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Direct Regioselective Oxidative Cross-Coupling of Indoles with Methyl Ketones: A Novel Route to C3-Dicarbonylation of Indoles

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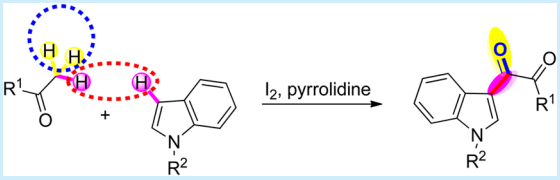
Supporting Information

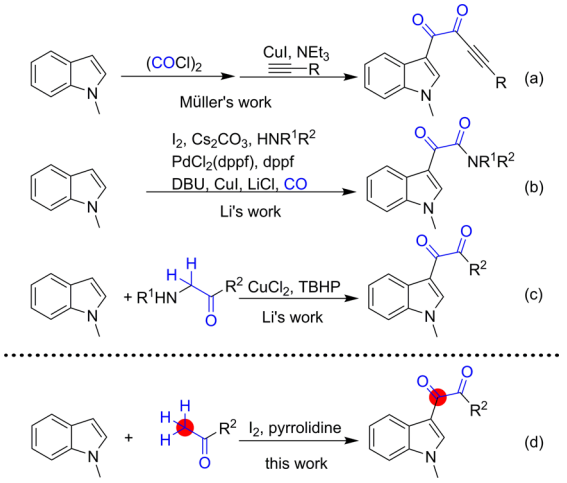
ABSTRACT: The first C3-dicarbonylation of indoles was realized through direct oxidative cross-coupling of indoles with methyl ketones in the presence of molecular iodine and pyrrolidine. This reaction constructed a highly efficient indolyl diketones scaffold, which might be regarded as a useful biological and pharmacological tool in the exploration of therapeutic A_{2B}AR modulators. The use of inexpensive molecular iodine and pyrrolidine and a broad substrate scope make this protocol very practical. Preliminary mechanistic studies indicate that two paths are involved in this process.



The oxidative coupling of two different C−H bonds has emerged as a powerful tool for the selective construction of C−C bonds and plays an integral part in organic synthesis.[1] Transition metals play an important role in many oxidative C−H/C−H coupling reactions;[2] This is because they can partake in a diverse range of electron transfer processes.[3] As a nonmetallic element, iodine also has diverse oxidation states and moderate redox potential. Molecular iodine has the lowest homolytic dissociation energy of the nonradioactive halogens, which makes it amenable to the single-electron-transfer process.[4] These properties led researchers to explore the use of molecular iodine in oxidative coupling reactions. In 2010, I_2-mediated intramolecular cyclization of enamines, via iodide intermediates, was realized by Li et al.[5] Recently, molecular iodine has also proven successful for the assembly of polycyclic spiroindoline scaffolds. This involves an intramolecular oxidative coupling of dianions derived from indole-embodied β-ketoamides[6] and has been applied to the total synthesis of an indole alkaloid.[7] Most recently, Itoh and Prabhu independently described a versatile molecular iodine catalyzed oxidative C−C bond formation reaction between tertiary amines and a carbon nucleophile.[8] Despite these promising results, the use of molecular iodine in oxidative coupling reactions is still a young and fascinating theme. Herein, we report our progress in the I_2-mediated dicarbonylation of indoles with methyl ketones.

The indole moiety is common in bioactive synthetic and natural products and occupies a privileged position in drug discovery.[9] Consequently, much attention has been paid to the synthesis of substituted indoles, through either construction or modification of indole rings. The electron-rich nature of the indole ring enables it to undergo direct C−H bond functionalization with electrophiles to form C−C bonds. However, up to now, only rare examples have been reported to realize the dicarbonylation of indoles.[10] The Müller group[11] reported a three-component approach to indolyl ynediones by a glyoxylation/Stephens−Castro coupling, in which the decarbonylative elimination was avoided (Scheme 1a). Li[12] developed a Pd-catalyzed direct dicarbonylation of indoles for synthesis of indole-3-α-ketoamides, which proceeded via an iodo-3-indole intermediate, followed by the sequential incorporation of two molecules of carbon monoxide (Scheme 1b). Li et al.[13] demonstrated an interesting route for the selective synthesis of 2-(1*H*-indol-3-yl)-2-oxo-carbonyls, and arylamines were generated concurrently as byproducts (Scheme 1c). Obviously, the direct utilization of methyl ketones as coupling partners with indoles for the construction of indolyl diketones would be an appealing approach (Scheme 1d).

Scheme 1. Dicarbonylation of Indoles



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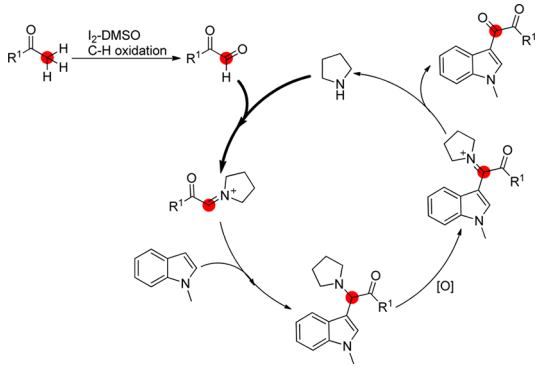
Inspired by previous reports of oxidative coupling α to nitrogen in tertiary amines,[14] we tried the direct coupling of indoles with iminium ions generated in situ from methyl ketones and secondary amines to form a cross-dyhydrogenative-coupling product (Scheme 2). These products can further undergo

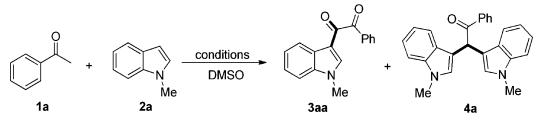
Scheme 2. Design Strategy: Direct and Selective Oxidative Cross-Coupling of Indoles with Methyl Ketones



oxidation to the second iminium ion, followed by hydrolysis, to realize the dicarbonylation of indoles, which may be conveniently transformed into highly conjugated polyheterocyclic compounds.[15] To the best of our knowledge, no examples of direct and selective oxidative cross-coupling of indoles with methyl ketones to construct indolyl diketone scaffolds have been reported.

To test this, acetophenone (**1a**) and *N*-methylindole (**2a**) were selected as model substrates. The reaction was successful in 25 mol % pyrrolidine over 12 h using 1.0 equiv of I_2 at 100 °C in DMSO. The products were a mixture of the desired 1-(1-methyl-1*H*-indol-3-yl)-2-phenylethane-1,2-dione (**3aa**, 15%) and the 2,2-bis(1-methyl-1*H*-indol-3-yl)-1-phenylethanone (**4a**, 43%).[16] Having obtained an initial and promising result, we next focused on the optimization of the reaction conditions. Increasing the amount of I_2 to 1.5 equiv, the yield increased to 80% (Table 1, entry 3). However, further increases in the amount of I_2 did not result in further increases in yield. The reaction was unable to occur in the absence of I_2 (Table 1, entry 5), indicating that molecular iodine is essential for the reaction. Under these conditions, various amines, such as piperidine, morpholine, and L-proline, were used to obtain the desired products in acceptable yields (Table 1, entries 6–8). However, *N*-methylaniline afforded **3aa** in only 25% yield (Table 1, entry 9), which indicated that the ability of the *N*-aryl subunit in stabilizing the charged iminium intermediate was unable to effectively promote the reaction. Interestingly, the reaction also resulted in the carbonylation of indole in the absence of amines (Table 1, entry 10), although less effectively, which can be attributed to the rapid oxidation of I_2.[17] The reaction could also proceed successfully when conducted at 90 °C (Table 1, entry 12).

Table 1. Optimization of the Reaction Conditions[a]

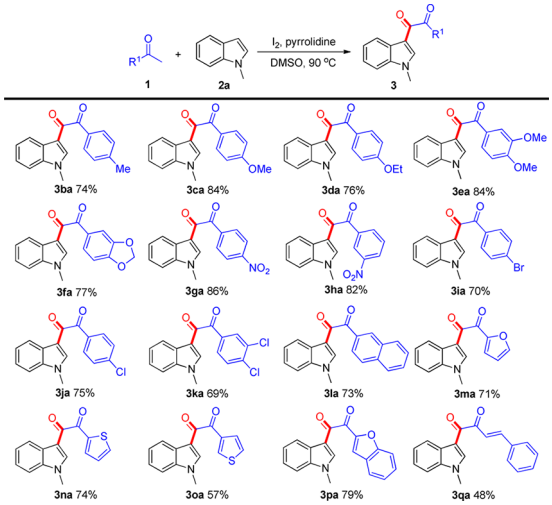


entry	I_2 (equiv)	cat.	temp (°C)	yield **3aa**/**4a**[b] (%)
1	1.0	pyrrolidine	100	15/43
2	1.2	pyrrolidine	100	73
3	1.5	pyrrolidine	100	80
4	2.0	pyrrolidine	100	78
5		pyrrolidine	100	0
6	1.5	piperidine	100	74
7	1.5	morpholine	100	70
8	1.5	L-proline	100	77
9	1.5	*N*-methylaniline	100	25
10	1.5		100	38
11	1.5	pyrrolidine	110	80
12	**1.5**	**pyrrolidine**	**90**	**80**
13	1.5	pyrrolidine	80	43/5
14	1.5	pyrrolidine	50	12/38

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (25 mol %), solvent (2 mL). [b]Isolated yields.

With the optimized conditions in hand, the generality and scope of the molecular iodine-pyrrolidine dicarbonylation of indoles was explored. The reaction demonstrated wide substrate scope in terms of the aromatic ketone unit (Scheme 3). Aryl

Scheme 3. Scope of Methyl Ketones[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), and I_2 (0.75 mmol) with pyrrolidine (25 mol %) in DMSO (2 mL) at 90 °C. [b]Isolated yield.

methyl ketones bearing electron-neutral (e.g., 4-Me), electron-rich (e.g., 4-OMe, 4-OEt, 3,4-OMe_2, 3,4-OCH_2O), and electron-deficient (e.g., 4-NO_2, 3-NO_2) phenyl rings were converted to the corresponding products in moderate to good yields (74–86%; **3ba**–**ha**). The electronic and steric properties of the aromatic ketones had little influence on the efficiency of this reaction. Much to our satisfaction, the optimized conditions were mild enough to allow a broad range of halogenated (e.g., 4-Br, 4-Cl, 3,4-Cl_2) substrates (69–75%; **3ia**–**ka**) to be reacted, which allowed for easy further functionalization. 2-Naphthyl methyl ketone also provided the expected product (**3la**) in 73% yield. Meanwhile, the optimized conditions could be applied to various heteroaryl ketones, including furanyl, thienyl, and benzofuryl methyl ketones, which gave the corresponding products in moderate to good yields (57–79%; **3ma**–**pa**). Moreover, the desired dicarbonylation could also be obtained in moderate yield from α,β-unsaturated methyl ketone (48%; **3qa**). Furthermore, the structure of **3ga** was unambiguously confirmed by X-ray crystallography. In addition, aliphatic methyl ketones, such as acetone, cyclohexanone, and methylethylketone, were also

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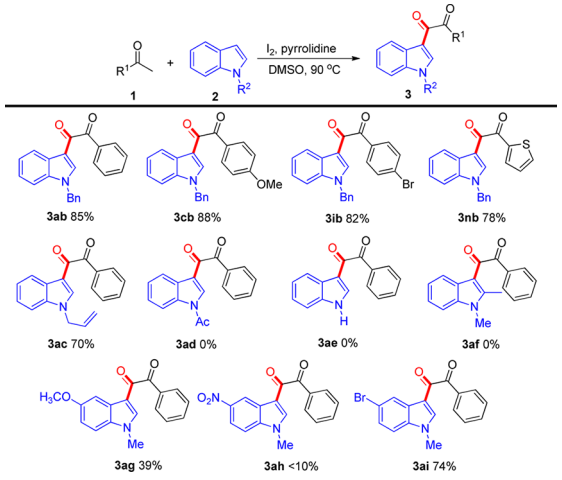
investigated. However, none of the desired products were observed under the standard conditions.

The scope of this reaction was subsequently extended to indole derivatives (Scheme 4). The oxidative coupling between

Scheme 4. Scope of Indoles and Methyl Ketones[a]



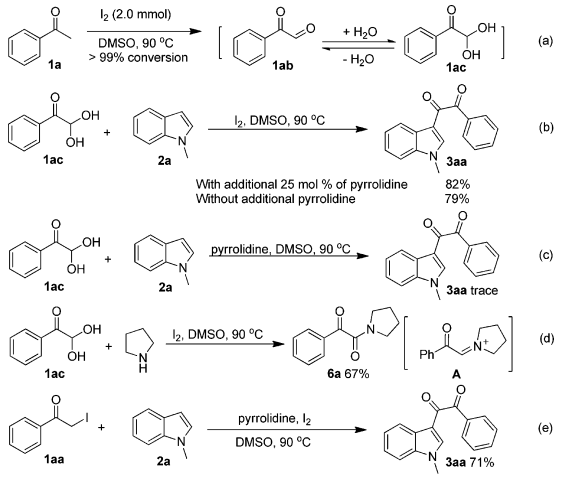
[a]Isolated yield.

methyl ketones and indoles with different *N*-protective groups proceeded smoothly, giving good yields (70−88%; **3ab**−**ac**). Noteworthily, the dicarbonylation products of *N*-benzyl indoles have been proven to be useful biological and pharmacological tools in understanding the therapeutic potential of A_{2B}AR modulators, and their 3-diketoindole scaffold might be useful in the design of new analogs.[18] Electron-withdrawing moieties (*N*-acetyl) prevented the reaction from proceeding due to decreased electron density in the indolyl ring. Unfortunately, *N*-H indole (R^2 = H) did not give the desired carbonylation product, likely due to the easy overoxidation of the *N*-H indole to the isatin.[19] Furthermore, different indole derivative were investigated. The electronic properties of the phenyl rings (**2g**−**i**) have a strong influence on the yield.

With the scope of the method established, the reaction mechanism was investigated. Acetophenone (**1a**) was reacted with I_2 in DMSO at 90 °C to give phenylglyoxal (**1ab**) and the corresponding hydrated species (**1ac**) in quantitative yield (Scheme 5a). The hydrated species (**1ac**) was subjected to the optimized reaction conditions and gave **3aa** in good yields, both with pyrrolidine (25 mol %) and without (Scheme 5b). This result demonstrates that **1ac** is an intermediate in the current reaction and also suggests there might be an alternative path in the absence of pyrrolidine. However, only trace amounts of **3aa** were detected when **1ac** and **2a** were reacted in the absence of I_2 (Scheme 5c). This suggested that molecular iodine plays an important role in this oxidative coupling process. In the absence of indole, substrate **1ac** was converted to 1-phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione **6a** in 67% yield (Scheme 5d), indicating that an iminium ion intermediate (**A**) might be reacting with indole to give the target product under the optimized conditions.[20] When the acetophenone substrate was replaced with α-iodo acetophenone (**1aa**), which was identified as a possible precursor of α-ketoaldehyde (**1ab**), the desired diketone product was also obtained in 71% yield (Scheme 5e).

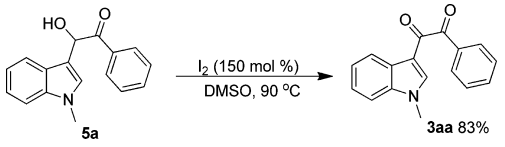
To further develop an understanding of the reaction mechanism, 2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-1-phenylethanone **5a**[21] was tested in the absence of pyrrolidine. To our

Scheme 5. Control Experiments



surprise, **5a** was converted to the carbonylation product in excellent yield in the presence of I_2 (Scheme 6). This reaction

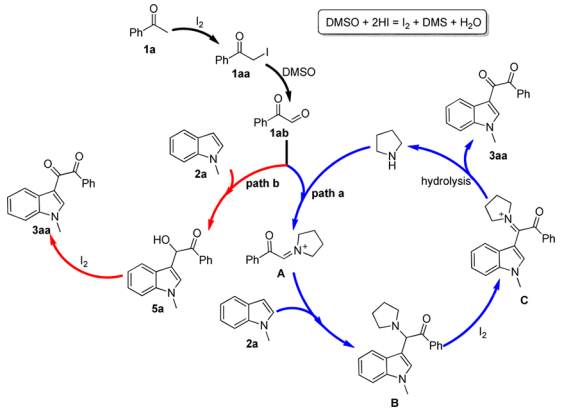
Scheme 6. Control Experiment



showed that **5a** could be the intermediate in the absence of pyrrolidine. Furthermore, the intermediate **5a** can reasonably account for the reactions (Table 1, entry 10 and Scheme 5b) which did not require the catalyst.

On the basis of the results in the current study and previous reports,[22] a possible mechanism has been proposed using acetophenone (**1a**) and *N*-methylindole (**2a**) as examples (Scheme 7). The initial reaction of I_2 with **1a** results in the

Scheme 7. Possible Mechanism



formation of an α-iodo ketone (**1aa**), which is converted to phenyl glyoxal by a subsequent Kornblum oxidation. In the presence of pyrrolidine (path a), pyrrolidine with the aldehyde group of **1ab** would generate an iminium ion intermediate **A** in situ, which then reacts with the nucleophilic indole to produce the intermediate **B** via a Friedel−Crafts-type reaction. Intermediate **B** is quickly converted into intermediate **C** in the presence of oxidants. Hydrolysis of intermediate **C** gives the

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desired product **3aa**, and the released pyrrolidine can start a new catalytic cycle. Without pyrrolidine as a catalyst (path b), the aldehyde group of **1ab** is activated by an excess of regenerated Lewis acid I_2.[17] The activated aldehyde group of phenylglyoxal would react with **2a** to give the intermediate **5a** directly, followed by further rapid oxidation by I_2 to afford **3aa**.[17]

In summary, we have developed a convenient and general method for the dicarbonylation of indoles via direct regioselective oxidative cross-coupling of indoles with methyl ketones in the presence of molecular iodine and pyrrolidine. These reactions proceed under mild conditions with high regioselectivity and show good functional group compatibility. Preliminary mechanistic studies indicate two paths are involved in this process. Further studies to elucidate a detailed mechanism and identify synthetic applications for this protocol are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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