

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: <https://www.tandfonline.com/loi/lsyc20>

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To cite this article: Ian Bento, Mabel Bernaldez, Ryden Noguchi & Joel Kawakami (2020) Ultrasound-assisted rapid reduction of nitroaromatics to anilines using gallium metal, *Synthetic Communications*, 50:9, 1404-1407, DOI: [10.1080/00397911.2020.1743317](https://doi.org/10.1080/00397911.2020.1743317)

To link to this article: <https://doi.org/10.1080/00397911.2020.1743317>



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Published online: 24 Mar 2020.



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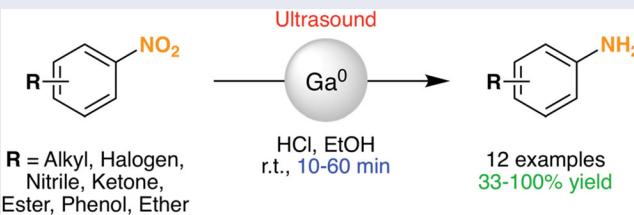
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ABSTRACT

The reduction of nitroaromatic compounds to anilines is widely used throughout organic synthesis. Typical methods of performing this transformation utilize hydrogenation over a pyrophoric catalyst or a finely divided reducing metal, which often affords heterogeneous mixtures that are difficult to purify. Herein, we report for the first time the use of gallium metal as a reducing agent in organic synthesis. The reaction proceeds under aerobic conditions and affords homogeneous mixtures for a convenient workup. Using this method, twelve anilines were obtained in 33% to quantitative yields with short reaction times of 10–60 minutes.

GRAPHICAL ABSTRACT



ARTICLE HISTORY

Received 18 October 2019

KEYWORDS

Aniline; gallium; metal; nitroaromatic; reducing; reduction; ultrasound

Introduction

The reduction of nitroaromatics to anilines remains an interesting organic transformation mediated by metals^[1a] or nonmetals.^[1b,c] The need for an aerobic and non-pyrophoric condition led to the investigation of methods involving indium as the reducing metal.^[2] Nitroaromatic reduction using indium produced minor amounts of anilines and mostly unreacted starting material. In addition, the crude reaction mixture afforded a colloidal, heterogeneous suspension making for a difficult workup, a problem often observed using tin, aluminum,^[3] zinc^[4] and iron^[5] as the reducing metal. We were intrigued to find scarce reports for using gallium,^[6a–d] a lighter metal within the same group as indium, as the reducing metal and no report of it for the reduction of nitroaromatic compounds.

Table 1. The reduction of nitroaromatic compounds to afford anilines using gallium in acidic ethanolic solution.

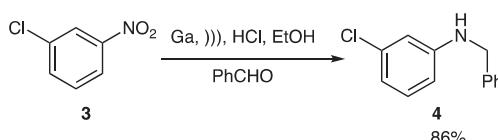
Entry	R ¹	R ²	R ³
1	H	H	Me
2	H	Me	H
3	Me	H	H
4	H	Cl	H
5	H	H	Br
6	H	H	I
7	H	H	CN
8	H	H	CH ₂ CN
9	H	H	OH
10	H	H	OBn
11	H	H	CO ₂ Me
12	H	H	Ac

^aNitroaromatic compounds were suspended in 1.5 N HCl in EtOH with 4 equiv. of Ga metal and sonicated until a homogeneous mixture was obtained. Work-up proceeded by (A) neutralization with NaOH and sonication followed by extraction with DCM; (B) neutralization with 2 M phosphate buffer (pH = 7.6) followed by extraction from Rochelle's salt (aq) with DCM; (C) Neutralization with NaOH followed by extraction from Rochelle's salt (aq) with DCM.

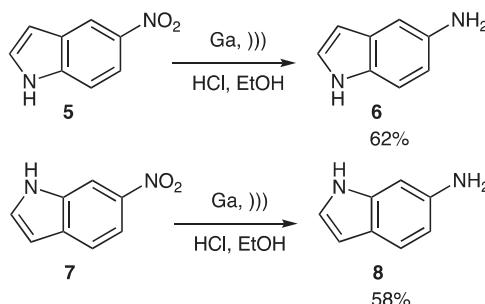
^bIsolated yields after chromatography on silica gel

Results and discussion

Initial attempts to use gallium in the reduction of nitroaromatic compounds produced only minute amounts of the aniline product with the bulk of the reaction material consisting of unreacted gallium metal. The use of acid to dissolve the metal was not successful. However, the use of an acid with sonication^[7] resulted in rapid dissolution of the gallium metal with complete conversion of nitroaromatic compounds to anilines in high yields. This reaction requires 4 equivalents of gallium metal, dissolved in 1.5 N HCl in ethanol as the optimized conditions. Critical to the success of the reaction was the complete dissolution of the gallium metal through ultrasonication. The dissolved gallium species in excess has yet to be elucidated. Attempts to substitute ethanol for water failed due to the insolubility of the nitroaromatic starting materials. Also, diminishing the concentration of HCl or substitution with formic, trifluoroacetic, *p*-toluenesulfonic or triflic acids resulted in lower yields of the aniline product. Replacing gallium with indium under these optimized conditions failed to afford appreciable amounts of the aniline product. The optimized conditions were applied to an array of nitroaromatic compounds (Table 1). The reduction of nitroarenes proceeded rapidly. Product yields were slightly lower for substrates bearing an electron withdrawing substituent (entries 7, 11 and 12). Chemoselectivity was observed in the reduction of nitro groups in the presence of a halogen atom (entries 4–6), a cyano group (entries 7 and 8), and a benzyl ether, or an ester (entries 10 and 11). The reduction proceeded well in the presence of a phenol functional group (entry 9). A slight decrease in yield is observed from the increased steric demand of an ortho methyl group (entry 3) relative to its less hindered meta and para counterparts (entries 1 and 2). The moderate yield observed for the



Scheme 1. Tandem *in-situ* nitro reduction followed by reductive amination.



Scheme 2. Nitro reduction of indoles. Reduction of 7 was performed on a gram-scale.

reduction of a nitro group in the presence of a ketone (entry 12) was primarily ascribed to the subsequent reductive amination with the aniline product. The simultaneous imine formation represents a limitation to this method. However, this side reaction inspired us to develop a creative tandem *in-situ* amination reaction as evidenced by performing the reduction of 3-nitrochlorobenzene in the presence of benzaldehyde (**Scheme 1**). The aqueous work up was optimized to afford a homogeneous biphasic extraction using DCM, avoiding a difficult heterogeneous mixture.

The method was applied to several heteroaromatic compounds. The reaction proceeded well in the presence of indoles (**Scheme 2**). The reduction of nitroindoles 5 and 7 afforded the corresponding anilines in good yields. Aniline 8 was isolated in 58% yield on a gram scale. Further scale up is feasible with several reaction vessels running in parallel in a single sonicator, all with rapid reaction times (<30 min).

Conclusion

The rapid reduction of nitroaromatic compounds with gallium as the reducing metal afforded anilines in high yields, and was shown to tolerate several functional groups susceptible to reduction. The reaction used non-pyrophoric reagents and did not require the need for a scrupulous anhydrous solution or inert atmosphere conditions. Gallium with its low melting point was easily handled as a molten liquid after heating in a warm water bath. Unlike other metals such as aluminum, zinc and tin, the reduction with gallium afforded a homogeneous solution for a less problematic workup.

Experimental

The following is a representative example. *p*-toluidine (**2A**): To a 25 mL round-bottom flask containing molten gallium (313 mg, 4.48 mmol, 4.0 equiv.) were added 4-nitrotoluene (154 mg, 1.12 mmol, 1.0 equiv.), EtOH (11.2 mL), and 12 N HCl (aq) (1.4 mL).

The flask was sonicated at r.t. for 15 min. The reaction mixture was basified with 2.74 M NaOH (aq) (8 mL), and sonicated for 10 min at r.t. to break up any precipitate formed. The reaction mixture was transferred to a 125 mL separatory funnel, diluted with water (20 mL) and extracted with DCM (3×20 mL). The combined extracts were dried over anhydrous Na_2SO_4 , passed through a short plug of silica gel, and solvent was removed by rotary evaporation to afford a colorless solid as the product (**2A**) in quantitative yield. ^1H NMR (300 MHz, CDCl_3) δ 6.97 (d, $J = 8.3$ Hz, 2H), 6.61 (d, $J = 8.3$ Hz, 2H), 3.53 (br s, 2H), 2.24 (s, 3H) ppm. ESI-MS (*m/z*): 108.4 $[\text{M} + \text{H}]^+$.

Supporting Information: Full experimental detail, ^1H spectra, MP, and LCMS-FIA (ESI^+) can be found via the “[Supplementary Content](#)” section of this article’s webpage.

Acknowledgments

We would like to thank Hawai’i Pacific University of the use of their nuclear magnetic resonance instrument. Also, our thanks to Dr. Paul Helquist at University of Notre Dame and Dr. David Kingston at Virginia Tech for useful commentaries while preparing our manuscript.

Funding

The work was supported by grants from the Alana Dung Research Foundation and NIH NIGMS INBRE under [Award number: P20GM103466].

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