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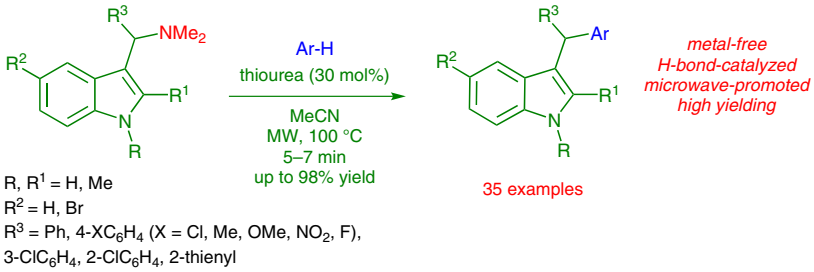
Hydrogen-Bond-Catalyzed Arylation of 3-(Aminoalkyl)indoles via C–N Bond Cleavage with Thiourea under Microwave Irradiation: An Approach to 3-(α,α-Diarylmethyl)indoles

Mohit L. Deb[*a]
Churnika Das[a]
Bhaskar Deka[a]
Prakash J. Saikia[b]
Pranjal K. Baruah[*a]

[a] Department of Applied Sciences, GUIST, Gauhati University, Guwahati 781014, Assam, India
baruah.pranjal@gmail.com
mohitdd.deb@gmail.com
[b] Analytical Chemistry Division CSIR-NEIST, Jorhat 785006, Assam, India



R, R^1 = H, Me
R^2 = H, Br
R^3 = Ph, 4-XC_6H_4 (X = Cl, Me, OMe, NO_2, F), 3-ClC_6H_4, 2-ClC_6H_4, 2-thienyl

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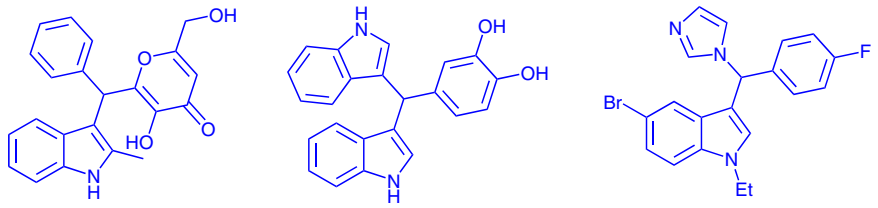
Abstract We have developed a simple and efficient method for the arylation of 3-(aminoalkyl)indoles with aryl alcohols and other aromatic nucleophiles through C–N bond cleavage under microwave irradiation to synthesize 3-(α,α-diarylmethyl)indoles. The method uses thiourea as catalyst, which is environmentally benign, water-tolerant and easy to handle. Notably, acid-sensitive substrates are tolerated under the reaction conditions. Thiourea activates the tertiary amine through double hydrogen bonding and converts it into a better leaving group. The reaction proceeds through the formation of vinylogous iminium ion as an intermediate.

Key words hydrogen-bond-catalyzed, thiourea, microwave, indoles, vinylogous iminium ion

Thiourea/urea based compounds are capable of forming double hydrogen bonds to substrates. This characteristic of thiourea compounds enables the development of attractive methods to activate proton-acceptor substrates such as carbonyl compounds or imine-like compounds. Thiourea and its derivatives are extensively utilized as organocatalysts, including in asymmetric catalysis.[1] Thiourea catalyzed reactions are easy to handle and do not require inert gas atmosphere. They work under mild and neutral conditions and, hence, acid-sensitive substrates are tolerated. Moreover, it is metal-free, relatively nontoxic, water-tolerant, and environmentally benign. Microwave-assisted reactions have several advantages compared with conventional thermal methods. Higher yield and shorter reaction time are two of the intriguing factors that may prompt organic chemists to choose this technique.[2]

The indole nucleus is an important structural motif in medicinal chemistry. Indole derivatives act as free radical scavengers and have a broad spectrum of antioxidant activity.[3] Furthermore, the indole nucleus is a vital component in several drugs used for the treatment of nausea and vomiting induced by chemotherapy, and used as antimitotic, antihypertensive and antineoplastic agents.[4]

C-3-Substituted indoles are the key units of many promising therapeutic agents.[5] They are venerable pharmacophores for medicinal chemists, especially in the neuroscience arena. They have a wide range of biological applications; for example, compound **A** is potent antifungal and antibacterial agent,[6] compound **B** is a HIV-1 integrase inhibitor,[7] and compound **C** functions as an aromatase inhibitor against breast cancer (Figure 1).[8]



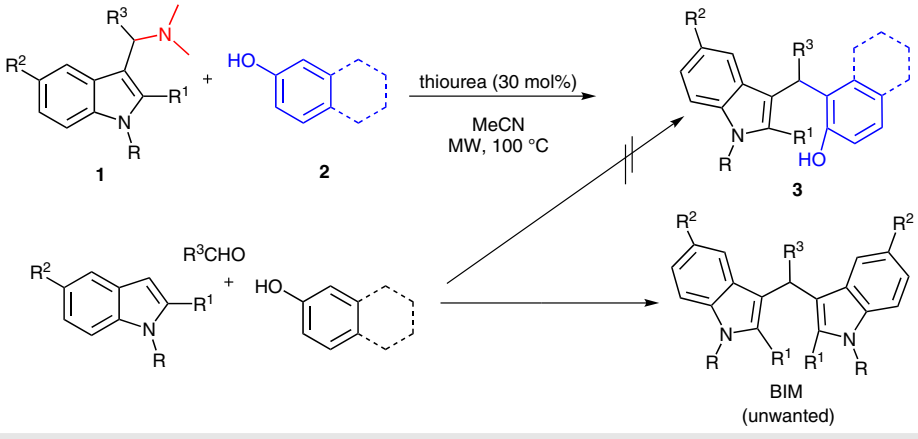
A, Antifungal, antibacterial **B**, HIV-1 integrase **C**, Aromatase inhibitor for breast cancer

Figure 1 Some bioactive indole derivatives

In this context, the synthesis and selective functionalization of indoles has been the focus of active research over the years. Aryl alcohols, such as naphthol derivatives, also possess many important biological properties, including antibacterial,[9a] anti-inflammatory,[9b] hypotensive and bradycardiac activities.[9c] Phenolic compounds, most of which are of plant origin, play a variety of important roles in plants. Most phenolic substances have important effects on the defense of plants against herbivores and pathogens.[10] They have strong antioxidant properties and therefore, function as protective agents against many free-radical-mediated diseases.[11]

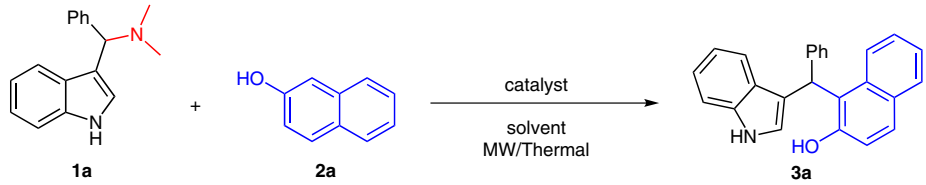
The bioactivity of 3-alkylated indoles (a selection are depicted in Figure 1) encouraged us to synthesize 3-(α,α-diarylmethyl)indoles **3**, bearing an aryl hydroxyl functional group. Only a few reports are available concerning the synthesis of **3**. Grimaud and co-workers described a method for the synthesis of similar compounds.[12] They used a three-component, one-pot approach involving phenol, aldehyde, and *N*-benzyl pyrazine and heating at reflux in toluene for more than two days. The resultant compounds were then treated with indole in the presence of $LiClO_4$ and dibromoethane. The main drawback of the procedure is the requirement for a long reaction time and relatively low yield of product. Jing and co-workers enantioselectively synthesized 3-substituted indoles having an aromatic hydroxyl group through the reaction of 2-naphthols and arenesulfonyl alkylindoles in the presence of asymmetric organocatalysts.[13] The key to this method is the cleavage of a C–S bond, catalyzed by the thiourea derivative. The reaction has further scope for improvement in terms of atom economy, substrate scope, reaction time, preparation of starting material, and catalyst. Wu and co-workers reported another enantioselective Friedel–Crafts reaction of indole with terminal 1,1-diarylalkene to synthesize phenolic derivatives of compound **3**.[14]

Despite the progress discussed above, the development of more proficient routes for the synthesis of such compounds is still required. In a continuation of our work[15] on the development of novel methodologies for the synthesis of valuable compounds, herein we disclose an efficient method for the synthesis of 3-(α,α-diarylmethyl)indoles through arylation of the 3-(aminoalkyl)indoles[16] with aryl alcohols through deamination (Scheme 1). We attempted to synthesize **3** by using a three-component, one-pot approach from indole, aldehyde and naphthol or phenol, and a range of Lewis and Brønsted acid catalysts were screened for this purpose. However, unfortunately we isolated only bisindolylmethanes (BIM) instead of the desired product **3**. Therefore, we switched our reaction route to a two-component strategy, wherein 3-(aminoalkyl)indoles **1** reacted with naphthols or phenols **2** in the presence of catalyst. We chose the synthesis of **3a** from the reaction of **1a** and **2a** as a model reaction for the optimization of the conditions (Table 1). Low yields were obtained under thermal conditions, irrespective of the catalyst and solvent used. A maximum yield of 64% was obtained by using *p*-TsOH as catalyst (20 mol%) and MeCN as solvent under reflux (Table 1, entry 4). Therefore, we performed the reaction under microwave irradiation in an attempt to improve the product yield. Interestingly, when the model reaction was performed in a microwave reactor, we found that, compared with the result obtained with *p*-TsOH as catalyst (80% of **3a**; entry 4), the use of thiourea (30 mol%) as catalyst in MeCN provided excellent yield of **3a** (96%; entry 10) within a few minutes. We also noted that whereas an increase in the catalyst loading did not increase the product yield, a reduction in catalyst loading had a detrimental influence on the yield (entries 11 and 9). Considering that a polar solvent might increase the yield, water was also used as solvent; however, we observed a decrease in the product yield in this case, which might be due to insolubility of the starting materials in H_2O (entry



Scheme 1 Synthesis of 3-(α,α-diarylmethyl)indoles

Table 1 Optimization of the Reaction Conditions[a]

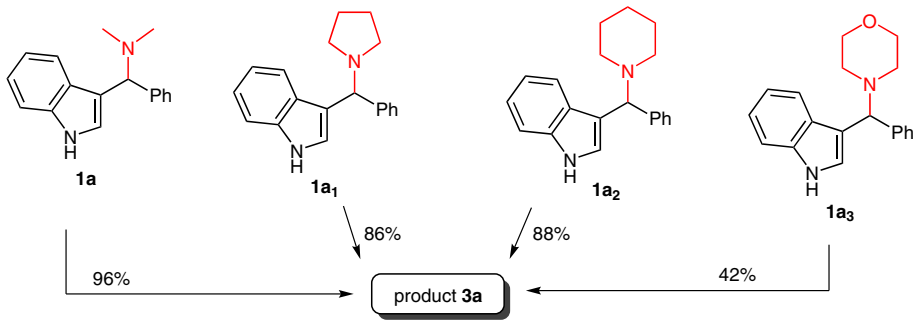


Entry	Catalyst (mol%)	Solvent	Time (min) MW [thermal]	Yield of **3a** (%)[b] MW [thermal]
1	–	–	8 [240]	trace [NR]
2	–	MeCN	8 [240]	trace [NR]
3	AcOH (20)	MeCN	8 [240]	25 [20]
4	*p*-TsOH (20)	MeCN	6 [180]	80 [64]
5	*p*-TsOH (25)	MeCN	6 [180]	80 [64]
6	*p*-TsOH (15)	MeCN	6 [180]	66 [52]
7	TFA (10)	MeCN	5 [180]	75 [55]
8	TFA (15)	MeCN	5 [180]	70 [55]
9	thiourea (20)	MeCN	6 [180]	75 [40]
10	thiourea (30)	MeCN	5 [180]	96 [45]
11	thiourea (40)	MeCN	5 [180]	96 [52]
12	thiourea (30)	H_2O	8 [240]	18 [trace]
13	thiourea (30)	$CHCl_3$	8 [240]	22 [trace]
14	thiourea (30)	toluene	8 [240]	15 [20]
15	thiourea (30)	EtOH	8 [240]	30 [25]
16	thiourea (30)	DMF	8 [240]	trace [10]
17	urea (30)	MeCN	8 [300]	20 [trace]

[a] Reaction conditions (unless otherwise noted): **1a** (1.0 mmol, 250 mg), **2** (1.0 mmol, 144 mg), 100 °C for reactions under microwave conditions; under thermal conditions, the reactions were carried out at reflux except for entry 1 and 16, where the temperature was 100 °C.
[b] Products were purified by column chromatography and yields are of isolated products. NR: no reaction.

12). To our knowledge, there is no report of thiourea-catalyzed C–N bond cleavage. In addition, one of the major advantages of the reaction is that the starting materials **1** for the reactions were smoothly prepared by using the three-component reaction of indole, aldehyde, and amine.[16b]

We then monitored the reaction of 2-naphthol with several 3-(aminoalkyl)indoles, and examined how changes of the amine moiety affected the yield of **3a**. It was observed that Betti bases of dimethylamine furnished the highest yield of the product (Scheme 2). To examine the efficiency and generality of this method, a range of substitut-



Scheme 2 Screening of 3-(aminoalkyl)indoles. *Reagents and conditions*: **1** (1.0 mmol), 2-naphthol (1.0 mmol), thiourea (30 mol%), 100 °C (MW), 5 min.

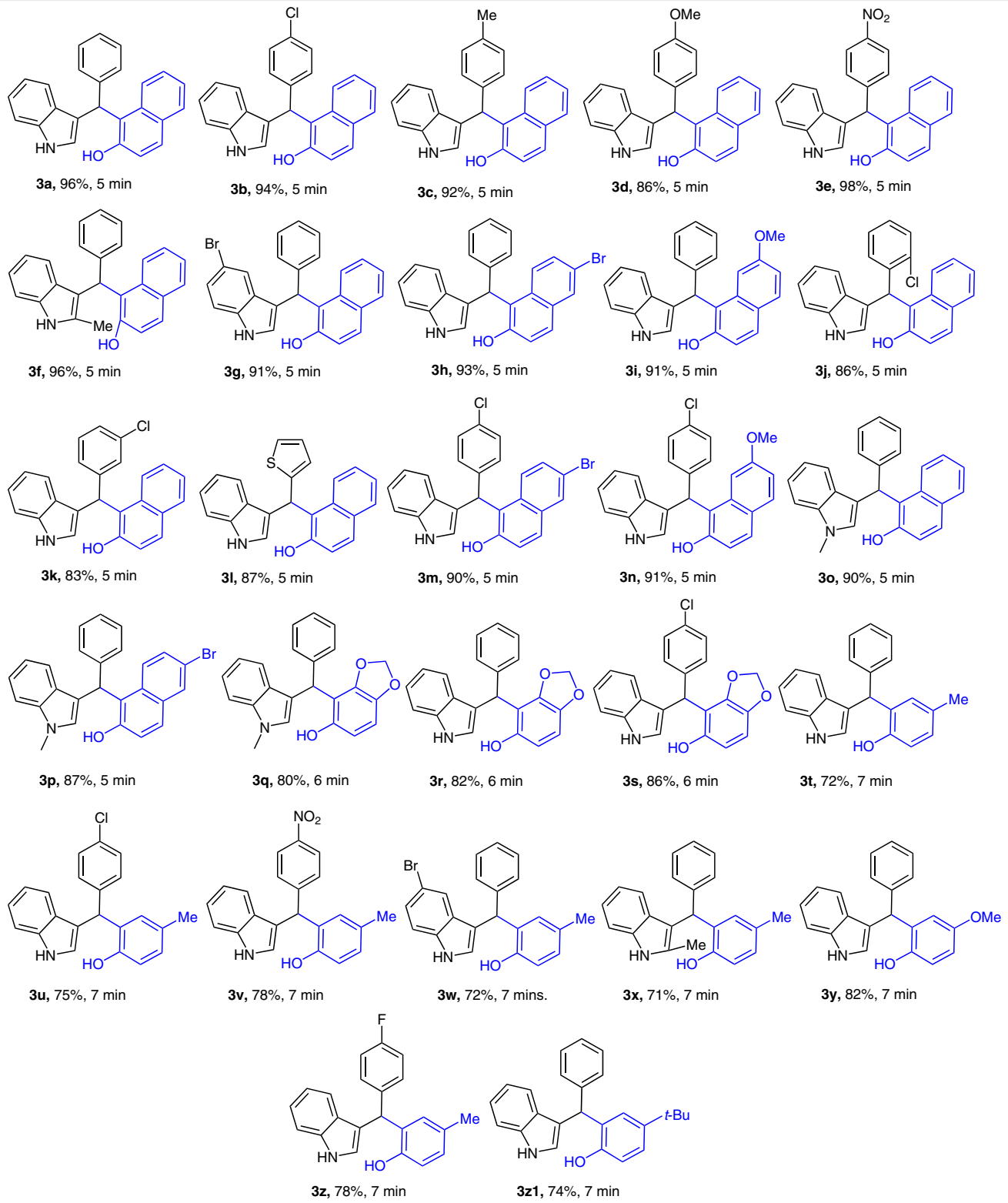


Figure 2 Substrate scope for the synthesis of 3-(α,α-diarylmethyl)indoles by using aryl alcohols as the nucleophilic source. *Reagents and conditions*: **1** (1.0 mmol), **2** (1.0 mmol), thiourea (30 mol%, 23 mg), MeCN (0.5 mL), 100 °C. Products were purified by column chromatography and yields are for the isolated products.

ed 3-(aminoalkyl)indoles and aryl alcohols were investigated under the optimized conditions; the results are summarized in Figure 2.[17]

The corresponding 3-(α,α-diarylmethyl)indoles, which contain a wide range of substituents, were obtained in good to excellent yields. To our delight, both electron-withdrawing and electron-donating substituents on the aryl ring (R^3) of **3** were well tolerated. Electron-donating groups on R^3 decreased the product yield, whereas electron-withdrawing groups increased the yield (**3d** vs. **3e**, Figure 2). As expected, we obtained lower yield of **3**, having a phenolic moiety (e.g., **3t**–**1**; Figure 2). Products **3** were characterized by NMR spectroscopic as well as X-ray crystallographic analyses (Figure 3).[18]

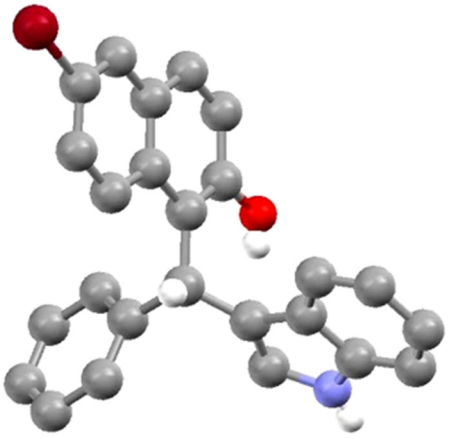


Figure 3 Crystal structure of **3h**; some hydrogen atoms have been removed for clarity

We next extended our reaction methodology by using other electron-rich aromatics such as indoles, methoxybenzenes, *N*,*N*-dimethylaniline, and pyrazoles as the nucleophilic sources and obtained very good yields of **3**. Reactions involving indole nucleophiles may provide an alternative route for the synthesis of unsymmetrical bisindolylmethanes **3aa**–**ad** (Figure 4) that are otherwise difficult to synthesize.

We propose a tentative mechanism for the reaction, which follows an elimination-addition pathway (Scheme 3). First, thiourea activates the amine moiety through double hydrogen bonding and converts it into a better leaving group. The reaction proceeds through the formation of vinylogous iminium ion (**A1**) as intermediate. The iminium ion is then attacked by a molecule of electron-rich aromatic nucleophile (**2**), giving **A2** (path a), which is subsequently aromatized to the desired product **3**. Similar mechanisms have good precedent in the literature.[19] We did not observe any product from the C-2 attack of indole by the nucleophile (path b).

In conclusion, we have developed a simple and efficient method for the synthesis of 3-(α,α-diarylmethyl)indoles containing an aromatic hydroxyl functional group such as naphthol and phenol. The strategy is also applicable to other electron-rich aromatics. The reaction does not require the use of any hazardous metal catalyst or Lewis acid. The method involves the inclusion of thiourea as catalyst, which is an environmentally benign, easy to handle and inexpensive reagent. Moreover, acid-sensitive substrates are tolerated under the reaction conditions. We anticipate that this method will offer an efficient and cost effective approach to

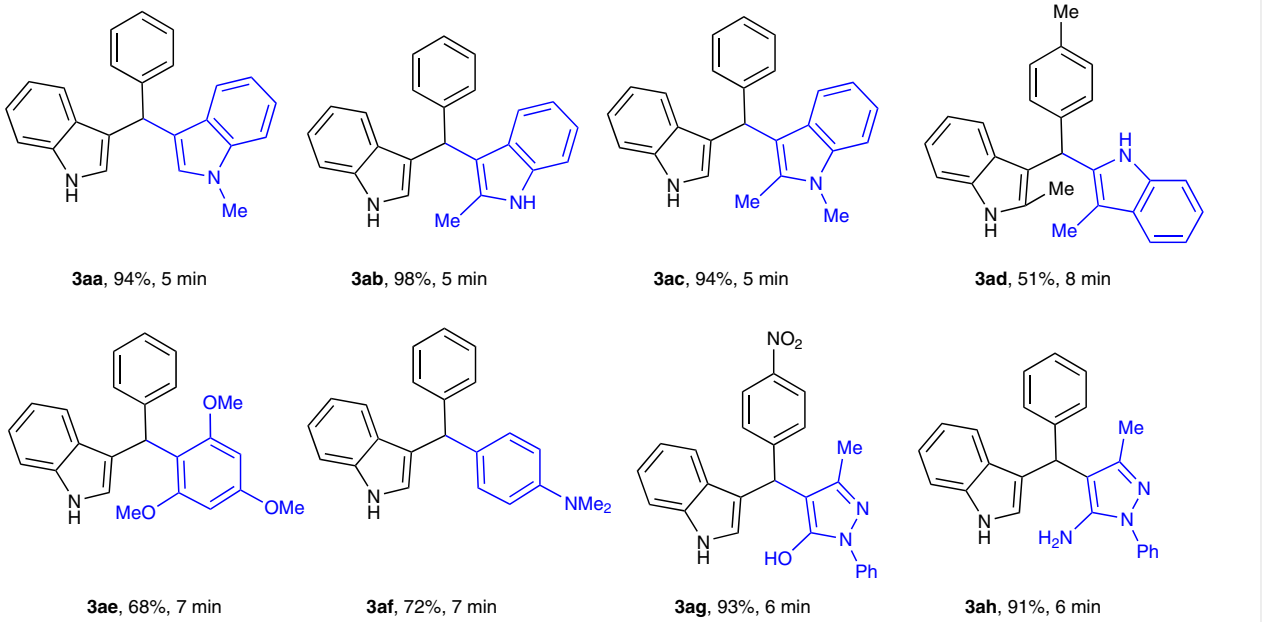
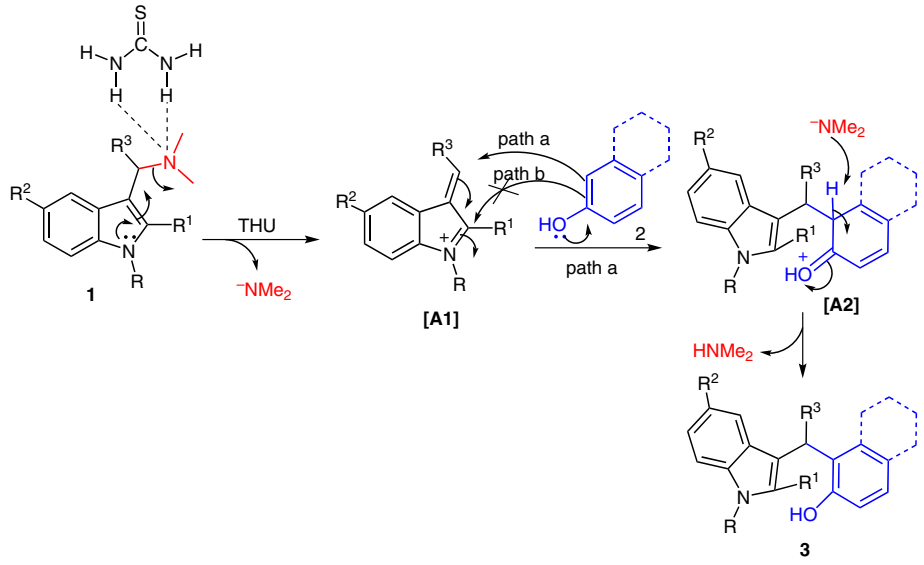


Figure 4 Substrate scope for the synthesis of 3-(α,α-diarylmethyl)indoles using electron-rich aromatics



Scheme 3 A tentative mechanism for the reaction; THU = thiourea

obtain this important class of compounds. Screening of biological activities of the synthesized compounds is underway and will be disclosed in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588887.

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(17) **Synthesis of 3a: Typical Procedure:** A solution of **1a** (1 mmol, 250 mg), 2-naphthol (1 mmol, 144 mg) and thiourea (30 mol%, 23 mg) in MeCN (0.5 mL) was irradiated in a closed vessel in a microwave reactor at 100 °C for the specified time. The progress of the reaction was monitored by TLC. Upon completion of the reaction, solvent was removed under vacuum and the crude mixture was purified by column chromatography (hexane/EtOAc) to obtain the desired product **3a**. Yield: 335 mg (96%); gray solid; mp 168–170 °C. IR (KBr): 3420, 3369, 3065, 2925, 1619, 1455, 1207, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.5 Hz, 1 H), 8.04 (br s, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.73 (d, *J* = 8.8 Hz, 1 H), 7.45–7.14 (m, 10 H), 7.02 (d, *J* = 8.8 Hz, 1 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 6.63 (s, 1 H), 6.50 (s, 1 H), 6.15 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 141.5, 137.0, 133.0, 129.5, 129.4, 128.9, 128.8, 128.6, 127.0, 126.8, 124.0, 123.1, 123.1, 122.5, 120.1, 119.6, 118.5, 117.5, 111.4, 40.9. Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.82; H, 5.34; N, 4.09.

(18) CCDC 1478603 (**3h**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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