Two Sulphur-containing Protecting Groups for Alcoholic Hydroxyl Functions

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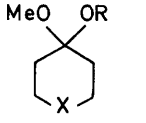
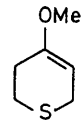
Summary Two achiral sulphur-containing protecting groups for alcoholic hydroxy-functions are described: the thioether acetal [as in (**1b**)] is slightly more labile, and the sulphone acetal [as in (**1c**)] is much less labile, to acidic hydrolysis than the methoxytetrahydropyranyl protecting group [as in (**1a**)].

IN the past few years, the development of procedures for the chemical synthesis of oligonucleotides has depended to a significant extent on the design of new protecting groups with very specific properties.[1] Thus, our work in the area of oligoribonucleotide synthesis led to the introduction[2] of the methoxytetrahydropyranyl group [as in (**1a**)] for the

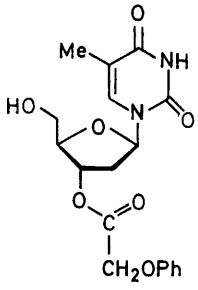
protection of alcoholic hydroxy-functions (ROH). The latter protecting group is particularly suitable for oligoribonucleotide synthesis in that it is achiral[2] and removable under sufficiently mild conditions of acidic hydrolysis.[3] Here we describe the use of two new sulphur-containing protecting groups [as in (**1b**) and (**1c**)] which are, respectively, slightly more and considerably less acid labile than the methoxytetrahydropyranyl group.



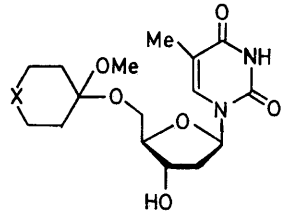
(1) a; X = O
b; X = S
c; X = SO_2



(2)



(3)



(4) a; X = O
b; X = S
c; X = SO_2

Treatment of (**3**) with an excess of (**2**)† in the presence of mesitylenesulphonic acid in dioxan at 20 °C, followed by deacylation of the neutralised products with methanolic ammonia gave the desired derivative (**4b**), which was isolated as a colourless crystalline compound (80%),‡ m.p. 156—157 °C. Treatment of (**4b**) with *m*-chloroperbenzoic acid (3 mol. equiv.) in chloroform gave[5] the corresponding sulphone (**4c**)‡ which was isolated as a crystalline compound (70%), m.p. 155 °C. The rates of acid-catalysed hydrolysis of (**4a**),[2] (**4b**), and (**4c**) are shown in the Table.

TABLE. *Half-times* ($t_{\frac{1}{2}}$) *of acid-catalysed hydrolysis of thymidine 5′-acetals at* 20°C.

Compound	[HCl]/M	$t_{\frac{1}{2}}$/min
(**4a**)	0·01	10·5[a]
(**4b**)	0·01[b]	2·0
(**4c**)	1·0	45

[a] See ref. 2b. [b] The hydrolysis of (**4b**) was carried out in aqueous dioxan (4:1 v/v).

It can be seen from the Table that (**4b**) undergoes hydrolysis *ca.* 5 times as rapidly as (**4a**). This ratio of hydrolysis rates may be correlated[2] with the reported ratio (*ca.* 4·4)[6] of the dissociation constants of morpholine and thiomorpholine. The exceptional stability of the sulphone acetal (**4c**) to acidic hydrolysis is noteworthy and indicative of the large inductive effect of the sulphone grouping. If second order kinetics for acetal hydrolysis are assumed,[7] it is apparent that a decrease in hydrolysis rate by a factor of more than 2×10^3 is introduced by oxidizing the thioether (**4b**) to the sulphone (**4c**).

Both of the above new protecting groups are achiral and are thus particularly suitable for use with chiral alcohols. Although there are some special situations, such as in 2′-deoxyribonucleoside chemistry, when a protecting group which is more acid labile than methoxytetrahydropyranyl would be desirable, it is likely that the much less labile sulphone acetal system [as in (**1c**)] will also be useful as a protecting group.

(*Received*, 10*th April* 1972; *Com.* 605)

† Prepared from (**1b**; R = Me) by the method described for its oxygen analogue;[2b] (**1b**; R = Me) was prepared by the usual procedure from tetrahydro-4*H*-1-thiopyran-4-one.[4]

‡ Satisfactory analytical and spectral data were obtained for compounds (**4b**) and (**4c**).

[1] For some of the leading references, see C. B. Reese 'Colloques Internationaux du C.N.R.S.,' Paris, 1970, No. 182, p. 319.
[2] (a) C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Amer. Chem. Soc.*, 1967, **89**, 3366; (b) *Tetrahedron*, 1970, **26**, 1023.
[3] B. E. Griffin, M. Jarman, and C. B. Reese, *Tetrahedron*, 1968, **24**, 639.
[4] E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, 1948, **70**, 1813.
[5] L. A. Paquette, *J. Amer. Chem. Soc.*, 1964, **86**, 4383.
[6] H. K. Hall, jun., *J. Amer. Chem. Soc.*, 1956, **78**, 2570.
[7] M. M. Kreevoy and R. W. Taft, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 3146, 5590.