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New route for the synthesis of *N*-alkyl-2-(phenylsulfonyl)anilines

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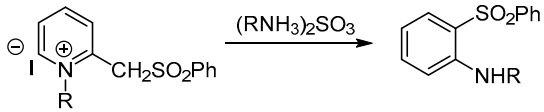


The main objective of this work was to study the rearrangement reactions of 1-alkyl-2-[(phenylsulfonyl)methyl]pyridinium iodides in the presence of various nucleophiles, leading to *N*-alkyl-2-(phenylsulfonyl)aniline derivatives. The best results were achieved with alkylammonium sulfites, leading to pyridine ring opening followed by recyclization to give diphenyl sulfone derivatives in up to 78% yields.

Keywords: alkylammonium sulfites, diaryl sulfones, 2-[(phenylsulfonyl)methyl]pyridine, pyridinium salts, sodium benzenesulfinate.

Sulfones have been proven as valuable synthons for the synthesis of a wide variety of biologically active heterocyclic systems.[1–5] In addition, Fadda and coworkers[6–15] have studied the recyclization of pyridinium salts to anilines in the presence of aqueous alkali, alkylamines, or alkylammonium sulfite. The nature and position of substituents in the pyridine ring have considerable effects on these types of reactions.

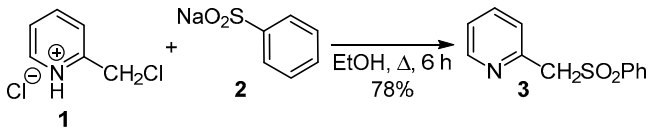
The aforementioned pyridine ring recyclization includes reactions involving the sp^3-carbon attached to position 2 of the pyridine ring and suggests that the recyclization could also involve more remote reactive groups.

The recyclization of pyridinium salts into anilines appears to be a fundamental type of pyridine ring transformation into benzene ring. In the present study, we report the effects of sulfonyl moiety as well as that of various amines on the recyclization of pyridinium salts. Thus, 2-[(phenylsulfonyl)methyl]pyridine (**3**) was selected as a key precursor for the synthesis of some hitherto unreported 2-(phenylsulfonyl)aniline derivatives with an expected broad spectrum of biological effects.

The reaction of 2-(chloromethyl)pyridine hydrochloride (**1**) with sodium benzenesulfinate (**2**) in refluxing ethanol furnished exclusively the corresponding 2-[(phenylsufonyl)-methyl]pyridine (**3**) in excellent yield (Scheme 1). The identity of compound **3** was confirmed by elemental analysis, the mass spectrum with a molecular ion peak with *m*/*z* 233 ([M]$^+$, 50%), and ^{1}H NMR spectrum which revealed a singlet signal at 5.00 ppm due to CH_2 protons.

Compound **3** was further used as a versatile reagent for the construction of several diaryl sulfone derivatives.

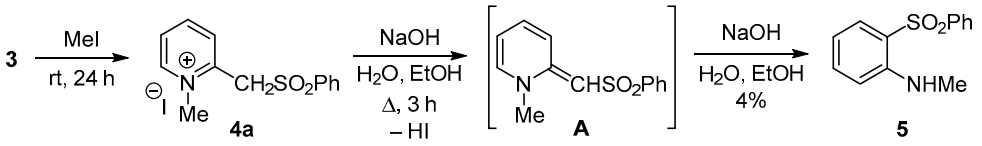
Scheme 1



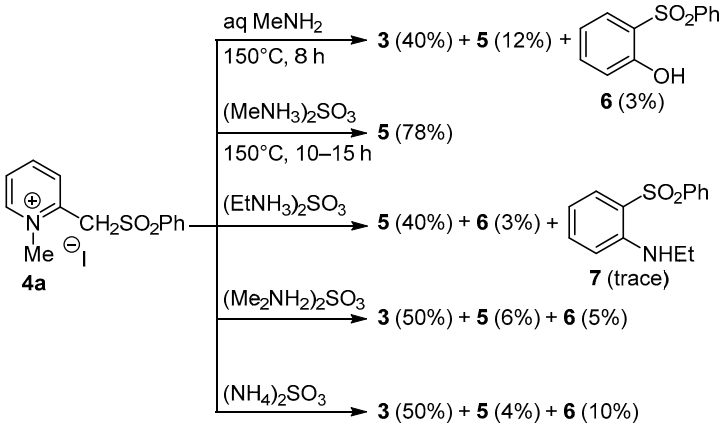
It was expected that the activation of 2-CH_2 group by the electron-withdrawing phenylsulfonyl substituent in the salt **4a** would facilitate the formation of the intermediate **A**, a key step in the reaction that occurs in the presence of NaOH. The treatment of the salt **4a** with aqueous sodium hydroxide solution ultimately led to *N*-methyl-2-(phenylsulfonyl)aniline (**5**) in 4% yield (Scheme 2), confirmed by mass spectrum featuring the molecular ion peak with *m*/*z* 247 ([M]$^+$, 60%) and ^{1}H NMR spectrum which showed singlet signals at 2.64 and 6.72 ppm for CH_3 and NH protons, respectively. However, when the same reaction was carried out in the presence of aqueous methylamine, it proceeded with the formation of a mixture containing compound **5** in a better yield (12%), as well as 2-(phenylsulfonyl)phenol (**6**) in 3% yield, and pyridine base **3** in 40% yield, resulting from parallel process of dealkylation by virtue of direct attack of the nucleophile on the N–Me bond (S_N2 mechanism). Since it has been reported that 2-picolinium salts do not undergo enamine rearrangement in aqueous ethanolic solutions of alkali or alkyl amines,[16] the formation of compound **5** in the present study indicates that the phenylsulfonyl group activates the 2-methylene group towards the rearrangement (Scheme 3).

On the other hand, in the presence of methylammonium sulfite as a recyclization reagent, the iodide **4a** underwent

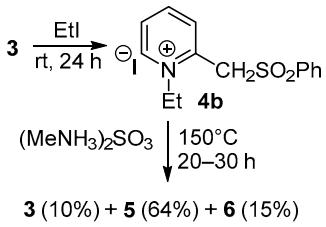
Scheme 2



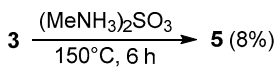
Scheme 3



Scheme 4



Scheme 5



rearrangement to *N*-methyl-2-(phenylsulfonyl)aniline (**5**) in a good yield (78%). The formation of compound **5** by the pathway shown in Scheme 3 was in line with a number of previously reported cases.[6–15,17,18,19]

In the present study, the action of methylammonium sulfite on 1-ethyl-2-(phenylsulfonylmethyl)pyridinium iodide (**4b**) led to the formation of a mixture of *N*-methyl-2-(phenylsulfonyl)aniline (**5**) (64%), 2-(phenylsulfonyl)-phenol (**6**) (15%), and compound **3** (10%) (Scheme 4). These results were in a good agreement with previously reported work.[10,11]

On the other hand, the reaction of ethylammonium sulfite with the *N*-methylpyridinium iodide **4a** gave compound **5** as the main product (40%) instead of *N*-ethyl-2-(phenylsulfonyl)aniline (**7**), which could not be detected in ^{1}H NMR spectrum (Scheme 3). However, GC-MS data of the mixture indicated that compound **7** was formed in a very poor yield. This shows that the substitution of methylamino group by ethylamino group occurs with great difficulty (Scheme 3).

The treatment of pyridinium iodide **4a** with dimethylammonium sulfite gave compounds **5** (6%) and **3** (50%), indicating that the secondary amine (dimethylamine) was not involved in the reamination reaction (Scheme 3). Thus, it was concluded that this type of reactions depends on the steric bulk of the attacking nucleophile.

When the nucleophile was less bulky, such as methylammonium sulfite, the reamination reaction was found to be facile. However, in the case of a bulkier nucleophile, such as ethylammonium sulfite, the increased steric hindrance greatly decreased the yield of the reamination product **7**. The bulky dimethylamino group in dimethylammonium sulfite prevented the exchange reaction, and therefore no 2-(dimethylamino)diphenyl sulfone was obtained. However, the high basicity of dimethylamine gave compound **6** in a considerable yield, which confirmed by mass spectrum showing a molecular ion peak with *m/z* 234 ([M]$^+$, 50%) and ^{1}H NMR spectrum showing a singlet signal at 10.13 ppm, assigned to the OH proton.

Based on the evidence that treatment of *N*-alkylpyridinium salts with aqueous ammonia[18] or ammonium sulfite[19,20] leads to dealkylation only, it seemed of interest to study the action of ammonium sulfite on compound **4a** (Scheme 3). In this case, recyclization was found to occur without the exchange of methylamino fragment by amino function, and the reaction products were identified as compounds **3** (50%), **5** (4%), and **6** (10%). The high yield of compound **3** may be attributed to its simultaneous formation *via* two pathways, one involving the *N*-dealkylation of pyridinium iodide **4a** by direct nucleophilic attack of the reagent at the *N*-methyl group, and the other (evidently the principal pathway) by opening of the pyridine ring, exchange of the methyl amine fragment for an amine fragment in the open structure, and subsequent ring formation giving the products shown in Scheme 3.

Based on the evidence that 2-picoline undergoes recyclization to *N*-methylaniline when treated with aqueous methylammonium sulfite,[17,20] the recyclization of unquaternized 2-[(phenylsulfonyl)methyl]pyridine (**3**) was studied. Thus, we found that the action of aqueous methylammonium sulfite on unquaternized 2-[(phenylsulfonyl)methyl]-pyridine (**3**) led to opening of the pyridine ring with exchange of the amine fragment for a methylamine fragment and the formation of the pyridinium salt recyclization product, i.e., *N*-methyl-2-(phenylsulfonyl)aniline (**5**), although it was obtained in a very low yield (8%, Scheme 5). However, the bulk of compound **3** was recovered unchanged. These results were in a good agreement with previously reported work.[10] There is no evidence for the formation of 2-(phenylsulfonyl)aniline as a product of recyclization reaction by spectroscopic data. All attempts to obtain the latter compound by treatment of compound **3** with aqueous ammonium sulfite failed.

The structures of all the compounds obtained were proved by a combination of spectral methods (IR, ^{1}H and ^{13}C NMR spectroscopy), mass spectrometric analysis, and by comparison with literature data.

Thus, heterocyclic sulfones have proven to be valuable synthons for the synthesis of a wide variety of potentially biologically active diaryl sulfones. We have reported here for the first time the synthesis of diaryl sulfones by using nucleophile-induced rearrangement of pyridinium salts bearing (phenylsulfonyl)methyl moieties, as these compounds are not always readily accessible by previously known methods.

Experimental

IR spectra were recorded for thin films on KBr disk on a Mattson 5000 FTIR spectrometer at the Faculty of Science, Mansoura University, Egypt. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker WPSY spectrometer (200 and 50 MHz, respectively) for DMSO-d_6 solutions with TMS as internal standard. The mass spectra were recorded with EI ionization (70 eV) on a Varian MAT 311 instrument at the Micro Analytical Center, Faculty of Science, Cairo University. Elemental analyses were carried out on a Heraeus MIKRO-K flask type Schöniger combustion apparatus at the Faculty of Science, Cairo University. Melting points were determined on a Gallenkamp digital melting point apparatus and were not corrected. The homogeneity of the products was checked by TLC with benzene as eluent. All alkylammonium sulfite reagents were prepared according to a previously reported method.[7]

Synthesis of 2-[(phenylsulfonyl)methyl]pyridine (3). A mixture of compound **1** (1.64 g, 0.010 mol) and sodium benzenesulfinate **2** (2.46 g, 0.015 mol) in absolute ethanol (30 ml) was refluxed for 6 h. The reaction mixture was left to cool at room temperature and poured into cold water. The solid product that precipitated was filtered off, washed thoroughly with water, dried, and recrystallized from absolute ethanol. Yield 78%, white crystals, mp 110–112°C (mp 111–112°C[21,22]). IR spectrum, ν, cm^{-1}: 1310 (SO_2). ^{1}H NMR spectrum, δ, ppm: 5.00 (2H, s, CH_2); 7.26–8.23 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 66.2; 120.9; 124.1; 128.3 (2C); 129.7 (2C); 133.7; 136.2; 137.6; 148.6; 158.6. Mass spectrum, *m*/*z* (I_{rel}, %): 233 $[M]^+$ (50). Found, %: C 61.65; H 4.63; N 5.85. $C_{12}H_{11}NO_2S$. Calculated, %: C 61.78; H 4.75; N 6.00.

Synthesis of 2-[(phenylsulfonyl)methyl]pyridinium iodides 4a,b (General method). A mixture of compound **3** (2.33 g, 0.01 mol) and methyl iodide (2.84 g, 0.02 mol) or ethyl iodide (3.12 g, 0.02 mol) was allowed to stand at room temperature for one day in pressure tube. The yellow crystals that formed were recrystallized from ethanol–ether, 3:1, to give compounds **4a** and **4b**, respectively.

1-Methyl-2-[(phenylsulfonyl)methyl]pyridinium iodide (4a). Yield 90%, mp 135°C. IR spectrum, ν, cm^{-1}: 1310 (SO_2). ^{1}H NMR spectrum, δ, ppm: 4.39 (3H, s, N–CH_3); 4.67 (2H, s, CH_2); 7.67–8.69 (9H, m, H Ar), in agreement with the literature.[23] ^{13}C NMR spectrum, δ, ppm: 40.6; 63.7; 125.4; 126.4; 128.3 (2C); 129.7 (2C); 133.7; 137.6; 145.6; 146.3; 151.3. Mass spectrum, *m*/*z* (I_{rel}, %): 247 $[M]^+$ (50). Found, %: C 41.52; H 3.60; N 3.64. $C_{13}H_{14}INO_2S$. Calculated, %: C 41.61; H 3.76; N 3.73.

1-Ethyl-2-[(phenylsulfonyl)methyl]pyridinium iodide (4b). Yield 82%, mp 156°C. IR spectrum, ν, cm^{-1}: 1310 (SO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.57 (3H, t, *J* = 8.0, CH_3); 4.67 (2H, s, CH_2); 4.80 (2H, q, *J* = 8.0, CH_2); 7.60–8.50 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 17.1; 56.1; 64.0; 125.4; 126.4; 128.3 (2C); 129.7 (2C); 133.7; 137.6; 145.6; 146.3; 151.3. Mass spectrum, *m*/*z* (I_{rel}, %): 262 $[M]^+$ (40). Found, %: C 43.10; H 4.01; N 3.50. $C_{14}H_{16}INO_2S$. Calculated, %: C 43.20; H 4.14; N 3.60.

Ring opening and recyclization of pyridinium salts 4a,b. Method I. Compound **4a** (3.74 g, 0.010 mol) was treated with 25% aqueous sodium hydroxide (10 ml) and ethanol (1 ml) to obtain a homogeneous solution, then heated for 3 h under nitrogen atmosphere, cooled, and extracted twice with ether. The ethereal extract was dried over anhydrous magnesium sulfate and chromatographed on a silica gel column (100/160 μm), eluting with benzene. Removal of solvent from the collected fractions under reduced pressure gave compound **5** as oil.

Method II. Aqueous methylamine (35%, 22.24 g, 0.71 mol) was added to compound **4a** (7.48 g, 0.020 mol). The mixture was heated in a pressure tube in silicone oil bath at 150°C for 8 h. The product was extracted with ether, dried over anhydrous magnesium sulfate, and chromatographed on silica gel (100/160 μm). Elution with benzene gave compounds **5**, **3** and **6**.

Method III: Reaction of pyridinium iodide **4a** with methylammonium sulfite. Aqueous methylammonium sulfite (35%, 25 ml) was added to pyridinium iodide **4a** (7.48 g, 0.02 mol), and the reaction mixture was heated in a pressure tube in silicone oil bath at 150°C for 10–15 h. The product was extracted with ether, dried over anhydrous magnesium sulfate and chromatographed on silica gel (100/160 μm) using benzene as eluent. The benzene eluate was evaporated under reduced pressure to give *N*-methyl-2-(phenylsulfonyl)aniline (**5**) along with the dealkylation product **3**.

Method IV. An aqueous solution of methylammonium sulfite (35%, 30 ml) was added to the pyridinium iodide **4b** (7.78 g, 0.020 mol), and the mixture was heated in pressure tube at 150°C for 20–30 h. The product was extracted with ether, dried over anhydrous $MgSO_4$ and separated by chromatography on a silica gel (100/160 μm) column using benzene as eluent to give compound **5**.

***N*-Methyl-2-(phenylsulfonyl)aniline 5**. Yield 4% (method I), 12% (method II), 78% (method III), 64% (method IV). R_f 0.65. IR spectrum, ν, cm^{-1}: 3450 (NH), 1310 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.64 (3H, s, CH_3); 6.72 (1H, s, NH); 6.84–7.97 (9H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 29.6; 112.4; 117.2; 118.1; 122.0; 124.1; 124.7; 128.3 (2C); 129.7 (2C); 133.7; 141.4. Mass spectrum, *m*/*z* (I_{rel}, %): 247 $[M]^+$ (60). Found, %: C 63.01; H 5.22; N 5.45. $C_{13}H_{13}NO_2S$. Calculated, %: C 63.14; H 5.30; N 5.66. The spectral data for compound **5** matched the literature.[24]

2-[(Phenylsulfonyl)methyl]pyridine (3). Yield 40% (method II), 10% (method IV), mp 110–112°C (mp 111–112°C[21,22]), R_f 0.55. Identical spectral data (IR, ^{1}H NMR, and mass spectra) with that obtained above.

2-(Phenylsulfonyl)phenol (6).[25–27] Yield 3% (method II), 15% (method IV), mp 52°C. R_f 0.58. IR spectrum, ν, cm^{-1}: 3455 (OH), 1300 (SO_2). ^1H NMR spectrum, δ, ppm: 6.98–7.97 (9H, m, H Ar); 10.13 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 115.7; 122.3; 128.3 (2C); 129.7 (3C); 130.3; 133.7; 141.4; 149.0; 153.1. Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (50). Found, %: C 61.40; H 4.15. $C_{12}H_{10}O_3S$. Calculated, %: C 61.52; H 4.30.

Ring opening and recyclization of pyridine derivative 3. Aqueous 35% methylammonium sulfite (25 ml) was added to 2-[(phenylsulfonyl)methyl]pyridine (**3**) (2.33 g, 0.01 mol), and the reaction mixture heated in a pressure tube for 60 h at 150°C. The resultant product was extracted with ether, dried ($MgSO_4$), and chromatographed on a silica gel (100/160 μm) column using benzene–ethyl acetate, 4:1, as eluent to give compound **5** (yield 8%) with identical IR, ^1H NMR, and mass spectral characteristics to those described above.

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