Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 5109–5115

# Ligand-, copper-, and amine-free one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-*endo-dig* cyclization

Sanjay S. Palimkar, P. Harish Kumar, Rajgopal J. Lahoti and Kumar V. Srinivasan*

*Division of Organic Chemistry, Technology, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India*

Received 5 January 2006; revised 22 February 2006; accepted 9 March 2006
Available online 17 April 2006

**Abstract**—Results of the optimized conditions for the one-pot synthesis of 2-substituted indoles via palladium acetate catalyzed tandem Sonogashira coupling 5-*endo-dig* cyclization at room temperature under ultrasonic irradiation and standard stirred conditions are described. Electron-donating and electron-withdrawing groups present in both coupling partners were well tolerated under these mild conditions. A copper-, ligand- and amine-free condition is an important feature of this protocol. Significant enhancement of reaction rates was observed for the reactions employing ultrasonic irradiation.


## 1. Introduction

Indole derivatives occur widely in natural products and possess unique biological activity.[1] Various 2-substituted indoles exhibit interesting pharmacological properties such as antithrombatic,[2] anti-cancer,[3] histamine $H_3$ receptor antagonism,[4] etc. Many synthetic methods for the construction of indole ring have been reported.[5] Among these palladium catalyzed annulation of *o*-halo anilines and alkynes has been employed widely due to the versatile nature of these protocols, increased functional group tolerance, and improved yields.[6]

The synthesis of indoles via Sonogashira reaction is generally carried out in two steps viz. the palladium–copper catalyzed Sonogashira cross coupling between 2-aminoaryl halide and alkyne followed by cyclization of the resulting 2-alkynylanilines. The various catalysts and promoters reported for the cyclization of 2-alkynylanilines include copper(I),[7] metal alkoxide,[8] fluorides,[9] Lewis acids,[10] gold(III),[11] and iodine.[12] Very recently Sakamoto et al. reported cyclization of 2-ethynylaniline derivatives to indoles catalyzed by copper(II) salts in aqueous medium.[13a] Konakahara et al. reported cyclization of 2-alkynylanilines catalyzed by Indium bromide.[13b] Also, several methods are reported for one-pot synthesis of indole via tandem Sonogashira coupling 5-*endo-dig* cyclization.[14] Most of these reported methods suffer from some drawbacks such as harsh reaction conditions, prolonged reaction period, and cumbersome isolation procedure. Many of these methods employ moisture sensitive phosphine ligands and phosphine based palladium catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ and also make use of copper iodide as co-catalyst. With the presence of copper(I) co-catalyst the Glaser type oxidative dimerization of alkynes[15] is encountered thus lowering chemoselectivity. In addition, the starting amines have a characteristic foul smell and industrial wastes containing them would require treatment for environmental purposes.

As a part of our continuing interest in palladium catalyzed carbon–carbon cross coupling reactions,[16] we recently reported the ultrasound promoted ligand- and copper-free Sonogashira reaction at ambient temperature.[16c] Our interest in exploring the potential of this reaction prompted us to extend studies to the palladium catalyzed one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-*endo-dig* cyclization. To the best of our knowledge, a copper-, ligand-, and amine-free one-pot synthesis of indole derivatives via Sonogashira coupling 5-*endo-dig* cyclization has not been reported. Herein, we wish to report an efficient one-pot synthesis of 2-substituted indoles via Sonogashira coupling 5-*endo-dig* cyclization under ligand-, copper-, and amine-free conditions at room temperature using ultrasound irradiation and standard stirred conditions, respectively. The methodology developed makes use of 2 mol % of $Pd(OAc)_2$ in the presence of $Bu_4NOAc$ as a base. Considerable rate enhancement and in most cases marginally improved yields were observed for the sonochemical reactions.

*Keywords*: Indole; Synthesis; 5-*endo-dig* Cyclization; Ultrasound.
* Corresponding author. Tel.: +91 20 25889089; fax: +91 20 25893614; e-mail: kv.srinivasan@ncl.res.in

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.035

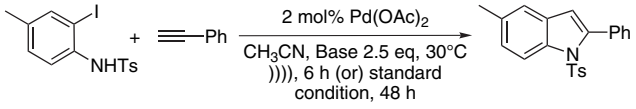
## 2. Results and discussion

Palladium catalyzed reactions are strongly dependent on a number of factors such as base, solvent, stabilizing ligand, temperature, and the combined effect of these. Based on our ongoing work on copper- and ligand-free palladium catalyzed C–C coupling reactions,[16c] our initial aim was to optimize the reactions conditions for this protocol under both ultrasound irradiation and standard stirred conditions at room temperature. For this purpose, we systematically evaluated the role of base and solvent for this synthetic protocol by subjecting 2-iodo-4-methyl-*N*-tosylbenzenamine to the tandem coupling–cyclization process. The results are summarized in Tables 1 and 2, respectively.

$Bu_4NOAc$ was found to be the most effective base (entry 14, Table 1). Other bases (entries 1–7, Table 1) were substantially less effective. Potassium-*tert*-butoxide failed to promote the reaction. Tetrabutylammonium salts are known to facilitate the reduction of $Pd(OAc)_2$ to catalytically active Pd(0) species.[17] Recently Verkade and Urgaonkar reported the $Bu_4NOAc$ promoted Sonogashira reaction.[18] We investigated the effect of counter anions (entries 10–14, Table 1) of the tetrabutylammonium salts. It was found that acetate and fluoride (entry 13 and 14, Table 1) promote this coupling–cyclization reaction whereas, bromide and hydroxide (entry 10 and 11, Table 1) did not promote the reaction. Even though $Bu_4NF$ (in THF 1 M solution) gave an appreciable yield nearly comparable to that with $Bu_4NOAc$ under standard stirred conditions, surprisingly, the yield was low under ultrasound irradiation.

Next, the above benchmark reaction using $Bu_4NOAc$ as the base was examined in various solvents. As is evident, from Table 2 acetonitrile was found to be the most suitable solvent. These tests showed that the optimal reaction conditions for synthesizing 2-substituted indoles required 2 mol % of $Pd(OAc)_2$, 2.5 equiv of $Bu_4NOAc$ and acetonitrile as the solvent.

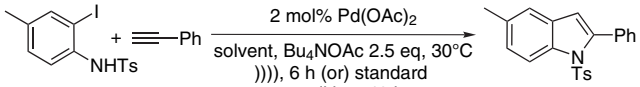
**Table 1**. Effect of base on Sonogashira coupling 5-*endo-dig*-cyclization reaction




| Entry | Base | Yield (%)[a] | |
|---|---|---|---|
| | | Ultrasonic irradiation | Standard stirred conditions |
| 1 | Diisopropyl amine | 7 | 6 |
| 2 | DABCO | 44 | 25 |
| 3 | $Et_3N$ | 23 | 26 |
| 4 | NaOAc | 4 | 5 |
| 5 | $Cs_2CO_3$ | 10 | 9 |
| 6 | $K_2CO_3$ | 13 | 12 |
| 7 | $K_3PO_4$ | 11 | 9 |
| 8 | Piperidine | 0 | 0 |
| 9 | KO$^t$Bu | 0 | 0 |
| 10 | $Bu_4NBr$ | 0 | 0 |
| 11 | $Bu_4NOH$ (in methanol 0.1 N) | 0 | 0 |
| 12 | $Bu_4NF$ (in water 75% solution) | 23 | 15 |
| 13 | $Bu_4NF$ (in THF 1 M solution) | 39 | 68 |
| 14 | $Bu_4NOAc$ | 74 | 71 |

[a] Isolated yields.

**Table 2**. Effect of solvent on Sonogashira coupling 5-*endo-dig*-cyclization reaction




| Entry | Solvent | Yield (%)[a] | |
|---|---|---|---|
| | | Ultrasonic irradiation | Standard stirred conditions |
| 1 | DMF | 50 | 32 |
| 2 | NMP | 0 | 0 |
| 3 | DMA | 5 | 14 |
| 4 | THF | 44 | 26 |
| 5 | $CH_3CN$ | 74 | 71 |
| 6 | $CH_3CN$ | 74[b] | 71[c] |
| 7 | Acetone | 50 | 49 |

[a] Isolated yields.
[b] Yield after 5 h.
[c] Yield after 30 h.

The reaction time was optimized for the benchmark reaction under both ultrasonic irradiation and standard stirred conditions. The isolated yields at various time intervals are given in Table 3. It can be observed for the reaction employing ultrasonic irradiation, the yield was found to increase up to 5 h after which there was no further conversion. Similarly, for the standard stirred conditions the isolated yield was optimized at 30 h.

**Table 3**. Optimization of reaction time for the benchmark reaction

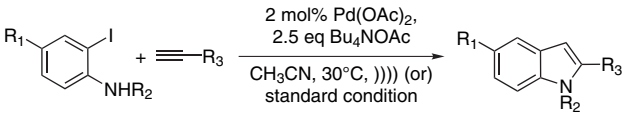
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Standard stirred conditions | Time (h) | 5 | 12 | 18 | 24 | 30 | 36 |
| | Yield (%)[a] | 39 | 48 | 58 | 64 | 71 | 71 |
| Ultrasonic irradiation | Time (h) | 3 | 4 | 5 | 6 | | |
| | Yield (%)[a] | 58 | 65 | 74 | 74 | | |

[a] Isolated yields.

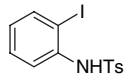
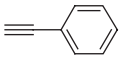
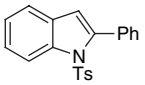
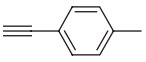
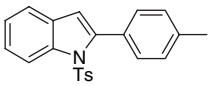
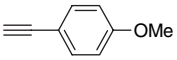
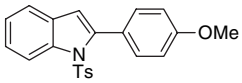
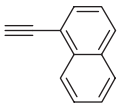
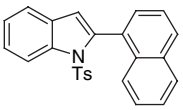
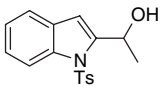
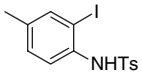
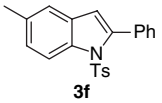
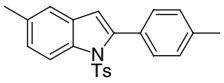
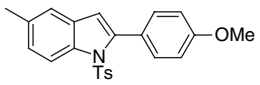
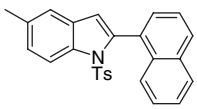
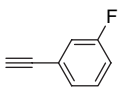
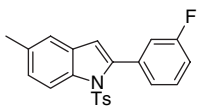
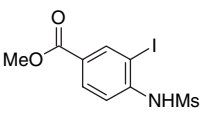
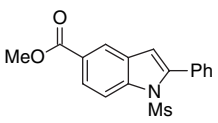
For the identical time (5 h) yield for the reaction employing ultrasonic irradiation was 74% in comparison to that for the standard stirred condition, which gave only 39% yield. This clearly shows significant enhancement in the reaction rate for the reaction employing ultrasonic irradiation.

To survey the generality of this protocol the optimized reaction conditions were applied to the synthesis of various 2-substituted indole derivatives. The results are summarized in Table 4. In all the cases, the reaction time was optimized as for the benchmark reaction. The time of reaction indicated in Table 4 is the optimized time after which no further conversion and improvement in the isolated yield were observed. We studied the effect of different substituents on *o*-iodoanilides and 1-alkynes. Both the unsubstituted *o*-iodoanilides and the substituted *o*-iodoanilides having an electron-donating group on the aromatic ring moiety gave indoles in good yields. It is noteworthy that even if $R_1$ (Table 4) is an electron-withdrawing group (–COMe, $–CO_2Me$, entries 11–18, Table 4) the reaction proceeded smoothly to afford the 2-substituted indoles in moderate yields. Another

**Table 4**. Synthesis of indole derivatives under silent conditions and ultrasound irradiation[a]

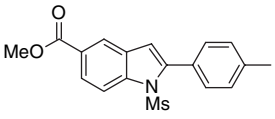
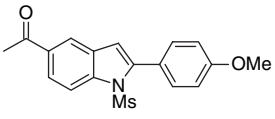
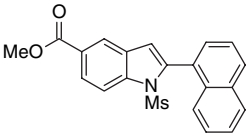
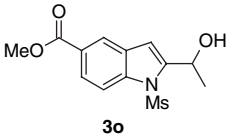
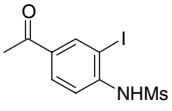
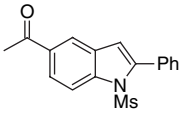
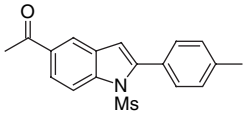
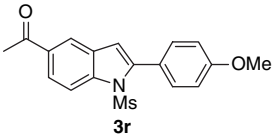



$R_1$ = H, $CH_3$, $CO_2Me$, COMe
$R_2$ = Ts, Ms
$R_3$ = Ph, p-tolyl, 4-methoxy phenyl, 3-fluoro phenyl, naphthyl, 1-hydroxy ethyl

| Entry | *o*-Iodoanilide **1** | 1-Alkyne **2** | Product **3** | Ultrasonic irradiation | | Standard stirred conditions | |
|---|---|---|---|---|---|---|---|
| | | | | Time (h) | Yield (%)[b] | Time (h) | Yield (%)[b] |
| 1 |  **1a** |  **2a** |  **3a** | 4 | 82 | 24 | 80 |
| 2 | **1a** |  **2b** |  **3b** | 5 | 71 | 30 | 69 |
| 3 | **1a** |  **2c** |  **3c** | 6 | 72 | 30 | 76 |
| 4 | **1a** |  **2d** |  **3d** | 6 | 63 | 24 | 67 |
| 5 | **1a** |  **2e** |  **3e** | 6 | 44 | 24 | 41 |
| 6 |  **1b** | **2a** |  **3f** | 5 | 74 | 30 | 71 |
| 7 | **1b** | **2b** |  **3g** | 5 | 90 | 36 | 87 |
| 8 | **1b** | **2c** |  **3h** | 5 | 90 | 36 | 74 |
| 9 | **1b** | **2d** |  **3i** | 6 | 42 | 30 | 46 |
| 10 | **1b** |  **2f** |  **3j** | 6 | 65 | 36 | 56 |
| 11 |  **1c** | **2a** |  **3k** | 6 | 51 | 12 | 43 |

(*continued*)

**Table 4**. (*continued*)

| Entry | *o*-Iodoanilide **1** | 1-Alkyne **2** | Product **3** | Ultrasonic irradiation | | Standard stirred conditions | |
|---|---|---|---|---|---|---|---|
| | | | | Time (h) | Yield (%)[b] | Time (h) | Yield (%)[b] |
| 12 | **1c** | **2b** |  **3l** | 6 | 54 | 12 | 58 |
| 13 | **1c** | **2c** |  **3m** | 6 | 60 | 12 | 54 |
| 14 | **1c** | **2d** |  **3n** | 6 | 61 | 12 | 60 |
| 15 | **1c** | **2e** |  **3o** | 6 | 58 | 12 | 56 |
| 16 |  **1d** | **2a** |  **3p** | 6 | 52 | 12 | 45 |
| 17 | **1d** | **2b** |  **3q** | 6 | 65 | 12 | 71 |
| 18 | **1d** | **2c** |  **3r** | 6 | 66 | 12 | 67 |

[a] Reaction conditions: 1.0 mmol 2-iodoanilide, 1.1 mmol alkyne, 0.02 mmol $Pd(OAc)_2$, and 2.5 mmol $Bu_4NOAc$ with 5 mL of acetonitrile.
[b] Isolated yields.

remarkable feature of this protocol is that the base sensitive ester group was not affected by our mild reaction conditions. Moreover, various substituted terminal alkynes reacted smoothly giving moderate to good yields.

Ultrasound as a non-thermal energy transfer source is well known to enhance reaction rates/yields/selectivity in organic synthesis and has found widespread application in synthetic organic chemistry.[19] Significant enhancement in rate of reaction (5–10 folds) and improved yields for the sonochemical reactions relative to the standard stirred reactions were observed (Table 4).

During the course of the reaction under standard conditions as well as ultrasound conditions we did not observe any uncyclized product. However, the formation of the homo-coupled product arising out of the terminal acetylene was observed to an extent of 2–8%. It should also be noted that we did not observe any reaction when 2-bromo-*N*-tosyl-benzenamine and phenyl acetylene was subjected to this coupling–cyclization protocol under the optimized reaction conditions. Moreover, the reaction of *o*-iodoaniline with the free amino group and phenyl acetylene using the standard reaction conditions yielded only Sonogashira coupled product in 92 and 82% yield by employing the ultrasonic irradiation and standard stirred conditions, respectively. It is worth noting that the *p*-toluene sulfonyl/methane sulfonyl groups were found to be stable under the mild reaction conditions of this protocol. The corresponding *N*-*p*-toluene sulfonyl/methane sulfonyl indoles **3a**–**r** were isolated in

moderate to good yields. These *N*-protected indole derivatives allow us the flexibility to further functionalize the indole nucleus.

## 3. Conclusion

In conclusion, we have developed a mild, efficient, and general one-pot synthesis of 2-substituted indoles at room temperature under ultrasound irradiation and standard stirred conditions in the absence of any ligand, copper, and amine by using $Pd(OAc)_2$ as the catalyst, $Bu_4NOAc$ as the base, in acetonitrile. Both electron-donating and electron-withdrawing substituents on the aryl ring of *o*-iodoanilides were tolerated.

## 4. Experimental

### 4.1. General

Melting points were recorded in open capillary using Buchi melting point B540 apparatus. Column chromatography was performed using silica gel (60–120 mesh size), and TLC was carried out using aluminum sheets precoated with silica gel 60F254. All solvents and chemicals used were reagent grade procured commercially and used without further purification. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance DPX 200 spectrometer. Infra red spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer. Elemental analysis was performed on Flash EA 1112 Thermo Finnigan instrument. The reactions were carried out in a thermostated (30±1 °C) ultrasonic cleaning bath at 50 kHz. The ultrasonic cleaner had an output power of 120 W and a power supply of 450 W. The tank dimensions were 290×240×150 mm with a liquid holding capacity of 9.5 L. The reactions were carried out in a RB flask of 10 mL capacity suspended at the center of the cleaning bath, 5 cm below the surface of the liquid. *o*-Iodoanilines were prepared according to the procedure described in the literature.[20]

### 4.2. General procedure for preparation of 2-substituted indoles

To the mixture of *o*-iodoanilide **1** (1 mmol), $Pd(OAc)_2$ (2 mmol %), and $Bu_4NOAc$ (2.5 mmol) in dry acetonitrile under argon atmosphere was added phenyl acetylene **2** (1.1 mmol). The reaction mixture was then stirred at room temperature or sonicated for the time as shown in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, acetonitrile was evaporated under reduced pressure, diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue thus obtained was purified by column chromatography using ethyl acetate/petroleum benzine as eluent to afford the desired product **3**. To the best of our knowledge, *N*-tosyl derivative of indoles **3** have not been previously reported and hence the complete characterization data is given as follows.

**4.2.1. 2-Phenyl-1-tosyl-1*H*-indole 3a.** Light brown solid; mp 145–147 °C; IR (film, cm$^{-1}$) 3019, 2400, 1450, 1374, 1215, 669; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.20 (s, 3H), 6.47 (s, 1H), 6.96 (d, $J$=8.13 Hz, 2H), 7.15–7.29 (m, 4H), 7.32–7.46 (m, 6H), 8.24 (d, $J$=7.58 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 113.2, 116.6, 120.5, 124.2, 124.5, 126.7, 129.1, 130.1, 130.6, 134.5, 138.1, 138.5, 142.2, 144.4. Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.79; H, 5.15; N, 4.27.

**4.2.2. 2-*p*-Tolyl-1-tosyl-1*H*-indole 3b.** Light brown solid; mp 108–110 °C; IR (film, cm$^{-1}$) 3027, 2922, 1597, 1504, 1449, 1188, 812, 752, 571; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.20 (s, 3H), 2.36 (s, 3H), 6.43 (s, 1H), 6.96 (d, $J$=8.08 Hz, 2H), 7.14–7.37 (m, 9H), 8.22 (d, $J$=8.58 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 113.2, 116.6, 120.5, 124.2, 124.5, 126.7, 129.1, 130.1, 130.6, 131.3, 134.6, 138.1, 138.5, 142.2, 144.4. Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.96; H, 5.28; N, 4.26.

**4.2.3. 2-(4-Methoxyphenyl)-1-tosyl-1*H*-indole 3c.** Light brown solid; mp 126–128 °C; IR (film, cm$^{-1}$) 3019, 2400, 1505, 1215, 668, 572; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.28 (s, 3H), 3.88 (s, 3H), 6.48 (s, 1H), 6.93–7.05 (m, 4H), 7.24–7.34 (m, 4H), 7.40–7.44 (m, 3H), 8.30 (d, $J$=8.28 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 55.2, 112.7, 112.9, 116.5, 120.4, 122.3, 124.1, 126.6, 127.4, 129.1, 129.5, 131.6, 134.9, 135.9, 137.5, 139.1, 144.1, 144.4, 160.0. Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N, 3.71. Found: C, 69.54; H, 4.72; N, 3.81.

**4.2.4. 2-(Naphthalen-1-yl)-1-tosyl-1*H*-indole 3d.** Light brown solid; mp 132–134 °C; IR (film, cm$^{-1}$) 3019, 2400, 1598, 1449, 1373, 667, 569; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.24 (s, 3H), 6.65 (s, 1H), 6.94 (d, $J$=8.06 Hz, 2H), 7.24–7.34 (m, 5H), 7.39–7.54 (m, 4H), 7.64 (d, $J$=8.79 Hz, 1H), 7.91 (dd, $J$=13.19, 8.06 Hz, 2H), 8.39 (d, $J$=8.79 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 113.6, 115.7, 120.7, 123.9, 124.4, 124.7, 125.7, 126.0, 126.2, 126.8, 127.9, 129.1, 129.4, 129.9, 132.9, 133.3, 135.2, 137.5, 138.7, 144.5. Anal. Calcd for $C_{25}H_{19}NO_2S$: C, 75.54; H, 4.82; N, 3.52. Found: C, 75.64; H, 4.52; N, 3.20.

**4.2.5. 1-(1-Tosyl-1*H*-indol-2-yl) ethanol 3e.** Light brown solid; mp 136–137 °C; IR (film, cm$^{-1}$) 3551, 3018, 2985, 2401, 1597, 1451, 1215, 668; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.67 (d, $J$=6.57 Hz, 3H), 2.33 (s, 3H), 3.48 (br s, 1H), 5.35 (q, $J$=6.57 Hz, 1H), 6.68 (s, 1H), 7.16–7.33 (m, 4H), 7.45–7.50 (m, 1H), 7.66 (td, $J$=8.33, 1.76 Hz, 2H), 8.09 (d, $J$=8.08 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 21.5, 62.6, 108.8, 114.7, 121.1, 123.8, 124.9, 126.3, 127.4, 129.1, 129.9, 135.6, 137.2, 144.8, 145.0. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.62; H, 5.32; N, 4.34.

**4.2.6. 5-Methyl-2-phenyl-1-tosyl-1*H*-indole 3f.** Light brown solid; mp 113–114 °C; IR (film, cm$^{-1}$) 3019, 2400, 1598, 1372, 1215, 668, 588; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.19 (s, 3H), 2.33 (s, 3H), 6.39 (s, 1H), 6.94 (d, $J$=8.31 Hz, 2H), 7.06–7.21 (m, 4H), 7.32–7.45 (m, 5H), 8.09 (d, $J$=8.52 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.2, 21.5, 113.5, 116.4, 120.6, 126.1, 126.7, 127.4, 129.1, 130.2, 131.4, 133.9, 134.6, 136.5, 142.2, 144.4.

Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.97; H, 5.21; N, 4.27.

**4.2.7. 5-Methyl-2-*p*-tolyl-1-tosyl-1*H*-indole 3g.** Light brown solid; mp 145–147 °C; IR (film, $cm^{-1}$) 3025, 2921, 1597, 1371, 1174, 811, 573; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.20 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 6.36 (s, 1H), 6.96 (d, $J$=8.00 Hz, 1H), 7.05–7.23 (m, 7H), 7.33 (td, $J$=8.21, 1.91 Hz, 2H), 8.08 (d, $J$=8.45 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.2, 21.4, 21.5, 113.2, 116.4, 120.5, 125.9, 126.8, 128.2, 129.1, 129.6, 130.1, 130.9, 133.8, 134.6, 138.5, 144.3. Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.85; H, 5.75; N, 3.92.

**4.2.8. 2-(4-Methoxyphenyl)-5-methyl-1-tosyl-1*H*-indole 3h.** Light brown solid; mp 138–139 °C; IR (film, $cm^{-1}$) 3028, 2924, 1611, 1506, 1371, 1175, 575; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.28 (s, 3H), 2.40 (s, 3H), 3.88 (s, 3H), 6.41 (s, 1H), 6.92–7.05 (m, 4H), 7.12–7.27 (m, 4H), 7.42 (td, $J$=8.83, 2.14 Hz, 2H), 8.16 (d, $J$=8.44 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.2, 21.4, 55.2, 112.7, 112.9, 116.3, 120.4, 122.8, 124.8, 125.8, 126.7, 129.1, 131.5, 133.8, 134.6, 136.3, 139.2, 142.1, 144.3, 159.9. Anal. Calcd for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.26; H, 5.35; N, 3.81.

**4.2.9. 5-Methyl-2-(naphthalen-1-yl)-1-tosyl-1*H*-indole 3i.** Light brown solid; mp 159–161 °C; IR (film, $cm^{-1}$) 3020, 2924, 1597, 1365, 1172, 592; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.25 (s, 3H), 2.46 (s, 3H), 6.58 (s, 1H), 6.95 (d, $J$=7.95 Hz, 2H), 7.21–7.36 (m, 5H), 7.41–7.55 (m, 3H), 7.66 (d, $J$=8.34 Hz, 1H), 7.85–7.96 (m, 2H), 8.26 (d, $J$=8.46 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.2, 21.3, 113.6, 115.5, 120.6, 124.4, 125.6, 126.1, 126.8, 127.4, 127.9, 129.1, 129.2, 129.4, 129.5, 129.9, 130.2, 130.3, 133.0, 133.3, 133.5, 135.2, 135.7, 138.8, 144.4. Anal. Calcd for $C_{26}H_{21}NO_2S$: C, 75.89; H, 5.14; N, 3.40. Found: C, 75.59; H, 5.03; N, 3.39.

**4.2.10. 2-(3-Fluorophenyl)-5-methyl-1-tosyl-1*H*-indole 3j.** Yellow Oil; IR (film, $cm^{-1}$) 2925, 2856, 1615, 1373, 757, 588; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.21 (s, 3H), 2.33 (s, 3H), 6.42 (s, 1H), 6.95–7.33 (m, 10H), 8.09 (d, $J$=8.33 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.2, 21.4, 114.2, 116.3, 116.7, 120.8, 126.1, 126.5, 126.7, 129.1, 130.6, 134.1, 136.6, 140.7, 144.6, 159.4, 164.3. Anal. Calcd for $C_{22}H_{18}FNO_2S$: C, 69.64; H, 4.78; F, 5.01; N, 3.69. Found: C, 69.54; H, 4.72; F, 4.98; N, 3.81.

**4.2.11. 1-Methanesulfonyl-2-phenyl-1*H*-indole-5-carboxylic acid methyl ester 3k.** Colorless solid; mp 131–132 °C; IR (film, $cm^{-1}$) 3019, 2400, 1717, 1375, 1216, 669; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.82 (s, 3H), 3.96 (s, 3H), 6.76 (s, 1H), 7.43–7.46 (m, 2H), 7.54–7.59 (m, 2H), 8.03–8.20 (m, 2H), 8.32 (d, $J$=1.75 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 40.4, 52.2, 112.6, 115.3, 123.1, 126.1, 127.8, 130.3, 131.4, 140.3, 142.9, 167.1. Anal. Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 62.31; H, 4.65; N, 4.47.

**4.2.12. 1-Methanesulfonyl-2-*p*-tolyl-1*H*-indole-5-carboxylic acid methyl ester 3l.** Colorless solid; mp 146–147 °C; IR (film, $cm^{-1}$) 3011, 2400, 1716, 1215, 669; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.48 (s, 3H), 2.86 (s, 3H), 4.01 (s, 3H), 6.77 (s, 1H), 7.30 (d, $J$=7.92 Hz, 2H), 7.50 (d, $J$=8.08 Hz, 2H), 8.10 (dd, $J$=7.27, 1.61 Hz, 1H), 8.22 (d, $J$=8.88 Hz, 1H), 8.36 (d, $J$=1.29 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 40.4, 52.1, 112.4, 115.3, 122.9, 125.9, 128.5, 130.2, 139.3, 143.1, 167.1. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.64; H, 4.88; N, 4.36.

**4.2.13. 1-Methanesulfonyl-2-(4-methoxyphenyl)-1*H*-indole-5-carboxylic acid methyl ester 3m.** Colorless solid; mp 144–146 °C; IR (film, $cm^{-1}$) 3019, 2400, 1716, 1290, 669; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.74 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 6.64 (s, 1H), 6.91 (d, $J$=8.73 Hz, 2H), 7.43 (d, $J$=8.83 Hz, 2H), 7.98 (dd, $J$=7.19, 1.64 Hz, 1H), 8.11 (d, $J$=8.73 Hz, 1H), 8.24 (d, $J$=1.19 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 40.4, 52.1, 55.3, 112.1, 113.3, 115.3, 118.9, 122.8, 123.4, 125.8, 129.8, 131.6, 140.2, 142.8, 160.3, 167.1. Anal. Calcd for $C_{18}H_{17}NO_5S$: C, 60.15; H, 4.77; N, 3.90. Found: C, 59.70; H, 4.59; N, 4.30.

**4.2.14. 1-Methanesulfonyl-2-(naphthalen-1-yl)-1*H*-indole-5-carboxylic acid methyl ester 3n.** Colorless solid; mp 144–146 °C; IR (film, $cm^{-1}$) 3020, 2400, 1715, 1375, 1215, 668; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.91 (s, 3H), 3.98 (s, 3H), 6.86 (s, 1H), 7.45–7.61 (m, 4H), 7.71 (d, $J$=8.97 Hz, 1H), 7.90–7.99 (m, 2H), 8.09–8.22 (m, 2H), 8.39 (d, $J$=1.65 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 41.1, 52.2, 112.9, 114.5, 123.2, 124.7, 125.5, 126.1, 126.2, 126.7, 128.4, 128.8, 129.2, 129.5, 129.9, 133.1, 133.3, 139.5, 139.9, 167.1. Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.87; H, 4.71; N, 3.94.

**4.2.15. 1-Methanesulfonyl-2-(1-hydroxyethyl)-1*H*-indole-5-carboxylic acid methyl ester 3o.** Colorless solid; mp 132–133 °C; IR (film, $cm^{-1}$) 3326, 3019, 2930, 2400, 1716, 1215, 668; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.72 (d, $J$=6.57, 3H), 3.24 (s, 3H), 3.95 (s, 3H), 5.39 (q, $J$=6.44 Hz, 1H), 6.78 (s, 1H), 8.03–8.05 (m, 2H), 8.28 (d, $J$=1.39 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.6, 41.3, 52.1, 62.1, 108.1, 113.7, 123.4, 126.2, 128.5, 131.1, 139.5, 145.4, 167.0. Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.56; H, 4.64; N, 4.44.

**4.2.16. 1-(1-Methanesulfonyl-2-phenyl-1*H*-indol-5-yl)-ethanone 3p.** Colorless solid; mp 170–171 °C; IR (film, $cm^{-1}$) 3019, 2919, 2400, 1681, 1374, 1215, 668; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.69 (s, 3H), 2.83 (s, 3H), 6.77 (s, 1H), 7.44–7.47 (m, 3H), 7.56 (dd, $J$=7.57, 2.24 Hz, 2H), 8.00 (dd, $J$=7.41, 1.40 Hz, 1H), 8.19 (d, $J$=8.87 Hz, 1H), 8.23 (s, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 26.7, 40.6, 112.7, 115.4, 121.8, 125.1, 127.8, 129.2, 130.3, 133.8, 140.3, 143.1, 197.5. Anal. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.15; H, 4.42; N, 4.52.

**4.2.17. 1-(1-Methanesulfonyl-2-*p*-tolyl-1*H*-indol-5-yl)-ethanone 3q.** Colorless solid; mp 138–139 °C; IR (film, $cm^{-1}$) 3019, 2400, 1678, 1375, 1216, 668; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.35 (s, 3H), 2.61 (s, 3H), 2.75 (s, 3H), 6.67 (s, 1H), 7.18 (d, $J$=7.75 Hz, 2H), 7.38 (d, $J$=8.17 Hz, 2H), 7.91 (dd, $J$=7.02, 1.70 Hz, 1H), 8.12 (d, $J$=9.56 Hz, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 21.3, 26.6, 40.4, 112.4, 115.3, 121.7, 124.8, 128.2, 128.4, 130.1,

133.5, 139.2, 140.2, 143.1, 197.6. Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 65.89; H, 4.93; N, 4.52.

**4.2.18. 1-(1-Methanesulfonyl-2-(4-methoxyphenyl)-1*H*-indol-5-yl)-ethanone 3r.** Colorless solid; mp 187–189 °C; IR (film, $cm^{-1}$) 3019, 2400, 1677, 1216, 758, 669; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.69 (s, 3H), 2.81 (s, 3H), 3.87 (s, 3H), 6.72 (s, 1H), 6.97 (td, $J$=8.87, 2.19 Hz, 2H), 7.49 (d, $J$=8.87, 2.19 Hz, 2H), 7.98 (dd, $J$=6.97, 1.74 Hz, 1H), 8.18 (d, $J$=8.71 Hz, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 26.7, 40.4, 55.2, 112.2, 113.3, 115.5, 121.6, 123.4, 124.8, 129.9, 131.6, 140.3, 143.1, 160.4, 197.6. Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.91; H, 4.91; N, 4.48.

## Acknowledgments

S.S.P. thanks CSIR, New Delhi for providing the Research Fellowship.

## References and notes

1. (a) Gribble, G. W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 207–257.
2. Young, W. B.; Kolesnikov, A.; Rai, R.; Sprengeler, P. A.; Leahy, E. M.; Shrader, W. D.; Sangalang, J.; Burgess-Henry, J.; Spencer, J.; Elrod, K.; Cregar, L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2253–2256.
3. Mackman, R. L.; Hui, H. C.; Breitenbucher, J. G.; Katz, B. A.; Luong, C.; Martelli, A.; McGee, D.; Radika, K.; Sendzik, M.; Spencer, J. R.; Sprengeler, P. A.; Tario, J.; Verner, E.; Wang, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2019–2022.
4. Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767–1770.
5. (a) Sundberg, R. J. *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 119–206; (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
6. For a recent review on indole synthesis see: Cacchim, S.; Giancarlo, F. *Chem. Rev.* **2005**, *105*, 2873–2920.
7. Castro, C. E.; Gaughn, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078.
8. (a) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699–7702; (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 31–32; (c) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823–1828; (d) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507–6511; (e) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Konchel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490.
9. Yasuhara, M. C.; Kanamori, Y.; Kaeko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534.
10. (a) Saulnier, M. G.; Fennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841–7844; (b) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280.
11. Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, *4*, 610–618.
12. (a) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539–541; (b) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037–1040.
13. (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958–10964; (b) Sakai, N.; Annaka, K.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 631–634.
14. (a) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305–1308; (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690; (c) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307–2310; (d) Zhang, H. C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanott, B. E. *Org. Lett.* **2000**, *2*, 89–92; (e) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028; (f) Cacchi, S.; Pabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846; (g) Suzuki, N.; Yasaki, S.; Yasuhara, A.; Sakamoto, T. *Chem. Pharm. Bull.* **2003**, *51*, 1170–1173; (h) Pal, M.; Subramanian, V.; Batchu, V. R.; Dager, I. *Synlett* **2004**, 1965–1969; (i) Chouzier, S.; Gruber, M.; Djakovitch, L. *J. Mol. Catal. A: Chem.* **2004**, *212*, 43–52; (j) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693–697.
15. (a) Siemen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657; (b) Fairlamb, I. J. S.; Bauerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, 632–633; (c) Batsanov, A. S.; Collings, J. C.; Fairlamb, I. J. S.; Holland, J. P.; Howard, J. A. K.; Lin, Z.; Marder, T. B.; Parsons, A. C.; Ward, R. M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 703–706.
16. (a) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, 1544–1545; (b) Rajagopal, R.; Jarikote, D. V.; Srinivasan, K. V. *Chem. Commun.* **2002**, 616–617; (c) Gholap, A. R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2005**, *70*, 4869–4872.
17. Reetz, M. T.; Masse, M. *Adv. Mater.* **1999**, *11*, 773–777.
18. Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752–5755.
19. (a) Luche, J. L. *Synthetic Organic Sonochemistry*; Plenum: New York, NY, 1998; (b) Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 443–451; (c) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2003**, *6*, 693–696; (d) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *3*, 147–150.
20. (a) Xiao, W. J.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9646–9652; (b) Ezquerra, J.; Pedregal, C.; Lamas, C. *J. Org. Chem.* **1996**, *61*, 5804–5812.