

## A Facile Synthesis of 3-Sulfonyl-Substituted Indole Derivatives<sup>1</sup>

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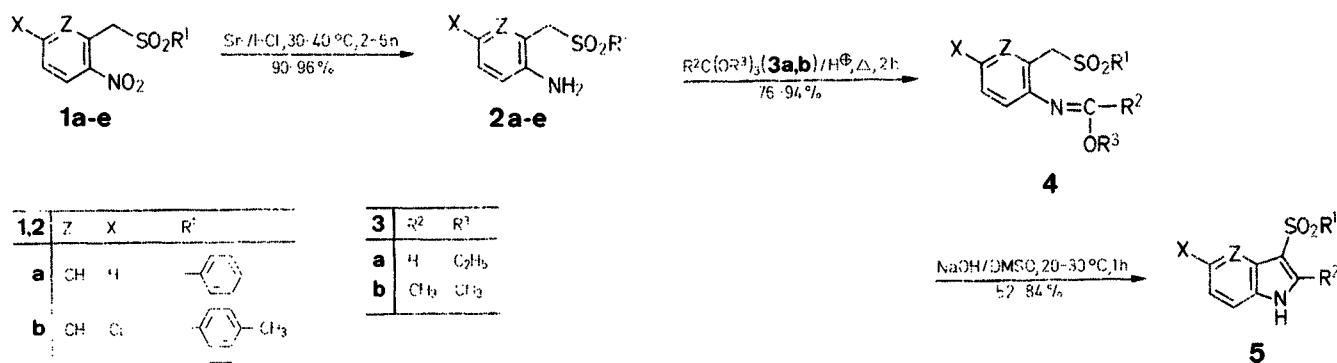
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A new method for the synthesis of 3-sulfonyl-substituted indole derivatives **5** was developed starting from the easily available products of the vicarious nucleophilic substitution of hydrogen in nitroarenes **1**.

Synthesis of indole derivatives is one of the most published problems in heterocyclic chemistry<sup>2</sup>. This is due to the great importance of the indole ring system in the chemistry of natural products, pharmaceuticals and fine chemicals.

In spite of extensive work on this field, only few indole derivatives containing sulfonyl groups in position 3 have been reported<sup>3</sup>. Recently we have shown<sup>4</sup> that 6-nitro-3-sulfonylphenyl indoles can be easily prepared via the vicarious nucleophilic substitution of hydrogen in *m*-isocyanonitrobenzene derivatives, followed by the in situ cyclization of the initially formed isocyanonitrobenzyl sulfones.

The vicarious nucleophilic substitution of hydrogen in aromatic nitro compounds with carbanions bearing leaving groups at the carbanionic center is a general process giving an easy access to substituted *ortho*- and *para*-nitrobenzyl sulfones<sup>5</sup>, sulfonamides<sup>5</sup>, cyanides<sup>6</sup>, etc. The *ortho*-isomers are particularly important, being valuable potential starting materials for the synthesis of a variety of heterocyclic systems. An efficient method of introduction of methylene phenyl sulfone substituent via the vicarious nucleophilic substitution of hydrogen *ortho* to the nitro group was recently developed in our laboratory<sup>7</sup>.



In this paper we report an efficient and simple synthesis of 3-sulfonyl-substituted indole derivatives **5** starting from readily available *ortho*-nitrobenzyl sulfones and sulfonamides **1**. Reduction of **1** was efficiently performed with tin in hydrochloric acid-methanol and the amino compounds **2**

Table 1. Amines **2** from Nitroderivatives **1**

Product No.	Yield [%]	m. p. [°C] <sup>a</sup>	Molecular formula <sup>b</sup>	I. R. (KBr) $\nu_{\text{NH}}$ [cm <sup>-1</sup> ]	<sup>1</sup> H-N.M.R. (Solvent/TMS) $\delta$ [ppm]
<b>2a</b>	90	172–173°	C <sub>13</sub> H <sub>13</sub> NO <sub>2</sub> S (247.3)	3475, 3390	Acetone- <i>d</i> <sub>6</sub> : 4.45 (s, 2H); 4.7 (br.s, 2H); 6.3–8.0 (m, 9H)
<b>2b</b>	90	137–138°	C <sub>14</sub> H <sub>14</sub> ClNO <sub>2</sub> S (295.8)	3450, 3380	CDCl <sub>3</sub> : 2.43 (s, 3H); 4.25 (br.s, 4H); 6.5–7.8 (m, 7H)
<b>2c</b>	94	163–164°	C <sub>11</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub> S (290.8)	3475, 3390	Acetone- <i>d</i> <sub>6</sub> : 3.2–3.8 (m, 8H); 4.3 (s, 2H); 4.9 (br.s, 2H); 6.8–7.4 (m, 3H)
<b>2d</b>	94	163–165°	C <sub>20</sub> H <sub>19</sub> NO <sub>2</sub> S (337.4)	3470, 3380	CDCl <sub>3</sub> : 2.43 (s, 3H); 4.2 (br.s, 2H); 6.6–7.8 (m, 12H)
<b>2e</b>	96	150–152°	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S (292.4)	3450, 3380	CDCl <sub>3</sub> : 2.4 (s, 3H); 3.35 (s, 3H); 3.9 (br.s, 2H); 4.48 (s, 2H); 6.4–7.8 (m, 6H)

<sup>a</sup> Uncorrected.

<sup>b</sup> Satisfactory microanalyses were obtained: C  $\pm$  0.35, H  $\pm$  0.16, N  $\pm$  0.23.

Table 2. Imidates **4** from Amines **2**

Product No.	Yield [%]	m. p. [°C] <sup>a</sup>	Molecular Formula <sup>b</sup>	I. R. (KBr) $\nu_{\text{C=N}}$ [cm <sup>-1</sup> ]	<sup>1</sup> H-N.M.R. (CDCl <sub>3</sub> /TMS) $\delta$ [ppm]
<b>4ab</b>	93	93°	C <sub>16</sub> H <sub>17</sub> NO <sub>3</sub> S (303.4)	1675	1.75 (s, 3H); 3.67 (s, 3H); 4.45 (s, 2H); 6.5–7.9 (m, 9H)
<b>4ba</b>	91	92–93°	C <sub>17</sub> H <sub>18</sub> ClNO <sub>3</sub> S (351.9)	1630	1.30 (t, 3H, <i>J</i> = 7.5 Hz); 2.38 (s, 3H); 4.08 (q, 2H, <i>J</i> = 7.5 Hz); 6.5–7.8 (m, 8H)
<b>4bb</b>	97	143–144°	C <sub>17</sub> H <sub>18</sub> ClNO <sub>3</sub> S (351.9)	1675	1.76 (s, 3H); 2.47 (s, 3H); 3.8 (s, 3H); 4.47 (s, 2H); 6.7–7.9 (m, 7H)
<b>4ca</b>	76	98–99°	C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>4</sub> S (346.8)	1640	1.43 (t, 3H, <i>J</i> = 7.0 Hz); 2.9–3.9 (m, 8H); 4.1–4.7 (m, 4H); 6.7–8.0 (m, 4H)
<b>4cb</b>	97	149–150°	C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>4</sub> S (346.8)	1670	1.93 (s, 3H); 3.1–4.0 (m, 11H); 4.27 (s, 2H); 6.8–7.8 (m, 3H).
<b>4da</b>	94	97–99°	C <sub>23</sub> H <sub>23</sub> NO <sub>3</sub> S (293.5)	1650	1.33 (t, 3H, <i>J</i> = 7.4 Hz); 2.38 (s, 3H); 4.13 (q, 2H, <i>J</i> = 7.4 Hz); 4.5 (s, 2H); 6.55–7.7 (m, 13H)
<b>4db</b>	94	142–143°	C <sub>23</sub> H <sub>23</sub> NO <sub>3</sub> S (393.5)	1675	1.83 (s, 3H); 2.43 (s, 3H); 3.83 (s, 3H); 4.53 (s, 2H); 6.7–8.0 (m, 12H)
<b>4ea</b>	82	111–112°	C <sub>17</sub> H <sub>23</sub> N <sub>2</sub> O <sub>4</sub> S (351.4)	1650	1.35 (t, 3H, <i>J</i> = 7.5 Hz); 2.38 (s, 3H); 3.55 (s, 3H); 4.22 (q, 2H, <i>J</i> = 7.5 Hz); 4.58 (s, 2H); 6.55 (d, 1H, <i>J</i> = 8.7 Hz); 7.0 (d, 1H, <i>J</i> = 8.7 Hz); 7.1–7.7 (m, 5H)
<b>4eb</b>	96	162–163°	C <sub>17</sub> H <sub>23</sub> N <sub>2</sub> O <sub>4</sub> S (351.4)	1670	1.9 (s, 3H); 2.43 (s, 3H); 3.5 (s, 3H); 3.83 (s, 3H); 4.58 (s, 2H); 6.67 (d, 1H, <i>J</i> = 9.0 Hz); 7.07 (d, 1H, <i>J</i> = 9.0 Hz); 7.2–7.9 (m, 4H)

<sup>a</sup> Uncorrected.

<sup>b</sup> Satisfactory microanalyses were obtained: C  $\pm$  0.26, H  $\pm$  0.22, N  $\pm$  0.16.

Table 3. Indoles **5** from Imidates **4**

Product No.	Yield [%]	m.p. [°C] <sup>a</sup>	Molecular formula <sup>b</sup>	I.R. (KBr) $\nu_{NH}$ [cm <sup>-1</sup> ]	<sup>1</sup> H-N.M.R. (DMSO- <i>d</i> <sub>6</sub> /TMS) $\delta$ [ppm]
<b>5ab</b>	84	132–133°	C <sub>15</sub> H <sub>13</sub> NO <sub>2</sub> S (271.3)	3200	2.7 (s, 3H); 7.1–8.1 (m, 9H); 12.1 (br.s, 1H)
<b>5ba</b>	65	181–182°	C <sub>15</sub> H <sub>12</sub> ClNO <sub>2</sub> S (305.8)	3340	2.33 (s, 3H); 7.4–7.9m, 7H); 8.23 (s, 1H); 12.1 (br.s, 1H)
<b>5bb</b>	83	268–270°	C <sub>16</sub> H <sub>14</sub> ClNO <sub>2</sub> S (319.8)	3320	2.33 (s, 3H); 2.9 (s, 3H); 7.1–8.2 (m, 7H); 12.2 (br.s, 1H)
<b>5ca</b>	54	174–175°	C <sub>12</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> S (300.8)	3220	2.8–3.9 (m, 8H); 6.9–7.4 (m, 4H); 12.1 (br.s, 1H)
<b>5cb</b>	64	248–250°	C <sub>13</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>3</sub> S (314.8)	3340	2.73 (s, 3H); 2.9–3.9 (m, 8H); 7.1–7.9 (m, 3H); 12.2 (br.s, 1H)
<b>5da</b>	73	180–181°	C <sub>21</sub> H <sub>17</sub> NO <sub>2</sub> S (347.4)	3280	2.37 (s, 3H); 7.2–8.0 (m, 12H); 8.06 (s, 1H); 12.1 (br.s, 1H)
<b>5db</b>	80	221–223°	C <sub>22</sub> H <sub>19</sub> NO <sub>2</sub> S (361.5)	3260	2.35 (s, 3H); 2.71 (s, 3H); 7.2–8.1 (m, 12H); 12.1 (br.s, 1H)
<b>5ea</b>	58	215°	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S (302.4)	3300	2.33 (s, 3H); 3.95 (s, 3H); 6.78 (d, 1H, <i>J</i> = 8.8 Hz); 7.3–8.4 (m, 5H); 12.0 (br.s, 1H)
<b>5eb</b>	52	235° (dec.)	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S (316.4)	3300	2.3 (s, 3H); 2.75 (s, 3H); 3.95 (s, 3H); 6.55 (d, 1H, <i>J</i> = 8.7 Hz); 7.25 (d, 2H, <i>J</i> = 8.2 Hz); 7.6 (d, 1H, <i>J</i> = 8.7 Hz); 8.0 (d, 2H, <i>J</i> = 8.2 Hz); 11.8 (br.s, 1H)

<sup>a</sup> Uncorrected.<sup>b</sup> Satisfactory microanalyses were obtained: C  $\pm$  0.44, H  $\pm$  0.24, N  $\pm$  0.13.

were isolated in high yields after basification of the reaction mixture (Table 1). The amines **2** were converted into the corresponding imidates **3** by refluxing with triethyl orthoformate (**3a**) or trimethyl orthoacetate (**3b**) in the presence of catalytic quantity of hydrochloric or toluenesulfonic acids<sup>8</sup> (Table 2). Finally the imidates **4** cyclize to indoles **5** when treated with powdered sodium hydroxide in dimethyl sulfoxide, in a process similar to the Madelung type condensation<sup>9</sup>. The indoles **5** were isolated upon neutralisation of the reaction mixture with aqueous ammonium chloride (Table 3).

The presented reaction sequence is a general method of preparation of 3-sulfonyl substituted indole derivatives including azaindoles<sup>10</sup> e. g. **5ea**, **5eb** and can be undoubtedly extended onto other similar systems. The structures of the products **2**, **4**, **5** were ascertained by <sup>1</sup>H-N.M.R. spectra and by microanalyses.

The following starting materials were prepared as described earlier: 2-Nitrobenzyl phenyl sulfone (**1a**)<sup>5</sup>, 5-chloro-2-nitrobenzyl tolyl sulfone (**1b**)<sup>5</sup>, 5-chloro-2-nitrobenzyl sulfonmorpholide (**1c**)<sup>5</sup>, 5-phenyl-2-nitrobenzyl tolyl sulfone (**1d**)<sup>5</sup> and 2-(6-methoxy-3-nitropyridylmethyl)-tolyl sulfone (**1e**)<sup>11</sup>. Other starting materials were commercial products.

#### 2-Amino-5-chlorobenzyl Tolyl Sulfone (**2b**); Typical Procedure:

To a suspension of 5-chloro-2-nitrobenzyl tolyl sulfone (**1a**; 6.5 g, 20 mmol) in methanol (50 ml) and concentrated hydrochloric acid (50 ml), tin foil (10 g) is added. The mixture is stirred at 30–40 °C until a sample shows negative test for the starting material (sample containing starting material turns deep blue when added to a solution of sodium methoxide in dimethyl sulfoxide, usually 2–6 h). The solids are filtered off and the filtrate is poured onto a mixture of ice and 10% aqueous sodium hydroxide (500 ml). The solid product is separated by suction filtration and recrystallized from ethanol/ethyl acetate (1:1); yield: 5.3 g (90%); m.p. 137–138 °C.

#### Imidates **4**; General Procedure:

Amine **2** (10 mmol), an orthoester **3a** or **3b** (5 ml) and *p*-toluenesulfonic acid (10 mg) are mixed together and refluxed for 2 h.

The mixture is cooled and hexane (25 ml) is added in order to precipitate the products. The imidates are collected by filtration and purified via recrystallization from hexane/ethyl acetate.

#### Indoles **5**; General Procedure:

To a solution of imidate **4** (5 mmol) in dimethyl sulfoxide (10 ml), powdered sodium hydroxide (1.0 g, 25 mmol) is added. The reaction mixture is stirred at 20–30 °C for 1 h and neutralized with 10% aqueous ammonium chloride (50 ml). The product is filtered and recrystallized from ethanol/ethyl acetate (1:1).

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