Chemoselective Cleavage of Benzyl Ethers, Esters, and Carbamates in the Presence of Other Easily Reducible Groups

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Abstract: Mild experimental conditions are reported that permit the selective cleavage of benzyl protecting groups in the presence of other easily reduced groups such as aryl chlorides and bromides, cyclopropanes, and alkenes, using triethylsilane and palladium chloride.

Key words: protecting group, hydrogenolysis, benzyl group, deprotection

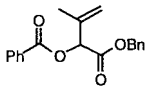
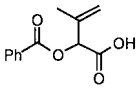
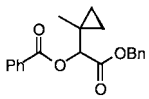
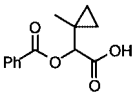
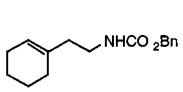
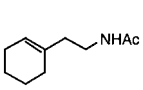
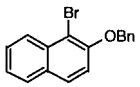
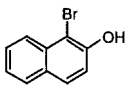
Protecting groups play a central role in modern organic synthesis,[1,2] and the ability or inability to achieve selective deprotection of one protecting group in the presence of another is key to the success or failure of a synthetic route. Related to this concept of orthogonality is a central requirement for a useful protecting group: that it can be removed selectively in the presence of other functional groups in the molecule.

The benzyl group plays a central role in many protecting groups for alcohols, carboxylic acids, and amines, among other functional groups.[1,2] Benzyl ethers and benzyloxymethyl ethers are commonly used protecting groups for alcohols, and benzyl esters offer respite from the normal nucleophilic acyl substitution mechanism commonly used for cleavage of esters. The benzyl carbamate or CBz group is one of the most widely used protecting group for amines.

A number of years ago, Sakaitani and Ohfune published a report[3] on reductive cleavage of benzyl and *tert*-butyl carbamates with trialkylsilanes that was based on an earlier description[4] by Birkofer and co-workers of the silane-promoted cleavage of benzyl carbamates, both catalyzed by palladium. We have found the Birkofer reaction conditions (Et_3SiH, $PdCl_2$, Et_3N, CH_2Cl_2) especially useful for removing benzyl carbamates in highly sensitive intermediates in the synthesis of the azinomycin family of antitumor agents,[5] where we found an aziridine *N*-CBz group would undergo facile cleavage in the presence of an alkene and vinylic bromide. None of these functional groups survived more traditional conditions for hydrogenolysis.

We have taken a more careful look at this reaction for cleavage of benzyl groups, and we have found these remarkably mild conditions to be compatible with a variety of easily reduceable functional groups such as alkenes, aryl chlorides, and cyclopropanes.[6] The conditions were not totally compatible with a more easily reduced aryl bromide. We feel that this method may be of use in systems where benzyl ethers, esters, or carbamates must be removed under exceptionally mild conditions in the presence of functional groups that would react with hydrogen over palladium metal.

Table Benzyl Group Hydrogenolysis Reactions

	Substrate	Product	Yield
1			71%
2			70%
3			68%
4			71%
5			66%

The results of our study are detailed in the Table. All reactions were performed under a standard set of reaction conditions involving catalytic palladium acetate, substoichiometric triethylamine, excess triethylsilane (1.5–2 equiv) in dichloromethane at room temperature. Reaction times varied from 10–12 h. Hydrogenolysis of benzyl esters in the presence of both an alkene (entry 1) and cyclopropane (entry 2) afforded the corresponding carboxylic acids directly in good yields. Similarly, benzyl carbamates could be removed in the presence of alkenes (entry 3), and in this case the crude reaction mixture was treated with acetyl chloride and Et_3N prior to isolation to facilitate purification. Aryl chlorides proved robust to the hydrogenolysis reaction conditions, and removal of the benzyl ether of *m*-chlorophenol (entry 4) afforded the corresponding phenol, which was isolated as the acetate ester to reduce losses from volatility. With relatively hindered

aryl bromides such as the benzyl ether of 1-bromo-2-naphthol (entry 5), hydrogenolysis was selective for the benzyl group, and the parent compound was isolated directly in moderate yield. In this instance and on occasion in others, some starting material remained, and forcing the reaction to completion allowed hydrogenolysis of the aryl bromide to compete with benzyl ether cleavage. This was a greater problem with less crowded aryl bromides such as the benzyl ether of *p*-bromophenol or benzyl ester of *p*-bromobenzoic acid, where bromide hydrogenolysis was fully competitive with benzyl group cleavage (data not shown), thus establishing a limitation of this methodology. With phenolic substrates, we observed the corresponding *O*-triethylsilylphenol as the intermediate product of the reaction, necessitating a separate desilylation reaction, which could be accomplished upon workup by treatment with either Bu_4NF or acetic acid under standard conditions.[7]

In summary, we have delineated the scope of the selective removal of benzyl groups using triethylsilane catalyzed by palladium acetate. We found complete selectivity for benzyl ester and carbamate removal in the presence of alkenes and cyclopropanes. In the presence of aryl chlorides, we could selectively remove a benzyl ether, but with aryl bromides, the selectivity was substrate dependent. In any event, this methodology increases the utility and orthogonality of benzyl protecting groups.

Cleavage of Benzyl Groups (Entry 1); General Procedure

A solution of $Pd(OAc)_2$ (11.7 mg, 0.052 mmol), Et_3SiH (0.25 mL, 1.6 mmol) and Et_3N (22 μL, 0.157 mmol) in anhyd CH_2Cl_2 (4 mL) was stirred at 23 °C under N_2 for 15 min. A solution of benzyl 2-benzoyloxy-3-methylbut-3-enoate (0.360 g, 1.16 mmol) was added dropwise. The mixture was stirred at 23 °C under N_2 for 12 h before quenching by the addition of sat. aq NH_4Cl (15 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (silica gel, 5% CH_3OH/CH_2Cl_2) provided the corresponding acid as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H, CH_3), 5.21 (s, 1H, C=CH), 5.36 (s, 1H, C=CH), 5.66 (s, 1H, C2-H), 7.44 (t, 2H, *J* = 7.7 Hz, ArH); 7.57 (t, 1H, *J* = 7.7 Hz, ArH); 8.08 (d, 2H, *J* = 8.3, ArH); 10.6 (br s, 1H, CO_2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 166.1, 137.9, 134.0, 130.4, 129.6, 129.0, 118.3, 76.4, 19.2.

HRMS (EI), *m*/*z* calcd for $C_{12}H_{12}O_4$:220.0743; found:220.0735.

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