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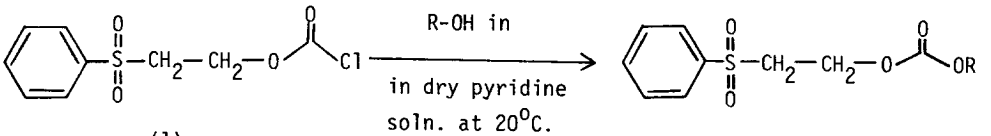
THE 2-PHENYLSULFONYLETHYLCARBONYL (PSEC) GROUP FOR THE PROTECTION OF THE HYDROXYL FUNCTION

Neil Balgobin, Staffan Josephson and Jyoti B. Chattopadhyaya*
Department of Microbiology, Biomedical Centre, University of Uppsala,
Box 581, S-751 23 Uppsala, Sweden

Abstract: The PSEC group may be used to protect the hydroxyl function in conjunction with a variety of acid and base labile protecting groups; the PSEC group may be removed by treatment of triethylamine (15 equiv.) in dry pyridine solution within 20 h at 20°C while other base labile protecting groups remained intact.

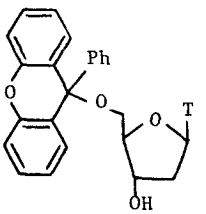
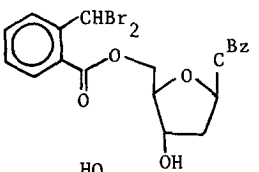
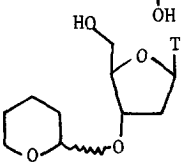
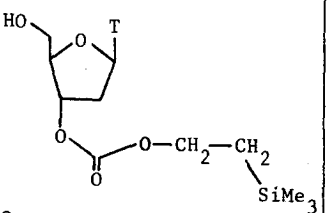
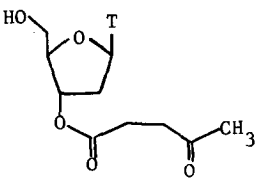
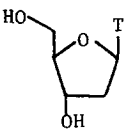
The protection of hydroxyl function constitute an important step in designing a strategy for a multistep chemical synthesis of oligosacharides and oligonucleotides. Several acid,[1] base labile protecting groups[1] along with the ones which are removable under virtually neutral conditions[2,3] have been proposed for this purpose. There are other categories of hydroxyl protecting groups which are removable either by mild lewis acids,[4,5] by fluoride ions[5,6] or by other means[7,8]. We now report that the 2-phenylsulfonylethylcarbonyl (PSEC) group, as shown in (2), a new hydroxyl protecting group which is removable quantitatively within 20 h at 20°C by the action of Et_3N, a non-nucleophilic base, (15 equiv.) in dry pyridine solution (15 ml/mmol). Alternatively, the PSEC group from (2) may be removed by mild alkaline hydrolytic conditions. Thus it is completely removable with M-NH_3 in dioxan-water (1:1 v/v) within 7 min. at 20°C or with 0.04 M K_2CO_3 in aqueous dioxan (1:1 v/v) at 20°C within a minute. The PSEC-group has the expected acid stability for over 10 days at 20°C in pH 2 (80% aq. acetic acid). The PSEC-derivative, as in (2), can be conveniently prepared by treating a pyridine solution (10 ml/mmol) of the substrate at 20°C with 2-phenylsulfonylethylchloroformate[9] (1) (1.3 equiv.) for 30 min. followed by a standard work-up. The Table illustrates the substrates (3) to (9), containing different standard protecting groups, whose PSEC-derivatives have been prepared.



(1) (2)

The Table also records the % isolated yields: (i) of formation of the PSEC-derivatives[18] of the substrates (3) to (9); (ii) of the recovery of the substrates[18] after the removal of the PSEC-group in presence of other protecting groups; (iii) and of the recovery yields of the hydroxy block containing the PSEC-group after the deprotection of the corresponding acid or base labile protecting group from the PSEC-derivatives[18] of (3) to (7). Thus, the examples in the Table clearly establish the synthetic applicability of the PSEC-group in conjunction with acid labile groups, like 9-phenylxanthen-9-yl (Pixyl)[10] and tetrahydropyranyl[1], and base labile groups like benzoyl[1], 2,2-dibromomethylbenzoyl[2], 2-trimethylsilylethylcarbonyl-(TMSEC)[5] and levulinyl-[3]. The selective removal of the PSEC-group from the PSEC-derivative of the substrate (4) is particularly interesting in view of the fact that the DBMB-group[2] has an almost identical lability to that of an acetyl group in an alkaline hydrolytic condition[11] ($t_{1/2}$ Ca. 90 min. at 20°C 0.15M aq. K_2CO_3 in dioxan solution, 1.6:1.0 v/v). It is also noteworthy that the selective removal of the DBMB-group by a virtually neutral condition[2] using $AgClO_4$ (16 equiv.),2,4,6-collodine (9 equiv.) in 98% aq. acetone for 1 h. followed by the treatment with morpholine (5 equiv.), the removal of the TMSEC-group[5,19] ($t_{1/2}$ ca. 7 h., dioxan-aq. NH_3 (d0.9), 1:1 v/v by the action of $ZnBr_2$ (10 equiv.) in CH_3NO_2 solution at 20°C and the removal of levulinyl

TABLE: PREPARATION OF THE PSEC-DERIVATIVES AND THE RECOVERY YIELDS.

SUBSTRATES	The formation of the PSEC-derivatives.	The selective removal of the PSEC-group in presence of other groups[a].	The selective removal of other groups in presence of the PSEC-group.
	% Yields	% Yields	% yields
(3) 	86.6	85.8	95.6
(4) 	99.0	98.2	73.6
(5) 	80.6	86.1	92.0
(6) 	88.0	87.3	96.0
(7) 	80.0	99.0	96.7
(8) 	73.6[b]	84.7[c]	
(9) CHOLESTEROL	74.0	96.5[d]	

[a] 15 equiv. of Et_3N in dry pyridine(15 ml/mmol) was used for deprotection of the PSEC-group (20h)

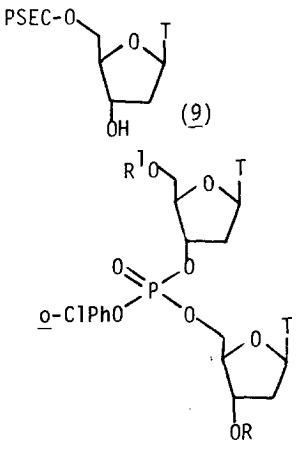
[b] 5'-O-PSEC derivative was selectively obtained.

[c] The 5'-O-PSEC derivative of (8) was first benzoylated at 3'-position and then the PSEC-group was removed to yield 3'-O-benzoyl thymidine.

[d] The deprotection took 70h under the usual condition.

group[3] (0.5 M hydrazine hydrate in pyridine-acetic acid, 3:1 v/v at 20°C) from the PSEC-derivatives of (4), (6) and (7) respectively should broaden the potential use of the PSEC-group in the synthesis of the natural products.

Finally, the application of the PSEC-group in oligodeoxyribonucleotide synthesis was investigated using a reported strategy.[12] Thus, the dimer block (10) was synthesized in 71.4% yield (powder) by reacting the 5'-O-PSEC thymidine (9) with a slight excess of o-chlorophenylphosphorobis-(1,2,4-triazolide) in CH_3CN-pyridine solution at 20°C for 30 min in an usual fashion followed by an addition thymidine (2 equiv.) and 1-methylimidazole (16 equiv.).[13] The reaction mixture was stirred for 45 min followed by a standard work-up and purification by column chromatography gave the pure (10). The 3'-hydroxyl function of the (10) was then blocked with the pixyl group[10] to obtain (11) in a quantitative yield. The 5'-hydroxy dimer block (12) was then prepared in 94% yield by the removal of the PSEC-group by the treatment of Et_3N (15 equiv.) in dry pyridine solution (15 ml/mmol) for 20 h. at 20°C. The 5'-protected dimer block (13) was conveniently prepared following a literature procedure.[14] A slight excess of the (13) was then reacted with the (12) under a usual condition in presence of an excess of 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole[12,15] to obtain the fully protected tetramer (14) in 94.4% yield. The tetramer (14) gave a pure 5'-hydroxy block (16) in 81% yield (powder), after the removal of the PSEC-group using the above Et_3N in pyridine reaction condition and a pure 5'-protected phosphodiester component (15) following a literature procedure[12,16]. The (16) was then coupled to the (15) in a standard way to obtain the fully protected octathymidylic acid (17) in 84% yield (powder). It should be added here that the 0.04M aq. K_2CO_3 in dioxan (1:1 v/v, 20°C, 6 min. T_2 & T_4 and 8 min for T_8) removed the PSEC-group from the fully protected dimer (11), tetramer (14) and the octamer (17) to their 5'-hydroxy components in 82.4, 64.3 and 47.7% yields as opposed to Et_3N (15 equiv.) in dry pyridine (20 h. at 20°C) condition which gave the respective 5'-hydroxy blocks in 94, 81 and 80.6% yields. The poorer yield of 5'-hydroxy components in the former conditions was clearly due to the removal of o-chlorophenyl group from



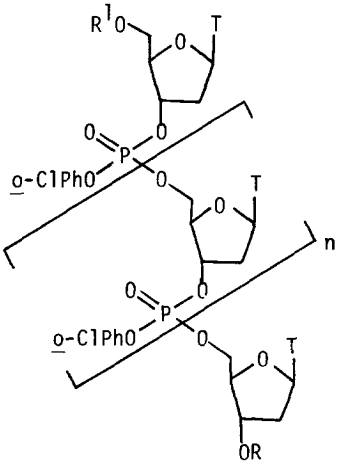
(9)

(10) R=H, R^1=PSEC

(11) R=Pixyl(Px), R^1=PSEC

(12) R=Px, R^1=H

(13) R= o-ClPhO-P(=O)-O$^-Et_3NH^+$, R^1=PSEC



(14) n=2, R^1=PSEC, R=Px

(15) n=2, R^1=PSEC and R= o-ClPhO-P(=O)-O$^-Et_3NH^+$

(16) n=2, R^1=H and R=Px

(17) n=6, R^1=PSEC and R=Px

from the internucleotide junctions. The final product (17) was deprotected in the following order: (i) replacement of the benzoyl group[16] at the 5'-end after the removal of the PSEC-group; (ii) treatment with syn-4-nitrobenzaldoximate ions[15]; (iii) aq. NH_3 (d0.9) for 24h. at 20°C;(iv) removal of the volatile matters and the treatment of the residue with 80% aq.acetic acid for 15 min. at 20°C. The oligonucleotide was then extracted into the aqueous phase by partitioning the reaction mixture with CH_2Cl_2 (10x5ml). The aqueous phase was then concentrated and examined by HPLC[16] (Permaphase AAX at 50°C; linear gradient: 0.01M KH_2PO_4, 0.0M KCl to 0.05M KH_2PO_4 and 0.7M KCl; pH 4.45) and the main peak in the elution profile contained more than 95% of the A_{260} O.D. units. An aliquot of this material was ^{32}P-labelled with ^{32}P-γ-ATP and kinase and electrophoresed on a 20% polyacrylamide gel[17]. An autoradiography revealed the presence of a single component of the expected mobility. The oligonucleotide was fully digested with Crotalus adamanteus snake venom phosphodiesterase confirming the presence of 3'→5' linkages in the octathymidylic acid. The ^{32}P-labelled octamer was also partially digested by the same enzyme and then it was electrophoretically shown to contain eight fragments of differently charged species as expected from octathymidylic acid[17].

Thus, it is clearly demonstrated that the PSEC group can indeed be successfully used as a hydroxyl protecting group. The obvious advantage with the PSEC-group seem to lie in the fact that one could conveniently introduce either electron withdrawing or lipophilic substituent, or a sutiable combination of the both, in the benzene ring in order to make the substituted 2-Phenylsulfonylethyl linkage more labile to a non-nucleophilic base to suit other needs.

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