2-(TOSYLAMINO)BENZYLTRIMETHYLAMMONIUM HALIDES AS PRECURSORS OF 2-SUBSTITUTED INDOLES[§]

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Abstract - The reactions of 2-(tosylamino)benzyltrimethylammonium halides (**1**) with dimethylsulfonium 2-oxo-2-phenylethylide (**6b**), dimethylsulfonium 2-ethoxy-2-oxo-ethylide (**6c**) and dimethylsulfonium cyanomethylide (**6d**) are useful synthetic routes to 2-substituted indoles (**8b-d**). The relationship between reaction conditions and selectivity is discussed.

Our work on the use of sulfur ylides in the synthesis of heterocyclic compounds[1-3] included the 2-(tosylamino)benzyltrimethylammonium halides (**1**) (Scheme 1). These compounds bear an electrophilic (CH_2N^+) and a nucleophilic site (NH-Tos) *ortho* each other. Thus, they are expected to react with sulfur ylides through a sequence of reactions leading to a five-membered ring cyclization.

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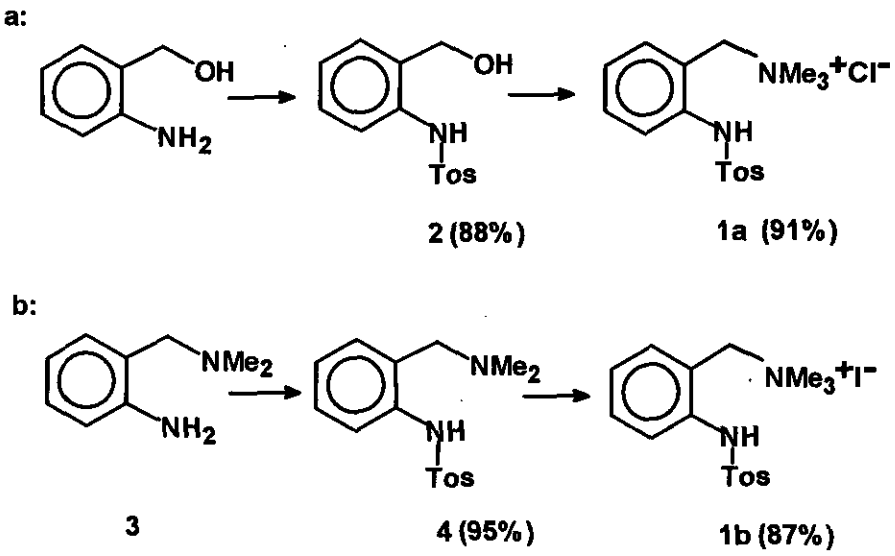
§ Dedicated to Professor Paolo Grünanger on the occasion of his 70th birthday.

Compounds (1) can be prepared easily by means of two simple and efficient routes. The first procedure (Scheme 1a) starts from *o*-aminobenzyl alcohol which, upon treatment with tosyl chloride, gives selectively the corresponding *N*-2-hydroxymethylphenyl-4-methylbenzenesulfonamide (2). The *N*-tosylated benzyl alcohol (2) is converted into the corresponding chloride which undergoes a nucleophilic substitution with trimethylamine leading to 1a. An alternative route to 1 for instance 1b (Scheme 1) requires the alkylation with methyl iodide of *N*-2-dimethylaminomethylphenyl-4-methylbenzenesulfonamide (4) prepared from *N,N*-dimethyl- 2-aminobenzenemethanamine (3) and tosyl chloride.

Scheme 1



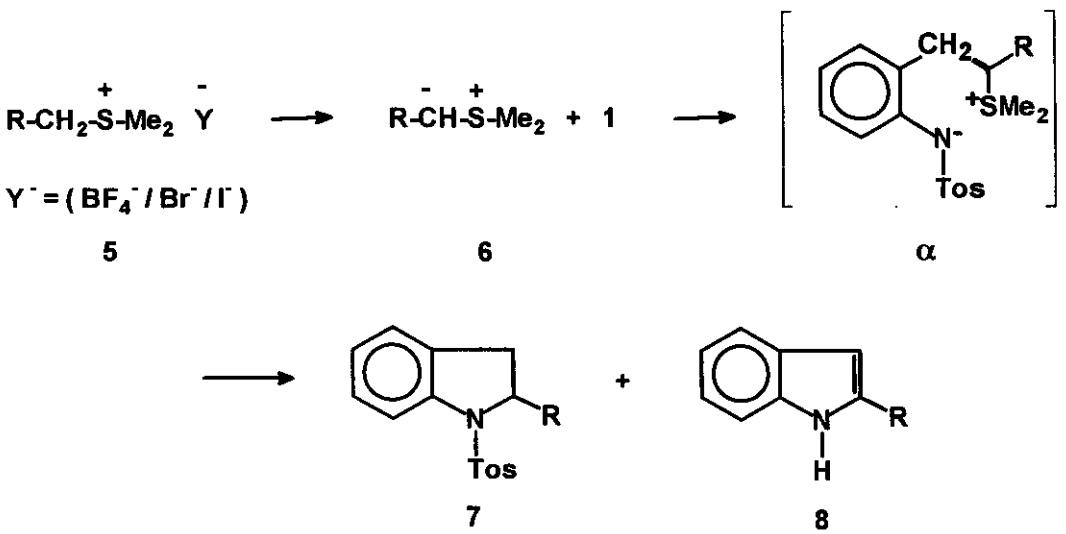
The optimization of the reactions of 1 with sulfur ylides (6) (Scheme 2) required subsequent experiments. When the stabilized ylides (6b-c), generated *in situ* from the corresponding sulfonium bromides (5b-c) in dimethyl sulfoxide (DMSO) and sodium hydride (NaH), were used in ratio 2.2 : 1 with respect to 1, a mixture of the dihydroindole derivative (7b) (59%) and *trans*-1,2,3-tribenzoylcyclopropane or 7c (42%) and *trans*-1,2,3-triethoxycarbonylcyclopropane was obtained respectively (see Experimental). The formation of by-products with a cyclopropane structure is usually observed in stabilized sulfur ylides chemistry[4] and in our case it can be explained as a basic acidic exchange between the NH hydrogen of 1 and the ylides (6b-c) with the formation of the aza-anion of 1 and the sulfonium salt (5b-c). Thus, the

presence of both the ylide and its precursor accounts for self-condensation which leads to the cyclopropane derivatives.

The reaction of 1 with the non-stabilized ylide (**6a**) gave only the dihydroindole derivative (**7a**) (76%).

The side-reactions of cyclopropanation could be overcome using the aza-anion of **1**, generated *in situ* from NaH in DMSO. When it reacted with 1.1 equivalent of the ylide (**6c**), no cyclopropane derivative was isolated, but a mixture of **7c** and **8c** was obtained with a yield of 21% and 36% respectively. Obtaining **8c** assumes that in the course of the reaction the ylide also behaves as a base promoting the elimination of 4-toluenesulfinic acid from the dihydroindole derivative.

Scheme 2



5, 6 { a: R=H; b: R=COPh; c: R=CO_2Et; d: R=CN; e: R=Tos;

7 { a: R=H; b: R=COPh; c: R=CO_2Et;

8 { b: R=COPh; c: R=CO_2Et; d: R=CN;

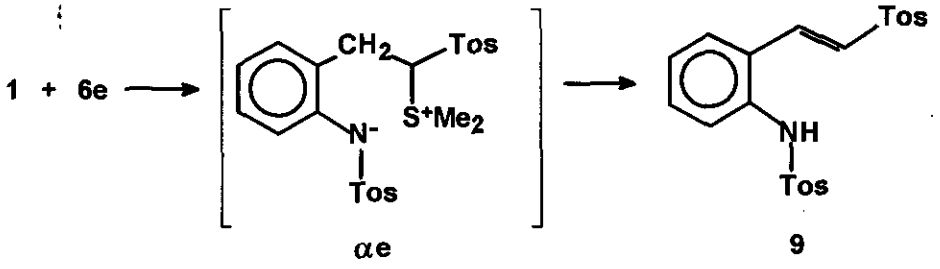
Finally, the indole derivatives were selectively obtained when the aza-anion of 1 was treated with 2.6 equivalents of the ylides (**6b-d**) in DMSO at 80°C. The indoles (**8b-c**) were isolated with yields of 82% and 80% respectively.

The reaction with **6d** gave the corresponding indole derivative (**8d**) with a low yield (16%). In the course

of the reaction the formation of by-products was observed. Among them a compound, whose analytical and physical properties were consistent with the *N*-2-(4-methylphenylsulfonyl)methylphenyl-4-methyl-benzenesulfonamide was isolated in appreciable yield (26%) (see Experimental). Its formation could be due to a nucleophilic substitution of the sodium 4-toluenesulfinate at the electrophilic site (CH_2N^+) of **1**.

These reactions may proceed through a nucleophilic substitution of the ylide at the benzylic carbon of **1**, favoured by the easy elimination of trimethylamine (Scheme 2). The corresponding sulfonium intermediates [α] undergo the ring closure by formation of the *N*-C bond with the elimination of dimethyl sulfide in the reactions with **6a-d**. The dihydroindoles obtained gain the aromaticity by the elimination of 4-toluenesulfinic acid to give the indoles (**8b-d**). The reaction with **6e** did not afford any indole derivatives, but a compound which was identified as **9**, on the basis of its analytical and spectroscopic properties (Scheme 3). It may form from the sulfonium intermediate [α**e**] which undergoes a base catalyzed dimethyl sulfide elimination leading to **9**.

Scheme 3



The reactions between the aza-anion of **1** and **6b-d** are useful synthetic routes to 2-substituted indole derivatives. Among the general synthetic methods known to prepare indole derivatives this could be classified as based on the ring closure by formation of the N-C(2) bond.[5]

We tried to verify the capability of **1** to participate in a reaction-sequence in which the nucleophilic site (NH-Tos) of **1** was initially involved. When compounds (**1**) were heated at 60-80°C in the presence of carbonyl compounds or isocyanates in the experimental conditions (base and solvent) which allowed us to

alkylate **1b** (see Experimental), no expected heterocyclic derivatives formed. After the work-up the starting materials were almost totally recovered. The stabilization of the aza-anion of **1** due to the tosyl group may decrease its reactivity. These results prompt us to continue the study on **1** as electrophiles.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were obtained with a Perkin -Elmer 298 spectrophotometer. ^1H Nmr spectra were recorded on a Bruker WP 80-SY and a Bruker AC 300 spectrometers. All chemical shifts are expressed in ppm (δ) values from tetramethylsilane as the reference. Mass spectra were determined on a VG Analytical 7070 EQ mass spectrometer with an attached VG Analytical 11/250 data system using EI and FAB tecniques. Chloroform ($CHCl_3$) was distilled from phosphorus pentoxide. DMSO was kept at 80°C for 8 h over calcium hydride and distilled at reduced pressure. Trimethylsulfonium iodide (**5a**) and *o*-aminobenzyl alcohol are commercially available. The sulfonium bromides (**5b**[6], **5c**[7] and tetrafluoroborate **5d**[8]) were prepared according to the reported procedures. The alkylation of methylthiomethyl *p*-tolylsulfone with trimethyloxonium tetrafluoroborate in acetonitrile gave 2.7 g (94%) of **5e** crystallized from ethanol, mp 192-194°C. Anal. Calcd for $C_{10}H_{15}O_2BF_4S_2$: C, 37.75; H, 4.75. Found: C, 37.60; H, 4.80.

N-2-Hydroxymethylphenyl-4-methylbenzenesulfonamide (**2**): A solution of 2-aminobenzyl alcohol (3.0 g, 24.4 mmol) and pyridine (2.3 g, 29.2 mmol) in dry $CHCl_3$ (90 ml) was treated dropwise with a solution of tosyl chloride (5.1 g, 27 mmol) in dry $CHCl_3$ (25 ml) at room temperature. The reaction mixture was left under magnetic stirring for 2 h. Then it was evaporated to dryness and the residue was taken up into ethyl acetate (50 ml) and washed with a saturated aqueous ammonium chloride solution (40 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The crude residue purified by crystallization from isopropyl alcohol gave **2** (5.9 g, 88%), mp146-148°C (lit.,[9] 148-150°C).

2-(4-Methylphenylsulfonylamino)benzyltrimethylammonium chloride **(1a):** A solution of **2** (5.0 g, 18 mmol) in dry $CHCl_3$ (70 ml) was added dropwise to thionyl chloride (1.6 ml, 22.2 mmol) in dry $CHCl_3$ (10 ml) at room temperature. The reaction mixture was left at 40°C for 12 h under magnetic stirring. Afterwards, it was slowly added to icy water (30 ml). The organic phase was separated and the aqueous layer extracted with $CHCl_3$ (2X20 ml). The combined organic extracts were dried over Na_2SO_4 and evaporated off. The solution of the crude *N*-2-chloromethylphenyl-4-methylbenzenesulfonamide (5.3 g, 18 mmol) in acetone (10 ml) was slowly added to a solution of trimethylamine (5.0 g, 85 mmoli) in acetone (15 ml) at 10°C. The reaction mixture was left 12 h at room temperature under magnetic stirring. Filtration of the suspension yielded a solid which was washed with the solvent (4 ml) and dried to give 5.8 g (91%) of **1a.** A sample was crystallized from isopropyl alcohol-diisopropyl ether (9:1), mp 154-155°C. Ir (nujol): 3040 cm^{-1}. ^1H Nmr (80 MHz, CD_3OD) δ: 2.35 (s, 3H, CH_3), 3.35 (s, 9H, NMe_3), 5.25 (s, 2H, CH_2), 6.85-8.0 (m, 9H, aromaticH and NH). Anal. Calcd for $C_{17}H_{23}N_2O_2ClS$: C, 57.53; H, 6.53; N, 7.89. Found: C, 57.34; H, 6.40; N, 7.71.

N,N-Dimethyl-2-aminobenzenemethanamine **(3):** A mixture of *N,N*-dimethyl-2-nitrobenzene methanamine[10] (5.0 g, 28 mmol) and tin (10.0 g, 84.2 mmol) was treated dropwise with a 10% sulfuric acid solution (51 ml) at room temperature. The reaction mixture was heated at 80°C for 3 h under mechanical stirring. Then it was cooled by an external ice-bath and treated dropwise with a 15% solution of sodium hydroxide until pH is basic. The aqueous suspension was filtered, the aqueous filtrate was extracted with ether (2x25ml) and the solid washed with the solvent several times. The combined organic phase was dried (Na_2SO_4) and evaporated off to give 3.6 g (86%)[11] of **3** as an oil which solidified upon standing, mp 36-37°C; a sample was purified by bulb to bulb distillation, bp 205 °C/20 mm Hg (lit.,[10] bp 107°C/14 mm Hg).

N-2-Dimethylaminomethylphenyl-4-methylbenzenesulfonamide **(4):** A solution of **3** (3.6 g, 24.1 mmol) in

pyridine (15 ml) was added dropwise to a solution of tosyl chloride (4.7 g, 24.7 mmol) in pyridine (20 ml), kept at -30°C. The reaction mixture was allowed to react for 2 h under magnetic stirring. The solvent was evaporated off and the residue was taken up in a 5% aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with ethyl acetate (2x30 ml). The combined organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by crystallization from diisopropyl ether-hexane (9:1) leading to 6.9 g (95%) of **4**, mp 100-102°C. ^{1}H Nmr (80 MHz, $CDCl_3$) δ: 2.15 (s, 6H, NMe_2), 2.35 (s, 3H, Me), 3.10 (s, 2H, CH_2), 6.85-7.70 (m, 8H, aromaticH), 9.50 (br s, 1H, NH). EI-ms m/z (rel. int. %): 304 (M^+, 10); 149 (100). Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C 63.13; H, 6.62; N, 9.20. Found: C 63.08; H, 6.57; N, 9.17.

2-(4-Methylphenylsulfonylamino)benzyltrimethylammonium iodide (**1b**): A solution of **4** (2.1 g, 7 mmol) in acetone (12 ml) was added to methyl iodide (9 ml) at room temperature. The reaction mixture was left overnight under magnetic stirring. Then it was filtered off and the precipitate purified by crystallization from ethanol to give 2.7 g (87%) of **1b**, mp 205-207°C. Ir (nujol): 3520 cm^{-1}. ^{1}H Nmr (300 MHz, DMSO-d_6) δ: 2.35 (s, 3H, Me), 3.00 (s, 9H, NMe_3), 4.70 (s, 2H, CH_2), 6.65-7.60 (m, 8H, aromaticH), 9.90 (br s, 1H, NH). FAB-ms m/z: 319 (M^+-127). Anal. Calcd for $C_{17}H_{23}N_2O_2IS$: C, 45.75; H, 5.19; N, 6.28. Found: C, 45.76; H, 4.98; N, 6.27.

Synthesis of the dihydroindole derivatives (**7a-c**): - Sodium hydride (55% mineral oil suspension, 0.065 g, 1.5 mmol) was freed of mineral oil by two washings and decantings with hexane and suspended in dry DMSO (7 ml). The suspension was heated at 50°C under magnetic stirring and nitrogen atmosphere until the hydrogen evolution ceased. Then, it was cooled at room temperature and added to the sulfonium salt (**5a-c**) (1.5 mmol) in dry DMSO (5 ml). A solution of **1** (0.3 g, 0.67 mmol) in dry DMSO (5 ml) was added to the solution of the ylide.The mixture was heated at 80°C for 3-5 h. Then it was cooled and neutralized with acetic acid. The solvent was evaporated off and the residue was taken up into water (20

ml) and dichloromethane (40 ml). The organic phase was separated, dried (Na_2SO_4) and evaporated off. The residue was purified by chromatography and the recovered product was recrystallized.

The reaction of **1** with **6a** gave **7a** (76%), mp 99°C (diisopropyl ether). ^{1}H Nmr (80 MHz, $CDCl_3$) δ: 2.30 (s, 3H, Me), 2.80 (t, 2H, J=8 Hz, CH_2), 3.90 (t, 2H, J=8 Hz, CH_2), 6.80-7.70(m, 8H, aromaticH). Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C; 65.78; H, 5.68; N, 5.22.

The reaction of **1** with **6b** gave **7b** (59%) mp 170-171°C (diisopropyl ether). Ir (nujol): 1780 cm^{-1}. ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, Me), 3.08 (dd, 1H, J=16.2, 5.4 Hz, CH), 3.37 (dd, 1H, J=16.2, 11 Hz, CH), 5.61 (dd, 1H, J=11, 5.4 Hz, CH), 6.59-8.05 (m, 13H, aromaticH). Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.93; H, 5.21; N, 3.81. *trans-1,2,3-Tribenzoylcyclopropane*(0.05 g, 0.14 mmol) recrystallized from ethanol mp 216-217°C (lit.,[6] 218-219°C).

The reaction of **1** with **6c** gave **7c,** recrystallized from diisopropyl ether (42%), mp 82-83°C. Ir (nujol): 1753 cm^{-1}. ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 1.30 (t, 3H, J=7.1 Hz, Me), 2.38 (s, 3H, Me), 3.07 (dd, 1H, J=16.3, 5.3 Hz, CH), 3.20 (dd, 1H, dd J=16.3, 10.4 Hz, CH), 4.25 (q, 2H, J=7.1 Hz, CH_2), 4.73 (dd, 1H, J=10.4, 5.3 Hz, CH), 6.90-7.30 (m, 8H, aromaticH). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found C, 62.41; H, 5.21; N, 4.01. *trans-1,2,3-Triethoxycarbonylcyclopropane*(0.033g, 0.13 mmol), purified by bulb to bulb distillation bp 130°C/1mm Hg, (lit.,[7] 110-113°C/1mm Hg).

General Procedure for the Reactions of **1** *with* **6b-e**. *Synthesis of the Indole Derivatives* (**8b-d**): - Sodium hydride (55% mineral oil suspension, 0.032 g, 0.75 mmol) freed of mineral oil by washings and decantings with hexane was suspended in dry DMSO (10 ml) and heated at 50°C for 30 min under magnetic stirring and nitrogen atmosphere. Then, it was cooled at room temperature and treated with a solution of **1** (0.67 mmol) in dry DMSO (3 ml). Then, this solution was added dropwise to a solution of the ylide (**6**) (1.8

mmol) in dry DMSO (7 ml) prepared from the corresponding sulfonium salts (**5**) according to the procedure described for the synthesis of **7a-c**. The mixture was heated at 60°C for 2 h with **6a** and at 80°C for 6 h with **6b-e**. The reaction mixture was subjected to the same work-up described above.

The reaction of **1** with **6b** gave **8b** (82%), mp 151-153°C (chloroform-hexane) (lit.,[12] 151-152°C).

The reaction of **1** with **6c** gave **8c** (80%), mp 124-125°C (dichloromethane-petrol ether) (lit.,[13] 126°C).

The reaction of **1** with **6d** gave **8d** (16%), mp 100°C (hexane) (lit.,[14] 101°C). *N-2-(4-Methylphenyl-sulfonyl)methylphenyl-4-methylbenzenesulfonamide* 26%, mp 152-154°C (isopropyl alcohol). Ir (nujol): 3330 cm^{-1}. ^1H Nmr (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, Me), 2.42 (s, 3H, Me), 4.00 (s, 2H, CH_2), 6.70-7.70 (m, 12H, aromaticH), 8.00 (br s, 1H, NH). EI-ms m/z: 415 (M^+, 35); 260 (100). Anal. Calcd for $C_{21}H_{21}NO_4S_2$: C, 60.70; H, 5.06; N, 3.37. Found: C, 60.53; H, 4.99; N, 3.17.

The reaction of **1** with **6e** gave *N-2-2-(4-methylphenylsulfonyl)ethenylphenyl-4-methylbenzenesulfonamide* (**9**) (39%), mp 193°C (toluene). Ir (nujol): 3220, 1615, 1600 cm^{-1}. ^1H Nmr (80 MHz, $CDCl_3$) δ: 2.35 (s, 3H, Me), 2.40 (s, 3H, Me), 6.50 (br s, 1H, NH), 6.65 (d, 1H, J=16.3 Hz, CH=), 7.10-7.90 (m, 13H, aromaticH and CH=). EI-ms m/z: 427 (M^+, 35); 272 (67); 117 (100). Anal. Calcd for $C_{22}H_{21}NO_4S_2$: C, 61.81; H, 4.95; N, 3.28. Found C, 61.75; H, 4.84; N, 3.34.

Alkylation of **1b** *with benzyl bromide*: - A mixture of **1b** (0.250 g, 0.63 mmol), potassium carbonate (0.085 g, 0.62 mmol) and a catalytic amount of tributylhexadecylphosphonium bromide in *N,N*-dimethylformamide (DMF) (6 ml) was stirred at room temperature for 15 min. A solution of benzyl bromide (0.115 g, 0.67 mmol) in DMF (2 ml) was added to the reaction mixture which was allowed to react overnight under magnetic stirring. The suspension was filtered and the filtrate was evaporated to dryness giving a solid which was purified by crystallization from isopropyl alcohol to give 2-(*N-(4-methylphenylsulfonyl)-N-(phenylmethyl))aminobenzyltrimethylammonium iodide* (0.25 g, yield 74%),[15]

mp 219-220°C. ^{1}H Nmr (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, CH_3), 3.00 (9H, s, NMe_3), 4.05 (d, 1H, J=13.4 Hz, CH), 4.32 (d, 1H, J=13.5 Hz, CH), 4.70 (d, 1H, J=13.5 Hz, CH), 5.16 (d, 1H, J=13.4 Hz, CH), 6.30-8.08 (m, 13H, aromaticH). Anal. Calcd for $C_{24}H_{29}N_2O_2IS$: C, 53.73; H, 5.45; N, 5.22. Found: C, 53.74; H, 5.38; N, 5.20.

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11. The reduction carried out with tin and hydrochloric acid[10] gave a mixture of **3** and *N,N*-dimethyl-2-amino-5-chlorobenzenemethanamine in the ratio of 3:1, upon integration of the two signals at δ: 3.40

(s, 2H, CH_2N) and 3.45 (s, 2H, CH_2N) in the ^1H nmr spectrum of the crude mixture. The chloro derivative was converted into the *N*-(2-dimethylaminomethyl-5-chlorophenyl)-4-methylbenzenesulfonamide as described for **3**, mp 89°C (dichloromethane). ^1H Nmr (300 MHz, $CDCl_3$) δ: 2.20 (s, 6H, NMe_2), 2.40 (s, 3H, Me), 3.00 (s, 2H, CH_2), 6.90-7.65 (m, 8H, NH and aromaticH). Anal. Calcd for $C_{16}H_{19}N_2O_2ClS$: C, 56.71; H, 5.65; N, 8.27. Found: C, 56.81; H, 5.46; N, 8.16.

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15.The alkylation of **1b** was also successfully carried out using *N*-ethyl-*N,N*-diisopropylamine in DMF at room temperature for 48 h.

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