An Efficient and Practical Method for Highly Chemoselective Hydrogenation of Nitrobenzylamines to Aminobenzylamine Hydrochlorides

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Abstract: Aqueous hydrochloric acid proved to be a very reliable modulator for adjusting the reactivity of palladium on carbon. Thus an efficient and practical method for the highly chemoselective hydrogenation of *N*,*N*-dialkylnitrobenzylamines to amino-*N*,*N*-dialkylbenzylamine hydrochlorides was established.

The method features convenient performance, easy work-up and high efficiency.

Keywords: amines; chemoselectivity; hydrogenation; palladium; reduction

Introduction

Palladium-catalyzed chemoselective hydrogenations have played an important role in modern organic synthesis, such as the well-known Rosenmund reduction and Lindlar reduction. Palladium on carbon (Pd-C) is a commercially available catalyst featured by a low price and easy regeneration. Pd-C-catalyzed hydrogenations have been widely employed in numerous organic transformations with high efficiency in both academic and industrial laboratories. Prominent among them are the catalytic hydrogenation of aromatic nitro groups^[1] and the catalytic hydrogenolysis of N,N-dialkylbenzylamines.^[2] Since these two transformations occur under very similar conditions (room temperature and atmospheric hydrogen pressure), low chemoselectivity was observed between them.^[3] In fact, no general and practical protocol by catalytic hydrogenation exists for this purpose to date, even though many efforts have been made to develop chemoselective Pd-C-catalyzed hydrogenations.^[4]

In past decades, amino-N,N-dialkylbenzylamines (2) have been gaining increasing importance in medicinal chemistry and organic chemistry.^[3,5,6] The most convenient preparations of them are the chemoselective reduction of the corresponding N,N-dialkylnitrobenzylamines (1). For example, TAK-779 was reported as the first small-molecule, non-peptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity.^[7] N-[(4-Aminophenyl)methyl]tetrahydro-N- methyl-2*H*-pyran-4-amine (**2c**) was recognized as both a key pharmacophore and an intermediate for the synthesis of TAK-779. As shown in Scheme 1, compound **2c** was prepared smoothly by a chemoselective reduction of N-[(4-nitrophenyl)methyl]tetrahydro-Nmethyl-2*H*-pyran-4-amine (**1c**) with a stoichiometric amount of SnCl₂ in aqueous HCl and was then converted into **2c**·2 HCl for easy purification. Unfortunately, the Pd-C- or Raney-Ni-catalyzed hydrogenation of **1c** was non-selective and led to hydrogenolyzed products **3** and **4c**.^[3a,b]



Scheme 1. *Conditions:* i) SnCl₂, aqueous HCl, 20–40 °C, 1 h; ii) aqueous HCl, *i*-PrOH; iii) Pd-C or Raney-Ni, H₂, room temperature.

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In our research project on the chemical biology, a series of amino-N,N-dialkylbenzylamines (2) derivatives was chosen as synthetic targets. The literature shows that the most reliable methods for the chemoselective transformation of 1 to 2, in practice, are those using reducing metals in acidic media, such as Fe, Sn or SnCl₂ in aqueous HCl.^[3,6] But, these methods are unavoidably associated with tedious work-ups and release of a large amount of hazardous wastes to the environment. Therefore, there is a great need to find a chemoselective catalytic hydrogenation method as an alternative. We report herein a novel method to accomplish this goal, which is characterized by adding a suitable amount of aqueous HCl to the conventional Pd-C-catalyzed system in MeOH. The method features convenient performance, easy work-up and high efficiency.

Results and Discussion

It is well known that: (1) the hydrogenation ability of the Pd-C catalyst is enhanced by a catalytic amount of HCl, but retarded with an excess amount of HCl (over 1 equivalent) due to the unproductive occupation of Pd-C catalytic sites by HCl molecules.^[8] (2) The Pd-C-catalyzed hydrogenation of nitrobenzene in the presence of CHCl₃ produced aniline hydrochloride in excellent yields, in which the hydrochloride came from the Pd-C-catalyzed hydrodechlorination of CHCl₃.^[9] These results strongly imply that the Pd-Ccatalyzed hydrogenation of N,N-dialkylnitrobenzylamines (1) in the presence of $CHCl_3$ could be a possible method to chemoselectively obtain amino-N,N-dialkylbenzylamines (2.2 HCl), because the catalytic ability of the Pd-C catalyst will be certainly retarded by the HCl produced from the dehydrochlorination of CHCl₃.

As was expected, when N,N-dimethyl-4-nitrobenzylamine (1a) was hydrogenated with Pd-C catalyst under 1 atmosphere hydrogen pressure at room temperature for 2 h in the presence of CHCl₃ (2 mL), the desired 4-amino-N,N-dimethylbenzylamine dihydrochloride (2a·2 HCl) was obtained as white crystals in 97 % yield. Only a 3 % yield of hydrogenolyzed products 3·HCl and 4a·HCl were detected. Unfortunately, the chemoselectivity of this method sharply decreased with increasing size of the substituents on the benzyl
 Table 1. Effect of the size of substituents on the chemoselectivity.



amine (Table 1). When **1c** was employed as a substrate, the undesired hydrogenolyzed products were obtained in 81% yields.

Control experiments proved that the undesired hydrogenolyzed products were produced totally in the first 5 min of the hydrogenation. During that period, just a small amount of HCl was released from the dechlorohydrogenation of CHCl₃. Thus, HCl actually enhanced rather than weakened the catalytic ability of the Pd-C catalyst.

Many attempts have been made to avoid the hydrogenolysis occurring at the beginning of the hydrogenation. By using compound 1c as a model substrate, we observed that the addition of anhydrous HCl made the catalyst lose its reactivity completely, while HOAc and TFA accelerated the hydrogenolysis of 1c significantly. Luckily, when a few drops of concentrated aqueous HCl were added to the hydrogenation system, the chemoselectivity for the conversion of 1c to $2c \cdot 2HCl$ was significantly improved to 78%. When CHCl₃ was replaced completely by the same amount of concentrated aqueous HCl (2 mL), the hydrogenation finished within 12 min and gave 2c·2HCl as the single product in almost quantitative vield (Scheme 2).

We found that water is essential to control the catalytic ability of Pd-C catalyst when HCl was used as an inhibitor. For example, when anhydrous HCl (2.5



Scheme 2.

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equivalents) was used in the Scheme 2, no hydrogenation occurred in 30 min. However, the hydrogenation finished within 15 min to give 2c·2 HCl in 99% yield after 1.0 mL of H₂O was added. Thus, we supposed that the occupation of Pd-C catalytic sites by HCl in the presence of H_2O may be a reversible process. Therefore, the catalytic ability of Pd-C catalyst with aqueous HCl is partially weakened to enable reduction of the aromatic nitro group, while the N,N-dialkylbenzylamine stays intact under these conditions.

Further experiments proved that at least 2.5 equivalents of aqueous HCl were required to guarantee the chemoselectivity (entry 3 in Table 2). Two equivalents of aqueous HCl are necessary for the formation of the product 2c·2HCl and 0.5 equivalents of aqueous HCl are enough to maintain the reactivity of Pd-C catalyst. The chemoselectivity is so good that the theoretical amount of hydrogen was absorbed exactly even with prolonged reaction time. More than 2.5 equivalents of aqueous HCl proved to have no negative effect (entry 4). However, less than 2.0 equivalents of aqueous HCl not only led to a cloudy endpoint of the hydrogenation (entry 1), but also dramatically affected the chemoselectivity with extended reaction time (entry 2). Clearly, these problems must have occurred at the end of the hydrogenation because two equivalents of aqueous HCl were completely captured as product $2c \cdot 2$ HCl was formed. Thus, the Pd-C catalyst was re-activated to lead to hydrogenolysis of the products. The effects of the amount of Pd-C catalyst on the hydrogenation are shown in entries 5

Table 2. Effect of amount of aqueous HCl on the chemoselective hydrogenation of 1c.^[a]

Entry	10% Pd-C [wt%]	aq. HCl ^[b] [mol equiv]	Time ^[c] [min]	2c ·2 HCl [%] ^[d]	3 ·HCl [%] ^[d]	4c ∙HCl [%] ^[d]
1	10	2.0	9(+10)	83	16	16
2	10	2.0	(+10) 9 (+60)	50	49	49
3	10	2.5	(+00) 12 (+60)	99	0	0
4	10	5.0	(+00) 12 (+60)	99	0	0
5	20	2.5	(+00) 5 (+20)	99	0	0
6	5	2.5	(+30) 15 (+30)	99	0	0

Hydrogenation was performed in MeOH at room temperature and 1 atmosphere pressure of H₂.

^[b] 37% aqueous HCl was used.

^[c] The number in parenthesis is the extended time after the absorption of the theoretical amount of hydrogen.

[d] Isolated yields are given and the ratios were determined by ¹H NMR.

and 6. The excellent chemoselectivity was obtained even with 20 wt % of Pd-C catalyst, while a satisfactory hydrogenation speed was maintained by using 5 wt % Pd-C catalyst.

As shown in Table 3, a wide range of concentrations of aqueous HCl can be used in the reaction. However, a dilute solution of aqueous HCl made the formation of the hydrochloride salt difficult because more water was brought into the reaction system (entries 2 and 3).

Table 3. Effect of concentration of aqueous HCl on the chemoselective hydrogenation of **1c**.^[a]

Entry	Concentration of aqueous HCl [%]	Volume [mL]	Time [min]	2c ·2HCl [%] ^[b]	3 ·HCl [%] ^[b]	4c ·HCl [%] ^[b]
1	37	0.63	12	99	0	0
2	18.5	1.25	10	98	0	0
3	9.25	2.50	10	98	0	0

^[a] 2.5 mmol of 1c and 10% Pd-C (10 wt%) were used in MeOH at room temperature and 1 atmosphere pressure of H_{2} . [b]

Isolated yields are given.

To generalize this highly chemoselective protocol, different N,N-dialkylnitrobenzylamines (1a-l) were tested. As shown in Table 4, they all gave the corresponding amine hydrochlorides (2a– $l\cdot n$ HCl) as single products in excellent yields. The hydrogenation of substrates with acyclic amines (1a-f) normally was completed within a few minutes, while those with cyclic amines (1g-i) took a little longer. Substrates **1g-i** were reported to be converted into **2g-i** in 43%, 75% and 1.9% yields, respectively, in conventional Pd-C catalyzed hydrogenations.^[3c] However, they were obtained as 2g-i-2HCl using our protocol in 97%, 95% and 96% isolated yields, respectively. This method is so efficient that the bulky N,N-dicyclohexylbenzylamine (1f) also gave 2f-2HCl in excellent chemoselectivity and yield. When 1k was employed as the substrate and 3.5 equivalents of aqueous HCl were used, the corresponding trihydrochloride 2k-3HCl (Figure 1) was obtained smoothly. It is noteworthy that 21.4 HCl (Figure 1), which could be an attractive dendrimeric core molecule, was obtained from 11 in excellent yield under extremely convenient conditions.

To explore the chemoselectivity of this method with other functional groups, the mixture of 1c with chlorobenzene, bromobenzene or octadec-1-ene was hydrogenated (Scheme 3). As a result, highly chemoselectivity between the aryl nitro group and the chlorobenzene was observed. The chlorobenzene was recovered in quantitative yield while 2c·2HCl was obtained in 98% yield. Unfortunately, the method had Table 4. Chemoselective hydrogenation of N,N-dialkylnitrobenzylamines (1a-j).



^[a] 2.5 mmol of 1c and 10% Pd-C (10 wt%) were used in MeOH at room temperature and 1 atmosphere pressure of H₂.

^[b] Isolated yields are given.^[a] Isolated as **2c**, see ref.^[3a]

^[b] Isolated as **2g**, **2h** and **2i**, see ref.^[3c]



no chemoselectivity between an aryl nitro group and aryl bromobenzene or octadec-1-ene, which was hydrogenated completely to give the corresponding benzene or octadecane.

Conclusions

We found that aqueous HCl is a very reliable modulator for adjusting the reactivity of the Pd-C catalyst. By addition of a suitable amount of aqueous HCl to a routine Pd-C-catalyzed hydrogenation system, an efficient and practical method for highly chemoselective hydrogenation of *N*,*N*-dialkylnitrobenzylamines to amino-*N*,*N*-dialkylbenzylamine hydrochlorides was established. The method features convenient performance, easy work-up and high efficiency. It is likely that the replacement of the routine procedures (using reducing metals in acidic media) by this method will also significantly reduce the release of hazardous wastes to the environment.

Figure 1.

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Scheme 3.

Experimental Section

Typical Procedure for the Hydrogenation of *N*-[(4-Nitrophenyl)methyl]tetrahydro-*N*-methyl-2*H*-pyran-4-amine (1c)

A mixture of 1c (626 mg, 2.5 mmol), 10% Pd-C (31.3 mg), and aqueous HCl (37%, 800 mg, ca. 8 mmol) in MeOH (30 mL) was stirred under H₂ at ambient temperature and atmospheric pressure until the absorption of hydrogen ceased (15 min). After the catalyst was filtered off, the filtrate was evaporated and Et₂O (20 mL) was added. The desired product 2c·2HCl was collected by filtration as yellowish crystals; yield: 726 mg (99%); mp 177-179°C (MeOH-Et₂O, lit.^[3a] 177–179 °C); IR: v=3429, 2951, 2858, 1611, 1575 cm⁻¹; ¹H NMR (D₂O): δ = 7.71 (d, J = 8.6 Hz, 2 H), 7.46 (d, J = 8.6 Hz, 2H), 4.58 (d, J = 13.1 Hz, 1H), 4.18 (d, J =13.1 Hz, 1 H), 4.01 (d, J=11.3 Hz, 2 H), 3.48–3.64 (m, 1 H), 3.38 (t, J=12.4 Hz, 2H), 2.64 (s, 3H), 2.06 (t, J=10.9 Hz, 2H), 1.77–1.94 (m, 2H); ¹³C NMR (D₂O): δ =133.4, 132.9, 131.1, 124.1, 66.2, 62.9, 55.8, 35.3, 28.0, 27.0; MS: m/z (%) = 221 (M+1, 2.4), 220 (M⁺, 18.0), 106 (100.0); anal. calcd. for C13H22Cl2N2O: C 53.25, H 7.56, N 9.55; found: C 53.23, H 7.57, N 9.54.

A similar procedure was used to convert the substrates **1a–j** chemoselectively to **2a–j**.

4-[(4-Methyl-1-piperazinyl)methyl]benzenamine Trihydrochloride (2k·3 HCl)

Using as similar procedure as that above and 3.5 equivalents of aqueous HCl, compound **2k**·3 HCl; mp 139–141 °C (MeOH-Et₂O). IR: v=3341, 2986, 2897, 1615 cm⁻¹; ¹H NMR (D₂O): $\delta=7.74$ (d, J=6.5 Hz, 2H), 7.43 (d, J=6.5 Hz, 2H), 4.46 (s, 2H), 3.50–3.70 (m, 8H), 2.91 (s, 3H); ¹³C NMR (D₂O): $\delta=140.2$, 129.3, 123.1, 50.1, 42.8, 41.0; MS: m/z (%) = 206 (M+1, 9.9), 205 (M⁺, 79.0), 106 (100.0); anal. calcd. for C₁₁H₂₂Cl₃N₃: C 45.80, H 7.05, N 13.35; found: C 45.91, H 7.04, N 13.57.

Tris-(4-nitrobenzyl)amine (11)

A mixture of 4-nitrobenzyl bromide (1.62 g, 7.5 mmol) and aqueous ammonia solution (25%, 5 mL) in anhydrous MeOH (2.5 mL), was heated in a sealed tube at 100 °C for

4 h. Then it was cooled to room temperature and poured into H₂O (20 mL). The resulting mixture was extracted with CH₂Cl₂ and the combined organic layers were dried over Na₂SO₄. Removal of the solvents yielded a yellow solid, which was recrystallized in EtOAc to give **11** as a light yellow crystal; yield: 0.72 g (68%); mp 170 °C (lit.^[10] 168 °C); ¹H NMR (CDCl₃): δ =8.20 (d, *J*=8.6 Hz, 6H), 7.58 (d, *J*=8.6 Hz, 6H), 3.70 (s, 6H); ¹³C NMR (CDCl₃): δ = 147.4, 146.0, 129.2, 123.8, 57.7.

Tris-(4-aminobenzyl)amine Tetrahydrochloride (2l·4HCl)

A mixture of tris(4-nitrobenzyl)amine (11, 634 mg, 1.5 mmol), 10% Pd-C (31.7 mg), and aqueous HCl (37%, 3.0 g) in MeOH (30 mL) was hydrogenated at ambient temperature and atmospheric hydrogen pressure for 310 min. After the catalyst was filtered off and MeOH was evaporated, the residue was dissolved in anhydrous ethanol (10 mL). Removal of ethanol (as an azeotropic mixture with water) yielded a light yellow solid, which was washed with anhydrous diethyl ether to give pure 21 4 HCl; yield: 680 mg (95%); mp >250°C (MeOH); IR: v = 3412, 2857, 1616, 1573 cm⁻¹; ¹H NMR (D₂O): $\delta = 7.56$ (d, J = 8.6 Hz, 6H), 7.42 $(d, J=8.6 \text{ Hz}, 6\text{H}), 4.30 \text{ (s, 6H)}; {}^{13}\text{C} \text{ NMR} (D_2\text{O}): \delta = 131.7,$ 131.6, 131.5, 123.8, 50.0; MS m/z (%): 227 (5.4), 122 (55.1), 121 (86.4), 107 (26.3), 106 (100.0), 94 (28.1); anal. calcd. for C₂₁H₂₈Cl₄N₄: C 52.74, H 5.90, N 11.71; found: C 52.86, H, 5.89, N 11.80.

Supporting Information

Characterization data and ¹H NMR and ¹³C NMR spectra for products **2a–I** are given in the Supporting Information.

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