A Facile Synthesis of 1-Arenesulfonylazetidines through Reaction of 1-Arenesulfonylaziridines with Dimethylsulfoxonium Methylide Generated under Microwave Irradiation

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Abstract: A simple, efficient and general method has been developed for the synthesis of 1-arenesulfonylazetidines through a one-pot reaction of 1-arenesulfonylaziridines with dimethylsulfoxonium methylide, generated under microwave irradiation, using alumina as solid support.

Key words: azo compounds, ring expansion, sulfur, ylides, heterocycles

Azetidines are an important group of nitrogen-containing heterocycles, which have continued to attract attention on account of their useful biological activities.[1–8]

However, there is a paucity of good synthetic methods for making these. Known ones, generally suffer from lack of generality, multiple steps and involve starting materials, which are difficult to obtain.[9–14]

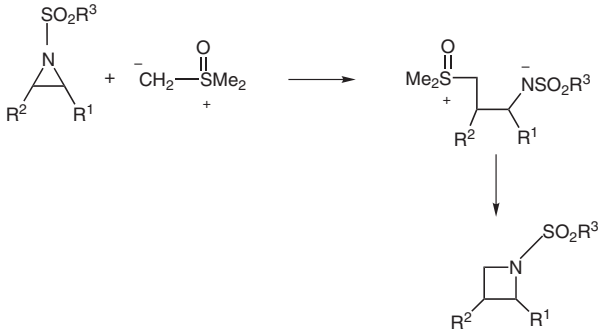
Different approaches for syntheses of 1-arenesulfonylazetidines have been reported, such as regioselective addition of 1,3-dicarbonyl dianions to *N*-sulfonyl aldimines,[15] homologation of α-amino acids,[16] cyclization of *tert*-butyl acetate,[17] photocyclization of 2-acyl-3-allylperhydro-1,3-benzoxazines,[18] α-alkylation of SAMP hydrazones with benzyloxymethyl chloride[19] and β-elimination of amino alcohols.[20,21]

We have shown previously[22–25] that methylene transfer from dimethylsulfoxonium methylide to 1-arenesulfonylaziridines leads in a fairly simple and general way to the corresponding azetidine through nucleophilic attack of the ylide on the aziridine followed by 4-*exo-tet* ring closure of intermediate **1** (Scheme 1).

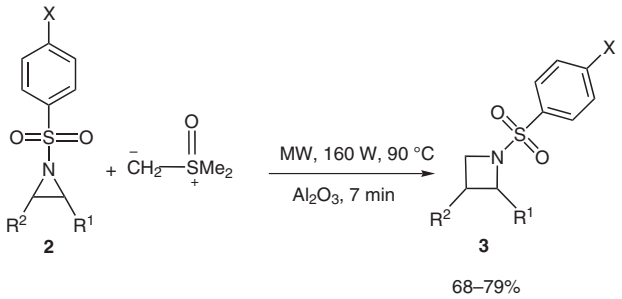
In all these reactions, however, side products accompanied azetidine formation and the yields were modest. Besides they involved use of solvents like DMSO and DMF.

In recent years, solvent-free syntheses utilizing microwave irradiation and surface mediation have received considerable attention because these are often environmentally benign, require shorter reaction times, are efficient, high-yielding and have easy workups.[26–30]

As part of our efforts to explore these types of reaction conditions,[31,32] we herein describe a facile procedure for obtaining 1-arenesulfonylazetidines through reaction of 1-arenesulfonylaziridines with dimethylsulfoxonium methylide (generated from trimethylsulfoxonium iodide and KOH) under microwave irradiation using alumina support (Scheme 2).



Scheme 1 Synthesis of 1-arenesulfonylazetidines through reaction of 1-arenesulfonylaziridines with dimethylsulfoxonium methylide



Scheme 2 Synthesis of 1-arenesulfonylazetidines under microwave irradiation

We performed ring expansion of 1-arenesulfonylaziridines **2a–k** by dimethylsulfoxonium methylide using microwave irradiation in solvent-free conditions (on Al_2O_3).[33] All reactions were carried out in sealed reaction vials by the focused microwave reactor Pelco with measurement and control of power and temperature by the thermocouple for the time given in Table 1.[34,35]

It may be noted that the reaction was successful only when alumina was used as the solid support; it failed when silica gel or montmorillonite K-10 or KSF were used as the solid support.

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Table 1 Various 1-Arenesulfonylazetidines[33] Synthesized[a]

Entry[b]	R^1	R^2	X	Time (min)	Temp. (°C)	Power (W)	Yield (%)[c]
3a	Ph	Ph (*cis*)	Me	7	90	160	78
3b	Ph	Ph (*trans*)	Me	3	110	320	79
3c	Ph	H	Me	7	90	160	68
3d	Ph	H	H	7	90	160	68
3e	Ph	H	Cl	7	90	160	70
3f	Me	Ph (*cis*)	Me	7	90	160	79
3g	C_6H_{13}	H	Me	7	90	160	75
3h	4-ClC_6H_4	H	Me	7	90	160	72
3i	4-BrC_6H_4	H	Me	7	90	160	71
3j	4-MeC_6H_4	H	Me	7	90	160	73
3k	Me	H	Me	7	90	160	75

[a] Reaction conditions: 1-arenesulfonylaziridines (1 mmol), trimethylsulfoxonium iodide (3 mmol), KOH (3 mmol).
[b] All new products were characterized by NMR, IR, mass and elemental analysis.
[c] Isolated, unoptimized yields.

The starting aziridines **2a–e** and **2h–j** were prepared from the appropriate olefin through a known three-step procedure used by us previously.[36] Aziridines **2f** and **2g** could be accessed by the Sharpless method[37] and **2k** by the Stephens method.[38] The mixture was irradiated with microwaves of appropriate power and for reaction times specified in Table 1.

Only a single product (as shown by TLC) was obtained and could be easily extracted with minimal use of solvents. It is clear from Table 1 that the reaction times were short and the yields were uniformly good.

The workup was simple and avoided the use of expensive bases for ylide generation. Entries 1 and 2 show that the reaction was stereospecific: *cis*-Aziridines yielded the *trans*-azetidines and the *trans*-aziridines led to the *cis*-azetidines. The geometry of these isomers was assigned on the basis of NMR observations and NOE experiment: coupling constant of vicinal *trans* protons (J = 7.5 Hz) was less than that of the *cis* protons (J = 9 Hz). C-2 proton *cis* to the phenyl ring in the *trans* isomer appeared ca. 0.4 ppm upfield from that in the *cis* isomer.[39] The 2,3-*cis* stereochemistry of vicinal hydrogens in **3a** was determined by NOE experiment. The peak for the C-2 hydrogen was enhanced (ca. 4%) on irradiation of the C-3 hydrogen (Figure 1).

These results indicate that methylene transfer to 1-arenesulfonylaziridines is stereospecific and leads to the inversion of configuration at the attacked carbon, thus lending support to the rational of this methodology. The regioselectivity of the reaction is substituent-dependent and governed by both steric and electronic factors. Entries 3–5 and 7–11 show that, only those azetidines were obtained, which corresponded to dimethylsulfoxonium methylide attack at less substituted carbon of aziridine ring. Entry 6 shows ylide attack at the carbon bearing phenyl rather than a methyl group, indicating the predominance of electronic effect.

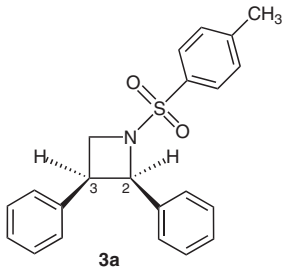

Figure 1

The improved yields of azetidines and the absence of side products could be due to the fact that, in solution phase conformational mobility adversely affects azetidine formation and results in side products.

In summary, we have described an experimentally simple and convenient process for the synthesis of 1-arenesulfonylazetidines. This protocol is fairly general and applicable to a wide variety of 1-arenesulfonylaziridines. The reaction is stereospecific as well as regioselective. The yields are good; reaction times are short, reaction conditions are benign and the workup procedure is simple.

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(33) **General Method for the Synthesis of 1-Arenesulfonyl-azetidines**: The pertinent aziridine (1 mmol), trimethylsulfoxonium iodide (3 mmol) and KOH (3 mmol) were loaded on neutral alumina (0.5 mmol) solid support. This mixture was irradiated with microwaves for the specified time (Table 1). Only a single product (as shown by TLC) was formed. The reaction was quenched by addition of cold H_2O. The product was extracted with EtOAc and purified by simple crystallization or through column chromatography on silica gel.
***cis*-2-Methyl-3-phenyl-1-(4-toluenesulfonyl)azetidine (3f)**: white crystalline solid; mp 105–106 °C; yield: 79%. IR: 1333, 1164 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (m, 5 H), 7.32 (s, 4 H), 4.26 (q, *J* = 7 Hz, 1 H), 3.93 (distorted d, *J* = 6 Hz, 2 H), 3.41 (m, 1 H), 2.39 (s, 3 H), 0.98 (d, *J* = 7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.2–137.4 (ArC), 63.02 (d), 53.47 (t), 38.17 (d), 21.42 (q), 17.02 (q). Anal. Calcd for $C_{17}H_{19}NSO_2$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.10; H, 6.40; N, 4.51. MS (FAB): *m*/*z* = 302 [MH^+].
2-Hexyl-1-(4-toluenesulfonyl)azetidine (3g): viscous oil; yield: 79%. IR: 1333, 1164 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, 2 H), 7.32 (d, 2 H), 3.42–3.77 (complex m, 3 H), 2.38 (s, 3 H), 1.84 (complex m, 2 H), 1.18–1.32 (m, 10 H, aliphatic), 0.81 (t, *J* = 7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.26–143.80 (ArC), 66.35 (d), 47.50 (t), 36.02 (t), 31.70 (t), 29.66 (t), 28.59 (t), 24.13 (t), 22.66 (t), 21.42 (q), 14.09 (q). Anal. Calcd for $C_{16}H_{25}NSO_2$: C, 65.08; H, 8.47; N, 4.74. Found: C, 64.88; H, 7.80; N, 4.30. MS (FAB): *m*/*z* = 296 [MH^+].
2-(4-Chlorophenyl)-1-(4-toluenesulfonyl)azetidine (3h): white crystalline solid; mp 108–109.5 °C; yield: 72%. IR: 1333, 1160 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (m, 4 H), 7.31 (s, 4 H), 4.89 (t, *J* = 8 Hz, 1 H), 3.77 (dd, *J* = 6, 8 Hz, 2 H), 2.40 (s, 3 H), 2.25 (m, *J* = 8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.83–139.14 (ArC), 65.11 (d), 47.43 (t), 25.89 (t), 21.41 (q). Anal. Calcd for $C_{16}H_{16}NSO_2Cl$: C, 59.72; H, 4.97; N, 4.35. Found: C, 59.72; H, 5.08; N, 4.07. MS (FAB): *m*/*z* = 322 [M^+].
2-(4-Bromophenyl)-1-(4-toluenesulfonyl)azetidine (3i): white crystalline solid; mp 118–119 °C; yield: 71%. IR: 1330, 1164 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (m, 4 H), 7.28 (s, 4 H), 4.78 (t, *J* = 8 Hz, 1 H), 3.78 (dd, *J* = 6, 8 Hz, 2 H), 2.38 (s, 3 H), 2.25 (m, *J* = 8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.83–139.14 (ArC), 65.15 (d), 47.43 (t), 25.89 (t), 21.42 (q). Anal. Calcd for $C_{16}H_{16}NSO_2Br$: C, 52.45; H, 4.37; N, 3.82. Found: C, 52.22; H, 4.44; N, 3.14. MS (FAB): *m*/*z* = 366 [M^+].
2-(4-Methylphenyl)-1-(4-toluenesulfonyl)azetidine (3j): white crystalline solid; mp 110–111 °C; yield: 71%. IR: 1334, 1163 (SO_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (m, 4 H), 7.02 (m, 4 H), 4.87 (t, *J* = 8 Hz, 1 H), 3.77 (dd, *J* = 6, 8 Hz, 2 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 2.28 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 123.3–140.29 (ArC), 65.83 (d), 47.27 (t), 25.83 (t), 21.4 (q), 21.38 (q). Anal. Calcd for $C_{17}H_{19}NSO_2$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.11; H, 5.95; N, 3.96. MS (FAB): *m*/*z* = 302 [MH^+].
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