CHEMISTRY LETTERS, pp. 2163-2166, 1994.

Proximately Assisted and Chemoselectively Cleavable Protecting Groups for Alcohols, 2-[2-(Arylmethyloxy)ethyl]benzoic Esters

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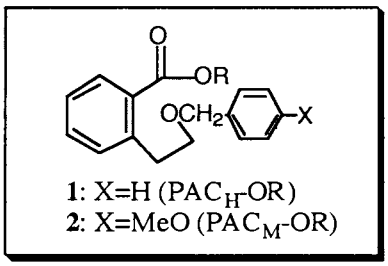
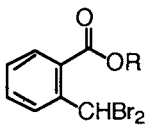
Alcohols were protected by esterification with new protecting reagents, 2-[2-(arylmethyloxy)ethyl]benzoic acids and the esters were chemoselectively deprotected in a proximately assisted manner even in the presence of acetyl, levulinyl, and silyl groups.

The benzoyl group is frequently employed for the protection of a hydroxyl function and the benzoate is more stable than the acetate. During our investigation on the synthesis of phosphatidylinositol phosphates,[1] we required the protection of an inositol hydroxyl group as a benzoate derivative which can be deprotected without injuring the glyceryl ester moieties of fatty acids. Intramolecular nucleophilic replacement is an attractive strategy for such deblocking purposes. Although this type of the deprotection reaction has been utilized for cleaving a variety of carboxylic esters,[2] they were mainly aliphatic esters such as 4-*O*-substituted 4-hydroxybutyrate.[2g] only **3**[2d] and **4**[2g),2i] were the benzoic esters with additional masked functionalities at the ortho position. However since these appendages are situated at the benzylic position, catalytic hydrogenation conditions can not be employed for deprotection. Furthermore, their applicability has not been available. As ideal protecting forms for our purposes, we have now devised 2-(2-benzyloxyethyl)benzoyl (**1**, PAC_H-OR) and 2-[2-(4-methoxybenzyloxy)ethyl]benzoyl derivatives (**2**, PAC_M-OR) referred to as the proximately assisted cleavable group with suffixes H and M meaning X=H and MeO. The benzyl moieties in **1** and **2** may be removed at the deprotection stage by various types of reactions depending on the derivatives: hydrogenolysis or the reaction with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or $AlCl_3$-$PhNMe_2$. We demonstrate here the wide applicability of PAC groups for the protection of alcohols.



1: X=H (PAC_H-OR)
2: X=MeO (PAC_M-OR)



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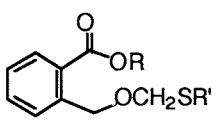
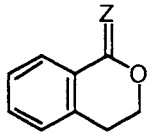
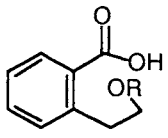


4 (R'=Me, ^{i}Pr)

The protecting reagents, PAC-OH **8**[3] and **9** were readily prepared in high overall yield starting from commercially available isochroman **5** according to the procedures shown in Scheme 1. The reaction of various alcohols with PAC-OH in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP)[4] afforded the corresponding benzoic esters, PAC-OR in excellent yields (Table 1).



5: Z=H x 2
6: Z=O

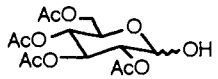


7: R=H[5]
8: R=$PhCH_2$
9: R=*p*-MeOPhCH_2

i (**5** to **6**): SeO_2 (100%); ii (**6** to **7**): NaOH then H_2SO_4 (98%);
iii (**7** to **8** or **9**): ArCH_2Cl, NaH (86% for **8**, 90% for **9**)

Scheme 1. Preparation of protecting reagents.

Table 1. Preparation of benzoic esters **1** and **2**[a]

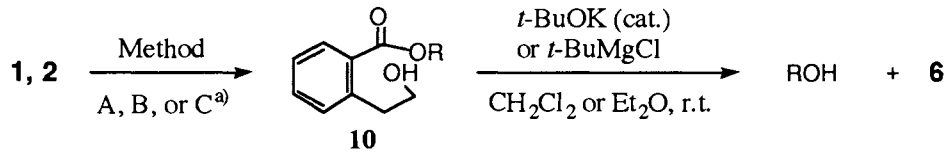
Run	X	ROH	PAC-OR	Yield, %
1	H	$Ph(CH_2)_3OH$	**1a**	100
2	H	$CH_3(CH_2)_{17}OH$	**1b**	87
3	H	3β-Cholestanol	**1c**	95
4	MeO	$CH_3(CH_2)_{17}OH$	**2a**	100
5	MeO	3β-Cholestanol	**2b**	100
6	MeO	Cholesterol	**2c**	95
7	MeO		**2d**[b]	95
8	MeO	$BzO(CH_2)_2CH(Me)OH$[c]	**2e**	87

a) A mixture of PAC-OH (1.2 equiv.) and an alcohol (1.0 equiv.) in CH_2Cl_2 (10 ml/1 g alcohol) was treated with DCC (1.5 equiv.) and DMAP (1.2 equiv.) at room temperature for about 4 h. b) α/β = ca. 1. c) Bz=benzoyl.

Deprotection of benzyloxybenzoates, PAC_H-OR **1** was first examined. Hydrogenolysis conditions using 5% Pd-C as a catalyst under a hydrogen atmosphere in ethyl acetate gave the debenzylated derivatives **10** which was then treated after filtration of the catalyst with a catalytic amount (10 mole%) of *t*-BuOK in CH_2Cl_2 at room temperature to afford the corresponding deblocked alcohol in excellent yields (Scheme 2 and Table 2). Use of $Pd(OH)_2$ in place of Pd-C realized the direct deprotection of 3β-cholestanyl ester **1c** (r.t., 27 h) affording cholestanol in 92% yield. Difference in reactivities of Pd-C and $Pd(OH)_2$ is now under investigation.

The cleavage of PAC_M-OR, **2** was accomplished by successive treatment with DDQ[6] or $AlCl_3$-*N*,*N*-dimethylaniline[7] as well as catalytic hydrogenolysis conditions and with *t*-BuOK. The procedure realized smooth deprotection of cholesteryl ester **2c** keeping the double bond intact in 86% yield by treatment with DDQ and subsequent with a catalytic amount of *t*-BuOK. The most desirable feature of **1** and **2** as protecting functions is that these ester groups are deblocked without affecting other acyl functions and protecting groups labile toward nucleophiles. To demonstrate this subject, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl methoxybenzyloxyethyl-benzoate **2d** was treated with DDQ or the aluminum reagent and with *t*-butoxide to give 1-hydroxy derivative successfully without migration of acetyl groups in a satisfactory yield (Runs 9 and 10 in Table 2). Selective removal of the parent benzoyl group instead of the PAC must be impossible in the presence of the more reactive acetyl one in the same molecule. The deprotection for 1-*O*-benzoyl-3-*O*-PAC_M derivative **2e** of 1,3-butanediol was successfully accomplished by treating with DDQ and then with *t*-BuMgCl (0.35 equiv) at -10 °C (Run 11 in Table 2). When *t*-BuOK was employed in this case, a serious amount of migration product, 3-*O*-benzoyl derivative was formed along with 1-benzoate. Usefulness of alkoxymagnesium salt was demonstrated in the

Grignard reagent-assisted removal of acyl functions.[8] The PAC_M group in the inositol derivatives **11** and **12** bearing the levulinyl and triethylsilyl groups was selectively removed in a similar manner (DDQ then *t*-BuOK) in 82 and 100% yields respectively. On the other hand, the levulinyl group was removed from **11** in a completely selective manner in 91% yield by treatment with hydrazine in pyridine and acetic acid.[2b]



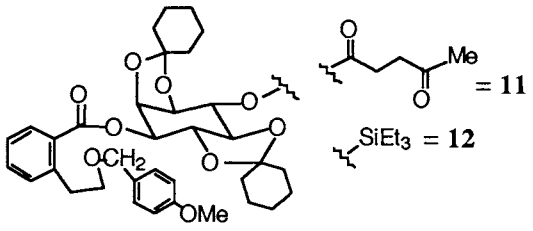
a) A: H_2, Pd-C, AcOEt, r.t.; B: DDQ, CH_2Cl_2-H_2O (18:1), 0 °C or r.t.; C: $AlCl_3$, $PhNMe_2$, CH_2Cl_2, r.t.

Scheme 2. Deprotection procedures.

Table 2. Deprotection of PAC-OR, **1** and **2**

Run	PAC-OR	Method[a)]	Reaction time[b)]		Yield, % of ROH[c)]
			1st step	2nd step	
1	**1a**	A	on	40 min	85
2	**1b**	A	2.5 h	30 min	89
3	**1c**	A	on	40 min	96
4	**1c**	A'[d)]	27 h	-	96
5	**2a**	B	3.0 h	30 min	94[e)]
6	**2a**	C	3.0 h	60 min	91
7	**2b**	B	3.0 h	15 min	98
8	**2c**	B	3.0 h	5 min	85[e)]
9	**2c**	B	3.0 h	10 min	84[f)]
10	**2d**	B	2.5 h	60 min	82
11	**2d**	C	1.0 h	60 min	88
12	**2e**	B	3.0 h	10 min	95[e,g)]

a) For explanation of methods used here, see Scheme 2. b) on = overnight. c) Overall yield. d) In Method A' $Pd(OH)_2$ was employed in place of Pd-C in Method A. e) Hydroxy intermediate **10** was purified by chromatography on silica gel while it was usually treated without purification with the base. f) Ethyl ether used as the solvent. g) In the 2nd step, *t*-BuMgCl (0.35 equiv) in place of *t*-BuOK was used in THF at -10 °C.



Isolation of the intermediate **10** was usually not necessary while, when a final deblocked alcohol such as stearyl alcohol can not be separated easily from *p*-methoxybenzaldehyde generated in the case of DDQ, its separation was carried out prior to the reaction with *t*-butoxide. Cyclization of **10** was completed within 15 min at

room temperature or even at -10 °C as monitored by TLC, however, in many cases described here, the reactions were continued from 30 to 60 min.

Deprotection of cholestanyl *p*-methoxybenzylbenzoate **2b** (Method B): A mixture of **2b** (251 μmol), DDQ (309 μmol), CH_2Cl_2 (2 ml), and H_2O (110 μml) was stirred for 3 h at r.t. and saturated aqueout $NaHCO_3$ solution and ethyl ether were added. The organic layer was washed with the same carbonate solution (twice) to remove the resultant hydroquinone and subsequently with brine, dried, filtered, and evaporated. The residue in CH_2Cl_2 (2 ml) was treated with *t*-BuOK (27 μmol) for 15 min at r.t. After addition of 1N HCl and ethyl ether, the organic layer was washed with H_2O and brine, dried, evaporated, and chromatographed to give cholestanol (98% yield).

Deprotection of stearyl p-methoxybenzylbenzoate **2a** (Method C): A solution of **2a** (175 μmol) in CH_2Cl_2 (1 ml) was treated with $AlCl_3$ (670 μmol) and *N,N*-dimethylaniline (710 μmol) for 3 h at r.t. After addition of 1N HCl and ethyl ether, the ethereal solution was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. After treatment of the residue with *t*-BuOK (21 μmol) for 60 min as above, stearyl alcohol was isolated in 91% yield by column chromatography on silica gel.

In summary, PAC_H and PAC_M groups can be introduced to the hydroxyl group in high yields. These esters were cleaved efficiently under various reaction conditions even in the presence of acetyl, levulinyl, and silyl groups in the same molecule. The protecting reagents, PAC_H-OH and PAC_M-OH are readily prepared. Therefore, PAC derivatives **1** and **2** can be utilized widely and efficiently for the protection of alcohols.

This work was financially supported in part by CIBA-GEIGY Foundation (Japan) for the Promotion of Science, and the Grant-in -Aid for Scientific Research on Priority Areas No. 06240105 from the Ministry of Education, Science and Culture, Japan.

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(Received August 26, 1994)