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Synthesis of novel 7-substituted 5,6-dihydroindol-2-ones via a Suzuki–Miyaura cross-coupling strategy

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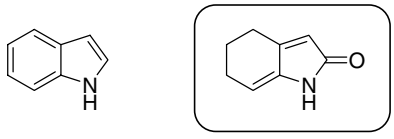
Abstract—A versatile method for the synthesis of new 7-substituted 5,6-dihydroindol-2-ones is described. The synthetic strategy proceeds through the use of the established palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of halogenated indol-2-ones and arylboronic acids/esters.

The indole heterocyclic system **1** is present in many naturally occurring alkaloids that exhibit medicinal and biological activity.[1–3] This system has been important in both the development of natural products chemistry and pharmaceuticals as it is a common building block for many complex molecular constructions.



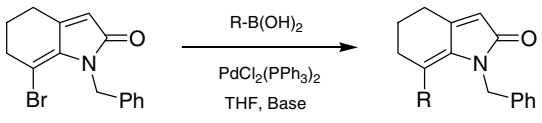
1 **2**

The great diversity of the biologically active indoles has prompted many to focus on the synthesis and functionalization of indoles.[4] More so, the ease of the Suzuki–Miyaura coupling reaction with various palladium catalytic systems to form aryl–aryl bonds has modernized many synthetic routes to electron-rich indoles.

A class of compounds that are yet to be researched systematically is that based on the 5,6-dihydroindol-2-one **2**. Such compounds are isosteres of the indoles and share similar structural motifs that could potentially possess similar biological activity. In addition, they also serve as an alternative precursor to the indoles.[5] Recently, indolone-nucleated compounds have gained much attention as a scaffold for the development of neuroprotective drugs in the treatment of neurodegenerative disease [6,7] and in the retrosynthesis of natural products.[8]

Recent syntheses have produced 2-, 3-, 4- and 6-substituted indolones with various pharmacological benefits.[6,9–13] However, the synthetic scope of 7-substituted dihydroindol-2-ones with different attached aryl substituents is limited with many of these compounds being subsets of larger complex molecules. Currently there is no general synthetic method reported in the literature to access such a system.

The palladium-catalyzed Suzuki–Miyaura aryl–aryl cross-coupling presents a viable established route to the 7-substituted derivatives via a direct coupling of halogenated indolones with arylboronic acids/esters. The key advantage of this coupling strategy lies in their high reactivity towards a vast range of easily available/synthesizable boronic acid/ester substrates and allows for the rapid preparation of a library of 7-substituted indol-2-ones as building blocks for various molecular constructions.



3 **4**

Scheme 1.

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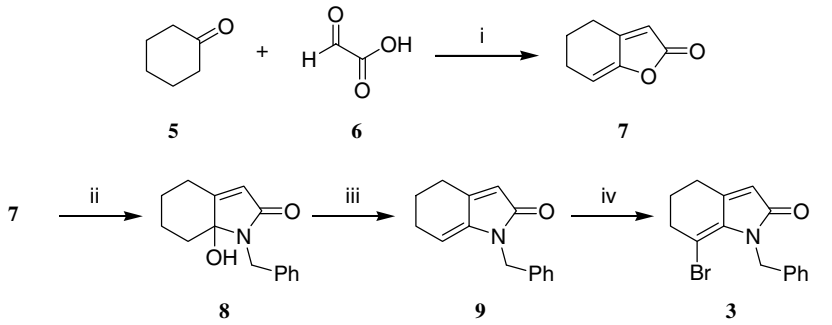


Scheme 2. Reagents and conditions: (i) H_3PO_4 (85%), 100 °C, 6 h, 40%; (ii) $BnNH_2$, CH_2Cl_2, reflux, 4 h, 68%; (iii) *p*-TsOH, $CHCl_3$, reflux, 2 h, 70%; (iv) NBS, CCl_4, reflux, 4 h, 63%.

Herein, we report the synthesis of novel 7-substituted 5,6-dihydroindol-2-ones **4** using a simple and efficient one-step procedure involving the palladium-catalyzed Suzuki–Miyaura coupling reaction (Scheme 1).

The reduced benzofuranone **7** provides a starting point for the direct synthesis of indolone **9**, in which a subsequent direct lactone-lactam conversion [14] would provide the basic reduced indolone scaffold. The reduced benzofuranone was obtained via the phosphoric acid catalyzed condensation and cyclization of cyclohexanone **5** and glyoxylic acid monohydrate **6** (Scheme 2).[15]

The reduced benzofuranone **7** was treated with benzylamine under reflux conditions to yield the intermediate hydroxy-dihydroindolone **8** as the only product (TLC monitoring) in moderate yield. This strategy of direct conversion of a benzofuranone to the dihydroindol-2-one was previously observed in the lactone-lactam conversion of fimbrolides to the corresponding dihydropyrrol-2-ones.[14]

A mechanistic scheme for the formation of hydroxy-dihydroindolone **8** incorporates formation of an amide intermediate followed by an intramolecular cyclization to generate the reduced indolone ring system.[14]

Dehydration of the intermediate hydroxy-compound to yield the basic indolone scaffold could be accomplished with common dehydrating agents such as phosphorus pentoxide or *p*-toluenesulfonic acid (*p*-TsOH). It was found that treatment with the latter under reflux conditions gave the cleanest reaction and the reduced indolone **9** was obtained in good yield.

The ensuing step involves conditioning the indolone for reaction at the 7-position. This was only attainable through selective halogenation due to the many reactive sites on the indolone as seen from the treatment with bromine that gave multiple products that were difficult to purify and characterize. Selective halogenation by treatment with *N*-bromosuccinimide (NBS) in CCl_4 provided the 7-bromo indolone **3** in good yield. Selective bromination at C-7 was evident as the ^1H NMR experiment showed only the loss of a multiplet peak at δ 5.50 ppm, which corresponds to H-7 of the starting material **9**. Further ^{13}C NMR data identified the carbon bearing the bromine substituent as C-7, with a value of δ 108.5 ppm.

The Suzuki–Miyaura coupling reaction was attempted with the 7-bromo derivative **3** under standard conditions using $PdCl_2(PPh_3)_2$ as the catalyst.[16] Preliminary investigation of the non-aqueous environment showed that THF was not a satisfactory solvent as the reaction proceeded very sluggishly and product yields were negligible.

Success was achieved by using a dual-solvent system THF/H_2O (6:1) and the phase transfer catalyst Bu_4NI. Cross-coupling with boronic acid **10a** gave product **4a** in good yield.

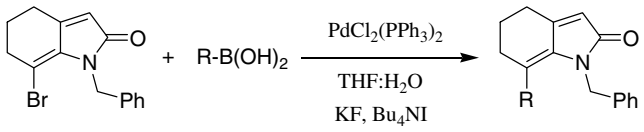
To optimize the reaction conditions, various solvents such as toluene or dioxane, and bases such as KF and CsF were investigated. The use of THF/H_2O and KF together was found to be the optimal conditions in terms of ease of workup and purification of the final products, while the product yields were relatively consistent.

It was postulated that the use of a dual-solvent reaction mixture ensures complete solvation of the reactants, especially the KF base in the aqueous phase and palladium in the organic phase, which catalyzed the coupling reaction efficiently.[17,18]

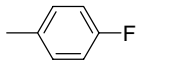
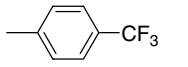
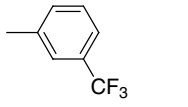
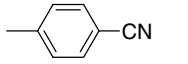
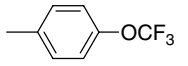
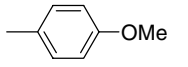
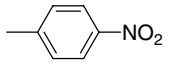
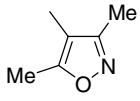
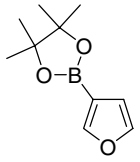
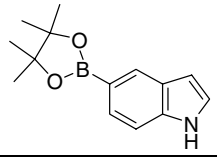
With these optimized reaction conditions, a variety of substituted arylboronic acids/esters **10a**–**k** were reacted with **3** yielding a library of new 7-substituted 5,6-dihydroindol-2-ones **4a**–**k** (Table 1).[19] All reported products were characterized by ^1H and ^{13}C NMR, IR spectra, mass spectra and elemental analyses.

In conclusion, a general versatile synthesis of new 7-substituted 5,6-dihydroindol-2-ones **4** bearing various functionalities has been developed. This reaction proceeds via an optimized palladium-catalyzed Suzuki–Miyaura cross-coupling reaction starting from a halogenated indolone **3**. This new series of 7-substituted 5,6-dihydroindol-2-ones offers access to many new building blocks for molecular constructions. These novel compounds are currently being evaluated for their biological activity.

Table 1. Reactions of 7-bromo dihydroindol-2-one with various boronic acids/esters via Suzuki–Miyaura cross-coupling[a]



3 **10** **4**

Entry	10	Coupling partner R	Product 4	Yield[b] (%)
1	**10a**		**4a**	70
2	**10b**		**4b**	67
3	**10c**		**4c**	67
4	**10d**		**4d**	91
5	**10e**		**4e**	75
6	**10f**		**4f**	67
7	**10g**		**4g**	68
8	**10h**		**4h**	80
9	**10i**		**4i**	52
10	**10j**[c]		**4j**	64
11	**10k**[c]		**4k**	68

[a] Reactions were carried out using a mixture of indolone **3**, boronic acid/ester **10** (1.5 equiv), KF (4 equiv), 5 mol % $PdCl_2(PPh_3)_2$, 5 mol % Bu_4NI, THF/H_2O (6:1) under refluxing conditions for 24 h.
[b] Isolated yields.
[c] Commercially available pinacol esters were used instead of the corresponding acid.

Acknowledgements

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19. *Representative procedure for the synthesis of* **4k**: Bromoindolone **3** (0.66 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (0.98 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.04 mmol) and tetrabutylammonium iodide (0.14 mmol) were suspended in tetrahydrofuran (20 mL). A solution of potassium fluoride in H_2O (2.0 M, 3 mL) was added and the mixture refluxed for 20 h. The solvent was evaporated and the residue extracted with dichloromethane. The organic phase was separated, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. Purification of the residue by chromatography on silica gel with ethyl acetate/dichloromethane (1:9, v:v) as the eluent gave **4k** (0.15 g, 68%) as a white solid, m.p. 208–212 °C. ^{1}H NMR (300 MHz): δ 1.85–1.93 (m, 2 H, CH_2), 2.56 (t, $J = 6.0$ Hz, 2H, CH_2), 2.67–2.72 (m, 2H, CH_2), 4.50 (s, 2H, NCH_2), 5.93 (s, 1H,

CH), 6.37–6.40 (m, 3H, H_{aryl}), 6.80–6.83 (m, 1H, H_{aryl}), 6.96–7.07 (m, 3H, H_{aryl}), 7.20–7.24 (m, 3H, H_{aryl}), 8.63 (br s, 1H, NH). ^{13}C NMR (75 MHz): δ 23.1 (CH_2), 24.7 (CH_2), 34.2 (CH_2), 44.4 ($\underline{C}H_2Ph$), 102.7 (CH_{aryl}), 110.5 (CH_{aryl}), 114.3 (CH), 120.9 (CH_{aryl}), 122.5 (CH_{aryl}), 125.0 (CH_{aryl}), 126.21 (CH_{aryl}), 126.26 ($2 \times CH_{aryl}$), 127.4 (C), 127.6 ($2 \times CH_{aryl}$), 128.9 (C), 130.0 (C), 134.4 (C), 135.3 (C), 137.8 (C), 150.1 (C), 172.2 (C=O). IR (Nujol, v, cm^{-1}): 3204, 1661, 1454, 1377, 1361, 1366, 1319, 711. UV (CH_3OH): λ_{max} 328.5 nm (ε 11470 cm^{-1} M^{-1}), 289.5 nm (ε 14240 cm^{-1} M^{-1}). HRMS (ESI): m/z 363.1487 ($M+Na^+$, $C_{23}H_{20}N_2ONa$ requires 363.1468).