Mild and Chemoselective Deacetylation Method Using a Catalytic Amount of Acetyl Chloride in Methanol

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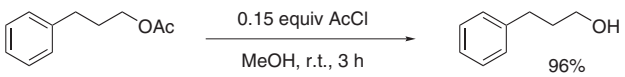
Abstract: Efficient deacetylation of alcohol acetates under mild acidic conditions was accomplished with a catalytic amount of acetyl chloride in methanol. Acetates of various primary, secondary, aromatic and sugar alcohols were successfully deprotected. Highly chemoselective removal of acetyl groups in presence of other commonly employed esters was also achieved in excellent yields. The reactivity of this transesterification-mediated deacetylation was found to be directly dependent upon the electronic and steric nature of the acetates.

Key words: acetyl chloride, acetate, catalytic, chemoselective, protecting group

Acetyl group has been frequently employed as a protecting group for alcohols based upon its ready installation and cleavage.[1] The acetylation/deacetylation protocol has gained much popularity in organic synthesis due to readily available precursors, clean spectroscopic indication of the products, and addition of minimal molecular weight, especially in carbohydrate chemistry.

However, in cases where different esters are present in one molecule, cleavage of an acetate under basic conditions often suffers from poor chemoselectivity. In relation to this, many methods have been developed for selective deacetylation in presence of other esters, in particular benzoate ester, such as 50% NH_3,[2a] guanidine,[2b] guanidine/guanidinium nitrate,[2c] DBU,[2d] Sm/I_2,[2e] Bu_2SnO,[2f] and magnesium in methanol.[2g] Most of the protocols mentioned above involve either basic or reductive methods. After a brief report on HCl-mediated deprotection of an acetate during leukotriene C-1 synthesis,[3a,b] several methods have successfully achieved selective acetyl cleavage under acidic conditions, including $HBF_4{\cdot}OEt_2$[3c,d] and *p*-TsOH.[3e,f]



Equation 1

From our ongoing research on the development of efficient protocol for the cleavage of alcoholic protecting groups, we encountered fast deprotection of acetate simply through the use of a catalytic amount of acetyl chloride in methanol. This is quite intriguing since the acetyl chloride is usually utilized as an acetylating reagent. On a model study, when acetyl chloride was introduced to the methanolic solution containing acetic acid 3-phenyl propyl ester, the acetyl group was deprotected cleanly within three hours at room temperature (Equation 1). Moreover, only a catalytic amount (15 mol%) of acetyl chloride was required for the removal of an acetyl group. This preliminary result prompted us to investigate the scope and selectivity of this protocol.

First, various solvents were examined and methanol was found to be an essential element for effective deacetylation. It was also found that the rate of acetate cleavage depends highly upon the Lewis basicity of the alcohol oxygen and steric environment. Deacetylation results on various substrates under optimized conditions are summarized in Table 1. Unhindered primary acetates (entries 1 and 3–6) underwent deacetylation smoothly with 15 mol% of acetyl chloride in methanol within a few hours. Hindered primary (entry 7) or secondary acetates (entries 2, 8, and 14) were also cleaved satisfactorily with slightly increased amount of acetyl chloride in prolonged reaction periods. In case of benzylic acetates, a significant influence of the *para*-substitution was noted on the rate of the reaction; while *p*-methylbenzyl alcohol acetate underwent deacetylation in 3.5 hours (entry 3), it took 20 hours for the *p*-nitro-substituted derivative (entry 4). This strongly indicates that the rate-determining step involves the initial protonation of the carbonyl oxygen. Allylic (entry 5) and propargylic (entry 6) acetates were deprotected without any structural rearrangement. Moreover, acetate removal of a serine derivative (entry 7) proceeded with no loss of stereochemical integrity, which is often a problem in basic hydrolysis. Application of this protocol to phenolic acetates was also successful. As in the case of benzylic acetates, the electronic nature of the substituents appeared to govern the rate of cleavage; electron donating methoxy group at the *para*-position of the benzene ring greatly accelerated the reaction (entry 10), whereas electron-withdrawing nitro group slowed the rate significantly (entry 12).

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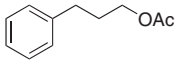
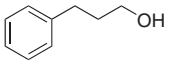
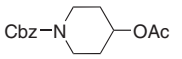
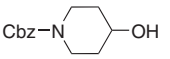
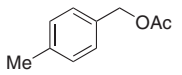
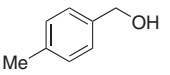
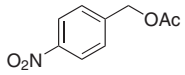
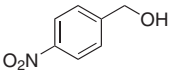
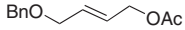
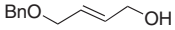
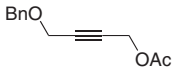
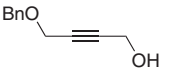
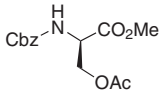
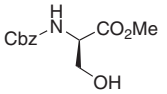
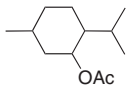
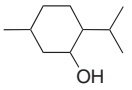
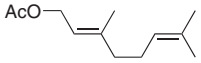
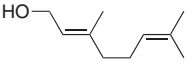
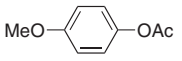
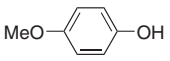
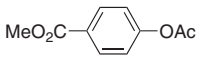
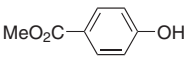
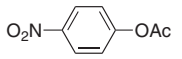
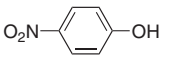
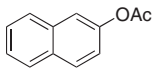
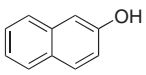
Table 1 Deprotection of Various Acetates Using a Catalytic Amount of Acetyl Chloride in Methanol

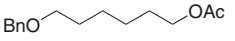
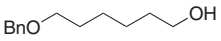
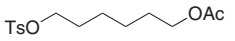
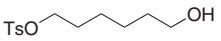
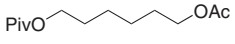
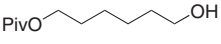
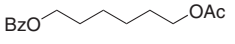
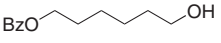
Entry	Substrate	Product[a]	Amount of AcCl, reaction time	Yield (%)[b]
1			15 mol%, 3 h	96
2			30 mol%, 4.5 h	89
3			15 mol%, 3.5 h	93
4			15 mol%, 21 h	96
5			15 mol%, 4.5 h	88
6			15 mol%, 4.5 h	93
7[c]			15 mol%, 15 h	91
8			30 mol%, 18 h	82
9			10 mol%, 4.5 h	74
10			15 mol%, 2 h	96
11			15 mol%, 5 h	99
12			15 mol%, 16 h	98
13			15 mol%, 3.5 h	98
14[d]	Cholestrol-Ac	Cholesterol	30 mol%, 16 h	91

[a] All products were identified by ^{1}H NMR and ^{13}C NMR spectra.
[b] Yields of isolated alcohols.
[c] No epimerization occurred during deacetylation; $[\alpha]_D^{28}$ 12.5 (*c* 1.00, MeOH).[4]
[d] Reaction was carried out in CH_2Cl_2–MeOH, 3:2 due to poor solubility of cholesterol in methanol.

To screen the chemoselectivity of the deacetylation reactions, 1,6-hexanediol monoacetates with various ω-alcohol substituents were examined (Table 2). Notably, when the deacetylation was carried out in the presence of benzyl (entry 1), *p*-toluenesulfonyl (entry 2), pivaloyl (entry 3), benzoyl (entry 4) and methyl ester (entry 7 of Table 1) groups, all the functional groups survived the deacetylation conditions and the desired monoalcohols were obtained in excellent yields (Table 2).

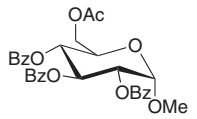
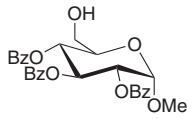
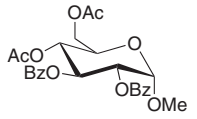
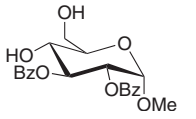
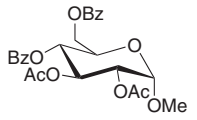
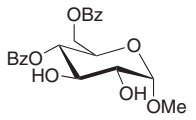
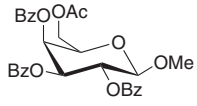
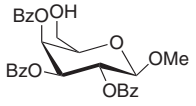
Chemoselective deacetylation of sugar acetate derivatives is important in light of the growing interest in glycopeptides and oligosaccharides. Extending our methodology toward sugar chemistry, we have examined various monosaccharide derivatives possessing both acetyl and benzoyl groups under the selective acetate cleavage conditions (Table 3). Due to steric congestion in the sugar derivative, 30–50 mol% acetyl chloride and longer reaction times were required for the removal of acetates. However, primary acetate moiety of glucose and galactose derivatives (entries 1 and 4, respectively) and both primary and secondary acetate moieties of glucose derivative (entry 2) were cleanly deprotected without touching the benzoyl group. Chemoselective removal of the 2,3-diacetates in the presence of primary benzoate group of glucose derivative was also successful providing 73% yield of the desired diol (entry 3). It is of a particular note that the deacetylation of the sugar derivatives occurred without any hint of epimerization at the anomeric stereocenter.

Table 2 Chemoselective Cleavage of Acetates in Presence of Other Esters[a]

Entry	Substrate	Product	Amount of AcCl, reaction time	Yield (%)[b]
1			15 mol%, 5 h	94
2			15 mol%, 4 h	94
3			15 mol%, 4.5 h	94
4			15 mol%, 4.5 h	92

[a] All products were identified by ^{1}H NMR and ^{13}C NMR spectra.
[b] Yields of isolated alcohols.

Table 3 Chemoselective Cleavage of Acetates in Sugar Derivatives in the Presence of Benzoyl Group[a]

Entry	Substrate	Product[b]	Amount of AcCl , reaction time	Yield (%)[c]
1[5a]			30 mol%, 22 h	93
2[5b]			50 mol%, 22 h	89
3			50 mol%, 24 h	73
4[5c]			30 mol%, 22 h	93

[a] Reaction was carried out in CH_2Cl_2–MeOH, 1:1 due to poor solubility of sugars in methanol.
[b] All products were identified by ^{1}H NMR and ^{13}C NMR spectra.
[c] Yields of isolated alcohols.

In summary, a simple and efficient deacetylation method was established using acetyl chloride in methanol, which is operationally very straightforward and chemoselective, utilizing only a catalytic amount of the reagent. The only by-product is methyl acetate, which can be easily removed by simple evaporation. Therefore in almost all the cases basic extraction and filtration through a pad of silica gel is sufficient to provide the desired alcohols in pure form.[6]

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(6) **Representative Procedure.**
To a magnetically stirred solution of acetic acid 3-phenylpropyl ester (1.43 g, 8.00 mmol) in MeOH (8 mL), was added acetyl chloride (0.084 mL, 1.2 mmol) at r.t. The mixture was stirred for 3 h at r.t. and the reaction was quenched upon addition of sat. aq $NaHCO_3$ solution (20 mL). The mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic extract was dried over anhyd $MgSO_4$, filtered and concentrated. The resulting residue was purified through a pad (ca. 5 cm) of silica gel column to provide the desired alcohol (1.05 g, 96% yield).