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THE 2-(METHYLTHIOMETHOXY)ETHOXYCARBONYL [MTMEC] PROTECTING GROUP

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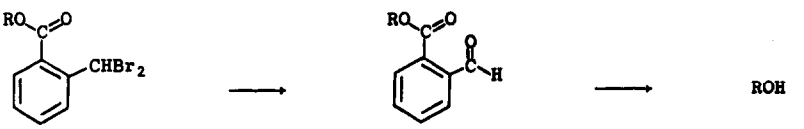
Summary: Alcohols (ROH) may be converted into their MTMEC derivatives (6) by acylation with 2-(methylthiomethoxy)ethoxycarbonyl chloride (5); the MTMEC "protected protecting group" may be removed by treatment first with Hg(II) perchlorate in the presence of 2,4,6-collidine or pyridine in acetone-water solution, followed by hydrolysis under very mild basic conditions.

A need has arisen in connection with our work on the synthesis of oligonucleotides[1] for acyl protecting groups which are removable under very mild basic conditions. As it is essential that these protecting groups should also be sufficiently stable to withstand the conditions necessary for phosphorylation and for the purification of intermediates, we have investigated the possibility of using "protected protecting groups" for this purpose. For example, we recently found[2] that while the 2-dibromomethylbenzoyl (DBMB) group [as in 1] is approximately as stable as the acetyl group to alkaline hydrolysis, it is readily transformed (Scheme 1) by treatment with silver perchlorate in the presence of 2,4,6-collidine in slightly wet acetone, into the exceptionally base-sensitive 2-formylbenzoyl group [as in 2]. The latter group may then be removed[2] by morpholinolysis under very mild conditions to give the desired unprotected alcohol (ROH).

Scheme 1

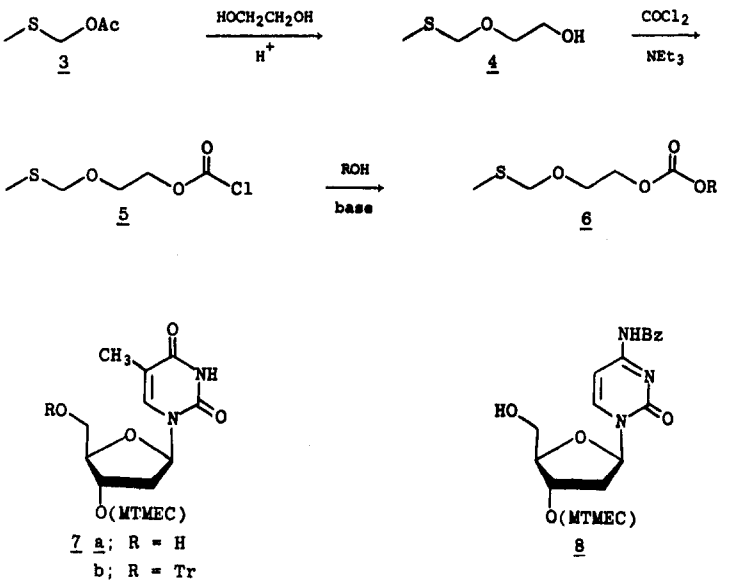


1 2

We now report that the 2-(methylthiomethoxy)ethoxycarbonyl (MTMEC) group [as in 6, Scheme 2] is another useful "protected protecting group" which may be removed by treatment with mercury (II) perchlorate in the presence of 2,4,6-collidine or pyridine in acetone-water (98:2 v/v), followed by alkaline hydrolysis under very mild conditions. When methylthiomethyl acetate (3), which may easily be prepared[3] on a relatively large scale and in 84% yield from dimethyl sulphoxide and acetic anhydride, is allowed to react (Scheme 2) with ethylene glycol in the presence of an acidic catalyst at room temperature and the products then subjected to alkaline hydrolysis, 2-(methylthiomethoxy)ethanol (4) is obtained in over 40% yield and may be isolated by fractional distillation as a colourless liquid (*ca.* 95% pure) in approximately 33% yield[4]. The required acylating agent, 2-(methylthiomethoxy)ethoxycarbonyl

chloride (MTMEC-Cl, 5) is then readily generated *in situ* by allowing 4 to react with one molecular equivalent of triethylamine and an excess (*ca.* 2 molecular equivalents) of phosgene in dioxan solution for 20 min at room temperature. When an alcohol (ROH) is treated with an excess of 5 in the presence of 1-methylimidazole in acetonitrile solution, the corresponding MTMEC ester (6) is obtained. Thus when 5'-O-(9-phenylxanthen-9-yl)thymidine[5] was allowed to

Scheme 2

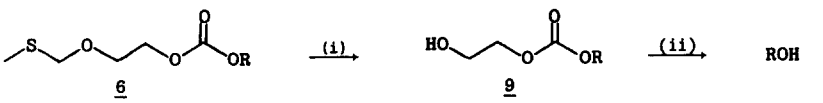


react with 5 (3 molecular equivalents) and 1-methylimidazole (5 molecular equivalents) in acetonitrile solution at room temperature for 1 hr, and the products treated with p-toluene-sulphonic acid in chloroform-methanol (9:1 v/v) solution for 2 min, 3'-O-(2-methylthiomethoxy) ethoxycarbonylthymidine (7a), m.p. 70-71°C, was obtained and isolated as a pure crystalline solid in 88% overall yield. In the same way, 8 was prepared from 5'-O-(9-phenylxanthen-9-yl) -4-N-benzoyl-2'-deoxycytidine[5] and isolated as a pure crystalline solid, m.p. 168-169°C, in 65% overall yield[6].

3'-O-(2-Methylthiomethoxy)ethoxycarbonyl-5'-O-tritylthymidine (7b), which was isolated as a crystalline solid in 72% yield from the products of the reaction between 5'-O-trityl-thymidine[8] and 5, was found to be a convenient substrate with which to carry out preliminary unblocking studies according to the procedure outlined in Scheme 3. When 7b (0.05 mmol), mercury (II) perchlorate (0.10 mmol), 2,4,6-collidine[9] (0.20 mmol) and acetone-water (9:1 v/v, 1.0 ml) were stirred together at room temperature, removal of the methylthiomethyl (MTM) group[10] was *ca.* 95% complete after 5 hr to give what is assumed to be 3'-O-(2-hydroxy)ethoxy-carbonyl-5'-O-tritylthymidine (corresponding to general formula 9, Scheme 3). When the latter intermediate was treated with M-ammonia in dioxan-water (1:1 v/v, 2.5 ml) for 15 min at room temperature, it was quantitatively converted into 5'-O-tritylthymidine (corresponding to ROH). Ethylene carbonate was presumably also obtained. The half-time for the removal of the MTMEC group from 7b by treatment with the M-ammonia reagent alone was *ca.* 20 hr at room temperature. It therefore follows that removal of the MTM part of the MTMEC "protected

protecting group" and the consequent release of a neighbouring hydroxy function (as in 9) leads to an approximately 500-fold increase in the rate of ammonia-promoted deacylation.

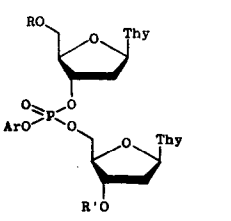
Scheme 3



6 9

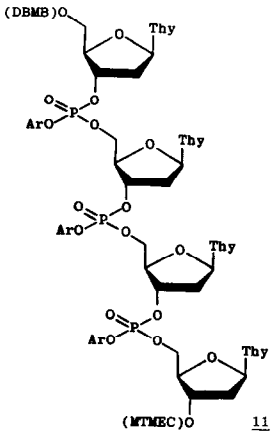
Reagents: (i) $Hg(ClO_4)_2$-2,4,6-collidine/Me_2CO-H_2O(9:1 v/v); (ii) M-NH_3/dioxan-water(1:1 v/v).

Finally, the use of the MTMEC protecting group in oligonucleotide synthesis was investigated. The fully-protected dinucleoside phosphate (10a) was obtained in 83% isolated yield by treating the triethylammonium salt of 5'-O-(2-dibromomethyl)benzoylthymidine 3'-(2-chlorophenyl) phosphate[11] with 7a in the presence of 1-(mesitylene-2-sulphonyl)-3-nitro-1,2,4-triazole (MSNT)[12,13] in pyridine solution. When 10a was allowed to react at room temperature with mercury (II) perchlorate (2 molecular equivalents) and pyridine (4 molecular equivalents) in acetone-water (98:2 v/v) for 3 hr and the products treated with 0.1 M-potassium carbonate in aqueous dioxan (1:1 v/v) for 6 min[14], the partially-protected dinucleoside phosphate (10b) was obtained. The latter material was isolated in 70% yield and was estimated (t.l.c.) to be >95% pure. The partially-protected dinucleoside phosphate (10c) with a free 5'-hydroxy function was obtained[2] in *ca.* 90% yield by allowing 10a to react at room temperature with silver perchlorate (10 molecular equivalents) in the presence of 2,4,6-collidine (10 molecular equivalents) in acetone-water (98:2 v/v) for 1 hr and then treating the products with morpholine (20 molecular equivalents) under the usual conditions[2]; this material was also estimated (t.l.c.) to be >95% pure. It therefore appears that the MTMEC group may be removed with a high degree of selectivity in the presence of a DBMB group and *vice versa*[15].



10 a; R = DBMB, R' = MTMEC
b; R = DBMB, R' = H
c; R = H, R' = MTMEC

Thy = thymin-1-yl;
Ar = 2-ClC_6H_4



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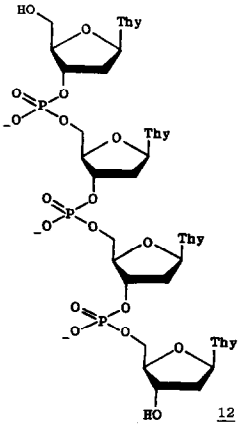

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The partially-protected dinucleoside phosphate (10b) was phosphorylated on its 3'-hydroxy function with an excess of 2-chlorophenyl phosphorodi-(1,2,4-triazolide)[11] in acetonitrile-pyridine solution and the resulting dinucleotide derivative was allowed to react with the 5'-unprotected dinucleoside phosphate (10c) in the presence of a twofold excess of MSNT (see above) in anhydrous pyridine solution. In this way, the fully-protected tetranucleoside triphosphate (11) was obtained and isolated, following chromatography of the products, as a homogeneous colourless solid in 86% yield; this material was completely unblocked by

treatment at room temperature first with a thirtyfold excess of the N^1,N^1,N^3,N^3-tetramethylguanidinium salt of *syn*-4-nitrobenzaldoxime[12] in aqueous dioxan (1:1 v/v) for 20 hr and then with 0.2 M-aqueous sodium hydroxide for 30 min. In this way, chromatographically homogeneous [DEAE Sephadex A25; h.p.l.c. (Partisil-10 SAX and μ Bondapak C_{18})] d[TTTT] (12) was obtained as the sole nucleotide product. This material underwent total digestion in the presence of *Crotalus adamanteus* snake venom and calf spleen phosphodiesterases to give the expected products in the correct ratios.

In conclusion, we believe that the above preliminary studies clearly establish that the MTMEC protecting group is useful in nucleoside and nucleotide chemistry. We further believe that it is likely to find important applications in other branches of natural products chemistry. It should be emphasized that the MTMEC has significant advantages over the simple MTM protecting group[10,16] inasmuch as it is both easier to introduce and it may, if required, be removed directly by treatment with alkali before its hemithioacetal moiety is cleaved.

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[3] L. Horner and P. Kaiser, Liebigs Ann. Chem. 626, 19 (1959).
[4] Methylthiomethyl acetate (3, 300g, 2.5 mol), ethylene glycol (277 ml, 4.96 mol) and Amberlyst 15 catalyst (6.25g) were stirred together at room temperature. After 23 hr, the catalyst was removed and a solution of sodium hydroxide (400g, 10 mol) in methanol-water (3:1 v/v, 1000 ml) was added to the stirred, cooled filtrate. The resulting solution was stirred for 2 hr at room temperature, neutralized with dilute hydrochloric acid and then concentrated to half volume under reduced pressure. After water (200 ml) had been added, the solution was extracted with dichloromethane (6 × 250 ml). Evaporation of the dried ($MgSO_4$) organic extracts gave crude 4 (197g, *ca.* 65% pure; corrected yield *ca.* 42%). The latter material (20g) was fractionated in a Nester-Faust NFT 51 spinning-band distillation apparatus to give nearly pure [*ca.* 95% by g.l.c. (Carbowax 20M, 165°C)] 2-(methylthiomethoxy)ethanol (4), b.p. 83-85°C/10 mmHg; yield 10.1g; ^{1}H n.m.r. ($CDCl_3$, 250 MHz): δ 2.17 (3H,s), 2.75 (1H,br.s), 3.66 (2H,m), 3.76 (2H,m), 4.70 (2H,s); M^+ = 122.0397 [Calc. for $C_4H_{10}O_2{}^{32}S$, 122.0401].
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[6] Crystalline 2'-O-methoxytetrahydropyranyl-3'-O-(2-methylthiomethoxy)ethoxycarbonyl derivatives of uridine and 4-N-benzoylcytidine[7] have also been prepared in satisfactory yields from appropriate starting materials.
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[8] J.P. Horwitz, J.A. Urbanski and J. Chua, J. Org. Chem. 27, 3300 (1962).
[9] 2,4,6-Collidine or pyridine is added to neutralize the perchloric acid which is released during the Hg^{++}-removal of the methylthiomethyl (MTM) group.
[10] E.J. Corey and M.G. Bock [Tetrahedron Letters 3269 (1975)] previously reported that the MTM group could be removed from protected primary alcohols by treatment with mercury(II) chloride in acetonitrile-water (4:1 v/v).
[11] J.B. Chattopadhyaya and C.B. Reese, Nucleic Acids Res. 8, 2039 (1980).
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[13] S.S. Jones, B. Rayner, C.B. Reese, A. Ubasawa and M. Ubasawa, Tetrahedron 36, 3075 (1980).
[14] 0.1 M-Potassium carbonate in aqueous dioxan (1:1 v/v) solution may conveniently be used as an alternative to ammonia for the second step of the removal of the MTMEC protecting group.
[15] It appears that, under the conditions required for the Hg^{2+}-promoted removal of the MTM moiety of the MTMEC protecting group, ≯5% hydrolysis of the dibromomethyl residue of the DBMB protecting group [to give 2-formylbenzoyl (as in 2)] occurs and that, under the conditions required for the Ag^+-promoted hydrolysis of the dibromomethyl residue in the DBMB protecting group, ≯5% removal of the MTM moiety of the MTMEC protecting group occurs.
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