Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3733–3738
Tetrahedron Letters

Indium-HI-mediated one-pot reaction of 1-(2-arylethynyl)-2-nitroarenes to 2-arylindoles

Ji Sook Kim [a], Joon Hee Han [a], Jung June Lee [a], Young Moo Jun [a]
Byung Min Lee [b], Byeong Hyo Kim [a,*]

[a] *Department of Chemistry, Kwangwoon University, Seoul 139-701, Republic of Korea*
[b] *Korea Research Institute of Chemical Technology, Taejon 305-600, Republic of Korea*

Received 28 February 2008; revised 31 March 2008; accepted 7 April 2008
Available online 9 April 2008

Abstract

While 1-(2-arylethynyl)-2-nitroarenes were reduced to 2-(2-arylethynyl)anilines in the presence of indium and $InCl_3$ in THF/H_2O (v/v = 5/1) at 50 °C, 1-(2-arylethynyl)-2-nitroarenes were reductively cyclized to 2-arylindoles with good yields in the presence of indium and aqueous HI in benzene.

Indole rings have been well known as the basic skeletons of pharmacologically and biologically active molecules.[1] Because of the wide-ranging applications of indoles, the development of efficient synthetic methods has continuously attracted the attention of many synthetic chemists since the classic Fischer indole synthesis was developed as a good tool for synthesizing bioactive indole compounds. Among the various indole syntheses, the metal-[2] or base[3]-catalyzed preparation of indoles starting from 2-alkynylanilines is one of the most efficient approaches for indole synthesis. However, one-pot reductive cyclizations of 1-(2-arylethynyl)-2-nitroarenes to indoles, which involves both the reductive reaction of the nitro group and following up with intramolecular cyclization, has not been reported yet, despite many studies have been performed on intramolecular metal-catalyzed hydroamination of alkynes leading to indoles. Even two-step cyclizations starting from 2-nitroarylacetylenes to indoles are shown rarely in the literature.[4]

In the view of synthetic tools, the use of indium for various organic transformations has been receiving increasing interest in the past decade for economic and environmental reasons.[5] In particular, the reactions mediated and catalyzed by indium in aqueous media have been focused on synthetic applications because of the ease of reactions that obviate the need for inflammable anhydrous organic solvents and inert atmosphere and also because of indium's green chemistry characteristics.[5b] Worth noting is the fact that the toxicity observed in many metals is little observed in indium, lending the metal its attractive green chemistry.

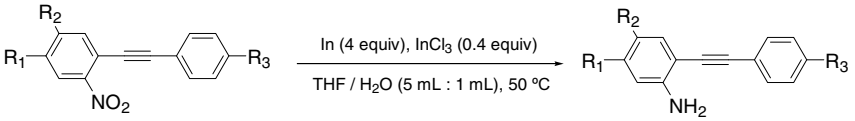
Consequently, considering the importance of bioactive indoles and the attractive green chemistry of indium, we combined them to develop a new synthetic methodology. Based on our previous work concerning the reductive heterocyclizations such as 2,1-benzisoxazoles,[6a,b] benzimidazoles,[6c] quinolines,[6d] and indazoles,[6b] we designed a new path for the indole ring formation starting from 2-ethynyl group substituted nitroarenes using indium metal, which can be triggered by the reductive reaction between the nitro group and indium toward indoles. Herein, we report the development of one-pot indole synthesis via indium-promoted reductive heterocyclization reactions.

Thus, the reductive cyclizations of 1-(2-arylethynyl)-2-nitroarenes using indium either in aqueous or in organic solution were examined for the development of a new synthetic path with indoles. Firstly, we attempted the

* Corresponding author. Fax: +82 2 942 4635.
E-mail address: bhkim@kw.ac.kr (B. H. Kim).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.032

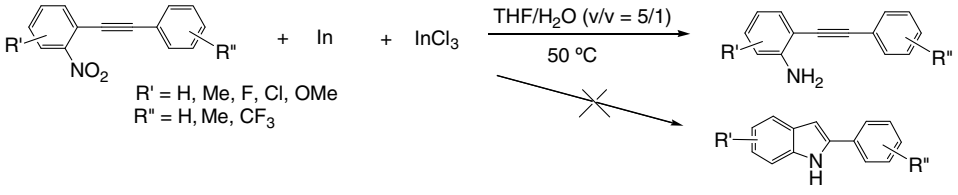
Table 1
Reductive reaction of 1-(2-arylethynyl)-2-nitroarene derivatives to 2-(2-arylethynyl)anilines in the presence of 4 equiv of indium and 0.4 equiv of $InCl_3$ in THF/H_2O (v/v = 5/1) at 50 °C[a]



Entry	Substrate			Time (h)	Product yield[b] (%)
	R_1	R_2	R_3		
1	H	H	H	5	87
2	CH_3	H	H	4	92
3	OCH_3	H	H	3	90
4	Cl	H	H	6	86
5	H	Cl	H	7	81
6	F	H	H	10	86
7	H	H	CH_3	5	83
8	CH_3	H	CH_3	4	82
9	OCH3	H	CH_3	3	83
10	Cl	H	CH_3	14	80
11	H	Cl	CH_3	14	84
12	F	H	CH_3	15	72
13	H	H	CF_3	6	83
14	CH_3	H	CF_3	6	86
15	OCH_3	H	CF_3	3	76
16	Cl	H	CF_3	14	88
17	H	Cl	CF_3	14	86
18	F	H	CF_3	16	69

[a] 0.5 mmol of substrate was used.
[b] Isolated yield.

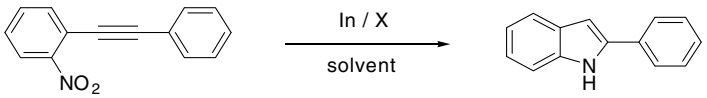
heterocyclizations of 1-(2-arylethynyl)-2-nitroarenes such as 1-nitro-2-(2-phenylethynyl)benzene in the presence of indium/indium(III) chloride as we believe that indium can transfer the electron to trigger the reductive reaction of the nitro group. Moreover, the $InCl_3$ may act as a Lewis acid to activate the triple bond to accept the anionic species of the reduced intermediate of the nitro group. Unfortunately, although various reaction conditions were examined, simply reduced products, 2-(2-arylethynyl)anilines, were obtained as a major product instead of indole formation. However, it is worth mentioning that it can be utilized as a useful methodology, if the simple reduction of nitro moiety is concerned. Thus, the reduction of 1-(2-arylethynyl)-2-nitroarenes was optimized for the synthesis of 2-(2-arylethynyl)anilines. In the presence of 4 equiv of indium and 0.4 equiv of $InCl_3$ in THF/H_2O (v/v = 5/1) at 50 °C, 1-(2-arylethynyl)-2-nitroarenes derivatives were reduced to 2-(2-arylethynyl)anilines in excellent yields as shown in Eq. 1 and Table 1. Although indole formation was failed with the $In/InCl_3$ condition, it will be worth to apply for the synthesis of anilines from nitroarenes as the reaction condition is quite mild with good yields.



(1)

To discover the appropriate reaction condition for the reductive cyclization of 1-(2-arylethynyl)-2-nitroarenes to indoles, not only wide range of Lewis acids or acids such as $InBr_3$, I_2, Br_2, AcOH, and HCl but also various solvents such as H_2O, alcohols, glycol, THF, CH_2Cl_2, pyridine, benzene, toluene, and some co-solvents were examined. However, any of the combination was not successful toward the desired cyclization reaction. After the various reaction conditions were examined, we could finally find out a proper acid and solvent for the reductive one-pot synthesis of indoles, that is, an optimized new condition for indium-catalyzed heterocyclizations to indoles. As shown

Table 2
Reductive cyclization reaction of 1-nitro-2-(2-phenylethynyl)benzene (0.5 mmol) to 2-phenylindole in the presence of indium/hydriodic acid under the various reaction conditions



Entry	Molar equiv				Aliquat 336	Solvent (mL)/temp (°C)	Time (h)	Yield[a] (%)
	In	I_2	HI	HCl				
1	4			40	1 drop	Benzene(15)/reflux	24	NR[c]
2	4	4				Benzene(15)/reflux	24	NR
3	4	4	40			Benzene(15)/reflux	10	43
4	4		40			Toluene(15)/50	24	36
5	4		40			CH_2Cl_2(15)/reflux	24	19[c]
6	4		40			Benzene(15)/50	24	16[b]
7	4		20		1 drop	Benzene(15)/rt	24	NR[c]
8	4		20		1 drop	Benzene(15)/50	24	14[c]
9	4		20		1 drop	Benzene(15)/reflux	7	32
10	4		30		1 drop	Benzene(15)/reflux	24	43
11	4		40		1 drop	Benzene(15)/reflux	8	52
12	4		40			Benzene(15)/reflux	24	35
13	4		60			Benzene(15)/reflux	12	44

[a] GC yield with an internal standard.
[b] NMR yield.
[c] Substrate was remained (entry 1: 50%, entry 5: 40%, entry 7: 20%, entry 8: 24%).

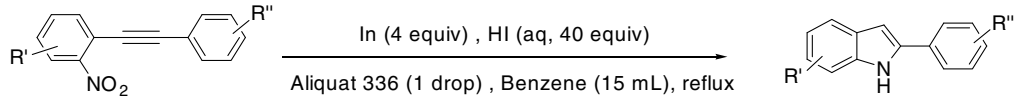
in Table 2, the cyclization of 2-nitroethynylbenzene to indole occurs in the presence of the hydriodic acid in benzene, whereas it does not occur even in the presence of the hydrochloric acid (Table 2, entry 1).

As indium in the presence of hydriodic acid turned out to have a reasonable reductive ability and trigger the cyclization toward indoles, the indium/hydriodic acid-promoted cyclization of 1-nitro-2-(2-phenylethynyl)benzene to indole was extended to cyclizations of variously substituted 1-(2-arylethynyl)-2-nitroarenes to test the synthetic utilization. Thus, the heterocyclizations of variously substituted 1-(2-arylethynyl)-2-nitrobenzene were examined using the optimized reaction conditions, that is, indium (4 equiv)/aq HI (40 equiv)/aliquat 336 (1 drop) in benzene at reflux (Table 3, entries 1–18). In most cases, the cyclization reaction appears to be generally applicable, as most of the substrates were consumed within 1–8 hours to give the corresponding indoles with reasonable yields.

As shown in Table 3, an interesting tendency of the substituent was observed. In general, the hyperconjugative electron-donating methyl group on either of the phenyl rings seems to enhance the reactivity in terms of fast reaction time and (similar or) improved yield compared with a similar compound that has no methyl group on the phenyl ring (e.g., entry 1 vs entries 2, 3; entry 5 vs entries 6, 7; entry 9 vs entries 10, 11; entry 13 vs entries 14, 15). On the other hand, the electronegative group or heteroatom on either of the phenyl rings tends to retard the reaction and reduce the yield as well. Especially, the reactions of trifluoromethyl substituted 1-nitro-2-(2-phenylethynyl)arenes such as 1-[2-[4-(trifluoromethyl)phenylethynyl]]-2-nitrobenzene (entry 4), 1-[2-[4-(trifluoromethyl)phenylethynyl]]-4-methyl-2-nitrobenzene (entry 8), and 4-chloro-1-[2-[4-(trifluoromethyl)phenylethynyl]]-2-nitrobenzene (entry 12) were retarded significantly and the yield was drastically lowered. In the case of 4-chloro-1-[2-[4-(trifluoromethyl)phenylethynyl]]-2-nitrobenzene, no major product was observed even with the extended reaction time of up to 2 days. The substitution of highly electronegative halogen atom such as fluoro atom on the phenyl ring also slowed down the reaction and lowered the yield as shown in entries 16, 17, and 18 in Table 3. Therefore, the hyperconjugation effect and electronegativity of the substituent seem to affect the reactivity, which may come from the variations in electron density of the triple bond between the two phenyl groups. Although the reaction path is not disclosed yet, it is obvious that 1-amino-2-(2-arylethynyl)arene is not a reaction intermediate, since 1-amino-2-arylethynylarene is not transformed into the corresponding indole by treating with HI or HI-In^{3+} (In^{3+} could be formed from the reduction of nitro group by indium) in aliquat 336/benzene at reflux. We presume that more reactive intermediate such as nitroso radical anion species may trigger the heteroannulation. We are now studying on theoretical calculations to explain the mechanistic considerations.

A typical procedure for the reductive heterocyclization is as follows: 2-Nitroethynylarene derivative (0.5 mmol) was added to a mixture of indium powder (230 mg, 2.0 mmol) and aliquat 336 (1 drop) in benzene (10 mL), and then hydriodic acid (4.5 mL, 20 mmol) in benzene (5 mL) was added. The reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with diethyl ether (30 mL), filtered through Celite, poured into 10% $NaHCO_3$ solution (30 mL), and extracted with diethyl ether (30 mL x 3). The combined organic extracts were

Table 3
Synthesis of 2-phenylindole derivatives under the optimized condition



(0.5 mmol)

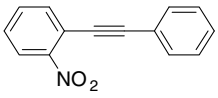
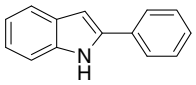
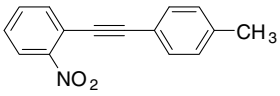
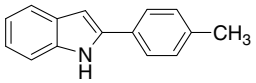
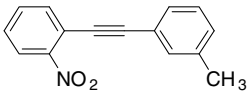
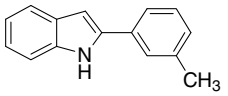
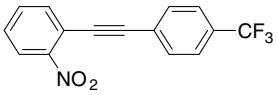
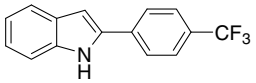
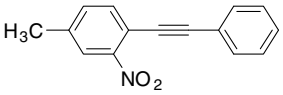
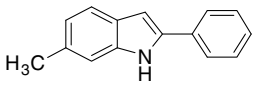
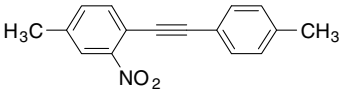
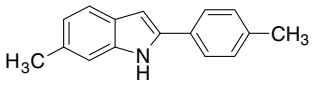
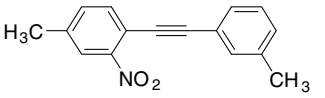
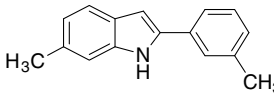
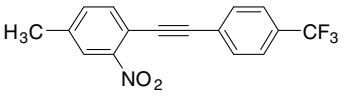
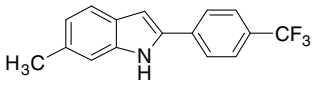
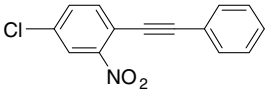
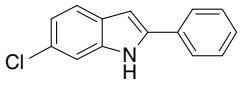
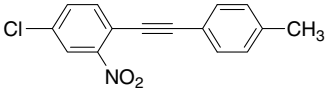
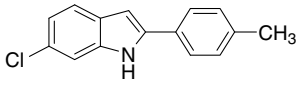
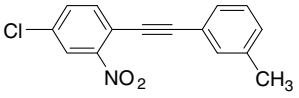
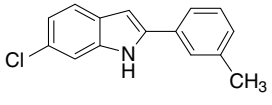
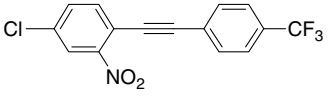
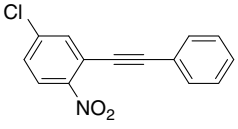
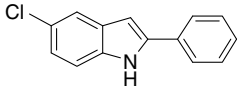
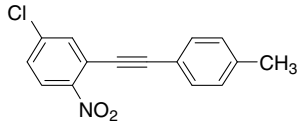
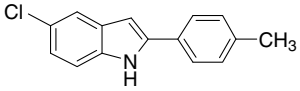
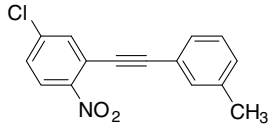
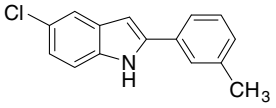
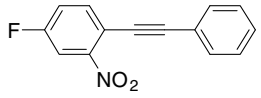
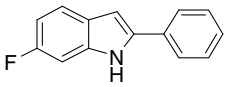
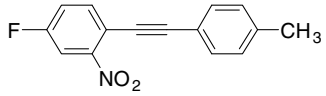
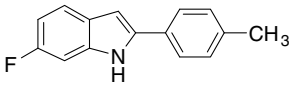
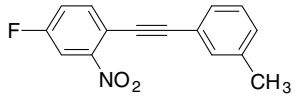
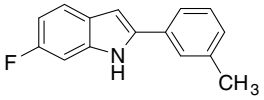
Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		8		50
2		2		60
3		2		55
4		16		18
5		6		64
6		1		58
7		1		63
8		12		17
9		6		50
10		4		50
11		4		53
12		48	—	No major product
13		8		54

Table 3 (*continued*)

Entry	Substrate	Time (h)	Product	Yield[a] (%)
14		3		57
15		3		61
16		12		44
17		3		45
18		6		35

[a] Isolated yield.

dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 2/98–20/80) through a silica gel column to give the corresponding 2-phenylindole, for the structures of 2-arylindoles were fully characterized by ^1H NMR, ^{13}C NMR, FTIR, MS, and HRMS.[7]

In conclusion, we have described a simple and efficient method for one-pot transformation of 2-nitroethynylarenes to the corresponding 2-arylindoles with good yields in the presence of indium and aqueous HI in benzene.

Acknowledgment

This work was supported by the RRC program of the Ministry of Commerce, Industry and Energy and partly by the Kwangwoon University in the year 2007.

References and notes

1. (a) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249–263; (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175–191; (c) McKay, M. J.; Carroll, A. R.; Quinn, R. J.; Hooper, N. A. *J. Nat. Prod.* **2002**, *65*, 595–597; (d) Somei, M.; Yamada, F.; Kurauchi, T.; Nagahama, Y.; Hasegawa, M.; Yamada, K.; Teranishi, S.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **2001**, *49*, 87–96; (e) Revial, G.; Jabin, I.; Lim, S.; Pfau, M. *J. Org. Chem.* **2002**, *67*, 2252–2256.
2. (a) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42–64; (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 2, pp 207–257; (c) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075; (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920; (e) Taylor, E. C.; Katz, A. H.; Salgado-Zamora, H.; McKillop, A. *Tetrahedron Lett.* **1985**, *26*, 5963–5966; (f) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799–1802; (g) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581–2584; (h) Rudisillt, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866; (i) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289–296; (j) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812; (k) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzalez, J. M. *J. Org. Chem.* **1996**, *61*, 5804–5812; (l) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001–1011; (m) Zhang, H. –C.; Ye, H.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751–4754; (n) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275–5278; (o) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277–1280; (p) Dai, W.-M.; Guo, D.-S.; Sun, L. P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2912–2919; (q) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843–3846; (r) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126–1136; (s) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527–1530; (t) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958–10964; (u) Sun, L.-P.; Dai, W.-M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7255–7258.
3. (a) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534; (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488–2490; (c) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699–7702; (d) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571–1587; (e) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409; (f) Sun, L.-P.; Huang, X.-H.; Dai, W.-M. *Tetrahedron* **2004**, *60*, 10983–10992.
4. Tokuyama, H.; Makido, T.; Han-ya, Y.; Fukuyama, T. *Heterocycles* **2007**, *72*, 191–197.
5. (a) Yamamoto, H.; Oshima, K. In *Main Group Metals in Organic Synthesis*; Wiley-VCH: Weinheim, 2004; Vol. 1, Chapter 8, pp 323–386; (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, 1997; (c) Li, C. J. *Tetrahedron* **1996**, *52*,

5643–5668; (d) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633–655; (e) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959–1982; (f) Kumar, S.; Pervinder, K.; Vijay, K. *Curr. Org. Chem.* **2005**, *9*, 1205–1235.

6. (a) Kim, B. H.; Jin, Y.; Han, R.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2000**, *41*, 2137–2140. 4244; (b) Han, R.; Son, K. I.; Ahn, G. H.; Jun, Y. M.; Lee, B. M.; Park, Y.; Kim, B. H. *Tetrahedron Lett.* **2006**, *47*, 7295–7299; (c) Kim, B. H.; Han, R.; Kim, J. S.; Jun, Y. M.; Baik, W.; Lee, B. M. *Heterocycles* **2004**, *62*, 41–54; (d) Han, R.; Chen, S.; Lee, S. J.; Qi, F.; Wu, X.; Kim, B. H. *Heterocycles* **2006**, *68*, 1675–1684.

7. Representative spectroscopic data of 6-fluoro-2-(4-methylphenyl)indole; TLC (20% ethyl acetate/hexane) R_f 0.45; mp 225–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.48–7.53 (m, 3H), 7.24 (d, 2H, $J = 8.3$ Hz), 7.06 (dd, 1H, $J = 9.7$, 2.3 Hz) 6.87 (ddd, 1H, $J = 9.8$, 8.7, 2.3 Hz) 6.73 (br s, 1H) 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.10, 158.74, 138.56, 138.53, 137.69, 136.67, 136.55, 129.73, 129.33, 125.84, 124.88, 121.19, 121.09, 108.98, 108.74, 99.23, 97.35, 97.09, 21.2; IR (Nujol) 3441, 3058, 2990, 1498, 1415, 1348, 1261, 908 cm^{-1}; GC–MS *m*/*z* (rel. intensity) 225 (M^+, 100), 209 (6), 196 (7), 183 (5), 112 (6), 99 (3); HRMS (EI) calcd for $C_{15}H_{12}FN$ 225.0953, found 225.0950.