2-Dibromomethylbenzoyl: An Acyl Protecting Group Removable Under Exceptionally Mild Conditions

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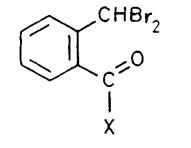
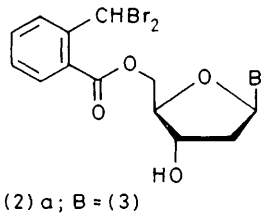
Summary 2-Dibromomethylbenzoate esters may be converted, at room temperature, into the corresponding alcohols in high yields by treatment first with silver perchlorate in the presence of 2,4,6-collidine in wet acetone or tetrahydrofuran and then with morpholine.

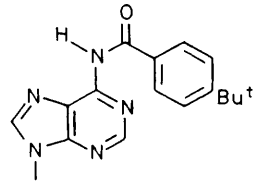
THERE has been a considerable need in the synthesis of oligonucleotides by the phosphotriester approach[1] for an *O*-acyl protecting group which is removable under virtually neutral conditions. A number of acyl protecting groups, including methoxy- and phenoxy-acetyl,[2] may be cleaved under relatively mild conditions of alkaline hydrolysis. However, the reaction conditions required are too drastic for the synthesis of oligonucleotides of even moderate chain length. Indeed, we have believed for some time that a 'protected protecting group' which is comparatively stable to both acid and alkali but which, after suitable modification, is removable under extremely mild conditions, is needed. It is further important, from practical considerations, that the protecting group should be easy to introduce and that the reagent required should be readily accessible. We now report that the 2-dibromomethylbenzoyl (DBMB) protecting group meets all these criteria.



(1) a; X = OH
b; X = Cl



(2) a; B = (3)
b; B = (4)
c; B = (5)
d; B = (6)



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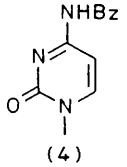

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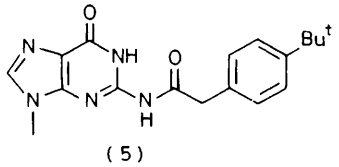

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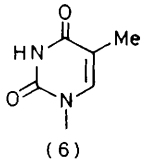


(6)

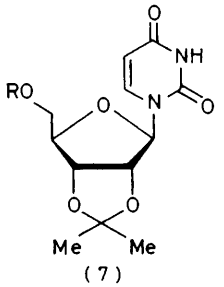
The required acylating agent, 2-dibromomethylbenzoyl chloride (**1b**) is prepared from 2-dibromomethylbenzoic acid (**1a**)† in the usual way by heating it, under reflux, with thionyl chloride; it may be purified by crystallization and isolated as a colourless solid, m.p. 53·5—54·5 °C.

TABLE. 2-Dibromomethylbenzoyl (DBMB) derivatives of alcohols.

Derivative	% Yield	M.p. (*t*/°C)
(**2a**)	71[a] (64)[b]	141—142
(**2b**)	69[a]	159—160 (decomp.)
(**2c**)	65[a]	154—157 (decomp.)
(**2d**)	76[a]	153 (decomp.)
(**7b**)	88[a]	185
(**8b**)	89[a]	132·5
(**9b**)	92[a]	184

[a] Based on corresponding hydroxy compound. [b] Based on 3′,5′-di-*O*-acetyl-2′-deoxyadenosine.

When a solution containing a slight excess of (**1b**) in acetonitrile is added dropwise to a solution of thymidine or the appropriate *N*-acyl derivative of 2′-deoxyadenosine, 2′-deoxycytidine, or 2′-deoxyguanosine in pyridine, regioselective acylation occurs to give the corresponding 5′-*O*-DBMB derivative (**2d**, **2a**, **2b**, or **2c**, respectively) as the major product. The latter compounds, which are required as building blocks in oligodeoxyribonucleotide synthesis, may be isolated from the products as pure crystalline solids‡ in satisfactory yields (Table). As expected, the yields of DBMB derivatives obtained from monohydric primary and secondary alcohols are greater. Thus, 2′,3′-



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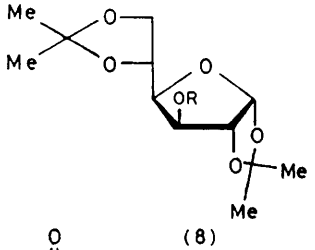

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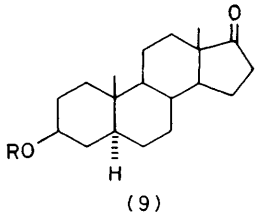


(9)

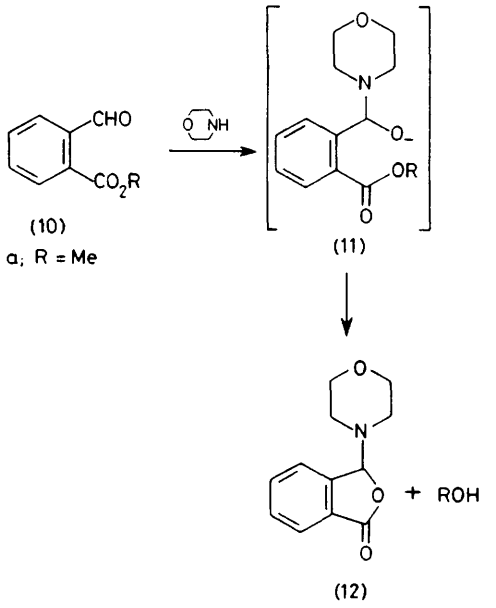
a; R = H
b; R = 2-$Br_2CH{\cdot}C_6H_4{\cdot}CO$

† 2-Dibromomethylbenzoic acid (**1a**) may be prepared on a large scale and in high yield by the direct bromination of *o*-toluic acid (E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, 1952, **17**, 1252). The crude product obtained, which will almost inevitably be contaminated with some 2-bromomethylbenzoic acid, may be purified by recrystallization from ethanol-water (9:1 v/v). The n.m.r. spectrum [$(CD_3)_2SO$] of recrystallized 2-dibromomethylbenzoic acid (**1a**), m.p. 166·5 °C, should display no absorption upfield from δ 7.

‡ Satisfactory spectroscopic and microanalytical data have been obtained for all new compounds described.

O-isopropylideneuridine (**7a**), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8a**), and 3β-hydroxy-5α-androstan-17-one (**9a**) may all be converted into their crystalline DBMB derivatives (**7b**, **8b**, and **9b**, respectively) in *ca.* 90% yields (Table).

Bender and his co-workers have reported[3] that the morpholine- and hydroxide ion-catalysed hydrolyses of methyl 2-formylbenzoate (**10a**) are among the fastest known non-enzymatic hydrolysis reactions of methyl esters. Thus at 25 °C, the half-time of hydrolysis of (**10a**) in carbonate buffer (pH 9·03) is *ca.* 32 s and its hydrolysis in 0·085 M-aqueous morpholine is virtually complete after 10 s. Bender *et al.* have proposed[3] that the morpholine-catalysed hydrolysis of (**10a**) proceeds (Scheme) *via* the cyclization of its morpholine adduct (**11**; R = Me) to give methanol and 3-morpholinophthalide (**12**). The latter compound (**12**) itself readily undergoes hydrolysis to give 3-hydroxyphthalide and morpholine. 2-Dibromomethylbenzoate esters (*i.e.*, DBMB derivatives of alcohols) such as (**2**) may be regarded as protected 2-formylbenzoate esters. When such DBMB derivatives are treated with silver perchlorate in the presence of 2,6-lutidine or 2,4,6-collidine (added to maintain a virtually neutral reaction medium) in slightly wet acetone or tetrahydrofuran solution at room temperature, they are readily converted into the corresponding 2-formylbenzoyl derivatives.§ Addition of morpholine then leads to rapid deacylation resulting in the release of the alcohol in high yield.



(10)
a; R = Me

(11)

(12)

SCHEME

The following procedure, which was used for the removal of the DBMB protecting group from (**7b**), may be used generally. A solution of compound (**7b**) (1·5 mmol), 2,4,6-collidine (4·5 mmol) and silver perchlorate (9·0 mmol) in tetrahydrofuran–water (95:5 v/v; 15 ml) was stirred at room temperature for 30 min. A solution of lithium bromide (18·0 mmol) in the same solvent mixture (10 ml) was then added and, after the removal of the precipitated silver bromide by filtration, morpholine (13·5 mmol) was added. The products were worked up after 6 min to give 2′,3′-*O*-isopropylideneuridine (**7a**) in 90% yield [76%, m.p. 160—162 °C, following crystallization from acetone–light petroleum (b.p. 40—60 °C)]. By a similar procedure in which the reactions were carried out in acetone–water (98:2 v/v) instead of in tetrahydrofuran–water, (**8b**) was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**8a**) in high yield [*ca.* 87%, m.p. 108 °C, following crystallization from light petroleum (b.p. 60—80 °C)].

In conclusion, we feel confident that the availability of such a protecting group, which is as stable as the acetyl group to alkaline hydrolysis and which may readily be removed under the exceptionally mild conditions described above, will prove to be of much value in the synthesis and transformations of oligonucleotides and other groups of sensitive compounds.

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§ 2-Dichloromethylbenzoate esters may be converted into the corresponding 2-formylbenzoyl derivatives in the same way. However, as silver ion-promoted solvolysis then proceeds more slowly, the DBMB is generally to be preferred to the 2-dichloromethylbenzoyl protecting group.

[1] C. B. Reese, Tetrahedron Report No. 56, *Tetrahedron*, 1978, **34**, 3143.
[2] C. B. Reese and J. C. M. Stewart, *Tetrahedron Letters*, 1968, 4273.
[3] M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, 1962, **84**, 4589; M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *ibid.*, 1965, **87**, 4545.