A safe and convenient synthesis of 4-benzyloxy-3-chloroaniline[1]

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Abstract

A convenient, safe, large-scale synthesis of the title compound 4-benzyloxy-3-chloroaniline is described. The commercially available 4-benzyloxy-3-chloronitrobenzene is reduced conveniently using $SnCl_2$ to afford 4-benzyloxy-3-chloroaniline in high yield, high purity, and free of tin residues. This process is suitable for kilogram-scale synthesis of the title compound.

Keywords: 4-Benzyloxy-3-chloroaniline, stannous chloride, reduction

Introduction

4-Benzyloxy-3-chloroaniline has been frequently used as a building block in the construction of potential anti-cancer,[2-7] anti-diabetes[6] and anti-viral[8] agents. Despite the widespread use of this compound, its preparation has not been thoroughly discussed in the literature except for a few limited examples involving small scale (milligrams to grams) preparations. The methods currently reported in the literature include: (1) reduction of 2-chloro-4-nitrophenol to 3-chloro-4-hydroxyaniline using Zn/NH_4Cl in $MeOH/H_2O$, followed by Boc protection of the amine, benzylation of the hydroxy group and deprotection of the Boc group,[9] (2) reduction of 4-benzyloxy-3-chloronitrobenzene by either Raney Ni[10] or Pd/C[4] catalyzed hydrogenation, and (3) reduction of 4-benzyloxy-3-chloronitrobenzene mediated by Fe powder in acetic acid[8] or NH_4Cl solution.[11,12] In connection with one of our development projects, we needed quick access to large amounts of this compound.

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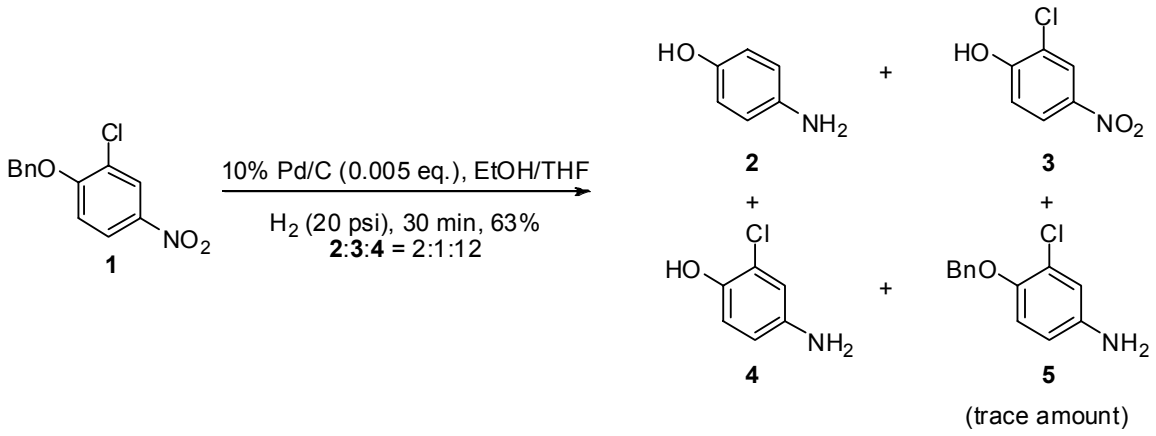
Results and Discussion

Although 4-benzyloxy-3-chloroaniline is commercially available, we quickly found that its purity did not always meet our specifications and could not be used directly. Some commercially available samples were contaminated with 4-amino-2-chlorophenol (**4**), most likely due to poor control during a hydrogenation step involving 4-benzyloxy-3-chloronitrobenzene (vide infra).

Following a brief survey of the reported procedures, we chose to avoid any large-scale process using hydrogenation conditions involving Raney nickel due to safety concerns associated with its use and the possibility of residual nickel being left in the final product. The reduction of 4-benzyloxy-3-chloronitrobenzene using traditional Pd/C catalyzed hydrogenation conditions has been reported for the preparation of 4-benzyloxy-3-chloroaniline but without detailed experimental procedures.[4] Although this approach was attractive to us, we envisioned that careful control of the reaction conditions would be needed to avoid the possible debenzylation and/or dechlorination.

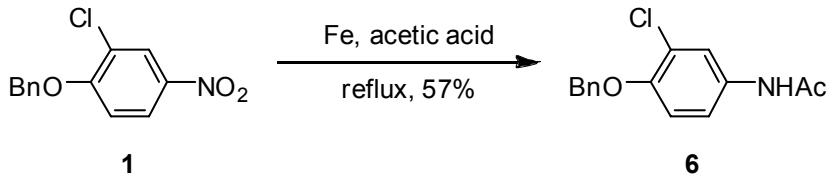
In order to test this reduction, we reacted 4-benzyloxy-3-chloronitrobenzene in ethanol:THF co-solvents (1:1 v/v) with 0.5 mol% of Pd on activated carbon under 20 psi of H_2 at ambient temperature. The reaction proceeded rapidly to afford, within 30 min, a reaction mixture containing compounds **2**, **3** and **4** with compound **4** as the major product. Only a trace amount of the desired compound **5** was detected (LC-MS and ^{1}H NMR analyses, Scheme 1).



Scheme 1. Hydrogenation of 4-benzyloxy-3-chloronitrobenzene.

Based on these findings we decided to explore preparing the title compound using non-hydrogenation conditions, starting with the commercially available 4-benzyloxy-3-chloronitrobenzene. We required the process to be simple and safe, and amenable for further scale-up. We first tried to reduce 4-benzyloxy-3-chloronitrobenzene in acetic acid with Fe powder since Fe powder in acetic acid has been known to reduce the nitro compounds successfully to their corresponding amines.[3,8,13] As expected, when 4-benzyloxy-3-chloronitrobenzene was heated with Fe powder in refluxing acetic acid, the nitrobenzene starting

material was quickly consumed. However, to our surprise the only product isolated was acetylaniline **6**: the acetylation product of the aniline intermediate (Scheme 2). Although we believed that the formation of this by-product could be controlled by adjusting the reaction conditions we chose not to pursue this route further because of the difficulty of removing acetic acid on large scale and the expected exothermic feature of this reaction.[13]



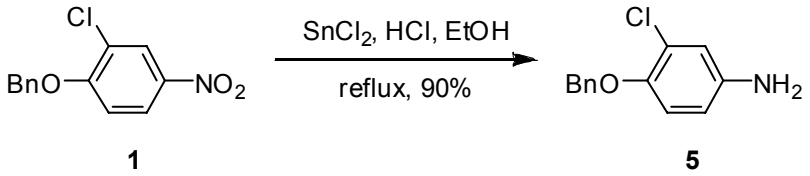
1 **6**

Scheme 2. Reduction of nitrobenzene **1** using Fe in acetic acid.

Reduction of 4-benzyloxy-3-chloronitrobenzene by powdered Fe in NH_4Cl solution[11,12] is also known and could be used for large scale preparation of 4-benzyloxy-3-chloroaniline. However, its workup requires tedious multiple extractions and filtrations. We therefore chose not to pursue this method. Stannous chloride is well known to reduce an aromatic nitro compound to the corresponding aniline under very mild reaction conditions, while a benzyl group and a chlorine functionality is stable under these conditions.[14] Further more, stannous chloride reduction of aromatic nitro compounds can usually be performed under homogeneous conditions, and we believed that one could precipitate the aniline products as their hydrochlorides directly from the reaction mixture. In fact, Bellamy et. al.[14] reported the reduction of 4-benzyloxynitrobenzene to 4-benzyloxyaniline using stannous chloride under neutral conditions. Under the conditions reported we encountered a thick suspension that made isolation of the product by extraction very difficult. We were glad to find that using acidic conditions afforded a more practical process for the preparation of the title compound. Thus when 4-benzyloxy-3-chloronitrobenzene was treated with 4 equivalent of $SnCl_2$ (or $SnCl_2 \cdot H_2O$) in acidic aqueous ethanol, the reduction proceeded smoothly and quickly to generate 4-benzyloxy-3-chloroaniline (**5**) without formation of any detectable debenzylated or dechlorinated side-products. Within one and a half hours, HPLC analysis and TLC analysis indicated that the starting material was completely consumed. Water was then added to the reaction mixture and the aniline hydrochloride precipitated as an easily filterable off-white solid. The solid was collected by simple filtration and washed with water to remove soluble inorganic salts. The wet cake was dried to afford the hydrochloride of the title compound in nearly quantitative yield.

To prepare the free base form of the title compound, the solid was treated with a 2N NaOH solution and extracted with dichloromethane or ethyl acetate. Alternatively, the wet cake was treated without drying with a 2N NaOH solution to pH 12, and the mixture extracted with dichloromethane or ethyl acetate, washed with brine, dried (Na_2SO_4), filtered and concentrated to afford the free base form of 4-benzyloxy-3-chloroaniline as an off-white solid. The purity of the product prepared in this method was satisfactory for our use (>99% by HPLC area analysis), and

the amount of residual Sn in the material was at the level of 1 ppm (Scheme 3).[15] If desired, the material can be further purified by recrystallization in ethyl acetate/heptane to generate 4-benzyloxy-3-chloroaniline as an off-white crystalline solid free of any tin residues.



1 **5**

Scheme 3. Stannous chloride reduction of 4-benzyloxy-3-chloronitrobenzene.

In summary, we have reported here that $SnCl_2$ effectively reduced 4-benzyloxy-3-chloronitrobenzene to form 4-benzyloxy-3-chloroaniline in excellent yield without cleaving either the benzyl group or the chlorine group. The process is simple, safe and can be easily scaled-up to provide larger amount of material in excellent purity and yield.

Experimental Section

4-Benzyloxy-3-chloroaniline (5). In a 5 L, 3-necked round bottom flask equipped with an overhead stirrer, a thermal couple and a water-cooled reflux condenser was added tin(II) chloride dihydrate (427.8g, 1.90 mol), ethanol (1250 mL) and concentrated HCl (250 mL). The mixture was stirred and heated to 70 °C to become a clear solution. To this hot solution was added portion-wise 3-chloro-4-benzyloxynitrobenzene (129.0 g, 0.48 mol, 5 portions over 30 min). The solution was kept slightly refluxing during the addition. After the addition, the mixture was heated for 1.5 hours at which time TLC and HPLC analysis indicated that no starting material remained. Water (1250 mL)[15] was added and the resulting solution was allowed to cool to room temperature. The product precipitated as a white solid during cooling. The mixture was further cooled and stirred for 30 min at 15 °C and the precipitation was collected by vacuum filtration through a Medium-sintered glass funnel, washed with water (2 x 250 mL then 500 mL), suction dried thoroughly and further dried in a vacuum oven at 50 °C under house vacuum until constant weight to afford 4-benzyloxy-3-chloroaniline hydrochloride as an off-white powder (131.1g, 99%). Mp (by DSC): 224.4 °C.

For the preparation of the free base form of 4-benzyloxy-3-chloroaniline, the drying step is not necessary. The wet solid was transferred to a 1 L 3-necked round bottom flask equipped with an overhead stirrer and dichloromethane (200 mL) was added. The suspension was cooled with an ice-water bath. NaOH solution (2 N) was added with stirring to adjust the solution to pH ~12 (300 mL of NaOH solution added). The mixture was transferred to a separatory funnel and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 200 mL). The combined organic phase was washed with brine (100 mL) and dried ($MgSO_4$), filtered

and concentrated in vacuo to afford the product as an off-white solid (90.0g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2 H), 7.39-7.29 (m, 3 H), 6.78 (d, J = 8.6 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.48 (dd, J = 2.8, 8.6 Hz, 1 H), 5.03 (s, 2 H), 3.46 (bs, 2 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 147.2, 141.4, 137.2, 128.5, 127.9, 127.4, 124.6, 117.18, 117.15, 114.2, 72.4; mp (by DSC): 58.4 °C; Anal. Calcd for $C_{13}H_{12}ClNO$: C 66.81, H 5.18, Cl 15.17, N 5.99. Found: C 67.01, H 5.21, Cl 15.13, N 5.93, Sn <1 ppm; MS (EI) *m/z* calcd for $C_{13}H_{13}ClNO$ (MH+) 234, found 234.

***N*-(4-(Benzyloxy)-3-chlorophenyl)acetamide (6).** To a dry 3-necked round bottom flask equipped with an overhead stirrer, a thermal couple and a water-cooled reflux condenser was added Fe (325 mesh, Aldrich, 13.24 g, 0.237 mol, 2.50 eq) and glacial acetic acid (100 mL). The mixture was heated to 50 °C. 4-Benzyloxy-3-chloronitrobenzene (**1**, 25.0 g, 94.8 mmol) was added to the hot suspension portion-wise in 1 hour, maintaining the reaction mixture to 80 – 85 °C. After the addition finished the mixture was heated to reflux (119.5 °C). The reaction was monitored by TLC analysis (SiO_2, EtOAc, R_f(**1**) = 0.9, R_f(**6**) = 0.5). When the reaction was complete (90 minutes), the reaction mixture was cooled to rt and filtered through a celite pad to remove the black solid. The filter cake was rinsed with glacial acetic acid (100 mL) and the combined filtrate was concentrated in rotary evaporator to get a dark solid. This solid was dissolved in sat. Na_2CO_3 solution until the pH value of the aqueous phase reached 12. The mixture was then extracted with EtOAc (3 x 250 mL). The combined extract was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in rotavap to afford an off-white solid. This solid was further dried in an oven under house vacuum at 50 °C until constant weight to afford compound **6** as an off-white solid (15.00g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.4 Hz, 1 H), 7.46-7.26 (m, 6 H), 7.20 (bs, 1 H), 6.89 (d, *J* = 8.9 Hz, 1 H), 5.12 (s, 2 H), 2.14 (s, 3 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 168.2, 151.1, 136.5, 131.9, 128.6, 128.0, 127.1, 123.6, 122.6, 119.6, 114.7, 71.3, 24.3; mp (by DSC) 140.2 °C; MS (EI) m/z calcd for $C_{15}H_{15}ClNO_2$ (MH+) 276, found 276.

Acknowledgements

We thank Dr. Xun Li and Mr. Scott Youells for helpful discussions.

References and Notes

1. *Caution! 4-Benzyloxy-3-chloroaniline is known to be mutagenic. Handling of this compound requires proper use of personal protective equipments (PPE).*
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15. The amount of water added is critical for controlling the residual tin in the final product. If too much water is added the Sn (IV) species are hydrolyzed to form a milky supernatant that contaminates the precipitated aniline hydrochloride. The Sn contamination in the hydrochloride cannot be totally removed in the free base formation step. This resulted in several occasions that the residual Sn in the isolated free base to be > 50 ppm. To avoid the hydrolysis of the Sn(IV) species, which is a side product from the oxidation of $SnCl_2$, we found that the amount of water added should be no more than the original amount of ethanol used. With control of the amount of water added to the reaction mixture the residual tin in the isolated aniline free base is at the level of 1 ppm.

