Article

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Metal-Free Photocatalyzed Cross Coupling of Bromo-Heteroarenes with Pyrroles

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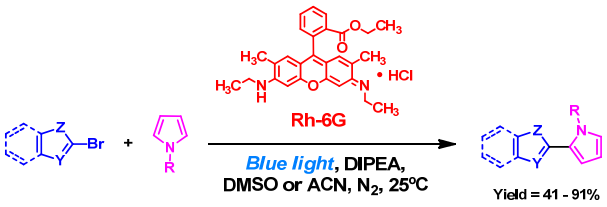
ABSTRACT: The excited radical anion of rhodamine 6G (Rh-6G) reduces heteroaryl bromides and chlorides to generate heteroaryl radicals that were successively trapped by pyrroles for the synthesis of heteroaromatic biaryls in moderate to excellent yields. The synthetically important photoredox catalytic C–H heteroarylation reaction works for a broad range of brominated electron rich heteroarenes and chlorinated heteroarenes bearing electron withdrawing groups. In addition, this methodology was applied to the formal synthesis of a benzimidazole derivative II with interesting pharmacological properties.



KEYWORDS: Photoredox catalysis, visible light, C–H heteroarylation, metal free reaction, pyrrole

1. INTRODUCTION

Heteroaromatic biaryls are an important structural motif in organic synthesis. They are present in polymers, advanced materials, liquid crystals, ligands, and molecules of medicinal interest.[1] For example, DB320 is a chemotherapeutic agent for *Trypanosomaevansi*, which causes surra, an animal pathogenic infection (Figure 1).[2] Benzafuranolderivative **I** acts as a potent retinoic acid receptor α antagonist,[3] while Wakayin is an alkaloid with anticancer activity (Figure 1).[4] Prodigiosin is a bright red tripyrrole pigment isolated from *Serratia marcescens*, showing biological activities such as antibacterial, anticoccidial, antimalarial and antifungal, and is often used as a biochemical tool (Figure 1).[5]

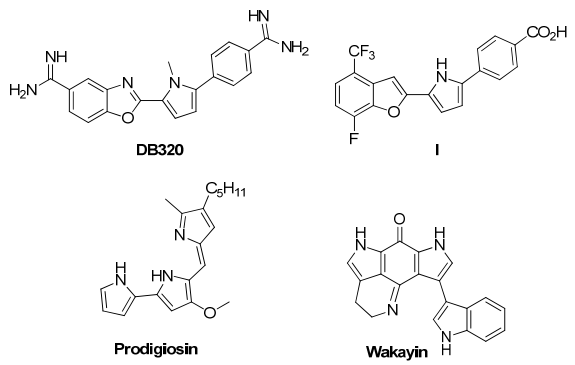
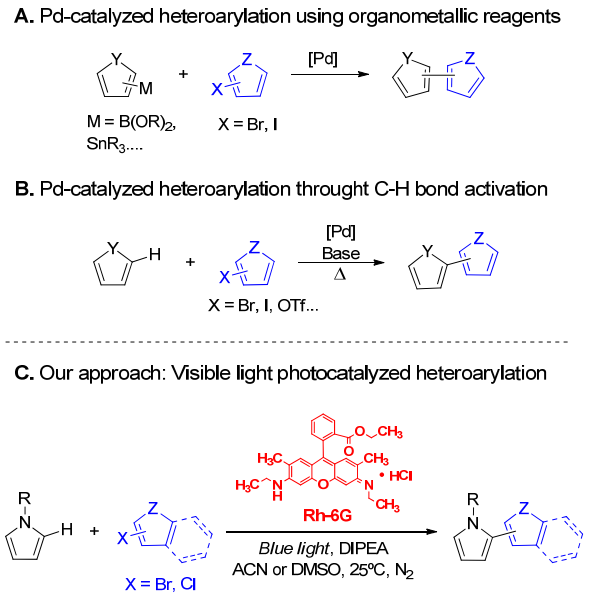


Figure 1. Bioactive compounds containing bi-heteroaryl moieties.

The abundance of the bi-heteroaryl moiety in many interesting compounds triggered the development of efficient methods for their synthesis. The typical preparation involves transition-metal catalyzed arylation reactions using pre-functionalized substrates. Palladium catalyzed C–C coupling starting form heteroaryl halides and organometallic species yields C2–C2′ and C2–C3′cross coupled diheteroarenes (eq. A, Scheme 1).[6] On the other hand, palladium catalyzed C–H bond arylation has emerged as a more direct and atom-economic alternative for the formation of such C–C bonds, because it avoids the use of pre-functionalized starting materials, and therefore, reduces the number of steps for the synthesis (eq. B, Scheme 1).[7] However, the use of transitions metals as catalyst of the reaction, and the use of high temperatures still remain a disadvantage.[8] As an alternative, visible light photoredox catalysis may provide an efficient method for the formation of C–C bonds.[9] Aryl halides (Ar–X) are activated by photoinduced electron transfer yielding the corresponding radical anions ($Ar–X^{\bullet-}$), which upon fragmentation (and by releasing halide anions) generate the corresponding aryl radicals that could be used for subsequent coupling reactions. However, the scope of such reactions is limited by the available reduction power of commonly known photocatalytic systems.[9c] Rhodamine 6G[10](Rh-6G) has recently been reported by us as a visible light photoredox catalyst with a high reduction potential.[11] The reduction potential of the radical anion, generated in situ, in its excited state reaches a value of *ca.*–2.4V vs SCE,[12] and has been applied for C–H arylation reactions using substituted aryl bromides.[11] We now apply the rho-

damine 6G catalytic system for the photocatalytic generation of heteroaryl radicals from commercially available, and bench-stable brominated and chlorinated substrates using DIPEA as a sacrificial electron donor under blue light (λ_{Ex} = 455 nm) irradiation at room temperature (25 °C). Subsequent trapping of heteroaryl radicals with a second heteroarene under C–H cross coupling conditions gives bi-heteroaryls in good to excellent yields (eq. C, Scheme 1).

Scheme 1. Synthesis of bi-heteroaryls.



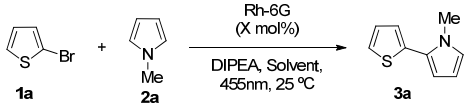
2. RESULTS AND DISCUSSION

Synthesis: The optimization of the reaction conditions was carried out by irradiating a mixture of 2-bromothiophene (**1a,** test substrate), *N*-methylpyrrole (**2a**), rhodamine 6G, and DIPEA, under nitrogen atmosphere using blue LEDs (Table 1).

Using 10 mol% catalyst, 1.5 equivalent of DIPEA in DMSO, 35% conversion to the final product was observed by GC (entry 1, Table 1). Different amounts of the sacrificial electron donor (*i.e.*, DIPEA) did not affect the reaction outcome (entries 2–4, Table 1). Then the reaction was carried out using 10 mol% catalyst in different solvents. DMF and NMP as solvent gave lower conversions than DMSO, while the reaction in acetonitrile afforded better result, with a 59% conversion of the bromide substrate giving the desired product (entries 5–7, Table 1).[13] The role of solvent in determining the yields of the photoredox catalytic chemical reaction is not fully understood at present. The Stern-Volmer quenching analysis demonstrates that quenching of Rh-6G excited states by DIPEA is faster in ACN than in DMSO (see Figure S2 in the Supporting Information). However, knowing that solvents also a play a crucial role in determining the stability and reactivity of radical intermediates (including the radical anion of rhodamine 6G), generated *in situ* during photoredox catalytic chemical reactions, the faster quenching of Rh-6G in ACN cannot fully account for the better isolated yields of compounds **3b**, **3d** and **3n–p**in DMSO.

Then the reaction was examined in the presence of 20 mol% catalyst loading, affording a 71% conversion in DMSO (45% isolated yield) and 92% conversion in ACN (65% isolated yield, see also the discussion below) (entries 8 and 9, Table 1). Control experiments without light, without catalyst or without DIPEA confirmed that all the components are necessary for the photoredox catalytic reaction to take place (entries 10–12).

Table1. Optimization of the reaction conditions for the photocatalyzed C–H heteroarylation.[a]



Entry	Rh-6G (mol%)	Solvent	DIPEA (eq.)	Time (h)	Conv.[b] (%)
1	10	DMSO	1.5	48	35
2	10	DMSO	1.0	48	40
3	10	DMSO	2.0	48	43
4	10	DMSO	2.5	48	40
5	10	DMF	1.5	48	35
6	10	ACN	1.5	48	59
7	10	NMP	1.5	48	23
8	20	DMSO	1.5	48	71 (45)[f]
9	20	ACN	1.5	48	92 (65)[f]
10[c]	20	ACN	1.5	48	0
11[d]	--	ACN	1.5	48	0
12[e]	20	ACN	--	48	0

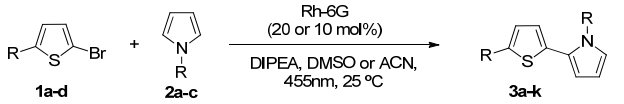
[a] The reactions were performed with 0.1 mmol of 2-bromothiophene **1a**, 1.8 mmol of *N*-methylpyrrole**2a**, and 1.5 mL of solvent. [b] Conversion to the final product determined by GC analysis after 48h. [c] Reaction in the dark. [d] Reaction with blue LED light, without catalyst. [e] Reaction without DIPEA. [f] In parenthesis is given the isolated product yield after flash chromatography.

With the optimized reaction conditions in hand (entry 8 or 9, Table 1), the reaction scope was explored with a range of substituted thiophenes and different pyrroles as radical trapping reagents (Table 2).

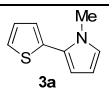
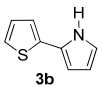
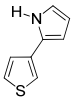
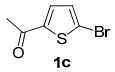
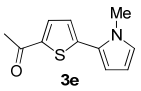
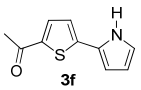
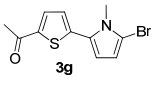
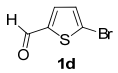
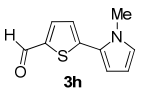
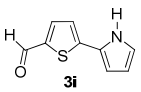
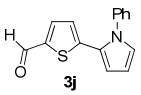
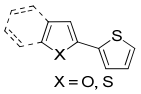
The reaction between 2-bromothiophene **1a** and pyrrole **2a** gave excellent conversion to the desired product **3a**, as monitored by GC, with 20 mol% catalyst in 48h using ACN as solvent of the reaction, but the high volatility of the final product allowed its isolation only in 65% yield (entry 1, Table 2). In the case of pyrrole **2b**, better results were obtained by carrying out the reaction in DMSO as solvent, but again the high volatility of **3b** allowed its isolation only in moderate yield (entry 2, Table 2). A similar situation was found for 3-bromothiophene **1b** in its reaction with pyrroles **2a** and **2b**. Although good conversion to the final products were observed by GC, the high volatility of **3c** and **3d**, only allowed their isolation in moderate yields (entries 3 and 4, Table 2). Thiophenes **1c** and **1d** bearing electron withdrawing substituents gave full conversion with 10 mol% catalyst loading in 24h in ACN or DMSO with pyrroles **2a–2d**. However, reactions in ACN allowed an easier isolation of the final products

3e–3j, that were obtained in excellent yields (entries 5–10, Table 2). The brominated pyrrol **2c** is an excellent trapping reagent in the reaction with **1c**, affording **3g** in good yield, that can be used as starting material for further functionalizations (entry 7, Table 2). Other heterocycles such as (benzo)furan or(benzo)thiophene do not act as radical trapping reagents and the radical coupling step with 2-bromothiophene **1a** does not occur (entry 11, Table 2). [14]

Table2. Scope of bromothiophenes used in the photocatalyzed C–H heteroarylation.[a]



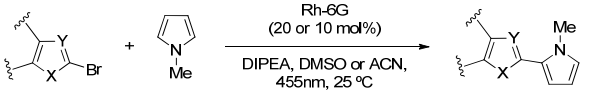
1a-d 2a-c 3a-k

Entry	Thiophene	Reactant	Product	Yield[b] (%)
1[c]	 1a	 2a	 3a	65[c,e]
2		 2b	 3b	41±15[d,e,g]
3	 1b	 2a	 3c	62[c,e]
4		 2b	 3d	49±15[d,e,g]
5	 1c	 2a	 3e	96[c,f]
6		 2b	 3f	72[c,f]
7		 2c	 3g	70[c,f]
8	 1d	 2a	 3h	84[c,f]
9		 2b	 3i	79[c,f]
10		 2d	 3j	91[c,f]
11	 1a	 X = O, S	 X = O, S	0[c,e]

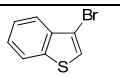
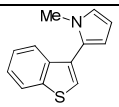
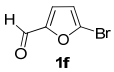
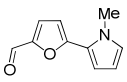
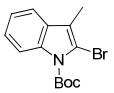
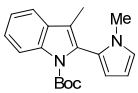
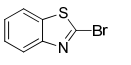
[a] Reaction conditions: Bromoheteroarene (0.1 mmol), pyrrole (1.8 mmol), Rh-6G (10 or 20 mol%), DIPEA (0.15 mmol), 1.5 mL solvent. [b] Isolated yield after flash chromatography. [c] Reaction carried out in ACN. [d] Reaction carried out in DMSO. [e] Yield after 48h, with 20 mol% catalyst loading. [f] Yield after 24h, with 10 mol% catalyst loading. [g] As this compound is quite volatile we were not able to remove the residual solvent form the final product after purification using flash column chromatography, and hence we give the range for the isolated chemical yield.

Next, the reaction scope was investigated with different electron-rich heterocycles, **1e–1j,** using *N*-methylpyrrole **2a** as a trapping reagent (Table 3 and Scheme 2). For compounds **1e–1g**, best results were obtained in ACN, whereas for compounds **1h–1j**, DMSO provided slightly better yields. Substituted thianaphthene **1e** and substituted furfural **1f** gave products **3k** (80%) and **3l** (81%) in very good isolated yields in the presence of 20 and 10 mol% catalyst, respectively (Table 3). Indole derivative **1g** gave 90% conversion to a mixture of Boc-deprotected indole, the dehalogenated reduced form (*via* hydrogen atom abstraction either from the radical cation of DIPEA or from the solvent),[11] and the desired product **3m** (isolated in 49% yield, Table 3). For the reaction of **1h–1j** 20 mol% catalyst loading was necessary for the complete conversion of the starting materials. Compounds **3n** and **3p** were isolated in good yields(87% and 79%,respectively, Table 3). However, compound **1i** gave the coupled product **3o** in moderate yield (51%) due to the formation of the dehalogenated reduced byproduct.

Table 3. Scope of bromo-heteroarenes for the photocatalyzed C-H heteroarylation.[a]



1e-l 2a 3l-s

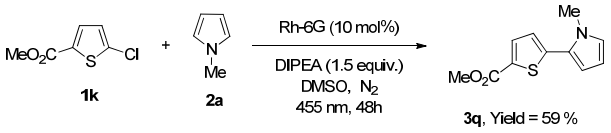
Entry	Heteroarene	T.R.	Product	Yield[b] (%)
1	 1e	 2a	 3k	80[c,e]
2	 1f	 2a	 3l	81[c,f]
3	 1g	 2a	 3m	49[c,e]
5	 1h	 2a	3n	87[d,e]
6	1i	2a	3o	51[d,e]
7	1j	2a	3p	79[d,e]

[a] Reaction conditions: Bromoheteroarene (0.1 mmol), *N*-methylpyrrole (1.8 mmol), Rh-6G (10 or 20 mol%), DIPEA (0.15 mmol), 1,5 mL solvent. [b] Isolated yield after flash chromatography. [c] Reaction carried out in ACN. [d] Reaction carried out in DMSO. [e] Yield after 48h, with 20 mol% catalyst loading. [f] Yield after 24h, with 10 mol% catalyst loading.

Notably, the regioselectivity of the reaction is controlled by the stability of the radical intermediates. Under the catalytic reaction conditions, in all cases, single regioisomers were obtained.

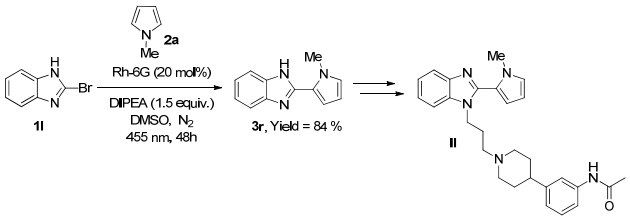
Although chloro-heteroarenes have higher reduction potentials than the corresponding brominated compounds, approaching the limits of the available reduction power byRh-6G,[15] the presence of electron withdrawing substituents decrease this reduction potential. Thus, the reaction of **1k** with **2a** in the presence of 10 mol% catalyst afforded **3q** in good yield after 48h (Scheme 2).

Scheme 2. Photocatalytic heteroarylation of chloro-heteroarene.



The methodology was also applied for the formal synthesis of compounds with biological activity. Starting from brominated imidazole **1l** and using *N*-methylpyrrole **2a** as radical trapping reagent, 20 mol% catalyst in DMSO in 48 h, product **3r** was obtained in 84% isolated yield (Scheme 3). Compound **3r** is an intermediate in the synthesis of the benzimidazole derivative **II** that is an MCH-R1 antagonist,[16] known to be involved in the control of food intake and body weight,[17] being one of the promising lead structures for obesity treatment (Scheme 3).

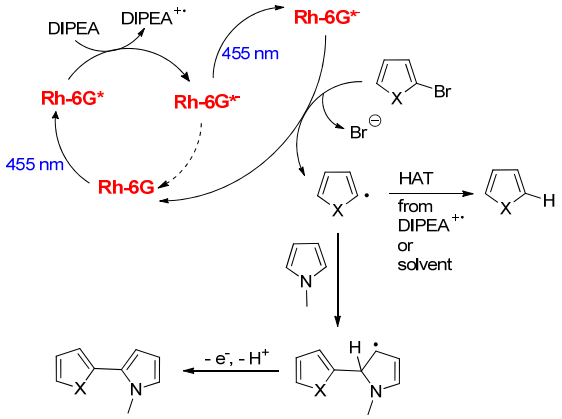
Scheme 3. Formal synthesis of the benzimidazole derivative II.



Mechanistic proposal: We assume the same catalytic cycle as reported previously for Rh-6G photocatalytic systems.[11] The catalytic cycle starts with the photoexcitation of Rh-6G with blue LEDs. Rh-6G in its excited state is able to accept an electron from a sacrificial electron donor (*i.e.*, DIPEA), yielding the radical anion of the Rh-6G (Rh-6G$^{\bullet-}$) and the radical cation of the DIPEA (DIPEA$^{\bullet+}$) (Scheme 4). The generated radical anion of Rh-6G absorbs a second photon (upon blue light irradiation) to reach its excited state that has a higher reduction potential and is therefore able to reduce the heteroaryl bromides by electron transfer, returning to its ground state, and yielding the heteroaryl radical by scission of the C–Br bond. Finally, this heteroaryl radical is trapped by pyrrole derivatives present in the media, yielding the biheteroaryl products after oxidation and rearomatization (Scheme 4).

The dehalogenated reduced byproduct, which is formed in notable amounts in some cases (e.g., for substrate **1i**),is formed by hydrogen atom transfer from the radical cation of DIPEA or from the solvent to the aryl radical.[11]

Scheme 4. Mechanistic proposal



3. CONCLUSSION

Photocatalytic cross–coupling of five membered brominated and chlorinated heteroarenes with pyrroles yields biheteroaryls. The strong reductive power of the excited radical anion of rhodamine 6G allows the reduction of a variety of heteroaryl bromides, and heteroaryl chlorides bearig electron withdrawing groups, giving the corresponding aryl radical, which is subsequently trapped by a pyrrol derivative present in the solution affording the target biaryls in good to excellent isolated yields. The simple photocatalytic protocol may be useful as metal–free alternative to the transition metal catalyzed cross coupling methods.

ASSOCIATED CONTENT

Supporting Information

Supporting Information Available:
[Full experimental data (PDF)]
This material is available free of charge via the Internet at http://pubs.acs.org.

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