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Rapid reduction of heteroaromatic nitro groups using catalytic transfer hydrogenation with microwave heating

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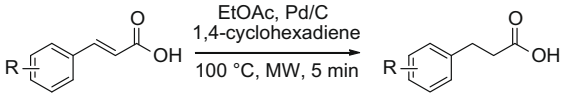
ABSTRACT

A method for the rapid, safe reduction of heteroaromatic and aromatic nitro groups to amines is described using catalytic transfer hydrogenation under microwave heating conditions. Commonly available Pd/C or Pt/C catalyst is extremely effective with 1,4-cyclohexadiene as the hydrogen transfer source. In the case of substrates containing potentially labile aromatic halogens, Pt/C is effective and results in little or no dehalogenation. In general, the reactions are complete within 5 min at 120 °C.

Aryl amines are important synthetic targets and intermediates. They are frequently encountered during the synthesis and optimization of biologically relevant molecules. One of the most frequent methods for the synthesis of aryl amines is by the reduction of aryl nitro groups which are obtained by the nitration of aromatic compounds.[1] Common methods for the reduction of nitro groups to amines include Zn,[2] Sn,[3] and Fe[4] in the presence of acid, $Sn(II)Cl_2$,[5] $TiCl_3$,[6] Raney Ni—hydrazine,[7] and catalytic hydrogenation.[8] Of these, catalytic hydrogenation is, perhaps, the most desirable procedure. Its main drawbacks are the requirement for handling and containing highly flammable hydrogen gas[9] and chemoselectivity in the presence of easily reduced functional groups such as halogens.

Microwave heating technology[10] enables safe access to high temperatures and pressures that can dramatically shorten reaction times.[11] Recently there have been a number of reports utilizing microwave heating and hydrogen transfer conditions[12] as an alternative to conventional hydrogenation using hydrogen gas.[13] The majority of these procedures use formate as a hydrogen transfer source which has the drawback that its reaction byproduct is CO_2 and may result in unsafe pressure in the microwave vial upon reaction completion. We have recently reported a new, microwave-enhanced procedure for the rapid and safe hydrogenation of alkenes under catalytic hydrogen transfer conditions (Scheme 1).[14]

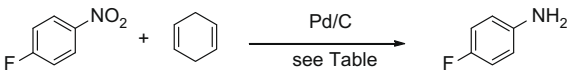
The key discovery in our previous work was that in the presence of a Pd/C catalyst, 1,4-cyclohexadiene acts as a highly active hydrogen donor,[15] generating only easily removable benzene as a reaction byproduct. Herein we report the extension of this hydrogenation methodology to the reduction of heteroaromatic and aromatic nitro groups.



Scheme 1. Transfer hydrogenation of alkenes with microwave heating.

Optimization of this reaction was performed on 4-fluoronitrobenzene as a test substrate (Table 1). We initially choose reaction conditions that worked well in our alkene hydrogenation case; specifically methanol as solvent, 2 mol % Pd[16], and 6 equiv of 1,4-cyclohexadiene (**2**) with microwave heating at 100 °C for 5 min. These reaction conditions only resulted in a 23% conversion to **3**

Table 1
Reduction of 4-fluoronitrobenzene with Pd/C—cyclohexadiene and microwave heating[a]



1 **2** **3**

Entry	Mol % Pd	Equiv 2	Solvent	Temp (°C)	Time (min)	% Conv.[b]
1	2	6	MeOH	100	5	23
2	5	6	MeOH	100	5	64
3	2	3	MeOH	100	5	12
4	3	19	MeOH	100	5	28
5	2	6	MeOH	100	20	98
6	5	6	MeOH	120	5	>99
7	5	6	EtOAc	120	5	10
8	5	6	CH_3CN	120	5	28
9	6	6	THF	120	5	19
10	2	6	MeOH	120	5	>99

[a] All reactions performed in methanol (2 mL), 0.50 mmol substrate, heated under microwave conditions.
[b] All % conversions determined by HPLC (AUC) at 254 nm.

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(Table 1, entry 1). HPLC analysis indicated that the transformation was extremely clean. The only compounds formed in the reaction were aniline **3** and benzene (from the concomitant dehydrogenation of the cyclohexadiene). Increasing the catalyst loading to 5 mol % led to a 64% conversion (Table 1, entry 2).

We next investigated the effect of the number of equivalents of 1,4-cyclohexadiene (Table 1, entries 3–4). Reducing from 6 to 3 equiv led to a 50% decrease in conversion from 23% to 12%. However, increasing from 6 to 19 equiv only led to a very modest increase from 23% to 28% conversion. The heating time and temperature had a much more pronounced effect on substrate conversion. Increasing the heating time from 5 min at 100 °C to 20 min resulted in a 98% conversion to **3** (Table 1, entry 5). Increasing the reaction temperature from 100 to 120 °C resulted in a >99% conversion to product in 5 min (Table 1, entry 6).

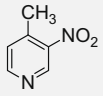
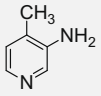
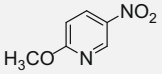
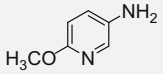
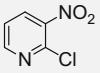
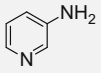
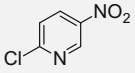
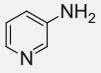
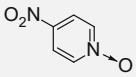
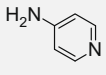
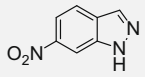
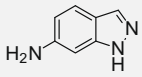
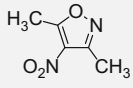
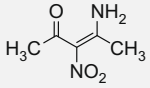
Methanol gives a 99% conversion at 120 °C within 5 min (Table 1, entry 6), while ethyl acetate, acetonitrile, and THF give, respectively, 10%, 28%, and 19% conversions under identical reaction conditions (Table 1, entries 7–9). Finally, reducing the catalyst loading in methanol from 5% to 2% while maintaining the reaction time and temperature at 5 min and 120 °C also results in a >99% conversion to **3** (Table 1 entry 10). These results led to a standard set of conditions for the remainder of the study namely 6 equiv of **2**, 5 mol % of catalyst, substrate 0.25 M in methanol, and microwave heating at 120 °C for 5 min. For scale-up the reaction concentration can be increased to 0.50 M with no adverse effect on reaction conversion or yield.[17]

We next turned our attention to expanding the substrate scope of the reduction reaction to nitro-pyridines and other nitro-heterocycles (Table 2). Utilizing our standard protocol, we observed essentially quantitative conversion of the nitro-heterocycles to the corresponding amino heterocycles. Pyridines **4** and **6** gave aminopyridines **5** and **7** in quantitative yields (Table 2, entries 1–2). Similarly, nitropyrazole **13** and nitroindazole **15** gave the corresponding amine compounds in quantitative yield (Table 2, entries 6–7). Reduction of 4-nitro-pyridine-*N*-oxide **11** gave a 90% yield of 4-aminopyridine **12** along with 10% of 4-aminopyridine-*N*-oxide (Table 2, entry 5). Surprisingly, increasing the equivalents of **2** from 6 to 8 and increasing the heating time from 5 to 10 min did not result in complete conversion to **12**. Reduction of chlorine-containing pyridines **8** and **10** gave exclusively the de-chlorinated amine **9** (Table 2, entries 3–4). As expected, hydrogenation of nitro-isoxazole **17** resulted in ring-opening *N–O* hydrogenolysis. However, there was no evidence for the further reduction of nitro-eneone **18** (Table 2, entry 8). It is worth noting that the highly polar and water soluble amino pyridines and pyrazines may be isolated in high yield and in a high state of purity with this method. Potentially troublesome aqueous workups and chromatography are avoided.

Since the use of Pd/C resulted in the complete de-chlorination of pyridines **8** and **10**, we explored alternative reaction conditions to provide the desired amino-chloropyridines (Table 3). Simply switching to 5 mol % Pt/C[17] gave a 71:29 ratio of **19**/**9** (Table 3, entry 1). In an attempt to improve selectivity we reduced the catalyst loading (Table 3, entries 2–4), reduced the equivalents of **2** (Table 3, entries 5–7), and lowered the reaction temperature (Table 3, entries 8–11). As can be seen lowering the catalyst loading or the reaction temperature results in incomplete conversions even with extended reaction heating. Additionally, significant amounts of oxime **20** are present in the product mixtures. Our best result was obtained by reducing **2** to 5 equiv while extending the reaction time to 8 min (Table 3, entry 7) giving a 79% yield of the desired 3-amino-2-chloropyridine **19** along with 2% of oxime **20** and 19% de-chlorinated pyridine **9**.

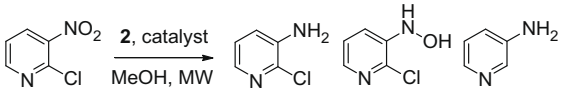
We next turned our attention to general nitro-aromatic compounds (Table 4) with a particular interest in investigating the chemoselectivity of halogenated aromatics. Both electron-rich (Table 4, entry 3) and electron-poor (Table 4, entries 4–7) substrates gave essentially quantitative conversion. Of particular note

Table 2
Catalytic reduction of nitro-heterocycles with cyclohexadiene and microwave heating[a]

Entry	Substrate	Product	% Conv.[b] (yield)
1	 **4**	 **5**	>99 (>99)
2	 **6**	 **7**	>99 (>99)
3	 **8**	 **9**	>99 (>99)
4	 **10**	 **9**	>99 (>99)
5	 **11**	 **12**	>99 (90)[c]
6	 **13**	 **14**	>99 (>99)
7	 **15**	 **16**	>99 (>99)
8	 **17**	 **18**	>99 (89)

[a] All reactions performed in methanol (2 mL), 0.5 mmol substrate, 6 equiv 1,4-cyclohexadiene, heated under microwave conditions at 120 °C for 5 min.
[b] Isolated yields.
[c] 10% of the *N*-oxide obtained.

Table 3
Reduction of 2-chloro-3-nitropyridine[a]



8 **19** **20** **9**

Entry	Equiv 2	Temp (°C)/time (min)	Catalyst (mol %)	8:19:20:9
1	6	120, 5	Pt, 5	0:71:0:29
2	6	120, 5	Pt, 1	33:12:53:1
3	6	120, 15	Pt, 1	12:36:50:2
4	6	120, 30	Pt, 1	8:58:32:2
5	4	120, 5	Pt, 5	4:49:44:3
6	5	120, 5	Pt, 5	0:75:8:18
7	5	120, 8	Pt, 5	0:79:2:19
8	5	100, 10	Pt, 4	22:25:53:0
9	5	100, 20	Pt, 4	12:45:42:1
10	5	100, 30	Pt, 4	7:60:32:1
11	5	100, 90	Pt, 4	0:75:0:25

[a] All reactions performed in methanol (2 mL), 0.50 mmol substrate, heated under microwave conditions.

Table 4
Catalytic reduction of nitro-arenes with cyclohexadiene and microwave heating[a]

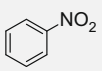
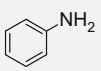
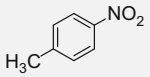
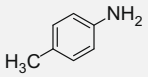
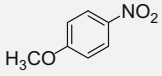
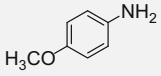
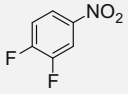
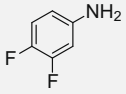
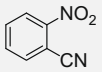
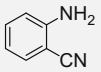
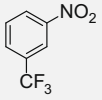
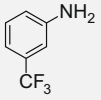
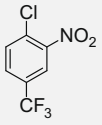
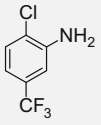
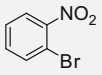
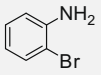
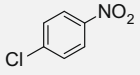
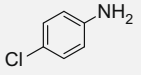
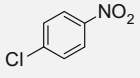
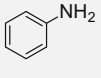
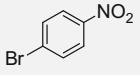
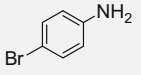
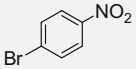
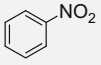
Entry	Substrate	Product	% Conv. (yield)[b]
1	 **21**	 **22**	>99 (70)
2	 **23**	 **24**	>99 (94)
3	 **25**	 **26**	>99 (98)
4	 **27**	 **28**	>99 (82)
5	 **29**	 **30**	>99 (98)
6	 **31**	 **32**	>99 (68)
7	 **33**	 **34**	>99 (89)
8	 **35**	 **36**	>99 (91)[c,d]
9	 **37**	 **38**	>99 (75)[c,d,e]
10	 **37**	 **22**	>99[d]
11	 **39**	 **40**	>99 (6.1)[c,d]

Table 4 (*continued*)

Entry	Substrate	Product	% Conv. (yield)[b]
12	 **39**	 **41**	>99[d]

[a] Unless otherwise noted, all reactions performed in methanol (10 mL), 5 mmol substrate, 6 equiv 1,4-cyclohexadiene, heated under microwave conditions at 120 °C for 5 min.
[b] Isolated yields.
[c] Catalyst is 5% Pt/C, 5 mol %.
[d] Reaction run on a 0.50 mmol scale in 2 mL methanol.
[e] 25% De-chlorinated aniline **22** obtained.

is the selective reduction of chlorine-containing **33** to **34** with Pd/C. In the case of 2-bromo-1-nitrobenzene **35** a 91% yield of the 2-bromoaniline **36** is obtained using Pt/C (Table 4, entry 8). The 4-halonitrobenzenes are more sensitive to dehalogenation than the 2-halo isomers. Whereas the 2-chloro compound **33** cleanly gives **34** using 5 mol % Pd/C (Table 2, entry 7), the 4-chloro compound **37** gives a quantitative yield of aniline **22** (Table 4, entry 10). By switching to a Pt/C catalyst, a 75:25 ratio of **38**/**22** is obtained (Table 4, entry 9). In the case of 4-bromo-1-nitrobenzene **39**, reduction using Pd/C unexpectedly gives a quantitative yield of nitrobenzene **41**. Switching the catalyst to Pt/C also gives complete consumption of the starting material. After filtration and concentration, the desired 4-bromo-aniline **40** is the only isolated product, albeit in low yield.[13e] This is perhaps due to unexpected volatility of the product or any side products.

In conclusion, we have developed a convenient, rapid, and safe procedure for the reduction of heteroaromatic and aryl nitro compounds to the corresponding anilines. Given the greater chemoselectivity observed with Pt/C, it may be the reagent of choice for this transformation. In analogy to traditional hydrogenation methods involving hydrogen gas, all that is required in the way of work-up and purification is a filtration to remove the spent catalyst and concentration to remove the solvent, volatile reagents, and byproducts. This is a significant advantage in cases of highly polar amino pyridines and pyrazines.

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16. The catalysts used in this study were either 5 wt % Pd (dry basis) Degussa type E101 O/W (~50 wt % H_2O) or 10 wt % Pd (dry basis) Degussa type E101 NE/W (~50 wt % H_2O). The Pt catalyst was 5 wt % Pt (dry basis) Degussa type F101 KYA/W (~50 wt % H_2O).
17. *A procedure for the synthesis of p-toluidine* (**24**) *is as follows*: A 20 mL Biotage microwave process vial with a stir bar was charged with 4-methyl-1-nitrobenzene (685 mg, 5 mmol), 10 wt % Pd/C (50% wet, 532 mg, 0.25 mmol), and methanol (10 mL). 1,4-Cyclohexadiene (3.00 mL, 32 mmol) was added and the vessel was capped and heated under microwave conditions at 120 °C for 5 min. The reaction was filtered through Celite and was evaporated to give *p*-toluidine (503 mg, 94%) as light brown crystals. This material had an identical HPLC retention time, APCI MS spectra, and ^{1}H NMR spectrum as authentic material.