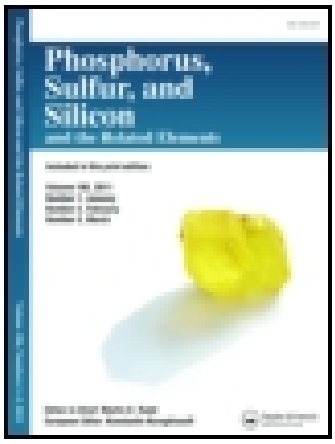

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A novel synthesis of arylsulfonyl hydrazine derivatives via the reaction of arylsulfonyl hydrazone salts and hydrazonoyl chlorides

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A novel synthesis of arylsulfonyl hydrazine derivatives via the reaction of arylsulfonyl hydrazone salts and hydrazonoyl chlorides

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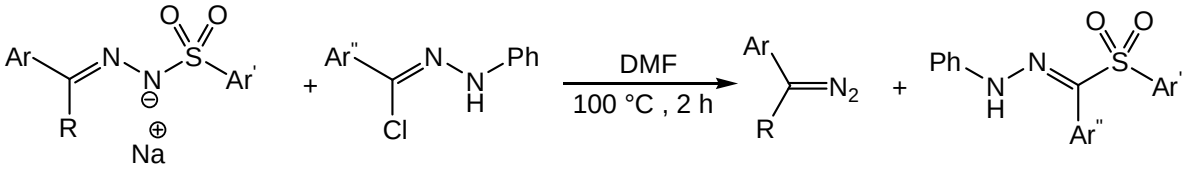
Abstract: An efficient method for the synthesis of arylsulfonyl hydrazines and diazo compounds via arylsulfonyl hydrazone salts is described. The reaction was performed in DMF using hydrazonoyl chlorides and sodium arylsulfonyl hydrazones, which were easily prepared from carbonyl compounds.



Key words: arylsulfonyl hydrazone salt; sulfone; diazo; arylsulfonyl hydrazine; hydrazonoyl chloride

INTRODUCTION

The sulfone functional group is frequently present in synthetic targets in medicinal chemistry research. For example, sulfone derivatives were found to be potent inhibitors for several enzymes such as cyclooxygenase-2, HIV-1 reverse transcriptase, and matrix metalloproteinase.[1-3] On the other hand, sulfones exhibit interesting chemical properties and are useful intermediates in organic synthesis.[4] Therefore, among the various sulfur-containing organic compounds sulfones occupy an important position.[5,6] The most common methods for sulfone preparation include the oxidation of sulfides[7-9] and the alkylation of sulfinate salts[10-13]. Though these methods are attractive for their simplicity, they are incompatible with numerous functional groups, including amines, olefins, and some nitrogen heterocycles.

Diazo compounds can be generated from their corresponding sulfonyl hydrazone salts, by photolysis,[14] vacuum pyrolysis,[15] thermolysis of a suspension in a suitable solvent ,[16-20] or thermolysis in a biphasic medium in the presence of a phase transfer catalyst (PTC).[21] We observed the formation of corresponding sulfonyl hydrazines and diazo compounds in good yields when hydrazone salts were heated in the presence of hydrazonoyl chlorides in DMF.

RESULTS AND DISCUSSION

Our studies commenced by thermal decomposition of sulfonyl hydrazine salts in the presence of hydrazonoyl chloride compounds in DMF. A facile reaction occurred affording two products of diazo **3** and arylsulfonyl hydrazine **4.** (Scheme 1)

Table 1 contains the results of our study. The structures of compounds **3a-3f** are well known in the literature.[22] The products of **4a-4f** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. For example, In the ^{1}H NMR spectrum of **4a**, the methyl protons resonated at δ = 2.38 ppm as singlet and NH group was discernible at δ = 7.70 ppm. The aromatic protons signals were visible between δ = 6.85 and δ = 7.69 ppm. The ^{1}H and ^{13}C NMR spectra of **4b-4f** were similar to those for **4a** except for the alkyl/aryl regions. Partial assignment of these resonances is given in the experimental.

A mechanistic rationalization for the reaction is given in Scheme 2. The initial event is the formation of the sodium arylsulfinate **5** and diazo **3** by thermolysis of hydrazone salt **1** in DMF.[23] The arylsulfinate ion can add to hydrazonoyl chloride **2** resulting in the formation of arylsulfonyl hydrazine derivatives **4**.

In summary, we have found a simple and efficient method for sulfonylation of hydrazonoyl chlorids by in situ generation of the diazo and sodium sulfinate compounds. Furthermore, we have designed the simplest route to access diazo compounds by thermolysis of hydrazone salts in DMF without any activation or modification. We hope that this method may successfully employ as the key step in the synthesis of products with unique properties for medicinal chemistry programs.

EXPERIMENTAL

Compounds arylsulfonyl hydrazone salt **1** and hydrazonoyl chloride **2** were prepared according to the literature[24,25]. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu-IR-460 spectrometer; $\bar{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: Bruker DRX-400 Avance instrument at 400.1 and 100.6 MHz, resp.; δ in ppm, J in Hz. MS: Finnigan-MAT-8430EI-MS mass spectrometer; at 70 eV; in *m/z* (rel. %). Elemental analyses: Vario EL III CHNOS elemental analyzer. Sample ^{1}H and ^{13}C NMR spectra for 4a and 4b are presented in the Supplemental Materials (Figures S 1 – S 4)

General procedure for the synthesis of 3 and 4*:* A solution of sodium arylsulfonyl hydrazone **1** (2 mmol) and hydrazonoyl chloride **2** (2.2 mmol) in DMF (7 mL) was heated at 100 °C for 2 h. The mixture was poured onto H_2O (10 ml), extracted with AcOEt (15 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using hexan/AcOEt (8:1) as eluent to give products **3 (**R_f = 0.69) and **4 (**R_f = 0.24).

1-Phenyl-2-((4-chlorophenyl)(*p*-tosyl)methylene)hydrazine (**4a**)

Pale yellow powder, yield: 0.29 g (76%), m.p. 137-140 °C. IR (KBr) (ν_{max}/cm^{-1}): 3270 (NH), 2925, 2346, 1585, 1507, 1283 (SO_2), 1140 (SO_2), 1082, 992, 591. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.38 (3 H, s, Me), 6.85-6.87 (3 H, m, 3 CH), 7.17 (2 H, d, ^3J = 8.4 Hz, 2 CH), 7.21 (2 H, d, ^3J = 8.4 Hz, 2 CH), 7.25 (2 H, d, ^3J = 8.4 Hz, 2 CH), 7.43 (2 H, d, ^3J = 8.4 Hz, 2 CH), 7.68-7.69 (2 H, m, 2 CH), 7.70 (1 H, b, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7 (Me), 113.9 (2 CH), 122.6 (CH), 124.5 (C), 128.9 (2 CH), 129.3 (2 CH), 129.6 (2 CH), 130.2 (2 CH), 131.3 (2 CH), 135.3 (C), 137.3 (C), 141.5 (C), 142.1 (C), 144.5 (C). EI-MS: 384

(M^+, 10), 141 (35), 91 (100), 77 (76). Anal. Calcd for $C_{20}H_{17}ClN_2O_2S$ (385.85): C 62.41, H 4.45, N 7.27, S 8.31%. Found: C 62.13, H 4.29, N 7.38, S 8.12 %.

1-Phenyl-2-((4-chlorophenyl)(phenylsulfonyl)methylene)hydrazine (**4b**)

Pale yellow powder, yield: 0.28 g (78%), m.p. 128-130 °C. IR (KBr) (ν_{max}/cm^{-1}): 3273 (NH), 2926, 2348 , 1585, 1504, 1283 (SO_2), 1141 (SO_2), 1082, 995, 689. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 6.47 (2 H, d, ^3J = 7.6 Hz, 2 CH), 6.88 (1 H, t, ^3J = 7.2 Hz, CH), 7.13-7.16 (3 H, m, 3 CH), 7.19-7.22 (4 H, m, 4 CH), 7.64-7.67 (4 H, m, 4 CH), 7.73 (1 H, b, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 112.6 (2 CH), 122.4 (CH), 124.0 (C), 128.7 (2 CH), 129.0 (2 CH), 129.2 (2 CH), 130.0 (2 CH), 130.3 (2 CH), 134.3 (CH), 136.7 (C), 139.5 (C), 141.8 (C), 144.9 (C). EI-MS: 370 (M^+, 10), 141 (40), 77 (100). Anal. Calcd for $C_{19}H_{15}ClN_2O_2S$ (370.83): C 61.53, H 4.07, N 7.55, S 8.64%. Found: C 61.34, H 4.12, N 7.45, S 8.75 %.

1-Phenyl-2-((*p*-tosyl)(*p*-tolyl)methylene)hydrazine (**4c**)

Pale yellow powder, yield: 0.29 g (80%), m.p. 118-121 °C. IR (KBr) (ν_{max}/cm^{-1}): 3274 (NH), 2928, 2313, 1585, 1506, 1286 (SO_2), 1145 (SO_2), 1076, 982, 595. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.34 (3 H, s, Me), 2.36 (3 H, s, Me), 6.86 (4 H, d, ^3J = 7.2 Hz, 4 CH), 7.11-7.15 (3 H, m, 3 CH), 7.20-7.24 (4 H, m, 4 CH), 7.68 (2 H, d, ^3J = 8.0 Hz, 2 CH), 7.86 (1 H, b, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.5 (Me), 21.6 (Me), 113.8 (2 CH), 122.2 (CH), 123.1 (C), 126.4 (C), 128.9 (2 CH), 129.2 (2 CH), 129.5 (2 CH), 129.7 (2 CH), 130.4 (2 CH), 136.2 (C), 141.2 (C), 142.4 (C), 144.2 (C). EI-MS: 364 (M^+, 8), 155 (63), 91 (100), 77 (65). Anal. Calcd for $C_{21}H_{20}N_2O_2S$ (364.44): C 69.20, H 5.53, N 7.68, S 8.79%. Found: C 69.45, H 5.44, N 7.58, S 8.69 %.

1-Phenyl-2-((phenylsulfonyl)(*p*-tolyl)methylene)hydrazine (**4d**)

Pale yellow powder, yield: 0.27 g (78%), m.p. 120-123 °C. IR (KBr) (ν_{max}/cm^{-1}): 3272 (NH), 2918, 2328 , 1567, 1521, 1287 (SO_2), 1136 (SO_2), 1080, 987, 593. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.43 (3 H, s, Me), 6.88-7.25 (7 H, m, 7 CH), 7.30 (2 H, d, ^3J = 7.9 Hz, 2 CH), 7.53 (2 H, d, ^3J = 7.7 Hz, 2 CH), 7.68 (1 H, t, ^3J = 7.2 Hz, CH), 7.80 (1 H, b, NH), 7.92 (2 H, d, ^3J = 7.9 Hz, 2 CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.4 (Me), 113.7 (2 CH), 122.2 (CH), 129.9 (C), 128.5 (2 CH), 128.9 (2 CH), 129.2 (2 CH), 129.6 (2 CH), 130.4 (2 CH), 133.2 (CH), 139.2 (C), 141.4 (C), 142.3 (C), 142.9 (C). EI-MS: 350 (M^+, 12), 209 (80), 141 (15), 91 (100), 77 (75). Anal. Calcd for $C_{20}H_{18}N_2O_2S$ (350.43): C 68.55, H 5.18, N 7.99, S 9.14%. Found: C 68.08, H 5.22, N 7.78, S 9.23 %.

1-Phenyl-2-(phenyl(tosyl)methylene)hydrazine (**4e**)

Pale yellow powder, yield: 0.28 g (80%), m.p. 115-117 °C. IR (KBr) (ν_{max}/cm^{-1}): 3276 (NH), 2921, 2310, 1585, 1506, 1285 (SO_2), 1139 (SO_2), 1015, 982, 565. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.45 (3 H, s, Me), 6.92-6.95 (4 H, m, 4 CH), 7.15-7.19 (3 H, m, 3 CH), 7.50-7.56 (5 H, m, 5 CH), 7.76 (2 H, d, ^3J = 8.2 Hz, 2 CH), 7.85 (1 H, b, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.6 (Me), 113.9 (2 CH), 122.3 (CH), 126.2 (C), 128.8 (2 CH), 129.2 (2 CH), 129.5 (2 CH), 129.7 (2 CH), 129.8 (2 CH), 130.8 (CH), 136.2 (C), 142.3 (C), 142.8 (C), 144.3 (C). EI-MS: 350 (M^+, 15), 155 (100), 141 (71), 91 (82), 77 (65). Anal. Calcd for $C_{20}H_{18}N_2O_2S$ (350.43): C 68.55, H 5.18, N 7.99, S 9.14%. Found: C 68.29, H 5.27, N 7.68, S 9.28 %.

1-Phenyl-2-(phenyl(phenylsulfonyl)methylene)hydrazine (**4f**)

Pale yellow powder, yield: 0.25 g (75%), m.p. 110-114 °C. IR (KBr) (ν_{max}/cm^{-1}): 3268 (NH), 2917, 2321, 1575, 1532, 1284 (SO_2), 1128 (SO_2), 1061, 928, 578. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 6.86-6.90 (5 H, m, 5 CH), 7.75-7.80 (4 H, m, 4 CH), 7.86-7.97 (6 H, m, 6 CH), 7.85 (1 H, b, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 113.8 (2 CH), 122.4 (CH), 126.0 (C), 128.8 (2 CH), 128.9 (2 CH), 129.2 (2 CH), 129.7 (2 CH), 129.8 (2 CH), 130.9 (CH), 133.5 (CH), 149.1 (C), 142.2 (C), 142.6 (C). EI-MS: 336 (M^+, 7), 195 (63), 141 (25), 105 (83), 91 (100), 77 (85). Anal. Calcd for $C_{19}H_{16}N_2O_2S$ (336.40): C 67.84, H 4.49, N 8.33, S 9.53%. Found: C 67.70, H 4.58, N 8.16, S 9.37 %.

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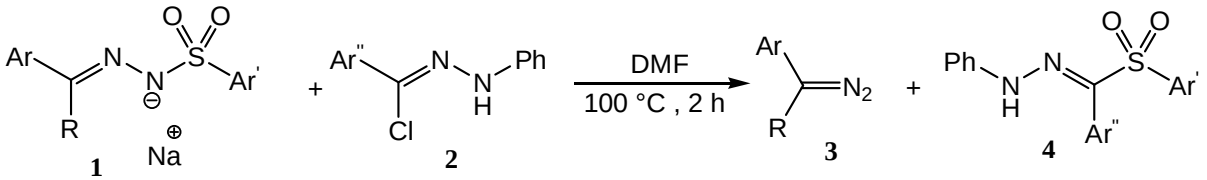
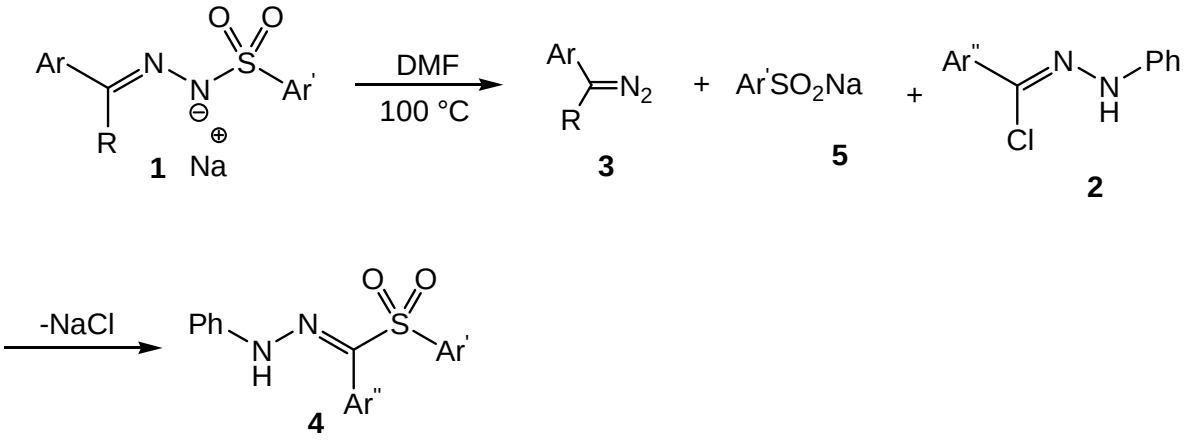


Scheme 1



Scheme 2

Table 1. Yields of diazo and arylsulfonyl hydrazine compounds from sodium arylsulfonyl hydrazones

Entry	R	Ar	Ar'	Ar''	Diazo	Arylsulfonyl hydrazine	Yield (3, 4)%
1	Me	4-$NO_2C_6H_4$	4-MeC_6H_4	4-ClC_6H_4	**3a**	**4a**	70, 76
2	Et	Ph	Ph	4-ClC_6H_4	**3b**	**4b**	80, 78
3	Me	4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	**3c**	**4c**	75, 80
4	Me	Ph	Ph	4-MeC_6H_4	**3d**	**4d**	73, 78
5	Me	4-ClC_6H_4	4-MeC_6H_4	Ph	**3e**	**4e**	72, 80
6	Ph	Ph	Ph	Ph	**3f**	**4f**	68, 75