^3J_{PH}$ 5.5 Hz, $^4J_{PH}$ 2.2 Hz); ^{19}F NMR (D_2O) δ_F -80.2, (d, $^1J_{PF}$ 933.0 Hz); ^{1}H NMR (D_2O) δ_H 8.26 (s, 1H), 8.16 (s, 1H), 6.26 (d, 1H), 5.45 (dd, 1H), 5.16 (dd, 1H), 4.62 (m, 1H), 4.12 (m, 2H), 1.65 (s, 3H), 1.40 (s, 3H); +ve FAB-MS m/z 412 (M + Na^+), 390 (M + H^+), 307, 289; Calcd for $C_{13}H_{17}FN_5O_6P$ m/z 389.

Adenosine 5'-O-ftriluoromethylphosphate (**14**). ^{31}P NMR (D_2O) δ_P -0.50 ppm (q, $^2J_{PF}$ 107.6 Hz; H-coupled, m); ^{19}F NMR (D_2O) δ_F -73.47 (d, J_{PF} 109.0 Hz); ^{1}H NMR (D_2O) δ_H 8.28 (s, 1H), 8.12 (s, 1H), 6.06 (d, 1H), 4.78 (t, 1H), 4.48 (t, 1H), 4.30 (m, 3H); +ve FAB-MS m/z 136, ($C_5H_6N_5^+$, 100 %), 400 (25 %, M + H^+), 422 (20 %, M + Na^+); Calcd for $C_{11}H_{13}F_3N_5O_6P$ m/z 399.

14. Myers, T.C., Nakamura, K. and Danielzadeh, A.B., *J. Org. Chem.*, 1965, **30**, 1517.

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