An Efficient Synthesis of *N*-Arylsulfonylindoles from Indoles and Arylsulfonyl Chlorides in the Presence of Triethylbenzylammonium Chloride (TEBA) and NaOH

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An efficient synthesis of *N*-arylsulfonylindoles from indoles and arylsulfonyl chlorides in the presence of triethylbenzylammonium chloride (TEBA) and NaOH at room temperature is described.

Keywords triethylbenzylammonium chloride (TEBA), *N*-arylsulfonylindole, indole, phase transfer catalyst

Introduction

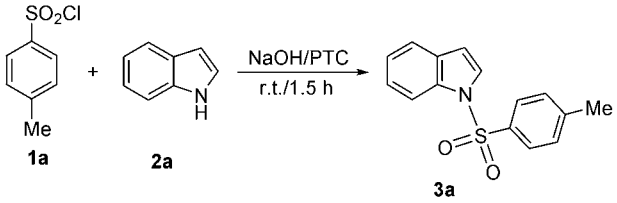
N-Arylsulfonylindole subunits have gained widespread interest due to their key role in medically important species, such as those displaying potent and selective ligation for the human serotonin 5-HT_6 receptor,[1-3] and potent antagonism against the peptidoleukotrienes.[4] Meanwhile, *N*-arylsulfonylindoles are often used as the intermediates, because of their robust behavior under a wide variety of reaction conditions, by protecting the NH group of the indoles with arylsulfonyl chlorides.[5,6]

Some harsh reaction conditions for the synthesis of *N*-arylsulfonylindoles have been described, such as using lithium diisopropylamide (LDA)/THF at －78 ℃,[7] over excess NaOH (nearly 9—10 equiv.),[8] and butan-2-one in reflux for long time.[2] Therefore, the development of mild and efficient methods for the synthesis of *N*-arylsulfonylindoles is very desirable. In continuation of our research interest in the development of mild and efficient methods for the synthesis of biological compounds,[9-12] herein we wish to report the preparation of *N*-arylsulfonylindoles from arylsulfonyl chlorides and indoles in the presence of triethylbenzylammonium chloride (TEBA) and NaOH.

Results and discussion

Firstly, we investigated the synthesis of *N*-(*p*-toluenesulfonyl)indole (**3a**) from *p*-toluenesulfonyl chloride (**1a**) and indole (**2a**) at room temperature for optimizing reaction conditions, and the results are summarized in Table 1. When the molar ratio of **1a**, **2a**, and NaOH was 1.1/1.0/1.5, the yield of **3a** was 60% after reaction for 1.5 h (Entry 1). When 0.1 equiv. of triethylbenzylammonium chloride (TEBA) was added as a phase transfer catalyst to the above reaction, the corresponding yield of **3a** was increased to 68% (Entry 3). When the equivalent of NaOH in the reaction was increased from 1.5 to 1.75, the corresponding yield of **3a** was increased from 60% to 82% (Entry 2). Especially when the molar ratio of **1a**, **2a**, NaOH to TEBA was 1.1/1.0/1.75/0.1, the corresponding yield of **3a** was increased to 93% (Entry 4). That is, the amount of NaOH and TEBA was

Table 1 Preparation of **3a** under different reaction conditions



Entry	Molar ratio				Isolated yield of **3a**/ %
	1a	**2a**	NaOH	PTC[a]	
1	1.1	1.0	1.5	0	60
2	1.1	1.0	1.75	0	82
3	1.1	1.0	1.5	0.1 (TEBA)[b]	68
4	1.1	1.0	1.75	0.1 (TEBA)	93
5	1.1	1.0	1.75	0.1 (CTAB)[c]	70
6	1.1	1.0	1.75	0.1 (*β*-CD)[d]	81
7	1.1	1.0	1.75	0.1 (PEG-600)[e]	82
8	1.1	1.0	1.75	0.1 (PEG-800)	87
9	1.1	1.0	1.75	0.1 (PEG-1000)	86
10	1.1	1.0	1.75	0.1 (TBAB)[f]	71

[a] PTC: phase transfer catalyst; [b] TEBA: triethylbenzylammonium chloride; [c] CTAB: hexadecyltrimethylammonium bromide; [d] *β*-CD: *β*-cyclodextrin; [e] PEG: poly(ethylene glycol); [f] TBAB: tetrabutylammonium bromide.

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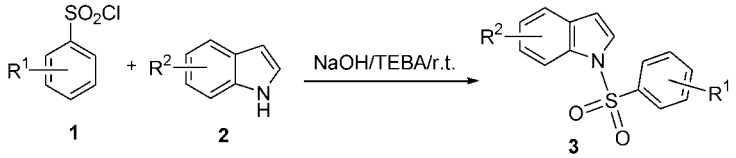
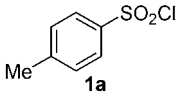
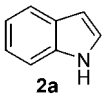
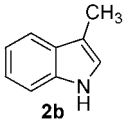
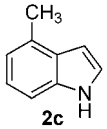
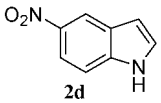
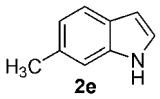
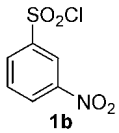
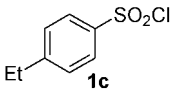
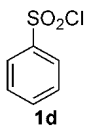
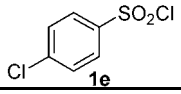
very crucial to this reaction. Meanwhile, the influences of other phase transfer catalysts, such as hexadecyltrimethylammonium bromide (CTAB, 70%, Entry 5), *β*-cyclodextrin (*β*-CD, 81%, Entry 6), poly(ethylene glycol)-600 (PEG-600, 82%, Entry 7), poly(ethylene glycol)-800 (PEG-800, 87%, Entry 8), poly(ethylene glycol)-1000 (PEG-1000, 86%, Entry 9), and tetrabutylammonium bromide (TBAB, 71%, Entry 10), were also examined. Obviously, TEBA was the most effective phase transfer catalyst for the synthesis of *N*-(*p*-toluenesulfonyl)indole.

Based upon the above findings, we further studied the synthesis of *N*-arylsulfonylindoles (**3a**—**3l**) from different arylsulfonyl chlorides (**1a**—**1e**) and indoles (**2a**—**2e**) in the presence of TEBA and NaOH at room

Table 2 Synthesis of *N*-arylsulfonylindoles in the presence of TEBA and NaOH



1 2 3

Entry	Arylsulfonyl chloride	Indole	Product	Yield/%
1	 **1a**	 **2a**	**3a** (1.5 h)[a]	93
2	**1a**	 **2b**	**3b** (2 h)	100
3	**1a**	 **2c**	**3c** (1.5 h)	91
4	**1a**	 **2d**	**3d** (1.5 h)	99
5	**1a**	 **2e**	**3e** (1.5 h)	100
6	 **1b**	**2a**	**3f** (2 h)	90
7	**1b**	**2b**	**3g** (1.5 h)	88
8	**1b**	**2c**	**3h** (1.5 h)	89
9	**1b**	**2e**	**3i** (1.5 h)	99
10	 **1c**	**2a**	**3j** (2 h)	92
11	 **1d**	**2a**	**3k** (1.5 h)	89
12	 **1e**	**2a**	**3l** (1.5 h)	95

[a] Values in parentheses represent the reaction time.

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temperature. As shown in Table 2, it can be seen that a variety of indoles, including those having electron-deficient and electron-rich substituents, were effective for this *N*-arylsulfonylation with arylsulfonyl chlorides. Good to excellent yields (88%—100%) were obtained (Table 2, Entries 1—12). For example, when 3-methylindole (**2b**) was reacted with **1a** in the presence of TEBA and NaOH for 2 h, the corresponding compound **3b** was obtained in a quantitative yield (Entry 2).

In conclusion, we have described an efficient and mild procedure for the synthesis of *N*-arylsulfonylindoles from indoles and arylsulfonyl chlorides in the presence of TEBA and NaOH. Good to excellent yields (88%—100%) and easy workup made it an attractive approach to prepare such important molecules.

Experimental

The materials were used as purchased. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co. Ltd.). Melting points were determined on a digital melting-point apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DMX 400 MHz instrument using TMS as an internal standard and $CDCl_3$ as a solvent. EI-MS was carried out with a Thermo DSQ GC/MS instrument.

General procedure for the synthesis of *N*-arylsulfonylindoles 3a—3l

The mixture of the *p*-toluenesulfonyl chloride **1a** (104.8 mg, 0.55 mmol), indole **2a** (58.6 mg, 0.5 mmol), NaOH (35 mg, 0.875 mmol), and TEBA (11.4 mg, 0.05 mmol) in dichloromethane (2 mL) in a 25 mL round bottomed flask was reacted at room temperature. When the reaction was complete after 1.5 h according to TLC analysis, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* and purified by PTLC to give **3a** in a 93% yield.

All the compounds were characterized by ^{1}H NMR, EI-MS and melting points.[13] The typical spectral data of **3a**: white solid, m.p. 83—84 ℃ (lit.[14] 87—88 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.33 (s, 3H), 6.65 (d, J= 4.8 Hz, 1H), 7.20—7.33 (m, 4H), 7.51 (d, J=10 Hz, 1H), 7.56 (d, J=4.4 Hz, 1H), 7.75 (d, J=10.8 Hz, 2H), 7.97 (d, J=10.8 Hz, 1H); EI-MS *m/z* (%): 271 (M^+, 100).

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