

Carbonyl Iron Powder: A Reagent for Nitro Group Reductions under Aqueous Micellar Catalysis Conditions

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(5) Supporting Information

ABSTRACT: An especially mild, safe, efficient, and environmentally responsible reduction of aromatic and heteroaromatic nitro-group-containing educts is reported that utilizes very inexpensive carbonyl iron powder (CIP), a highly active commercial grade of iron powder. These reductions are conducted in the presence of nanomicelles composed of TPGS-750-M in water, a recyclable aqueous micellar reaction medium. This new technology also shows broad scope and scalability and presents opportunities for multistep one-pot sequences involving this reducing agent.

eveloping, modifying, and optimizing methodologies for nitro group reductions has a rich history in organic chemistry.¹ Most existing methods have undesirable aspects, such as high pressures and/or temperatures, pyrophoric materials, toxic or dangerous reagents, high-boiling or egregious dipolar, aprotic solvents, precious or toxic metals, long reaction times, expensive ligands, commercially unavailable materials, lack of selectivity, and highly variable yields. The more common traditional approaches oftentimes focus on catalytic hydrogenation utilizing a variety of catalysts or stoichiometric reducing agents such as formic acid,² hydrazine,³ and silanes.⁴ Various metals have also played an important role, including tin, zinc, platinum, and nickel.⁵ Iron-based reagents, in particular, have been fundamental to these reductions, with Fe/HCl and Fe/NH₄Cl as textbook cases.⁶ Nonetheless, these reagents are considered relatively harsh and may be functionalgroup-intolerant; from a modern perspective, they are certainly not environmentally friendly. Herein we describe the use of commercially available, inexpensive, and safe carbonyl iron powder (CIP), which can be used under micellar catalysis conditions in water for the facile and efficient reduction of functionalized aryl and heteroaryl nitro-group-containing compounds.

CIP (Figure 1) is a free-flowing powder produced in large quantities by BASF via thermal decomposition of liquid $Fe(CO)_5$.⁷ That process affords the reagent as uniform spherical particles (2–3.5 μ m average diameter) suitable for direct use. Bulk quotes for one metric ton range from \$5000 to \$8000 (i.e., \$5–8/kg),⁸ which categorizes this reagent as inexpensive as well as practical. Its high purity makes it also suitable for a variety of industrial uses, such as in electronic parts, in the synthesis of industrial diamonds, and as an absorber of microwave radiation. Its use in organic synthesis,



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Figure 1. Carbonyl iron powder (CIP).

and specifically for nitro-group-containing intermediates en route to active pharmaceutical ingredients, however, has not been tested, notwithstanding reports on other types of iron powders that have been applied for similar purposes.⁶

The use of CIP is remarkably straightforward, as none of the typical additives are needed for this reduction; no ligands, hydride, external gases and resulting pressure, or special equipment is required. Only NH₄Cl is needed, (presumably) to clean the CIP surface during the reaction. Reductions take place in water containing nanoreactors composed of the designer surfactant TPGS-750-M (2 wt %) between rt and 45 °C, typically with high functional group tolerance and in excellent isolated yields.

By way of comparison, other reagents, in particular alternative processes based on iron metal⁶ (e.g., Fe/NH₄Cl), required refluxing aqueous EtOH under dilute conditions. Such conditions lead to considerable waste generation upon workup, as this is not a recyclable reaction mixture. Attempts to use commonly available 325 mesh iron powder under the same aqueous nanomicellar conditions at 45 °C gave highly variable and unreliable results, with some substrates going to

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completion while others were only partially reduced. Moreover, this form of iron is rather abrasive, as was evident from its impact on Teflon-coated stir bars. While not a major issue in an academic setting, this could be troublesome and costly at scale. No such problem was observed using CIP.

The addition of cosolvents⁹ such as THF and EtOAc improved the reaction processability and stirring on occasion and frequently shortened the reaction time (Scheme 1). Some

Scheme 1. Substrate Scope for CIP-Mediated Nitro Group Reductions



substrates (e.g., precursors to products 2, 6, and 19) were fully reduced at ambient temperature, although the reaction times were notably longer than for those treated with CIP at 45 °C. In comparison to earlier processes developed using micellar catalysis conditions, the CIP method is similar to that based on zinc;¹⁰ however, iron is a notable improvement from a sustainability perspective in terms of earth abundance¹¹ and presents no complications with stirring in large-scale reactions. No aggregation of solids using CIP was noted at any point, including during the scale-up experiment (vide infra). Use of prior technology based on Fe/ppm Pd nanoparticles (NPs) for similar reductions, while not leading to any solids of consequence, can lead to foaming due to hydrogen gas evolution from NaBH₄ (or KBH₄) being added to the aqueous mixture, which can present difficulties when scaling reactions.^{12,13} Introduction of a cosolvent can decrease the extent of foaming but may necessitate the use of a larger vessel to ensure that any foaming can be accommodated. CIP, on the other hand, with no gas evolution involved, obviates these practical considerations. Furthermore, while educts bearing electronwithdrawing groups proved to be very reactive toward Fe/ppm

Pd NPs,^{12a} those with electron-donating residues appear to be the most receptive to reduction with CIP. Thus, these reagents appear to be complementary.

As the examples in Scheme 1 show, several functional groups are unaffected under the standard reaction conditions. These include, notably, a free hydroxyl group as in product 3, aryl fluorides, chlorides, and bromides (e.g., products 1, 7 and 14), CF_3 residues (e.g., 1), amides, esters, ketones, and carbamates. Several pyridyl- or pyridyl-like-containing educts were also studied, affording products 18-22 (Scheme 2), documenting





that this important heteroaromatic ring remains unaffected (i.e., not reduced) using CIP under these conditions. In general, therefore, the functional group compatibility appeared to be excellent. By contrast, the use of CIP under identical conditions but in organic solvents (MeOH, THF, EtOAc, or DMF) led to no product formation. All attempts to extend this methodology to analogous alkyl nitro compounds met with failure, as in several cases none of the anticipated primary amines were observed.

Increasing the scale of a reduction under our standard conditions was performed, going in this case from the typical 100 mg reaction to one that generates ca. 3.5 g of amine product (Scheme 3). Unlike the use of Zn/NH_4Cl , which

Scheme 3. Scale-Up Reaction: (a) Ammonium Chloride, CIP, and Nitro Compound; (b) After Addition of EtOAc Cosolvent and 2 wt % TPGS-750-M/H₂O; (c) After Stirring for 20 min at 45 $^{\circ}$ C



produces copious amounts of solids that can inhibit stirring,¹⁰ no notable changes in either physical appearance or reaction outcome were seen, suggesting that this is a scalable method.

On the basis of the multitude of processes that can now be run in the same aqueous medium containing TPGS-750-M,¹⁴ a tandem series of three reactions was run in a single pot (Scheme 4). The sequence was designed with special emphasis Scheme 4. Tandem Three-Step, One-Pot Sequence: (A) Completed S_NAr Reaction; (B) Completed Suzuki–Miyaura Coupling; (C) Completed Nitro Group Reduction



on the use of the nitro group to aid in an S_NAr reaction,¹⁵ followed by a Suzuki–Miyaura cross-coupling, and finally reduction of the nitro group. The nitro reduction proved to be robust for this step and was unaffected by the complex mixture present from the previous two steps, leading to amine **24** in a global yield of 89% over three steps.

The aqueous reaction medium containing nanoreactors composed of TPGS-750-M is fully recyclable (Table 1), with

Table 1. Recycling of Aqueous TPGS-750-M

Br CI	P (5 equiv), NH₄Cl wt % TPGS-750-M THF (10 vol %) 45 °C, 2 h	(3 equiv) /H ₂ O Br	
	reaction	first recycle	second recycle
isolated yield (%)	95	93	96
E factor (organic solvent)	5.5	5.5	5.5
E factor (including water)	16.5	5.5	5.5

no loss in reaction yield. Moreover, as expected, the E Factors¹⁶ associated with this chemistry as a measure of greenness are low.¹⁷ In addition, the CIP present retains enough residual reactivity to mediate a second reduction, but only upon addition of NH_4Cl (Table 2). Adding more CIP and NH_4Cl to the reaction vessel containing the same TPGS-750-M allows for the continued use of the aqueous reaction mixture for three consecutive recycles (Table 3).

In conclusion, a readily available and inexpensive reagent, carbonyl iron powder (CIP), has been identified that can be applied to valuable nitro group reductions, especially at the

Table 2. Recycling of the Aqueous Reaction Medium and CIP

	reaction	first recycle	second recycle
isolated yield (%)	94	92	NR
reaction time (h)	2	5	N/A
equiv of NH ₄ Cl added	none	3	3

Table 3. Recycling Using Repeated Addition of CIP and $\rm NH_4Cl$

	reaction	first recycle	second recycle	third recycle
isolated yield (%)	94	93	93	96
reaction time (h)	2	2	2	2.5
equiv of CIP added	none	2.5	2.5	2.5
equiv of NH ₄ Cl added	none	3	3	3

gram scale and beyond, under environmentally responsible reaction conditions. The reagent and reaction medium are both recyclable and can be applied to sequential processes in a onepot sequence. This new technology relies on iron, the one element among the transition metals that is both of great synthetic value and not endangered. While many alternative processes exist, including those with iron, few are of recent vintage and cognizant of the importance of the selection of reagents, the energy invested, and the avoidance of organic solvents from the perspective of sustainability.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03216.

Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra (PDF)

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