

Removal of Acyl Protecting Groups Using Solid NaOH and a Phase Transfer Catalyst

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Abstract: Acetyl-, benzoyl- and pivoyl-protected alcohols and phenols undergo smooth deacylation in a two-phase system of powdered NaOH and Bu₄NHSO₄ in THF or CH₂Cl₂.

Key words: protecting groups, alcohols, phase-transfer catalysis, acyl groups, deprotection

As synthetic targets have become increasingly complex, the importance of protecting groups has grown.^{1–3} Although silyl ethers have achieved prominence as a means of protecting alcohols, acyl protecting groups continue to be widely used and development of new methods for their removal remains an area of active research.³ Generally, acetyl-, benzoyl- and pivoyl-protecting groups are removed via alkaline hydrolysis.^{1,2} A number of uses of hydroxide^{4–6} and alkoxide-containing reagents^{6–12} have been described for deacylation under homogeneous conditions. But, to the best of our knowledge, solid-liquid heterogeneous systems have not been pursued despite possible advantages such as ease of application, simple workup and inexpensive, relatively safe reagents.¹³ During our studies on the selective deprotection of silyl-protected phenols, we discovered that a two-phase system of solid NaOH in 1,4-dioxane containing a phase transfer catalyst¹⁴ also hydrolyzed acetyl-protected alcohols as well as methyl esters.¹⁵ We have now investigated the generality of this method for the removal of acyl protecting groups and wish to report our findings.

Desilylation of aryl silyl ethers was best effected using 1,4-dioxane as solvent.¹⁵ Hoping to use a more common, readily-available solvent and to optimize the amount of NaOH needed, a series of reactions was run in CH₂Cl₂ or THF with varying quantities of NaOH (Table 1). Yields of the isolated alcohol were compared and, although CH₂Cl₂ was useful, slightly better results were obtained using THF. Additionally, 10 equivalents of powdered NaOH provided the highest yields with larger excesses of NaOH failing to improve yields. No attempt to adjust the amount of phase transfer catalyst was made.

With optimized reaction conditions in hand, a series of acetyl-, benzoyl- and pivoyl-protected alcohols was prepared and subjected to the reaction conditions and the

Table 1 Effect of Solvent and Quantity of NaOH on Deacetylation^a

Equiv of NaOH	THF	CH ₂ Cl ₂
3	68%	51%
5	75	62
8	88	76
10	93	89

^a Isolated yields are given; all products were spectrally identical with the authentic alcohol.

products were isolated (Table 2). The reaction is general for acyl-protected 1° alcohols as well as acetyl- and benzoyl-protected 2° alcohols. It is noteworthy that, after the usual reaction time of 3 hours, a pivoyl-protected 2° alcohol (entry **3c**) was largely unreacted with only 7% of hydrolyzed product being recovered. After 24 hours, however, a more satisfactory yield was achieved. This result is being investigated as a possible means of selective deprotection.^{9–11}

The stability of silyl-protected alcohols to these conditions is illustrated by the recovery of a TIPS-protected alcohol from a deacetylation reaction (entry 6). This result is in accord with our earlier observation that, under these reactions conditions, silyl-protected alcohols are stable while aryl silyl ethers undergo desilylation.¹⁵

When subjected to these conditions, acyl-protected phenols produced interesting results. Initial attempts to deprotect 4-*t*-butylphenyl acetate **1a** produced modest results. However, when dry THF was used, the reaction mixture was purged with argon and the reaction was conducted under an inert atmosphere, the yield of 4-*t*-butylphenol **2** was considerably improved (Scheme 1). When open to the air, deacylation reactions of acyl-protected phenols produced considerable quantities of brightly-colored baseline residue. But when air was excluded, little or no such material formed. Benzoyl- and pivoyl-protecting groups were also removed to produce 4-*t*-butylphenol in good yield (Scheme 1).

The effect of steric hindrance due to neighboring *ortho* substituents was also examined. Although reaction times of 16–18 hours were required, 2,6-dimethylphenyl acetate

Table 2 Deprotection of Acyl-Protected Alcohols^a

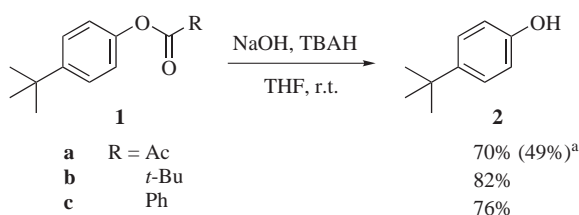
Entry	Substrate	Product/yield
1		 a R = Me 93% b Ph 96% c <i>t</i> -Bu 95%
2		 a R = Me 55% b Ph 88%
3		 a R = Me 93% b Ph 54% (94%) ^b c <i>t</i> -Bu 7% (63%) ^b
4		 92% ^b
5		 87%
6		 75%

^a All products were identified with 300 MHz ¹H NMR and compared with authentic alcohol.

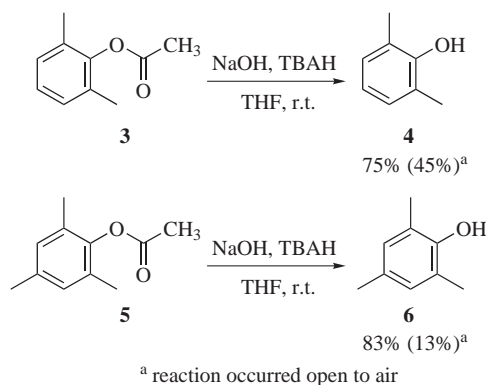
^b Reaction time was 24 hours.

3 and 2,4,6-trimethylphenyl acetate **5** were deprotected using this method (Scheme 2).

A typical procedure is as follows: The acyl-protected alcohol (1 equiv), powdered NaOH (10 equiv), Bu₄NHSO₄ (0.5 equiv) and THF (5 mL/mmol of substrate) were combined in a round-bottomed flask, purged with argon and stirred under an inert atmosphere at room temperature. When TLC indicated the disappearance of starting material (typically 3 hours), the mixture was filtered through a Celite pad (phenol products were filtered through acidic alumina), washing with Et₂O. Evaporation of the solvent followed by column chromatography yielded the deprotected alcohol. Powdered NaOH was prepared by grinding NaOH pellets with a mortar and pestle in a glovebox un-



^a reaction occurred open to air

Scheme 1**Scheme 2**

der an inert atmosphere. THF was distilled from sodium-benzophenone prior to use.

In summary, we have devised a new method for the removal of acetyl-, benzoyl- and some pivoyl-protecting groups from acyl protected alcohols utilizing a two-phase system with tetrabutylammonium hydrogen sulfate as phase transfer catalyst. Furthermore, based on our previous work,¹⁵ this method does not affect alkyl silyl ethers but does deprotect aryl silyl ethers.

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