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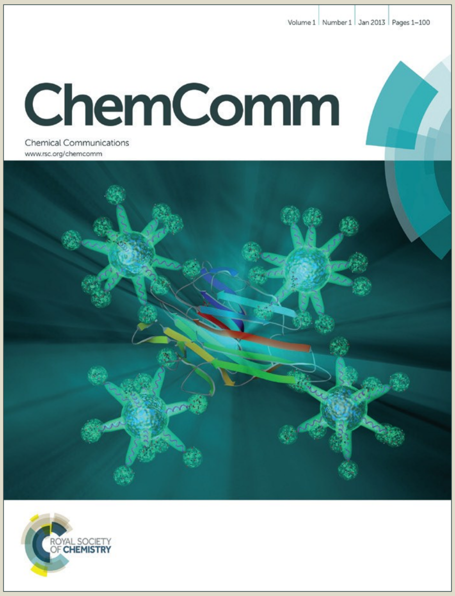

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Synthesis of Pyrrolo[1,2-*a*]quinolines and Ullazines by Visible Light mediated one- and twofold Annulation of *N*-Arylpyrroles with Arylalkynes†

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1-(2-Bromophenyl)-1*H*-pyrrole and 1-(2,6-dibromophenyl)-1*H*-pyrrole react in the presence of catalytic amounts of rhodamine 6G (Rh-6G) and *N,N*-diisopropylethylamine (DIPEA) under blue light irradiation with aromatic alkynes and subsequently cyclize intramolecularly to form pyrrolo[1,2-*a*]quinoline and ullazines. The reactions proceed at room temperature, avoid transition metal catalysts, and provide the target compounds in one pot in moderate to good yields. Mechanistic investigations suggest that the photo excited Rh-6G is reduced by DIPEA to form the corresponding radical anion Rh-6G$^{\bullet-}$, which is again excited by 455 nm light. The excited radical anion of Rh-6G donates an electron to the aryl bromide giving an aryl radical that is trapped by aromatic alkynes. The intermediate vinyl radical cyclizes intramolecularly and yields the product after rearomatization.

Fused nitrogen containing heterocycles are structural elements of biologically active natural products[1] or active pharmaceutical ingredients (APIs) and find applications in organic materials.[2] Among them, pyrrolo[1,2-*a*]quinolines, pyrazolo[1,5-*a*]quinolines, and ullazines are of particular importance. Some of their derivatives show antitumor,[3] antibacterial[4] or antimicrobial[5] activities; they activate caspases or induce apoptosis[6] and are used as organic semiconductors,[7] in host–guest chemistry[8, 9] or as liquid crystals.[10, 11] Also, the pyrazolo derivatives, *e.g.*; 4-phenylpyrazolo[1,5-*a*]quinoline show anti reproductive utility.[12] Ullazines have found applications in optoelectronics, as organic sensitizer for solar-cell and show very good electron transport properties.[13]

Several methods for the synthesis of fused nitrogen-containing heterocycles have been reported; many apply direct arylation reactions. These include palladium-catalyzed reactions,[14, 15, 16, 17] 1,2-alkyl migration,[18] DDQ-mediated intramolecular cyclizations,[19] flash vacuum pyrolysis,[20] photosubstitution reactions,[21] and alkyne-carbonyl metathesis.[22] Lautens *et al*. reported a palladium catalyzed direct arylation of geminal dibromo-olefins with a boronic acid *via* tandem Suzuki-Miyura coupling reaction.[23] Larock *et al.* reported a copper catalyzed tandem synthetic methodology for the synthesis of pyrrolo- and indolo[2,1-*a*]isoquinolines.[24] Recently, Baxendale *et al*. developed a method for the synthesis of pyrrolo[1,2-*a*]-quinolines based on an allene cascade reaction in batch and flow mode.[25] Miyura *et al*. described the coupling of phenylazoles with internal alkynes in the presence of a rhodium catalyst and a copper oxidant.[26] Also, the same group reported the formation of indolo[1,2-*a*][1,8]naphthyridines by rhodium catalyzed dehydrogenative coupling *via* rollover cyclometallation[27]. Dumitrescu *et al.* developed the synthesis of pyrrolo[2,1-*a*]isoquinolines by multicomponent 1,3-dipolar cycloaddition.[28] However, all the current synthetic methods require base, specific ligands, high temperature and transition metal catalysts, multi-step processes, and in some cases both cyclized and non-cyclized products are formed, which are difficult to separate. Transition metal free visible light photoredox catalysis is an attractive mild, selective and efficient alternative for the synthesis of pyrrolo[1,2-*a*]quinolines, pyrazolo[1,5-*a*]quinolines, and ullazines by one and two fold annulation of *N*-aryl pyrroles/pyrazoles with aryl alkynes. We report here a one-step visible light mediated metal free direct arylation of 1-(2-bromophenyl)-1*H*-pyrrole, 1-(2-bromophenyl)-1*H*-pyrazole, 3-bromo-2-(1*H*-pyrrol-1-yl)pyridine and 1-(2,6-dibromophenyl)-1*H*-pyrrole with simple aromatic alkynes providing pyrrolo[1,2-*a*]quinolines, pyrazolo[1,5-*a*]quinolines, pyrrolo[1,2-*a*][1,8]naphthyridine and ullazine compounds, respectively. This method utilizes blue light, the organic dye rhodamine 6G (**Rh-6G**) as photocatalyst and *N,N*-diisopropylethylamine (DIPEA) as electron donor.

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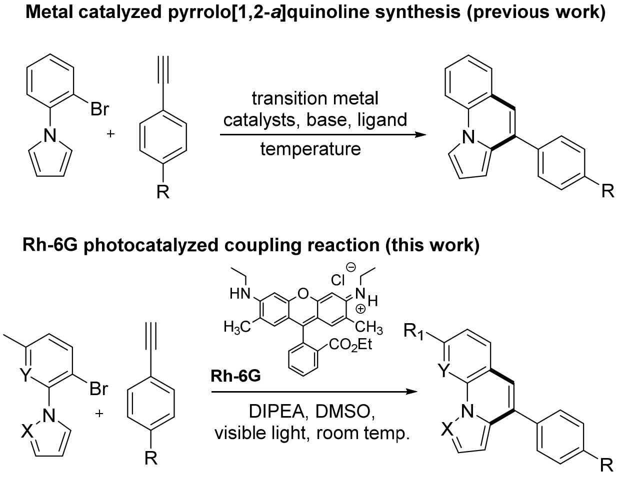
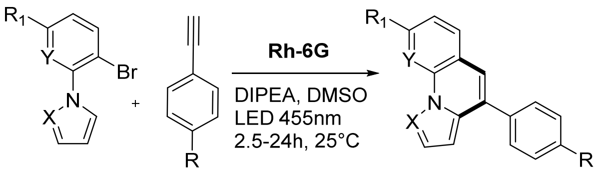


Scheme 1 Pyrrolo[1,2-*a*]quinoline syntheses.

First, the annulation reaction of aryl halide **1a** with aryl alkyne **2a** (entry 1) in the presence of Rh-6G (20 mol%) as the photocatalyst in DMSO at 25 °C under visible light irradiation (blue LEDs: λ_{max} = 455 ± 15nm) was investigated. Under the reaction conditions Rh-6G photo-bleaches and 20 mol% catalyst loading was required. The annulated pyrrolo[1,2-*a*]quinoline **3a** was obtained in 60% yield in 24 hours. This synthetic approach uses the high reduction power of the excited stable radical anion Rh-6G$^{\bullet-}$[29, 30] obtained upon photoirradiation of the xanthene dye under nitrogen with visible light in the presence of *N,N*-diisopropylethylamine (DIPEA). Our photocatalytic method allows the activation of electron rich heteroarenes with a redox potential up to *ca.* –2.4 V *vs* SCE, which is not accessible using common photocatalysts,[31, 32] for C–C bond formation. The synthesis of fused heterocycles combines an intermolecular radical addition to alkynes with an intramolecular cyclization reaction. To improve the efficiency of this method, the reaction conditions were optimized trying various solvents, electron donors, varying the amount of catalyst and of the starting materials. DMSO was found to be the best solvent for the photoreaction using 0.07 mol/L substrate concentrations, 20 equiv. of the alkyne and 2.2 equiv. of DIPEA. Notably, excess amount of alkynes (unreacted alkynes were recovered during isolation) were used to avoid the dehalogenated byproduct[30, 33] formed upon hydrogen atom abstraction of the generated aryl radical from the radical cation of DIPEA or from the solvent.[34, 35] The cyclized product was obtained in good yield with 20 mol% of the photocatalyst. We used a thin layer (1.0 mm) glass reactor with 1.5 ml volume to have an optimal exposure of the reaction mixture for irradiation (for details see ESI). Control reactions confirmed that light, the photocatalyst, and an electron donor are needed for the reaction to occur. Having identified the optimized reaction conditions, we examined the scope of the reaction with substituted aryl halides and alkynes. The products were obtained in moderate to good yields (Table 1). It is observed that the reaction is much faster with neutral and electron rich alkynes, and comparatively slower in the presence of electron withdrawing alkynes. The products (entry 5-13) in Table 1 were obtained in shorter time, but the reaction stops before full conversion. Adding one extra nitrogen to the system increases the redox potential of the aryl halide, hence, slows down the reaction. 1-(2-Bromophenyl)-1*H*-pyrazole (1d) has a redox potential of ~ –2.4 V *vs* SCE (Table 1, entry 14–15) and 3-bromo-2-(1*H*-pyrrol-1-yl)pyridine (**1e**) has a redox potential of ~ –2.1 V *vs* SCE (Table 1, entry 16–17). The observed low yields may be attributed to the slow reaction rates owing to the high reduction potentials of the substrates[36] representing the limit of the photocatalyst scope, or due to the competing light absorption (*i.e.,* the inner filter effect) of the colored products with the catalyst and/or its radical anion (see Fig. **2**). In addition, trace amount of dehalogenated starting material was isolated as by-product.[34, 35]

Table 1 Synthesis of Pyrrolo[1,2-*a*]quinoline.



Entry	Aryl Bromide[a]	R_1	Alkyne[a]	R	Product	Yield[b,c]
1	**1a**[d]	H	**2a**	H	**3a**	60
2	**1a**[d]	H	**2b**	CH_3	**3b**	51
3	**1a**[d]	H	**2c**	OCH_3	**3c**	50
4	**1a**[d]	H	**2d**	F	**3d**	48
5	**1b**[d]	$COCH_3$	**2a**	H	**3e**	56
6	**1b**[d]	$COCH_3$	**2b**	CH_3	**3f**	54
7	**1b**[d]	$COCH_3$	**2c**	OCH_3	**3g**	75
8	**1b**[d]	$COCH_3$	**2d**	F	**3h**	50
9	**1b**[d]	$COCH_3$	**2e**	Cl	**3i**	50
10	**1c**[d]	CF_3	**2a**	H	**3j**	52
11	**1c**[d]	CF_3	**2b**	CH_3	**3k**	56
12	**1c**[d]	CF_3	**2c**	OCH_3	**3l**	41
13	**1c**[d]	CF_3	**2d**	F	**3m**	41
14	**1d**[e]	H	**2a**	H	**3n**	39
15	**1d**[e]	H	**2c**	OCH_3	**3o**	35
16	**1e**[f]	H	**2a**	H	**3p**	49
17	**1e**[f]	H	**2b**	CH_3	**3q**	50

[a] The reaction was performed with **1(a–e)** (0.1 mmol), **2(a–e)** (20 equiv.), DIPEA (2.2 equiv.), and **Rh-6G** (20 mol%) in 1.5 mL of DMSO. [b] Isolated yields after purification by flash column chromatography using silica gel. [c] for the reaction times see ESI. [d] X, Y = C (entry 1-13), [e] X = N, Y = C (entry 14 and 15), [f] X = C, Y = N (entry 16 and 17).

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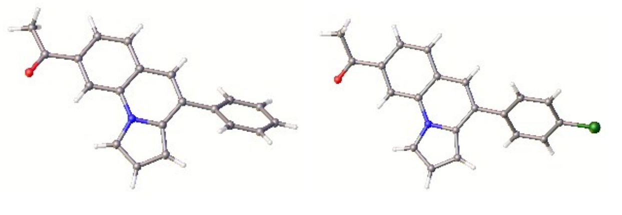
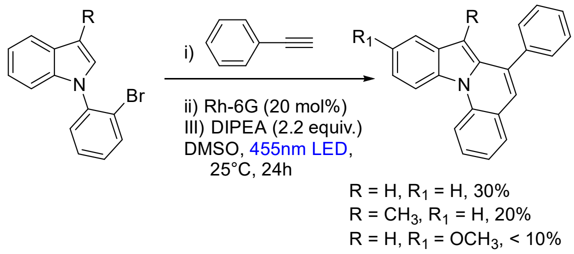


3e **3i**

Fig. 1 Crystal structures of compounds **3e** and **3i**.

Extending the scope of the reaction by replacing the pyrrole moiety by indole resulted in low yields for the transformation. A likely rational for the lower reactivity and yields of indoles in the cyclization reaction is the enforced unfavourable substitution at the 2 position.[37]



Scheme 2 Indolo[1,2-*a*]quinoline syntheses.

Next, we explored the photocatalytic synthesis of ullazines. First derivatives of these class of compounds were prepared in 1983 by Balli *et al.* [38] in 9 steps with very poor yields. Takahasi's route[39] showed no regioselectivity and required harsh conditions. Grätzel's synthesis[40] uses $InCl_3$ and requires four steps. The photoredox reaction yields ullazines in one pot. Using the optimized reaction condition, the annulation reaction was carried out between the dibromo compound **1d** and aryl alkynes. The results are summarized in Table 2. The observed low yields are due to the extremely high reduction potentials of quinoline intermediates and intensively colored products that inhibit the reaction by competing in absorption with the catalyst and/or it's radical anion (see **Fig. 2**). Although not quantified, most of the unreacted starting materials could be recovered during the purification process.

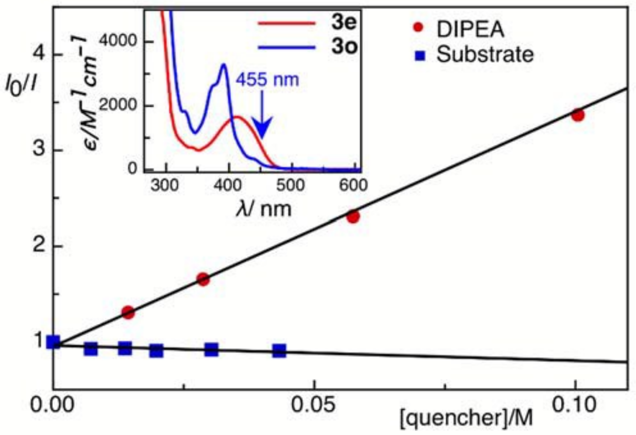
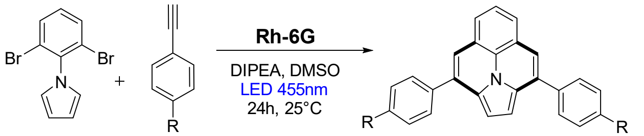


Fig. 2 Stern-Volmer quenching plot of **Rh-6G** in the presence of DIPEA and **1b** (test substrate). In the inset, absorption spectra of compounds **3e**, and **3o** are shown.

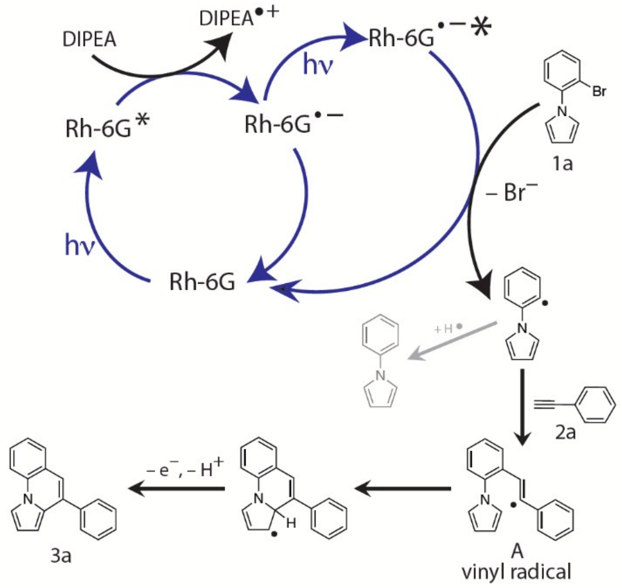
Table 2 Synthesis of ullazines.



Entry	Substrate	Alkyne	R	Product	Yield[b]
1	**1f**	H	**2a**	**3r**	45
2	**1f**	CH_3	**2b**	**3s**	30
3	**1f**	OCH_3	**2c**	**3t**	30

The reaction was performed with **1f** (0.1 mmol), **2(a–c)** (20 equiv.), DIPEA (2.2 equiv.), and **Rh-6G** (0.2 equiv.) in 1.5 mL of DMSO.
[b] Isolated yields after purification by flash column chromatography using silica gel.

Based on previous results,[30] spectroscopic investigations, and our experimental observations we propose the following mechanism (Scheme 3) for the cyclization reaction. Upon photoexcitation with blue light (λ_{max} = 455nm),[41] **Rh-6G** is photoreduced in the presence of DIPEA to the stable radical anion **Rh-6G**$^{\bullet-}$, which is again excited by blue light and transfers an electron to the *N*-aryl bromide **1a** forming **Ar-Br**$^{\bullet-}$ while regenerating the neutral **Rh-6G**. While the radical anion of rhodamine 6G (**Rh-6G**$^{\bullet-}$) can also be generated with green light, the blue light excitation is required to photoexcite it again. Using blue light for both steps simplifies the experimental set up. The reduction potential of **Rh-6G**$^{\bullet-}$ (*ca.* –1.0) is not sufficient to reduce the *N*-aryl bromide substrates investigated here. Fragmentation of the radical anion **Ar-Br**$^{\bullet-}$ generates the aryl radical, which reacts intermolecularly with the alkyne **2a** to form the vinyl radical **A**. This vinyl radical cyclizes intramolecularly giving the annulated product **3a** after oxidation and rearomatization. The formation of the dehalogenated product is due to hydrogen atom abstraction by the intermediate aryl radical either from the radical cation of DIPEA or from the solvent.



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Scheme 3 Proposed reaction mechanism.

In conclusion, the first photocatalytic synthesis of pyrrolo[1,2-*a*]quinolines and ullazines was accomplished starting from *N*-aryl halides and aryl alkynes. This method provides in a single step mild and efficient access to different types of substituted pyrrolo[1,2-*a*]quinolines, pyrazolo[1,5-*a*]quinolines, pyrrolo[1,2-*a*][1,8]naphthyridine and ullazines avoiding transition metal catalysts, bases, ligands, and high temperature.

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