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Selective Reduction of Halogenated Nitroarenes with Hydrazine Hydrate in the Presence of Pd/C

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Abstract

A large variety of halogenated nitroarenes have been selectively reduced with hydrazine hydrate in the presence of Pd/C to give the corresponding (halogenated) anilines in good yield.

Keywords

reduction; nitroarenes; hydrazine hydrate; palladium on carbon; aromatic amines; transfer hydrogenation

Aromatic amines are important precursors and key intermediates for the synthesis of medicines, dyes, agricultural chemicals, and polymers.[1] Reduction of the corresponding nitroarenes constitutes one of the most efficient methods for the synthesis of aniline-containing compounds. Traditionally, nitroarenes were reduced by a metal and an acid, a methodology developed by Bechamp in 1854[2] which has been replaced by catalytic hydrogenation with less toxic and hazardous by-products.[3]

However, catalytic hydrogenation has two drawbacks: 1) the danger and inconvenience of handling highly flammable hydrogen gas and 2) the low selectivity in the reduction of functionalized nitroarenes. Catalytic transfer hydrogenation, using in situ hydrogen production, has emerged as the best solution in the last century. Different catalytic metals, such as iron, palladium, and platinum, have been utilized to carry out nitro reductions. But for highly functionalized substrates with liable halogen-based functional groups reduction selectivity is a major problem.[4]

In our development of novel kinase inhibitor fragments,[5] a highly selective and versatile reduction of a halogenated nitroarene was required. Numerous selective reductions on chlorinated nitroarenes have been reported with the problem of enhanced reductive dehalogenation caused by an in situ produced amino group.[6] Therefore, a mild, universal strategy for the selective reduction of halogenated nitroarenes is highly desired to replace

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harsher (for example Zn/H^+) or non-selective conditions. Herein, we report a simple, efficient, and highly selective reduction of halogenated nitroarenes.

Among the variety of catalytic metals, palladium catalysts are most extensively used.[6b,7] Hydrazine, as an indirect hydrogen source, has been shown to be effective in nitro reduction.[8] Thus, our study started with evaluating the reduction of 1-bromo-4-(*tert*-butyl)-2-nitrobenzene (**1a**) by Pd/C and hydrazine. At first, **1a** was totally reduced to 3-(*tert*-butyl) aniline (**2a**) in a sealed tube with 10% Pd/C and ten equivalents of hydrazine in one hour. Under the same conditions, except utilizing open reflux heating, 2-bromo-5-(*tert*-butyl)aniline (**3a**) was obtained in five minutes. These two reactions were exceptionally clean, quick, and convenient for work-up (Scheme 1).

Considering the only difference between the two reductions was an opened or sealed environment, we conclude that hydrogen pressure plays a vital role in determining reaction progression. For better observation and monitoring of the direct pressure in the reaction vessel, microwave irradiation was employed. Microwave irradiation has been used as an efficient alternative to conventional heating in the last two decades.[9] Several microwave-assisted catalytic transfer hydrogenations have been reported recently.[10] As expected, **2** was obtained exclusively through microwave heating in about 30 minutes. The pressure rose to about 6 psi, which progressed **1a** to a full reduction.

To optimize reduction conditions, extensive studies were conducted on catalyst loading, heating, and solvent. After confirming methanol as the best solvent for nitro reductions (Table 1, entries 1 and 2), 5% Pd/C was found adequate without lowering yield (Table 1, entry 3). The optimized selective reduction conditions are listed under method A (entry 3).

With conventional heating, one hour was needed for full reduction (Table 1, entry 4), while microwave irradiation could reduce the reaction time to 30 minutes (Table 1, entry 5). After carefully optimizing the temperature, 120 °C was found to be ideal for the shortest reaction time (15 min) and highest yield (Table 1, entries 6–8). Higher temperatures cause higher pressure in the reaction vessel, which permits facile dual nitro and halogen reductions. A higher catalyst loading (20%) did not improve the reaction yield (Table 1, entry 9), while a lower catalyst loading (5%) caused a substantial decrease in yield (Table 1, entry 10). Correspondingly, methanol is the best solvent for total reduction (Table 1, entry 11). The optimized full reduction conditions are found under method B (Table 1, entry 8).

With optimal conditions in hand, we investigated the substrate scope and generality of the reduction on a variety of bromo-, chloro-, and iodonitroarenes, as demonstrated in Table 2. Simple nitroarenes were tested first under methods A and B, and the corresponding anilines and halogenated anilines were obtained in high yield (Table 2, entries 1 and 2). Bromonitroarenes, unlike chloronitroarenes, have been sparsely investigated for chemoselective reductions utilizing palladium, because C–Br bonds are more catalytically active than C–Cl bonds.[6] We were pleased to identify, through the utilization of our system in Table 1, that nitro groups with various halogenated substituents could be selectively reduced under open reflux conditions while total reductions were achieved with microwave irradiation (Table 2, entries 3–5).

Electron-donating groups, such as amino groups, have been found to impair chemoselectivity. When substrates containing amino groups were utilized (Table 2, entries 6–10), dehalogenation cleavage was observed under reflux. This was easily remedied by completing the reaction at room temperature. Similarly, dinitro substrates could be selectively reduced at room temperature with higher catalyst loading (entry 11). We then investigated substrates with two halogen substituents. Monodehalogenation occurred under reflux, while a selective nitro reduction occurred at room temperature (Table 2, entries 12–14). Notably, the highly palladium active C–I bond is not affected by the mild conditions (Table 2, entry 14).

We decided to extend our research on heteroaromatics to investigate the full scope of the nitroarene reduction. Pyridines, as electron-deficient heterocycles, showed a good yield and selectivity (Table 2, entries 15 and 16). Nitro groups on fused bicyclic ring systems such as indole can also be selectively reduced (Table 2, entry 17), which renders this methodology very attractive for indole ring containing pharmaceuticals.[11]

Unfortunately, cyano groups were also reduced under the reduction conditions (Table 2, entry 18). And it is noteworthy that the yield substantially decreased with the presence of a fluorine group (Table 2, entries 19 and 20).

Because of the convenient workup, Pd/C could be recycled with filtration after the reaction. The chemoselective reaction recyclability was measured on substrate **1a** and conversion to **2a** was determined by LC–MS (Table 3). There is no major catalytic activity loss for up to four cycles.

In summary, we have developed a highly efficient, selective reduction of halogenated nitroarenes. Several advantages compared to other methods exist: (1) The chemoselectivity can be conveniently controlled by applying different heating methods with the same catalyst system. (2) The methodology works on bromo, chloro, iodo and multihalogenated substrates. (3) The methodology works on normal arenes and hetereoarenes. (4) As a heterogeneous catalyst, Pd/C can be recycled up to four times with minimal loss of catalytic activity.

Acknowledgments

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References and Notes

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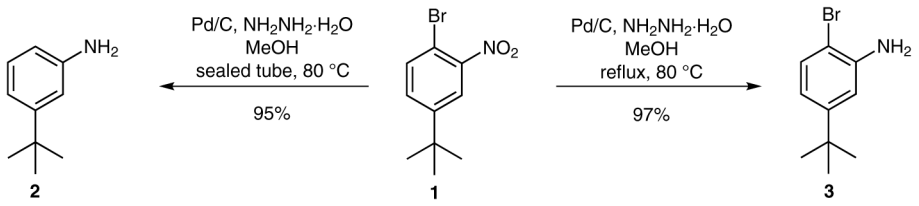
12. **General Procedures; Method A**: To a mixture of halogenated nitroarene (1 mmol), Pd/C(5%), and MeOH (5 mL) was added $NH_2NH_2{\cdot}H_2O$ (10 mmol), and the resulting solution was heated at 80 °C reflux condition for 5 min. Then the mixture was filtered and concentrated in vacuo. The crude material was purified by flash column chromatography using hexanes and EtOAc. **Method B**: To a mixture of halogenated nitroarene (1 mmol), Pd/C(10%), and MeOH (5 mL) was added $NH_2NH_2{\cdot}H_2O$ (10 mmol), and the resulting solution was heated at 120 °C by Biotage Initiator Classic microwave synthesizer for 15 min. The mixture was filtered and condensed in vacuo. The crude material was purified by flash column chromatography using hexanes and EtOAc. **2-Bromo-5-(*tert*-butyl)aniline (3a)**: compound **3a** was prepared in 95% yield according to the general procedure (Method A). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 2.3 Hz, 1 H), 6.66 (dd, *J* = 8.3, 2.4 Hz, 1 H), 4.02 (br s, 2 H), 1.27 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 143.5, 132.0, 117.0, 113.1, 106.3, 34.5, 31.2 (3 × C).

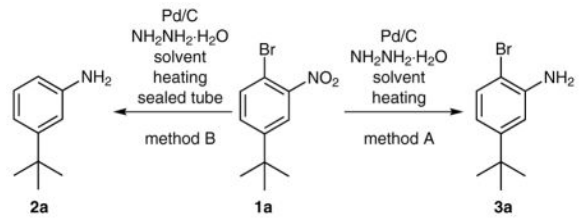


Scheme 1.

Selective reduction on bromo-4-(*tert*-butyl)-2-nitrobenzene **1** under different heating conditions

Table 1

Optimization of Reduction Conditions



Entry	Temp (°C)	Catalyst loading	Solvent	Time (min)	Product	Yield (%)[a]
1	80[b]	10%	MeOH	5	3	95
2	80[b]	10%	EtOH	5	3	86
3	**80**[b]	**5%**	**MeOH**	**5**	**3**	**95**
4	80[c]	10%	MeOH	60	2	95
5	80[d]	10%	MeOH	30	2	96
6	100[d]	10%	MeOH	30	2	95
7	120[d]	10%	MeOH	30	2	96
8	**120**[d]	**10%**	**MeOH**	**15**	**2**	**95**
9	120[d]	20%	MeOH	15	2	94
10	120[d]	5%	MeOH	15	2	79
11	120[d]	10%	EtOH	15	2	85

[a] Isolated yield.

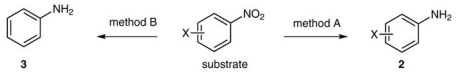
[b] Heating was performed under reflux condition.

[c] Heating was performed in sealed tube.

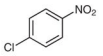
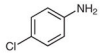
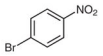
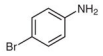
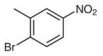
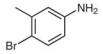
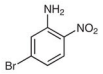
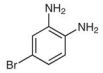
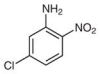
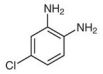
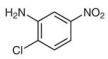
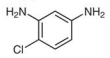
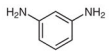
[d] Heating was performed in a microwave reactor.

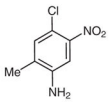
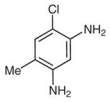
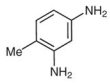
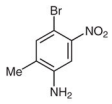
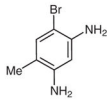
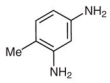
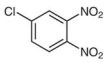
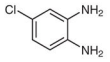
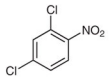
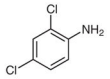
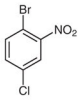
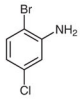
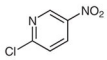
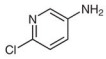
Table 2

Substrate Scope



3 substrate 2

Entry 1	Substrate	Product yield and ratio[a] (method A)[b]	Product yield[a] (method B)[c]
1	 **1b**	 **2b** (93%) 14:1	 **3b** (90%)
2	 **1c**	 **2c** (94%) 15:1	 **3b** (90%)
3	 **1d**	 **2d** (92%) 14:1	 **3b** (92%)
4	 **1e**	 **2e** (93%) 16:1	 **3e** (92%)
5	 **1f**	 **2f** (95%) 14:1	 **3b** (91%)
6	 **1g**	 **2g** (95%)[d] 18:1	 **3g** (96%)
7	 **1h**	 **2h** (93%)[d] only product	 **3g** (97%)
8	 **1i**	 **2i** (95%)[d] only product	 **3i** (96%)

9	 **1j**	 **2j** (94%)[d] 14:1	 **3j** (91%)
10	 **1k**	 **2k** (92%)[d] 15:1	 **3j** (97%)
11	 **1l**	 **2l** (90%)[d] 11:1	 **3g** (89%)
12	 **1m**	 **2m** (90%)[d] 12:1	 **3b** (88%)
13	 **1n**	 **2n** (89%)[d] 10:1	 **3b** (91%)
14	 **1o**	 **2o** (88%)[d] 9:1	 **3b** (92%)
15	 **1p**	 **2p** (87%) 10:1	 **3p** (89%)
16	 **1q**	 **2q** (85%) 9:1	 **3p** (84%)

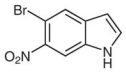
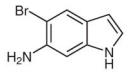
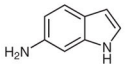
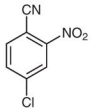
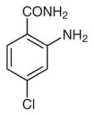
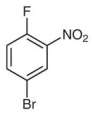
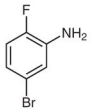
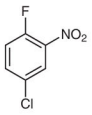
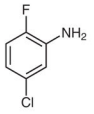
17	 **1r**	 **2r** (91%) 12:1	 **3r** (87%)
18	 **1s**	 **2s** (84%) 9:1	 **3e** (86%)
19	 **1t**	 **2t** (37%) 3:1	 **3t** (29%)
20	 **1u**	 **2u** (25%) 2.5:1	 **3u** (27%)

Table 3

Recyclability

Time	**1st**	**2nd**	**3rd**	**4th**	**5th**
Conversion	100	98	95	90	80

[a]Reaction conditions: **1a** (1 mmol), Pd/C (13 mg), $NH_2NH_2{\cdot}H_2O$ (10 mmol), MeOH (5 mL), 80 °C, 5 min.