A Convenient Method to Aniline Compounds Using Microwave-Assisted Transfer Hydrogenation

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Abstract: The reduction of mononitro and dinitro aromatic compounds to their aniline analogues using microwave-assisted transfer hydrogenation has been demonstrated. The optimised conditions used, with some examples, are described herein.

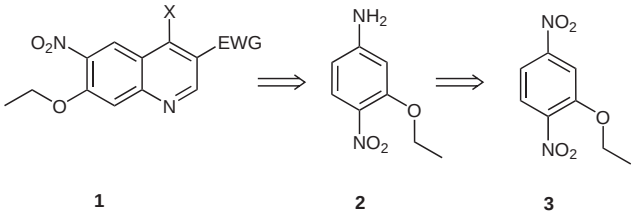
Key words: microwave, transfer hydrogenation, nitroaromatic, anilines

There are a wide variety of methods, which can be used to convert aromatic nitro groups to their corresponding anilines. These include the use of metal catalysts in the presence of hydrogen such as iron,[1] ruthenium,[2] rhodium,[3] cobalt,[4] palladium,[5] platnium,[6] or in the presence of mineral acids, tin,[7] iron[8] and zinc.[9] The use of catalytic transfer hydrogenation with palladium is also a useful method to achieve this transformation.[10] It has been demonstrated also that dinitro aromatic compounds can be selectively monoreduced to the corresponding aniline compound in the presence of controlled amounts of hydrogen using palladium[11] or cyclohexene.[10]

Microwave-assisted hydrogenation has been demonstrated previously using zinc in the presence of ammonium chloride or ammonium formate as the cation source[12] but also with sodium hydrogen sulfide in the presence of acid.[13] We wish to report our preliminary results and observations for a microwave-assisted transfer hydrogenation of aromatic nitro compounds using a number of methylcyclohexenes.

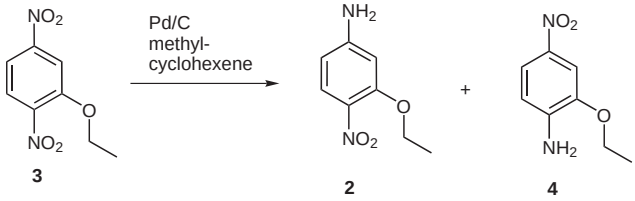
Initially, we were looking for a robust reliable method for reduction of aromatic mononitro and dinitro aromatic compounds to use as multifunctional building block starting materials (Scheme 1). However, in the case of dinitro aromatic species, we felt that there was a strong possibility of dinitro reduction using many of the methods described and so were interested in investigating the use of catalytic transfer hydrogenation as a possible controlled approach for synthesising key nitroaniline intermediate building block compounds.

Previously described conventional transfer hydrogenation one-pot experiments using methylcyclohexenes[10] often required long reaction times under vigorous heating in order to achieve the desired product. Therefore, we incorporated the use of microwave technology to assist in our rapid screening of suitable reaction conditions to investigate the conversion of **3** as described in Scheme 2. This gave the advantage of rapidly achieving high reaction temperatures as well as cleaner reaction profiles, in shorter reaction times, advantages associated with microwave-assisted techniques.[14]



Scheme 1 Rationalisation for the synthesis of (**1**) via [3-(ethyloxy)-4-nitrophenyl]amine (**2**). EWG = electron-withdrawing group, X = halogen.

In an attempt to formulate a generalised set of reaction conditions, a number of solvents were screened in the reaction including ethanol, methanol, acetone, acetonitrile, tetrahydrofuran, toluene–acetonitrile (1:1), dimethylformamide, dimethylsulfoxide and dimethylsulfoxide–water (1:1) and it was found that protic alcohol solvents, e.g. methanol or ethanol were most suitable for this reaction and these became our solvents of choice for further investigations.



Scheme 2 Catalytic transfer hydrogenation of 2-(ethyloxy)-1,4-dinitrobenzene (**3**) to the 3-(ethyloxy)-4-nitroaniline (**2**) and 2-(ethyloxy)-4-nitroaniline (**4**).

Upon initial subjection of **3** in ethanol to transfer hydrogenation conditions using cyclohexene as the hydrogen source, it was found that a mixture of regioisomers **2** and **4** was obtained in a ratio of 2:1 (Figure 1). These were readily separable by HPLC and after initial characterisation of each individual isomer by NMR spectroscopy[15] we were able to establish conditions for monitoring this reaction by HPLC.

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A time profile was carried out for the reaction described in Scheme 2 using cyclohexene, 1-methylcyclohexene and 4-methylcyclohexene in order to determine a generic optimum reaction time (Figure 1).

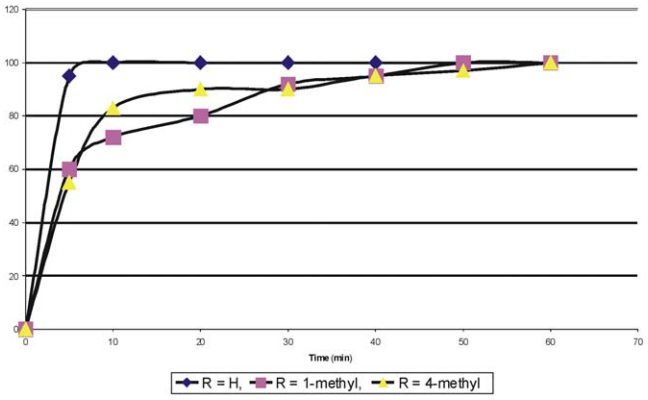


Figure 1 Percentage conversion[a] of 2-(ethyloxy)-1,4-dinitrobenzene (**3**) to 3-(ethyloxy)-4-nitroaniline (**2**) and the 2-(ethyloxy)-4-nitroaniline (**4**) vs. time with a number of *R*-cyclohexenes in ethanol. Temp. = 80 °C. [a] Conversion (%) determined by HPLC.

Using cyclohexene in ethanol at 80 °C, it was found after two minutes, that a conversion of ca. 80% was observed and full conversion was achieved after prolonged heating for greater than ten minutes. Lower conversions were observed when 1-methyl- and 4-methylcyclohexenes were compared under similar conditions. Full conversion was observed after one hour for both at 80 °C, however, to avoid the benzene side product from cyclohexene oxidation, it was decided to continue further studies using 1- and 4-methylcyclohexenes. Subsequent studies concluded that using 1-methylcyclohexene at higher temperatures for ten minutes resulted in complete conversion to the desired product mixture with similar regioselectivities being demonstrated and this observation was extended to a number of substrates.

Having chosen our hydrogen transfer substrate, it was decided to investigate the effect of increased amounts of methylcyclohexene in the reaction mixture. It was found that there was little or no regiospecificity in compound **3** for the 2- over the 5-position on the aromatic ring demonstrated in the reaction when a low (1 equiv) or high concentration (50 equiv) of 1-methylcyclohexene was used. Indeed it was also found that the 5-nitro compound **4** was present in the reaction mixture as the minor component in all cases, while no evidence for the dianiline was observed in any case.

From our experience with this reaction, a generalised set of conditions for screening alternative substrates was summarised in entry 9 (Table 1). Using standard quantities of methylcyclohexene (5 equiv) and the palladium catalyst (10%) each substrate in Table 2 (Scheme 3) was screened rapidly using the described conditions in order to determine conversion for the given set of conditions.

Interestingly, it was found under the conditions of reaction that a degree of tolerance was exhibited by a number

Table 1 Conditions Investigated for Transfer Hydrogenation

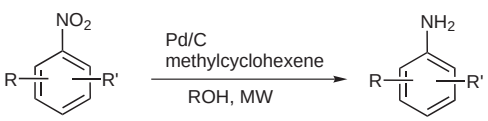
Entry	Solvent	Temp (°C)	Time (min)
1	MeOH	80	5–20
2	MeOH	100	5–20
3	MeOH	120	5–20
4[a]	MeOH	160	Variable
5[a]	EtOH	80	5–20
6	EtOH	100	5–20
7	EtOH	120	5–20
8	EtOH	160	Variable
9[b]	ROH	120	20

[a] 4-Methylcyclohexene used in place of 1-methylcyclohexene.
[b] Suggested conditions for new evaluations.

of functional groups. In one case (entry 13) it was found that the benzylic type double bond was preserved under the described conditions. Complete saturation of the double bond as well as reduction of the nitro group by using an excess of the transfer reagent at higher temperatures or prolonged reaction times could also be achieved.[16] It was found also that both the acetophenone (entry 5) and methyl ester (entry 6) nitrobenzene derivatives were also stable under the conditions described with high conversions.

In general, it can be seen that both *ortho* and *para* substituents, either electron-withdrawing, electron-donating or a combination of both, are tolerated to a high degree. However, it was found that the 4-dimethylaminoethylphenoxy nitrobenzene did not undergo reaction using a temperature of 160 °C for 60 minutes. This could be attributed to possible chelating effects of the flexible dimethylamino chain and the catalyst.

Interestingly, it was also found that the *para*-halo-nitrobenzenes exhibited unusual behaviour under the standardised set of reaction conditions. Whereas the strongly electron-withdrawing *para*-fluoronitrobenzene underwent complete reaction (entry 12), the *para*-chloronitrobenzene underwent partial conversion to the desired component (entry 11) with the major side product identified as being the dehalogenated aniline. The *para*-bromonitrobenzene did not undergo complete reduction to the desired material under these conditions resorting instead to a volatile unidentified intermediate. It appears that the increased electronegativity of the halogens (Br < Cl < F) has a significant effect on the outcome of this reaction for these analogues.



Scheme 3

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Table 2 Transfer Hydrogenation of Nitroaromatic Compounds

Entry	R	R′	Reaction time (min)	Conversion, yield (%)[a]	Product
1	H	H	10	95 (65)	NH_2
2	4-OMe	H	10	95 (95)	NH_2
3	2-Me	H	20	70 (50)	NH_2
4	2,6-Me	H	20	82 (60)	NH_2
5[b]	2-COMe	H	10	95 (95)	NH_2
6[b]	4-CO_2Me	H	10	95 (95)	NH_2
7	2-CHO	H	20	20 (–)	NH_2
8[c]	2-OH	4-NO_2	10	95 (54)	2-NH_2-5-NO_2
8[c]	2-OH	4-NO_2	10	95 (31)	2-NO_2-5-NH_2
9[c,d]	2-OC_2H_5	4-NO_2	5	95 (71)	2-NH_2-5-NO_2
9[c,d]	2-OC_2H_5	4-NO_2	5	95 (22)	2-NO_2-5-NH_2
10[b]	4-NO_2	H	20	95 (95)	NH_2
11	4-Cl	H	15	95 (60)[e,f]	NH_2
12	4-F	H	15	95 (63)	NH_2
13	2-(CH)-2-Py[17]	H	90	65 (40)	NH_2
14	Indazole[17]	–	15	70 (48)	NH_2

[a] Conversion (%) determined by HPLC-MS, yield (%) refers to major products, which were isolated and purified prior to analysis.
[b] 4-Methylcyclohexene can be used.
[c] Two products separated and identified.
[d] An optimum temperature of 95 °C can be used with cyclohexene.
[e] Unsubstituted aniline identified as the main side product (40%).
[f] Yield estimated by ^{1}H NMR spectroscopy.

In the case of the model reaction described in Scheme 2, it was found that the less sterically hindered product **2** was favoured under the described set of conditions used, while the side product **4** was the minor component in all cases. When the corresponding phenol analogues were reduced (entries 9) it was found that the main component recovered was the *ortho* aniline in favour of the *para* aniline. This reversal of selectivities may be attributed to a change in the electronics on the ring as a result of the removal of the ethyl group, but also as a result of the additional internal hydrogen bond interaction possible between the phenolic OH and the *ortho* nitro group.

In summary, we have demonstrated a general method for reduction of nitro aromatic systems, which is amenable to a high throughput screening for reaction conditions under the suggested set of general conditions. Although in our model reaction, total regioselectivity could not be demonstrated with **3**, it was found that the regioisomers were easily separated and isolated leading to a greater diversity of starting monomers for key building block intermediates.

General Procedure for Microwave-Assisted Catalytic Transfer Hydrogenation of Aromatic Nitro Compounds

To a microwave vial [EMRYS Process Vial (5 mL)] was added palladium on carbon (10%), a solution of the nitro compound (1 equiv) in MeOH (5 mL) and the 1-methylcyclohexene (5 equiv). The vial was sealed and allowed to react in the Biotage initiator sixty™ microwave synthesiser with stirring for 10 min at a hold temperature of 80 °C. Upon completion, the reaction vessel was cooled using compressed air and the solution was filtered through Celite® then concentrated under vacuum to give the crude compound. Where required, the crude reaction mixture was subjected to chromatography on silica gel (eluent: cyclohexane–EtOAc, 0–100%). All isolated compounds were characterised by ^{1}H NMR and ^{13}C NMR spectroscopy, LCMS, HRMS where possible and were in good agreement when compared with literature.

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(15) Each isomer was separated and characterised by ^{1}H NMR and ^{13}C NMR spectroscopy. For each isomer, an NOE was observed between the NH_2 and the aromatic proton.

(16) The conversion of 2-[(*E*)-2-(4-pyridinyl)ethenyl]aniline to the 2-[2-(4-pyridinyl)ethyl]aniline required microwave conditions of 180 °C, 120 min in EtOH.

(17) **3-(Ethyloxy)-4-nitroaniline.**
Synthesised using heating time of 3 min. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 1.35 (t, *J* = 8 Hz, 3 H, CH_3), 4.05 (q, *J* = 8 Hz, 2 H, CH_2), 6.18 (d, *J* = 8 Hz, 1 H, ArH), 6.24 (s, 1 H, ArH), 6.53 (br s, 2 H, NH_2), 7.78 (d, *J* = 8 Hz, 1 H, ArH), 7.71 (d, *J* = 8 Hz, ArH). ^{13}C NMR [75 MHz, $(CD_3)_2SO$]: δ = 14.8, 64.5, 96.9, 105.9, 127.2, 129.3, 156.3, 156.5. MS (EI, 70 eV): *m/z* (%) = 182.97 (100). HRMS-FAB: *m/z* calcd for $C_8H_{10}N_2O_3$ $[M + H]^+$: 183.0770; found: 183.0775.
2-(Ethyloxy)-4-nitroaniline.
Synthesised using heating time of 3 min. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 1.37 (t, *J* = 8 Hz, 3 H, CH_3), 4.10 (q, *J* = 8 Hz, 2 H, CH_2), 6.40 (br s, 2H, NH_2), 6.64 (d, *J* = 8 Hz, 1 H, ArH), 7.54 (s, 1 H, ArH), 7.71 (d, *J* = 8 Hz, ArH). ^{13}C NMR [75 MHz, $(CD_3)_2SO$]: δ = 14.5, 63.9, 106.3, 110.8, 119.6, 135.4, 143.6, 146.1. MS (EI, 70 eV): *m/z* (%) = 182.85 (100). HRMS-FAB: *m/z* calcd for $C_8H_{10}N_2O_3$ $[M + H]^+$: 183.0770; found: 183.0775.
2-[(*E*)-2-(4-pyridinyl)ethenyl]aniline.
Synthesised using heating time of 90 min. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 5.51 (s, 2 H, NH_2), 6.55 (t, *J* = 4 Hz, 1 H, ArH), 6.65 (d, *J* = 8 Hz, 1 H, ArH), 6.96 (d, *J* = 16 Hz, 1 H, CH), 7.01 (m, 1 H, ArH), 7.47 (d, *J* = 8 Hz, 1 H, ArH), 7.57 (br d, *J* = 4 Hz, 2 H, ArH), 7.67 (d, *J* = 16 Hz, 1 H, CH), 8.51 (br s, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.7, 116.6, 119.4, 120.61, 123.7, 125.7, 128.8, 129.5, 145.1, 146.3, 149.2. MS (EI, 70 eV): *m/z* (%) = 197.0 (100). HRMS-FAB: *m/z* calcd for $C_{13}H_{13}N_2$ $[M + H]^+$: 197.1083; found: 197.1079.
1*H*-Indazol-6-amine
Synthesised using heating time of 15 min. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 5.18 (s, 2 H, NH_2), 6.48 (dd, *J* = 8, 4 Hz, 1 H, ArH), 6.50 (s, 1 H, CH), 7.35 (d, *J* = 8 Hz, 1 H, ArH), 7.71 (s, 1 H, ArH) 12.3 (s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 89.6, 111.5, 114.7, 119.7, 132.3, 141.1, 146.8. MS (EI, 70 eV): *m/z* (%) = 134.02 $[M + H]^+$ (100). HRMS-FAB: *m/z* calcd for $C_7H_7N_3$ $[M + H]^+$: 134.0717; found: 134.0718.

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