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RAPID COMMUNICATION

Iodine-catalyzed regioselective C-3 arylation of indoles with *p*-quinols

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Abstract. Iodine-mediated highly convenient strategy for the C-3 arylation of indoles with *p*-quinols is presented. The present work surpasses in forming a C–C bond at the *meta*-position of the phenols, which is traditionally challenging to functionalize. This protocol further leads the way to have ascendable, forthright access to phenol-assimilated heterocycles which have powerful applications both in synthetic and medicinal chemistry.

Keywords. C-3 arylation of indoles; *meta*-functionalized phenols; indole-phenol hybrids; regioselective reaction.

1. Introduction

Indole and its derivatives are found over a diverse range of natural products and pharmaceutically active compounds.[1–3] They are widely known for their anti-cancer activity especially in case of breast cancer and cervical cancer because of their endowment to boost the breakdown of estrogen in the human body. In addition to their antioxidant,[4] antidepressant[5] activities, indoles are found in many organic compounds such as amino acid tryptophan, pigments and alkaloids.[6] It is a no-brainer that indole acts as an enamine towards electron-deficient species and favors the Michael addition towards α,β-unsaturated ketones and aldehydes.[7] Traditionally, the combination of two moieties results in the synthesis of hybrid scaffolds that individually show the biological activity of both coupling partners. With this aim, we studied the formation of hybrid scaffolds of indole and *p*-quinol entities. Quinols show significant biological activities in natural products[8–11] (Figure 1) and also behave as intermediates in the synthesis of various biologically potent frameworks.[12] Remarkably, 4-hydroxy-4-alkyl-2,5-cyclohexadienones or *p*-quinol derivatives behave as double Michael-type acceptors which show challenging prochiral behaviour[1] for the enantioselective desymmetrization with high regioselectivity.[13] Moreover, these cross-conjugated cyclohexadienones have an attribute to take part in dienone-phenol rearrangement *via* a C–C bond shift.

C-3 arylindoles are ubiquitous core heterocyclic compounds. As a result of the essence of substituted indoles, the most commonly known protocols for direct C-3 functionalization reactions of indoles were introduced *via* transition metal-based catalysts *viz.*, copper and its nanoparticles,[14–16] rhodium[17–19] and palladium[18–26] with ligands. Several other methodologies have also been described for the synthesis of the C-3 arylation of indoles.[17–29] In 2005, Koulouri and co-workers described the acid-catalyzed protocol for arylation on indole.[27] More recently, Zhang *et al.*, designated the transition metal-free direct arylation on indole by photoredox catalysis.[28] Furthermore, Ribagorda and co-workers reported the asymmetric synthesis of C-3 arylated indoles.[1] In 2011, Fan *et al.*, reported the synthesis of C-aryl indoles through *in situ* oxidative dearomatization of *p*-cresols in methanol followed by Michael addition with indoles.[29] However, these protocols have some innate drawbacks, such as harsh conditions, narrow substrate scope and poor yields. Intrigued by the multiple applications of hybrid molecules, herein we present an iodine-

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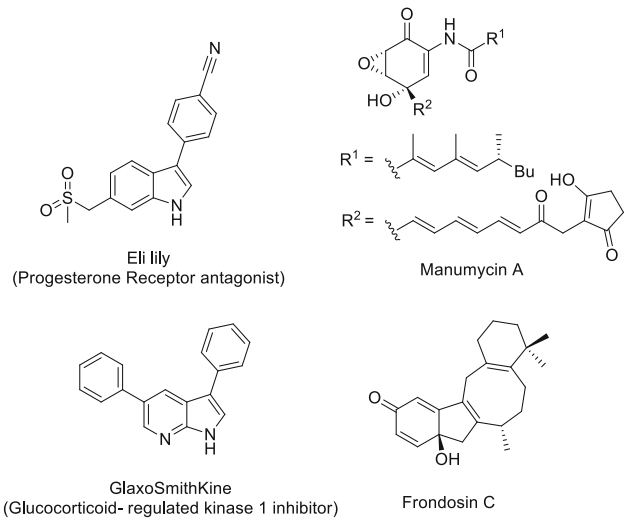


Figure 1. Bioactive compounds containing *p*-quinol and indole units.

catalyzed rapid protocol for the regioselective synthesis of C-aryl indole-phenol hybrids.

2. Results and Discussion

In a pilot experiment, we began our study by choosing *p*-quinol **1a** and *N*-methylindole (**2a**) as model substrates for C-3 arylation. At the outset, the reaction of **1a** and **2a** was carried out at room temperature in the presence of 25 mol% of I_2 in dichloromethane. To our delight, C-3 arylated indole **3**, resulting from the Michael addition of indole **2a** onto *p*-quinol **1a** followed by aromatization, was obtained in 75% yield in 1 min (Table 1, entry 1). Encouraged by these initial findings, the reaction conditions have been screened to improve the yield of the product **3**. For that, a series of reagents such as $ZnCl_2$, $AlCl_3$, TFA and *p*-TSA·H_2O were examined to evaluate their effect in the reaction. However, in the presence of Lewis/Brønsted acid, the desired product was not observed (entries 2–5). Then we continued the reaction in the presence of iodine by switching the solvent to improve the yield of the product **3**. Thus, we tested solvents such as ethyl acetate, methanol, ethanol, THF, toluene, hexane, acetonitrile in the reaction between *p*-quinol **1a** and indole **2a** (entries 6–12).

Among all the tested solvents, the reaction showed the excellent compatibility in ethyl acetate and provided the product **3** in 96% yield (entry 6). Subsequently, we performed the reaction with variable concentrations of catalyst I_2 and observed that the decreasing loading of iodine was not affecting much the efficiency of the reaction. The reaction with 10 mol% of I_2 delivered the C-3 aryl indole **3** in 96% yield (entry 13), and a further decrease in the reagent loading to 5 mol% resulted in the formation of **3** in a similar productivity (entry 14). Thus, 5 mol% of iodine was found to be optimal loading to effect the indole-phenol coupling transformation.

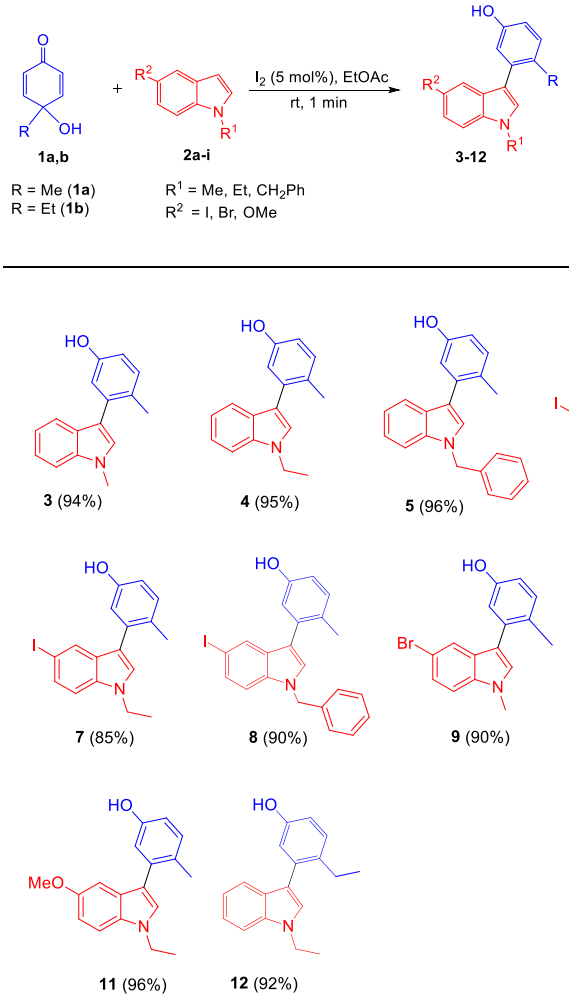
With the optimal conditions established for the synthesis of C-3 aryl indoles, the substrate scope was explored by using various indoles **2a–i** and 4-hydroxy-4-alkyl-2,5-cyclohexadienones **1a–c**. As shown in Scheme 1, there is no significant effect on the reaction

Table 1. Optimization of conditions for C-3 arylation of *N*-methylindole with *p*-quinols.[a]

Entry	Solvent	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	DCM	I_2 (25)	1	75
2	DCM	$ZnCl_2$ (25)	60	–
3	DCM	$AlCl_3$ (25)	60	–
4	DCM	TFA (25)	60	–
5	DCM	*p*-TSA·H_2O (25)	60	–
6	EtOAc	I_2 (25)	1	96
7	MeOH	I_2 (25)	60	–
8	EtOH	I_2 (25)	60	–
9	THF	I_2 (25)	60	–
10	Toluene	I_2 (25)	60	–
11	Hexane	I_2 (25)	60	–
12	ACN	I_2 (25)	1	25
13	EtOAc	I_2 (10)	1	96
14	EtOAc	I_2 (5)	1	94

[a]Reaction conditions: *p*-quinol (**1a**, 0.2 mmol), indole (**2a**, 0.2 mmol), catalyst, solvent (3 mL).

[b]Isolated yield of product **3**.



Reaction conditions: **1a,b** (0.2 mmol), **2a–i** (0.2 mmol) and I_2 (5 mol %), ethyl acetate (3 mL) stirred at rt for 1 min.

Scheme 1. Substrate scope of indoles with **1a**.

of *p*-quinols with *N*-protected indoles carrying groups such as methyl, ethyl and benzyl in terms of yield.

Notably, *N*-protected indoles bearing electron-withdrawing groups at C-5 position such as bromo and iodo gave the desired arylated products **6–10** in a very high yield. The indole bearing electron-donating group such as methoxy group at C-5 position was amenable to the reaction with *p*-quinol **1a** and provided the hybrid structure **11** in excellent yield.

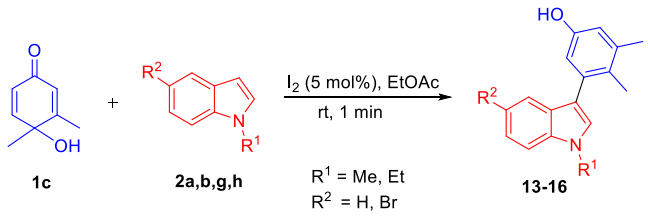
Similarly, the reaction of 4-hydroxy-3,4-dimethyl-cyclohexa-2,5-dien-1-one (**1c**) with indoles **2a**, **b**, **g**, **h** provided the corresponding C-aryl indole derivatives 13–16 in 87–95% yield (Scheme 2).

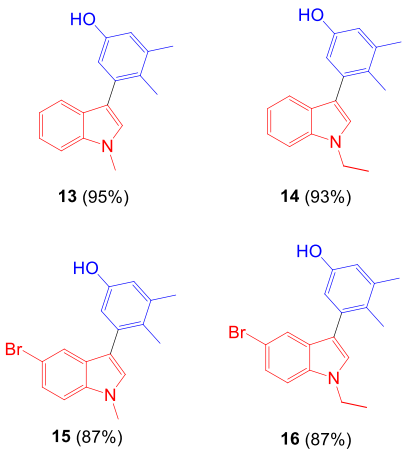
To our surprise, the reaction of *p*-quinol **1c** with iodoindoles **2e**, **f** under the optimized conditions led to the formation of Michael adducts **17** and **18** in very high yield (Scheme 3).

After successfully carrying out the reactions of *p*-quinols with substituted indoles, we turned our attention to extend the scope of the present protocol using sulfur and oxygen containing heterocycles such as 2-methylfuran, 2-ethylfuran and 2-methylthiophene as donors in the reaction with *p*-quinol **1a**. These reactions resulted in the formation of hybrid compounds **19–21** in excellent yield (Scheme 4).

Encouraged by this green and ecological protocol for the synthesis of C-3 aryl indoles and to establish the utility of this procedure, a gram-scale reaction was performed between *p*-quinol **1a** (8.0 mmol) and *N*-methylindole (**2a**, 8.1 mmol) in presence of iodine and the product C-3 aryl indole 3 was obtained in 90% yield (Scheme 5).

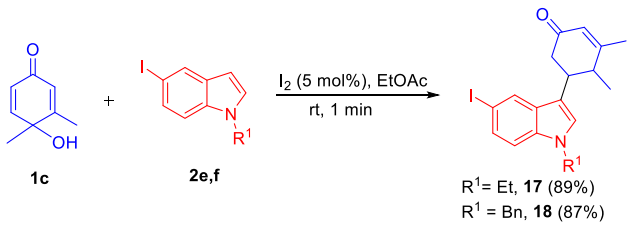
The synthesized hybrid compounds were thoroughly characterized by modern analytical tools. The





Reaction conditions: **1c** (0.2 mmol), **2** (0.2 mmol) and I_2 (5 mol %), ethyl acetate (3 mL) stirred at rt for 1 min

Scheme 2. Substrate scope of indoles with **1c**.



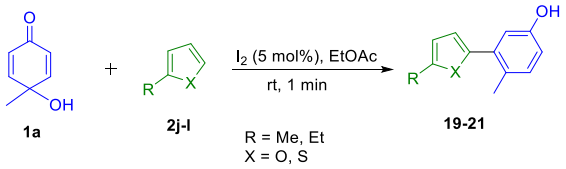
Reaction conditions: **1c** (0.2 mmol), **2** (0.2 mmol) and I_2 (5 mol %), ethyl acetate (3 mL) stirred at rt for 1 min

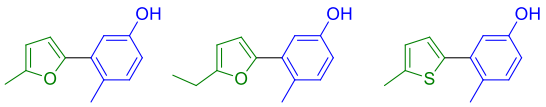
Scheme 3. Reaction of **1c** with iodoindoles **2e, f**.

structure of arylindole **15** was further confirmed by its single-crystal X-ray analysis[30] (Figure 2).

3. Conclusions

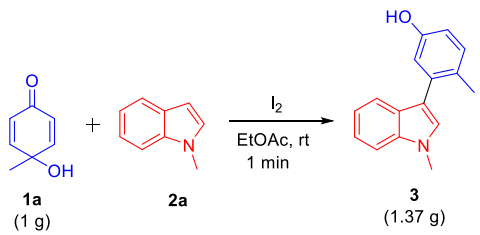
In summary, we have exemplified a novel route to access C-3 arylated indoles *via* a proficient, metal-free, Lewis acid-mediated protocol. The present simple and rapid methodology utilize readily available substrates for Michael addition of heterocyclic systems such as indoles, furans and thiophene to *p*-quinols and subsequent aromatization. The method illustrated here is a straightforward clean, high yielding route for the rapid synthesis of C-aryl indoles which lead the way for the endowment of important biological scaffolds.



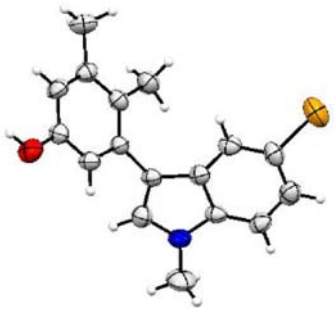


Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol) and I_2 (5 mol %), ethyl acetate (3 mL) stirred at rt for 1 min.

Scheme 4. Reaction of **1a** with five-membered heterocycles.



Scheme 5. Gram-scale synthesis of **3**.



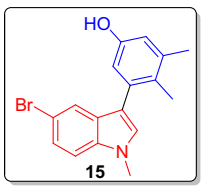


Figure 2. ORTEP diagram of crystal structure of **15**.

Supplementary Information (SI)

Figure S1, Characterization data and ^{1}H NMR and ^{13}C NMR spectra data are available at www.ias.ac.in/chemsci.

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