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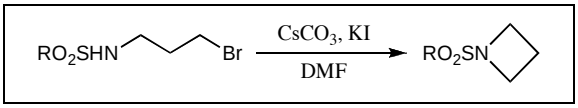

A convenient method for the synthesis of N-arylsulfonyl azetidines using *N*-(3-bromopropyl)-arylsulfonamide with cesium carbonate and potassium iodide in DMF is reported. The reaction conditions are optimized and seven N-arylsulfonyl azetidines have been synthesized in good yield using this method. The structures of compounds **2a** and **2e** were determined by X-ray crystallography.

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INTRODUCTION

Azetidines are valuable compounds in pharmaceutical research [1-4]. However, azetidines represent one of the more difficult group of amines to synthesize because of the unfavorable enthalpy of activation in four-membered ring formation [5]. The development of effective methods for the synthesis of azetidines has posed a challenge for more than one hundred years since azetidines were first prepared in low yield in 1888 by treatment of 3-bromopropylamine with a base [6].

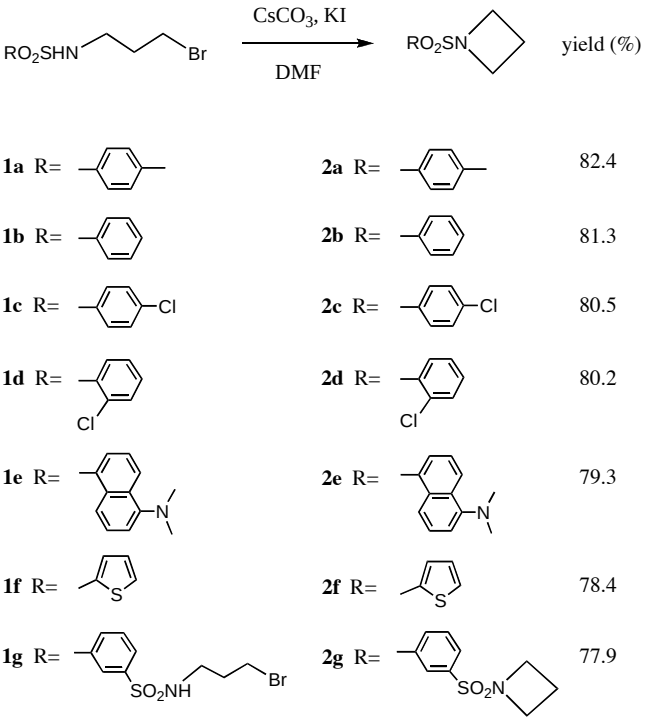
Several methods have been utilized to synthesize N-arylsulfonylazetidines and include alkylation of a primary amine with the bis-triflate of a 1,3-propanediol species [7], methylene transfer from dimethyloxosulphonium methylide to azetidines [8], cyclization of ditoslyloxypropanes with sulfonamines [9], cyclization of *N*-[ω-(phenylseleno)propyl]sulfonamines [10], and cyclization of 3-chloropropyl sulfonamines [11]. Strong bases such as sodium metal or sodium hydroxide have been used, but these lead to competing elimination reactions and dimerization to bisazacyclooctane sulfonamides and these reactions are always run in ethanol at reflux temperature.

Recently, while investigating the synthesis of resorcin-[4]arene derivates, a convenient method for the synthesis of N-arylsulfonyl azetidines was discovered. Herein, are described the syntheses of N-arylsulfonylazetidines by the reaction between *N*-(3-bromopropyl)aryl sulfonamide and cesium carbonate and potassium iodide in DMF.

RESULTS AND DISCUSSION

During optimization of the reaction conditions, it was found that there are three key factors involved in this reaction: base, solvent and the nature of the leaving group. Vaughan, *et al.* [11] reported that in the dehydrohalogenation of 3-chloropropylsulfonamines, deprotonation of the sulfonamine is necessary. Recently, we found that cesium carbonate is a sufficiently strong base to deprotonate 3-halopropylaryl sulfonamide to form *N*-arylsulfonyl azetidines. However, it is notable that when a weaker base such as potassium carbonate or stronger base such as sodium hydroxide is used, the reaction is unsuccessful. And with these substrates, which bear alkyl substituents on sulfonamine, the reaction is also unsuccessful. Secondly, the solvent plays an important role in the reaction yield. Because the deprotonation of the sulfonamine is the key step during the reaction, polar solvents favor the reaction. The solubility of cesium carbonate is greater in polar solvents than in nonpolar solvents. It was found that in the dehydrohalogenation of *N*-(3-bromopropyl)-4-methylbenzenesulfonamide the reaction yield can reach about 80% when the DMF is used

Scheme 1. Synthesis of compounds **2a-g**.



as the solvent. However, only about a 10% yield was obtained when the solvent is dichloromethane or benzene. Thirdly, the leaving group plays an important role in the reaction. Potassium iodide converts *N*-(3-bromopropyl)-arylsulfonamide to the more reactive *N*-(3-iodopropyl)-arylsulfonamide. It was found that the reaction is unsuccessful without potassium iodide.

The structures of compounds **2a** and **2e** were determined utilizing X-ray crystallography. Compound **2a** or **2e** was obtained in the form of air-stable, colorless crystals by slow evaporation from a solution of **2a** or **2e** in methanol. The perspective view of compound **2a** is shown in Figure 1.

Examination of the crystal structure of **2a** shows that the angle between the plane of the four-membered ring and the plane of benzene is close to 90°. The angles within the four-membered ring are close to 90° with C(11)-N(1)-C(13) slightly larger [90.66(10)] than the others. The average value of the endocyclic N-C bonds [1.505(18)] and C-C bonds [1.539(2)] are in agreement with the value obtained in 1-(diphenylmethyl)azetidin-3-ol [12].

The perspective view of compound **2e** is shown in Figure 2. Examination of the crystal structure of **2e** shows that its structure is very similar to that of **2a**.

CONCLUSION

We report a convenient method for the synthesis of *N*-arylsulfonyl azetidines using *N*-(3-bromopropyl)aryl-sulfonamide with cesium carbonate and potassium iodide in DMF. Seven N-arylsulfonyl azetidines have been synthesized in good yield using this method. The structures of compounds **2a** and **2e** have been determined by X-ray crystallography.

EXPERIMENTAL

General. *N*-(3-Bromopropyl)arylsulfonamides **1** were prepared according to literature methods [13]. All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ (TMS as internal reference), unless otherwise specified, at 300 MHz and 75 MHz, using a Varian 300 MHz NMR spectrometer.

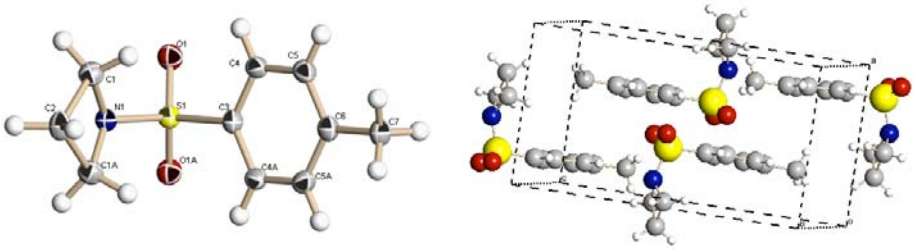


Figure 1. Molecular structure of **2a**.

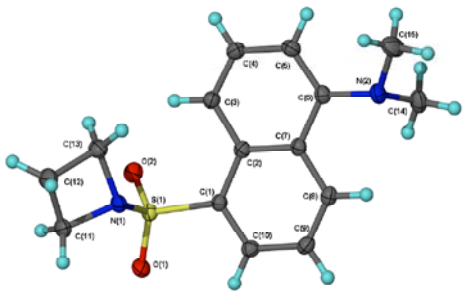


Figure 2. Molecular structure of **2e**.

The mass spectral measurements were obtained using a Kratos MS80 mass spectrometer. Column chromatography was performed on Merck silica gel 230-400 mesh ASTM. Microanalyses were in agreement with theoretical values (0.4%). Elemental analyses were performed by the Galbraith Laboratories, Knoxville, Tenn.

General method for synthesis of 2. To a stirred suspension of **1** (0.001 mol) in DMF (10 mL), cesium carbonate (0.001 mol) and potassium iodide (0.001 mol) were added. The resulting mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography, eluted with dichloromethane, to afford the desired product **2**.

1-(Toluene-4-sulfonyl)-azetidine (2a), this compound was obtained in the form of white crystals by recrystallization from methanol in 82.4% yield. m.p. 119-121° (reported 120° [14]). ^{1}H NMR ($CDCl_3$) δ (ppm): 2.07 (m, 2H, CH_2), 2.47 (s, 3H, CH_3),

Table 1

Crystal data and Structure Refinement of Compound **2a** and **2e**

	2a	**2e**
Empirical formula	$C_{10}H_{12}NO_2S$	$C_{15}H_{18}N_2O_2S$
Formula weight	210.27	290.37
Temperature (K)	110(2)	110(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic
Space group	Pnma	P2(1)/n
Unit cell dimensions		
a (Å)	7.4237(7)	11.5918(7)
b (Å)	9.7647(10)	10.0015(6)
c (Å)	13.5192(14)	12.6481(8)
α (°)	90	90
β (°)	90	109.0880(10)
γ (°)	90	90
Volume ($Å^3$)	980.01(17)	1385.74(15)
Z	4	4
D_{calc} (Mg/m^3)	1.425	1.392
Absorption coefficient (mm^{-1})	0.302	0.237
F(000)	444	616
Crystal size (mm^3)	0.20 x 0.17 x 0.05	0.30 x 0.20 x 0.20
Theta range for data collection (°)	4.17 to 24.98	4.08 to 28.13
Index ranges	-8<=h<=8	-15<=h<=15
	-11<=k<=11	-13<=k<=13
	-13<=l<=16	-16<=l<=16
Reflections collected	6496	13657
Independent reflections	865 [R(int) = 0.0305]	3422 [R(int) = 0.0198]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	865 / 0 / 73	3422 / 0 / 183
Goodness-of-fit on F^2	1.067	1.053
Final R indices [I>2sigma(I)]	R_1 = 0.0499	R_1 = 0.0448
	wR_2 = 0.1222	wR_2 = 0.1134
R indices (all data)	R_1 = 0.0536,	R_1 = 0.0480
	wR_2 = 0.1290	wR_2 = 0.1173
Largest diff. peak and hole ($e.Å^{-3}$)	0.874 and -0.322	0.558 and -0.375

3.77 (t, 4H, CH_2), 7.27-7.37 (dd, *J* = 0.9, 4.8 Hz, 4H, ArH), ^{13}C NMR ($CDCl_3$) δ (ppm): 15.25, 21.58, 50.83, 128.40, 129.70, 143.92. MS (ESI) ($CHCl_3$): 212 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; O, 15.15; S, 15.18. Found: C, 56.48; H, 6.31; N, 6.30; O, 14.21; S, 13.92.

1-Benzenesulfonyl-azetidine (2b), this compound was obtained as a liquid in 81.3% yield. ^1H NMR ($CDCl_3$) δ (ppm): 2.06 (m, 2H, CH_2), 3.77 (t, 4H, CH_2), 7.56-7.66 (m, 3H, ArH), 7.82-7.86 (m, 2H, ArH), ^{13}C NMR ($CDCl_3$) δ (ppm): 15.20, 50.87, 128.23, 129.04, 133.05. MS (ESI) ($CHCl_3$): 198 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; O, 16.22; S, 16.26. Found: C, 54.44; H, 5.74; N, 7.40; O, 16.60; S, 15.82.

1-(4-Chlorobenzenesulfonyl)-azetidine (2c), this compound was obtained in the form of white crystals by recrystallization from methanol in 80.5% yield. m.p. 116-118°. ^1H NMR ($CDCl_3$) δ (ppm): 2.11 (m, 2H, CH_2), 3.80 (t, 4H, CH_2), 7.55-7.59 (m, 2H, ArH), 7.77-7.82 (m, 2H, ArH), ^{13}C NMR ($CDCl_3$) δ (ppm): 15.26, 50.97, 129.42, 129.69. MS (ESI) ($CHCl_3$): 232 $[M+H]^+$. Anal. Calcd. for $C_9H_{10}ClNO_2S$: C, 46.65; H, 4.35; Cl, 15.30; N, 6.05; O, 13.81; S, 13.84. Found: C, 46.41; H, 4.23; Cl, 15.60; N, 6.21; O, 14.02; S, 13.54.

1-(2-Chlorobenzenesulfonyl)-azetidine (2d), this compound was obtained as a liquid in 80.2% yield. ^1H NMR ($CDCl_3$) δ (ppm): 2.21 (m, 2H, CH_2), 4.04 (t, 4H, CH_2), 7.56-7.62 (m, 3H, ArH), 8.01-8.04 (m, H, ArH), ^{13}C NMR ($CDCl_3$) δ (ppm): 14.93, 51.06, 126.84, 131.26, 131.95, 132.61, 133.60, 136.01. MS (ESI) ($CHCl_3$): 232 $[M+H]^+$. Anal. Calcd. for $C_9H_{10}ClNO_2S$: C, 46.65; H, 4.35; Cl, 15.30; N, 6.05; O, 13.81; S, 13.84. Found: C, 46.35; H, 4.18; Cl, 15.58; N, 6.14; O, 14.50; S, 13.25.

1-[5-(Dimethyl-amine)-naphthalenyl-1-sulfony]-azetidine (2e), this compound was obtained in the form of white crystals by recrystallization from methanol in 79.3% yield, m.p. 77-79°. ^1H NMR ($CDCl_3$) δ (ppm): 2.11 (m, 2H, CH_2), 2.87 (s, 6H, CH_3), 3.90 (t, 4H, CH_2), 7.16-7.19 (dd, *J* = 0.9, 7.8 Hz, 1H, ArH), 7.24-7.57 (m, 2H, ArH), 8.21-8.23 (dd, *J* = 0.9, 7.2 Hz, 1H, ArH), 8.38-8.41 (dd, *J* =0.9, 8.7 Hz, 1H, ArH), 8.54-8.57 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ (ppm): 15.04, 45.44, 50.21, 115.20, 120.03, 123.19, 128.04, 130.53, 130.83. MS (ESI) ($CHCl_3$): 291 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65; O, 11.02; S, 11.04. Found: C, 61.72; H, 6.30; N, 9.24; O, 10.18; S, 11.05.

1-(Thiophene-2-sulfonyl)-azetidine (2f), this compound was obtained in the form of white crystals by recrystallization from methanol in 78.4% yield, m.p. 66-68°. ^1H NMR ($CDCl_3$) δ (ppm): 2.09 (m, 2H, CH_2), 3.84 (t, 4H, CH_2), 7.21-7.24 (m, H, ArH), 7.62-7.64 (m, H, ArH), 7.70-7.72 (m, H, ArH), ^{13}C NMR ($CDCl_3$) δ (ppm): 14.99, 51.29, 127.77, 132.65, 133.41. MS (ESI) ($CHCl_3$): 204 $[M+H]^+$. Anal. Calcd. for $C_7H_9NO_2S_2$: C,

41.36; H, 4.46; N, 6.89; O, 15.74; S, 31.55. Found: C, 41.16; H, 4.51; N, 6.82; O, 15.87; S, 31.64.

1,3-Bis[sulfonyl-azetidine]-benzene (2g), this compound was obtained in the form of white crystals by recrystallization from methanol in 77.9% yield, m.p. 179-181°. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.15 (m, 4H, CH_2), 3.86 (t, 8H, CH_2), 7.80-7.85 (m, H, ArH), 8.10-8.13(m, 2H, ArH) 8.30-8.31 (m, H, ArH), ^{13}C NMR ($CDCl_3$) δ (ppm): 15.27, 51.17, 127.62, 130.14, 132.23, 136.86. MS (ESI) ($CHCl_3$): 317 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{16}N_2O_4S_2$: C, 45.55; H, 5.10; N, 8.85; O, 20.23; S, 20.27. Found: C, 45.32; H, 5.18; N, 8.24; O, 20.41; S, 20.85.

X-ray crystallography. Crystallographic measurements were carried out on a Siemens P4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and a 12 kW rotating generator. The data were collected at 110 K. The structures were solved and refined using the programs SHELXS-97 (Sheldrick, 1997) and SHELXL (Sheldrick, 1997). The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs.

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