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Relay Visible-Light Photoredox Catalysis: Synthesis of Pyrazole Derivatives via Formal [4 + 1] Annulation and Aromatization

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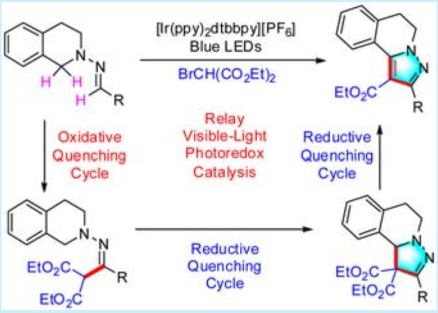
Supporting Information

ABSTRACT: A relay visible-light photoredox catalysis strategy has been accomplished. Three successive photoredox cycles (one oxidative quenching cycle and two reductive quenching cycles) are engaged in a single reaction with one photocatalyst. This strategy enables formal [4 + 1] annulation of hydrazones with 2-bromo-1,3-dicarbonyl compounds, which functionalizes three C−H bonds of hydrazones. This method affords rapid access to a complex and biologically important pyrazole scaffold in a step-economical manner with high efficiency under mild conditions.



Visible light photoredox catalysis has recently emerged as a powerful synthetic tool to achieve important organic transformations.[1] Either a reductive or an oxidative quenching cycle can be employed to initiate single-electron-transfer events (Scheme 1a).[2] The merger of photoredox catalysis with other catalysis methods, such as transition-metal catalysis,[3] acid catalysis,[4] and organocatalysis,[4a,5] has also been discovered to achieve novel reaction modes or functionalization of inert bonds, which visible-light photoredox catalysis is incapable of accomplishing itself. Despite these advances, the synthetic potential of visible-light photoredox needs to be further developed. We envisage that multiple quenching cycles can be involved in a single reaction, which can convert simple starting materials to sophisticated and valuable molecules (Scheme 1b).[6]

This relay visible light photoredox catalysis strategy can be demonstrated by formal [4 + 1] annulation[7] of hydrazone **A** with diethyl 2-bromomalonate (Scheme 1c). Three major events are involved in this transformation: (1) photoredox-catalyzed oxidative coupling of hydrazone **A** with diethyl 2-bromomalonate via an oxidative quenching cycle to give hydrazone **B**; (2) photo-oxidation of hydrazone **B** to the hydrazinium through a reductive quenching cycle followed by an intramolecular Mannich reaction to provide dihydropyrazole **C**; (3) decarboxylation and photo-oxidation of dihydropyrazole **C** via another reductive quenching cycle to give final pyrazole **D**. The overall outcome of this reaction is to convert three C−H bonds to three C−C bonds, resulting in a pyrazolo[5,1-*a*]isoquinoline framework[8] in a step-economical manner with high efficiency. Pyrazoloisoquinolines are biologically important heterocycles that display pregnancy terminating activity and *anti*-reproductive properties.[9] This relay visible light photoredox catalysis strategy will enrich the synthetic potential visible-light photoredox catalysis and enable more novel reaction modes.

This rationale was examined by photoredox-catalyzed formal [4 + 1] annulation of hydrazone **1a** with diethyl 2-bromomalonate (**2a**) (Table 1). A mixture of **1a** and diethyl 2-bromomalonate **2a** (1:1.0 ratio) in acetonitrile with [Ir(ppy)$_2$dtbbpy][PF$_6$] (**I**) as the photocatalyst, anhydrous K$_2$HPO$_4$, and 4 Å molecular sieve (MS) as additives was irradiated by a 5 W blue LED. The desired product **3a** was afforded in 20% yield after 16 h irradiation (Table 1, entry 1). The dosage of bromide **2a** was then carefully optimized (entries 2−6). It was found that the best ratio between the substrates **1a** and **2a** was 1:2.5, and the yields were obtained up to 81% (entry 4). The other photocatalysts, such as Ir(ppy)$_3$ (**II**) and Ru(bpy)$_3$Cl$_2$ (**III**), gave 40% and 54% yields of the desired product **3a**, respectively (entries 7 and 8). No other bases and solvents could give improved results (entries 9−12). It was found that both photocatalyst and visible light irradiation were crucial to this transformation and neither photocatalyst nor light could be absent (entries 13 and 14).

With the optimized reaction conditions established, we next sought to explore the scope and limitation of this transformation (Scheme 2). First, a variety of hydrazones were examined to react with diethyl 2-bromomalonate **2a**. Aromatic aldehyde-derived *N*-tetrahydroisoquinoline hydrazones could efficiently react with diethyl 2-bromomalonate **2a** under the optimized conditions to give the corresponding pyrazoles **3a−k** in 46−81%. The substituents could be electron-donating groups (MeO, Me), halides (F, Cl, Br), an electron-with-

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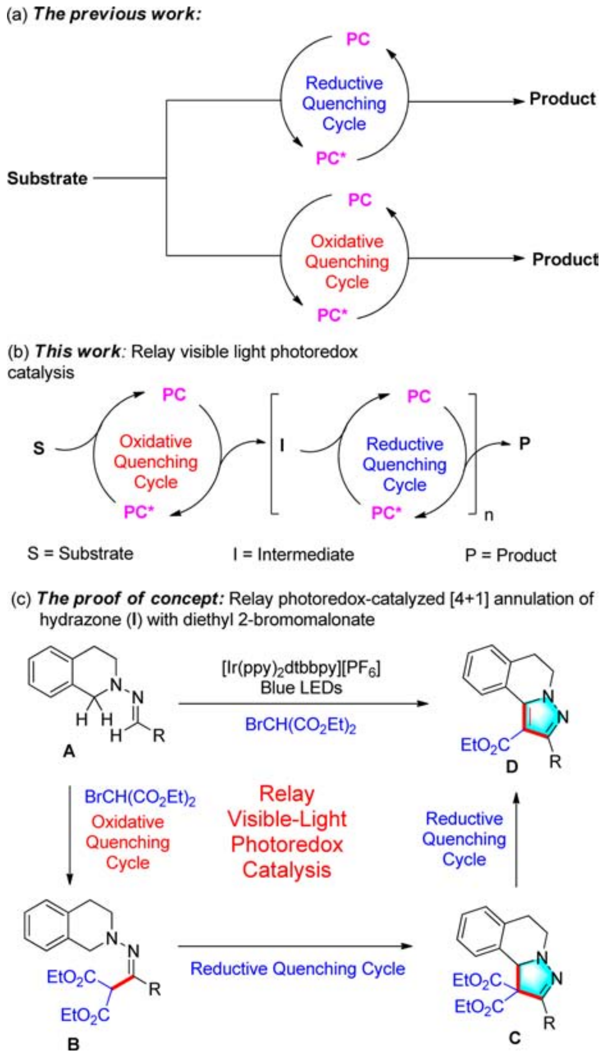
Scheme 1. Relay Visible-Light Photoredox Catalysis

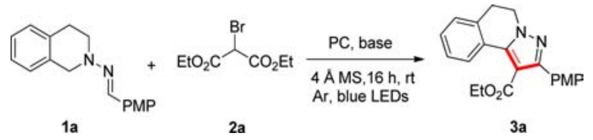


drawing group (CF_3), and even thiophene. Aliphatic aldehyde-derived hydrazones were also suitable in this reaction whether they were linear (**3l**, 67% yield) or cyclic (**3m**, 77% yield). 5-Chlorotetrahydroisoquinoline-derived hydrazone also went through this transformation smoothly to give the desired pyrazole **3n** in 74% yield. Benzylmethylhydrazine-derived hydrazone worked well to afford the corresponding pyrazole **3o** in 65% yield.

Various 2-bromo-1,3-dicarbonyl compounds were then employed in this reaction (Scheme 3). Dimethyl 2-bromomalonate (**2b**) could be annulated with hydrazone **1a** to give pyrazole **3p** in satisfactory yield, the structure of which was established unambiguously by X-ray diffraction analysis.[10] Interestingly, when bromoacetoacetate (**2c**) or bromobenzoylacetate (**2d**) was subjected to standard conditions, both of them gave deacylation product **3a** in 70% and 75% yields, respectively, without any decarboxylation product.[11] When acetoacetone- or benzoylacetone-derived bromides **2e** or **2f** reacted with hydrazone **1a**, both of them gave pyrazole **3q**. From these experiments, it can be concluded that the leaving propensity in this transformation is acetyl group (−COMe) > benzoyl group (−COPh) > ester (−CO_2Et).

To understand this relay visible light photoredox catalysis further, control experiments were conducted as shown in

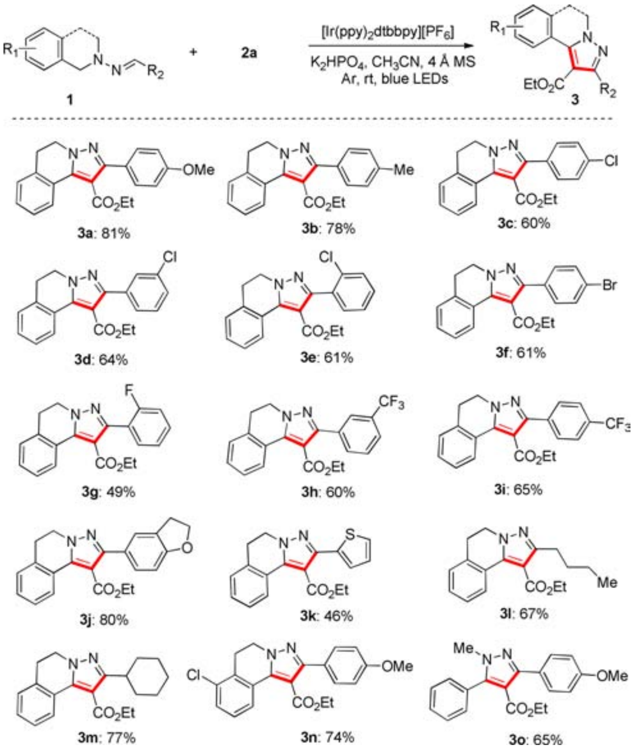
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	base	solvent	ratio (**1a**/**2a**)	yields[b] (%)
1	**I**	K_2HPO_4	CH_3CN	1:1.0	20
2	**I**	K_2HPO_4	CH_3CN	1:1.5	45
3	**I**	K_2HPO_4	CH_3CN	1:2.0	56
4	**I**	K_2HPO_4	CH_3CN	1:2.5	81
5	**I**	K_2HPO_4	CH_3CN	1:3.0	68
6	**I**	K_2HPO_4	CH_3CN	1:3.5	63
7	**II**	K_2HPO_4	CH_3CN	1:2.5	54
8	**III**	K_2HPO_4	CH_3CN	1:2.5	40
9	**I**	K_2CO_3	CH_3CN	1:2.5	60
10	**I**	$NaHCO_3$	CH_3CN	1:2.5	57
11	**I**	K_2HPO_4	DMF	1:2.5	59
12	**I**	K_2HPO_4	DMA	1:2.5	48
13[c]	**I**	K_2HPO_4	CH_3CN	1:2.5	0
14	none	K_2HPO_4	CH_3CN	1:2.5	0

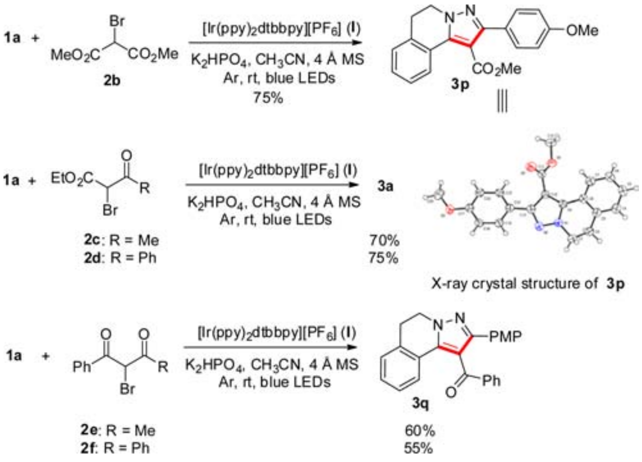
[a] Reaction conditions: **1a** (0.2 mmol), **2a**, photocatalyst (0.002 mmol, 1 mol %), base (0.6 mmol, 3.0 equiv), anhydrous solvent (2 mL), 4 Å molecular sieves (MS) (100 mg), 5 W blue LED irradiation for16 h, argon atmosphere, room temperature. [b] Yields of the isolated product. [c] In the dark. PMP = 4-methoxyphenyl.

Scheme 2. Scope for Synthesis of the 5,6-Dihydropyrazolo[5,1-*a*]isoquinoline[a]



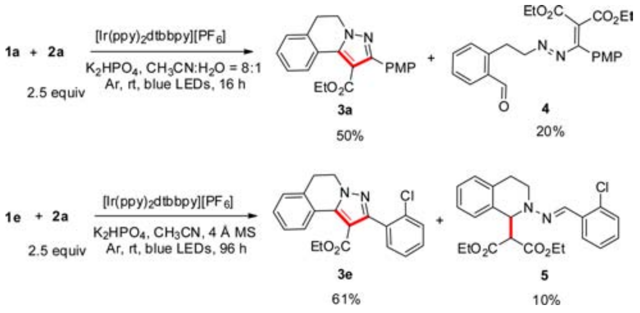
[a] Reaction conditions: hydrazone **1** (0.2 mmol), diethyl 2-bromomalonate **2a** (0.5 mmol, 2.5 equiv), anhydrous K_2HPO_4 (0.6 mmol, 3 equiv), photocatalyst **I** (0.002 mmol, 1.0 mol %), anhydrous CH_3CN (2 mL), 4 Å MS (100 mg), argon atmosphere, 5 W blue LED irradiation at room temperature. The reaction time varied from 16 to 100 h. All yields were based on isolated products.

Scheme 3. Reactions of Hydrazone 1a with Bromides 2b−f



Scheme 4. When annulation of hydrazone **1a** with bromide **2a** was carried out in wet acetonitrile, the desired product **3a** was isolated in 50% yield together with 20% yield of aldehyde **4**. Aldehyde **4** was supposed to be generated from hydrolysis followed by oxidation of hydrazinium salt **10a** (vide infra). The existence of hydrazinium ion could be further supported by the formation of the oxidative coupling product **5** during the reaction of **1e** and **2a**.

Scheme 4. Control Experiments



On the basis of the results of control experiments and our previous works,[12] a plausible mechanism is suggested in Scheme 5. The reaction starts from oxidative quenching of the excited stated photocatalyst Ir(III)* by bromide **2a** to give radical **6** and Ir(IV).[2b] Addition of the radical **6** onto hydrazone **1a** affords nitrogen-centered radical **7**,[12c,13a] which is oxidized by Ir(IV) to close the first photocatalytic cycle and generate hydrazinium ion **8**. Deprotonation of **8** provides hydrazone **9**, which serves as a reductive quencher to initiate the second photocatalytic cycle. Photoxidation of hydrazone **9** gives hydrazinium ion **10** with bromide **2a** via a reductive quenching cycle. The hydrazinium ion **10** exists as two equilibrium species **10a** and **10b**. When water is introduced into the reaction mixture, hydrazinium **10a** can be hydrolyzed followed by oxidation to give aldehyde **4**, as we observed. Hydrazinium ion **10b** can undergo intramolecular Mannich reaction to produce dihydropyrazole **12**.[12a] The key intermediates hydrazone **9** and dihydropyrazole **12** could be observed in high-resolution mass spectrometry (for details, see the Supporting Information). Decarboxylation of dihydropyrazole **12** gives dihydropyrazole **13**, which acts as a reductive quencher to initiate the third photocatalytic cycle. Dihydropyrazole **13** is photochemically oxidized with bromide **2a** to give compound **14**.[13b,c] Ultimately, deprotonation of **14** gives the final product **3a**.

In summary, we have developed a relay visible-light photoredox catalysis strategy. By employing this strategy, formal [4 + 1] annulation of hydrazones with 2-bromo-1,3-dicarbonyl compounds can be achieved to give pyrazole derivatives in a step-economical manner with high efficiency under mild conditions. Three discrete photocatalytic cycles (one oxidative quenching cycle and two reductive quenching cycles) cooperate to accomplish this goal. We believe this relay visible-light photoredox catalysis strategy can enable more novel reaction modes, which are to be investigated in our laboratories.

■ ASSOCIATED CONTENT

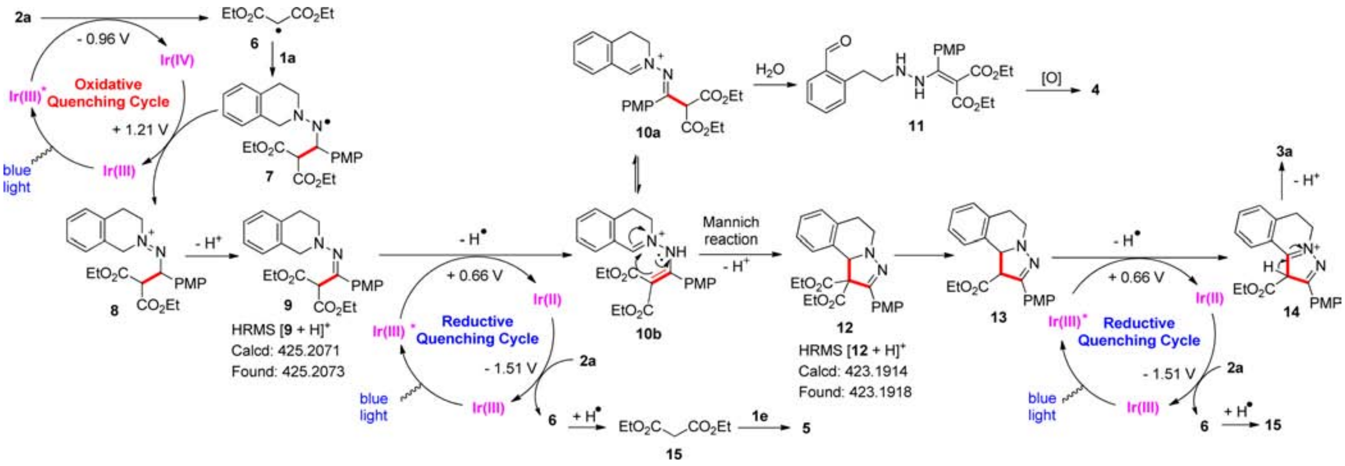
Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03497.

Characterization data for all of the new products (PDF)

X-ray crystal data of **3p** (CIF)

Scheme 5. Proposed Mechanism



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Notes

The authors declare no competing financial interest.

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