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HCl/DMF for enhanced chemoselectivity in catalytic hydrogenolysis reactions

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ABSTRACT

An improved, chemoselective hydrogenolysis method has been developed. By employing a solvent-acid combination (i.e., DMF–aq HCl) we were able to favor debenzylation rather than aromatic hydrogenation and acid-mediated bond cleavage which are the two main drawbacks of these reactions. The generality of the method, which was primarily developed as a solution to a carbohydrate problem, is shown by the successful hydrogenolysis of 1,8-naphthalide, a previously unsolved problem.

Due to the ease of formation, the chemical stability and an array of mild methods for deprotection, the benzyl group is often preferred for protection of hydroxy groups, amines, and thiols in synthetic organic chemistry. The most common method for selective debenzylation is metal-catalyzed hydrogenolysis, and palladium is usually the preferred catalyst due to less probability of saturation of aromatic structures, in contrast to platinum and ruthenium catalysts.[1]

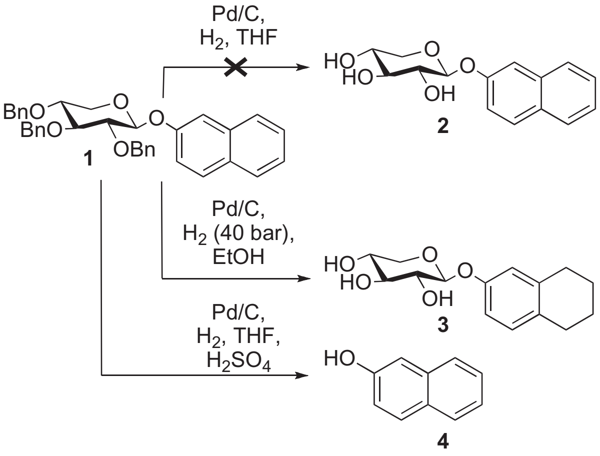
Palladium on activated charcoal (Pd/C) and palladium hydroxide [$Pd(OH)_2$] are the two most widely used types of palladium for these reactions, and common solvents include ethanol, acetic acid, tetrahydrofuran, hexanol, and toluene.[1] In addition, strong acids, such as hydrochloric acid or perchloric acid, might be used to protonate the ether oxygen atoms and thereby facilitate the debenzylation.[2] It has also been shown that chloride anions have a general rate-accelerating effect on the hydrogenolysis reactions, probably due to the formation of a highly active palladium oxochloride complex on the surface of the catalyst.[3]

In a recent project aimed at anti-tumor drugs based on naphthoxylosides we encountered unexpected selectivity problems.[4] Despite the general belief that catalytic debenzylations are simple, some cases show unusually low chemoselectivity. The straightforward debenzylation of compound **1** proved to be such an example. In preliminary investigations we tested palladium on activated charcoal (Pd/C) from several suppliers in a range of solvents (e.g., methanol, THF, ethyl acetate and acetic acid). To our great surprise, at ambient pressure, compound **1** was inert to these conditions, except for partial saturation of the naphthol residue. Moreover, the reaction in EtOH at increased hydrogen pressure (34 atm) resulted in complete saturation of the outer ring of the naphthalene unit to give compound **3** (Scheme 1). Finally, addition of acids, for example, hydrochloric or sulfuric acid, mainly resulted in cleavage of the acid-sensitive glycosidic bond to release naphthol **4**. We therefore initiated a study to find a new, efficient, and selective method for hydrogenolysis of compounds containing acid-sensitive groups as well as aromatic residues prone to saturation.

There is a plethora of palladium reagents recommended for debenzylation. Unfortunately, most reagents suitable for hydrogenolysis of benzyl ethers are also appropriate for aromatic ring hydrogenation. Since the first choice, that is, Pd/C, was not active enough, we turned our attention to the more active Pearlman's catalyst, that is, [$Pd(OH)_2$].[5]

Catalytic debenzylation of the model compound **1**, using palladium hydroxide gave good conversions in several solvents. Unfortunately, all the reactions were accompanied by saturation of the outer naphthalene ring to yield substantial amounts of compound **3** (Table 1). The formation of **3** persisted regardless of the solvent or the amount of catalyst. We were unable to separate **2** from **3** using standard purification methods.

Since the initial studies using Pearlman's catalyst resulted in unacceptable amounts of partly saturated product we then turned



Scheme 1. Reaction outcomes from the debenzylation of compound **1**.

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Table 1
Benzyl cleavage using Pearlman's catalyst

Amount of catalyst (wt %)	Solvent	Degree of saturation[a] (%)
10	EtOAc	20
20	AcOH	22
20	EtOH	No reaction
20	THF	12
100	THF	23

[a] Calculated from the crude ^{1}H NMR spectra.

to a Degussa type catalyst, which has proven valuable in earlier hydrogenolysis studies.[6] The Degussa type catalyst comprises Pd/C with 10% Pd loading (dry basis) on a wet support (50% water).

This particular catalyst was used in a series of debenzylation reactions of **1** under atmospheric pressure of hydrogen, varying the solvent (Table 2). The resulting reaction mixtures were analyzed by TLC in 1-h intervals for the first 4 h, which indicated that the fastest consumption of the starting material took place in DMF, followed by acetone and THF. The reactions in CH_3CN, EtOAc, Et_2O, toluene, 1,4-dioxane, and CH_2Cl_2 were not complete after 36 h.

Unfortunately, all the reactions were accompanied by partial saturation. Acetone proved to be the best solvent with only 13% saturation. However, it is known that preconditioning of the catalyst by simply purging the catalyst with hydrogen gas before addition of the substrate can improve the reaction. Thus, preconditioning of the Degussa type catalyst reduced substantially the proportion of saturation to low levels, that is 1% and 2% in acetone and DMF, respectively. Although these reactions gave clean conversions the yields obtained were generally low (approximately 50%).

To improve the yields and to further suppress saturation of the aromatic moiety, we introduced acid additives. Several different acids were tested using the Degussa catalyst in acetone. Although sulfuric acid accelerated significantly the reaction rate (**1** was consumed after 1 h) it gave a substantial degree of saturation (2–12%) accompanied by glycosidic bond cleavage. Trifluoroacetic acid resulted in slow conversion, the reactions were complete only after 19 h and also saturation of the aromatic moiety (3–13%). Acetic acid proved the least useful additive since these reactions were not complete even after 29 h. In contrast, addition of hydrochloric acid (37%) gave good results with respect to conversion. The reactions turned out to be dependent on the equivalents of acid used (Fig. 1). However, the conversions were accompanied by some saturation, 1–2%, and the substoichiometric yields were due to acid-catalyzed glycosidic bond cleavage yielding naphthol **4**. The yields were also clearly dependent on the work-up method. The reactions that were simply concentrated showed decreased yields of the product with increased amounts of HCl used. In contrast, neutralization with triethylamine generally increased the yields significantly. To confirm the acid-directed hydrolysis, we performed a simple experiment where compound **1** was dissolved in acetone-containing sulfuric acid, which clearly indicated the formation of naphthol.

Table 2
Benzyl cleavage using the Degussa type catalyst

Solvent	Degree of saturation without preconditioning[a] (%)	Degree of saturation with preconditioning[a] (%)
DMF	17	2
Acetone	13	1
THF	44	25

[a] Calculated from the crude ^{1}H NMR spectra.

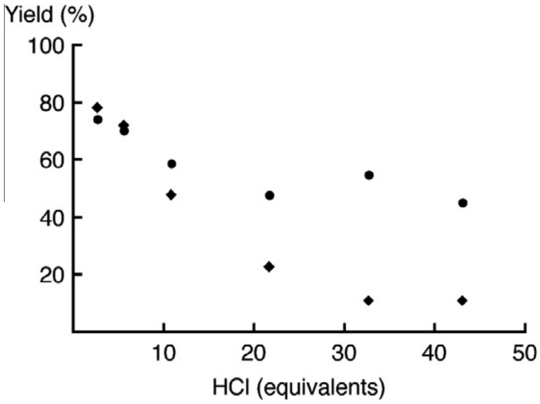


Figure 1. Debenzylation of compound **1** using the Degussa catalyst in acetone with the addition of HCl. Simple work-up with evaporation (diamonds) generally gave lower yields compared to neutralization with triethylamine (circles).

To moderate the effect of the acid, while keeping the concentration of the activating chloride anions constant, we changed the solvent from acetone to DMF. The protonated form of acetone has a pK_a of -7, similar to that of HCl.[7] On the contrary, DMF is more basic with a pK_a of the conjugated acid that is protonated DMF, of approximately -1.[8] A series of experiments in DMF was then conducted using 10% Pd/C (Degussa type) and different equivalents of HCl (Fig. 2).

The reactions in DMF showed a clearly different behavior with a maximum 88% isolated yield using 22 equiv of acid.[9] No saturated compound was found, nor was any glycosidic bond cleavage observed. In the search for alternative sources of chloride anions, LiCl and CsCl were used in similar reactions in both DMF and acetone. Generally, LiCl had a higher activating effect compared to CsCl, but neither gave results comparable with HCl, nor led to completion of these reactions, even after five days.

Subsequently, the conditions were tested under high pressure (50 bar). According to the ^{1}H NMR spectrum of the crude reaction mixture, the deprotection of **1** was successful and no saturation or glycosidic bond cleavage was observed. This stresses the role of DMF in the chemoselectivity of these hydrogenolysis reactions, allowing debenzylation, but preventing saturation and acid hydrolysis.

To further evaluate the role of DMF, and to reduce possibly its amount and thus simplifying laboratory manipulations, we tested DMF as an additive (Table 3). Although the reaction rates and yields of the product varied, the principle of using DMF/HCl as additives for selective debenzylation without the risk of over-saturation or acid-related side reactions was proved.

Finally, a number of commercially available palladium-based catalysts were submitted to these conditions, to evaluate the

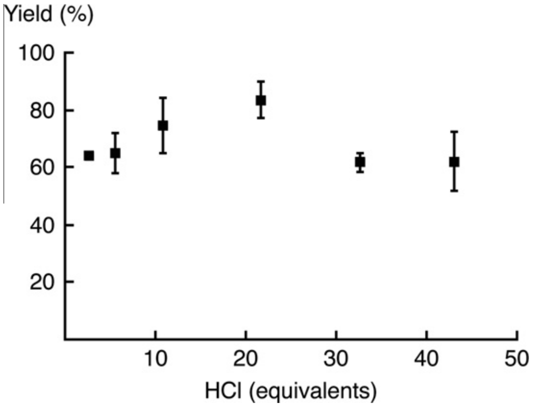


Figure 2. Debenzylation of compound **1** using the Degussa catalyst in DMF with the addition of HCl. Each data point represents at least two experiments.

Table 3
The use of DMF as an additive

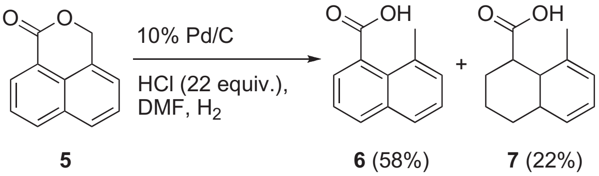
Solvent	Reaction time (h)	Yield of **2** (%)
CH_3CN	45	46
Et_2O	29	41
Toluene	Not complete (46 h)	–
Acetone	1.5	66
CH_2Cl_2	Not complete (46 h)	–
EtOAc	6	50
THF	5	54

General conditions: HCl (22 equiv), DMF (1 mL) in solvent (3 mL).

Table 4
The use of other palladium catalysts in DMF with the addition of HCl

Palladium catalyst	Reaction time (h)	Conversion[a] (**2**) (%)
10% Pd/C (Aldrich)	2.5	72
10% Pd/C, unreduced (Acros)	8	71
10–20% $Pd(OH)_2$ (Aldrich)	8	79
10% Pd/C, dry (AlfaAesar)	8	71

[a] Calculated from ^1H NMR spectra.



Scheme 2. Chemoselective hydrogenolysis of 1,8-naphthalide.

importance of the catalyst. The reactions were conducted in DMF with addition of HCl (aq 37%, 22 equiv.) at ambient pressure (Table 4).

The new conditions for debenzylation that is aq HCl in DMF, proved very useful since all the tested catalysts gave good conversions without any side reactions. However, the required reaction times were longer and the yields slightly lowered compared to the Degussa catalyst.

To prove the general usefulness of this method, we examined the hydrogenolysis of 1,8-naphthalide **5** which gave the expected 8-methyl-1-naphthoic acid (**6**) in 58% yield (Scheme 2).[10]

Chemoselective hydrogenolysis of 1,8-naphthalide was, until now, an unsolved problem. Pourahmady et al. originally submitted 1,8-naphthalide **5** to different hydrogenolysis conditions, but all attempts led to a mixture of tetralin products.[11] The problem turned out to be the energetically favorable release of *peri* strain of 1,8-disubstituted naphthalenes under normal palladium-catalyzed hydrogenolysis conditions.[12] Even though it is possible to obtain the acid by other means,[13] our results allude to the general usefulness of this method for complicated deprotections.

To conclude, we have reported new reaction conditions, that is 10% Pd/C Degussa type catalyst in DMF using aqueous hydrochloric acid as an additive, for catalytic debenzylation without side reactions such as saturation of aromatic residues or decomposition of acid-labile groups. The palladium is activated by the hydrochloric acid, and DMF buffers the proton activity. Using these conditions we were able to isolate compound **2** in 88% yield without any sign of saturation or acid-mediated cleavage of the glycoside. The usefulness of the method was further verified in a previously unsolved hydrogenolysis problem.[13,14]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.142.

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