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Graphical Abstract

A visible-light promoted cascade of Glaser coupling/annulation has been developed for one-pot synthesis of polysubstituted pyrazoles from alkynes and hydrazines. The reaction features mild reaction conditions, readily availible starting materials and green oxidant (O_2).

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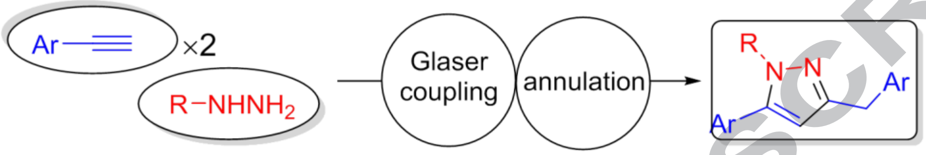

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Visible-Light Promoted One-Pot Synthesis of Pyrazoles from Alkynes and Hydrazines

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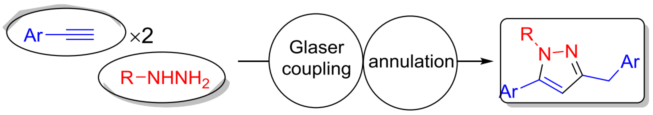
ABSTRACT

A visible-light promoted cascade of Glaser coupling/annulation has been developed for one-pot synthesis of polysubstituted pyrazoles from alkynes and hydrazines. The method features mild reaction conditions, readily availible starting materials and green oxidant (O_2). It works for a wide range of substituted phenyl acetylene and hyrazines with good functional group tolerance and efficiency. Mechanistic pathways including photochemical irridiation, intramolecular hydrogen-atom-abstraction (HAT) and enamine-to-imine tautomerization was proposed for the transformation.

The synthesis of privileged pyrazole framework has gained major research effort from the synthetic community due to their prevalence in many natural products and synthetic pharmaceuticals,[1] as well as versatile utility as precursors to *N*-heterocyclic carbenes (NHCs),[2] ligands for transition-metal-catalyzed cross-coupling reactions,[3] and directing groups for C−H activations[4]. Many traditional methods for their preparation have mainly focused on annulations initiated by the condensation of a monosubstituted hydrazine with a carbonyl, such as cyclocondensation of 1, 3-dicarbonyl or α, β-unsaturated carbonyl compounds with hydrazines.[5] However, these methods usually suffer from harsh conditions like high reaction temperature, microwave irradiation or hazard oxidants, which are contrary to the concept of green chemistry. As a result, the development of more environmentally benign processes toward the synthesis of pyrazole derivatives continues to be a topic of current interest in contemporary synthetic chemistry.



Scheme 1. A visible-light promoted cascade of Glaser coupling/annulation of alkynes with hydrazines.

Recently, visible light-induced photocatalytic strategy has received increasing attention from the synthetic community due to the inexhaustible, environmentally friendly and efficient characteristics of sunlight.[6] In contrast to conventional thermal reactions, photocatalytic processes are initiated by the generation of various reactive species, frequently without stoichiometric activation reagents under mild conditions. Application of these reactive intermediates can result in numerous synthetically useful bond formations in a predictable and selective manner, thus giving rise to the flourishment of photocatalysis in almost every subjects of organic synthesis. It is worth mentioning that the synthesis of heterocycle compounds has benefit a lot from the development of such catalytic system, as the past decades have witnessed a wealth of novel methodologies for the synthesis of different heterocycles like pyrazoles, pyridines, pyrroles, etc.[7] For the synthesis of pyrazoles, Xiao and Chen developed an oxidative deprotonation electron transfer strategy for the photoredox catalytic generation of hydrazonyl radicals from ketone hydrazones, which could undergo intramolecular radical cyclization reaction to give pyrazole derivatives.[8] Chen group reported a practical and efficient CF_3 radical-mediated nucleophilic cyclization of β, γ-unsaturated hydrazones for the synthesis of CF_3-containing pyrazolines employing visible-light photoredox catalysis.[9] Zhu group accomplished a visible-light photoredox catalyzed cascade of the $C(sp^2)$−H/$C(sp^3)$−H bond functionalization of aldehyde hydrazones for the synthesis of complex fused dihydropyrazoles.[10] Zhu and Yu developed a novel [4 + 1] annulation of aldehyde hydrazones with diethyl 2-bromomalonate for the synthesis of pyrazoloisoquinolines by exploiting a relay photoredox catalysis strategy.[11] We developed a selective and high yielding synthesis of polysubstituted pyrazoles through a visible light photoredox

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catalysis promoted reaction of hydrazine with Michael acceptors.[12a]

As a continuation of our interest in such area,[12] herein we report a visible-light promoted cascade of Glaser coupling/annulation of alkynes with hydrazines for the synthesis of polysubstituted pyrazoles (Scheme 1). Initially phenyl acetylene **1a** and hydrazine hydrate **2a** were chosen as the model substrates to study the reaction conditions. The reaction was carried out by exposing phenyl acetylene **1a** to air in the presence of copper catalyst and photocatalyst under the irradiation of 12 w blue LED bulb, followed by the addition of hydrazine hydrate **2a** when **1a** was consumed. At first, different photocatalysts (2 mol%) were evaluated with reactions in DMSO in the presence of CuI (20 mol%) under room temperature, and it is found that Rhodamine B, Eosin Y and Methylene blue were able to promote the reaction to some extent, resulting in the formation of desired product **3a** with yields from 38-51% (Table 1, entries 1-3), while Ru(bpy)$_3$Cl$_2$ gave a yield up to 77% (Table 1, entry 4). Instead of CuI, different copper salts including CuCl, CuCl$_2$, Cu(OTf)$_2$ and Cu(OAc)$_2$ were tested in the reaction using Ru(bpy)$_3$Cl$_2$ as the photocatalyst, and they could not improve the outcome of the reaction (Table 1, entries 5-8). The screening of solvents revealed that DMSO was superior to THF, DMF and MeOH (Table 1, entries 9-11), while CH$_3$CN, AcOEt or DCM did not work for this reaction at all, resulting in no desired product (Table 1 entries 12-14). The reaction was further optimized by varying the equivalents of hydrazine hydrate **2a**. A decrease in the yield of the reaction was observed when the amount of hydrazine hydrate **2a** was reduced from 4.0 equivalents to 2.0, 2.5 or 3.0 equivalents (Table 1 entries 15-17). On the other side, increasing the equivalents of hydrazine hydrate **2a** to 5 also led to inferior outcomes (Table 1, entry 18), probably due to additional side reaction. So DMSO, CuI, Ru(bpy)$_3$Cl$_2$ and 4.0 equivalents of hydrazine hydrate **2a** were chosen as the optimized conditions.

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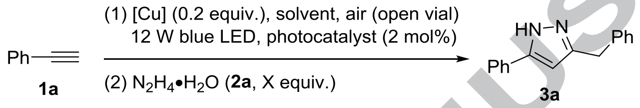
Table 1. Optimization of reaction conditions[a]

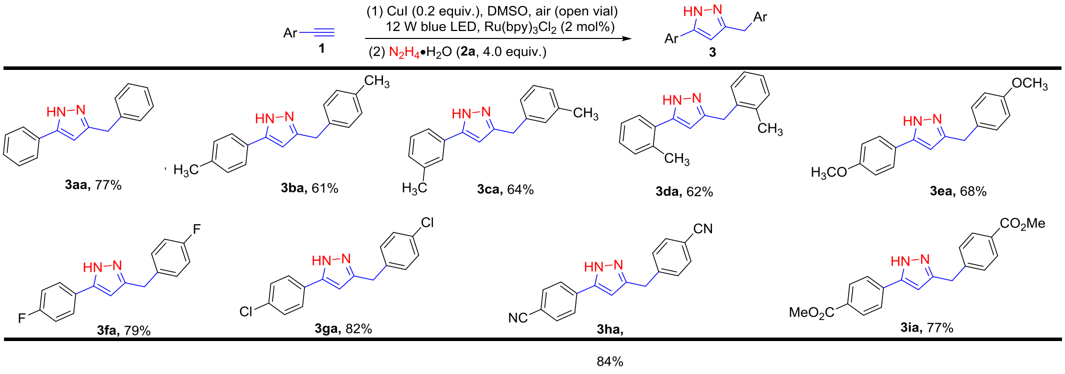


entry	solvent	[Cu]	photocatalyst	X	Yield %
1	DMSO	CuI	Rhodamine B	4.0	38
2	DMSO	CuI	Eosin Y	4.0	51
3	DMSO	CuI	Methylene blue	4.0	42
4	**DMSO**	**CuI**	**Ru(bpy)$_3$Cl$_2$**	**4.0**	**77**
5	DMSO	CuCl	Ru(bpy)$_3$Cl$_2$	4.0	64
6	DMSO	CuCl$_2$	Ru(bpy)$_3$Cl$_2$	4.0	60
7	DMSO	Cu(OTf)$_2$	Ru(bpy)$_3$Cl$_2$	4.0	56
8	DMSO	Cu(OAc)$_2$	Ru(bpy)$_3$Cl$_2$	4.0	69
9	THF	CuI	Ru(bpy)$_3$Cl$_2$	4.0	48
10	DMF	CuI	Ru(bpy)$_3$Cl$_2$	4.0	32
11	CH$_3$OH	CuI	Ru(bpy)$_3$Cl$_2$	4.0	45
12	CH$_3$CN	CuI	Ru(bpy)$_3$Cl$_2$	4.0	0
13	AcOEt	CuI	Ru(bpy)$_3$Cl$_2$	4.0	0
14	DCM	CuI	Ru(bpy)$_3$Cl$_2$	4.0	0
15	DMSO	CuI	Ru(bpy)$_3$Cl$_2$	2.0	58
16	DMSO	CuI	Ru(bpy)$_3$Cl$_2$	2.5	62
17	DMSO	CuI	Ru(bpy)$_3$Cl$_2$	3.0	70
18	DMSO	CuI	Ru(bpy)$_3$Cl$_2$	5.0	68

[a] 0.5 mmol of **1a**, 2.0 mmol of **2a**, 0.1 mmol of copper catalyst, 0.01 mmol of photocatalyst, 2 mL of solvent, open vial, irradiated by 12 W blue LED bulb at room temperature.

[b] isolated yield.

Table 2. Reaction of hydrazine hydrate **2a** with different aryl acetylenes **1**[a]

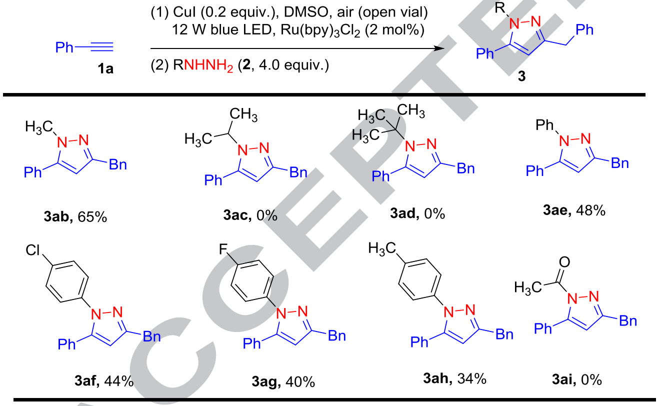


[a] 0.5 mmol of **1**, 2.0 mmol of **2a**, 0.1 mmol of CuI, 0.01 mmol of Ru(bpy)$_3$Cl$_2$, 2 mL of DMSO, open vial, irradiated by 12 W blue LED bulb at room temperature.

With the optimized conditions in hand, we proceeded to evaluate the scope and generality of this cascade reaction. Firstly, a wide range of aryl acetylenes **1** could react with hydrazine hydrate **2a**, leading to desired pyrazole products with moderate to good isolated yields(**3aa**–**3ia**). Aryl acetylenes bearing electron-withdrawing groups on benzene ring gave relatively higher yields than the ones with electron-donating groups (**3fa**–**3ia** *vs* **3ba**–**3ea**), and 4-ethynylbenzonitrile **1h** with a –CN group could undergo this reaction to form desired product **3ha** in up to 84% yield. The steric nature of the substrates was shown to have little influence on the reaction efficiency, as substrates **3ba**–**3da** with a methyl group on para, meta and ortho position of benzene ring respectively could be converted to the corresponding pyrazoles in nearly same yields. Notably, a series of functional groups, such as methoxy, nitrile and ester, were all well tolerated under the reaction conditions, leading to desired products in good yields (**3ea**, **3ha** and **3ia**). The reaction of two alkynes with different aryl groups was also studied, unfortunately it gave poor selectivity for homo-/cross-coupling.

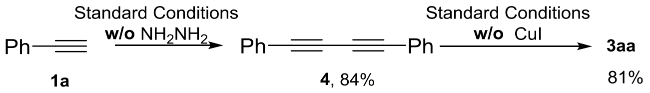
We next examined substituted hydrazines **2** in the cascade reaction with phenyl acetylene **1a**. As showed in Table 3, this reaction allows both alkyl and aryl substitution of hydrazine, leading to tri-substituted pyrazoles in moderate yields. The reaction of methyl hydrazine **2b** and phenyl acetylene **1a** can generate pyrazole **3ab** with a yield of 65%**,** while the reaction of *iso*-propyl or *tert*-butyl hydrazine did not give any desired products, probably due to the steric hindrance (**3ac** and **3ad**). Notably, various aryl hydrazines with different groups on benzene ring were also found to work for the reaction, leading to corresponding pyrazoles **3ae-3ah**. Unfortunately, electron-deficient hydrazine, such as acetohydrazide **2i** could not undergo this transformation, probably due to its relatively lower nucleophilicity compared to alkyl and aryl substituted hydrazines.

Table 3. Reaction of phenyl acetylene **1a** with substituted hydrazines **2**[a]



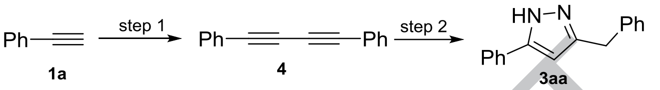
3ab, 65%
3ac, 0%
3ad, 0%
3ae, 48%
3af, 44%
3ag, 40%
3ah, 34%
3ai, 0%

[a] 0.5 mmol of **1a**, 2.0 mmol of **2**, 0.1 mmol of CuI, 0.01 mmol of Ru(bpy)$_3$Cl$_2$, 2 mL of DMSO, open vial, irradiated by 12 W blue LED bulb at room temperature



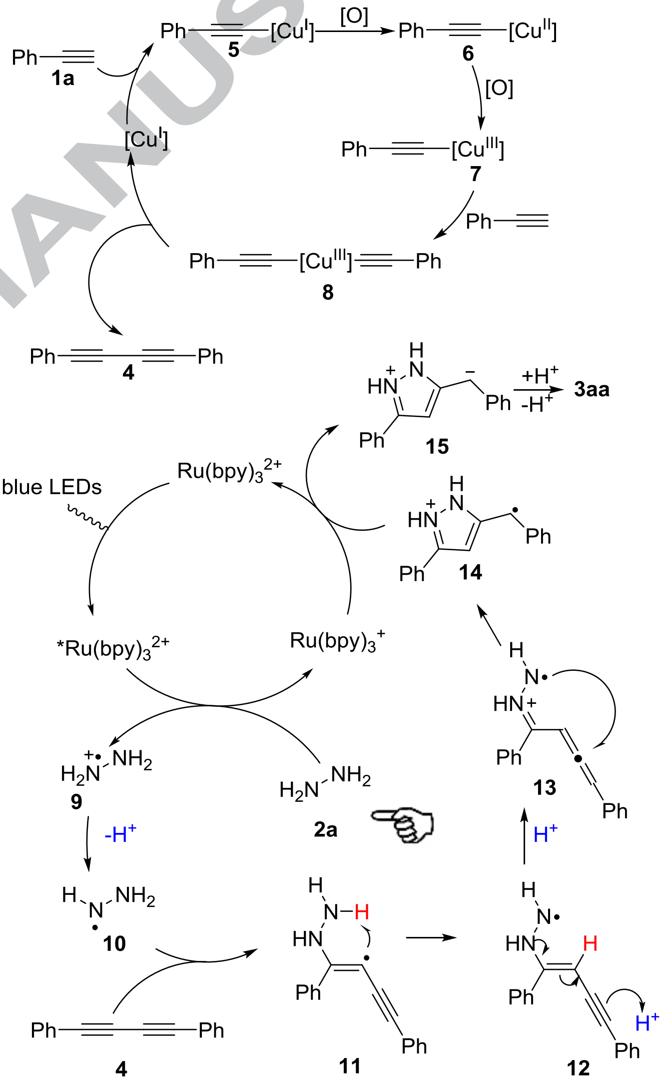
Scheme 2. Stepwise results of the synthesis

For insight into the reaction mechanism, a stepwise synthesis (Scheme 2) was performed by firstly subjecting **1a** to standard conditions without hydrazine, and **4** was isolated in 84% yield. Then **4** was treated with hydrazine under standard conditions in the absence of CuI, and the desired product **3aa** was obtained in 87% yield. Also control reactions focusing on the role of photocatalysis in this strategy were carried out (Scheme 3). By turning on/off light or photocatalyst, it is found that light is indispensable for the first step (Glaser coupling) of the cascade reaction, while photocatalyst can accelerate the coupling, but is not essential. For the second step, both light and photocatalyst are indispensable, as no desired product **3aa** is detected from the reaction in absence of photocatalyst in dark environment.



Variation from the standard conditions	step 1	step 2
No *hv*	✗	✗
No photocatalyst	✓	✗
No *hv*, no photocatalyst	✗	✗

Scheme 3. Control reactions by turning on/off *hv* or photocatalyst



Scheme 4. Plausible mechanistic pathways for the reaction

On the basis of these experimental observations and our previous study of hydrazines,[12,13] a plausible mechanism is proposed for this cascade reaction (Scheme 4). The first step almost resembles a typical Glaser reaction, as it goes through several copper acetylide complexes, accompanied by the valence changes of copper which is proposed to be accomplished by photochemical process in the presence of oxygen. By studying the

UV-Vis absorption of phenyl acetylene, CuI and the mixture of the two (see section 6 of Supporting Information), it is found that the absorption of the mixture is red shifted to the region almost within the spectrum of household blue LEDs compared to phenyl acetylene or CuI alone. This result indicates that the generated copper complex (intermediate **5** and **6**) could be irradiated by blue light, hence be oxidized through photochemical process. The second step is initiated by the irradiation of Ru^{II} photocatalyst to its excited state $Ru^{II}*$ which is then reductively quenched by **2a** with concomitant generation of radical ion **9** and Ru^{I}. Upon deprotonation, radical ion **9** is converted to radical **10** which attacks diyne **4** to form radical intermediate **11**. Through an intramolecular hydrogen-atom-abstraction (HAT) and enamine-to-imine tautomerization, **11** is converted to **13** via **12** by abstracting a proton. Then intramolecular attack of allene group by the nitrogen radical within intermediate **13** generates radical **14**. Finally, an oxidative quench of Ru^{I} by radical **14** regenerates Ru^{II} photocatalyst, along with the formation of **15** which readily transforms to desired product **3aa** upon proton transfer.

In conclusion, we have developed a visible-light promoted cascade of Glaser coupling/annulation for the synthesis of polysubstituted pyrazoles from readily available alkynes and hydrazines. The method employs very mild reaction conditions and uses air as the terminal oxidant, which makes the process environmentally benign. Various substituted phenyl acetylene and hyrazines undergo this reaction smoothly, leading to desired products with good functional group tolerance and efficiency. Photocatalysis was proven to be essential for these transformation and a plausible mechanism featuring intramolecular hydrogen-atom-abstraction (HAT) and enamine-to-imine tautomerization was proposed for this transformation.

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Supplementary Material

Highlights

- Simple one-pot reaction for preparation of pyrazoles from alkynes and hydrazines.
- Mild conditions: visible-light promoted; room temperature; O_2 as the Oxidant.
- Easy reaction set-up.
- Functional group tolerance.