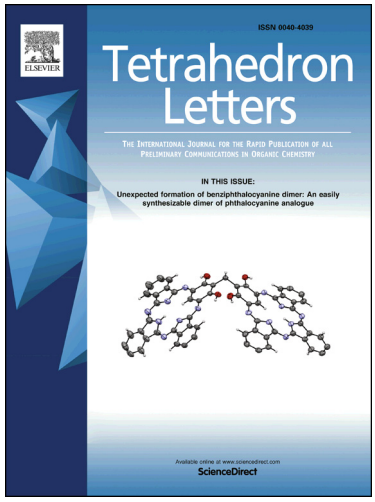


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PII: S0040-4039(17)30998-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.08.009
Reference: TETL 49199

To appear in: *Tetrahedron Letters*

Received Date: 8 July 2017
Revised Date: 2 August 2017
Accepted Date: 3 August 2017

Please cite this article as: Chen, X-L., Ai, B-R., Yu-Dong, Zhang, X-M., Wang, J-Y., Hexafluoro-2-propanol-assisted quick and chemoselective nitro reduction using iron powder as catalyst under mild conditions, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.08.009

## Graphical Abstract

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**Hexafluoro-2-propanol-assisted quick and chemoselective nitro reduction using iron powder as catalyst under mild conditions**

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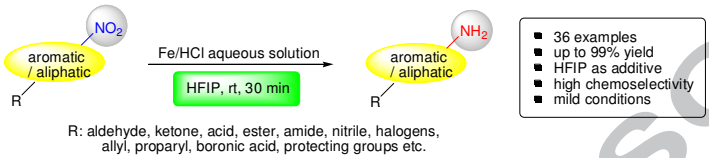


R: aldehyde, ketone, acid, ester, amide, nitrile, halogens, allyl, proparyl, boronic acid, protecting groups etc.

Tetrahedron Letters
journal homepage: www.elsevier.com

# Hexafluoro-2-propanol-assisted quick and chemoselective nitro reduction using iron powder as catalyst under mild conditions

Xu-Ling Chen[a], Bai-Ru Ai[a], Yu-Dong[a], Xiao-Mei Zhang[a,b] and Ji-Yu Wang[a ,b, *]

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ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

*Keywords:*
Hexafluoro-2-propanol
Nitro reduction
chemoselective
mild conditions

ABSTRACT

Hexafluoro-2-propanol as the promoter for the quick nitro reduction using a combination of iron powder and 2 N HCl aqueous solution is reported. This methodology has several positive features, as it is of room temperature, remarkably short reaction time. A wide range of substrates including those bearing reducible functional groups such as aldehyde, ketone, acid, ester, amide, nitrile, halogens, even allyl, propargyl and heterocycles are chemoselectively reduced in good to excellent yields, even on gram scale. Notably, the highly selective reduction of 3-nitrophenylboronic acid is achieved quantitatively. The reduction is also tolerant of common protecting groups, and aliphatic nitro compound, 1-nitrooctane can be reduced successfully.



## Introduction

Aliphatic or aromatic amines are widely used as important intermediates in the synthesis of chemicals such as dyes, antioxidants, conducting polymers, photographic, pharmaceutical and agricultural chemicals.[1] While numerous methods have been reported in the literature for the synthesis of amine, the reduction of nitro group represents one of the most straightforward entries to aliphatic or aromatic amines. It is known that reductions via catalytic hydrogenation utilizing catalysts such as Pd/C, $PtO_2$, Raney nickel and other transition metals are largely employed.[2] However, these methods lack functional group compatibility and often require high-pressure equipment. Alternatively, transfer hydrogenation has received high interest.[3] In 2016, Thomas group reported the reduction of nitroarene with high selectivity using iron (III) catalyst and silane.[4] More recently, PVP-Pd nanoparticles have been developed by Martín group for the reduction of nitro group under mild conditions.[5] Unfortunately, these methods suffered from sophisticated catalysts or ligands and the use of expensive hydride source silane. Classically, stoichiometric metal-mediated reductions of nitro compound under acidic conditions have been well developed.[6] Although it is effective in scaled industrial process, this method still tends to suffer from a limited substrate scope due to the severity. In 2014, Lipshutz group studied the zinc-mediated reduction of nitro compound in solution containing nanomicelles surfactant TPGS-750-M.[7] While chemoselectivity is impressively high, this protocol has limitations due to the cost and complexity of the surfactant TPGS-750-M. Hence, an objective to develop a more simple and efficient nitro reduction method with excellent chemoselectivity is still highly desirable.

Hexafluoro-2-propanol (HFIP) is a useful solvent, cosolvent, and additive in organic synthesis with a nearly unique set of properties including high ionizing power, strong hydrogen bond donating ability, mild acidity, and low nucleophilicity. All of these properties are favorable for an array of valued organic transformations, and accordingly, HFIP has drawn special attention of a number of investigators.[8] For example, HFIP is an ideal solvent for generating reactive electrophilic species and allowing them to react with the desired nucleophilic species.[9] In particular, electrophilic aromatic substitution reactions (e.g. Friedel-Crafts type reactions) have been shown to often proceed well in HFIP without the need for any acid catalyst.[10] In addition, Cheng et al. studied the Pd (II)-catalyzed C-H alkylation of arenes with epoxides in HFIP.[11] HFIP was effectively applied by Pappo group as a solvent in the iron-catalyzed oxidative cross-coupling of phenols.[12] However, fewer examples of HFIP employed in reduction have been reported. Several work focused on stoichiometric iron-mediated reductions of nitro compound but limited in the weak tolerance of functionalities, long reaction time and need of heating.[6d, 6e] To further widen the range of the HFIP applications, we performed the iron powder catalyzed nitro reduction reaction in the presence of HFIP. Surprisingly, we achieved the amine successfully and quickly in good yield under mild conditions. Herein, we would like to report the HFIP-assisted nitro reduction catalyzed by iron powder with 2 N HCl aqueous solution as hydrogen source under mild conditions.

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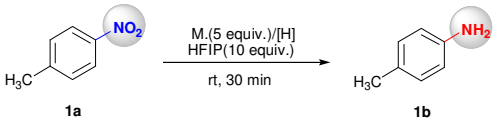
**Table 1.** Optimization of reaction conditions for the reduction[a]




1a 1b

| entry | metal | [H][b] | additive | Yield (%)[c] |
|---|---|---|---|---|
| 1 | Zn | HCl (2 N) | HFIP | 82 |
| 2 | Mg | HCl (2 N) | HFIP | / |
| 3 | Sn | HCl (2 N) | HFIP | 88 |
| 4 | Fe | HCl (2 N) | HFIP | 99 |
| 5 | Cu | HCl (2 N) | HFIP | / |
| 6 | Fe | $H_2O$ | HFIP | 13 |
| 7 | Fe | AcOH | HFIP | 91 |
| 8 | Fe | $NH_4Cl$ [d] | HFIP | / |
| 9 | Fe | HCOOH | HFIP | / |
| 10 | Fe | $CF_3COOH$ | HFIP | 68 |
| 11 | Fe | HCl (2 N) | EtOH | 36 |
| 12 | Fe | HCl (2 N) | MeOH | 45 |
| 13 | Fe | HCl (2 N) | $(CH_3)_2CHOH$ | 27 |
| 14 | Fe | HCl (2 N) | THF | 41 |
| 15 | Fe | HCl (2 N) | dioxane | 37 |
| 16 | Fe | HCl (2 N) | EtOH/HFIP (5/1)[e] | 48 |
| 17 | Fe | HCl (2 N) | EtOH/HFIP (3/2)[e] | 66 |
| 18 | Fe | HCl (2 N) | EtOH/HFIP (1/1)[e] | 78 |

[a]Unless otherwise noted, all reactions were carried out using 1.0 eq. of nitro substrate (0.6 mmol), 0.75 mL HFIP (10 eq.), 5.0 eq. of iron powder (3.0 mmol) and 6 mL HCl (2 N aqueous solution) at room temperature for 30 min.

[b] [H]: Hydrogen source.

[c]Isolated yield.

[d]Saturated $NH_4Cl$ solution was used.

[e] 0.9 mL of EtOH/HFIP (v/v) was used.

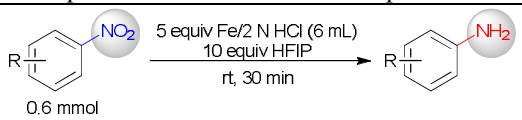
## Results and discussion

Preliminary experiments were carried out with 1-methyl-4-nitrobenzene as model substrate using different metal catalysts, hydrogen sources, and additives. Iron, the most abundant transition metal, was selected as the stoichiometric reductant with 99% reduction of the nitro group to amine (Table 1, entry 4). No product was obtained with magnesium powder and copper powder (Table 1, entries 2 and 5), while zinc powder and stannum powder gave amine in moderate to good yields (Table 1, entries 1 and 3). The use of different hydrogen sources revealed efficient reduction to amine in 99% yield with 2 N HCl aqueous solution. Obviously, reduction was not observed in the case of $NH_4Cl$ and HCOOH (Table 1, entries 8 and 9). Starting substrate was not consumed completely in the presence of AcOH and $CF_3COOH$ (Table 1, entries 7 and 10). Additive had a significant influence on the reduction in terms of reactivity. Replacing HFIP with other alcohols, THF or dioxane gave a significant drop in yield (Table 1, entries 11-15). In terms of EtOH-HFIP, with the ratio of HFIP increasing, the yield added up to highest at 50% HFIP (Table 1, entries 16-18). These results pointed to the promotion of HFIP for the reduction reaction.

Using these optimized conditions, reduction of structurally diverse nitro compounds was carried out to investigate the scope of this method. A series of aromatic nitro substrates containing functional groups such as methyl, methoxy, methylthio, hydroxyl, amino were all successfully reduced (Table 2, entries 2-4, 11, 12, 14 and 15). And the reduction of halogen-substituted nitrobenzenes proceeded without dehalogenation[13] or homocoupling[14] and the amines were obtained in high yields (Table 2, entries 5-10). In general dehalogenation of halogen-substituted aromatic nitro compounds takes place with earlier reported methods such as catalytic hydrogenation[2] or $Pd(OAc)_2$/MHS[15] and $S_8$/mild base[16]. In addition, Ts and benzylic protecting groups on both O and N atoms survived the reduction conditions (Table 2, entries 13, 16 and 17). An array of reactive functionalities including aldehyde, ketone, amide, nitrile and carboxylic moieties were tolerated, indicating the complete chemoselectivity and moderate to good reactivity of the developed system for these challenging substrates (Table 2, entries 18-22). In contrast to classical hydrogenation[17], subjected to the nitro reduction conditions, reducible functionalities like allyl and propargyl were found to be stable (Table 2, entries 23 and 24). Importantly, the selective reduction of the nitro group in the presence of $-B(OH)_2$ functionality proceeded smoothly in 83% yield (Table 2, entry 25). Industrially important naphthalen-1-amine could be prepared from 1-nitronaphthalene in good yield (Table 2, entry 27). Various heterocyclic nitroarenes were converted to corresponding amines without affecting heterocyclic ring (Table 2, entries 28-33). In the case of substituted dinitrobenzene excellent chemoselectivity was observed (Table 2, entry 34). When 1-nitrooctane was treated with the developed reduction conditions, we obtained the octan-1-amine hydrochloride in 82% yield (Table 2, entry 35). Aminaphtone precursor was produced from the corresponding nitro compound successfully (Table 2, entry 36) without atering the quinone and ester moieties of the compound, once again demonstrating the strong preference for selective nitro group reduction. Additionally, the intermediate can be used in the synthesis of Aminaphtone, an agent for antivaricose therapy.[18]

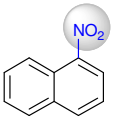
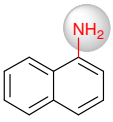
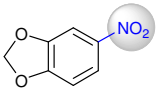
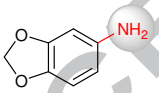
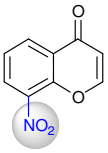
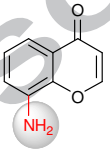
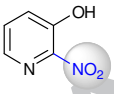
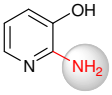
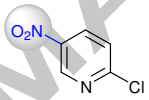
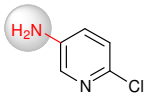
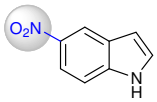
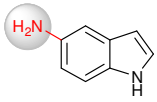
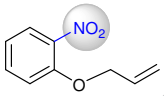
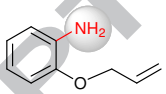
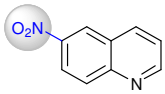
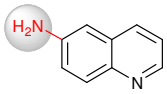
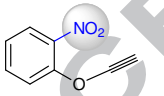
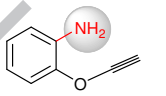
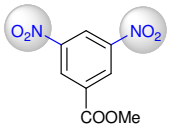
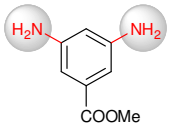
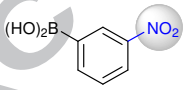
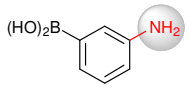
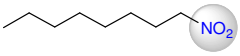
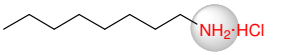
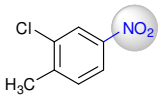
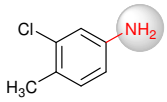
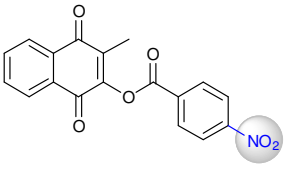
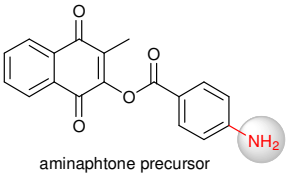
The applicability of the methodology was evaluated using the reactions on gram scale (Scheme 1). Performing the reduction reaction with 4-nitrobenzonitrile on a decagram scale, we achieved the amine in 90% yield. In the case of heteroaromatic substrates, this method also successfully gave the amines on gram scale. What's more, the heterocycles are important building

**Table 2.** Scope of the reduction of nitro compounds[a,b]




0.6 mmol

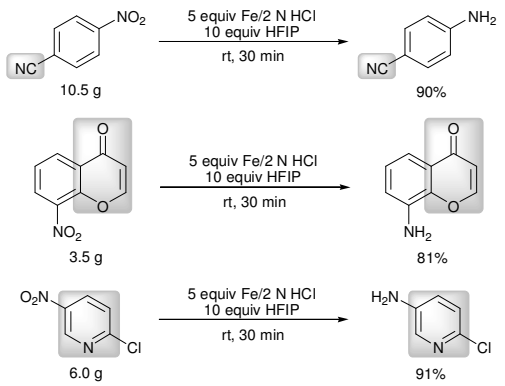
- R: various functionalities (e.g. halogens, ester, amide, allyl)
- herteroarmatic
- aliphatic

| Entry | Substrate | Product | Yield (%) | Entry | Substrate | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | R = H | | 97 | | | | |
| 2 | R = 4-CH3 | | 99 | | | | |
| 3 | R = 2-OCH3 | | 75 | 27 |  |  | 60 |
| 4 | R = 4-OCH3 | | 78 | | | | |
| 5 | R = 4-F | | 76 | | | | |
| 6 | R = 3-Cl | | 80 | 28 |  |  | 64 |
| 7 | R = 4-Cl | | 84 | | | | |
| 8 | R = 2-Br | | 80 | | | | |
| 9 | R = 4-Br | | 86 | 29 |  |  | 83 |
| 10[d] | R = 4-I | | 71 | | | | |
| 11 | R = 4-SMe | | 90 | | | | |
| 12 | R = 2-NH2 | | 85 | | | | |
| 13[d] | R = 4-NHBn | | 85 | 30 |  |  | 70 |
| 14 | R = 2-OH | | 82 | | | | |
| 15 | R = 4-OH | | 82 | | | | |
| 16 | R = 4-OBn | | 82 | 31 |  |  | 96 |
| 17 | R = 4-OTs | | 85 | | | | |
| 18 | R = 2-CHO | | 63 | | | | |
| 19 | R = 4-Bz | | 93 | | | | |
| 20[c,d] | R = 4-COOH | | 99 | 32 |  |  | 51 |
| 21 | R = 2-CONH2 | | 84 | | | | |
| 22 | R = 4-CN | | 91 | | | | |
| 23[c] |  |  | 89 | 33 |  |  | 83 |
| 24[c] |  |  | 70 | 34 |  |  | 67 |
| 25 |  |  | 83 | 35 |  |  | 82 |
| 26 |  |  | 83 | 36 |  |  aminaphtone precursor | 76 |

[a] Unless otherwise noted, all reactions were carried out using 1.0 eq. of nitro substrate (0.6 mmol), 0.75 mL HFIP (10 eq.), 5.0 eq. of iron powder (3.0 mmol) and 6 mL HCl (2 N aqueous solution) at room temperature for 30 min.

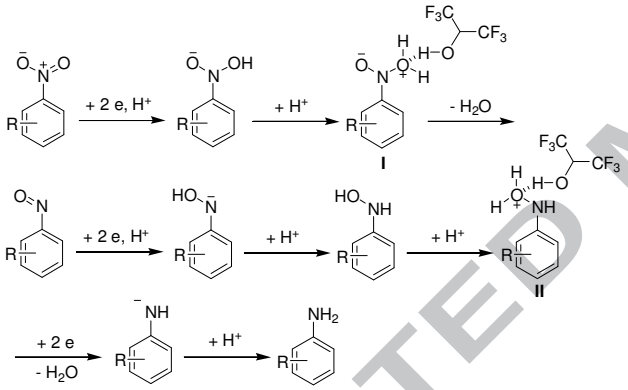
[b] Isolated yields; [c] AcOH instead of HCl (2 N aqueous solution); [d] At 40 °C.

blocks in the synthesis of pharmaceuticals and natural products, suggestive of the potential utility of the reduction protocol.




**Scheme 1.** The gram-scale reduction reactions

It is generally accepted that the direct reduction of nitrobenzene to aniline proceeds via nitrosobenzene and N-phenylhydroxylamine intermediates (Scheme 2). We noticed that hydrogen bond forming mechanisms have been proposed in other HFIP-promoted reactions.[19] We assumed that hydrogen bonding existing in intermediates **I** and **II** would be the driving force for the removal of water. Thus, the transformation can take place under very mild conditions. Overall, HFIP can efficiently promote the nitro reduction reduction as a hydrogen bond donor.




**Scheme 2.** The reaction pathway for the nitro reduction

## Conclusion

In conclusion, an efficient and practical method has been developed for chemoselective reduction of nitro groups, which was carried out using a combination of iron powder and 2 N HCl aqueous solution in the presence of HFIP under mild conditions. The reduction is chemoselective for nitroaromatic compounds bearing a wide range of reactive functional groups (e.g. aldehyde, ketone, acid, ester, amide, nitrile, halogens, allyl, propargyl). In addition, compatibility with common protecting groups and heteroaromatic substrates has been demonstrated. 1-nitrooctane was smoothly reduced in good yield. Also, aminaphtone precursor was achieved successfully.

## Acknowledgments

This work is supported by Science and Technology Department of Sichuan Province under grant number 2015JY0171.

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Highlights:

- Hexafluoro-2-propanol-assisted quick reduction of nitro groups is reported.
- This method features very mild conditions (e.g. room temperature, short time, etc.).
- This protocol is tolerant of a number of challenging substrates (up to 36 examples).
- The nitro reduction is also applicable in gram scale.