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Selective removal of a benzyl protecting group in the presence of an aryl chloride under gaseous and transfer hydrogenolysis conditions

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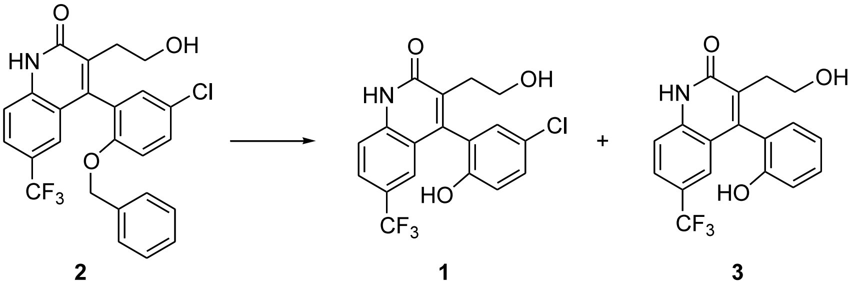
Abstract—Selective removal of a benzyl protecting group in the presence of an aryl chloride using Pd/C under gaseous and transfer hydrogenolysis conditions is described. The addition of chloride salts to the debenzylation reaction provides excellent selectivity. © 2003 Elsevier Science Ltd. All rights reserved.

4-Aryl-quinolin-2(1*H*)-ones are modulators of the large-conductance, calcium-activated potassium (Maxi-K and BK) channels and are potentially useful in the treatment of diseases which arise from dysfunction of cellular membrane polarization and conductance.[1] During process development of 4-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyethyl)-6-(trifluoromethyl)-2(1*H*)-quinolinone (**1**), debenzylation of the aryl chloride **2** via hydrogenolysis with palladium on carbon (Pd/C) proved troublesome (Scheme 1). Competitive dechlorination afforded the deschloro analog **3**, which was difficult to purge by selective crystallization of **1**. Thus, we needed to develop conditions for a more chemoselective hydrogenolysis which minimized formation of the undesired byproduct.

In early screening, we found that the use of platinum oxide (Adams' catalyst) or platinum on carbon provided the desired selectivity, but complete removal of the benzyl group in **2** was not achieved. We thus returned to palladium catalysts and focused our attention on the effect of hydrogenolysis conditions on the course of the reaction. Our initial finding was that the ratio of **1**:**3** correlated directly with the dielectric constant of the solvent employed, in line with the observations of others.[2] Thus, the deschloro analog **3** was observed to form in up to 35% yield in solvents such as methanol with high dielectric constant (32.7 at 25°C), while solvents with low dielectric constant such as ethyl acetate (6.02 at 25°C) or methylene chloride (9.08 at 25°C) provided product with deschloro levels of only 1–2%. Although this initial screening demonstrated a high selectivity for debenzylation using ethyl acetate, the product **1** was poorly soluble in this solvent and tended to precipitate out on the catalyst, dramatically inhibiting the reaction rate.



Scheme 1.

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Selective hydrogenolysis of benzyl groups in the presence of an aryl chloride in acidic media have been reported.[2–4] When the reaction was carried out over Pd/C in 5 mol% hydrochloric acid/ethanol, the ratio of **1**:**3** increased to 40/1. Larger amounts of acid further increased the selectivity, unfortunately, however, at the cost of a dramatically slower reaction rate.[2]

In a recent study on the active Pd/C species in dechlorinations,[5] cationic Pd was inferred to be responsible for chemisorption of substates prior to reduction. We reasoned that chloride salts might selectively deactivate the Pd/C catalyst by chelating to the cationic Pd sites, while not deactivating the sites for the debenzylation. We describe herein the results of a study which demonstrate a novel approach to achieving both high chemoselectivity *and* reaction rate by the use chloride salts under gaseous or transfer hydrogenolysis conditions.

Tetrabutylammonium chloride (TBACl) was examined as chloride source for hydrogenations over Pd/C in methanol and ethyl acetate (Table 1). In methanol, the ratio of product to deschloro (**1**:**3**) increased dramatically from 3.3:1 to 57:1 when 1.1 equiv. of TBACl was used. The level of deschloro **3** could be further decreased (but not eliminated) by use of higher levels of TBACl. When a large excess of TBACl (5 equiv.) was used, a new impurity was observed and the debenzylation did not go to completion, possibly indicating 'overtoxification' of the catalyst. TBACl also detered debenzylation in EtOAc. However, in this solvent the reaction stalled at 25% conversion when only 0.1 equiv. of TBACl was used.

The benefits of chloride salts in the selective transfer hydrogenolysis of **2** were much more pronounced than in gaseous hydrogenolysis. In hopes of taking advantage of the dual functions of formic acid as hydrogen donor and acidic medium, selective hydrogenolysis of **2** with formic acid in methanol was investigated (Table 2). Unfortunately, no reaction occurred under these conditions. Although ammonium formate has been reported to be superior to formic acid as a hydrogen donor due to the high hydrogen-donating ability of formate ion, it is also highly effective in dehalogenation of aryl chlorides.[6] In line with this report, we found that transfer hydrogenation of **2** in methanol gave exclusively deschloro analog **3**. On the other hand, in ethyl acetate an 18:1 ratio of **1**:**3** was observed. The chloride salt deactivating effect on selectivity was striking when ammonium chloride was added to the reaction in MeOH. Although the debenzylation reaction was slow and stalled around 93% conversion, the product/deschloro ratio was 172:1.

Sodium hypophosphite has been recommended as a mild hydrogen donor in the hydrogenolysis of benzyl ethers.[7] The transfer hydrogenation has been proposed to occur via isomerization of the phosphoryl form of (NaO)H_2PO to the hydroxide (NaO)(HO)PH form followed by dissociation of the P–H bond.[8] In this study, we found that use of this reagent in MeOH/water afforded a 17:1 ratio of **1**:**3**. A possible explanation of this effect is the difference in pH of the reaction mixtures: the $HCOONH_4$ reaction mixture is basic (pH ~9), while that of sodium hypophosphite is moderately

Table 1. TBACl effect on the ratio of **1**/**3**[a]

TBACl (equiv.)	Solvent	**3** (AP[b])	**1** (AP)	**2** (AP)	**1**/**3** ratio
0	MeOH	22.8	75.7	0.2	3.3:1
0.5	MeOH	2.4	96.2	–	40:1
1.1	MeOH	1.7	96.6	0.1	57:1
5.0	MeOH	0.9	91.3	1.0	101:1
0	EtOAc	2.5	94.6	–	39:1
0.1	EtOAc	–	24.6	75.4	

[a] Hydrogenations were carried out at ambient temperature and 40 psi over 18 h. The catalyst used was 5% Pd/C from Johnson Matthey. The loading was 10% w/w relative to **2**. The results were determined by HPLC monitored at 235 nm.

[b] AP stands for HPLC area percent.

Table 2. Ratios of **1**/**3** and conversions for different hydrogen donors, chloride salts and solvents

Hydrogen donor (equiv.)	Solvent	Chloride	Time (h)	Ratio (**1**/**3**)	Conversion[c] (%)
HCOOH (6 equiv.)	MeOH		16	–	0
[a]$HCOONH_4$ (2 equiv.)	MeOH		16	0/100	100
[a]$HCOONH_4$ (2 equiv.)	MeOH	NH_4Cl (8.8 equiv.)	21	172/1	93
[a]$HCOONH_4$ (2 equiv.)	EtOAc		16	18/1	76
[b]NaH_2PO_2 (2 equiv.)	MeOH/water (2/1)		16	17/1	100
[b]NaH_2PO_2 (2 equiv.)	MeOH/water (2/1)		23	5/1	100
[b]NaH_2PO_2 (2 equiv.)	MeOH/water (2/1)	NaCl (15 wt%)	2.5	120/1	98
[b]NaH_2PO_2 (2 equiv.)	MeOH/water (2/1)	NaCl (15 wt%)	23	33/1	100
[b]NaH_2PO_2 (2 equiv.)	MeOH/water (2/1)	NaCl (20 wt%)	23	82/1	86

[a] *Reaction conditions*: **2** (50 mg, 0.11 M), catalyst (10% Pd/C from Degussa, 10% w/w), 65°C.

[b] *Reaction condition*: **2** (0.08 M), catalyst (10% Pd/C from Johnson Matthey), 65°C.

[c] (Product+deschloro)/(product+deschloro+starting material).

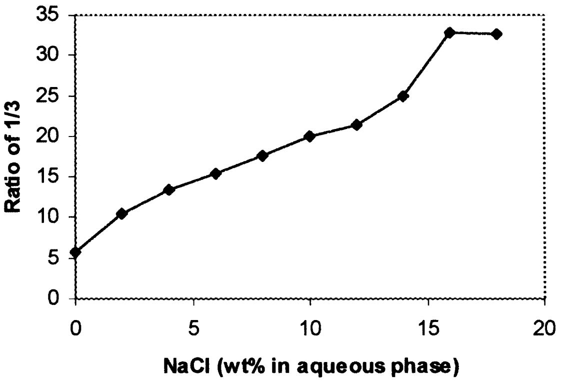

Figure 1. *Reaction conditions*: **2** (50 mg, 0.08 M), NaH_2PO_2 (2 equiv.), catalyst (10% Pd/C, 10% w/w), MeOH/aq. NaCl, 2:1 (v/v), temperature (65°C).

acidic (pH ~4). As noted earlier, dehalogenation is faster under basic and neutral conditions but slower in the presence of acid.[2]

Employing sodium hypophosphite, it was found that sodium chloride effectively suppresses the level of deschloro byproduct, even under the prolonged heating conditions (23 h) required to achieve complete debenzylation. We also found that the length of reaction time as well as the amount of NaCl affected the ratio of **1**:**3** (Table 2). In order to investigate the effect resulted from the concentration of NaCl and to achieve complete debenzylation across the range of concentrations, the results of the following reactions were compared after 23 h (Fig. 1). Hydrogenolysis reactions were conducted with various mixtures of MeOH and aq. NaCl in which the MeOH/aq. NaCl ratio was maintained at 2:1 v/v, but the amount of NaCl in the aqueous component was varied from 0–20 wt%. As shown in Figure 1, the ratio of product/deschloro increased from 5:1 to 33:1 as the NaCl concentration in the aqueous component increased from 0 to 18 wt%. However, the ratio reached a plateau around 15 wt% NaCl. When 20 wt% NaCl was used, the debenzylation reaction stalled at 86% conversion, although the ratio of product/deschloro was 82:1. No further dechlorination was observed, indicating 'over-toxification' of dechlorination site on the catalyst as well. To avoid the potential catalyst poisoning due to high salt concentration and to maximize the ratio of the product/deschloro without compromising the yield, the optimal NaCl concentration was determined to be 15±3 wt% and the average ratio of the product/deschloro was between 88:1 to 120:1 with 98% conversion after 2.5 h.

Based on the above results, the transfer hydrogenolysis reaction was demonstrated on gram-scale using sodium hypophosphite in the presence of 12 wt% NaCl solution to afford product **1** in 93% isolated yield with product/deschloro ratio as high as 120:1.

In conclusion, we have demonstrated a highly selective gaseous and transfer hydrogenolysis of a benzyl protecting group in the presence of an aryl chloride in the synthesis of quinolinone (**1**) using chloride salts to suppress an undesired dehalogenation reaction.

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