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Letter

Synthesis of Indolyl Phenyl Diketones through Visible-Light-Promoted Ni-Catalyzed Intramolecular Cyclization/Oxidation Sequence of Ynones

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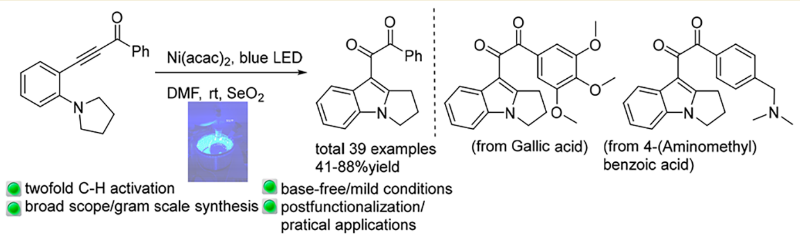
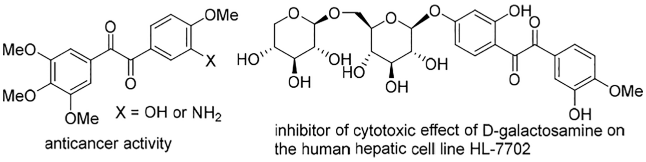


ABSTRACT: The combination of visible light catalysis and Ni catalysis has enabled the synthesis of indolyl phenyl diketones through the cyclization/oxidation process of ynones. This reaction proceeded under mild and base-free conditions and showed a broad scope and feasibility for gram-scale synthesis. Several natural products and biologically interesting molecules could be readily postfunctionalized by this method.

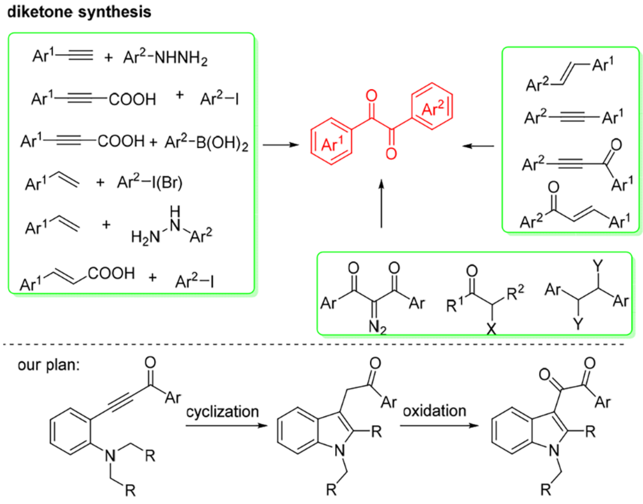
KEYWORDS: *diketones, photocatalysis, Csp^3−H bond functionalization, ynones, nickel, cyclization*

Aryl diketones, also called benzyls, are versatile synthetic intermediates in the synthesis of *N*-containing heterocycles[1] and relevant compounds.[2] They are ubiquitous subunits of natural products and biologically active molecules.[3] For example, benzyls (Scheme 1, left) exhibited excellent antiproliferative activity on a nanomolar scale on four human tumor cell lines. There are three existing routes (Scheme 2) for the synthesis of diketones: (1) the oxidation of unsaturated motifs, such as alkynes, alkenes, ynones, and enones;[4] (2) the coupling of unsaturated components with electrophiles (or nucleophiles);[5] and (3) others, which include oxidation of diazo compounds, *α*-ketones, and alcohols (or halides).[6] The main limitation of these methodologies is the requirement of the substituents present on diketones to be preinstalled on the starting material, itself. To increase the molecule complexity, it is highly desirable to realize simultaneous generation of substituents during diketone formation. With our continuous endeavors on ynone conversions,[7] we envisioned that the

Scheme 1. Biologically Active Molecules with Diketone Structure



Scheme 2. State of the Art on Synthesis of Diketones and Our Plan



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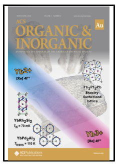

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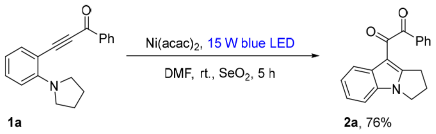
Table 1. Reaction Conditions Optimization[a]



entry	change from the standard conditions	yield (%)[b]
1	none	76
2	$NiCl_2(PPh_3)_2$ instead of $Ni(acac)_2$	trace
3	$Ni(cod)_2$ instead of $Ni(acac)_2$	40
4	$NiCl_2[P(CH_3)_3]_2$ instead of $Ni(acac)_2$	28
5	$Ni(dppf)Cl_2$ instead of $Ni(acac)_2$	trace
6	$Ni(PPh_3)_4$ instead of $Ni(acac)_2$	trace
7	$NiCl_2$ instead of $Ni(acac)_2$	trace
8	254 nm UV instead of blue LED	trace
9	365 nm UV instead of blue LED	trace
10	filament lamp instead of blue LED	trace
11	DMSO instead of DMF	no reaction
12	*o*-xylene instead of DMF	29
13	THF instead of DMF	50
14	dioxane instead of DMF	trace
15	EtOAc instead of DMF	16
16	DCE instead of DMF	trace
17	air instead of SeO_2	49
18	$CuCl_2$ instead of SeO_2	
19	$Cu(OAc)_2$ instead of SeO_2	20
20	BQ instead of SeO_2	
21	MnO_2 instead of SeO_2	
22	*m*-CPBA instead of SeO_2	
23	BPO instead of SeO_2	15
24	*t*-BuOOH instead of SeO_2	
25	AgOAc instead of SeO_2	30

[a] Ynone **1a** (0.2 mmol, 1.0 equiv) and catalyst (0.02 mmol, 10 mol %) in solvent (2 mL) under irradiation using light source with oxidant (0.3 mmol, 1.5 equiv) at room temperature for 5 h. [b] Isolated yield.

cyclization of tertiary amine-substituted ynone through Csp^3-H bond functionalization[8,9] and subsequent oxidation would provide indolyl- and phenyl-substituted diketones. Toward this goal, herein, a visible-light-induced Ni-catalyzed strategy[10] for the synthesis of indolyl[11] phenyl diketones through double Csp^3−H bond functionalization under base-free and mild conditions has been disclosed.

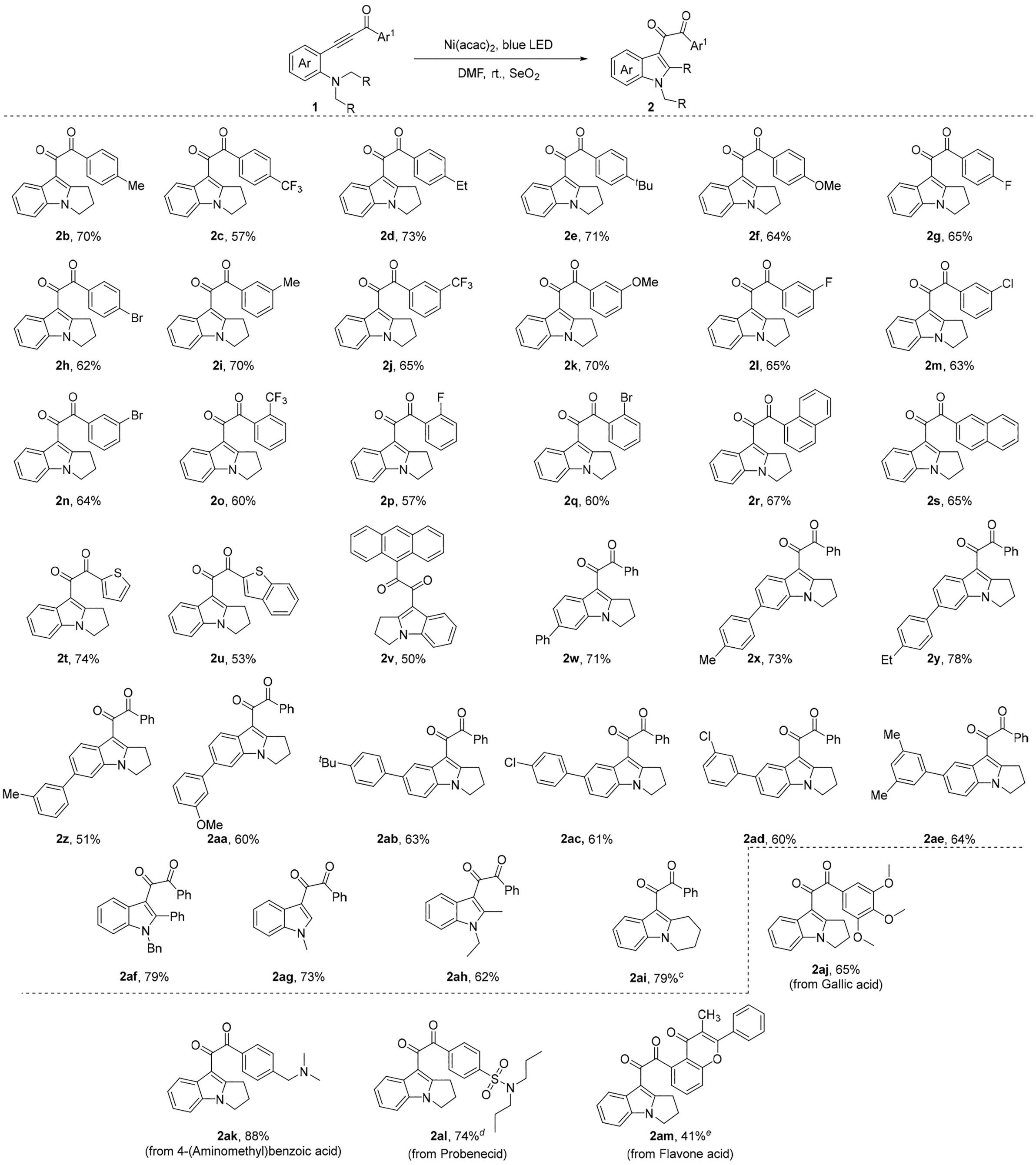
Initially, **1a** was used as the model substrate. After extensively studying a series of reaction parameters, phenyl indolyl dione product **2a** was obtained in 76% yield when 10 mol % of Ni(acac)$_2$ was used as the catalyst and SeO$_2$ (1.5 equiv) was used as the oxidant in DMF with irradiation of a 15 W blue LED lamp (464 nm) for 5 h (Table 1). The screening of different nickel catalysts showed that the expected product could be formed in decent yields only with Ni(cod)$_2$ or NiCl$_2$[P(CH$_3$)$_3$]$_2$, whereas other Ni catalysts failed (entries 2−7). Irradiation with a 254 nm UV, 365 nm UV, or filament lamp as the light source provided only trace yields of the product (entries 8−10). Next, a range of solvents were screened (entries 11−16). The expected cyclization could proceed in EtOAc, *o*-xylene, and THF to produce **2a** in 16%, 29%, and 50% yields, respectively. Next, a series of commonly used oxidants was tested (entries 17−25). With air, Cu(OAc)$_2$, BPO, or AgOAc as the oxidant, **2a** was produced in 15−49% yields, whereas other oxidants failed to give the product.

After the establishment of optimal reaction conditions, the scope of various substituted ynones with a pyrrolidinyl group for the cyclization reaction was tested (Scheme 3). Ynones with substituents on both the benzoyl group and aniline smoothly underwent the expected diketone formation reaction and assembled into the corresponding products in 51−78% yields. Functional groups, such alkyl (**2b−e**, **2i**), highly useful halides (**2g,h**; **2l−n**; **2p,q**), methoxyl (**2f**, **2k**), and CF$_3$ (**2c**, **2j**, **2o**) on the benzoyl group, were well tolerated and afforded the desired products in moderate to good yields. In general, the cyclization−oxidation reaction was not sensitive to the electronic nature of the substituent. In addition, ynones bearing naphthyl group provided the desired products (**2r**, **2s**) in 65−67% yields. Moreover, ynones containing heterocycles, such as thiophenyl and benzothiophenyl rings, furnished the corresponding diketones (**2t**, **2u**) in 53−74% yields. To our delight, a ynone bearing an anthracene group produced the corresponding diketone (**2v**) in 50% yield. In addition, ynones derived from aryl-substituted anilines delivered the cyclized products in 51−78% yields (**2w−ae**). This diketone formation reaction could be extended to benzyl, methyl, ethyl, and piperidinyl-substituted ynones, which generate corresponding products in 62−79% yields (**2af−i**). Importantly, natural products and biologically interesting molecules-derived ynones smoothly undertook the cyclization/oxidation sequence to provide envisioned products in 41−88% yields (**2aj−m**), thereby demonstrating the postfunctionalization capability of this approach.

The synthetic application of this methodology was demonstrated by the gram-scale synthesis and selective transformations of adducts (Scheme 4). When the model reaction was scaled up to 6.0 mmol with a diluted concentration and prolonged reaction time, **2a** was produced in 63% yield (1.1 g). The selective 1,2-addition between **2a** and PhMgBr proceeded to give **3** in a 69% yield. After condensation between **2a** and 1,2-diaminobenzene in MeOH at 80 °C for 12 h, quinoxaline product **4** was afforded in excellent yield. The hydrazone formation reaction between **2a** and phenylhydrazine readily gave **5** in a 74% yield. By the employment of a classic Pd(0) catalytic system, the coupling between **2q** and phenylboronic acid afforded product **6** in an 84% yield. The structures of **3** and **5** were established by X-ray crystallography.

Next, some preliminary investigations were conducted to study the reaction mechanism (Scheme 5). First, the UV−vis absorbance spectra of **1a**, Ni(acac)$_2$, and SeO$_2$ in MeOH were recorded, wherein **1a** showed strong absorption in the visible light region. When the reaction was conducted in dark, the starting material was recovered with no formation of the desired product. This demonstrated the key role of light irradiation in this reaction. In the presence of radical scavengers (4.0 equiv), the efficiency of reactions dropped dramatically, which suggests that a radical process should be involved in this reaction. Intermediate **G** was isolated from the reaction mixture, which was treated with standard conditions to give **2a** in 83% yield. In addition, the ON/OFF experiment showed that continuous irradiation was essential for this transformation, and a radical chain process was unlikely to be involved. Furthermore, Stern−Volmer luminescence quenching experiments (see the Supporting Information) indicated that ynone and Ni(acac)$_2$ might form a metal complex through coordination. Next, irradiation of a mixture of **1a**, Ni(acac)$_2$, and SeO$_2$ in DMF with blue LEDs for 5 min with 5,5-

Scheme 3. Scope of Diketone Formation[a,b]

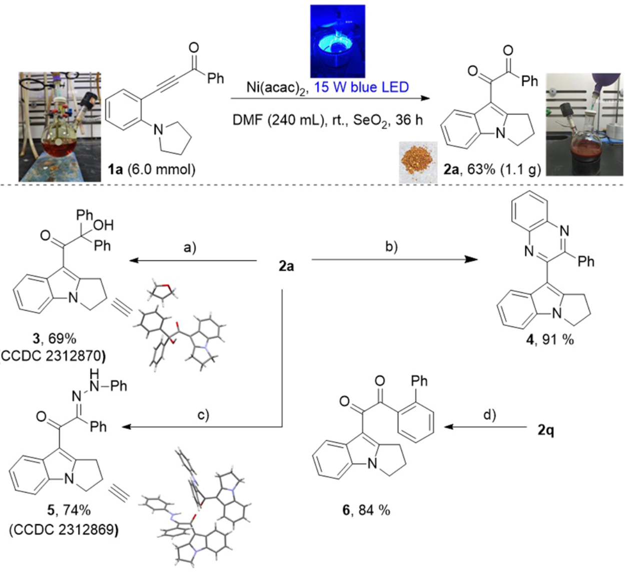


[a]Ynone **1** (0.2 mmol, 1 equiv), Ni(acac)$_2$ (0.02 mmol, 10 mol %), and SeO$_2$ (0.3 mmol, 1.5 equiv) in DMF (2 mL) under irradiation using 15 W blue LED at room temperature for 5 h. [b]Isolated yield. [c]Ni(acac)$_2$ (20 mol %), SeO$_2$ (6.0 equiv), 24 h. [d]Reacted at 40 °C for 12 h. [e]Twenty-four hours.

dimethyl-pyrroline *N*-oxide (DMPO) as radical spin-trapping agent displayed EPR signals, which could be assigned to carbon radical adduct **C**-DMPO (see the Supporting Information). We then envisioned a possible reaction mechanism on the basis of these results and previous reports.[9,10] Compound **1a** and Ni(acac)$_2$ form intermediate **A** through coordination. Under photo irradiation, **A** is converted into diradical intermediate **B** by releasing Ni(acac)$_2$.[12] The intramolecular 1,8-HAT[13,14] of **B**[15] gives intermediate **C**, which next coordinates with Ni(acac)$_2$ to offer intermediate **D**. The intramolecular radical addition to triple bond on **D** produces adjacent diradicals intermediate **E**. Then, **E** tautomerizes to allene intermediate **F**, which further undertakes [1,3]-hydride transfer and isomerization to access intermediate **G**. After tautomerization, **G** is transformed into enol intermediate **H**, which is then oxidized by SeO$_2$ to give diketone product.[16]

This is the first report on photoinduced Ni-catalyzed synthesis of indolyl phenyl diketones from ynones via twin Csp^3−H bond functionalizations. This transformation proceeded smoothly under mild and base-free conditions to produce a wide range of indolyl phenyl diketones in moderate

Scheme 4. Synthetic Applications[a]



[a]Reaction conditions: (a) **2a** (0.2 mmol, 1.0 equiv) and PhMgBr (0.6 mmol, 3.0 equiv) in THF (2 mL) under Ar at −78 °C to room temperature for 12 h; (b) **2a** (0.2 mmol, 1.0 equiv) and 1,2-diaminobenzene (0.4 mmol, 2.0 equiv) in MeOH (2 mL) under Ar at 80 °C for 12 h; (c) **2a** (0.2 mmol, 1.0 equiv), phenylhydrazine (0.3 mmol, 1.5 equiv), and HOAc (0.1 mmol, 50 mol %) in EtOH (2 mL) under Ar at 90 °C for 18 h; (d) **2q** (0.2 mmol, 1.0 equiv), phenylboronic acid (0.2 mmol, 1.0 equiv), Pd(PPh$_3$)$_4$ (0.004 mmol, 2 mol %), and Na$_2$CO$_3$ (0.62 mmol, 3.1 equiv) in toluene/MeOH (3/2, 3 mL) under Ar at 90 °C for 12 h.

to good yields. Preliminary mechanistic studies indicated that a radical process could be involved in this reaction and that photoirradiation was an indispensable factor for the success of this conversion. Various derivatizations of the coupled product were conducted, which demonstrated the potential synthetic applications. Detailed mechanistic studies are ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

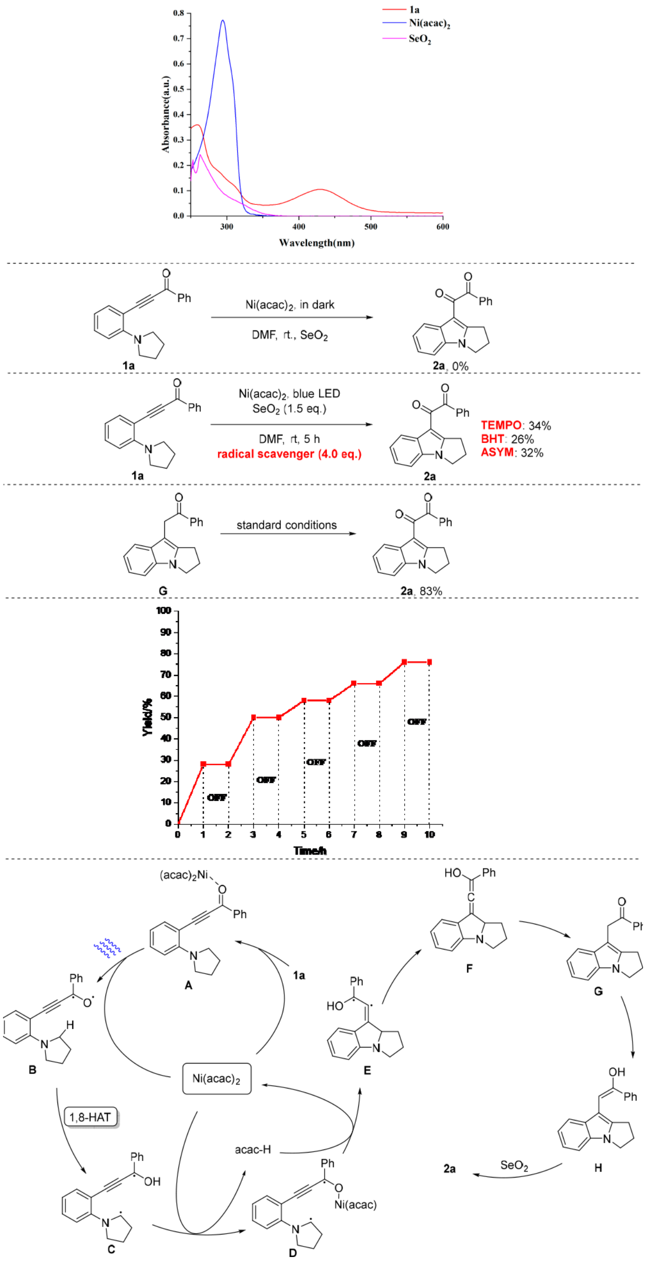
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.3c00060.

General information; materials; general procedure for the synthesis of derivatives **1a**−**1am**; purification and characterization of derivatives **1a**−**1am**; procedure for the synthesis of derivatives **2a**−**2am**; procedure for the gram synthesis of **2a**; procedures for the synthesis of compounds **3**−**6**, as well as their purification and characterization; procedures for control experiments; NMR spectra of **1a**−**1am**; NMR spectra of **2a**−**2am**; and NMR spectra of derivatives **3**−**6** and **G** (PDF)

Accession Codes

CCDC 2312869−2312870 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

Scheme 5. Investigation of the Reaction Mechanism



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Author Contributions

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Notes

The authors declare no competing financial interest.

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