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Highly regioselective ring-opening of aziridines with arenesulfinates on water: a facile access to β-amino/vinyl sulfones

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ABSTRACT

We have developed a LiBr catalyzed efficient synthesis of β-amino sulfones from readily available aziridines and sodium sulfinates in good to excellent yields. The synthetic potential of β-amino sulfones has also been demonstrated by their facile conversion to the corresponding vinyl sulfones. The use of water as reaction media, atom-economy and isolation of products by simple filtration in the case of solid β-amino sulfones are certain green virtues of the synthetic protocol.

1. Introduction

β-Amino sulfones have widely been recognized for their interesting biological properties. They are valuable HIV protease inhibitors,[1] matrix metalloproteinase inhibitors[2] and DNA alkylating agents for cancer treatment[3] (Fig. 1). In addition, they readily undergo electrophilic substitution in the α-position acting as versatile intermediates in the synthesis of α-amino acids,[4] amino alcohols,[5] substituted uridines and adenosines,[6] alkaloids,[7] β-lactams[8] and nitrogen heterocycles.[9] Despite their importance, the synthesis of β-amino sulfones has been less explored. The most common methods available for their preparation include use of amino acids as substrates,[10] stereoselective addition of sulfonyl carbanions to *N*-sulfinyl imines[11] and intramolecular[12] and intermolecular[6,9a,13] aza-Michael additions to α,β-unsaturated sulfones. However, these methods suffer from drawbacks like tedious multi-step transformations, low yields, non-green conditions and expensive reagents.

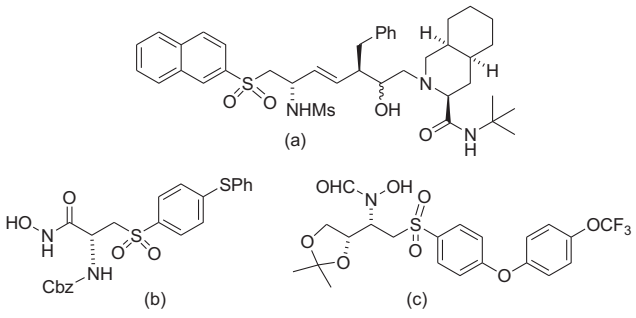

Fig. 1. Examples of β-amino sulfone-containing enzyme inhibitors.

Aziridines are well-known synthetic intermediates and starting materials owing to their inherent ring strain, which makes them highly susceptible to nucleophilic attack. Nucleophilic ring-opening reactions of aziridines hold a prominent place in organic synthesis since they lead to 1,2-bifunctional systems, which are potent structural motifs for the synthesis of wide variety of valuable products. In view of the generation of such important functionalized systems, a plethora of oxygen, nitrogen and sulfur nucleophiles have been reported for the ring-opening reactions of aziridines.[14] To the best of our knowledge, there is no report on the ring-opening reaction of aziridines with sulfinate nucleophiles although it would offer a direct approach for the synthesis of substituted β-amino sulfones. However, Hou and co-workers have reported an unexpected transfer of tosyl group of *N*-tosylimines to aziridines catalyzed by *N*-heterocyclic carbene.[15] The use of such expensive and difficult-to-handle substrates and catalyst, strictly limits the synthetic viability of the process. On the other hand, numerous examples of the ring-opening reactions of epoxides with sulfinates are reported in the literature.[16] Recently, we have

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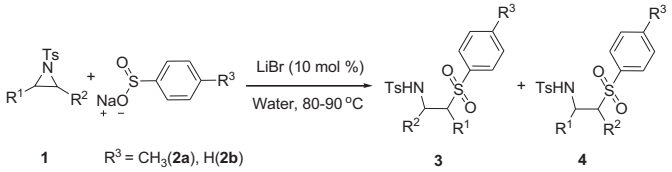
disclosed a method for the synthesis of terminal as well as internal vinyl sulfones employing the sulfinate nucleophile mediated ring-opening reaction of terminal epoxides in aqueous medium.[16g] Encouraged by our previous findings we became interested in the nucleophilic ring-opening of aziridines with sulfinates.

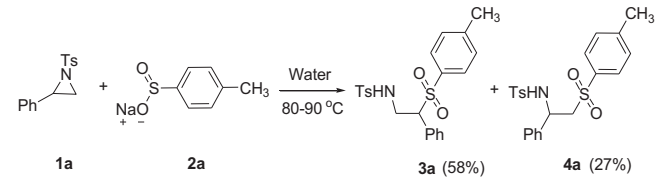
Over the recent years, tremendous efforts have been devoted towards the development of environmentally benign synthetic methodologies. Replacement of hazardous classical solvents with highly ecofriendly aqueous medium has emerged as one of the most commendable moves in this direction.[17] Besides being inexpensive and environmentally benign, water as a reaction medium offers an easy approach for the separation of organic reagents or catalysts. As part of our efforts to devise novel greener synthetic methodologies using easily available substrates[16g,18,19a] and to overcome the limitations associated with the synthesis of β-amino sulfones, we herein report the first synthetic route to β-amino sulfones on water employing LiBr catalyzed nucleophilic ring-opening of aziridines with arenesulfinates (Scheme 1).



Scheme 1. Synthesis of β-amino sulfones in aqueous media.

2. Results and discussion

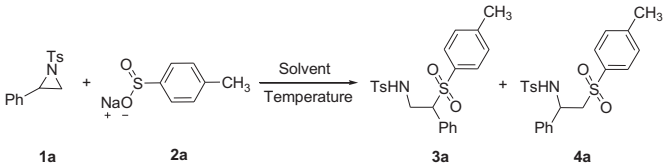
We commenced our study with the model reaction of *N*-tosylaziridine **1a** with sodium *p*-toluenesulfinate **2a** on water at rt. Not very encouraging results were obtained at rt even after 24 h, so we heated the reaction mixture to 50–60 °C. This resulted in the formation of a mixture of regioisomers of β-amino sulfone **3a** (34%) and **4a** (16%) after 8 h. It is quite evident from this fact that during the nucleophilic attack, electronic factors were dominating the steric factors since the attack of the bulky sulfinate nucleophile took place at the hindered benzylic carbon of aziridine **1a** to produce **3a** as the major product. On increasing the temperature to 80–90 °C, the overall yield of the reaction was increased but there was not any significant change in the regioselectivity of the reaction (Scheme 2) (Table 1, entries 1–3).



Scheme 2. Model reaction for the synthesis of β-amino sulfones on water.

The reaction was also tried in some organic solvents. At rt as well as at reflux no product could be isolated in the case of less polar solvents (Table 1, entries 4, 5). This may be attributed to the insolubility of salt **2a** in these organic solvents. Addition of a few drops of water to the reaction mixture in CH_3CN or 1,4-dioxane, slightly promoted the reaction at rt and heating the reaction mixture to reflux did not produce any encouraging results (Table 1, entries 6–9). Though the reaction proceeded well in polar solvents like methanol and ethanol at reflux but the overall yield was lesser than that in water without significant improvement in the regioselectivity as well (Table 1, entries 10, 11). So water remained the solvent of choice for further study.

Table 1
Optimization of solvent for the synthesis of β-amino sulfones[a]

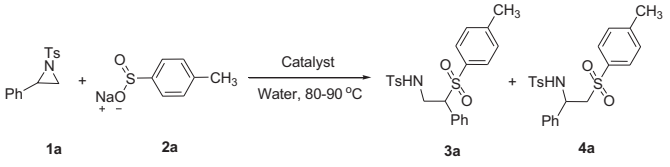


Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)		Regioselectivity[c]
				3a	**4a**	(**3a**:**4a**)
1	Water	rt	24	17	10	64:26
2	Water	50–60	8	34	16	68:32
3	Water	80–90	6	58	27	69:31
4	1,4-Dioxane	Reflux	8	Nil	Nil	—
5	Acetonitrile	Reflux	8	Nil	Nil	—
6	Acetonitrile–water (9:1)	rt	24	20	12	61:39
7	Acetonitrile–water (9:1)	Reflux	10	33	19	63:37
8	Dioxane–water (9:1)	rt	24	14	7	65:35
9	Dioxane–water (9:1)	Reflux	10	30	15	66:34
10	Methanol	Reflux	8	42	16	72:28
11	Ethanol	Reflux	8	44	19	70:30

[a] Reaction conditions: *N*-tosylaziridine **1a** (1.0 mmol), sodium *p*-toluenesulfinate (1.0 mmol), solvent (5 mL).
[b] Isolated yield after column chromatography.
[c] As determined by ^{1}H NMR integration of the α- and β-proton signals of the two regioisomeric sulfones **3a** and **4a** in the crude product.

The regioselectivity of the reaction was not satisfactory so we decided to employ a Lewis acid. A number of Lewis acids were tested and the best results were obtained with 10 mol % of LiBr (Table 2). With the use of LiBr, the reaction could be performed even at rt with decent yield and almost complete regioselectivity in favour of **3a** though longer time was needed (Table 2, entry 2). On heating the reaction mixture to 80–90 °C, the reaction was completed in 3.5 h without any appreciable change in regioselectivity (Table 2, entry 3). Thus, the presence of 10 mol % of LiBr not only accelerated the reaction but also enhanced the yield as well as regioselectivity (Table 2, entries 3, 11). The significant improvement

Table 2
Optimization of catalyst for the synthesis of β-amino sulfones[a]



Entry	Catalyst	Mol %	Time (h)	Yield[b] (%)		Regioselectivity[c]
				3a	**4a**	(**3a**:**4a**)
1	LiCl	10	8	48	10	83:17
2	LiBr	10	15	68	4	94:6[d]
3	LiBr	10	3.5	89	4	96:4
4	LiBr	5	8	73	12	86:14
5	LiBr	15	3.5	89	4	96:4
6	LiI	10	7	50	13	79:21[e]
7	$FeCl_3$	10	9	32	13	70:30
8	$FeBr_3$	10	9	40	13	76:24
9	$CuCl_2$	10	8	26	14	66:34
10	$CuBr_2$	10	7	32	15	69:31
11	—	—	6	58	27	69:31

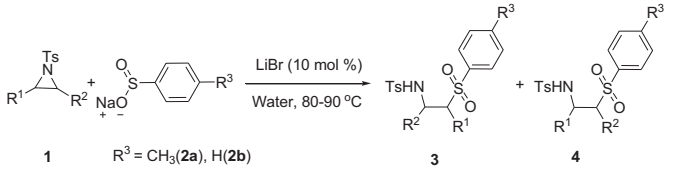
[a] Reaction conditions: *N*-tosylaziridine **1a** (1.0 mmol), sodium *p*-toluenesulfinate (1.0 mmol), water (5 mL).
[b] Isolated yield after column chromatography.
[c] As determined by ^{1}H NMR integration of the α- and β-proton signals of the two regioisomeric sulfones **3a** and **4a** in the crude product.
[d] Reaction was carried out at rt.
[e] In addition to 50% of **3a** and 13% of **4a**, 2-iodo-2-phenyl-*N*-tosylethanamine was isolated in 18% yield.

in regioselectivity in the presence of LiBr may be attributed to the fact that the carbocationic character of the benzylic carbon, induced by the resonance effect of the phenyl group in *N*-tosylaziridine **1a**, is enhanced by the coordination of LiBr with the nitrogen atom of the aziridine ring, which results in the predominant formation of the ring-opened product **3a** by the nucleophilic attack at the benzylic carbon. LiBr is a mild Lewis acid, which has been employed as an efficient, green, and inexpensive catalyst to carry out various synthetic trasformations.[16g,19]

As far as the isolation of the product is concerned, when the reaction was performed with 1 equiv of **1a** and 1.2 equiv of **2a** on water at 80–90 °C using LiBr (10 mol %), the product **3a** could be isolated as a white solid by simple filtration followed by successive washing with water and toluene. Thus, water not only acted as a solvent in the reaction but also very effectively facilitates isolation of the product.

With the optimized conditions, scope of the reaction was investigated for the synthesis of various β-amino sulfones and the results are compiled in Table 3. The generality of the protocol was demonstrated across a range of aziridines using two sulfinate salts. In general, 2-arylaziridines bearing an electron-donating substituent afford better yield of β-amino sulfones than that with an electron-withdrawing group (Table 3, entries 1–6). The more nucleophilic *p*-toluenesulfinate gave slightly higher yields than benzenesulfinate. In the case of terminal aliphatic aziridines (Table 3, entries 8–10, 14–16), the nucleophilic attack took place exclusively at the terminal carbon atom of the aziridine ring. Aziridines bearing an aryl substituent were preferably attacked at the benzylic carbon to produce the ring-opened products (Table 3, entries 1–6, 12, 18). Under similar conditions, cyclic aziridines gave trans products as confirmed by coupling constants in ^{1}H NMR spectroscopy (Table 3, entries 11, 17).

Table 3
Synthesis of β-amino sulfones **3** and **4**[a]



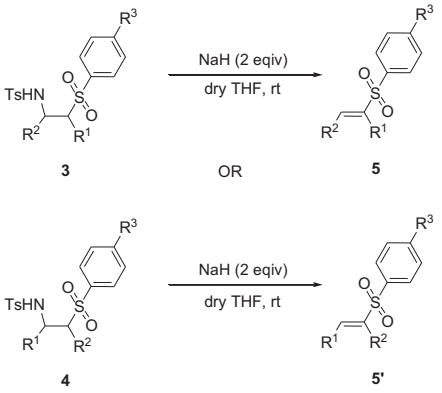
1 R^3 = CH$_3$(**2a**), H(**2b**) 3 4

Entry	R^1	R^2	**2**	Product	Time (h)	Yield[c,d] (%)		Regioselectivity[e] (**3**:**4**)
						3	**4**	
1	Ph	H	**2a**	**3a**[b], **4a**	3.5	89	4	96:4
2	*p*-ClC$_6$H$_4$	H	**2a**	**3b**, **4b**	4.5	77	8	91:9
3	*p*-MeC$_6$H$_4$	H	**2a**	**3c**, **4c**	4.0	91	3	97:3
4	Ph	H	**2b**	**3d**, **4d**	4.0	82	4	95:5
5	*p*-ClC$_6$H$_4$	H	**2b**	**3e**, **4e**	5.5	74	7	92:8
6	*p*-MeC$_6$H$_4$	H	**2b**	**3f**, **4f**	4.5	82	5	94:6
7	H	H	**2a**	**4g**[b]	3.5	—	86	—
8	*n*-Bu	H	**2a**	**3h**[b], **4h**	5.5	—	77	0:100
9	*n*-Hexyl	H	**2a**	**3i**[b], **4i**	5.0	—	71	0:100
10	C$_{16}$H$_{33}$	H	**2a**	**3j**[b], **4j**	7.0	—	69	0:100
11	–(CH$_2$)$_4$–		**2a**	**4k**[b]	5.5	—	74	—
12	Ph	CH$_3$	**2a**	**3l**[b], **4l**	4.0	75	10	88:12
13	H	H	**2b**	**4m**	3.5	—	82	—
14	*n*-Bu	H	**2b**	**3n**, **4n**	7.0	—	73	0:100
15	*n*-Hexyl	H	**2b**	**3o**, **4o**	7.0	—	68	0:100
16	C$_{16}$H$_{33}$	H	**2b**	**3p**, **4p**	7.5	—	67	0:100
17	–(CH$_2$)$_4$–		**2b**	**4q**	6.5	—	66	—
18	Ph	CH$_3$	**2b**	**3r**, **4r**	6.0	71	11	86:14

[a] For the experimental procedure, see Experimental.
[b] β-Amino sulfones **3**/**4** are known compounds and their spectroscopic data were in agreement with the literature data.[15]
[c] Isolated yield after column chromatography/filtration.
[d] All compounds (**3** and **4**) gave C, H and N analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.
[e] As determined by ^{1}H NMR integration of the α- and β-proton signals of the two regioisomeric sulfones **3a** and **4a** in the crude product.

The presented methodology has remarkable potential for the synthesis of vinyl sulfones, which have exceptional biological significance[20] and synthetic utility.[21] Previously, we have prepared vinyl sulfones by mere heating of epoxides and arenesulfinates on water in the presence of LiBr.[16g] In the case of aziridines we did not obtain any such results. Instead, the prepared β-amino sulfones **3** and **4** were treated with strong bases like NaH and ^{t}BuOK in dry THF at rt to yield the corresponding vinyl sulfones in good yields. The toluenesulfonamide group acted as the leaving group in the reaction.[22] The yield of vinyl sulfones was slightly better in the case of NaH (76%) than with ^{t}BuOK (68%). We also attempted the reaction in water with NaOH but a complex mixture containing aziridine as the major product was formed. The protocol is superior to other methods of vinyl sulfone synthesis as it gives the opportunity to prepare terminal vinyl sulfones for which lesser methods are available in the literature as compared to the other internal isomer.[23] The process is general and works well with good yields of vinyl sulfones (Table 4).

Table 4
Synthesis of vinyl sulfones[a]



Entry	Compound **3** or **4**	Product[b]	Time (h)	Yield[c] (%)
1	**3a**	**5a**	12	72
2	**3c**	**5c**	14	67
3	**3e**	**5e**	10	75
4	**4k**	**5'k**	15	68
5	**4n**	**5'n**	18	65

[a] For the experimental procedure, see Experimental.
[b] Vinyl sulfones **5** and **5'** are known compounds and their spectroscopic data were in agreement with the literature data.[16g,24]
[c] Isolated yield after column chromatography.

3. Conclusions

In summary, we have described a LiBr catalyzed highly regioselective approach for the synthesis of β-amino sulfones from easily accessible starting materials on water. This is the first report on the aziridine ring-opening with the commercially available inexpensive arenesulfinates. Environmentally benign reaction conditions and easier purification of products opens up a new green pathway for the synthesis of β-amino sulfones. The synthetic potential of the prepared β-amino sulfones has been demonstrated by their conversion to vinyl sulfones in good yields.

4. Experimental

4.1. General

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 IR spectrophotometer and ^{1}H NMR spectra were

recorded on a Bruker Avance II (400 MHz) FT spectrometer in $CDCl_3$ using TMS as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in $CDCl_3$ and TMS was used as internal reference. Mass (EI) spectra were recorded on JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. All chemicals used were reagent grade and were used as received without further purification. Reactions for the synthesis of vinyl sulfones (Section 4.3) were performed using oven-dried glassware. Organic solutions were concentrated using a Buchi rotary evaporator. Column chromatography was carried out over silica gel (Merck 100–200 mesh) and TLC was performed using silica gel GF254 (Merck) plates.

4.2. General procedure for the synthesis of β-amino sulfones 3 and 4

A mixture of aziridine **1** (1.0 mmol), LiBr (10 mol %) and sodium sulfinate **2** (1.2 mmol) in water (5 mL) was stirred at 80–90 °C for 3.5–7.5 h (Table 3). After completion of the reaction (monitored by TLC), the mixture was cooled to rt and extracted with EtOAc (3×5 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of EtOAc/*n*-hexane (1:19) as eluent to afford an analytically pure sample of β-amino sulfones **3** or **4** (Table 3, entries 8–11, 14–17). In the case of solid products, after completion of the reaction, the resulting solution was cooled to rt, the precipitate was filtered and washed with cold water and then with toluene to afford an analytically pure sample of β-amino sulfones **3** (Table 3, entries 1–6, 12, 18) or **4** (Table 3, entries 7 and 13).

*4.2.1. N-[2-(4-Chlorophenyl)-2-tosylethyl]-4-methylbenzenesulfonamide (**3b**).* Yield (0.36 g, 77%) as a white solid; mp 169–171 °C; [found: C, 57.01; H, 4.62; N, 3.19 $C_{22}H_{22}ClNO_4S_2$ requires C, 56.95; H, 4.78; N, 3.02%]; R_f (20% EtOAc/hexane) 0.31; IR (KBr) ν_{max} 3281, 1598, 1335, 1315, 1302, 1289, 1159, 742 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 2.40 (s, 3H), 2.47 (s, 3H), 3.59–3.69 (m, 1H), 3.88–3.97 (m, 1H), 4.13–4.19 (m, 1H), 5.22–5.26 (dd, 1H, *J*=7.9, 5.3 Hz), 6.90–6.92 (d, 2H, *J*=7.8 Hz), 7.12–7.40 (m, 8H), 7.71–7.74 (d, 2H, *J*=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 20.8, 21.3, 41.0, 68.8, 127.4, 128.0, 128.5, 128.9, 129.7, 130.4, 131.1, 132.0, 134.1, 136.6, 143.0, 144.7; EIMS (*m*/*z*) 463, 465 (M^+, M^++2).

*4.2.2. N-[2-(p-Tolyl)-2-tosylethyl]-4-methylbenzenesulfonamide (**3c**).* Yield (0.40 g, 91%) as a white solid; mp 210–213 °C; [found: C, 62.16; H, 5.50; N, 3.24 $C_{23}H_{25}NO_4S_2$ requires C, 62.28; H, 5.68; N, 3.16%]; R_f (20% EtOAc/hexane) 0.35; IR (KBr) ν_{max} 3283, 1599, 1336, 1312, 1306, 1288, 1158, 745 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 2.34 (s, 3H), 2.39 (s, 3H), 2.47 (s, 3H), 3.57–3.66 (m, 1H), 3.86–3.94 (m, 1H), 4.12–4.17 (m, 1H), 5.21–5.25 (dd, 1H, *J*=7.8, 5.3 Hz), 6.91–6.93 (d, 2H, *J*=7.7 Hz), 7.00–7.38 (m, 8H), 7.71–7.73 (d, 2H, *J*=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 20.8, 21.3, 24.2, 41.0, 68.9, 127.4, 128.1, 128.5, 128.9, 129.7, 130.3, 133.3, 134.1, 135.3, 136.6, 143.1, 144.8; EIMS (*m*/*z*) 443 (M^+).

*4.2.3. N-[2-Phenyl-2-(phenylsulfonyl)ethyl]-4-methylbenzenesulfonamide (**3d**).* Yield (0.34 g, 82%) as a white solid; mp 173–175 °C; [found: C, 60.34; H, 5.04; N, 3.49 $C_{21}H_{21}NO_4S_2$ requires C, 60.70; H, 5.09; N, 3.37%]; R_f (20% EtOAc/hexane) 0.34; IR (KBr) ν_{max} 3284, 1598, 1336, 1314, 1305, 1289, 1158 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 2.47 (s, 3H), 3.59–3.66 (m, 1H), 3.88–3.94 (m, 1H), 4.14–4.18 (m, 1H), 5.21–5.25 (dd, 1H, *J*=7.8, 5.2 Hz), 6.90–6.92 (d, 2H, *J*=7.8 Hz), 7.15–7.83 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.2, 41.0, 68.9, 126.5, 127.3, 128.0, 128.5, 128.9, 129.7, 130.3, 132.2, 134.9, 137.1, 136.6, 143.0; EIMS (*m*/*z*) 415 (M^+).

*4.2.4. N-[2-(4-Chlorophenyl)-2-(phenylsulfonyl)ethyl]-4-methylbenzenesulfonamide (**3e**).* Yield (0.33 g, 74%) as a white solid; mp 188–191 °C; [found: C, 56.26; H, 4.36; N, 3.03 $C_{21}H_{20}ClNO_4S_2$ requires C, 56.05; H, 4.48; N, 3.11%]; R_f (20% EtOAc/hexane) 0.32; IR (KBr) ν_{max} 3285, 1597, 1334, 1315, 1303, 1289, 1156, 740 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 2.46 (s, 3H), 3.59–3.69 (m, 1H), 3.88–3.97 (m, 1H), 4.15–4.20 (m, 1H), 5.22–5.26 (dd, 1H, *J*=7.9, 5.2 Hz), 6.91–6.93 (d, 2H, *J*=7.7 Hz), 7.12–7.43 (m, 9H), 7.70–7.73 (d, 2H, *J*=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 21.1, 41.1, 68.8, 127.4, 128.1, 128.5, 129.0, 129.9, 130.3, 131.1, 132.0, 133.5, 136.6, 137.2, 143.0; EIMS (*m*/*z*) 449, 451 (M^+, M^++2).

*4.2.5. N-[2-(Phenylsulfonyl)-2-p-tolylethyl]-4-methylbenzenesulfonamide (**3f**).* Yield (0.35 g, 82%) as a white solid; mp 220–223 °C; [found: C, 61.36; H, 5.49; N, 3.08 $C_{22}H_{23}NO_4S_2$ requires C, 61.51; H, 5.40; N, 3.26%]; R_f (20% EtOAc/hexane) 0.34; IR (KBr) ν_{max} 3283, 1598, 1335, 1315, 1303, 1289, 1157, 745 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 2.35 (s, 3H), 2.47 (s, 3H), 3.59–3.66 (m, 1H), 3.88–3.94 (m, 1H), 4.13–4.17 (m, 1H), 5.21–5.25 (dd, 1H, *J*=7.9, 5.3 Hz), 6.91–6.93 (d, 2H, *J*=7.9 Hz), 7.01–7.38 (m, 9H), 7.71–7.73 (d, 2H, *J*=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 21.1, 24.2, 41.1, 69.0, 127.3, 128.0, 128.5, 128.9, 129.7, 130.3, 134.9, 135.3, 135.9, 136.6, 137.1, 143.1; EIMS (*m*/*z*) 429 (M^+).

*4.2.6. N-[2-(Phenylsulfonyl)]-4-methylbenzenesulfonamide (**4m**).* Yield (0.28 g, 82%) as a white solid; mp 130–133 °C; [found: C, 53.19; H, 4.94; N, 4.01 $C_{15}H_{17}NO_4S_2$ requires C, 53.08; H, 5.05; N, 4.13%]; R_f (20% EtOAc/hexane) 0.25; IR (KBr) ν_{max} 3281, 1596, 1335, 1289, 1162, 1146, 1082 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 2.46 (s, 3H), 3.18–3.23 (m, 2H), 3.33–3.41 (m, 2H), 5.38–5.41 (t, 1H, *J*=6.1 Hz), 7.31–7.85 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5, 37.0, 55.2, 127.1, 127.9, 129.7, 130.1, 135.8, 136.4, 138.2, 143.8; EIMS (*m*/*z*) 339 (M^+).

*4.2.7. N-[1-(Phenylsulfonylhexan-2-yl)]-4-methylbenzenesulfonamide (**4n**).* Yield (0.29 g, 73%) as a colourless oil; [found: C, 57.52; H, 6.44; N, 3.26 $C_{19}H_{25}NO_4S_2$ requires C, 57.69; H, 6.37; N, 3.54%]; R_f (20% EtOAc/hexane) 0.22; IR (KBr) ν_{max} 3282, 2959, 2932, 2871, 1598, 1317, 1292, 1159, 1145, 1086 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 0.75 (t, 3H, *J*=5.2 Hz), 1.02–1.12 (m, 4H), 1.59–1.62 (m, 1H), 1.80–1.88 (m, 1H), 2.47 (s, 3H), 3.09–3.13 (dd, 1H, *J*=6.6, 14.4 Hz), 3.31–3.36 (dd, 1H, *J*=4.5, 14.1 Hz), 3.50–3.56 (m, 1H), 5.23–5.26 (d, 1H, *J*=7.2 Hz), 7.30–7.78 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.6, 21.0, 21.5, 22.2, 28.1, 49.6, 59.6, 127.0, 127.7, 129.5, 130.1, 133.5, 136.8, 139.1, 143.5; EIMS (*m*/*z*) 395 (M^+).

*4.2.8. N-[1-(Phenylsulfonyl)octan-2-yl]-4-methylbenzenesulfonamide (**4o**).* Yield (0.29 g, 68%) as a colourless oil; [found: C, 59.67; H, 6.81; N, 3.37 $C_{21}H_{29}NO_4S_2$ requires C, 59.54; H, 6.90; N, 3.31%]; R_f (20% EtOAc/hexane) 0.23; IR (KBr) ν_{max} 3283, 2957, 2928, 2860, 1598, 1319, 1290, 1163, 1088 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 0.80 (t, 3H, *J*=7.2 Hz), 0.93–1.17 (m, 8H), 1.47–1.58 (m, 1H), 1.73–1.85 (m, 1H), 2.46 (s, 3H), 3.09–3.17 (m, 1H), 3.33–3.39 (m, 1H), 3.43–3.52 (m, 1H), 5.56–5.58 (d, 1H, *J*=7.7 Hz), 7.23–7.35 (m, 5H), 7.61–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8, 21.5, 22.3, 24.9, 28.3, 31.3, 33.8, 49.5, 59.6, 127.0, 127.8, 129.5, 129.9, 134.5, 136.7, 139.3, 143.4; EIMS (*m*/*z*) 423 (M^+).

*4.2.9. N-[1-(Phenylsulfonyl)octadecan-2-yl]-4-methylbenzenesulfonamide (**4p**).* Yield (0.38 g, 67%) as a colourless oil; [found: C, 66.01; H, 8.64; N, 2.64 $C_{31}H_{49}NO_4S_2$ requires C, 66.03; H, 8.76; N, 2.48%]; R_f (20% EtOAc/hexane) 0.20; IR (KBr) ν_{max} 3281, 2919, 2849, 1599, 1321, 1150, 1094 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) 0.88 (t, 3H, *J*=6.6 Hz), 0.97–1.32 (m, 28H), 1.59–1.67 (m, 1H), 1.79–1.88 (m, 1H), 2.47 (s, 3H), 3.13 (dd, 1H, *J*=6.0, 13.6 Hz), 3.36 (dd, 1H, *J*=4.5,

13.6 Hz), 3.49–3.61 (m, 1H), 5.10–5.13 (d, 1H, *J*=6.9 Hz), 7.26–7.38 (m, 5H), 7.61–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 14.06, 21.5, 22.6, 25.2, 28.8, 29.2, 29.6, 31.8, 33.9, 49.8, 59.6, 127.2, 127.8, 129.5, 129.9, 134.7, 136.9, 139.6, 143.5; EIMS (*m*/*z*) 563 (M^+).

*4.2.10. N-[2-(Phenylsulfonyl)cyclohexyl]-4-methylbenzenesulfonamide (**4q**).* Yield (0.26 g, 66%) as a colourless oil; [found: C, 57.75; H, 5.76; N, 3.44 $C_{19}H_{23}NO_4S_2$ requires C, 57.99; H, 5.89; N, 3.56%]; R_f (20% EtOAc/hexane) 0.22; IR (KBr) ν_{max} 3255, 2940, 2865, 1596, 1452, 1335, 1312, 1302, 1290, 1161, 1143 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) 1.14–1.37 (m, 4H), 1.53–1.61 (m, 1H), 1.69–1.74 (m, 1H), 1.82–1.89 (m, 1H), 2.41–2.46 (m, 1H), 2.46 (s, 3H), 3.01 (td, 1H, *J*=10.5, 3.6 Hz), 3.28–3.38 (m, 1H), 6.32 (s, 1H), 7.30–7.38 (m, 5H), 7.63–7.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5, 22.5, 23.2, 25.3, 28.7, 51.4, 64.6, 127.2, 128.8, 129.5, 129.9, 133.5, 135.1, 139.9, 143.4; EIMS (*m*/*z*) 393 (M^+).

*4.2.11. N-[1-Phenyl-1-(phenylsulfonyl)propan-2-yl]-4-methylbenzenesulfonamide (**3r**).* Yield (0.30 g, 71%) as a white solid; mp 134–138 °C; [found: C, 61.83; H, 5.68; N, 3.17 $C_{22}H_{23}NO_4S_2$ requires C, 61.51; H, 5.40; N, 3.26%]; R_f (20% EtOAc/hexane) 0.33; IR (KBr) ν_{max} 3226, 1597, 1325, 1287, 1163, 1136, 1083 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) 1.53 (d, 3H, *J*=5.7 Hz), 2.43 (s, 3H), 4.12–4.18 (m, 2H), 5.72 (d, 1H, *J*=7.7 Hz), 7.01–7.18 (m, 6H), 7.21–7.34 (m, 6H), 7.69–7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 19.5, 21.5, 51.5, 74.2, 127.1, 128.0, 128.4, 128.9, 129.3, 129.9, 130.4, 130.8, 133.6, 138.3, 137.4, 143.4; EIMS (*m*/*z*) 429 (M^+).

4.3. General procedure for the synthesis of vinyl sulfones 5/5′

A mixture of β-amino sulfone **3** or **4** (1.0 mmol) and NaH (2.0 mmol) in dry THF was stirred at rt for the required time (Table 4). After completion of the reaction (monitored by TLC), the mixture was extracted with EtOAc (3×5 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a mixture of EtOAc/*n*-hexane (1:24) as eluent to afford an analytically pure sample of vinyl sulfones **5**/**5′** (Table 4).

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References and notes

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