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$InBr_3$-catalyzed sulfonation of indoles: a facile synthesis of 3-sulfonyl indoles

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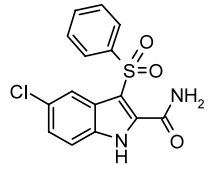
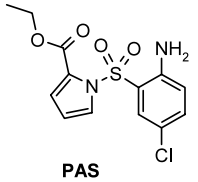
Abstract—Indoles react smoothly with sulfonyl chlorides in the presence of a catalytic amount of indium tribromide at ambient temperature to afford the corresponding 3-arylsulfonyl indole derivatives in high yields with high regioselectivity.

Aryl sulfones and sulfoxides are interesting functional groups possessing manifold reactivity for conversion to a variety of organosulfur compounds in the field of drugs and pharmaceuticals.[1] In particular, aryl sulfones have received much attention as powerful anti-HIV-1 agents.[2] Indol-3-yl and pyrrol-2-yl aryl sulfones are found to be highly potent and structurally novel non-nucleoside reverse transcriptase inhibitors (NNTRIs) for example L-737,126 and PAS.[3,4]



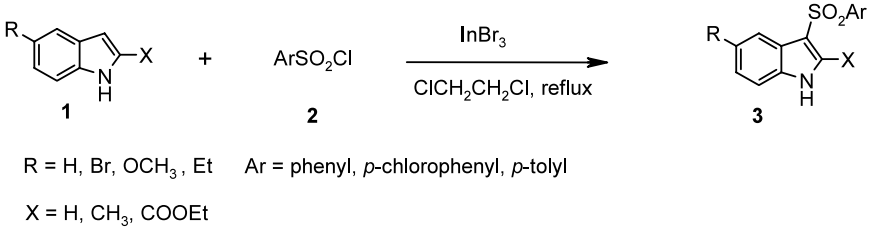
L-737,126



PAS

Indolyl aryl sulfones are generally prepared by indirect methods which involve the oxidation of indol-3-yl sulfides to the corresponding sulfones.[3] Alternative methods such as chlorosulfination and direct mesylation of more substituted indoles have also been reported.[4] In view of the importance of indolyl aryl sulfones as non-nucleoside reverse transcriptase inhibitors, a direct and one-pot approach for their synthesis is needed. In recent years, indium halides have evolved as mild and water-tolerant Lewis acids imparting high regio-, stereo- and chemoselectivity in various organic transformations.[5] Compared to conventional Lewis acids, indium halides have advantages of water stability, recyclability and operational simplicity. Particularly, indium tribromide is found to be a more effective catalyst than conventional Lewis acids in promoting various transformations including glycosidation, thioacetalization, cyanation of ketones and conjugate addition reactions.[6,7]

In this letter we highlight our results on the electrophilic sulfonylation of indoles with sulfonyl chlorides using a catalytic amount of indium bromide. Thus treatment of indole **1** (R = H) with phenylsulfonyl chloride **2** (Ar = Ph) in the presence of 10% $InBr_3$ in 1,2-dichloroethane afforded 3-phenylsulfonyl-1*H*-indole **3b** in 87% yield (Scheme 1).



Scheme 1.

Keywords: indium reagents; sulfonylation; indoles; indolyl aryl sulfones.
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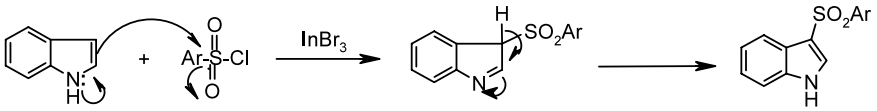
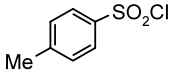
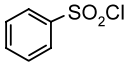
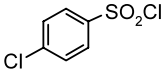
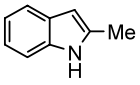
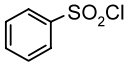
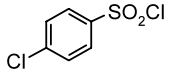
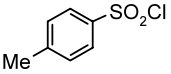
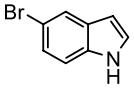
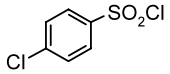
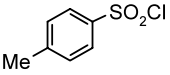
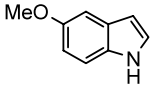
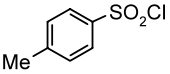
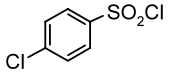
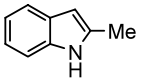
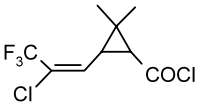
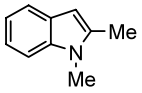
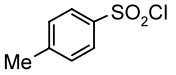
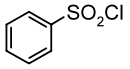
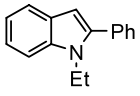
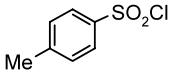
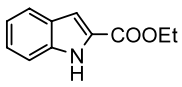
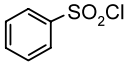


Scheme 2.

Table 1. Indium tribromide-catalyzed sulfonation of indoles[a]

Entry	Indole	Sulfonyl chloride	Product[a]	Yield(%)[b]	Time(h)
a			**3a**	90	8.0
b	"		**3b**	87	7.5
c	"		**3c**	85	9.0
d			**3d**	95	6.0
e	"		**3e**	90	7.5
f	"		**3f**	93	6.5
g			**3g**	78	9.5
h	"		**3h**	82	9.0
i			**3i**	91	6.5
j	"		**3j**	89	7.5
k			**3k**	85	6.0
l			**3l**	70	7.0
m			**3m**	92	6.0
n			**3n**	65	9.0
o			**3o**	82	7.5

a:All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
b: Isolated and unoptimized yields.

A variety of indoles reacted smoothly with sulfonyl chlorides under similar conditions to give the corresponding 3-arylsulfonyl indole derivatives in high yields.[8] In all cases, the reactions proceeded efficiently in dichloroethane at reflux temperature with high regioselectivity. No *N*-substituted products were observed under these reaction conditions. This is probably due to the stabilization of the imine–enamine complex by the Lewis acid during sulfonylation as shown in Scheme 2.

The nature of the substituents on the aromatic ring shows some effects on this conversion. Activated indoles gave the products in excellent yields (see Table 1). However, the treatment of *N*-protected indoles such as *N*-ethyl or *N*-methyl derivatives with *p*-toluene sulfonyl chloride in dichloroethane at 75–80°C for 7–9 h afforded the corresponding 3-phenylsulfonyl indole derivatives in 65 and 70% yields, respectively. All products were characterized by ^{1}H NMR, IR and mass spectroscopy and also by comparision with authentic compounds.[3,4] In contrast, metal triflates such as $In(OTf)_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$ gave the products in moderate yields (45–60%). The best results were obtained when indium tribromide was used as the catalyst. Similar yields and selectivity were also obtained with 10% $ZrCl_4$ and 10% $BiCl_3$ under similar conditions. However, in the absence of catalyst, the reaction of phenyl sulfonyl chloride and indole did not yield any product even after a long reaction time under reflux. This method does not require any additives or anhydrous conditions and no precautions need to be taken to exclude moisture from the reaction media. The solvents 1,2-dichloroethane and toluene were found to give the best results. An acid chloride also reacted smoothly with 2-methyl indole to generate a 3-acyl derivative under similar conditions (entry k). The scope of indium tribromide-catalyzed sulfonylation of indoles was investigated with respect to various indoles and sulfonyl chlorides and the results are presented in Table 1.

In summary, indium tribromide was found to be a novel and highly efficient Lewis acid catalyst for the direct synthesis of 3-arylsulfonyl indole derivatives from indoles and aryl sulfonyl chlorides under mild reaction conditions. This method is also useful for the acylation of indoles with acid halides.

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References

1. (a) Holland, H. L. *Chem. Rev.* **1988**, *88*, 473–485; (b) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135–1178.
2. McMohan, J. B.; Gulakowsky, R. J.; Weislow, O. S.; Schoktz, R. J.; Narayanan, V. L.; Clanton, D. J.; Pedemonte, R.; Wassmundt, F. W.; Buckheit, R. W., Jr.; Decker, W. D.; White, E. L.; Bader, J. P.; Boyd, M. R. *Antimicrob. Agents. Chemother.* **1993**, *37*, 754–760.
3. (a) Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharrides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291; (b) Artico, M.; Silvestri, R.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, G.; Scintu, F.; La Colla, P. *J. Med. Chem.* **2000**, *43*, 1886–1891.
4. (a) Unangst, P. C.; Connor, D. T.; Stabler, S. R. *J. Heterocyclic Chem.* **1987**, *24*, 817–820; (b) Shen, J.-K.; Katayama, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1871–1877; (c) Shen, J.-K.; Katayama, H. *Chem. Pharm. Bull.* **1992**, 2879–2884; (d) Silvestri, R.; De Martino, G.; Sbardella, G. *Org. Prep. Proced. Int.* **2002**, *34*, 507–510.
5. (a) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149; (c) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16; (b) Ghosh, R. *Indian J. Chem.* **2001**, *40B*, 550–557.
6. (a) Bandini, M.; Giorgio Cozzi, P.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett.* **2001**, *42*, 3041–3043; (b) Ceschi, M. A.; Felix, L. A.; Peppe, C. *Tetrahedron Lett.* **2000**, *41*, 9695–9699; (c) Bandini, M.; Giorgio Cozzi, P.; Giocomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704.
7. (a) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett.* **2002**, *43*, 5437–5440; (b) Yadav, J. S.; Reddy, B. V. S. *Synthesis* **2002**, 511–514.
8. *Experimental procedure*: A mixture of indole (2 mmol), sulfonyl chloride (2.5 mmol) and $InBr_3$ (10 mol%) in dichloroethane or toluene (10 mL) was stirred at reflux temperature for an appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure indolyl aryl sulfone. Spectral data for selected products:
3-(4-Methylphenylsulfonyl)-1*H*-indole (3a): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.20 (s, 3H), 6.78–6.85 (m, 4H), 6.97–7.10 (m, 2H), 7.20–7.30 (m, 2H), 7.45 (d, 1H, $J=8.0$ Hz), 8.15 (brs, NH). IR (KBr) ν: 3325, 1579, 1445, 1380, 1296, 1226, 1141, 1090, 751 cm^{-1}. EIMS: m/z: 271 M$^+$, 206, 195, 178, 130, 119, 82, 47. Anal. calcd for $C_{15}H_{13}NO_2S$ (271.33): C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.51; H, 4.91; N, 5.23; S, 11.76. HRMS calcd for $C_{15}H_{13}NO_2S$: 271.0667. Found: 271.0673.
3-(4-Chlorophenylsulfonyl)-2-methyl-1*H*-indole (3e): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 6.80–6.95 (m, 2H), 7.05–7.25 (m, 5H), 7.50 (d, 1H, $J=8.0$ Hz), 8.05 (brs, NH, 1H). (KBr) ν: 3327, 1580, 1441, 1387, 1298, 1225, 1144, 1091, 757 cm^{-1}. EIMS: m/z: 305 M$^+$, 273, 207, 162, 147, 73, 55. Anal. calcd for $C_{15}H_{12}ClNO_2S$ (305.77): C, 58.92; H, 3.96; Cl, 11.59; N, 4.58; S, 10.48. Found: C, 58.85; H, 3.88; Cl, 11.66; N, 4.67; S, 10.39. HRMS calcd for $C_{15}H_{12}ClNO_2S$: 305.0277. Found: 305.0281.
5-Methoxy-3-(4-methylphenylsulfonyl)-1*H*-indole (3i): ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.80 (s, 3H), 6.80

(dd, 1H, $J=1.8$, 8.0 Hz), 6.90–6.98 (m, 4H), 7.05 (d, 1H, $J=8.0$ Hz), 7.15 (d, 1H, $J=8.0$ Hz), 7.20 (d, 1H, $J=8.0$ Hz), 8.10 (brs, NH, 1H). IR (KBr) v: 3333, 1580, 1440, 1389, 1299, 1227, 1149, 1097, 760 cm^{-1}. FAB Mass: m/z: 301 M^+, 275, 246, 185, 165, 123, 109, 91, 75, 41. Anal. calcd for $C_{16}H_{15}NO_3S$ (301.35): C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.68; H, 5.11; N, 4.71; S, 10.71. HRMS calcd for $C_{16}H_{15}NO_3S$: 301.0772. Found: 301.0779.

3-(2-Chloro-3,3,3-trifluoro-(*E*)-1-propenyl)-2,2-dimethylcyclopropyl-2-methyl-1*H*-3-indolylmethanone (3k): ^1H NMR (200 MHz, $CDCl_3$) δ: 1.30 (s, 3H), 1.60 (s, 3H), 2.35 (dd, 1H, $J=8.1$, 8.5 Hz), 2.60 (s, 3H), 2.98 (d, 1H, $J=8.1$ Hz), 7.20–7.35 (m, 4H), 7.85 (d, 1H, $J=8.0$ Hz), 8.65 (brs, NH, 1H). IR (KBr) v: 3345, 3089, 1620, 1415, 1297, 1108, 967, 770 cm^{-1}. EIMS: m/z: 355 M^+, 297, 262, 197, 158, 130, 103, 77, 39. Anal. calcd for $C_{18}H_{17}ClF_3NO$ (358.78): C, 60.77; H, 4.82; Cl, 9.96; F, 16.02; N, 3.94. Found: C, 60.81; H, 4.87; Cl, 9.89; F, 16.19; N, 3.99. HRMS calcd for $C_{18}H_{17}ClF_3NO$: 356.1029. Found: 356.1025.