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Two-Step Continuous Synthesis of Dicarbonyl Indoles via I_2/DMSO-Promoted Oxidative Coupling: A Green and Practical Approach to Valuable Diketones from Aryl Acetaldehydes

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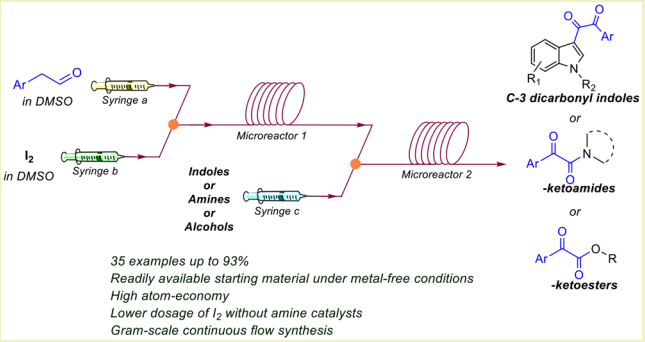
Supporting Information

ABSTRACT: A green and practical method for the synthesis of C-3 dicarbonyl indoles from aryl acetaldehydes and indoles was developed under I_2/DMSO conditions, employing an assembled two-step continuous flow system. Moderate to good yields of dicarbonyl indole derivatives have been achieved by consuming a lower dosage of iodine and shorter reaction time without amine catalysts added, which presents major advantages over reactions in a traditional batch. Moreover, this method was also compatible with the synthesis of α-ketoamides and α-ketoesters by adjusting the reaction parameters of a continuous flow system, which indicates its good universality. And a possible mechanism was proposed based on DMSO[18] isotopic labeled experiments.



KEYWORDS: *Continuous-flow synthesis, Microreactors, Diketones, Metal-free, Oxidative coupling*

INTRODUCTION

Indole derivatives are widespread in natural products, pharmaceutical molecules, and agrochemicals.[1−5] Owing to the excellent features, functional modification of indoles is an important research topic in organic and medicinal chemistry.[6−11] Notably, C-3 dicarbonyl indoles containing indolyl diketone scaffolds have attracted lots of interest from chemists all over the world because of not only their remarkable biological and pharmacological activities but also their wide application as precursors for various organic transformations.[12−16] Recent studies have disclosed that some dicarbonyl indole derivatives could behave as positive or negative allosteric modulators of A_{2B}AR and represent new pharmacological tools useful for the development of therapeutic agents to treat pathological conditions related to an altered functionality of A_{2B}AR.[17,18] In addition, α-ketoamides and α-ketoesters as kinds of well-known and valuable diketones have been also widely researched in organic synthesis and pharmaceutical chemistry by chemists worldwide.[19−24] Consequently, green and practical approaches to these valuable diketones from readily available starting materials are still desirable.

Traditionally, the diketones structural moieties used to be generated from oxalyl chloride, α-ketoacyl halides, or α-ketoacids. These methods are general; however, some drawbacks include a high cost and reagents or byproducts that are both toxic and hazardous. In the past decades, transition-metal-catalyzed oxidative dehydrogenative coupling of C−X bonds are widely studied in modern synthetic chemistry.[25−30] Most methods to C-3 dicarbonyl indoles were realized by Pb or Cu-catalyzed oxidative cross-coupling of indoles with α-amino ketones,[31,32] α-hydroxyketones,[33] or 2-oxoaldehydes.[34,35] Nonetheless, metal catalysts are usually expensive, poisonous, or air-sensitive, which may cause amplification effects and restrict its application in industrial production.

In recent years, synthetic methodologies under metal-free conditions have been widely studied for the oxidative coupling reaction, which overcome the drawbacks of the expensive, poisonous, and air-sensitive properties of metals or organometallics. For example, Ahmed and co-workers reported an aminocatalytic cross-coupling approach via iminium ions to dicarbonyl indoles from 2-oxoaldehydes with indoles.[36] In almost the same time, Wu's group developed a novel route to C3-dicarbonylation of indoles by direct regioselective oxidative cross-coupling of indoles with acetophenones in I_2/DMSO/pyrrolidine conditions.[37] Beyond that, some other methods utilizing I_2/DMSO conditions have been also reported.[38−42] However, there still exist some drawbacks in these methods mentioned above: (1) they consume a large dosage of iodine at

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Scheme 1. A Green and Practical Approach to Valuable Diketones from Aryl Acetaldehydes

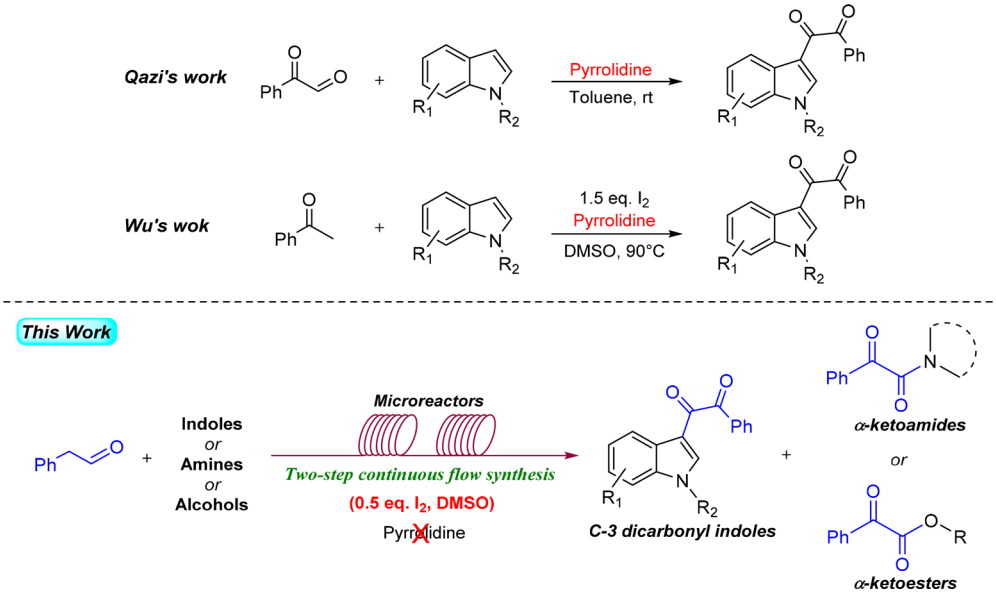
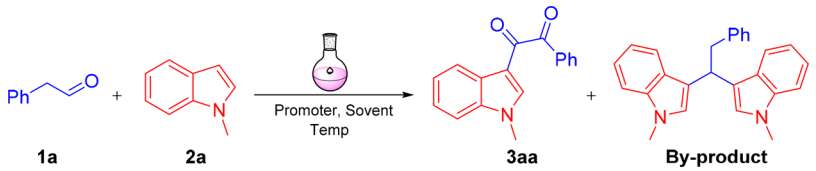


Table 1. Optimization of Reaction Conditions in Batch[a]



entry	promoter (equiv)	solvent	temp (°C)	yield[b] 3aa/by
1	NIS	DMSO	90	22
2	TBAI	DMSO	90	17
3	TBAB	DMSO	90	trace
4	KI	DMSO	90	28
5	I_2	DMSO	90	36/33
6	I_2	DMF	90	0
7	I_2	ACN	90	0
8	I_2	H_2O	90	13
9	I_2	dioxane	90	trace
10	I_2	toluene	90	0
11	I_2	DMSO	80	32/42
12	I_2	DMSO	100	40/30
13	I_2	DMSO	110	40
14	I_2	DMSO	120	39
15	I_2 (1.2)	DMSO	100	45
16	**I_2 (1.5)**	**DMSO**	**100**	**53/27**
17	I_2 (2.0)	DMSO	100	54
18	I_2 (2.5)	DMSO	100	55
19	**I_2 (1.5)**	**DMSO**	**100**	**59/13**[c]

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), promoter (1.0 equiv) dissolved in 2 mL of solvent stirred at 90 °C for 15 h in the sealed flask. [b]Isolated yields. [c]Reaction conditions: **1a** (1.0 mmol) and I_2 (1.5 mmol) dissolved in 2 mL of DMSO were heated for 4 h in a sealed flask. **2a** (1.5 mmol) in DMSO (1.0 mL) was added, and heating continued for 11 h.

a high reaction temperature (ref 37), and (2) they employ amine catalysts to enhance the oxidative coupling process (ref 36). Consequently, decreasing the dosage of iodine and removal of amine catalysts will make these methods more green and practical.

Similarly, our previous work found that iodine in the microfluidic chip has higher reaction efficiency to synthesize α-ketoesters than that in a batch.[43] On the basis of our study of flow chemistry and inspired by the pioneering work of Wu's group, we intended to choose aryl acetaldehydes as novel coupling partners with indoles for the construction of dicarbonyl indoles. Herein, we develop a green and practical method for the synthesis of C-3 dicarbonyl indoles via I_2/DMSO-promoted oxidative coupling of aryl acetaldehydes with indoles in a two-step continuous flow system, where phenyl glyoxal **C** as an important intermediate is generated in the first

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Scheme 2. Strategy to Synthesize C-3 Dicarbonyl Indoles from Aryl Acetaldehydes with Indoles

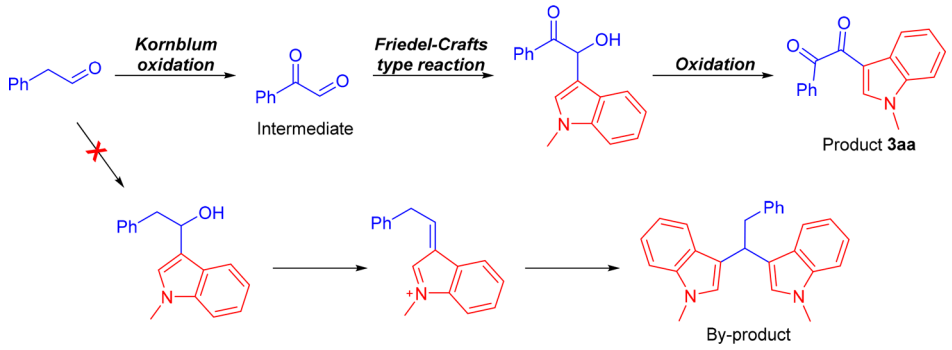
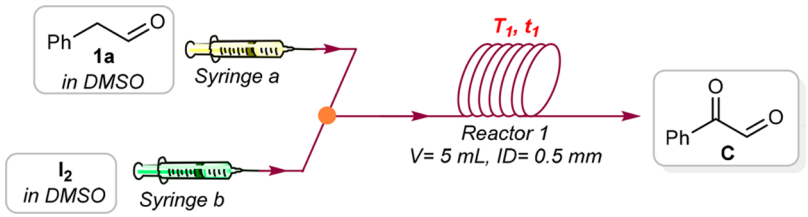


Table 2. Optimization of the First Step[a]



entry	I_2 (equiv)	T_1 (°C)	$rate_{a,b}$ (mL/min)	t_1 (min)	yield C[b]
1	0.3	90	0.5	5.00	48
2	0.5	90	0.5	5.00	66
3	0.8	90	0.5	5.00	67
4	1.0	90	0.5	5.00	66
5	0.5	80	0.5	5.00	58
6	0.5	100	0.5	5.00	72
7	0.5	110	0.5	5.00	83
8	0.5	120	0.5	5.00	80
9	0.5	110	0.6	4.17	77
10	**0.5**	**110**	**0.4**	**6.25**	**92**
11	0.5	110	0.3	8.33	90
12	0.5	110	0.2	12.50	84

[a]Reaction conditions: solution A, 10 mmol **1a** dissolved in 10 mL DMSO; solution B, I_2 dissolved in 10 mL DMSO; V_1 = 5 mL, flow $rate_a$ = flow $rate_b$ (mL/min). [b]HPLC yield.

step and then reacts with indoles to produce C-3 dicarbonyl indoles in moderate to good yields, consuming only 0.5 equiv of I_2 in the absence of amine catalysts. Moreover, the synthesis of α-ketoamides and α-ketoesters was also implementable in this two-step continuous flow system (Scheme 1).

RESULTS AND DISCUSSION

At the beginning of our study, phenylacetaldehyde **1a** and 1-methylindole **2a** were chosen as the model reaction to identify an appropriate promoter and its suitable reaction conditions in a batch. The results were summarized in Table 1. First, the model reaction was carried out in the presence of different iodine source promoters, such as NIS (N-iodosuccinimide), TBAI (tetrabutylammonium iodide), TBAB (tetrabutylammonium bromide), KI, and I_2 in 2 mL of DMSO at 90 °C for 15h (Table 1, entries 1−5). As expected, I_2 exhibited the best promoted activity with 36% yield of product **3aa**, while 33% byproducts (bis-indolyl-alkanes) were also isolated simultaneously (Table 1, entry 5). Solvents were next tested, but the yield turned out to be pretty poor when DMSO was replaced (Table 1, entries 6−10), indicating that DMSO serves an important role in this transformation. Raising the reaction temperature to 100 °C could contribute to 40% yield of product **3aa** (Table 1, entry 12). As 1.5 equiv of I_2 was loaded, the yield of **3aa** reached 53%. Nevertheless, further increasing iodine did not result in obvious improvement of the yield (Table 1, entries 15−18), likely due to the rapid oxidation of I_2 and its sublimation at high temperature in the batch. In addition, considering the reaction mechanism compound **2a** was added after **1a** was oxidized under an I_2/DMSO atmosphere, and the yield of product **3aa** was increased to 59%, the generation of byproducts was a 13% yield (Table 1, entry 19). As shown in Scheme 2, our strategy was designed as the synthesis of C-3 dicarbonyl indoles going through Kornblum oxidation, Friedel−Crafts type reaction, and oxidation processes. However, during this process, the dehydration between acetaldehydes and indoles inescapably generates byproducts, leading to the generation of byproducts.

In recent years, continuous flow chemistry as an innovative and effective technique for reaction profiling and optimization has been widely researched and developed in academic, pharmaceutical, and fine chemical production.[44−55] In addition, it has prominent edges for aiding in scale up of reactions owing to its fast mixing of reagents, larger specific surface area, higher mass and heat transfer capacity, and favorable safety profile, which could contribute to higher yields or selectivity over batch

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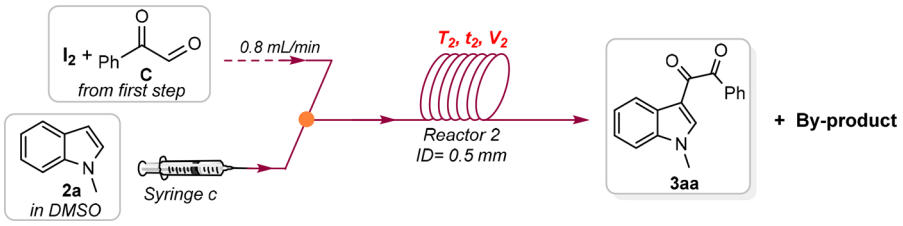
Table 3. Optimization of the Second Step[a]



entry	T_2 (°C)	rate$_c$ (mL/min)	t_2 (min)	V_2 (mL)	yield **3aa**/by[b]
1	100	0.8	6.25	10.0	56
2	110	0.8	6.25	10.0	59
3	120	0.8	6.25	10.0	63
4	130	0.8	6.25	10.0	60
5	120	0.6	6.25	8.8	43
6	120	1.0	6.25	11.3	69
7	120	1.2	6.25	12.5	76
8	120	1.4	6.25	13.8	75
9	120	1.2	7.00	14.0	84
10	**120**	**1.2**	**7.50**	**15.0**	**88/Trace**
11	120	1.2	8.00	16.0	85
12	120	1.2	8.50	17.0	87

[a]Reaction conditions: solution C, 10 mmol **2a** dissolved in 20 mL DMSO. The adjustment of flow rate$_c$ and V_2. [b]Isolated yield.

processes.[56−66] As for these dicarbonyl indoles, α-ketoamides, and α-ketoesters transformation from acetaldehydes, a two-step continuous flow system that divides this reaction into two microreactors may effectively work for avoiding the side reaction mentioned above and improving the products' yield. Moreover, I_2 that reacts in this continuous-flow microreactor is difficult to sublimate and has a higher reaction efficiency than that in the batch.

In order to improve the yield of product **3aa** avoiding increasing the dosage of I_2 or adding amine catalysts, we tried to optimize this reaction in an assembled two-step continuous flow system on the basis of the optimal conditions in the batch. The results were summarized in Tables 2 and 3. At the first step, phenylacetaldehyde **1a** was pumped to microreactor 1 under I_2/DMSO conditions to generate phenyl glyoxal **C**, which is the key intermediate to synthesize **3aa**. As shown in Table 2, 10 mmol of phenylacetaldehyde **1a** dissolved in 10 mL of DMSO was added to syringe a; I_2 dissolved in 10 mL of DMSO was added to syringe b. The volume of microreactor 1 is 5 mL, and the inner diameter is 0.5 mm. The rate of the two syringes keeps the same, and the reaction time could be regulated by changing the flow rate of syringes. Initially, I_2 was scanned from 0.3 to 1.0 equiv, and it was observed that when 0.5 equiv of I_2 was taken into the continuous flow system at 90 °C for 5 min, a 66% yield of phenyl glyoxal **C** was obtained (Table 2, entries 1−4). In order to further improve the yield, temperature (T_1) and residence time (t_1) were subsequently screened in the presence of only 0.5 equiv of I_2 (Table 2, entries 5−12). Surprisingly, 92% yield of phenyl glyoxal **C** was generated at 110 °C for 6.25 min (flow rate$_a$ = flow rate$_b$ = 0.4 mL/min; Table 2, entry 10), which could also be used as a more efficient and prominent method to prepare 2-oxoaldehyde derivatives than previous synthetic methods that employed stoichiometric I_2 or SeO_2.[67−70]

Following the good yield of intermediate **C** generated in microreactor 1, the second step was subsequently optimized to produce the target product **3aa**, where phenyl glyoxal **C** was treated with *N*-methylindole **2a** in microreactor 2 under I_2/DMSO conditions. As shown in Table 3, 10 mmol of **2a** dissolved in 20 mL of DMSO was added to syringe c. The inner diameter of microreactor 2 is 0.5 mm, and the volume could be changed by adjusting the length of the PTFE tube. The reaction time was regulated by changing the flow rate of syringe c and the volume of the microreactor. Meanwhile, the molar ratio between **1a** and **2a** could also be adjusted in accordance with the flow rate$_c$. First, the temperature of microreactor 2 was scanned from 100 to 130 °C for 6.25 min (rate$_c$ 0.8 mL/min; Table 3, entries 1−4). To our delight, a 63% yield of target product **3aa** could be obtained at 120 °C (Table 3, entry 3), which exceeded the best result obtained in the batch (Table 1, entry 19). Inspired by this result, flow rate$_c$ was scanned with the residence time fixed on 6.25 min at 120 °C (Table 3, entries 5−8). The results showed that 76% yield of **3aa** was obtained when flow rate$_c$ was at 1.2 mL/min, which was equal to 1.5 equiv of *N*-methylindole **2a** added to react with phenyl glyoxal **C** in microreactor 2 (Table 3, entry 7). On this basis, residence time (t_2) was prolonged by enlarging the microreactor volume with the flow rate$_c$ fixed at 1.2 mL/min (Table 3, entries 9−12). It was observed that an 88% yield of target product **3aa** was obtained when the residence time was prolonged to 7.5 min, with only a trace amount of byproduct detected (Table 3, entry 10). And a further long residence time could not make the yield higher (Table 3, entries 11 and 12).

Additionally, different inner diameters (ID) of microreactors, including 0.5 mm, 0.8 mm, and 1.0 mm ID were tested on the yield of product **3aa** as a function of dosage of iodine with other parameters constant, and the same reaction was also carried out in a batch. As shown in Figure 1, the results clearly demonstrate that the same dosage of I_2 in the continuous flow microreactors has a better reaction efficiency on this reaction and produces a higher product yield than that in a batch. Moreover, it is easy to find that the thinner the microchannels were, the higher the products yield obtained. On one hand, this is almost certainly due to the better mass and heat transfer in continuous flow microreactors, where residence time could be controlled precisely. On the other hand, this transformation has

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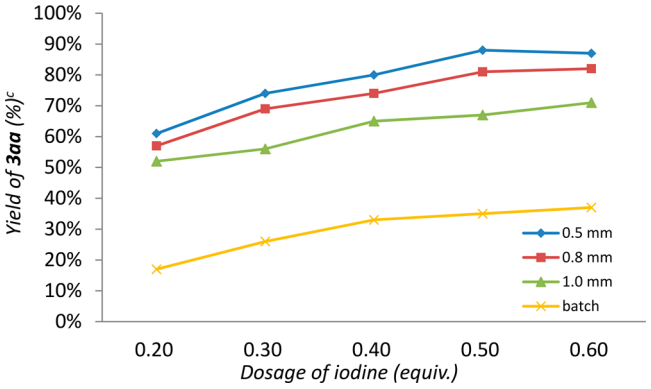

Figure 1. Effect of different inner diameters of microreactors and batch on the yield of dicarbonyl indole **3aa** as a function of dosage of iodine. (a) Reaction conditions flow: solution A, 10 mmol of **1a** dissolved in 10 mL of DMSO; solution B, 5 mmol I_2 dissolved in 10 mL of DMSO; solution C, 10 mmol of **2a** dissolved in 20 mL of DMSO; V_1 = 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; V_2 = 15 mL, flow rate$_c$ = 1.2 mL/min, T_2 = 120 °C. (b) Reaction conditions batch: **1a** (1.0 mmol), **2a** (1.5 mmol), and different dosage of I_2 dissolved in 2 mL of DMSO stirred at 100 °C for 15 h in 100 mL sealed flask. (c) Isolated yield.

been logically divided into two parts (microreactor 1 and 2) to reduce the generation of side reactions and improve reaction efficiency, which is another reason why the flow system performs better than the batch system.

With the optimized continuous flow reaction conditions in hands, the scope of substrates was explored, and the results were summarized in Scheme 3. First, the effect of different electron-withdrawing (F, Cl, Br, NO_2) and electron-donating (OMe, Et, Me) substituents on the aryl group of phenylacetaldehyde was examined, and all substrates reacted smoothly with *N*-methylindole to produce the corresponding products in 75−91% yields (Scheme 3, **3aa**−**3ja**).

Meanwhile, no obvious electronic effect was detected in this reaction when the methyl substituent was attached on different positions of the substrates (Scheme 3, **3ha**−**3ja**). In addition, aromatic rings, such as 1-naphthaleneacetaldehyde, 2-thiopheneacetaldehyde, and 2-pyridineacetaldehyde were all well-behaved in this dicarbonylation reaction, affording 81%, 84%, and 67% yields of corresponding products, respectively (Scheme 3, **3ka**−**3ma**). Next, a wide range of indoles **2** were also explored. It was found that indoles with different N-protective groups, such as methyl, benzyl, and propenyl, could react smoothly with **1a** to produce corresponding products in moderate to good yields (Scheme 3, **3aa**, **3ab**, and **3ae**). In addition, 61% yield of **3al** could be generated from N−H indole, which was not feasible in Wu's work. Notably, as potential A_{2B}AR antagonists, 1-benzyl-3-ketoindole derivatives **3ab**, **3ac**, and **3ad** were synthesized successfully when 1-benzylindole was pumped into this continuous flow system, demonstrating the potential value of our method in future marketing applications. Moreover, 2-substituted (Me, Ph) and 5-substitued (Br, NO_2, OMe) indoles were also tested. The results showed that most of them were tolerated under optimized reaction conditions, except for strongly electron-withdrawing substituents that may decrease electron density on the indole ring, such as N-acetyl and 5-nitron substituted indoles (Scheme 3, **3af**−**3ak**).

To further explore the universality of this method, the scope of other nucleophiles was examined under these continuous synthesis conditions as shown in Scheme 4. To our delight, when the reaction parameters were slightly adjusted, both secondary amines and alcohols were feasible in this method, which reacted smoothly with phenylacetaldehyde **1a** under I_2/DMSO conditions to produce corresponding diketone products α-ketoamides (Scheme 4, **4a**−**4d**) and α-ketoesters (Scheme 4, **5a**−**5i**), respectively, in moderate to good yields. However, no desired α-ketoamide products were detected when primary amines and anilines were subjected to this transformation.

In order to get insights into the role of DMSO and the reaction mechanism, ^{18}O-labeled isotope experiments were performed. As shown in Figure 2, when the model reaction between **1a** and **2a** was carried out in the presence of iodine and ^{18}O-labeled DMSO, the ^{18}O-labeled product **O^{16}O^{18}−3aa** was highly detected by ESI-MS analysis at $[M + H]^+$ 266.1085 and $[M + Na]^+$ 288.0894, indicating that DMSO acts as an oxygen donor for the generation of C-3 dicarbonyl indoles.

On the basis of the isotope experiments above and previous reports, a plausible mechanism was proposed in Scheme 5. In microreactor 1, Compound **B** is first generated from the iodination of phenylacetaldehyde **1a**, which subsequently undergoes Kornblum oxidation to produce phenyl glyoxal **C** with the release of HI and DMS under I_2/DMSO conditions. After that, the reaction mixture flows into microreactor 2, where I_2 activates the aldehyde group of **C** and indole **2a** attacks the activated aldehyde group of **C**, affording the benzoin intermediate **D**, and follows by further rapid oxidation by I_2 and DMSO to produce the C-3 dicarbonyl indoles product **3a**.

CONCLUSION

In conclusion, a green and practical two-step continuous flow synthetic method has been developed to produce C-3 dicarbonyl indoles from phenylacetaldehydes and indoles under I_2/DMSO conditions. Moderate to good yields of dicarbonyl indole derivatives were achieved by consuming a lower dosage of iodine and a shorter reaction time, especially in the absence of amine catalysts, which presents major advantages over this reaction in a traditional batch. Moreover, the applicability of this work was extended by developing the two-step continuous synthesis method to α-ketoamides and α-ketoesters from aldehydes, which demonstrates that the method has good universality with a wide substrate scope. This method was expected to contribute to a new facet to the preparation of diketones and have good application prospects.

EXPERIMENTAL SECTION

General Procedure for Continuous Synthesis of Compound 3. A total of 10 mmol of aryl acetaldehydes **1** was dissolved in 10 mL of DMSO, which was extracted to syringe a. A total of 5 mmol of I_2 was dissolved in 10 mL of DMSO, which was extracted to syringe b. A total of 10 mmol of indoles **2** was dissolved in 20 mL of DMSO, which was extracted to syringe c; V_1 = 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; and V_2 = 15 mL, flow rate$_c$ = 1.2 mL/min, T_2 = 120 °C. Saturated thiosulfate solution was injected to quench the reaction mixture at 1.0 mL/min. The outflow of the reaction mixture was collected in a conical flask and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and solvent was removed under a vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum (hexane/ethyl acetate 60:1), affording the desired product **3** in good yields.

General Procedure for Continuous Synthesis of Compound 4. A total of 10 mmol of phenylacetaldehyde **1a** was dissolved in 10

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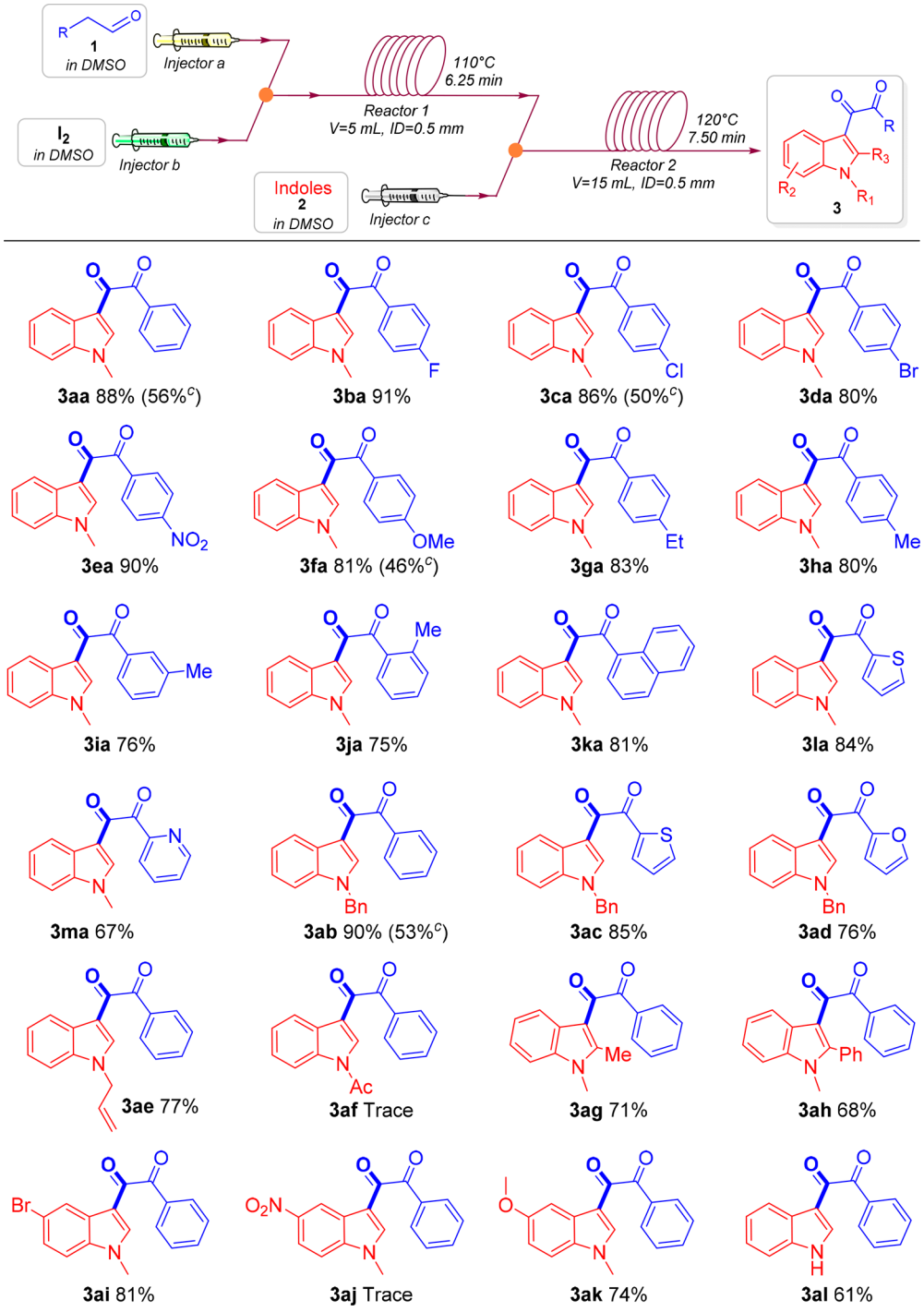
Scheme 3. Substrate Scope of Aldehydes with Indoles[a]



[a]Reaction conditions flow: solution A, 10 mmol **1** dissolved in 10 mL of DMSO; solution B, 5 mmol of I_2 dissolved in 10 mL of DMSO; solution C, 10 mmol of **2** dissolved in 20 mL of DMSO; V_1 = 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; V_2 = 15 mL, flow rate$_c$ = 1.2 mL/min, T_2 = 120 °C. [b]Isolated yield. [c]Reaction conditions batch: **1** (1.0 mmol) and I_2 (1.5 mmol) dissolved in 2 mL of DMSO were heated at 100 °C for 4 h in a sealed flask. **2** (1.5 mmol) in DMSO (1.0 mL) was added, and heating continued for 11 h.

mL of DMSO, which was extracted to syringe a. A total of 5 mmol of I_2 was dissolved in 10 mL of DMSO, which was extracted to syringe b. A total of 10 mmol amines was dissolved in 20 mL of DMSO, which was extracted to syringe c; V_1 = 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; V_2 = 15 mL, flow rate$_c$ = 1.2 mL/min, T_2 = 90 °C. Saturated thiosulfate solution was injected to quench the reaction mixture at 1.0 mL/min. The outflow of the reaction mixture was collected in a conical flask and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under a vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum (hexane/ethyl acetate 5:1), affording the desired product **4** in good yields.

General Procedure for Continuous Synthesis of Compound 5. A total of 10 mmol of phenylacetaldehyde **1a** was dissolved in 10 mL of DMSO, which was extracted to syringe a. A total of 5 mmol of I_2 was dissolved in 10 mL of DMSO, which was extracted to syringe b. A total of 10 mmol of alcohols was dissolved in 20 mL of DMSO,

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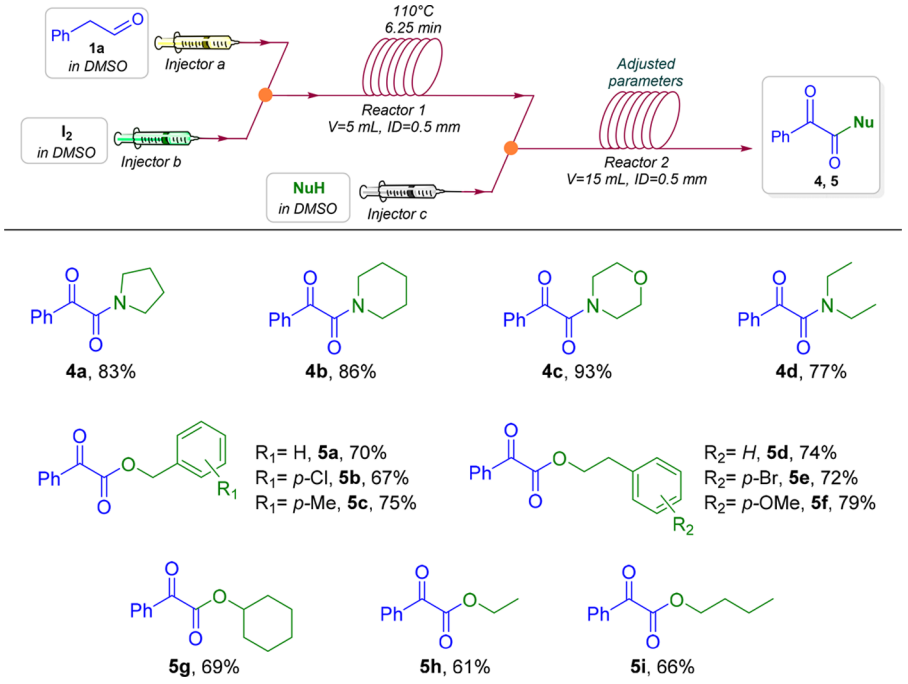
Scheme 4. Scope of Continuous Synthesis Towards Other Nucleophiles[a,b]



[a]Reaction conditions flow: solution A, 10 mmol **1a** dissolved in 10 mL of DMSO; solution B, 5 mmol I_2 dissolved in 10 mL of DMSO; solution C, 10 mmol amines dissolved in 20 mL of DMSO; V_1= 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; V_2 = 15 mL, flow rate$_c$ = 1.2 mL/min, T_2 = 90 °C. [b]Reaction conditions flow: solution C, 10 mmol alcohols dissolved in 20 mL of DMSO; V_2 = 25 mL, flow rate$_c$ = 1.6 mL/min, T_2 = 100 °C. [c]Isolated yield.

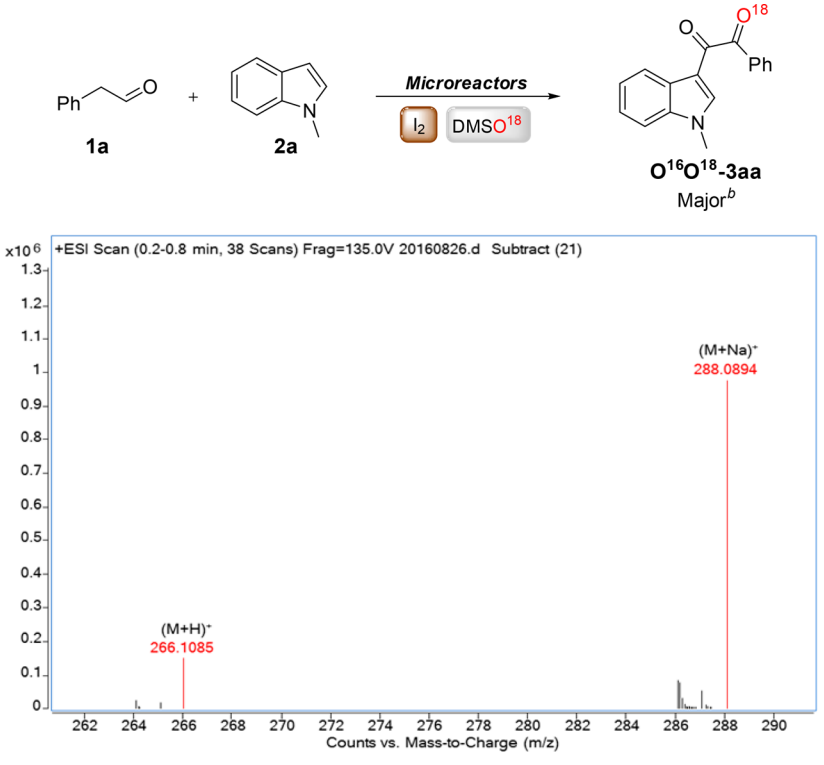


Figure 2. Isotope experiments. (a) Reaction conditions: solution A, 10 mmol **1** dissolved in 10 mL DMSO; solution B, 5 mmol I_2 dissolved in 10 mL DMSO; solution C, 10 mmol **2** dissolved in 20 mL DMSO; V_1 = 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; V_2 = 15 mL, flow rate$_c$ = 1.2 mL/min, T_2 = 120 °C. (b) Isolated yield.

which was extracted to syringe c; V_1 = 5 mL, flow rate$_a$ = flow rate$_b$ = 0.4 mL/min, T_1 = 110 °C; V_2 = 25 mL, flow rate$_c$ = 1.6 mL/min, T_2 = 100 °C. Saturated thiosulfate solution was injected to quench the reaction mixture at 1.0 mL/min. The outflow of the reaction mixture was collected in a conical flask and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent

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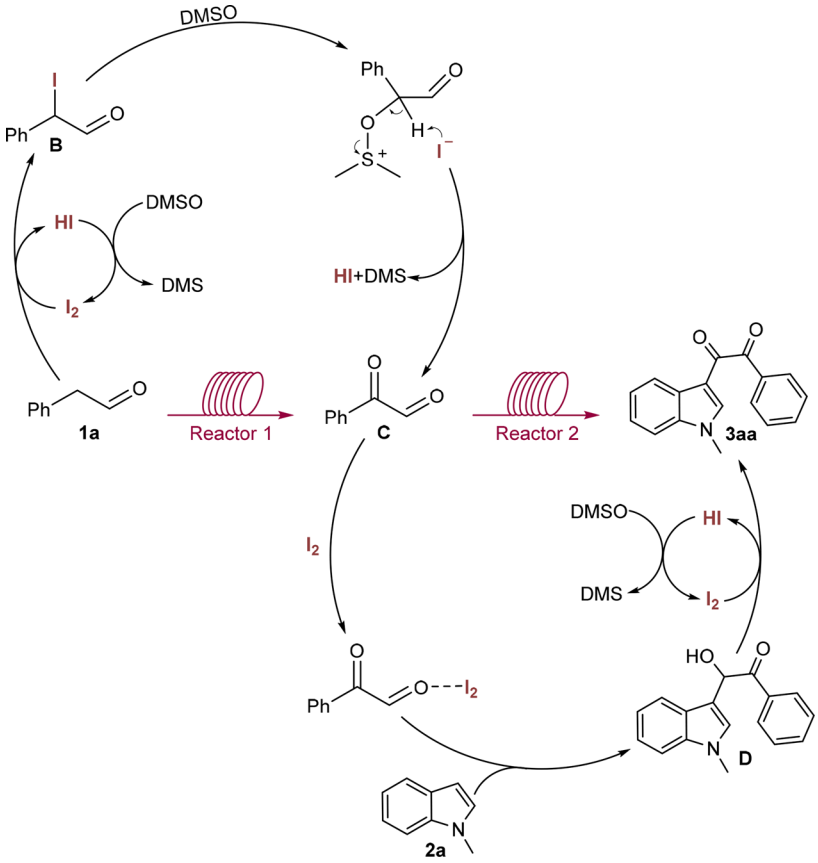
Scheme 5. Possible Mechanism



was removed under a vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum (hexane/ethyl acetate 50:1), affording the desired product **5** in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.8b01339.

General experimental, analytical data of products, ^{1}H NMR and ^{13}C NMR spectra of products, and introduction of assembled two-step continuous flow system (PDF)

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Notes

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