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Graphical Abstract





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Visible-light-mediated Gomberg-Bachmann reaction: an efficient photocatalytic approach to 2-aminobiphenyls

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online An efficient, metal-free and highly selective protocol for the synthesis of 2-aminobiphenyls via visible-light-mediated arylation of anilines using aryl diazonium salts (Gomberg-Bachmann reaction) has been reported. The reaction is an example of photoredox catalysed direct $C(sp^2)$ -H arylation of anilines using eosin Y as an organophotoredox catalyst. The presented visible-light-mediated environmentally sustainable approach has the potential to earn a decent position among the classical and contemporary methods for the synthesis of aminobiaryls.

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Keywords: Anilines Aryl diazonium salts Visible light Aminobiphenyls

Aryl-aryl radical coupling reactions seem to offer a very convenient route for the synthesis of biaryls but are known to be associated with a number of challenges. The unavoidable side reactions accompanying the desired intermolecular radical aryl-aryl couplings are, in fact, the major challenge.¹ Circumvention of this problem is generally done by using substrate as the solvent² or by carrying out the intramolecular version of the specific reaction.³ An impeccable solution to this issue can be the use of visible-light for such reactions keeping in mind the unique selectivity displayed by visible-light-mediated radical reactions.⁴ These reactions also offer additional advantages of pronounced sustainability in terms of cost and environmental concerns. However, only a few visible-light-mediated radical aryl-aryl couplings have been reported till date⁵ and the scope of new developments in this area is enormous.

The aromatic nucleus of anilines is ubiquitous in an array of natural products and pharmaceuticals. It also finds important applications in numerous other industries, viz. dye, rubber, explosives etc.⁶ Typically, arylation of anilines can be efficiently accomplished by the Suzuki,⁷ Stille,⁸ or Ullmann⁹ cross-coupling reactions which require transition metals and prefunctionalization of the aniline. The direct C-H arylation of anilines via visible-light-mediation can prove to be a state-of-the-art alternative to the aforementioned typical reactions.

Aryl diazonium salts are well known aryl radical precursors which can be easily photoreduced to give aryl radicals.¹⁰ In 2011, the research group of Sanford has reported ligand directed C–H arylation reactions using aryl diazonium salts using a combination of visible-light photoredox and palladium catalysis.^{5a} Also, König et al.^{5b} and Heinrich et al. ^{5c} have independently reported arylation of arenes/heteroarenes

using the same salts via visible-light photoredox catalysis. However, to the best of our knowledge, there is no report in the literature on the visible-light-mediated arylation of anilines using arenediazonium salts as aryl radical precursors (visible-lightmediated Gomberg-Bachmann reaction). Notably, Heinrich et al. have also previously reported the radical Gomberg-Bachmann reaction using anilium hydrochlorides, diazonium salts and substoichiometric amount of TiCl₃ in acidic aqueous conditions where large excess (20 equiv) of anilium hydrochlorides was used to avoid homocoupling.^{11a} An excess use of the substrate and reductant makes the method less economical and it also suffers from limited substrate scope and selectivity issues (formation of meta substituted product along with ortho substituted product). However, the same group has also previously reported a number of other radical arylations of anilines using arylating agents other than diazonium salts which address the regioselectivity issue.11b-d



Scheme 1. Visible-light-mediated arylation of anilines.

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Recently, König and co-workers have described the visible-lightmediated radical C(sp²)-H arylation of anilines with acceptorsubstituted (hetero)aryl halides (Scheme 1a).^{5d} Yu et al. have reported the arylation of aniline with phenols via visible-light photoredox/nickel dual catalysis but under their reaction conditions, arylation of the C(sp³)-H bonds of anilines has taken place (Scheme 1b).¹² All the above factors and our previous work on visible-light photoredox catalysis,¹³ prompted us to develop a more efficient photocatalytic protocol for the Gomberg-Bachmann reaction. We report herein the results obtained when anilines **1** were treated with arenediazonium tetrafluoroborates **2** in the presence of eosin Y as an organophotoredox catalyst under visible-light irradiation (Scheme 1c).

To test the feasibility of our proposed strategy, initial trials were carried out using *N*,*N*-dimethyl-*p*-toluidine **1a** and phenyl diazonium tetrafluoroborate **2a** as model substrate/reagent and eosin Y as an organophotoredox catalyst (1 mol %) in acetonitrile under irradiation with green light emitting diodes (LEDs; 2.50 W, $\lambda = 535$ nm). Pleasingly, the desired product **3a** was formed in 66% yield in 12 hours (Table 1, entry 1). Before proceeding further, we conducted some control

Table 1. Optimization of experimental conditions^a



Entry	Photocatalyst (mol %)	Solvent	Time (h)	Yield (%) ^b
1	Eosin Y (1 mol %)	MeCN	12	66
2	-	MeCN	18	traces
3°	Eosin Y (1 mol %)	MeCN	18	traces
4	Eosin Y (1 mol %)	H_2O	18	60
5	Eosin Y (1 mol %)	DMF	18	65
6	Eosin Y (1 mol %)	DMSO	18	78
7	Eosin Y (1 mol %)	$MeCN/H_2O(5:1)$	12	70
8	Eosin Y (1 mol %)	MeCN/H ₂ O (10 : 1)	12	87
9	Eosin Y (1 mol %)	DMF/H ₂ O (10 : 1)	12	79
10	Eosin Y (1 mol %)	DMSO/H ₂ O (10 : 1)	12	81
11	Rose Bengal (1 mol %)	MeCN/H ₂ O (10 : 1)	12	64
12 ^d	Ru(bpy) ₃ Cl ₂ (1 mol %)	MeCN/H ₂ O (10 : 1)	12	88
13°	Eosin Y (1 mol %)	MeCN/H ₂ O (10 : 1)	12	87
14	Eosin Y (1 mol %)	MeCN/H ₂ O (10 : 1)	14	87
15	Eosin Y (0.5 mol %)	MeCN/H ₂ O (10 : 1)	12	58
16	Eosin Y (2 mol %)	MeCN/H ₂ O (10 : 1)	12	87
17 ^f	Eosin Y (1 mol %)	MeCN/H ₂ O (10 : 1)	12	78

^a Reaction conditions: **1a** (1 mmol), catalyst (1 mol %), **2a** (3 equiv.), solvent 5 mL, green LEDs, 12-18 h, under a nitrogen atmosphere. ^b Isolated yield.

° No light.

^d Irradiation with blue LEDs.

^e 5 equiv. **2a**.

experiments to test the necessity of photocatalyst and visiblelight in our reaction. The absence of either of the two reaction parameters led to the formation of product in traces (entries 2 and 3). Thus, we were encouraged to employ a wide set of reaction conditions to decide the best solvent system and catalyst for our proposed scheme. The results of some selected optimization conditions have been reported in Table 1. As regards the solvent, the reaction was tried in MeCN, water, DMF and DMSO (entries 1, 4-6). In fact, the solvent combination of acetonitrile and water in 10:1 ratio gave the best yield of product under the initial reaction conditions (entries 4-10). In view of our prime concern to develop a metal-free protocol, eosin Y (entries 8, 11 and 12) was identified as the best catalyst under irradiation with visible-light (green LEDs). The role of eosin Y as an organophotoredox catalyst is welldocumented in the literature¹⁴ and previously our research group has also reported a number of synthetic transformations using this organic dye as a photoredox catalyst.^{13a-g}

The diazonium salt was used in excess (3 equiv) with respect to aniline because dimerisation of a small amount of aryl radicals was also observed as a side reaction. Furthermore, the yield of biaryl did not increase on using a modest excess of the diazonium salt (entry 8 versus 13). On increasing the reaction time from 12 to 14 h, there was no increase in the yield of the product (entry 14). The catalyst loading of 1 mol % was found to be the optimum loading for the reaction (entry 8 versus 15 and 16). It was also observed that on diluting the reaction mixture, the yield of the product considerably decreased (entry 17).

Once the optimum reaction conditions were decided, we moved on to investigate the scope of the reaction with respect to the aniline and arenediazonium salt (Table 2). Both alkyl and methoxy substituents on the aromatic ring were well tolerated in the case of anilines, affording the corresponding biaryls 3a-c in high yields. Also, Cl, F and CN groups were compatible with the established photoredox conditions (3d-g). When no substituent at position 4 of the aromatic ring of N,Ndimethylaniline was present, both o- and p-substituted products were obtained in the ratio 2:1, respectively (3h). Not only N, Ndimethylaniline but anilines with different substituents at the nitrogen atom also performed well in the reaction (3i, j). It was observed that arylation occurs predictably at the ortho- and para-positions with respect to the amino substituent. Specifically, N,N-dialkylated anilines have been used as substrates by us because mono-alkylated and non-alkylated anilines quickly form triazenes under the present reaction

f Solvent 7 mL.

conditions. As far as arenediazonium salts are concerned, a broad range of substituents were found to be tolerated. Both electron-withdrawing and electron-donating substituents on the aromatic ring of diazonium salts provided the corresponding biaryls in good to moderate yields (**3k-s**). The diazonium salts bearing strongly electron-withdrawing substituents such as p-NO₂ or p-CN were also compatible with our reaction conditions

(3r and 3s). However, anilines 1 bearing an electron-donating group on the aromatic ring appear to react faster and afford slightly higher yields in comparison to those having an electron-withdrawing group (Table 2, products 3a-c versus 3d-g). In the case of diazonium salts 2, electron- withdrawing group on the aromatic ring gave better yield of the products in shorter



^a For experimental procedure, see Ref. 17.

^b Isolated yield of the purified products **3**.

^c All compounds gave satisfactory spectral (¹H NMR, ¹³C NMR and HRMS) data.

^d Ratio of regiomers arylated at labeled carbon 2, 2' and 4, respectively.

e Ratio of ortho- and para-phenyl regiomers, respectively.

reaction time in comparison to those having an electrondonating group (Table 2, products 3k-n versus 3o-s). The high yields for products 3a, 3b, 3o, 3p and 3q are remarkable because compounds bearing a benzylic position are usually prone to hydrogen abstraction by the aryl radical as reported in many Gomberg-Bachmann reactions.¹⁵ However, the high yields in our case can be attributed to the simultaneous activation of the aryl ring of aniline via a SET from R₂N- group under visible light photoredox catalysis which leads to arylation of the aromatic ring exclusively.¹⁶ Naphthyldiazonium salt also gave a decent yield of the product (3t) under our reaction conditions.

No biaryl formation could be detected when two equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) were added to the reaction mixture under standard conditions suggesting a radical pathway. The formation of phenyl-TEMPO adduct was confirmed by its MS (HRMS (ESI): calcd for C₁₅H₂₃NO [M+H]⁺ 234.1858, found 234.1855). Based on this result and previous literature,^{5b,10} a plausible mechanism has been proposed in Scheme 2. A SET from the excited state of eosin Y to the arenediazonium salt 2 leads to the formation of aryl radical I. This aryl radical I is trapped by the aryl ring of aniline 1 to form radical intermediate II. The oxidation of radical II by the eosin Y radical cation generates the carbocation intermediate III and completes the visible-lightmediated catalytic cycle. Finally, rearomatization of carbocation III by proton loss provides the 2-aminobiphenyl product 3.

In summary, we have developed a metal-free visiblelight-mediated radical approach for the introduction of aryl group into the aniline ring. It offers an efficient and highly selective method for the synthesis of 2-aminobiphenyls from anilines and aryl diazonium salts employing eosin Y as an under mild organophotoredox catalyst conditions. cost-effectiveness, Environmental sustainability, broad substrate scope and simple methodology are some of the adorning features of the present protocol which makes its addition to the arsenal of synthetic strategies creditable.



Scheme 2. Plausible mechanism for the formation of 2-aminobiphenyls.

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- 17. General procedure for the synthesis of compounds **3**: A solution of aniline **1** (1 mmol), arenediazonium salt (3 equiv.) and eosin Y (1 mol %) in CH₃CN/H₂O 10:1 (5 mL) was irradiated with visible light (green light emitting diodes (LEDs), $\lambda_{max} = 535$ nm, 2.5 W) under a nitrogen atmosphere with stirring at rt for 12/18 h (Table 2). After completion of the reaction (monitored by TLC), water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography using a mixture of hexane/ethyl acetate (49:1) as eluent to afford an analytically pure sample of product **3**.
 - Characterization data of representative compounds 3:

Compound **3a**:¹⁸ H NMR (400 MHz, CDCl₃) δ : 7.58 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.28-7.24 (m, 1H), 7.05 (d, J = 10.8 Hz, 2H), 6.97 (d, J = 8.0 Hz, 1H), 2.50 (s, 6H), 2.31 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 148.8, 141.8, 134.3, 132.3, 130.8, 128.6, 128.4, 128.2, 126.4, 117.6, 43.5, 20.5. HRMS (ESI): calcd for C₁₅H₁₇N [M+H]⁺ 212.1434, found 212.1436. Compound **3g**:¹⁸ ¹⁴H NMR (400 MHz, CDCl₃) δ : 7.52-7.38 (m, 6H), 7.33-7.30 (m, 1 H), 6.95 (d, J = 7.5 Hz, 1H), 2.65 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ : 154.1, 140.3, 135.5, 132.2, 131.8, 128.6, 127.9, 127.2, 119.8, 116.7, 101.9, 42.5. HRMS (ESI): calcd for C₁₅H₁₄N₂ [M+H]⁺ 223.1230, found 223.1227. Compound **3n**: ¹⁴H NMR (400 MHz, CDCl₃) δ : 7.54-7.50 (m, 2H), 7.07 (d, J = 10.8 Hz, 2H), 7.03-6.98 (m, 2H), 6.95 (d, J = 10.8 Hz, 1H), 3.85 (s, 3H), 2.54 (s, 6H), 2.30 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 158.2, 141.8, 134.3, 133.8, 130.8, 129.6, 128.6, 126.4, 117.5, 113.6, 55.2, 43.30, 20.50. HRMS (ESI): calcd for C₁₆H₁₉NO [M]⁺ 241.1467, found 241.1468.

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Highlights

- Metal-free one-pot approach to 2aminobiphenyls.
- The direct C(sp²)-H arylation of anilines with diazonium salts.
- Eosin Y as an organophotoredox catalyst.
- Visible-light-mediated Gomberg-Bachmann reaction.

Tetrahedron

Graphical Abstract



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