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Efficient synthesis of bulky 4-substituted-isatins via microwave-promoted Suzuki cross-coupling reaction

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ABSTRACT

Indoline-2,3-diones (isatins) and their derivatives are important heterocycles found in nature and present in numerous bioactive compounds. Very few examples related to the synthesis of 4-substituted-arylisatins have been reported before. Utilizing microwave irradiation, the synthesis of bulky 4-substituted-arylisatins via a Suzuki cross-coupling has been developed with a wide range of substrates. All the reactions proceeded smoothly and afforded moderate to excellent yields of products, which indicating that electronic effects and steric modifications have little effect on this reaction.

Introduction

Indoline-2,3-diones (isatins) and their derivatives are important heterocycles found in nature and present in numerous bioactive compounds which can act as inhibitors of apoptosis,[1a,b] anticonvulsants,[1c] and other antiviral,[1d,e] anti-bacterial, and anti-fungal agents.[1f] For example, as shown in Figure 1 and 5-(3′-methylbuten-2′-yl)isatin and 6-(3′-methylbuten-2′-yl)isatin, isolated respectively from *Chaetomium globosum* and *Streptomyces albus*, have been described as novel antifungal compounds.[2] Indirubin is the active ingredient of Danggui Longhui Wan, a mixture of plants that is used in traditional Chinese medicine to treat chronic diseases. It is also found in Chinese medicinal herbs *Isatis indigotica* and *Strobilanthes cusia*.[3] Methisazone and the β-thiosemicarbazone of *N*-methyl isatin (IBT) have also been described as smallpox chemoprophylactic agents.[1d,3a] In addition, the isatins are broadly used as an important intermediate in organic synthesis and technical supramolecular applications.[4,5]

Two traditional methods have been developed for the synthesis of isatins.[4,6–9] The first one involves a strong acid- or base-mediated condensation of aniline with diethyl ketomalonate,[6] oxalyl chloride,[7] or chloral hydrate.[8] The other method involves the functionalization of preexisting aromatic rings.[9] Although these approaches provided useful access to substituted indoline-2,3-diones, they suffered from some drawbacks, such as relatively harsh reaction conditions, narrow range of substrates, and poor yields. Recently, modern synthetic protocols for the syntheses of isatin and its derivatives have been established, including C–H oxidation/acylation of formyl-*N*-arylformamides[10a] and Suzuki cross-coupling reaction from iodoisatins.[10b] However, these methods could be used to synthesize only 5-, 6-, or 7-substituted-isatins,[10b–h] and very few examples related to the synthesis of 4-substituted-isatins could be found.[10b] Thus, the development of an efficient method to prepare 4-substituted-isatins is of great interest.

Microwave irradiation has emerged as a powerful technique for promoting a variety of chemical reactions.[11] The main benefits of performing reactions under microwave irradiation conditions are significant enhancements in rate and higher product yields. During recent years, we have developed some new methods for efficient synthesis of heterocyclic compounds under microwave irradiation.[12] Herein, as a continuation of our research on the synthesis of structurally diverse heterocyclic compounds, we report the synthesis of isatin derivatives bearing bulky substituents on position-4 via a Suzuki cross-coupling under microwave irradiation.

Result and discussion

The 4-iodoindoline-2,3-dione derivatives were prepared by using a previously reported synthetic strategy.[13] Then, the reaction between 4-iodoindoline-2,3-dione (1) and phenylboronic acid (**3**a) was selected as a model to optimize the conditions for the palladium-catalyzed cross-coupling reaction. As shown in Table 1, as compared to the conventional heating methods, microwave

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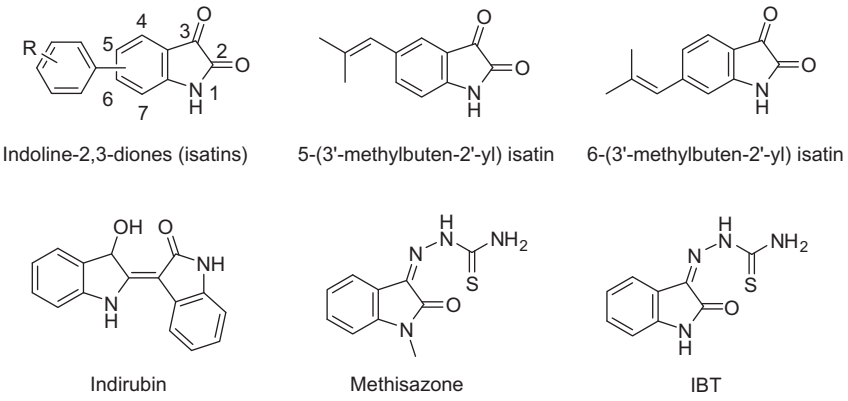


Figure 1. Pharmacologically active indoline-2,3-diones (isatins) and their derivatives.

irradiation can dramatically accelerate the reactions and increase the reaction yields. In addition, the temperature showed a marked effect on the reaction. The yield was notably increased to 92% when the reaction was carried out at 130 °C under microwave irradiation (Table 1, entries 2, 3 and 5).

Next, we investigated the effect of the stoichiometric ratio of the reactants was investigated. If the ratio of 4-iodoindoline-2,3-dione to phenylboronic acid was decreased from 1:1.2 to 1:1, it was necessary to increase the reaction temperature to maintain shorter reaction time and higher yields (Table 1, entries 3–6). Furthermore, the presence of the $Pd(PPh_3)_4$ catalyst was critical to the reaction and without it, no reaction was observed. For the base additive, $NaHCO_3$ was more effective than K_2CO_3 (Table 1, entries 6–10).

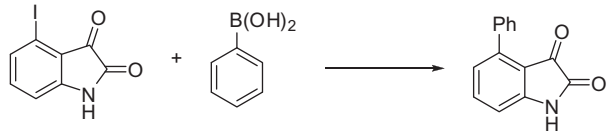
With the optimized conditions defined, the substrate scope was further investigated by employing a variety of arylboronic acids substituted with electron-donating and electron-withdrawing groups. As shown in Table 2, significant structural variations in the arylboronic acid components were well tolerated and afforded the corresponding 4-substituted-isatins in moderate to good yields. Both electron-rich and electron-poor aryl boronic acids could be successfully utilized in this transformation. Even potentially problematic groups, such as nitro and trifluoromethyl, did not show significant effects on the transformation and afforded acceptable to moderate yields of products (Table 2, 14 and 15). It should be noted that incorporation of halogen-substituents at the *ortho*, *meta* or *para* positions in arylboronic acids did not retard the reaction, demonstrating that steric modification can be accomplished without compromising the efficiency of the process (Table 2, 5–7 and 11–13). More importantly, the reaction proved to be tolerant of valuable but unstable substituents, such as formyl and acetyl (Table 2, compounds **17** and **18**).

Very promisingly, polysubstituted phenylboronic acids, furan-2-ylboronic acid, thiophen-2-ylboronic acid, dibenzofuran-4-ylboronic acid, naphthalen-1-ylboronic acid, and benzofuran-2-ylboronic acid also reacted with 4-iodoindoline-2,3-dione very well and gave moderate to excellent yields of products (Table 2, 19–31).

In order to investigate the effects of steric hindrance on the reaction, the reaction between 4-iodo-5-methylindoline-2,3-dione and various boronic acids was examined. As shown in Table 2 (compounds **32**–**39**), all the reaction proceeded smoothly and afforded moderate to excellent yields of products, which indicating that the *ortho*-methyl has little steric effect on the cross-coupling reaction.

Finally, we also extended the substrates to alkyl and alkenyl boronic acids. Not surprisingly, the process showed good functional group compatibility for the alkenyl reagents (Table 2, compounds **40**–**42**). However, alkyl reagents did not reacted with 4-iodoindoline-2,3-diones under the investigated conditions.

Table 1
Optimization of the reaction conditions[a]



1 3a 4

Entry	Temp (°C)	1:3a	Catalyst	Base	Time	Yield[b] (%)
1	110[c]	1:1.2	$Pd(PPh_3)_4$	$NaHCO_3$	98 h	32
2	[d]MW:110	1:1.2	$Pd(PPh_3)_4$	$NaHCO_3$	65 min	54
3	MW:120	1:1.2	$Pd(PPh_3)_4$	$NaHCO_3$	6 min	71
4	MW:120	1:1	$Pd(PPh_3)_4$	$NaHCO_3$	20 min	67
5	MW:130	1:1.2	$Pd(PPh_3)_4$	$NaHCO_3$	3 min	92
6	MW:130	1:1	$Pd(PPh_3)_4$	$NaHCO_3$	5 min	92
7	MW:130	1:1	$Pd(PPh_3)_4$	Na_2CO_3	5 min	73
8	MW:130	1:1	$Pd(PPh_3)_4$	K_2CO_3	5 min	59
9	MW:130	1:1	None	$NaHCO_3$	5 min	No reaction
10	MW:130	1:1	$Pd(PPh_3)_4$	None	5 min	No reaction

[a] Unless otherwise noted, all the reactions were carried out at 0.2 mmol scale in the solution of DME (3 mL) and H_2O (0.6 mL) with 5 mol % of $Pd(PPh_3)_4$, 2 equiv of base, protected by N_2.
[b] Isolated yields.
[c] Conventional heating method.
[d] Microwave irradiation.

Conclusion

In summary, we have developed a convenient method for the synthesis of bulky 4-substituted-isatins from 4-iodoisatins by using microwave-assisted Suzuki cross-coupling reactions. The reaction is applicable to a wide range of substrates and produces a variety of densely functionalized bulky 4-substituted-isatins in good to excellent yields within a very short time.

Experimental section

General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography (FC) was performed using 200–300 mesh silica gel.

^1H NMR spectra were recorded on 400/600 (400/600 MHz) spectrophotometers. Chemical shifts (δ) are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, DMSO: 2.50 ppm). Data are reported as follows: chemical shift,