An Improved Synthesis of *N*-Sulphonyl-1*H*-azepines under Solid–Liquid Phase-Transfer Catalysis Conditions

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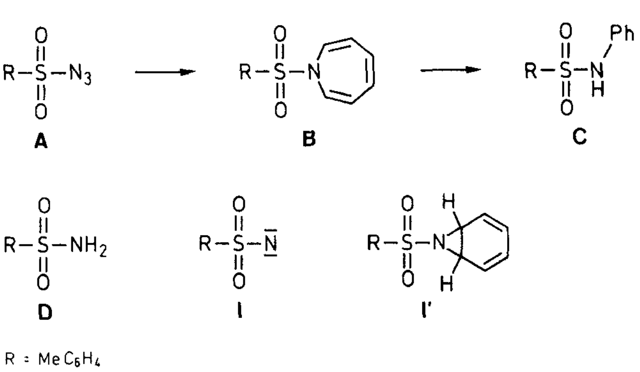
The synthesis of novel *N*-sulphonyl-1H-azepines is described starting from arylsulphonyl chlorides in a one-pot operation making use of solid–liquid phase-transfer catalysis technique (benzene/sodium bicarbonate). Good yields were obtained under moderate reaction conditions.

Recently, the facile synthesis of *N*-sulphonyl-1*H*-azepines in significant yields by the nitrene insertion reaction in the benzene ring under nitrogen pressure has been reported from our laboratory, in which it was also shown that pressure has a remarkable effect on such insertion product formation involving ring expansion.[1] The interest in the azepine ring systems has been generated because of their presence in a number of drugs.[2] The rhoeadine alkaloids have benzazepine as the basic structure.[3] The *N*-sulphonylazepines described in this report may exhibit promising biological activity. In continuation of our research in azepine chemistry, we have synthesized *N*-sulphonyl-1*H*-azepines in high yields under moderate reaction conditions starting from arylsulphonyl chlorides instead of arylsulphonyl azides. The nucleophilic substitution of chlorine by the azido group as well as the nitrene insertion into benzene ring has been performed in a one-pot operation making use of solid–liquid phase-transfer catalysis (PTC) techniques.

Azacycloheptatriene (Azepine) can exist in four tautomeric forms, *viz.* 1*H*-, 2*H*-, 3*H*, and 4*H*-azepines. The *N*-unsubstituted 1*H*-azepines are rare since they are unstable and tautomerize to the 3*H*-isomer.[4,5] X-ray and NMR analysis indicated that the azepines are non-planar and exist predominantly in the boat conformation.[6] Hückel molecular orbital calculations on 1*H*-azepine had indicated extensive localisation of electrons on nitrogen and the carbon–carbon double bonds, from which it was concluded that 1*H*-azepines should exhibit marked polyene character.[7] The stability of 1*H*-azepines is enhanced by electron-withdrawing substituents, especially at the 1-position. Alkoxycarbonyl nitrenes[8] and cyanonitrenes[9] provided good yields in the synthesis of *N*-substituted 1*H*-azepines via nitrene insertion in aromatic hydrocarbons. However, sulphonylnitrenes are not very effective in this regard.[10]

Thermal decomposition of sulphonyl azides in aromatic solvents occurs slowly at 120 °C. The decomposition is unimolecular,[11] leading to a singlet nitrene.[12] This is followed by addition to the aromatic ring to give a benzaziridine intermediate. The kinetic evaluation[13] of these reactions in our laboratory indicated the reaction pathway as shown in Scheme 1. The kinetic data generated indicate that both the steps, *viz.* the formation of the azepine **B** and the subsequent conversion to the sulphonanilide **C**, are kinetically controlled.

It has been observed that *N*-alkoxycarbonylazepines are more stable than *N*-sulphonylazepines, and they rearrange to their corresponding anilides only on treatment with acids. On the basis of the above observation Breslow[11] suggested that the sulphonylazepine **B** rearranges to the sulphonanilide **C** under the reaction conditions due to the presence of acidic sulphonamide **D**, which is formed in the reaction. Our earlier studies[1] proved experimentally the role of acidic sulphonamide **D** in the rearrangement of sulphonylazepine into sulphonanilide **C**. When sulphonylazepine was refluxed in benzene in the presence of acidic sulphonamide **D**, the azepine underwent complete rearrangement into the sulphonanilide **C** in agreement with the suggestion of Breslow.



Scheme 1

Having been established consistantly the reason for poor yields of *N*-sulphonylazepines due to the formation of acidic sulphonamide in the reaction, which rearranges the azepine into sulphonanilide, it was thought to neutralize the acidity of sulphonamide during the reaction using a weak base such as sodium bicarbonate. To make sodium bicarbonate soluble in the reaction medium under anhydrous conditions, solid–liquid PTC techniques was employed.

As expected, in the presence of sodium bicarbonate under solid–liquid PTC conditions, thermolysis of sulphonyl azide in benzene gave improved yields of *N*-sulphonylazepines. The concentration profiles of the reactants and products in typical reaction sequence of thermolysis of sulphonyl azides in benzene at 125 °C in the presence of sodium bicarbonate (solid–liquid PTC) and in the absence of sodium bicarbonate are shown in the Figure. The curves have been plotted by analysing aliquots of reaction mixtures at different intervals of time by HPTLC. The concentration profile clearly indicates that the rearrangement of *N*-sulphonylazepine into sulphonanilide is minimum in the case of the reactions performed under solid–liquid PTC conditions in the presence of sodium bicarbonate. The enhanced selectivity results in improved yields of *N*-sulphonylazepines (45–80%) in comparison to the yields (15–40%) obtained in the absence of sodium bicarbonate. Moreover, the formation of sulphonamide **D**, the product of hydrogen abstraction by sulphonylnitrene intermediate **I**, is also reduced considerably.

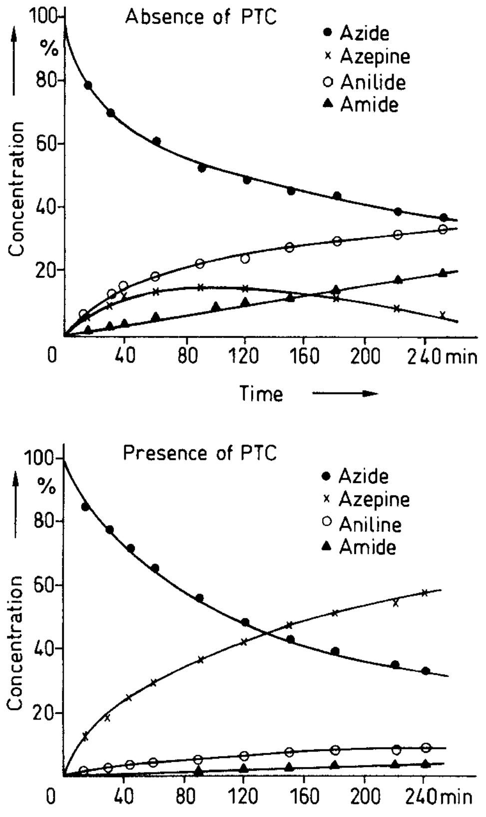
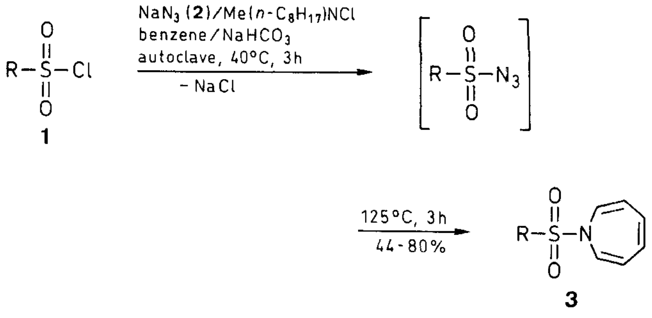


Figure: Concentration-time curves of 4-methylbenzenesulfonyl azide thermolysis in benzene at 125 °C.

Further, the solid–liquid PTC technique is extended to the in situ preparation of sulphonyl azide from the corresponding sulphonyl chlorides. The solid–liquid PTC facilitated the nucleophilic substitution of chlorine by the azido group as well as the nitrene insertion reaction, thus avoiding the handling of hazardous and explosive sulphonyl azides. In other words, *N*-sulphonylazepines could be prepared directly by the reaction of aromatic substrates with sulphonyl chlorides and sodium azide powder by using appropriate solid–liquid PTC technique.

Several *N*-sulphonylazepine derivatives **3a–g** have been prepared from the corresponding sulphonyl chlorides **1a–g**. The sulphonyl chlorides are stirred in benzene in an autoclave at 40 °C with a suspension of powdered sodium azide and sodium bicarbonate in the presence of methyltrioctylammonium chloride (PTC) for 3 hours and subsequently at 125 °C for 3 hours (Scheme 2, Table).

All the *N*-sulphonylazepines **3a–g** (previously unknown azepines **3d–g**) synthesized have been characterized by spectral data and microanalysis. The IR spectra of **3a–g** show vinylic C=C frequencies in the range of $\nu = 1638$, 1645 and 1600–1620 cm^{-1} for the azepinyl ring system.



1,3	R	1,3	R
a	Ph	e	4-MeOC$_6$H$_4$
b	4-MeC$_6$H$_4$	f	4-O$_2$NC$_6$H$_4$
c	4-BrC$_6$H$_4$	g	4-FC$_6$H$_4$
d	4-ClC$_6$H$_4$		

Scheme 2

The absence of the characteristic absorption band of NH group near $\nu = 3200$–3400 cm^{-1}, further confirms the azepinyl ring system. In the ^{1}H NMR spectra, the aromatic proton signals are seen in the range of $\delta = 6.8$–8.3 and the azepinyl ring protons appeared as multiplets in the range of $\delta = 5.6$–6.0. The mass spectra showed significant molecular ion peaks (M$^+$). The major fragment occured by the cleavage of S–N bond, which gives the azepinium ion at $m/z = 92$ and is the base peak in all compounds. The other fragment which is seen in moderately good abundance is arylsulphonyl ion (M$^+$ – 92). The azepinium ion at m/z 92 fragments further by loss of HCN and acetylene giving peaks at m/z = 65 (M$^+$ – 27) and m/z = 66 (M$^+$ – 26).

Features of the present method are:

- Synthesis of *N*-sulphonylazepines starting from sulphonyl chlorides instead of sulphonyl azides. Nucleophilic substitution of chlorine by the azido group as well as the nitrene insertion in one-pot operation under solid–liquid PTC conditions;
- Avoids handling of hazardous and explosive sulphonyl azides as these are prepared in situ;
- Thermolysis of arylsulphonyl azides at temperatures lower than their decomposition temperatures and under moderate pressures;
- Improved yields due to the minimal rearrangement of the azepines to the sulphonanilides, and due to the minimal formation of sulphonamide.

The arylsulphonyl chlorides **1** are commercially available and were purchased from Fluka, or Aldrich and were used without further purification. Commercial grade NaN$_3$ was used without further purification/activation. Benzene and hexane are Analar grade chemical solvents used after purification by standard methods.

General Procedure for the Thermolysis of Benzenesulphonyl Azides in Benzene (Concentration – Time Curves):

In a typical run, the 4-methylbenzenesulfonyl azide (**A**; 4 g, 0.005 mol) and benzene (200 g, 2.56 mol) were charged into an autoclave (Parr bench-top mini reactor of 300 mL capacity provided with a heater, stirrer, pressure gauge, thermocouple, temperature controller and a sample removal system in the form of a loop with inlet and outlet valves, fabricated out of a copper tube of 11 in.x 0.01

Table. *N*-Sulphonylazepines **3a**–**g** Prepared

Product	Yield[a] (%)	mp (°C)[b]	Molecular Formula[c] or Lit. mp (°C)	IR (Nujol)[d] ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS)[e] δ	MS[f] *m/z* (%)
3a	80	133	132–133[17]	1645, 1625, 1455, 1360, 1175	7.62 (m, 5H_{arom}), 5.76 (m, 6$H_{azepinyl}$)	233 (15), 92 (100), 65 (38), 39 (15)
3b	48	167	169[1]	1645, 1620, 1580, 1455, 1360, 1170	2.40 (s, 3H, CH_3), 7.70 (m, 5H_{arom}), 5.80 (m, 6$H_{azepinyl}$)	247 (48), 183 (6), 156 (17), 92 (100), 66 (64), 64 (39)
3c	68	132	131–134[17]	1640, 1618, 1585, 1570, 1455, 1298, 1270, 1170	7.70 (d, 2H, H-2′, H-6′), 7.40 (d, 2H, H-3′, H-5′), 5.80 (m, 4H, H-2, H-4, H-5, H-7), 5.70 (m, 2H, 3-H, 6-H)	312 (12), 247 (7), 217 (17), 92 (100), 65 (68), 64 (36)
3d	71	122–123	$C_{12}H_{10}ClNO_2S$ (267.6)	1640, 1618, 1585, 1570, 1455, 1298, 1270, 1170	7.80 (d, 2H, H-2′, H-6′), 7.30 (d, 2H, H-3′, H-5′), 5.80 (m, 4H, H-2, H-4, H-5, H-7), 5.70 (m, 2H, H-3, H-6)	267 (28), 203 (4), 188 (2), 175 (14), 112 (19), 92 (100), 69 (42), 65 (71), 64 (39)
3e	44	111–112	$C_{13}H_{13}NO_3S$ (263.2)	1645, 1600, 1580, 1455, 1375, 1270, 1165, 1040	7.70 (d, 2H, H-3′, H-5′), 6.80 (d, 2H, H-2′, H-6′), 5.80 (m, 4H, H-2, H-4, H-5, H-7), 5.70 (m, 2H, H-3, H-6), 3.80 (s, 3H, MeO)	263 (71), 199 (3), 184 (9), 171 (13), 108 (27), 92 (100), 66 (49), 65 (74), 64 (35)
3f	76	175	$C_{12}H_{10}N_2O_4S$ (278.2)	1680, 1612, 1545, 1455, 1345, 1222, 1108, 1048	8.20 (d, 2H, H-3′, H-5′), 7.80 (d, 2H, H-2′, H-6′), 5.80 (m, 6$H_{azepinyl}$)	278 (6), 91 (100), 66 (9), 65 (38), 64 (11)
3g	72	semisolid	$C_{12}H_{10}FNO_2S$ (251.2)	1640, 1620, 1585, 1570, 1455, 1295, 1270, 1179	7.70 (d, 2H, H-2′, H-6′), 7.40 (d, 2H, H-3′, H-5′), 5.70 (m, 6$H_{azepinyl}$)	251 (26), 187 (8), 172 (4), 158 (15), 92 (100), 65 (62), 64 (31)

[a] Yield of isolated product **3** based on **1**.

[b] Uncorrected, measured with a Mettler-FP 5 apparatus.

[c] Satisfactory microanalyses obtained: C ±0.27, H ±0.15, N ±0.30.

[d] Perkin-Elmer FTIR 1720 X.

[e] Bruker WH-90 FTNMR spectrometer.

[f] Recorded on a Hewlett-Packard 5930-A spectrometer.

in. id). The reactor was purged with N_2 and heated slowly to raise the temperature to 125 °C in 30 min. The final pressure recorded on the gauge at 125 °C was 480 psi. The generated N_2 in the reaction and the vapour pressure of benzene at reaction temperature contributing towards the increase in pressure. The samples were removed at 125 °C at various intervals of time. In a typical run, in presence of $NaHCO_3$ under solid–liquid PTC conditions, the azide **A** (4 g, 0.005 mol), benzene (200 g, 2.56 mol), $NaHCO_3$ (1.68 g, 0.02 mol) and Me (n-C_8H_{17})$_3$ NCl (0.202 g, 0.0005 mol) were charged into the autoclave and the reaction was conducted as described above.

Procedure for Sample Removal: During each sample removal, the outlet valve of the sample tube was closed and the inlet valve opened to let the mixture enter inside the loop. The inlet valve was then closed immediately. The loop was cooled externally by dipping in cold H_2O and the outlet valve opened to remove the mixture inside the loop. Each time nearly 4–5 mL of the sample was removed.

High performance Thin Layer Chromatographic (HPTLC) Analysis:
The HPTLC estimations of **A**, **B**, **C** and **D** were carried out on Camag TLC Scanner-2. The sample of mixture, withdrawn at different intervals of time, was washed with distilled H_2O (2 x 5 mL). The samples were spotted in volume of 1 μL each, with an automatic spotting device on silica plate. The plates were eluted in a mixture of benzene and hexane (Analar grade) (50:50, v/v) in a development tank. The standard solution of the pure components were also spotted and eluted under identical conditions. The estimations were done by calculating the areas under the recorded peaks. Each estimation was a mean of at least four consecutive spottings and elutions.

Preparation of Standard Compounds: The standard compounds were prepared according to the method reported in literature. (**A**) 4-methylbenzenesulphonyl azide, mp 20–21 °C (Lit.[14] mp 19–20 °C); (**B**) 1-(4-methylbenzenesulphonyl)-1*H*-azepine, mp 167 °C (dec) (Lit.[1] mp 167 °C); (**C**) 4-methylbenzenesulphonanilide, mp 103 °C (Lit.[15] mp 103 °C); (**D**) 4-methylbenzenesulphonamide, mp 136 °C (Lit.[16] mp 136 °C).

Synthesis of *N*-sulphonyl-1*H*-azepines (3) from Sulphonyl Chlorides (1); General Procedure:
The sulphonyl chloride derivatives **1** (0.005 mol), benzene (200 g, 2.56 mol), NaN_3 (4 g, 0.005 mol), $NaHCO_3$ (1.68 g, 0.02 mol) and Me(n-C_8H_{17})$_3$NCl (0.202 g, 0.0005 mol) were charged into an autoclave. The reactor was purged with N_2 and the mixture was stirred at 40 °C for 3 h. Then the mixture was heated slowly to the temperature of 125 °C and maintained at this temperature for another 3 h. The final pressure recorded on the gauge at 125 °C was 460–480 psi. The mass was cooled and discharged from the autoclave. The mass was filtered and washed with distilled H_2O thoroughly. Benzene was removed under vacuum. The resulting reddish yellow mass was adsorbed on neutral alumina and chromatographed through a column of neutral alumina by eluting with hexane/benzene (60:40) to yield *N*-sulphonyl-1*H*-azepines. After solvent removal and recrystallization from petroleum ether (60–80 °C), analytically pure compounds listed in the Table were obtained.

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