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Direct Synthesis of 2,3-Diaroyl Quinolines and Pyridazino[4,5-*b*]quinolines via an I_2-Promoted One-Pot Multicomponent Reaction

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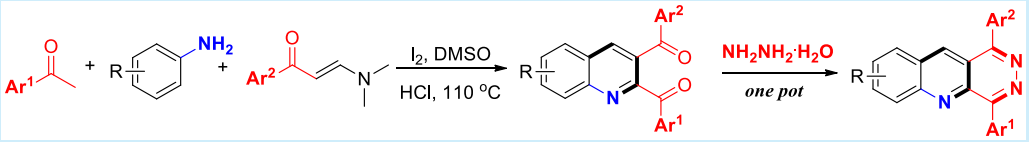
Supporting Information



ABSTRACT: The first synthesis of 2,3-diaroyl quinolines via a formal [3 + 2 + 1] cycloaddition of enaminones, aryl methyl ketones, and aryl amines is disclosed. This reaction efficiently affords a 1,4-dicarbonyl scaffold, which is a useful building block for constructing complex fused heterocycles. Furthermore, the 1,4-dicarbonyl scaffold has been used directly to prepare pyridazino[4,5-*b*]quinoline skeletons in one-pot.

The 1,4-Dicarbonyl compounds are readily available and versatile building blocks that can be used to prepare carbocyclic and heterocyclic compounds,[1] and many convenient and efficient methods for their synthesis have been developed. Currently, typical methods for preparing 1,4-dicarbonyl compounds can be mainly summarized into six categories: (i) conjugate additions of in situ-generated acyl radicals or acyl anions to Michael acceptors;[2] (ii) chain extensions of 1,3-dicarbonyls;[3] (iii) oxidative couplings of enolates;[4] (iv) additions of homoenolate equivalents to electrophilic acyl derivatives;[5] (v) nucleophilic substitutions of α-haloketones with highly reactive enolates;[6] and (vi) enolate heterocouplings[7] (Scheme 1). Despite recent significant advances in the construction of chain 1,4-dicarbonyl scaffolds, the direct synthesis of cyclic or heterocyclic 1,4-dicarbonyl compounds, such as quinoline skeletons containing 1,4-dicarbonyl units, has rarely been reported.[8]

Quinolines are privileged aromatic aza-heterocycles widely found in modern pharmaceuticals and natural products. Methods for their synthesis, which include named reactions, have been widely studied.[9,10] Among these elegant methods, the Povarov reaction is among the most effective, enabling the rapid assembly of quinolines via the formal [4 + 2] cycloaddition of electron-poor 2-azadienes to electron-rich dienophiles. Recently, several quinoline syntheses using the Povarov reaction as a key transformation have been reported.[10] However, the latest developments in the Povarov reaction are mainly reflected in the synthesis of quinolines containing only one carbonyl group. To our knowledge, the direct use of two different carbonyl precursors, such as electron-deficient α,β-unsaturated ketones, as starting materials to synthesize quinolines containing 1,4-dicarbonyl units via a Povarov reaction has yet to be reported and remains challenging. Povarov-type reactions have mainly been focused on electron-rich alkene substrates.

Therefore, we envisioned using enaminones as α,β-unsaturated ketone surrogates, through $HNMe_2$ elimination, and as carbonyl precursors simultaneously to prepare quinoline skeletons bearing dicarbonyl units via a Povarov-type reaction. These structures could then be further functionalized to obtain pyridazino[4,5-*b*]quinolines skeletons in one pot (Scheme 1).

Initially, we use aryl methyl ketones (**1a**), *p*-toluidine (**2a**), and enaminone (**3a**) as model substrates in the presence of $CuCl_2$ and I_2 in DMSO at 100 °C afforded (6-methylquinoline-2,3-diyl)bis(phenylmethanone) **4a** in 46% yield (Table 1,

Scheme 1. Synthesis of 1,4-Dicarbonyl Compounds

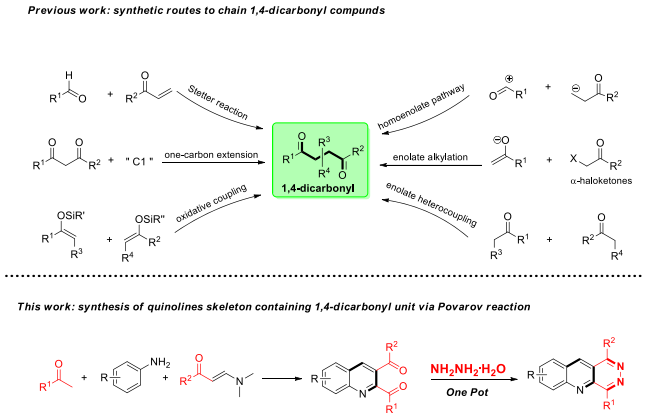


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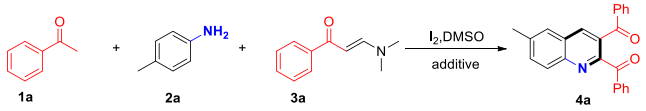
Table 1. Optimization of Reaction Conditions[a]



entry	temp (°C)	I_2 (equiv)	additive	yield[b] (%)
1	100	1.6	$CuCl_2$	46
2	90	1.6	$CuCl_2$	40
3	110	1.6	$CuCl_2$	52
4	120	1.6	$CuCl_2$	50
5	130	1.6	$CuCl_2$	45
6	110	1.0	$CuCl_2$	47
7	110	2.0	$CuCl_2$	50
8	110	2.5	$CuCl_2$	49
9	110	1.6	$ZnCl_2$	55
10	110	1.6	$FeCl_3$	53
11	110	1.6	TFA	68
12	110	1.6	TfOH	65
13	110	1.6	HCl	72
14	110	1.6	HI	62
15	110	1.6		42
16[c]	110	1.6	HCl	70
17[d]	110	1.6	HCl	69
18[e]	110	1.6	HCl	67

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), additive (0.2 mmol), I_2 (1.6 mmol) and DMSO (3.0 mL) within 24 h unless noted. [b]Isolated yields. [c]Hydrochloric acid 1.0 mmol. [d]Hydrochloric acid 1.5 mmol. [e]Hydrochloric acid 2.0 mmol.

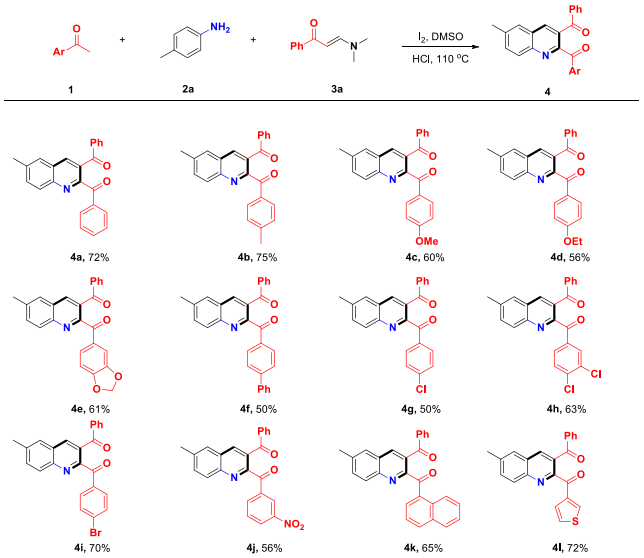
entry 1). Encouraged by the results, we began to screen the reaction conditions to further improve the yield. First, the reaction was screened at a temperature ranging from 90 to 130 °C, and the results showed that the optimum reaction temperature was 110 °C (Table 1, entries 2−5).

Then, different amounts of iodine were screened, finding that 1.6 equiv of iodine has the best effect (Table 1, entries 6−8). Moreover, various Bronsted acids and Lewis acids are screened to increase the yield of the reaction, with hydrochloric acid determined to be the optimal additive (Table 1, entries 9−15). We also tested the amount of hydrochloric acid on the yield of the reaction. The best results were seen with 20 mmol % hydrochloric acid (Table 1, entries 16−18).

After the best reaction conditions were established, we next investigated the scope of this Povarov reaction using a variety of different aryl ketones. To our satisfaction, various acetophenone derivatives were compatible with this reaction under the optimized reaction conditions, providing the desired products in moderate to good yields (Scheme 2). Aryl methyl ketones substituted with electron-donating group and electron-withdrawing group (including methyl, methoxyl, ethoxyl, 3,4-methylenedioxyl, chloro, bromo, and nitro groups) could participate smoothly in this reaction, giving the corresponding products in good yields (**4a**−**4j**, 50%−75%). Notably, sterically hindered substrate 1-naphthyl methyl ketone reacted smoothly in this transformation, furnishing desired product **4k** in 65% yield. Furthermore, 3-acetylthiophene was investigated under the optimized reaction conditions, affording corresponding product **4l** in 72% yield.

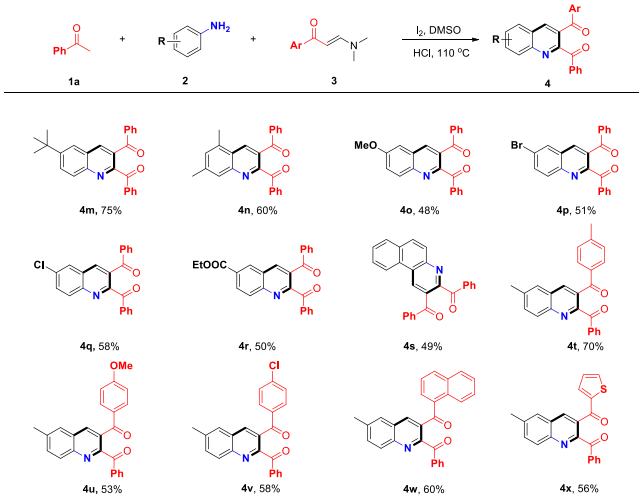
Next, we tested a variety of substituted anilines and enaminones to further extend the reaction scope (Scheme 3). Anilines substituted with electron-rich (4-C$(CH_3)_3$, 3,5-dimethyl, 4-OMe), halogen (4-Cl, 4-Br), and electron-deficient

Scheme 2. Scope of Aryl Methyl Ketone Substrates[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), hydrochloric acid (0.2 mmol), I_2 (1.6 mmol) in DMSO (3.0 mL) at 110 °C for 24 h. [b]Isolated yields.

Scheme 3. Scope of Anilines and Enaminones[a,b]



[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), hydrochloric acid (0.2 mmol), I_2 (1.6 mmol) in DMSO (3.0 mL) at 110 °C for 24 h. [b]Isolated yields.

(4-CO_2Et) were tolerated in this reaction, and the corresponding 2,3-diaroyl quinolines were obtained in moderate yield (**4m**−**4r**, 48%−75%). Notably, 2-naphthylamine was conducted in this reaction, affording desired product **4s** in 49% yield. Furthermore, we investigated the substrate scope of different enaminones in the reaction. Enaminone derivatives bearing different phenyl ring substituents (including 4-Me, 4-OMe, 4-Cl, and 4-Br) performed smoothly in this reaction, and desired products **4t**−**4w** were obtained in 53%−70% yields. A heteroaryl functionalized enaminone was also tolerated in the reaction, affording desired product **4x** in 56% yield. Furthermore, we also tested alkyl reactants, including alkyl ketones, alkyl amines, and alkyl enaminones under the optimized reaction conditions. To our disappointment, alkyl reactants were not compatible with this transformation.

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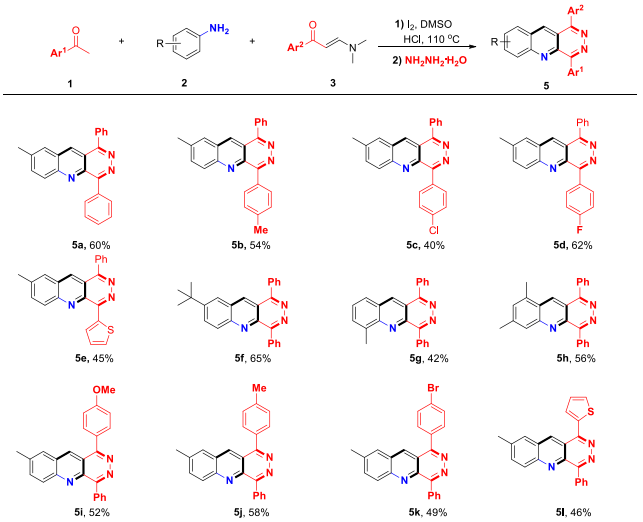
Polycyclic structures containing quinoline skeleton are frequently found in natural products and pharmaceuticals.[11] Therefore, the development of efficient and concise methods for constructing polycyclic heterocycles containing quinoline skeleton in one pot is highly desirable. Note that quinoline skeletons contain 1,4-dicarbonyl units bearing two electrophilic sites, which can serve as useful intermediate for the preparation pyridazine. To our delight, we succeeded in the highly efficient and concise synthesis of various pyridazino[4,5-*b*]quinoline skeletons using this method (Scheme 4). Aryl methyl ketones,

Scheme 4. Synthesis of Various Pyridazino[4,5-*b*]quinoline Skeletons[a,b]

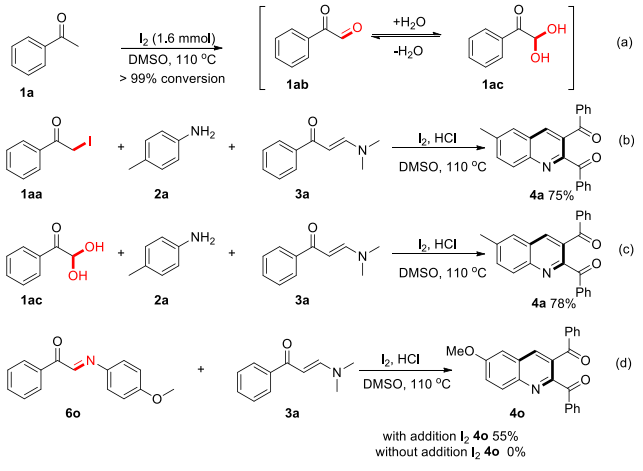


[a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), hydrochloric acid (0.2 mmol), I_2 (1.6 mmol) in DMSO (3.0 mL) at 110 °C for 24 h, and then 10 equiv of hydrazine hydrate was added to the reaction for 10 min. [b]Isolated yields.

anilines, and enaminones attached with different substituents were tolerated in this transformation, and the desired products **5a**−**5l** were obtained in 40%−65% yields.

To further investigate the mechanism of the reaction, some control experiments were conducted (Scheme 5). The phenylglyoxal **1ab** and corresponding hydrated species **1ac** was afforded in quantitative yield by the reaction of

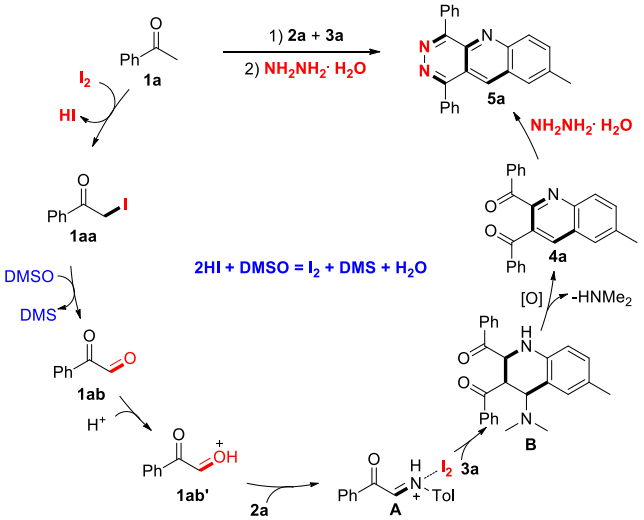
Scheme 5. Control Experiments



acetophenone (**1a**) and iodine in dimethyl sulfoxide (DMSO) at 110 °C (Scheme 5a). Next, the reaction of *α*-iodoacetophenone **1aa**, *p*-toluidine (**2a**), and enaminone (**3a**) under the standard conditions gave **4a** in 75% yield (Scheme 5b). Hydrated species **1ac** also reacted smoothly in this multicomponent reaction, and the **4a** was obtained in 78% yield (Scheme 5c). These results revealed that *α*-iodoacetophenone **1aa** and phenylglyoxal **1ac** were important intermediates for this reaction. Moreover, product **4o** was obtained in 55% yield by the reaction of C-acylimine **6o** and enaminone (**3a**) under optimized reaction conditions. However, this multicomponent reaction did not proceed without the addition of iodine. These results implied that C-acylimine was a key intermediate in this Povarov reaction and indicated that iodine played an important role in the Povarov/oxidation process.

On the basis of the above results and previous studies,[10,12] a plausible mechanism is proposed (Scheme 6). Acetophenone

Scheme 6. Proposed Mechanism



(**1a**) is converted to phenylglyoxal **1ab** with the release of HI and dimethyl sulfide (DMS) via sequential iodination/Kornblum oxidation. Then, intermediate **1ab′** activated by acid is attacked by *p*-toluidine (**2a**), affording iminium ion **A**, which reacts with enaminone (**3a**) to generate intermediate **B**. Finally, **4a** is obtained via elimination of $HNMe_2$ and oxidative aromatization. This quinoline formed in situ contains two activated carbonyl groups that can be further functionalized to afford pyridazino[4,5-*b*]quinoline **5a** via a one-pot, two-step protocol.

In conclusion, we have disclosed a concise protocol for the direct synthesis of 2,3-diaroyl quinolines using a simple carbonyl precursor and aryl amine. This multicomponent reaction enriched the scope of 1,4-dicarbonyl compounds synthesized by the Povarov reaction. Furthermore, the 2,3-diaroyl quinoline generated in situ is endowed with two activated electrophilic sites that can be functionalized to afford pyridazino[4,5-*b*]quinolines in one pot. The application of this method is being further studied in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00685.

Crystal data and structure refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, torsion angles (PDF)

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1866721 contains 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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