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## Rapid and Convenient Conversion of Nitroarenes to Anilines under Microwave Conditions Using Non-precious Metals in Mildly Acidic Medium

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## Abstract

Nitroarenes are reduced to the corresponding aniline derivatives using iron or zinc under mild conditions under microwave heating conditions. Mild acidity is provided by ammonium chloride in an aqueous methanol medium. The conditions are tolerant to other functional groups, with the exception of bromoalkyl derivatives, which yield complex reaction mixtures; otherwise, yields are generally quite high (80-99%).

## **GRAPHICAL ABSTRACT**



KEYWORDS: nitroarenes; anilines; reduction; iron; zinc; microwave chemistry

#### **INTRODUCTION**

Anilines are among the oldest and most indispensible organic intermediates for both laboratory-scale and commercial synthesis.<sup>[1]</sup> Moreover, the aniline and anilide substructures are widely distributed among natural products of biological interest.<sup>[2,3]</sup>

Consequently, access to this privileged moiety remains a high priority for the synthetic chemist.<sup>[4]</sup>

Owing to the ease and versatility of aromatic nitration,<sup>[5,6]</sup> the reduction of nitroarenes is among the most convenient methods for the preparation of anilines. Although well established, this approach continues to provide a platform for useful innovation.<sup>[7,8]</sup> Next to catalytic hydrogenation,<sup>[9]</sup> Béchamp-inspired<sup>[10]</sup> conditions find the greatest application, thanks to practical simplicity and broad functional group tolerance. A particularly mild variation features ammonium chloride as an acidifying agent, which has been used in combination with zinc in aqueous<sup>[11,12]</sup> and methanolic<sup>[13]</sup> medium, iron in aqueous ethanol<sup>[14,15]</sup> and aqueous acetone,<sup>[16]</sup> and indium in aqueous ethanol.<sup>[17–19]</sup> In connection with our ongoing work in adapting workhorse synthetic transformations for rapid microwave protocols,<sup>[20,21]</sup> we were interested in studying how well these modified Béchamp conditions would behave in a dedicated microwave reactor.

## **RESULTS & DISCUSSION**

A comparison of some of the literature conditions (Table 1) reveals modest variation in reaction parameters, as well as significant differences in cost. Whereas reductions with iron and zinc are relatively inexpensive, using indium as the reductant costs almost \$1000 per mole of nitroarene converted (entry 3). Another factor impacting the utility of the method is the speed with which the metals effect reduction in mildly acidic medium at elevated temperatures. Thus, a few commonly available metals were surveyed by reaction with nitrobenzene in aqueous ammonium chloride for 5 min at 120°C (Table 2).

Interestingly, zinc, iron, and indium led to the highest conversions (entries 1-3). It is noteworthy that the results do not cleanly correlate to parameters such as standard reduction potentials, but rather depend upon physicochemical characteristics, such as the robustness of the passive oxide layers.<sup>[22]</sup> These results demonstrate that iron and zinc are the most attractive reductants from both economic and kinetic standpoints.

Since this process is a six-electron reduction, and zinc is a two-electron reductant, theoretically only three equivalents of zinc are necessary. However, in practice an excess is needed to achieve rapid and full conversion (Table 3). Carrying out the reaction with nitrobenzene and a deficiency (2 equiv) of zinc leads to an almost equimolar mixture of nitrobenzene, aniline, and phenylhydroxylamine (entry 1). With a slight excess of zinc (4 equiv), some residual phenylhydroxylamine is still present after 5 min (entry 2). Best results are achieved with a twofold excess of reductant (entry 3). This does not appear to be a surface area phenomenon, as granular zinc gives essentially the same results as zinc dust (entry 5). The method can also be conveniently run on a 5-mmol scale with equal efficiency (entry 6). It is worth noting that a control experiment using open reflux provided predominantly phenylhydroxylamine and no aniline (entry 7).

A variety of nitroarenes were then examined to explore the scope of this procedure (Table 4). Thus, the substrate was taken up in methanol, diluted with an equal volume of saturated ammonium chloride, treated with 6 equiv of iron or zinc, and heated in a sealed tube under microwave irradiation for 5 min at 120 °C. A variety of functional groups were tolerated, including esters, ketones, aldehydes, amides, and halogens; and many

products were isolated without the need for column chromatography. Notable exceptions included nitrophenyl acetate (entry 5), which underwent concomitant hydrolysis under the reaction conditions, and bromoalkyl derivatives (entries 10 and 11), which suffered decomposition and provided complex reaction mixtures that proved recalcitrant to purification.

The two metals gave comparable results, each having its own practical advantage. Iron is more readily available, but it tends to complicate the subsequent cleaning of glassware and equipment. Zinc is much tidier to work with, but it is more pyrophoric than iron and it conforms less to green chemical principles, as it is listed among the endangered elements because of increasing global demand.<sup>[23]</sup> While a purely aqueous system could be used in some cases, an alcohol co-solvent led to more consistent results in our hands, presumably due to the limited water solubility of some starting materials.

In summary, the Béchamp reduction of nitroarenes using ammonium chloride as an acidifier is well behaved under sealed-tube microwave heating conditions, rapidly providing the corresponding aniline derivatives in high purity in most cases. The speed and operational simplicity of this method makes it a particularly attractive protocol for laboratory-scale synthesis.

#### **EXPERIMENTAL**

#### **General Procedure For The Reduction Of Nitroarenes 1**

To a 10 mL microwave vial was added the nitroarene (0.50 mmol), zinc dust (3.00 mmol), MeOH (1.0 mL), and sat. aq NH<sub>4</sub>Cl. The vial was sealed and heated at 120 °C for 5 min. The reaction mixture was transferred to a separatory funnel containing sat aq Na<sub>2</sub>CO<sub>3</sub> (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 8 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to provide anilines **2**.

#### **Spectral Data For Selected Compounds**

Aniline (2a).<sup>[24]</sup> The general procedure provided 2a (46.1 mg, 99%) as a light amber oil with physical properties identical to those found in the literature: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.18 (t, *J* = 7.8 Hz, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 2H), 3.58 (br s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  146.41, 129.43, 118.73, 115.29.

*p*-Methoxyaniline (2c).<sup>[25]</sup> The general procedure, followed by column chromatography (30% EtOAc/hexane), provided 2c (45.6 mg, 74%) as a brown solid with physical properties identical to those found in the literature: mp 53-55 °C (lit. 56-59 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.74 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 3.30 (br s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.93, 139.91, 116.55, 114.88, 55.83.

**Ethyl** *p***-aminobenzoate (2d).**<sup>[19]</sup> The general procedure provided **2d** (76.8 mg, 93%) as a buff solid with physical properties identical to those found in the literature: mp 87-89 °C (lit. 88-90 °C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.83 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* =

8.7 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.93 (br s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 166.95, 151.05, 131.63, 119.89, 113.85, 60.45, 14.51.

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## SUPPORTING INFORMATION

Full experimental detail, <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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|       |           |                    |                     | 1   | 1   |                   | 1   |               |
|-------|-----------|--------------------|---------------------|-----|-----|-------------------|-----|---------------|
| Entry | metal     | eq                 | solvent system      | T°C | t   | cost              | ref |               |
|       | (eq)      | NH <sub>4</sub> Cl |                     |     | (h) | (\$) <sup>a</sup> |     |               |
| 1     | Fe (n.r.) | 3.0                | water/acetone       | 57  | 2-5 | 2.59              | 16  |               |
|       |           |                    | (1:2.5)             |     |     |                   |     | $\mathcal{L}$ |
| 2     | Zn (7.25) | 2.0                | water               | 80  | 0.5 | 5.87              | 12  | R             |
| 3     | In (4.0)  | 10                 | water/ethanol (1:2) | 78  | 2.5 | 933               | 19  |               |

Table 1. Typical conditions for metal-mediated reduction in NH<sub>4</sub>Cl solution.

<sup>a</sup>cost of metal to convert 1 mol of nitroarene; prices taken from the Sigma-Aldrich web

catalog (www.sigmaaldrich.com); for cost calculation, 7.25 eq of iron were assumed.

Table 2. Efficacy of various metals in reducing nitrobenzene.<sup>a</sup>

|       | NO <sub>2</sub> – | metal<br>NH₄CI   |                    | 2                |   |
|-------|-------------------|------------------|--------------------|------------------|---|
| 1a    | l                 | H <sub>2</sub> O | 2a                 |                  |   |
| entry | metal             | E <sup>0</sup>   | equiv <sup>b</sup> | conv             |   |
|       |                   | (V)              |                    | (%) <sup>c</sup> | X |
| 1     | Zn                | -0.76            | 3.5                | 93               |   |
| 2     | Fe                | -0.41            | 3.5                | 88               |   |
| 3     | In                | -0.34            | 7.0                | 81               |   |
| 4     | Mg                | -2.83            | 3.5                | 51               |   |
| 5     | Ni                | -0.23            | 3.5                | 24               |   |
| 6     | Al                | -1.66            | 2.3                | 7                |   |
| 7     | Ti                | -1.63            | 3.5                | 3                |   |

<sup>a</sup>conditions: 0.5 mmol PhNO<sub>2</sub>, 2.5 mL H<sub>2</sub>O, 2.0 equiv NH<sub>4</sub>Cl; 5 min @ 120°C

<sup>b</sup>stoichiometry standardized to give 7.0 equiv of electrons

<sup>c</sup>conversion determined by HPLC

N.C.C.R.

| entry          | Zn      | reaction | )     |      |  |
|----------------|---------|----------|-------|------|--|
|                | (equiv) | 1a       | 2a    | 3    |  |
| 1              | 2.0     | 37%      | 34%   | 29%  |  |
| 2              | 4.0     | 0%       | 89%   | 11%  |  |
| 3              | 6.0     | 0%       | > 99% | < 1% |  |
| 4              | 8.0     | 0%       | > 99% | < 1% |  |
| 5°             | 6.0     | 0%       | >99%  | < 1% |  |
| 6 <sup>d</sup> | 6.0     | 0%       | >99%  | < 1% |  |
| $7^{\rm e}$    | 6.0     | 9%       | 0%    | 91%  |  |

 Table 3. Impact of metal stoichiometry.<sup>a</sup>

Ph-NH<sub>2</sub> +

2a

Ph-NHOH

3

Zn

NH<sub>4</sub>Cl MeOH/H<sub>2</sub>O

Ph-NO<sub>2</sub>

1a

<sup>a</sup>conditions: 0.5 mmol PhNO<sub>2</sub>, 1.0 mL MeOH, 1.0 mL sat'd NH<sub>4</sub>Cl; 5 min @ 120°C

<sup>b</sup>molar ratio determined by NMR

<sup>c</sup>granular zinc used instead of zinc dust

<sup>d</sup>run on a 5.0 mmol scale

<sup>e</sup>heated under reflux for 5 min

Table 4. Anilines prepared by the reduction of nitroarenes.<sup>a</sup>



| entry | R                                   | product | isolated         | l yield          |   |
|-------|-------------------------------------|---------|------------------|------------------|---|
|       |                                     |         | Zn               | Fe               | × |
| 1     | -H                                  | 2a      | 99               | 90               |   |
| 2     | -Me                                 | 2b      | 95               | 94               |   |
| 3     | -OMe                                | 2c      | 74               | 91               |   |
| 4     | -CO <sub>2</sub> Et                 | 2d      | 93               | 95               | 2 |
| 5     | -OAc                                | 2e      | 18               | 32               |   |
| 6     | -CHO                                | 2f      | 34               | 95               |   |
| 7     | -C(O)Me                             | 2g      | 95               | 97               |   |
| 8     | -Br                                 | 2h      | 94               | 91               |   |
| 9     | -Cl                                 | 2i      | 95               | 90               |   |
| 10    | -CH <sub>2</sub> Br                 | 2j      | <38 <sup>b</sup> | <10 <sup>b</sup> |   |
| 11    | -CH <sub>2</sub> CH <sub>2</sub> Br | 2k      | <33 <sup>b</sup> | 17               |   |
| 12    | -NH <sub>2</sub>                    | 21      | 82               | 64               |   |
| 13    | -NHAc                               | 2m      | 86               | 65               |   |

<sup>a</sup>conditions: 0.5 mmol ArNO<sub>2</sub>, 3.0 mmol metal, 1.0 mL MeOH, 1.0 mL sat'd NH<sub>4</sub>Cl; 5

min @ 120°C; conversion cost (including work-up) per mole of substrate: Fe, \$3.04; Zn,

\$5.76

<sup>b</sup>complex reaction mixture