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Intramolecular Reductive Cyclization of *o*-Nitroarenes via Biradical Recombination

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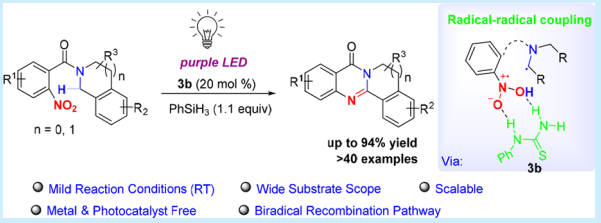
Supporting Information

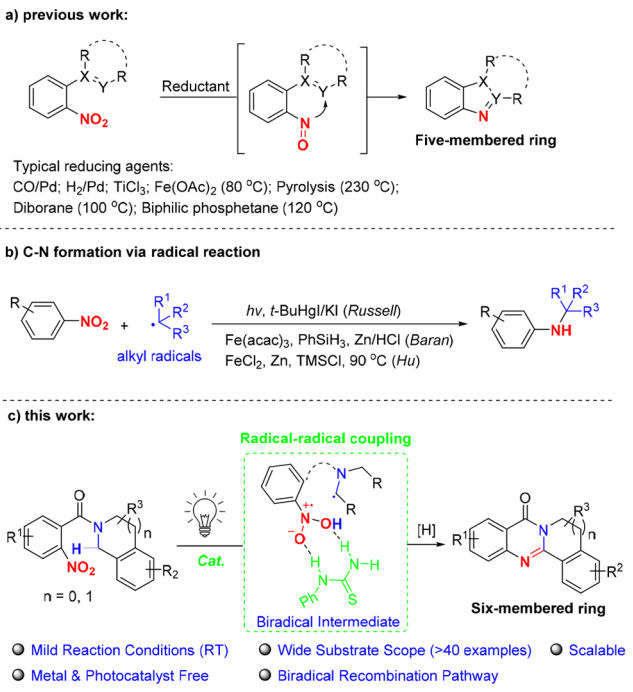
ABSTRACT: A visible-light-induced/thiourea-mediated intramolecular cyclization of *o*-nitroarenes under mild conditions is realized for the first time, which provides an efficient and environmentally friendly way to access pharmaceutical relevant quinazolinone derivatives. The reaction can be easily extended to gram level by using a continuous-flow setup with high efficiency. Mechanistic investigation including control experiments, transient fluorescence, UV−vis spectra, and DFT calculations suggests that the formation of active biradical intermediates via intramolecular single electron transfer (SET) is key stage in the catalytic cycle.



The development of catalytic methods for direct conversion of the nitro group into other functional groups has received a lot of attention from the synthesis community.[1] The nitroarenes are the desired building blocks for this transformation due to their widespread availability and appealing synthetic diversities.[2,3] Since the initial discovery by Reissert[4] (named as Reissert indole synthesis), a variety of useful strategies have been developed for the reductive cyclization of o-functionalized nitroarenes to construct N-containing heterocycles such as indoles[5−8] and carbazoles,[9] which are important structural units in both natural products and synthetic pharmaceuticals.[10] Generally, these transformations could be accomplished by using stoichiometric quantities of a reductant (such as zinc dust,[3] Grignard reagent,[5] phosphite,[6] [Mo-$(CO)_6$],[7] $TiCl_3$,[8a] CO/Pd,[8b,c] or diborane[8d]), which convert the nitro group into reactive nitrogen species (Scheme 1a). Very recently, the biphilic phosphetane and iron phenanthroline complexes were demonstrated as efficient oxygen-atom transfer catalysts for the reductive cyclization of *o*-nitroarenes by the Radosevich group[11] and the Driver group,[12] respectively. However, despite the great progress that has been made in this field, there are still some limitations (e.g., five-membered *N*-heterocycles were generally built, stoichiometric amounts of reductant, specialized reactors, high pressures of CO, high temperatures, or toxic reagents), which disfavor the use of these transformations, particularly on a large scale. Consequently, the development of efficient, scalable, facile, and environmentally friendly methods for this transformation is still highly desirable.

Visible-light-induced photochemistry has undergone a dramatic development over the past decade.[13] As a photosensitive protecting group, the *o*-nitrobenzyl compounds are also widely exploited in photoimaging and biochemistry,[14] but there are only limited examples in organic synthesis by using their photorearrangement.[15] Additionally, previous reports

Scheme 1. Intramolecular Cyclization of *o*-Nitroarene Derivatives



have already shown that alkyl radicals can react readily with nitroarenes.[16] Russell and co-workers have demonstrated that the photoinduced *tert*-butyl radicals could react with both nitroarenes and nitrosoarenes to generate N-alkylated prod-

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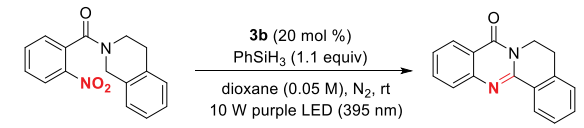
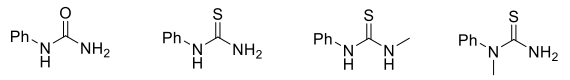
ucts. Recently, Baran and Hu reported the iron-catalyzed hydroamination and reductive coupling approach to synthesize aryl amines from nitroarenes using simple olefins and alkyl halides as the radical sources, respectively (Scheme 1b). Considering the biradical species were proposed as intermediates in the photochemistry of *o*-nitrobenzyl compounds,[17] we speculated that reasonable substrate design combined with the suitable photochemistry reaction conditions (under visible-light irradiation) would enable the intramolecular reductive cyclization of *o*-nitroarene via biradical recombination. Herein, we report the first metal-free visible-light-induced/thiourea-mediated intramolecular reductive cyclization of *o*-nitroarenes to synthesize a series of polycyclic quinazolinone derivatives[18] without external photocatalysts (Scheme 1c). In addition, the reaction can be easily scaled up by using a continuous-flow system under mild conditions.

In general, in the primary photorearrangement, the irradiation of *o*-nitrobenzyl compounds with intramolecular 1,5-HAT (HAT = hydrogen atom transfer) will generate the *aci*-nitro tautomers, which have strong absorption around 400 nm. To start our investigation, the purple LED (395 nm) was chosen as the light source, as well as *o*-nitrobenzamide **1a** as the standard substrate, for optimization studies. Initial screening revealed that the best results were obtained by using a catalytic amount of phenylthiourea as catalyst with 1.1 equiv of $PhSiH_3$ as a terminal reductant in dry 1,4-dioxane under purple LED (395 nm) irradiation at room temperature (for more details, see SI, Tables S1–S4). Under these optimized conditions, the quinazolinone **2a** was obtained in 94% yield (Table 1, entry 1). The use of both phenylthiourea and $PhSiH_3$ was critical for achieving high yields, and only 24% and 48% of **2a** were obtained in the absence of phenylthiourea or $PhSiH_3$, respectively (Table 1, entries 2–3). The solvents have a great influence on the reaction, and only trace products were obtained in DMF and alcohol, which were commonly used in reductive coupling reaction by using a nitro group as the nitrogen source (Table 1, entry 4).[3a,16b] Among the thioureas and silanes screened, phenylthiourea and $PhSiH_3$ proved to be the most effective at facilitating transformation (Table 1, entries 5–9; for more detail, see SI). The yield of **2a** decreased to 71% with reducing the amount of $PhSiH_3$ to 0.5 equiv (Table 1, entry 10). The reaction of **1a** under air atmosphere only leading to **2a** in 33% yield indicated that the reaction was sensitive to oxygen and water (Table 1, entry 11). Finally, no product was detected for the control experiment in the dark, indicating that the light was essential for this reaction (Table 1, entry 12).

With optimal conditions in hand, we investigated the generality of this protocol. As shown in Scheme 2, a broad

Table 1. Optimization of Reaction Conditions[a]

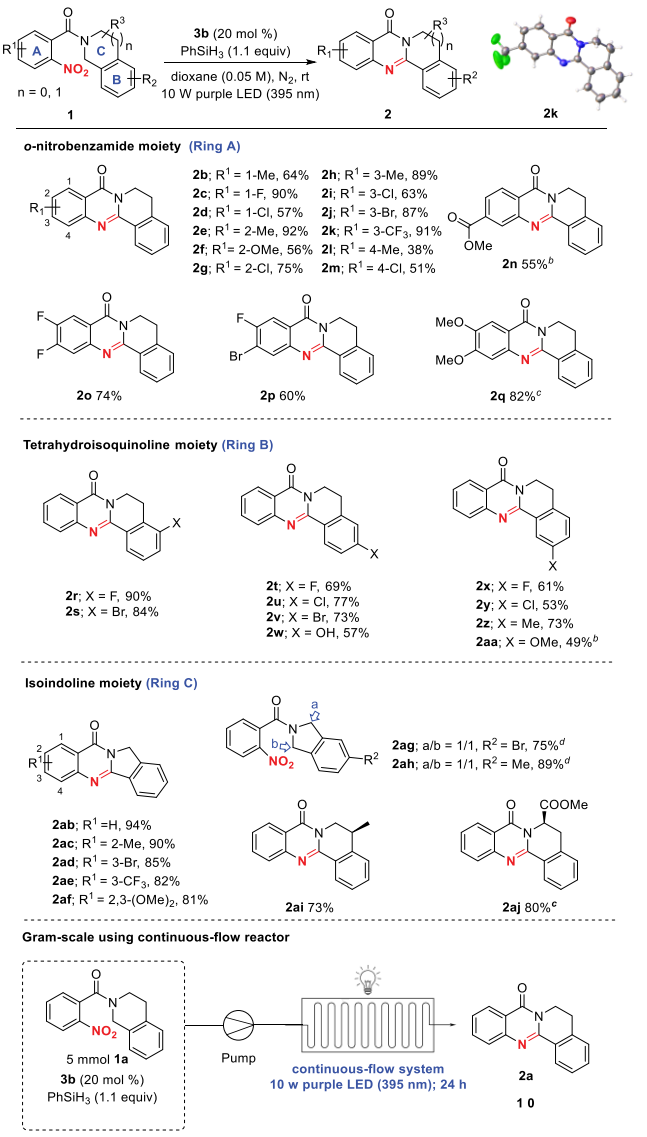




entry	variation from the "standard conditions"	yield[b] (%)
1	none	94
2	without phenylthiourea	24
3	without $PhSiH_3$	48
4	DMF or EtOH instead of dioxane	trace
5	**3a** instead of **3b**	31
6	**3c** instead of **3b**	59
7	**3d** instead of **3b**	72
8	$HSi(Et)_3$ instead of $PhSiH_3$	51
9	$HSi(OMe)_3$ instead of $PhSiH_3$	64
10	0.5 equiv $PhSiH_3$	71
11	under air	33
12	without light	NR

[a]Reactions were performed on a 0.05 mmol scale in dry 1,4-dioxane (1.0 mL) at rt for 24 h under nitrogen. [b]Isolated yield. NR = no reaction.

Scheme 2. Scope of *o*-Nitrobenzamide Compounds[a]



[a]Reaction condition: phenylthiourea **3b** (20 mol %), $PhSiH_3$ (1.1 equiv), and **1a** (0.05 mmol) in dry 1,4-dioxane (1.0 mL) under 10 W purple LED (395 nm) at rt for 24 h. Isolated yield. [b]Reaction time was 36 h. [c]Reaction time was 12 h. [d]Isolated combined yields. Isomer ratios were determined by analysis of the ^1H NMR spectra of isolated products.

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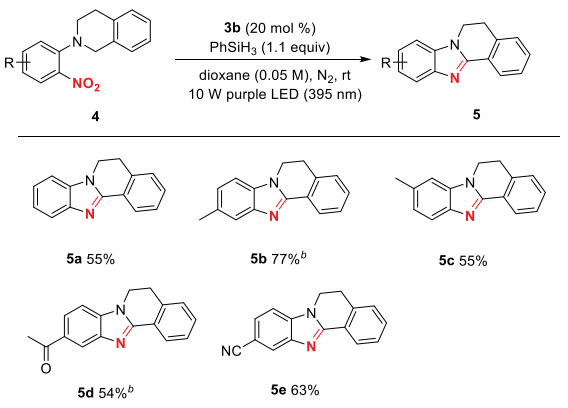
range of *o*-nitrobenzamides participated in the reaction, affording a series of polycyclic quinazolinone derivatives in good to high yields (up to 94% yield, **2b**–**2aj**). The results indicated this method is insensitive to electronics of the substituents on the *o*-nitroarene moiety, and both electron-donating and electron-withdrawing groups, as well as electro-neutral groups, at different positions of benzene ring A were well tolerated in the reaction (**2b**–**2q**), although substrates with substituents at the 4-position generally gave lower yields in some cases (**2l** and **2m**). The substrates **2o**, **2p**, and **2q** with disubstituted phenyl groups (ring A) underwent the reductive cyclization smoothly to afford the corresponding quinazolinones in high yields. Similarly, benzene ring B of the tetrahydroisoquinoline moiety bearing various electronic properties in different position was also compatible in the reaction (49–90% yields **2r**–**2aa**). To our delight, it was found that the isoindoline (ring C) derivatives with a range of electronically diverse aryl groups were also tolerable and showed high efficiency in the transformation (75–94% yields of **2ab**–**2ah**). Moreover, the substrates with methyl or ester group substituted on ring C performed well, delivering the corresponding products **2ai** and **2aj** with good outcomes, respectively. To further demonstrate the synthetic utility of this method, a simple continuous-flow setup was assembled for the scale up to the gram scale, which has potential application in industry (**2a**, 80% yield, 1.0 g/24 h). After investigating the scope of *o*-nitrobenzamides, the reaction was next explored to varieties of *o*-nitroaniline compounds (Scheme 3). Under the

Scheme 3. Scope of *o*-Nitroaniline Compounds[a]

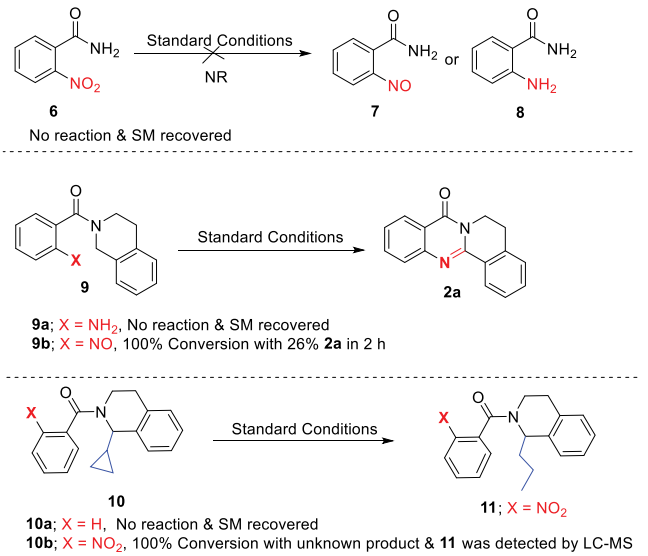


[a]Reaction conditions: Phenylthiourea **3b** (20 mol %), $PhSiH_3$ (1.1 equiv), and **1a** (0.05 mmol) in dry 1,4-dioxane (1.0 mL) under 10 W purple LED (395 nm) at rt for 12 h. Isolated yield. [b]Reaction time was 48 h.

optimal conditions, the corresponding tetracyclic imidazole products **5a**–**5e** were observed with moderate to good yields. All of these results showed that this transformation exhibited excellent functional group tolerance, and the reactive groups such as halides, ketone, ester, hydroxy, and cyano groups do not affect the outcomes.

To identify the mechanism of the reaction, several control experiments were performed (Scheme 4). First, the *o*-nitrobenzamide **6** was subjected to the standard conditions, and no reduction products **7** or **8** were detected with almost all starting material **6** recovered, suggesting that silane cannot directly reduce the nitro group under the optimal conditions. Moreover, no cyclization product **2a** was obtained for the

Scheme 4. Control Experiments[a]



[a]Reaction condition: phenylthiourea **3b** (20 mol %), $PhSiH_3$ (1.1 equiv), and **1a** (0.05 mmol) in dry 1,4-dioxane (1.0 mL) under 10 W purple LED (395 nm) at rt for 12 h. Isolated yield. SM = starting material

aniline **9a** treated with the standard conditions, and only 26% yield of **2a** was given in 2 h for *o*-nitrosoarene **9b**. Thus, direct cyclization of *in situ* formed active aniline or *o*-nitrosoarene can be ruled out as the main reaction pathway. Notably, compared to no reaction of **10a** (X = H), 100% conversion of starting material was observed but without cyclization product, when the *o*-nitroarenes **10b** (X = NO_2) bearing a cyclopropyl moiety (radical clock) were utilized under the optimal conditions. The ring-opened product **11** (X = NO_2) was detected by LC-MS analysis, supporting the involvement of biradical intermediate in the reaction. Furthermore, the reaction of **1a** with *N*-methyl-substituted phenylthiourea such as **3c** and **3d** gave the cyclization product only in lower yield, indicating that both NH group and NH_2 group of the phenylthiourea were essential for this transformation, which might help stabilize the photoactive biradical intermediate via hydrogen-bonding interaction (for more details, see SI, Table S5).

To further understand the mechanism of the reaction, transient fluorescence and UV–vis spectra,[19] as well as DFT calculation, were performed (for more details, see SI). A triplet biradical intermediate **IV** was located at the UB3LYP-D3(BJ)(PCM, 1,4-dioxane)/def2-SVP theoretical level, and the corresponding SOMOs with unpaired electrons were visualized in Figure 2. According to the Salem rules, these two SOMOs with different orientation could interact rapidly to form a C–N bond. On the basis of the experimental results, DFT calculations, and previous reports,[17e] we envisioned that the cyclization might undergo the biradical recombination pathway (Figure 1): first, the irradiation of *o*-nitrobenzamide **1a** with internal 1,7-HAT generates the *aci*-nitro tautomer intermediate **I**, in which the ground state reactant **1a** was first excited to triple state **I** with high reactivity. The energy barrier in this step was predicted to be 3.7 kcal/mol, indicating that this process was facile to occur. Sequentially, the thiourea interacted with intermediate **II** by hydrogen bonding, forming a molecular complex intermediate **III**. This step was exothermic by 62.7 kcal/mol, suggesting that the thiourea

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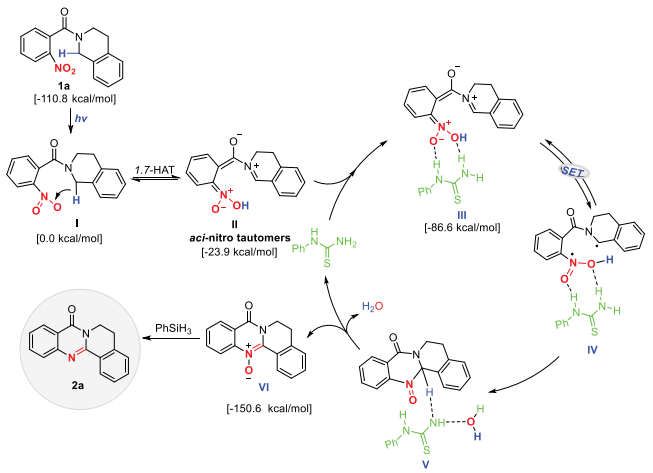

Figure 1. Proposed mechanism.

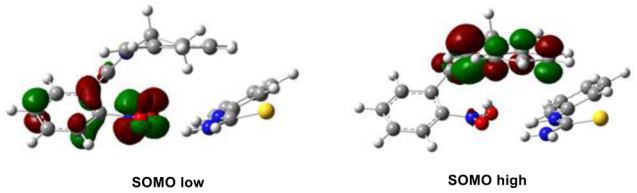

Figure 2. Visualization of the frontier orbitals (SOMOs) in triplet biradical intermediate **IV** (isovalue = 0.04).

would stabilize intermediate **II**. The photoactive intermediate **III** undergoes intramolecular single electron transfer (SET) to form triplet-phased biradical intermediate **IV** (Figure 1). Then, formation of H_2O and recombination of the radical pair ensure the C−N formation, accompanied with the construction of a six-membered ring intermediate **V**. The basic N atom in thiourea abstracted the H atom from **V**, affording intermediate **VI**.[20] Finally, the quinazolinone product **2a** was obtained via reduction of the resulting intermediate **VI** in the presence of $PhSiH_3$.

In conclusion, we established intramolecular reductive cyclization of *o*-nitroarenes for the synthesis of useful quinazolinone derivatives with visible light, thiourea, and terminal reductant silane. Mild reaction conditions, broad substrate scope, and facile procedure show the potential for the practical synthesis. Moreover, the reaction can be easily scaled up when combined with flow chemistry. Mechanistic studies suggested that the reaction undergoes a biradical recombination pathway. Further application of this novel strategy in intermolecular reactions is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00191.

General procedures, analytical data, NMR spectra, and DFT calculation data (PDF)

Accession Codes

CCDC 1888418 and 1888420 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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