Deprotection of Masked Steroidal Alcohols by Hydride Transfer

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Summary Hydride transfer to the trityl cation is a useful method for the deprotection of masked alcohols and should be applicable to other masked functional groups

IMPLICIT in the proposed mechanism for the oxidation of acetals by hydride transfer[1] is the oxidation of benzyl, benzyloxycarbonyl, tetrahydropyranyl and bismethylenedioxy protecting groups for the hydroxy-group

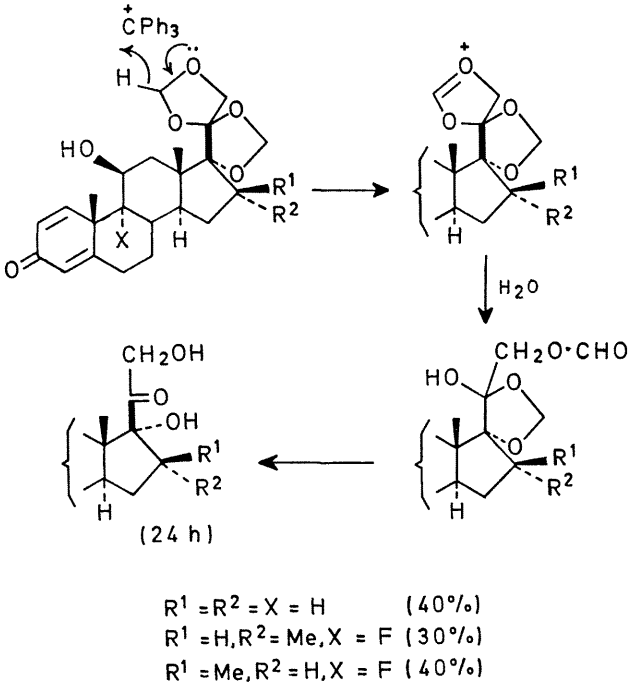
Several benzyl ethers were prepared and treated with tritylfluoroborate [1,2] The results (Table 1) demonstrate

TABLE 1

Ether	Temp.	Time of reaction	Product	Method	Yield (%)
$PhCH_2OMe$ [3a]	20°	2 h	PhCHO	P.l.c.[a]	75
p-$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}OMe$ [3b]	20	10 min	p-$MeO{\cdot}C_6H_4{\cdot}CHO$ ..	P.l.c.	25
p-$(PhCH_2{\cdot}O){\cdot}C_6H_4{\cdot}NO_2$ [3c]	Reflux	4 days	p-$HO{\cdot}C_6H_4{\cdot}NO_2$ ..	P.l.c.	50
p-$(PhCH_2{\cdot}O{\cdot}CH_2){\cdot}C_6H_4$ [3d]	20	14 h	PhCHO	N.m.r.	>90
$PhCH_2{\cdot}O{\cdot}Chol$ [3e]	20	4 h	Cholesterol	G.l.c.	60
			Cholest-4-en-3-one ..	G.l.c.	20
p-$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}O{\cdot}Chol$	20	30 s	Cholesterol	G.l.c.	75—85
3,5-Me_2,4-$OMe{\cdot}C_6H_2{\cdot}O{\cdot}Chol$ ..	20	5 min	Cholesterol	G.l.c.	85—90
Cholesterol	20	6 h	Cholest-4-en-3-one ..	G.l.c.	50

[a] Plate layer chromatography.

that the benzyl hydrogen atoms are sufficiently basic to give a benzyloxonium ion (Scheme 1). To determine the



$R^1 = R^2 = X = H$ (40%)
$R^1 = H, R^2 = Me, X = F$ (30%)
$R^1 = Me, R^2 = H, X = F$ (40%)

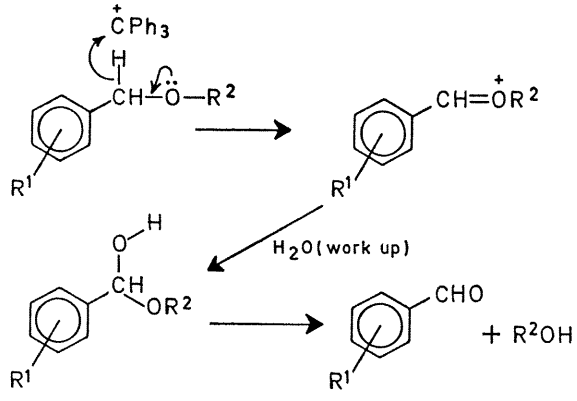
SCHEME 1

nature of the non-oxidised part of the benzyl ethers some cholesterol benzyl ethers were prepared (Table 1). The relative rates of debenzylation parallel the rate of hydrolysis of the corresponding benzyl chlorides.[4a-e]

The extension of this procedure to the benzyloxycarbonyl protecting group is shown in Table 2. Benzyloxycarbonyl cholesterol did not react at all, presumably because electron withdrawal by the carbonyl group induces electron shift opposite to that required to stabilise a benzyloxonium ion. Reactions at 0° were generally cleaner. The observed order of reactivity of the substituted benzyl esters is in accordance with the order of their reactivity in solvolyses.[4a-e]

The above method offers an extremely mild and neutral procedure for the deprotection of benzyl ethers and benzyloxycarbonyl esters or for the oxidation of benzyl ethers to aldehydes.

The bismethylenedioxy (BMD) protecting group offers a method of masking αα′-dihydroxy-ketones. The BMD derivatives of prednisone[5] (Scheme 2; $R^1 = R^2 = X = H$),



SCHEME 2

dexamethasone ($R^1 = H$, $R^2 = Me$, $X = F$), and betamethasone ($R^1 = Me$, $R^2 = H$, $X = F$) were treated with

TABLE 2

Ester	Temp.	Time of reaction	Yield (%)
$PhCH_2{\cdot}O{\cdot}C(O){\cdot}O{\cdot}Chol$ [5]	20°		No reaction
p-$MeO{\cdot}C_6H_4{\cdot}CH_2{\cdot}O{\cdot}C(O){\cdot}O{\cdot}Chol$	20	4·5 min	60—80
	0	6 min	90
3,5-Me_2,4-$MeO{\cdot}C_6H_2{\cdot}CH_2{\cdot}O{\cdot}C(O){\cdot}O{\cdot}Chol$ ..	20	16 min	80
3,4-$(MeO)_2{\cdot}C_6H_3{\cdot}CH{\cdot}O{\cdot}C(O){\cdot}O{\cdot}Chol$ ..	20	1—2 min	
	0	15 min	90
	−20	2 h	
3,4,5-$(MeO)_3C_6H_2{\cdot}CH_2{\cdot}O{\cdot}C(O){\cdot}O{\cdot}Chol$ ..	20	1 h	70

The product was cholesterol, determined by g.l.c.

tritylfluoroborate (24 h). (See Scheme 2). The 21-*O*-formate was not isolated but its presence, before hydrolysis (Na_2CO_3–H_2O), was indicated by spectral data (τ 1·9, 1HS), ν_{max} 1725 cm^{-1}.

Finally cholesterol tetrahydropyranyl ether on treatment with tritylfluoroborate gave cholesterol (67%) and tritylmethane (100%).

It is clear that this method of deprotecting masked hydroxy-groups should be applicable to other functional groups (*e.g.* NH, CO_2H, OAr *etc.*).

All new compounds gave satisfactory spectral and microanalytical data.

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† All reactions were carried out in dichloromethane and worked-up by quenching with aqueous sodium hydrogen carbonate. Chromatographic separation of tritylmethane was essential.

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