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Indium powder as the reducing agent in the synthesis of 2-amino-1,1'-biphenyls

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ABSTRACT

An improved and simplified In-based protocol for the reduction of 2-nitro-1,1'-biphenyls to the corresponding 2-amino-1,1'-biphenyls is disclosed. The method utilizes only a stoichiometric quantity of indium powder as the reducing reagent along with a stoichiometric quantity of ammonium chloride. The work-up is very simple, it requires only a simple filtration of the post-reaction mixture whereupon the reaction medium is removed under reduced pressure. The method was also proven to operate with a variety of functional groups to provide high to excellent yields of the target 2-amino-1,1'-biphenyls. A proposal for a reaction mechanism is also provided.

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Introduction

For a project dedicated to the synthesis of the 1*H*-carbazole scaffold, we have previously disclosed a highly efficient method for the synthesis of 2-nitro-1,1'-biphenyls by means of the Suzuki cross coupling reaction (Scheme 1).¹ For the subsequent step, which encompasses reduction of the 2-nitro-1,1'-biphenyl intermediate to the corresponding 2-amino-1,1'-biphenyl, we were searching for a reliable, simple, and efficient reduction method. To approach the target 1*H*-carbazole frameworks, we planned to use the combined C–H functionalization and C–N bond formation as disclosed by Buchwald and collaborators,² or the newly reported iridium(III) catalyzed intramolecular C–H amination method by Miura and collaborator.³

Numerous methods exist for the Ph–NO₂ \rightarrow Ph–NH₂ transformation, including catalytic hydrogenation with Pd/C⁴ or Raney nickel,⁵ Pd catalyzed reduction using silicon hydride as the reducing agent,⁶ and the Bechamp reduction that involves treatment of the nitroaromatic with iron and hydrochloric acid.⁷

Additionally, protocols encompassing either SnCl₂,⁹ TiCl₃,¹⁰ Zn,¹¹ Sm,¹² or sodium dithionite (Na₂S₂O₄)¹³ as reducing agents constitute functioning methods developed for the nitroarene to aniline transformation. A method disclosed by Moody and collaborators¹⁴ attracted our attention due to its simplicity involving the treatment of nitroarene with elemental In in an ammonium chloride solution.



Scheme 1. Outline for the synthesis of 2-amino-1,1'-biphenyls,⁸ a key intermediate for the synthesis of 1*H*-carbazoles.

Results and discussion

In order to utilize the Moody method,¹⁴ a highly diluted substrate mixture in ethanol should be treated with a large excess of indium powder and a saturated solution of aqueous ammonium chloride for a long reaction time, up to 72 h. We began to investigate this method with our substrate 2-nitro-1,1'-biphenyl, trials that proved to function perfectly well. Chromatographic analysis of the post-reaction mixture revealed full conversion of the substrate to the desired 2-amino-1,1'-biphenyl (Scheme 2, entry 1). However, the subsequent workup procedure required several steps including filtration, pH adjustment, extraction, solvent removal, and finally column chromatography, which only provided a low isolated yield (41%) of our target 2-amino-1,1'-biphenyl.

It turned out that the work-up procedure resulted in decomposition or other loss of the target reduction product and in some occasions we also observed ring closure to give the 1*H*-carbazole frameworks, but only in small quantities. Although, with considerable challenges to implement this reduction method, we found





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Scheme 2. Indium reduction of 2-nitro-1,1'-biphenyls to 2-amino-1,1'-biphenyls.

that it looked attractive due to its simplicity, which spurred us to explore, adapt, and simplify the Moody method for our aminobiphenyl application.

To the best of our knowledge, the In reduction method has not been thoroughly investigated from a mechanistic point of view. Nevertheless, for us it was reasonable to draw a parallel to the Zn powder reduction method, which would require two or three equivalents of In for each nitro group depending on the final oxidation state of the oxidized indium.

Therefore, we reduced the amount of indium, $7 \rightarrow 3.5$ equiv, an alteration that still provided quantitative yields (measured with GC) of the 2-amino-biphenyl. Further lowering the quantity of In to only 2 equiv afforded a yield of 87% (GC). This experiment was repeated with prolonged reaction time, 150 min (Scheme 2, entry 4), which successfully provided the target molecule in quantitative yields (GC). The achieved results suggested a mechanism where In ends up at an oxidation state of +3, see our proposal for a mechanism in Scheme 3. During this experimentation we also observed that the particle size of the indium powder was important in relation to the reaction rate and overall performance of the reaction. For the reduction experiments, we utilized a freshly opened container of indium powder (100 mesh, 99.99%) to achieve a quantitative conversion in almost all trials. However, the reactivity of the indium as a reductant was observed to be impaired even at few days of storage when stored under a normal atmosphere at room temperature, which we believe is due to surface oxidation.

A scope and limitation of the reduction method was evaluated by means of a small library of various substituted 2-nitro-1,1'biphenyls (Table 1). Unfortunately, the hitherto developed method was revealed to operate in low to medium yields only.

These results (Table 1) encouraged us to further explore the experimental variables with the goal to improve the outcome. The reaction temperature was raised (78 \rightarrow 120 °C) and for this purpose the reaction was conducted in a sealed tube reactor. The solvent (EtOH) volume was lowered (10 \rightarrow 4 mL) and a lowered quantity of ammonium chloride was utilized [16 mmol (0.85 g)¹⁵ \rightarrow 1.03 mmol (0.055 g)]. These conditions were explored with a library composed of fifteen 2-nitro-1,1'-biphenyls (Table 2). The results show that the method provides high to excellent yields in all cases and displays a good functional group tolerance. The achieved results also suggest that the developed method is consistent with the proposed mechanism resulting in an oxidation of In to In⁺² and thus requiring 3 equiv of elemental In.



Scheme 3. Mechanism proposal for the In promoted reduction of the Ar-NO₂ group.

Table 1

Introductory exploration of an improved procedure for the reduction of 2-nitro-1,1'biphenyl to 2-amino-1,1'-biphenyl





^a Yield based on GC (isolated yield after column chromatography).

 $^{\rm b}$ Additional In powder (2 equiv) and aq satd NH_4CI (3 mL) was added after 3 h in an attempt to attain higher conversion and yield.

Table 2

Exploration of the scope and limitation of the In promoted reduction of 2-nitro-1,1'biphenyl to 2-amino-1,1'-biphenyl⁸



2-Nitro-biphenyl Yield^a (%) Entry 2-Amino-biphenvl 1 91 NO-NH HOOD ноос 2 75 3 95 69^b 4 ΝO₂ ΝH₂ 5 92 NO2 NH 94^b 6

(continued on next page)

Table 2 (continued)



^a Isolated yield.

Advantages of the improved indium reduction method comprise a considerably simplified work-up and high purity of target product. When the reduction was completed at 3 h, ethyl acetate was added to the post reaction mixture and the solid inorganics could be filtered off. The resulting filtrate was dried over Na₂SO₄ and the solvent was removed under reduced pressure using a rotary evaporator. The target 2-amino-1,1-biphenyls were isolated in yields in the range of 69–96%.

Conclusions

In conclusion, we have explored and improved a method suitable for the preparation of 2-amino-1,1'-biphenyls by reduction of the corresponding 2-nitro-1,1'-biphenyls. A stoichiometric quantity of indium powder (3 In: 1 substrate) with ethanol as the reaction medium was revealed to be necessary. The lowered reduction reagent loading gives rise to a simple work-up, namely only filtration of the post reaction mixture followed by evaporation of the solvent. This is in contrast to previous methods, which required column chromatography for purification of the reaction product. Furthermore, the method displays a high functional group tolerance to provide high to excellent yields, demonstrated with a series of 2-nitro-1,1'-biphenyls. A proposal for a reaction mechanism is described based on analogy with the Zn reduction and experimental observations, namely the required quantities of the elemental In as reduction reagent.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02. 007.

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- 8. General procedure: 2-Nitrobiphenyl (1 mmol, 0.2 g) was dissolved in EtOH (4 mL) and transferred to a tube reactor. Then, a mixture of NH_4CI (2 mmol, 0.107 g) in H_2O (1.2 mL) and indium powder (3 mmol, 0.344 g, 99.99% 100 mesh, use preferably a freshly opened bottle or stored under Ar) were added whereupon a magnetic stirrer bar was transferred to the tube. The tube was then sealed and the reaction mixture was stirred and heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (30 mL). The resulting mixture was filtered through a pad of celite to remove the catalyst. Another portion (20 mL) of ethyl acetate was used to wash through the filter pad. The resulting transparent organic phase was dried over Na_2SQ_4 , filtered and the solvent was removed under reduced pressure using a rotary evaporator to obtain the target compound.
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^b Product was not isolated, measured by GC.