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2-(TRIMETHYLSILYL)ETHYL CHLOROFORMATE: A CONVENIENT REAGENT FOR PROTECTION OF HYDROXYL FUNCTION

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Summary: 2-(Trimethylsilyl)ethyl chloroformate reacts with alcohols to give carbonates in high yield. n-Bu_4NF in THF(0.2M) solution for 10 min or $ZnBr_2$ or $ZnCl_2$ in CH_3NO_2 for 10 min regenerate the alcohol at 20°C.

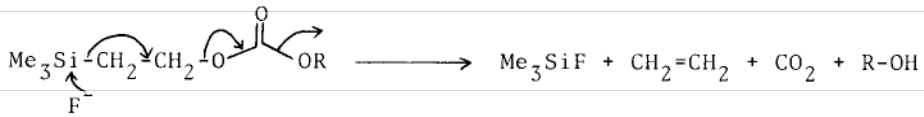
Sieber[1] first introduced 2-(trimethylsilyl)ethyl group for protection of carboxyl function in peptide chemistry. This group was removable by fluoride ions (Ca. 2.1M, 3 min at 24°C). Lipshutz and Pegram[2] have employed this group to prepare 2-(trimethylsilyl)ethoxymethyl (SEM) chloride which these workers have used to protect the hydroxyl group of a variety of substrates in the presence of diisopropylethylamine (4-5 equiv.) in CH_2Cl_2 solution at 25-40°C. The SEM group was removable with 2M solution of n-Bu_4NF in dry THF at 45°C within 5-24h.

We now report that 2-(trimethylsilyl)ethyl chloroformate (1)[3], an easily accessible reagent[4], can be conveniently used for the protection of hydroxyl function of different substrates. The 2-(trimethylsilyl)ethoxycarbonyl(TMSEC) derivatives (3) are stable in 80% acetic acid at 20°C for over 170h. The TMSEC group could, therefore, be safely used in conjunction with other acid labile protecting groups like ethers, acetals or ketals. The TMSEC derivatives

$$Me_3Si\text{-}CH_2\text{-}CH_2\text{-}O\text{-}COCl + HO\text{-}R \xrightarrow[20°C]{\text{pyridine}} Me_3Si\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CO_2R$$

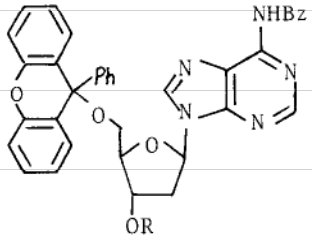
(1) (2) (3)

are, as expected, susceptible to alkaline hydrolysis at 20°C (dioxan-aq.NH_3 (d0.9) 1:1 v/v, $t_{1/2}$ Ca.7h.). The TMSEC derivatives can be convenintly prepared in high yield by treating a dry pyridine solution of an alcohol (5ml/mmol) at 20°C with the reagent (1.2 equiv.) for 30 min. Table I lists the alcohols whose derivatives have been prepared and examined for the deprotection study. The TMSEC group can be cleaved by F^- to unmask the hydroxyl function in a relatively mild reaction condition compared to SEM derivatives[2]. Thus, TMSEC group can be smoothly removed from esters in dry THF solution with 0.2M n-Bu_4NF at 20°C under 10 min. to obtain the desired alcohol. Presumably this facile removal of TMSEC group is due to the release of CO_2 (bp -78°C / 760 mm), a relatively inert and a sparingly soluble moiety compared to formaldehyde (bp -21°C / 760 mm) which is generated

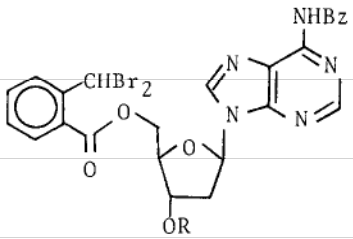


(3) (2)

during F^- promoted cleavage of SEM drivatives[2]. In two actual examples, we have synthesized 5'-O-(9-phenylxanthen-9-yl)-3'-O-TMSEC-6-N-m-chlorobenzoyl-2'-deoxyadenosine(4) and 5'-O-(2,2-dibromomethylbenzoyl)-3'-O-(TMSEC)-6-N-m-chlorobenzoyl-2'-deoxyadenosine(5) starting from (6) and (7) respectively. 9-Phenylxanthen-9-yl protecting group[7] ($t_{1/2}$ Ca.90 secconds in 80% acetic acid, pH 2, at 20°C. Alternatively it could be completely removed under 2 min. by the action of 4-toluensulphonic acid.H_2O,2 equiv., in 2% ethanol-$CHCl_3$ at 20°C) from (4) and 2,2-dibromobenzoyl group[8] (removable under a neutral condition: $AgClO_4$(16 equiv.) and 2,4,6-collidine(9 equiv.) in 98% aq.acetone for 1h. at 20°C followed by treatment with morpholine (3 equiv.) for 2 min.) from (5) could be cleanly deprotected to generate the corresponding 5'-hydroxy derivatives quantitatively. Similarly, (6)



(4),R = TMSEC
(6),R = H



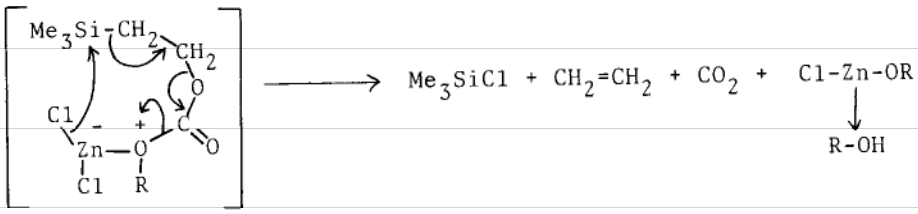
(5),R = TMSEC
(7),R = H

and (7) could be regenerated from (4) and (5) respectively in 94 and 97% yield by the action of 0.2M F^- (4 equiv.) in dry THF at 20°C. Thus it is clearly demonstrated that TMSEC group can be conveniently used in conjunction with an acid labile and acyl protecting groups.

Further, the TMSEC group can also be smoothly removed in a completely different set of conditions. Thus, it is cleaved in an anhydrous condition, in dry CH_3NO_2 solution (10 ml/mmol), using lewis acids like $ZnCl_2$ or $ZnBr_2$ (15 equiv.) under 10 min. at 20°C. This reaction is only specific for the removal of 2-(trimethylsilyl)-ethyl carbonate linkage (2a-e). The benzyl, isobutyl and allyl carbonates of (2c) were completely inert under the above reaction condition.It should be mentioned that the $ZnCl_2$ or $ZnBr_2$ mediated deprotection of (3) was a much slower process when the reaction was performed in CH_2Cl_2 solution at 20°C. Thus it required Ca. 180 min. for complete deprotection of 5'-O-TMSEC-thymidine to thymidine in CH_2Cl_2 solution (with 15 equiv. of $ZnCl_2$ or $ZnBr_2$) while a parallel experiment in CH_3NO_2 was complete under 10 min.

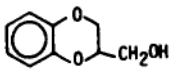
It is interesting to note that naked nucleophiles like Cl^- and Br^- (KCl or KBr in dry DMF in conjunction with 18crown6) did not have any efect on (2c) and the by-products formed during $ZnCl_2$ mediated deprotection of (2c) in CH_3NO_2 have been identified as Me_3SiCl, ethylene and CO_2. Thus it strongly suggest that the formation of a complex like (8) may be actually

involved during the reaction which opens up in a concerted fashion by neighbouring group participation, as shown in (8) to give the observed products.



(8)

Table 1: Reactions of alcohols with TMSEC-Cl and the regeneration of alcohols from the derivatives(3).

2	Substrate	% yield of TMSEC derivatives[5]	% yield regeneration of alcohols		
			0.2M F^-	$ZnCl_2$	$ZnBr_2$
a.	Cholesterol	85.4	94.0	81.0[c+]	82.5[c+]
b.	4-Nitroethanol	88.3	93.5	83.7	65.7
c.	Thymidine	65.0[b+]	87.5	87.0[c+] 90.0	88.0[c+] 92.0
d.	m-Nitrophenol	96.7	90.0	83.0	80.6
e.		88.9	94.0	89.0	80.0[c+] 89.0

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

[c+] reactions were performed in CH_2Cl_2 solutions (10ml/mmol) at 20°C.

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References and notes:

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5. Correct microanalyses, ^{1}H-NMR and I.R have been obtained for all new compounds.
6. The identity of alcohols have been established by comparison with authentic samples(T.l.c.,mp.,I.R. and ^{1}H-NMR).
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