Tetrahedron 65 (2009) 8434–8439

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Benzotriazole: an efficient ligand for the copper-catalyzed N-arylation of indoles

Akhilesh Kumar Verma [a,b,c,*], Jaspal Singh [a], Richard C. Larock [c,*]

[a] Synthetic Organic Chemistry Research Laboratory, Dr. B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi 110007, India
[b] Department of Chemistry, University of Delhi, Delhi 110007, India
[c] Department of Chemistry, Iowa State University of Science and Technology, Ames, IA, USA

ARTICLE INFO

*Article history:*
Received 26 November 2008
Received in revised form 20 July 2009
Accepted 21 July 2009
Available online 25 July 2009

*Keywords:*
Benzotriazole
Dihalobenzene
CuI
Indole
N-arylation

ABSTRACT

A general, efficient, and inexpensive method for the N-arylation of indoles using a catalytic system derived from CuI and benzotriazole is reported. Selective mono N-arylation of indoles with *ortho*-dihaloarenes has also been successfully achieved in good yields using this protocol.



## 1. Introduction

*N*-Arylindoles are an important class of compounds because of the significant pharmacological, biological, and chemical activities and their presence in bioactive natural products.[1] *N*-Arylindoles are of interest as antipsychotic agents,[2] antiallergic,[3] COX-2 inhibitors,[4] angiotensin II antagonists,[5] melatonin receptor MT1 agonists,[6] herbicides,[7] and as selective ligands for the G2 binding sites.[8] Beside their biological activity, they are also used as a synthetic intermediates for the preparation of other biologically active compounds.[9] Much attention has been focused on these heterocycles and various synthetic strategies have been developed for the N-arylation of indoles and other heterocycles. During the past few years significant advances have occurred in the development of cross-coupling methodology, traditionally, these *N*-arylindoles have been prepared by nucleophilic aromatic substitution or by Ullman type coupling,[10] which have limitations because of high temperatures and stoichiometric amounts of copper reagent required, plus long reaction times, and low yields.[11] Despite the recent development of Pd-catalyzed C–N bond forming reactions,[12] the copper-catalyzed N-arylation of azoles and other nitrogen heterocycles with aryl halides promoted by various ligands has attracted much attention due to its economy and efficiency.[13,14] To date there have been numerous copper-mediated or copper-catalyzed methods published to allow for such transformation. The ligands, which have been disclosed to promote copper-catalyzed N-arylation of indoles and other heterocycles includes diamines,[15] oxime-phosphine oxides,[16] amino acids,[17] and phosphoramidite,[18] pyrrolidinylmethylimidazole,[19] and *trans*-2,3-diarylpiperazine,[20] diimines,[21] aminoarenethiolates,[22] 2-aminopyrimidines-4,6-diol,[23] hydroxyquinoline,[24] 4,7-dimethoxy-1,10-phenanthroline,[25] 2-oxocyclohexanecarboxylate[26] and *N*-hydroxyimides,[27] pyridine functionalized 1,3 diketone,[28] and hydrazones.[29]

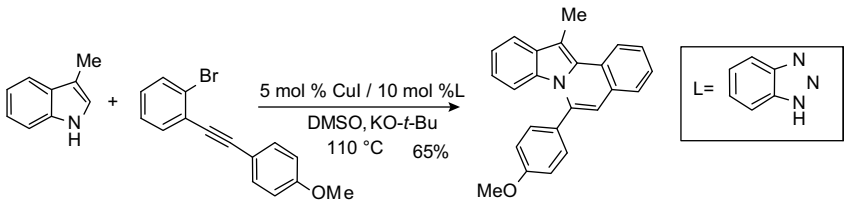
1-(2-Halo-phenyl)indoles and pyrroles are important intermediates for the synthesis of indolo[1,2-*f*]phenanthridines and indolo[1,2-*a*]quinolines, an important class of biologically active compounds.[3] However, the reported synthesis of this type of intermediate is very low yielding (22%)[3] and thus new synthetic methods are needed. Herein, we report a very simple and cost effective catalytic system consisting of commercially available benzotriazole and copper(I) halides, which efficiently catalyzes the N-arylation of indoles. Selective mono N-arylation of indoles and pyrroles by *o*-dihaloarenes has also been achieved in good yields using this catalytic system.

## 2. Results and discussion

In a continuation of recently developed methods for copper-catalyzed C–N and C–S coupling reactions using benzotriazole[30] as a ligand and its application in the tandem synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines by the addition of *N*-heterocycles onto *ortho*-haloarylalkynes, followed by intramolecular arylation (Scheme 1),[31] we hereby expand the application of this ligand to the synthesis of *N*-arylindoles.

* Corresponding authors. Tel.: +91 11 27666272; fax: +91 11 27666248.
*E-mail address:* averma@acbr.du.ac.in (A.K. Verma).

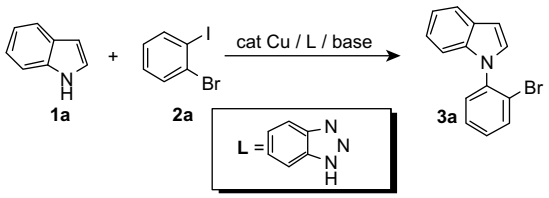
0040-4020/$ – see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tet.2009.07.050




**Scheme 1.**

The arylation of *N*-heterocycles with dihalobenzene has not been much explored and reported synthesis of this type of intermediate are low yielding, thus, it is a longstanding problem, we therefore chose to focus initial studies on the evaluation of the behavior of benzotriazole in the selective N-arylation of *o*-haloarenes with indoles. This was determined during a preliminary survey of reaction conditions with the use of indole and bromoiodobenzene. To identify the optimal reaction conditions for the reaction, a number of copper catalysts, including CuI, CuCl, CuBr, $Cu_2O$, and $Cu(OAc)_2$, and several different organic solvents and bases were examined in the reaction of indole (**1a**) with 2-bromoiodobenzene (**2a**). The results of these experiments are summarized in Table 1.

**Table 1**
Optimization studies[a]




| Entry | L/mol % | L/mol % | Base | Solvent | Time (h)/°C | Yield[b] % |
|---|---|---|---|---|---|---|
| 1 | CuI/10 | — | KO-*t*-Bu | DMF | 24/110 | 0 |
| 2 | CuI/10 | 20 | KO-*t*-Bu | DMF | 30/110 | 39 |
| 3[b] | CuI/10 | 20 | KO-*t*-Bu | DMSO | 30/110 | 46 |
| 4 | CuI/10 | 20 | KO-*t*-Bu | Dioxane | 30/110 | 29 |
| 5 | CuI/10 | 20 | KO-*t*-Bu | Toluene | 30/110 | 25 |
| 6 | CuI/10 | 20 | NaO-*t*-Bu | DMSO | 30/110 | 31 |
| 7 | CuI/10 | 20 | $Cs_2CO_3$ | DMSO | 30/110 | 29 |
| 8 | CuI/10 | 20 | $K_3PO_4$ | DMSO | 30/110 | 63 |
| 9 | CuI/10 | 20 | $K_3PO_4$ | DMSO | 30/120 | 65 |
| 10 | CuI/5 | 10 | $K_3PO_4$ | DMSO | 30/120 | 53 |
| 11 | CuCl/10 | 20 | $K_3PO_4$ | DMSO | 30/120 | 20 |
| 12 | CuBr/10 | 20 | $K_3PO_4$ | DMSO | 30/120 | 18 |
| 13 | $Cu_2O$/10 | 20 | $K_3PO_4$ | DMSO | 30/120 | Trace |
| 14 | $Cu(OAc)_2$/10 | 20 | $K_3PO_4$ | DMSO | 30/120 | 20 |

[a] All reactions were performed with **1a** (0.5 mmol) with **2a** (1 equiv) under standard conditions under an argon atmosphere unless otherwise indicated.
[b] Isolated yields.

We first allowed indole **1a** (0.5 mmol) to react with 1 equiv of 2-bromoiodobenzene (**2a**), 10 mol % of CuI, and 2 equiv of KO-*t*-Bu in 1.0 mL of DMF at 110 °C for 24 h. The desired coupling product **3a** was not observed (Table 1, entry 1). However, the addition of 20 mol % of benzotriazole ligand to the reaction afforded the desired product **3a** in a 39% yield (Table 1, entry 2). From entries 3–5, it is apparent that the solvent has a significant influence on the reaction; DMSO was found to be quite successful for the transformation. Compound **3a** was obtained in 46% yield, when DMSO was used as the solvent, instead of DMF (Table 1, entry 3). When we used dioxane and toluene as solvents, the desired product **3a** was obtained in only 29 and 25% yields, respectively (Table 1, entries 4 and 5). Different bases were tested in this reaction system, but $K_3PO_4$ proved to be most effective (Table 1, entries 6–8). Decreasing the catalyst loading from 10 to 5 mol % adversely affected the yield of the product, since compound **3a** was obtained in only a 53% yield (Table 1, entry 10). The coupling product **3a** was obtained in 65% yield when the reaction was carried out at 120 °C (Table 1, entry 9). Other copper catalysts CuCl, CuBr, $Cu_2O$, and $Cu(OAc)_2$ were found to be inferior (Table 1, entries 11–14).

After optimized reaction conditions were obtained, the scope of the reaction was investigated and the results are summarized in Table 2. The reaction of **1a**, 3-methylindole(**1b**), and 5-methoxyindole (**1c**) with **2a**, 1,2-diiodobenzene (**2b**), and 2,3-dibromopyridine (**2c**) afforded the selective mono coupling products **3a–g** in good yields using our standard reaction conditions (Table 2, entries 1–7). We extended the substrate scope of this reaction by replacing the indole with a pyrrole. Thus treatment of pyrrole (**1d**) with **2a** and **2b** afforded the corresponding products **3h** and **3i** in 61 and 52% yields, respectively (Table 2, entries 8 and 9). Further the reaction of 1,2-iodobenzene **2b** was performed with 2 equiv of indole **1a** to obtain1,2-diarylated product **5m**. It is noteworthy that instead of obtaining di-substituted product **5m**, we obtained mono arylated product **3b** in 68% yield along with reduced product **5n** in 10% yield (Scheme 2).

The scope of the N-arylation of indoles with various substituted aryl and heteroaryl iodides has been examined. Aryl and heteroaryl iodides with electron-donating groups in the *ortho* or *para* position afforded the coupling products in good yields (Table 3; entries 1, 2, 4, 5, 6, 11, and 12). However, the coupling of *p*-tolyl bromide with 3-methylindole (**1b**) gave the corresponding coupling product in a lower yield when compared to the aryl iodide (Table 3, entries 5 and 6). The reaction of 2-iodopyridine (**2c**) with **1a** and **1b** afforded the coupling products **5c** and **5f** in 92 and 93% yields (Table 3, entries 3 and 7). The presence of electron-withdrawing cyano and nitro groups in the *ortho* position of the aryl halide provided the coupling products in excellent yields in 8 h at 80 °C (Table 3, entries 9 and 10).

## 3. Conclusion

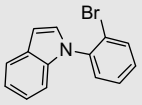
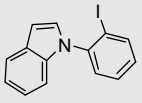
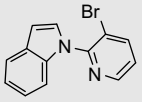
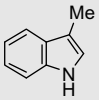
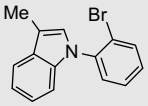
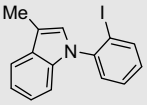
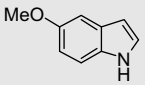
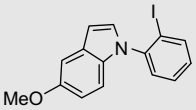
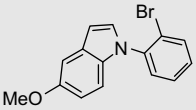
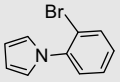
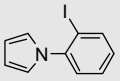
In conclusion, we have developed an inexpensive and experimentally simple method for the synthesis of *N*-arylindoles. The process has been successfully applied to the preparation of important intermediates such as 1-(2-halo-phenyl)indole and pyrrole in good yields. The protocol is palladium free and avoids the use of expensive and air sensitive ligands. Further studies on the scope of this reaction are currently underway in our laboratory.

## 4. Experimental

### 4.1. General

All reagents used were AR grade. Melting points were determined using a Buchi B-540 melting point apparatus. $^1H$ (300 MHz) and $^{13}C$ NMR (75 MHz) and $^1H$ (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded on a Bruker 300 NMR and Varian 400 NMR spectrometer, respectively in $CDCl_3$ (with TMS for $^1H$ and chloroform-*d* for $^{13}C$ as internal references) unless otherwise stated. HRMS and CHN analyses were recorded on Kratos MS50TC double focusing magnetic sector mass spectrometer and on Elementar, Vario EL III. Column

**Table 2**
Selective mono N-arylation of indoles and pyrrole with *o*-dihalobenzenes[a]

| Entry | Indole | | *o*-Dihalobenzene | | Product | | % Yield[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | **1a** |  | **2a** |  | **3a** | 65 |
| 2 | | **1a** |  | **2b** |  | **3b** | 65 |
| 3 | | **1a** |  | **2c** |  | **3c** | 85 |
| 4 |  | **1b** | | **2a** |  | **3d** | 72 |
| 5 | | **1b** | | **2b** |  | **3e** | 70 |
| 6 |  | **1c** | | **2b** |  | **3f** | 68 |
| 7 | | **1c** | | **2a** |  | **3g** | 70 |
| 8 |  | **1d** | | **2a** |  | **3h** | 61[c] |
| 9 | | **1d** | | **2b** |  | **3i** | 52[c] |

[a] All reactions were carried out using 0.5 mmol of the *N*-heterocycle **1** and 1.0 equiv of *o*-dihaloarene **2** in the presence of CuI (10 mol %), **L** (20 mol %), and $K_3PO_4$ (2 equiv) in 1.5 mL of DMSO at 120 °C for 30 h.
[b] The yields are based on the product isolated by column chromatography.
[c] The reaction was carried out 100 °C.

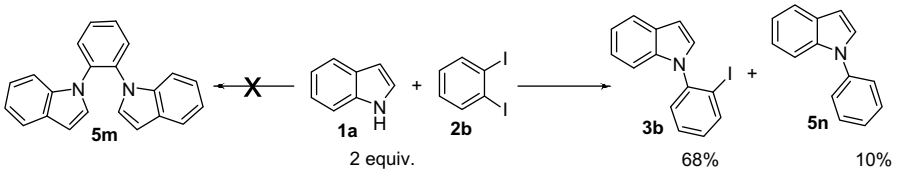
chromatography was performed on silica gel (100–200 mesh). The reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets with silica gel 60 F254 (Merck).

All glassware was oven dried, evacuated, and purged with nitrogen prior to use. All reaction temperature refers to bath temperatures.

## 4.2. General procedure for the synthesis of *N*-aryl heterocycles

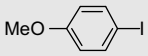
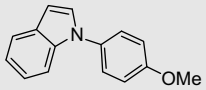
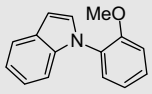
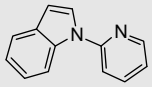
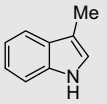
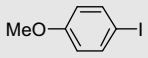
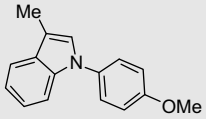
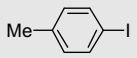
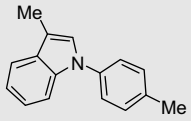
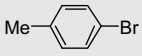
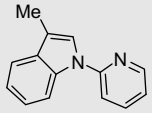
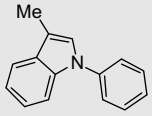
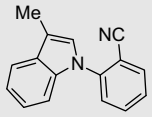
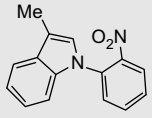
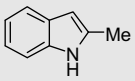
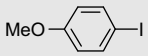
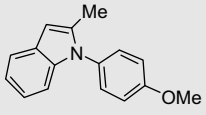
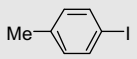
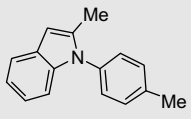
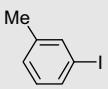
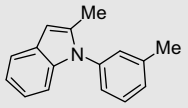
The appropriate quantity of CuI and ligand L was added to a 5 mL round bottom flask containing the aryl halide (0.5 mmol), nitrogen heterocycles (1.1 equiv), and KO-*t*-Bu or $K_3PO_4$ (2 equiv) in 2.0 mL of DMSO. The flask was sealed with a cap containing a PTFE septum. The mixture was then heated at 120 °C until the aryl halides were consumed, as determined by TLC. The reaction mixture was washed with ethyl acetate and water. The organic layer was then washed with brine and dried over $Na_2SO_4$. The solvent was removed in vacuo and the crude residue was purified by column chromatography on silica gel using hexanes or a mixture of hexane and ethylacetate as eluent. *N*-Arylheterocycles were isolated in the yields reported in Table 2 and 3.

*4.2.1. 1-(2-Bromo-phenyl)-1H-indole (**3a**)*[9a]. Colorless oil, 1% EtOAc/hexanes, $R_f$ 0.48; $^1$H NMR ($CDCl_3$) $\delta$: 7.79 (1H, d, *J* 8.24 Hz), 7.73–7.71 (1H, m), 7.47–7.44 (2H, m), 7.36–7.32 (1H, m), 7.25 (1H, d, *J* 3.12 Hz),




**Scheme 2.**

**Table 3**
Reaction of aryl and heteroaryl halides with indoles[a]

| Entry | Indole | | Arylhalide | | Product | | % Yield[b] |
|---|---|---|---|---|---|---|---|
| 1 |  | **1a** |  | **4a** |  | **5a** | 87 |
| 2 | | **1a** |  | **4b** |  | **5b** | 78 |
| 3 | | **1a** |  | **4c** |  | **5c** | 92 |
| 4 |  | **1b** |  | **4a** |  | **5d** | 89 |
| 5 | | **1b** |  | **4d** |  | **5e** | 91 |
| 6 | | **1b** |  | **4e** | | **5e** | 55 |
| 7 | | **1b** |  | **4c** |  | **5f** | 93 |
| 8 | | **1b** |  | **4f** |  | **5g** | 85 |
| 9 | | **1b** |  | **4g** |  | **5h** | 98[c] |
| 10 | | **1b** |  | **4h** |  | **5i** | 96[c] |
| 11 |  | **1c** |  | **4a** |  | **5j** | 87 |
| 12 | | **1c** |  | **4d** |  | **5k** | 89 |
| 13 | | **1c** |  | **4i** |  | **5l** | 90 |

[a] All reactions were carried out using 0.5 mmol of the *N*-heterocycle **1** and 1 equiv of aryl or heteroaryl halide **4** in the presence of CuI (10 mol %), **L** (20 mol %), and KO-*t*-Bu (2 equiv), in 1.0 mL of DMSO at 120 °C for 24 h.
[b] The yields are based on the product isolated by column chromatography.
[c] Reaction was carried out at 80 °C for 8 h.

7.22–7.17 (2H, m), 7.14–7.11 (1H, m), 6.72 (1H, d, *J* 3.12 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 137.1, 134.2, 129.9, 129.6, 128.8, 128.5, 122.5, 121.9, 120.8, 120.5, 110.7, 102.9; HRMS: $MH^+$, found 270.99857. $C_{14}H_{10}BrN$ requires 270.99966.

*4.2.2. 1-(2-Iodo-phenyl)-1H-indole (**3b**).* White solid, mp: 57–58 °C; 1% EtOAc/hexanes, $R_f$ 0.51; $^1$H NMR ($CDCl_3$) $\delta$: 8.03 (1H, dd, *J* 1.64, 8.96 Hz), 7.72–7.70 (1H, m), 7.49 (1H, td, *J* 1.66, 8.5 Hz), 7.39 (1H, dd, *J* 2.12, 8.32 Hz), 7.22–7.16 (4H, m), 7.07–7.04 (1H, m), 6.71 (1H, dd, *J* 0.82, 3.4 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 142.2, 140.4, 136.8, 130.1, 129.6, 129.4, 128.8, 128.5, 122.5, 121.2, 120.4, 110.9, 103.3, 97.8; HRMS: $MH^+$, found 318.98647. $C_{14}H_{10}IN$ requires 318.98580.

*4.2.3. 1-(3-Bromo-pyridin-2-yl)-1H-indole (**3c**).* Colorless oil, 5% EtOAc/hexanes, $R_f$ 0.42; $^1$H NMR ($CDCl_3$) $\delta$: 8.48 (1H, d, *J* 3.6 Hz), 8.03 (1H, dd, *J* 1.6, 6.3 Hz), 7.59 (1H, dd, *J* 1.3, 5.4 Hz), 7.43 (1H, d, *J* 3.3 Hz), 7.35 (1H, d, *J* 8.1 Hz), 7.28–7.08 (3H, m), 6.63 (1H, d, *J* 3.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 150.2, 147.8, 143.3, 135.9, 129.0, 127.7, 123.3, 120.98, 129.95, 115.7, 111.9, 104.4; HRMS: $MH^+$, found 271.98542. $C_{13}H_9BrN_2$ requires 271.99491.

*4.2.4. 1-(2-Bromo-phenyl)-3-methyl-1H-indole (**3d**).* Colorless oil; 1% EtOAc/hexanes, $R_f$ 0.46; $^1$H NMR ($CDCl_3$) $\delta$: 7.79 (1H, d, *J* 8.0 Hz), 7.68–7.66 (1H, m), 7.45 (2H, q, *J* 8.0 Hz), 7.32 (1H, t, *J* 8.0 Hz), 7.23–7.21 (2H, m), 7.13–7.11 (1H, m), 7.06 (1H, s), 2.44 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 138.9, 137.1, 134.1, 129.9, 129.3, 129.1, 128.4, 126.4, 122.4, 121.9, 119.8, 119.2, 112.5, 110.7, 9.9; HRMS: $MH^+$, found 285.01668. $C_{15}H_{12}BrN$ requires 285.01531.

*4.2.5. 1-(2-Iodo-phenyl)-3-methyl-1H-indole (**3e**).* White solid, mp: 71–72 °C, 1% EtOAc/hexanes, $R_f$ 0.51; $^1$H NMR ($CDCl_3$) $\delta$: 7.99 (1H, d, *J* 7.6 Hz), 7.63–7.61 (1H, m), 7.42 (1H, t, *J* 7.4 Hz), 7.31 (1H, d, *J* 7.6 Hz), 7.19–7.13 (2H, m), 7.12 (1H, d, *J* 7.6 Hz), 7.01–6.99 (1H, m), 6.96 (1H, s), 2.3 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 142.4, 140.3, 137.1, 129.7, 129.6, 129.3, 129.0, 126.2, 122.4, 119.8, 119.2, 112.5, 110.8, 97.7, 9.9; HRMS: $MH^+$, found 333.00194. $C_{15}H_{12}IN$ requires 333.00145.

*4.2.6. 1-(2-Iodo-phenyl)-5-methoxy-1H-indole (**3f**).* Colorless oil, 2% EtOAc/hexanes, $R_f$ 0.45; $^1$H NMR ($CDCl_3$) $\delta$: 8.04 (1H, dd, *J* 1.4, 6.4 Hz), 7.50 (1H, td, *J* 1.2, 7.6 Hz), 7.40 (1H, dd, *J* 1.6, 6.4 Hz), 7.21–7.17 (3H, m), 6.98 (1H, d, *J* 8.8 Hz), 6.88 (1H, dd, *J* 2.4, 6.4 Hz), 6.66 (1H, dd, *J* 0.4, 2.8 Hz), 3.90 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 154.6, 142.2, 140.3, 132.1, 129.9, 129.5, 129.3, 129.2, 128.9, 112.6, 111.6, 102.9, 102.7, 97.7, 55.9; HRMS: $MH^+$, found 348.99689. $C_{15}H_{12}INO$ requires 348.99637.

*4.2.7. 1-(2-Bromophenyl)-5-methoxy-1H-indole (**3g**)[9b].* Colorless oil, 2% EtOAc/hexanes, $R_f$ 0.45; $^1$H NMR ($CDCl_3$) $\delta$: 7.80 (1H, d, *J* 8.0 Hz), 7.46 (2H, m), 7.35 (1H, m), 7.24 (1H, d, *J* 4.0 Hz), 7.18 (1H, d, *J* 2.8 Hz), 6.98 (1H, d, *J* 8.0 Hz), 6.88 (1H, d, *J* 8.0 Hz), 6.65 (1H, d, *J* 4.0 Hz), 3.88 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 154.4, 138.7, 134.0, 132.3, 129.9, 129.2, 129.1, 128.9, 128.5, 121.9, 112.6, 111.4, 102.8, 102.6, 55.6; HRMS: $MH^+$, found 301.01097. $C_{15}H_{12}BrNO$ requires 301.01023.

*4.2.8. 1-(2-Bromo-phenyl)-1H-pyrrole (**3h**)[9a].* Colorless oil, 1% EtOAc/hexanes, $R_f$ 0.51; $^1$H NMR ($CDCl_3$) $\delta$: 7.71 (1H, dd, *J* 1.02, 6.9 Hz), 7.42–7.34 (2H, m), 7.25 (1H, dd, *J* 2.0, 6.04 Hz), 6.90 (2H, t, *J* 2.06 Hz), 6.37 (2H, t, *J* 2.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 140.5, 133.9, 128.9, 128.4, 128.3, 122.4, 120.0, 109.3; HRMS: $MH^+$, found 220.98517. $C_{10}H_8BrN$ requires 220.98401.

*4.2.9. 1-(2-Iodo-phenyl)-1H-pyrrole (**3i**).* White solid, mp: 114–116 °C; 1% EtOAc/hexanes, $R_f$ 0.51; $^1$H NMR ($CDCl_3$) $\delta$: 7.92 (1H, dd, *J* 1.04, 6.88 Hz), 7.39 (1H, td, *J* 1.08, 6.68 Hz), 7.29 (1H, dd, *J* 1.4, 6.4 Hz), 7.08 (1H, td, *J* 1.5, 6.3 Hz), 6.80 (2H, t, *J* 2.04, Hz), 6.33 (2H, t, *J* 2.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 144.1, 140.1, 129.5, 129.1, 128.2, 122.3, 109.3, 96.0; HRMS: $MH^+$, found 268.97074. $C_{10}H_8IN$ requires 268.97015.

*4.2.10. 1-(4-Methoxy-phenyl)-1H-indole (**5a**)[12c].* White solid, mp: 57–59 °C; $^1$H NMR ($CDCl_3$) $\delta$: 7.72–7.69 (1H, d, *J* 7.5 Hz), 7.49–7.41 (3H, m), 7.31–7.29 (1H, d, *J* 3.3 Hz), 7.26–7.15 (2H, m), 7.06–7.03 (2H, m), 6.68–6.67 (1H, d, *J* 3.0 Hz), 3.89 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 158.20, 136.28, 132.80, 128.90, 128.26, 125.95, 122.11, 120.98, 120.04, 114.69, 110.33, 102.84, 55.56. CHN Calcd C: 80.69, H: 5.87, N: 6.27, found C: 80.65, H: 5.86, N: 6.22.

*4.2.11. 1-(2-Methoxy-phenyl)-1H-indole (**5b**)[12g].* Colorless oil; $^1$H NMR ($CDCl_3$) $\delta$: 7.77–7.73 (1H, m), 7.51–7.34 (4H, m), 7.33–7.12 (3H, m), 6.72 (1H, d, *J* 3.0 Hz), 6.59 (1H, d, *J* 3.3 Hz), 3.85 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 158.20, 136.28, 132.80, 128.90, 128.26, 125.95, 122.11, 120.98, 120.04, 114.69, 110.33, 102.84, 55.56; HRMS: $MH^+$, found 224.10155 $(M+H)^+$. $C_{14}H_{10}IN$ 223.09971.

*4.2.12. 1-Pyridin-2-yl-1H-indole (**5c**).* Colorless oil; $^1$H NMR ($CDCl_3$) $\delta$: 8.58–8.57 (1H, m), 8.22–8.19 (1H, d, *J* 8.1 Hz), 7.85–7.79 (1H, d, *J* 3.0 Hz), 7.73–7.72 (1H, d, *J* 3.0 Hz), 7.68–7.66 (1H, d, *J* 7.5 Hz), 7.57–7.50 (1H, m), 7.32–7.09 (3H, m), 6.73–6.71 (1H, d, *J* 3.3 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 152.5, 149.0, 138.4, 135.0, 130.4, 123.1, 122.6, 121.2, 121.1, 120.1, 114.6, 112.9, 105.5; HRMS: $MH^+$, found 194.1998. $C_{13}H_{10}N_2$ requires 194.0844.

*4.2.13. 1-(4-Methoxy-phenyl)-3-methyl-1H-indole (**5d**).* Colorless oil; $^1$H NMR ($CDCl_3$) $\delta$: 7.69–7.57 (1H, m), 7.46 (1H, s), 7.36 (1H, d, *J* 6.3 Hz), 7.18–7.09 (3H, m), 7.08–7.05 (3H, m), 3.78 (3H, s), 2.39 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 154.34, 136.92, 128.93, 128.38, 128.11, 127.93, 126.73, 121.80, 121.82, 119.25, 118.84, 112.38, 111.69, 110.77, 55.72, 9.68; CHN for $C_{16}H_{15}NO$, C: 80.98, H: 6.37, N: 5.90; found C: 80.93, H: 6.35, N: 5.89.

*4.2.14. 3-Methyl-1-p-tolyl-1H-indole (**5e**)[15].* White solid, mp: 42–44; $^1$H NMR ($CDCl_3$) $\delta$: 7.65–7.52 (2H, m), 7.37 (1H, d, *J* 8.1 Hz), 7.32–7.12 (6H, m), 2.43 (3H, s), 2.40 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 137.4, 136.0, 135.6, 130.3, 129.6, 125.5, 123.9, 123.5, 122.2, 119.5, 119.1, 112.3, 110.3, 20.9, 9.6; CHN for $C_{16}H_{15}N$: C: 80.84, H: 6.83, N: 6.33; found C: 80.80, H: 6.81, N: 6.28.

*4.2.15. 3-Methyl-1-pyridin-2-yl-1H-indole (**5f**).* Colorless oil, 5% EtOAc/hexanes, $R_f$ 0.43; $^1$H NMR ($CDCl_3$) $\delta$: 8.55–8.53 (1H, m), 8.23–8.21 (1H, d, *J* 8.4 Hz), 7.82–7.76 (1H, m), 7.61–7.59 (1H, d, *J* 7.2 Hz), 7.52 (1H, s), 7.47–7.44 (1H, dd, *J* 7.8, 0.6 Hz), 7.33–7.19 (2H, m), 7.14–7.09 (1H, m), 2.38 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 152.6, 148.8, 138.2, 135.3, 131.0, 123.2, 123.1, 120.7, 119.4, 119.0, 114.8, 114.0, 113.0, 9.7; HRMS: $MH^+$, found 208.3041. $C_{14}H_{12}N_2$ requires 208.1000.

*4.2.16. 3-Methyl-1-phenyl-1H-indole (**5g**)[12j].* Pale amber oil; $^1$H NMR ($CDCl_3$) $\delta$: 7.64–7.62 (m, 1H), 7.58–7.56 (1H, m), 7.52–7.47 (3H, m), 7.37–7.30 (2H, m), 7.27–7.15 (3H, m), 2.40 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 137.6, 131.02, 129.53, 129.17, 125.84, 125.45, 123.97, 122.30, 119.7, 119.16, 112.78, 110.35, 9.58; HRMS: $MH^+$, found 207.10601. $C_{15}H_{13}N$ requires 207.10480.

*4.2.17. 2-(3-Methyl-indol-1-yl)-benzonitrile (**5h**).* White crystal, mp: 127–129 °C; 5% EtOAc/hexanes, $R_f$ 0.38; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$: 7.35(1H, dd, *J* 1.5, 6.3 Hz), 7.76–7.64 (2H, m), 7.62–7.59 (1H, m) 7.46 (1H, dt, *J* 1.2, 6.6 Hz), 7.33 (1H, dd, *J* 2.7, 3.9 Hz), 7.31–7.22 (3H, m), 2.43 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$: 142.2, 136.3, 134.5, 133.8, 129.9, 127.0, 126.8, 125.5, 122.8, 120.6, 119.4,

114.2, 110.2, 109.3, 40.9, 9.6; HRMS: $MH^+$, found 232.1923. $C_{16}H_{12}N_2$ requires 232.1000.

*4.2.18. 3-Methyl-1-(2-nitro-phenyl)-1H-indole (**5i**).* Yellow solid, mp: 73–74 °C; 2% EtOAc/hexanes, $R_f$ 0.40; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$: 8.04–8.01 (1H, dd, *J* 1.3, 6.9 Hz), 7.74 (1H, dt, *J* 1.5, 6.5 Hz), 7.66–7.12 (3H, m), 7.25–7.14 (3H, m), 6.6 (1H, s), 2.40 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$: 145.9, 136.7, 133.5, 133.1, 129.6, 129.4, 127.7, 125.5, 125.2, 122.9, 120.4, 119.4, 114.4, 119.3, 9.6; HRMS: $MH^+$, found 252.2508. $C_{15}H_{12}N_2O_2$ requires 252.0899.

*4.2.19. 1-(4-Methoxy-phenyl)-2-methyl-1H-indole (**5j**)*[12i]. White solid, mp: 69–71; $^1$H NMR ($CDCl_3$) $\delta$: 7.58–7.54 (1H, m), 7.28–7.23 (2H, m), 7.12–7.05 (4H, m), 7.02 (1H, d, *J* 2.1 Hz), 6.37 (1H, s), 3.89 (3H, s), 2.27 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 158.97, 138.49, 137.35, 130.63, 129.16, 128.03, 120.85, 119.81, 119.46, 114.56, 109.96, 100.70, 55.53, 13.25; HRMS: $MH^+$, found 237.2458. $C_{16}H_{15}NO$ requires 237.1154.

*4.2.20. 2-Methyl-1-p-tolyl-1H-indole (**5k**)*[12c]. Yellow oil; $^1$H NMR ($CDCl_3$) $\delta$: 7.57–7.54 (1H, m), 7.34–7.32 (2H, d, *J* 8.1 Hz), 7.26–7.22 (2H, m), 7.13–7.06 (3H, m), 6.39 (1H, s), 2.46 (3H, s), 2.29 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 138.24, 137.58, 137.14, 135.27, 130.02, 128.46, 127.77, 121.08, 120.26, 119.85, 110.03, 100.94, 21.19, 13.33; HRMS: $MH^+$, found 221.1658. $C_{16}H_{15}N$ requires 221.1204.

*4.2.21. 2-Methyl-1-m-tolyl-1H-indole (**5l**).* Colorless oil, 1% EtOAc/hexanes, $R_f$ 0.52; $^1$H NMR ($CDCl_3$) $\delta$: 7.58–7.54 (1H, m), 7.42–7.37 (1H, t, *J* 7.5 Hz), 7.25–7.19 (1H, m), 7.15–7.04 (5H, m), 6.38 (1H, s), 2.42 (3H, s), 2.29 (3H, s); $^{13}$C NMR ($CDCl_3$) $\delta$: 139.4, 138.1, 137.8, 137.0, 129.1, 128.5, 128.4, 128.1, 124.9, 120.9, 119.8, 119.5, 110.0, 101.06, 21.3, 13.4; $C_{16}H_{15}N$; HRMS: $MH^+$, found 221.1398. $C_{16}H_{15}N$ requires 221.1204.

*4.2.22. 1-Phenyl-1H-indole (**5n**)*[12g]. Colorless oil; $^1$H NMR ($CDCl_3$) $\delta$: 7.7–7.67 (1H, m), 7.58–7.53 (1H, m), 7.51–7.48 (4H, m), 7.37–7.32 (2H, m), 6.25–7.14 (2H, m), 6.68 (1H, d, *J* 3.0 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 139.8, 135.8, 129.6, 129.3, 128.0, 126.5, 124.4, 122.4, 121.2, 120.4, 110.5, 103.6; HRMS: $MH^+$, found 193.1008. $C_{14}H_{11}N$ requires 193.0891.

## Acknowledgements

The research work was supported by Department of Science and Technology (DST), Govt. of India and National Institute of General Medicine (GM 070620 and GM 079593), USA. A.K.V. was awarded BOYSCAST fellowship from DST, Ministry of Science and Technology, Govt. of India for the promotion of Science for young Scientist. J.S. is thankful to CSIR, India for the SRF.

## Supplementary data

$^1$H NMR and $^{13}$C NMR spectra of all the synthesized compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.050.

## References and notes

1. (a) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Elsevier: Oxford, 1996; (b) Craig, P. N. In *Comprehensive Medicinal Chemistry*; Drayton, C. J., Ed.; Pergamon: New York, NY, 1991; Vol. 8.
2. (a) Perregaard, J.; Arnt, J.; Bogeso, K. P.; Hyttel, J.; Sanchez, C. *J. Med. Chem.* **1992**, *35*, 1092–1101; (b) Andersen, K.; Liljefors, T.; Hyttel, J.; Perregaard, J. *J. Med. Chem.* **1996**, *39*, 3723–3738.
3. Unangst, P. C.; Connor, D. T.; Stabler, S. S.; Weikert, R. J.; Carethers, M. E.; Kennedy, J. A.; Thueson, D. O.; Chestnut, J. C.; Adolphson, R. L.; Conroy, M. C. *J. Med. Chem.* **1989**, *32*, 1360–1366.
4. Sano, H.; Noguchi, T.; Tanatani, A.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem.* **2005**, *13*, 3079–3091.
5. Jahangir Stabler, S. R. *Synth. Commun.* **1994**, *24*, 123–129.
6. Spadoni, G.; Balsamini, C.; Bedini, A.; Diamantini, G.; Di Giacomo, B.; Tontini, A.; Tarzia, G.; Mor, M.; Plazzi, P. V.; Rivara, S.; Nonno, R.; Pannacci, M.; Lucini, V.; Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **1998**, *41*, 3624–3634.
7. Pallos, F. M.; Matheus, C. J. U.S. Patent 5,739,353 (filed: November 1, 1996).
8. (a) Perregaard, J.; Moltzen, E. K.; Meier, E.; Sanchez, C. *J. Med. Chem.* **1995**, *38*, 1998–2008; (b) Sanchez, C.; Arnt, J.; Costall, B.; Kelly, M. E.; Naylor, R. J.; Perregaard, J. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1323–1332; (c) Wust, F. R.; Kniess, T. *J. Labelled Compd. Radiopharm.* **2005**, *48*, 31–43; (d) Sarges, R.; Howard, H. R.; Koe, H. B. K.; Weissman, A. *J. Med. Chem.* **1989**, *32*, 437–444.
9. (a) Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761–1764; (b) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431–5434.
10. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384; (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–854.
11. Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456.
12. (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernaćndez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828; (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-oman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580; (c) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403–1406; (d) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481–483; (e) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729–7737; (f) Jiang, L.; Buchwald, S. L. Palladium-Catalyzed Aromatic Carbon–Nitrogen Bond Formation. In *Metal-catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 699–760; (g) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729; (h) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925–934; (i) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173; (j) Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851–856.
13. For recent reviews, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439; (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; (c) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.
14. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
15. Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.
16. Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553–6560.
17. Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496–499.
18. Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435–4443.
19. Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 2737–2743.
20. Periasamy, M.; Vairaprakash, P.; Dalai, M. *Organometallics* **2008**, *27*, 1963–1966.
21. Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607–5622.
22. Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241–5244.
23. Xie, Y.; Pi, S.; Wang, J.; Yin, D.; Li, J. *J. Org. Chem.* **2006**, *71*, 8324–8327.
24. Liu, L.; Frohn, M.; Xi, N.; Dominguez, C.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2005**, *70*, 10135–10138.
25. Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779–2782.
26. Lv, X.; Bao, W. J. *J. Org. Chem.* **2007**, *72*, 3863–3867.
27. Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943–8946.
28. Xi, Z.; Liu, F.; Zhou, Y.; Chen, W. *Tetrahedron* **2008**, *64*, 4254–4259.
29. Mino, T.; Harada, Y.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 614–620.
30. (a) Verma, A. K.; Singh, J.; Sankar, V. K.; Chaudhary, R.; Chandra, R. *Tetrahedron Lett.* **2007**, *48*, 4207–4210; (b) Verma, A. K.; Singh, J.; Chaudhary, R.; Chandra, R. *Tetrahedron Lett.* **2007**, *48*, 7199–7202.
31. Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138–1143.