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Synthesis of biphenyl anilines using iodo phenylformamides via a one-pot Suzuki coupling reaction

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Abstract

We have developed a novel and economical synthesis of biphenyl anilines via a one-pot Suzuki coupling reaction with iodo phenylformamides. This literature is an unprecedented approach to biphenyl anilines replacing costly aminophenylboronic acids with economical iodo anilines for the preparation of biphenyl anilines. It also provides a viable synthesis toward substituted biphenyl anilines where the required aminophenylboronic acids are not readily available.

Keywords: One-pot Suzuki coupling reaction; Iodo phenylformamides; Biphenyl formamides and substituted biphenyl formamides; Biphenyl anilines and substituted biphenyl anilines

Biphenyl aniline, a subclass of biaryl compounds, has been recognized as a privileged structure in drug discovery. Its derivatives have been pursued as anti-phlogistic, analgesic, anti-obesity, and anti-tumor agents.[1] The synthesis of biphenyl aniline usually incorporates the traditional Suzuki coupling reaction between aryl boronic acids and aryl halides.[1,2] However, in practice, this strategy is often limited by the availability and the cost of boronic acids. In connection with a drug discovery project, we required numerous biphenyl anilines in multi-gram quantities, denoted by the generic structure **1** (Fig. 1). In the original synthesis of **1**, the un-substituted analogues ($R' = H$) were assembled via Suzuki cross-coupling reactions of 4-aminophenylboronic acid or 4-nitrophenylboronic acid with appropriate aryl bromides **2** (Scheme 1).[1b] In the latter case, the nitro group was reduced to afford **1** by catalytic hydrogenation or Fe/HCl reduction.[3] While the original

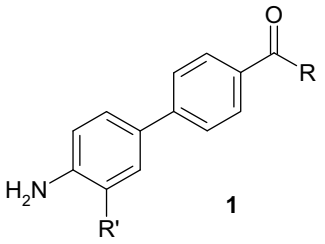

Fig. 1.

synthesis was useful in obtaining **1** in small quantities, it had significant limitations. First and foremost, the costs of 4-amino and 4-nitrophenylboronic acids were high,[4] and the quantities provided by commercial sources were insufficient for scale-up of **1**; the supply of substituted nitro/amino phenylboronic acids could not be identified. Furthermore, coupling reactions with 4-aminophenylboronic acid often gave variable results, and column chromatography was required for obtaining pure aniline product. Finally, in the cases where 4-nitrophenylboronic acid was used in the coupling reaction, the reduction of the nitro to amino group was complicated by a competing

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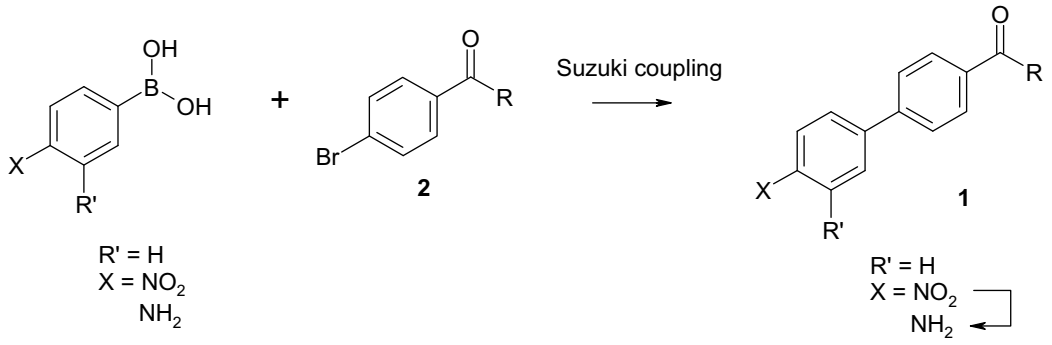
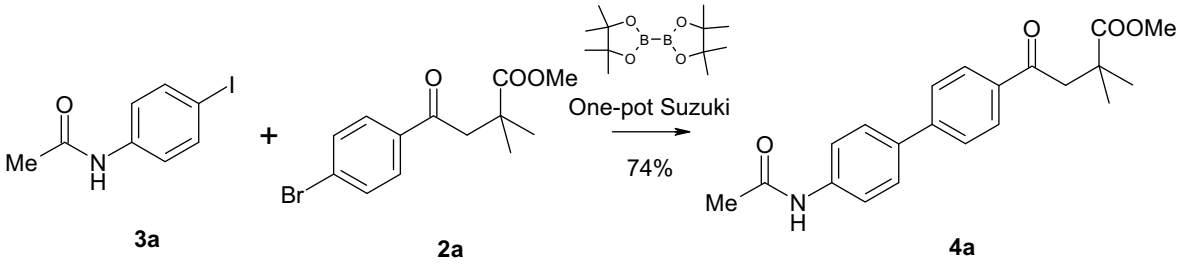


Scheme 1. The original synthesis of biphenyl anilines **1**.

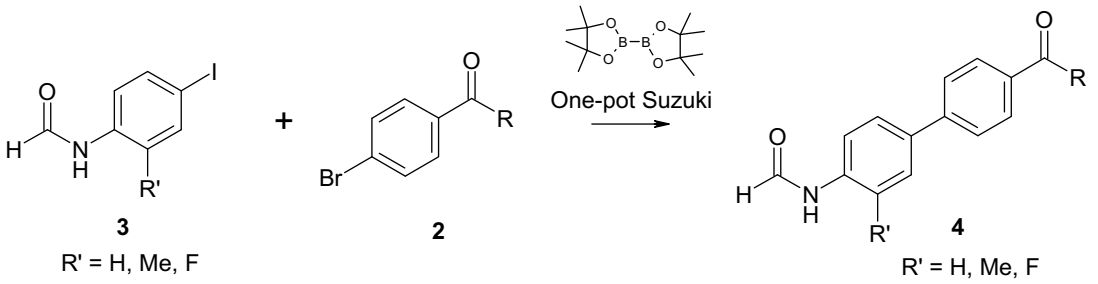
reduction of the benzylic carbonyl group on the other side of the biphenyl.

Miyaura pioneered the use of arylboronates, more readily accessible than boronic acids, for the cross-coupling reaction to afford biaryls.[5] We recently expanded the use of this methodology by developing a convenient one-pot protocol via aryl boronates generated in situ.[6] This one-pot procedure allows coupling reactions between two aryl halides without the need for boronic acids. In search for a scaleable and economical synthesis of biphenyl aniline **1**, we investigated amino and protected amino phenyl halides as boronate precursors in the one-pot Suzuki coupling reaction. Although amide aryl halides are known to cross couple with boronic acids,[7] there is very limited literature precedent of amide aryl boronate in Suzuki coupling reactions. We started out with 4-iodoaniline, a readily available and low-cost starting material, in forming its corresponding aniline boronate. Not surprisingly, we found the reaction to be difficult presumably due to the electron-donating amino group. However, we envisioned that its amide derivatives were considerably less electron-donating, therefore boronate formation and subsequent cross-coupling with aryl bromide **2** would be more likely to occur. In this Letter, we wish to describe a novel and efficient synthesis of biphenyl aniline moiety **1** from iodo phenyl formamides via one-pot Suzuki coupling reactions.

We first chose iodo acetamide **3a**, readily prepared from 4-iodoaniline with acetyl chloride, as the boronate precursor in the one-pot Suzuki coupling reaction. Although using aryl bromide **2** as boronate precursor was not the focus in this study, it is worth noting that boronate formed from **2a** did not react well with **3a** in the cross-coupling reaction. In contrast, boronate generated in situ from **3a** smoothly coupled with **2a** to afford biphenyl acetamide **4a** in 74% yield (Scheme 2). In the following step, **4a** was treated under strong acidic conditions in order to produce aniline **1**.[8] However, **4a** was stable in conc. HCl at an elevated temperature for days: no desired product was observed. Thus, we examined other amino protecting groups such as BOC and the formyl group. Although less popular than BOC, the formyl group is also known as a choice for amino protection.[9] Following a standard one-pot Suzuki protocol,[6] BOC protected 4-iodoaniline provided an insignificant amount of the desired biphenyl product, while the same reaction with formamides afforded much better results. The formamide derivatives **3b**, **3g**, and **3h** were prepared in quantitative yields by treating appropriate anilines in formic acid/acetic anhydride.[10] One-pot Suzuki coupling reaction between **3** and bromides **2** occurred smoothly (Scheme 3), and the results are shown in Table 1. In most cases, biphenyl **4** was cleanly formed and isolated without chromatography. Specifically, biphenyls **4b–f** were obtained cleanly in satisfactory yields (64–70%) after a simple trituration (entries 1–5). Substituted biphenyl formanilides **4g–i** were also prepared in moderate yields (entries 6–9). Except for **4g** where a slower reaction was observed, hydrolysis of the biphenyl formanilides **4** readily occurred under mild acidic conditions to afford anilines **1** in near quantitative yields (Scheme 4).[9a] Compared with the original preparation of **1**, savings realized by this alternative synthesis were significant.[11] Notably, biphenyl anilines **1g–i** obtained in this fashion were inaccessible by

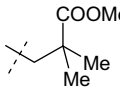
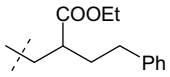
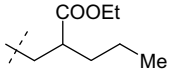
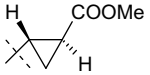
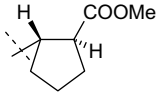
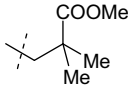
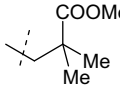
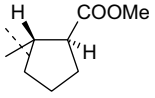


Scheme 2. Synthesis of biphenyl acetamide from 4-iodo phenylacetamide via one-pot Suzuki coupling reaction.



Scheme 3. Biphenyl formamide synthesis via one-pot Suzuki coupling reaction.

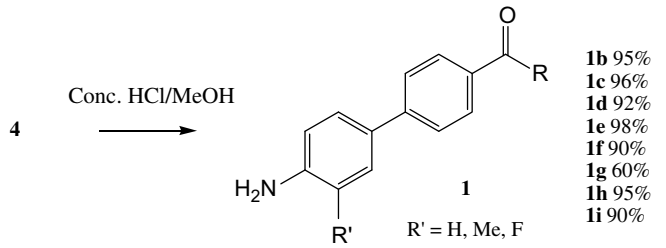
Table 1
Synthesis of biphenyl formamide **4** from iodo formamide **3** and aryl bromide **2**

Entry	Formamide **3** R′=	Aryl bromide **2** R=	**4** (% Yield[a])
1	H **3b**		**4b** (68)
2	H **3b**		**4c** (65)
3	H **3b**		**4d** (64)
4	H **3b**		**4e** (67)
5	H **3b**		**4f** (70)
6	Me **3g**		**4g** (30)[b]
7	F **3h**		**4h** (65)
8	F **3h**		**4i** (65)[b]

[a] Isolated yield.
[b] Not optimized and the product was purified by column chromatography.

normal Suzuki coupling reaction due to the unavailability of the corresponding boronic acids. We also made efforts to replace iodoaniline by bromo analog for further economical benefit. Unfortunately, the coupling reactions suffered from poor yields due to a much slower boronate formation under the same reaction conditions.

In summary, iodo phenyl formamides readily undergo one-pot Suzuki reaction via boronate generated in situ with phenyl bromides to afford biphenyl formamides. Subsequent acid hydrolysis of the formamides provides biphenyl anilines, highly desirable intermediates, in good overall yields.



Scheme 4. Biphenyl aniline **1** from the hydrolysis of biphenyl formamide **4**.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, and ^{1}H NMR and LCMS data of compounds **1** and **4**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.157.

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4. At the present time, 4-nitrophenylboronic acid and 4-aminophenylboronic acid cost $5,000/mol and $31,000/mol, respectively (estimated based on catalog prices).
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11. Cost for the most expensive reagent, bis(pinacolato)diboron ($2,000/mol, estimated based on catalog price), was less than 10% of 4-aminophenylboronic acid.