An efficient stereo selective synthesis of benzyl, (benzimidazol-2-yl)-methyl and (6H-imidazo[4,5-*e*][2,1,3]benzothiadiazol-7-yl)methyl styryl sulfones

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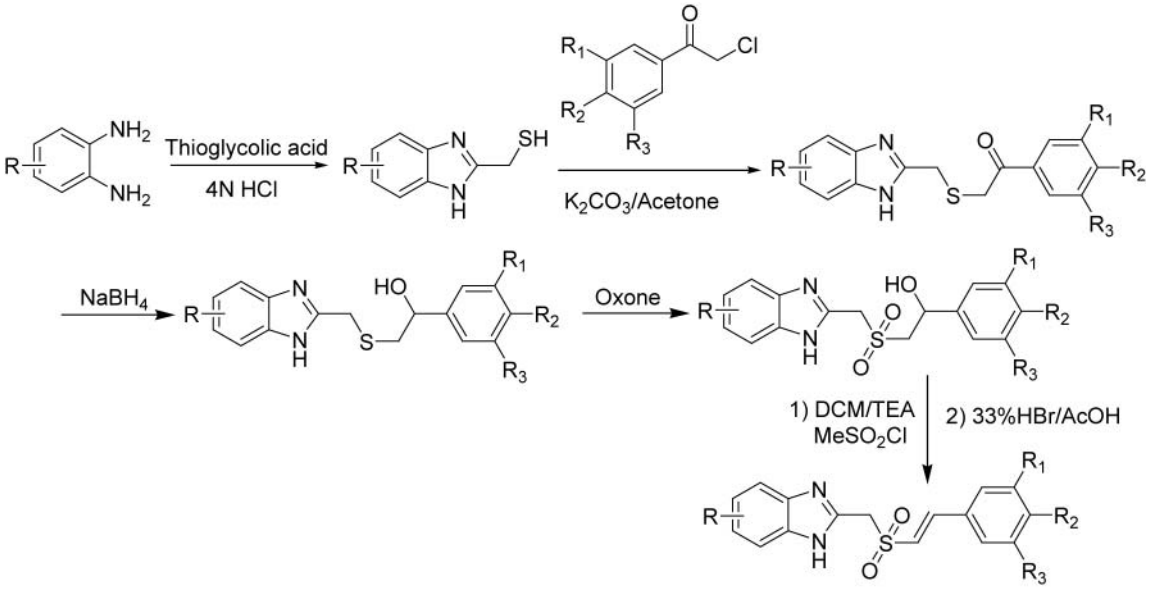
A facile and an efficient one-pot synthesis of (*E*)-styryl sulfones is described by condensation of 2-(chloromethyl)benzimidazoles or 7-(chloromethyl)-6*H*-imidazo[4,5-*e*][2,1,3]benzothiadiazole or benzyl bromides with sodium (*E*)-styryl sulfinates in DMF gave corresponding styryl sulfones. They have been prepared in good yields, in the absence of any catalyst.

Keywords: benzimidazole, benzyl bromide, sodium (*E*)-styryl sulfinates, styryl sulfone, one-pot synthesis

Over last four decades, the use of styryl sulfones in organic chemistry and medicinal chemistry has increased dramatically. Styryl sulfones have been employed in many synthetic methodologies as intermediates, enabling the preparation of great number of functionalised products, such as natural products and bioactive substances. The functional group is found in numerous biologically interesting compounds.

Styryl sulfone is a functional group that appears in a number of biologically active compounds, including those for the treatment of cancer[1–3] and inhibitors for several enzymes such as cyclooxygenase-2(COX-2).[4] Benzimidazole derivatives are useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest[5–10] and substituted benzimidazole derivatives have found applications in diverse therapeutic areas such as anti-ulcer agents, anti-cancer agents and anthelmintic species, to name just a few[11–14]. Recently, it has been reported that certain styryl sulfone derivatives like FRI-20 inhibit the tumour cell growth and viability by inhibiting the MAPK signal transduction pathway[3]. These compounds regulate the ERK and inhibit the proliferation of breast and prostate tumour cells in a dose-dependent manner with out affecting normal cell growth. The cell growth inhibitory activity of these compounds is dictated by the nature and position of the functional groups. In view of the wide range of biological activities exhibited by styryl sulfones and benzimidazoles, we became interested in incorporating these moieties in one molecule, which will be expected to enhance the biological activity compared to simple styryl sulfones. Based on the above observations, we wish to report an economical and efficient one pot synthesis of some substituted (*E*)-styryl sulfones (**3, 5** and **7**).

It has been reported[3] (Scheme 1) that the synthesis of the title compounds require a multi-step synthesis *i.e.* five steps. The overall yields of the end products were between 33 and 50%. While our procedures involve the overall yield of model compounds ranging from 80 to 86%. Recently, Evans *et al.*[15] reported the synthesis of sytyl sulfones (**7**) by a five-step process. The first step involves reaction of benzyl mercaptan with paraformalin. The second step is condensation between (benzyl thio)methyl chloride and triethylphosphite to yield diethyl (benzylthio)methyl phosphonate. This on oxidation with sodium bromate in acetic acid gave the corresponding diethyl (benzylsulfonyl)methylphosphonate. This on treatment with sodium hydride in tetrahydrofuran followed by reaction with aromatic aldehyde resulted in the formation of styryl sulfones. The overall yields of the literature method is 77–83%, while our methodology gave the overall yield of the related compounds in 86–92%. Alhough the above methodologies are quite useful, they have some limitations such as tedious procedures, harsh reaction conditions, the requirement of the isolation of intermediates, longer reaction times and overall yields are lower. It is thus evident that there remains a scope



Scheme 1

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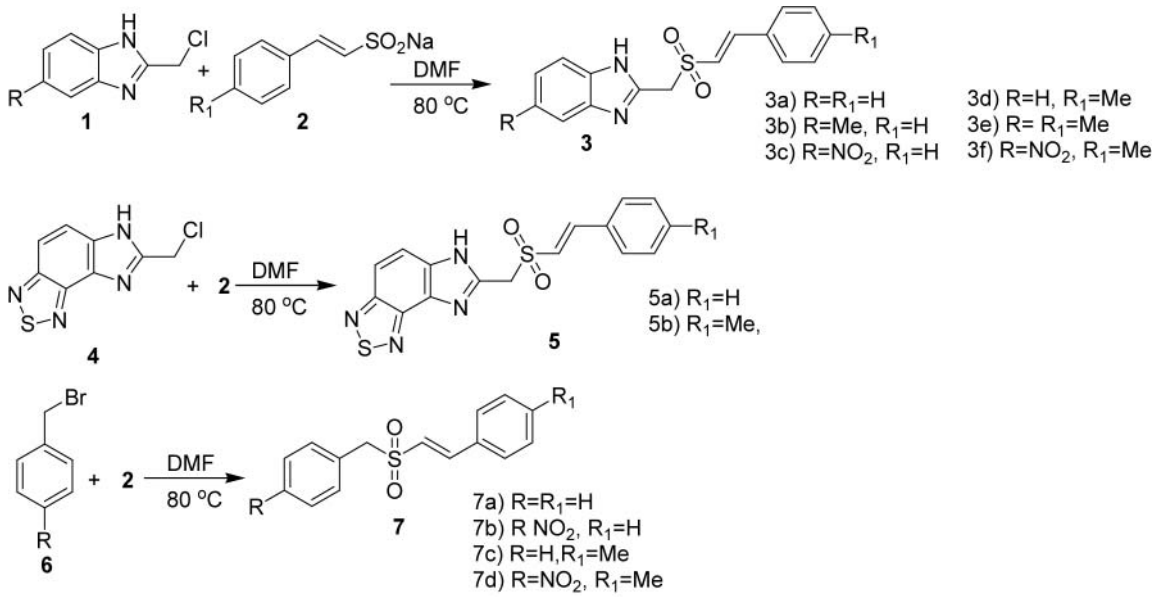

Scheme 2

for the development of clean and efficient methodologies of the title compounds. We have developed a novel one-pot synthesis of styryl sulfones in good yields when compared to alternative available methods in the literature. Our method of synthesis of styryl sulfones (Scheme 2) is highly stereoselective. During the condensation of 2-(chloromethyl)benzimidazo les(**1**)or7-(chloromethyl)-6H-imidazo[4,5-*e*][2,1,3]benzothiadiazole (**4**) or benzyl bromides (**6**) with styryl sodium sulfinates, no change in the configuration occurred in the products formation. The configuration of styryl sufinates is also carried forward to the end product. Thus the reactions are highly stereo selective even though there is a possibility of isomerisation in the end product to give both (*E*) and (*Z*) but we got only (*E*)-styryl sulfones.

Results and discussion

The required benzimidazolyl styryl sulfones were prepared by the condensation of appropriate 2-(chloromethyl)benzimidazole and 7-(chloromethyl)-6*H*-imidazo[4,5-*e*][2,1,3]benzothiadiazole with sodium styrene sulfinate. The reaction proceeded well and produced (*E*)-styryl sulfones at 80 °C in DMF in 86% yield. Higher yields were obtained by prolonging the reaction time. Among the solvents tested, DMF gave the best result, with the use of alternative solvents failing to improve the yields of products. These promising results encouraged us to explore the generality of this reaction and the results are summarised in Table 1. It was found that a wide variety of halides, such as benzimidazole and benzyl halides, were all suitable for this reaction, giving the desired products in good yields. These examples, in particular, demonstrate the superiority of the present approach for forming styryl sulfones over previously described methods. Using the conditions detailed here, harsh reaction conditions and complex operational processes can be avoided.

Table 1 Optimisation of reaction for the formation of **3a** under range of conditions

Entry	Solvent	Time/h	Isolated yield/%[a]
1	DMF	8	66
2	DMF	10	70
3	DMF	12	86
4	DMF	16	87
5	Ethanol	12	50
6	THF	12	48
7	DMSO	12	56
8	CH_3CN	12	42
9	Toluene	12	51

[a]Reagents and conditions: 2-(chloromethyl)benzimidazole (1 mmol) sodium E-styrenesulfinate (1.25 mmol), 80 °C temperature in given solvent.

Experimental

All the reagents and solvents were purchased from commercial sources and were used without further purification unless otherwise stated. Styrene-β-sulfonyl chlorides[16] and sodium (*E*)-stryrenesulfinates[17] were prepared by literature procedures. The 2-(chloromethyl) benzimidazole derivatives were prepared by Philip's condensation of *o*-phenylinediamines with chloroacetic acid using 4N hydrochloric acid as cyclising agent.[3] The same procedure has been extended for the preparation of 7-(chloromethyl)-6H-imidazo[4,5-*e*][2,1,3]benzothiadiazole (**4**). Melting points were determined in open capillaries with a Cintex melting point apparatus Mumbai, India and were uncorrected. CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyser. The purity of the compounds was checked by TLC plates (E.Merek, Mumbai, India). IR spectra (KBr) were recorded on a BrukerWM-4(X) spectrometer (577model). ^{1}H NMR spectra were recorded on a Bruker WM-300 spectrometer in δ ppm using TMS as internal standard. Mass spectra (EI-MS) were determined on Perkin-Elmer (SCIEX API-2000, ESI) at 12.5eV.

*General procedure for the synthesis of benzyl, (benzimidazol-2-yl) methyl and (6H-imidazo[4,5-e][2,1,3]benzothiadiazol-7-yl)methyl styryl sulfones (***3a–f***,* **5a–b**, **7a–d***)*

A mixture of the sodium (*E*)-styrenesulfinate (1.25 mmol) and the 2-(chloromethyl)benzimidazole (**1**) (1 mmol) or **4** (1 mmol) and DMF (10mL) was added to 25 mL flask equipped with a magnetic stirrer and the mixture was stirred at 80 °C for 12 hours. After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and solid separated was filtered, dried and the crude product was purified by column chromatography (ethyl acetate/hexane 3:7). All the other compounds were prepared similarly.

Spectral and analytical data for styryl sulfones

2-[(Styrylsulfonyl)methyl]-1H-benzimidazole (**3a**): Time: 12 h, yield 86%, m.p. 142–144 °C. IR (KBr, γ_{max} cm^{-1}): 1139, 1330 (SO_2), 1455 (C=N), 1612 (C=C), 3377 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 4.93 (s, 2H, –CH_2), 7.20–7.23 (m, 4H, ArH), 7.47–7.72 (m, 7H, ArH). EI-MS 299 [M+H]$^+$. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.4; H, 4.73; N, 9.39. Found: C, 64.45; H, 4.76; N, 9.36%.

5-Methyl-2-[(styrylsulfonyl)methyl]-1H-benzimidazole (**3b**): Time: 12 h, yield 84%, m.p. 168–170 °C. IR (KBr, γ_{max} cm^{-1}): 1124, 1332 (SO_2), 1450 (C=N), 1612 (C=C), 3142 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 2.39 (s, 3H, CH_3), 4.78 (s, 2H, –CH_2), 6.46 (d, 1H, *J* = 15 Hz, styryl), 6.98–7.02 (m, 2H, ArH) 7.17–7.25 (m, 6H, ArH), 7.70 (d,1H, ArH). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.35; H, 5.20; N, 8.92%.

5-Nitro-2-[(styrylsulfonyl)methyl]-1H-benzimidazole (**3c**): Time: 12 h, yield 86%, m.p. 176–178 °C. IR (KBr, γ_{max} cm^{-1}): 1114, 1341(SO_2), 1474 (C=N), 1626(C=C), 3300(NH), ^{1}H NMR (DMSO-d_6, δ ppm): 4.69 (s, 2H, –CH_2), 6.61(d, 1H, *J* = 15 Hz, styryl), 7.45–7.52 (m, 5H, ArH), 7.68–7.72 (m, 2H, ArH), 8.08–8.11 (m, 2H, ArH). Anal. Calcd for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 55.92; H, 3.89; N, 12.30%.

2-[(4-Methyl styrylsulfonyl)methyl]-1H-benimidazole (**3d**): Time: 12 h, yield 80%, m.p. 180–182 °C. IR (KBr, γ_{max} cm^{-1}): 1137, 1329 (SO_2), 1456 (C=N), 1611 (C=C), 3377 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 4.99 (s, 2H, –CH_2), 6.53 (d, 1H, styryl), 6.97–7.02 (m, 3H, ArH), 7.13–7.63 (m, 6H, ArH), EI-MS 313[M+H]$^+$. ^{13}C NMR ($CDCl_3$ δ ppm), 21.2, 55.4, 112.5, 119.8, 123.1, 123.4, 126.4, 130.4, 133.5, 134.5, 139.7, 143.0. Anal Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.40; H, 5.11; N, 8.99%.

5-Methyl-2-[(4-methylstyrylsulfonyl)methyl]-1H-benzoimidazole (**3e**): Time: 12 h, yield 84%, m.p. 188 °C. IR (KBr, γ_{max} cm^{-1}): 1125, 1326(SO_2), 1449 (C=N), 1610 (C=C), 3344 (NH). ^{1}H NMR (DMSO-d_6, δ ppm): 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.78 (s, 2H, –CH_2), 6.31(d, 1H, styryl), 7.19–7.60 (m, 8H, ArH). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.29; H, 5.59; N, 8.51%.

5-Nitro-2-[(4-methylstyrylsulfonyl)methyl]-1H-benzimidazole (**3f**): Time: 12 h, yield 82%, m.p. 188–190 °C. IR (KBr, γ_{max} cm^{-1}): 1119, 1344 (SO_2), 1477 (C=N), 1626 (C=C), 3303(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 4.99 (s, 2H, –CH_2), 6.61 (d, 1H, styryl), 7.25–7.28 (m, 2H, ArH), 7.42–7.43 (m, 3H, ArH), 7.59–7.61 (m, 3H, ArH). Anal. Calcd for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.10 ; H, 4.28 ; N, 11.79%.

(6H-Imidazo[4,5-e][2,1,3]benothiadiazol-7-yl)methyl styryl sulfone (**5a**): Time: 14 h, yield 78%, m.p.197–198 °C. IR (KBr, γ_{max} cm^{-1}): 1126, 1332 (SO_2), 1455 (C=N), 1604(C=C), 3323 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 4.8 (s, 2H, –CH_2), 7.60–7.70 (m, 4H, ArH), 7.80–7.95 (m, 5H, ArH). Anal. Calcd for $C_{16}H_{12}N_4O_2S_2$: C, 53.92; H, 3.39; N, 15.72. Found: C, 53.98; H, 3.32; N, 15.76%.

(6H-Imidazo[4,5-e][2,1,3]benothiadiazol-7-yl)methyl-4-methyl-styryl sulfone (**5b**): Time: 14 h, yield 74%, m.p. 204–206 °C. IR (KBr, γ_{max} cm^{-1}): 1133, 1328 (SO_2), 1445 (C=N), 1608 (C=C), 3328 (NH). ^{1}H NMR ($CDCl_3$, δ ppm): 2.7 (s, 3H, Me), 4.75 (s, 2H, –CH_2), 7.20–7.40 (m, 4H, ArH), 7.60–7.80 (m, 4H, ArH). Anal. Calcd for $C_{17}H_{14}N_4O_2S_2$: C, 55.12; H, 3.8; N, 15.12. Found: C, 55.10; H, 3.80; N, 15.10%.

*General procedure for the synthesis of benzyl styryl sulfones (***7a–d***):* A mixture of the sodium (*E*)-styrenesulfinate (1.25 mmol) and the benzyl bromide(1 mmol) and DMF (10 mL) was added to a 10 mL flask equipped with a magnetic stirrer and the mixture was stirred at 80 °C for 12 hours. After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and solid separated was filtered dried and the crude product was purified by column chromatography (ethyl acetate/hexane 2:8). All the other compounds were prepared similarly.

1-[(E)-2-(Benzylsulfonyl)vinyl]benzene (**7a**): Time: 8 h, yield 92%, m.p. 144–146 °C, [ref.[15] m.p. 145–146 °C]. IR (KBr, γ_{max} cm^{-1}): 1117, 1309 (SO_2), 1607 (C=C). ^{1}H NMR ($CDCl_3$,δ ppm): 4.32 (s, 2H, –CH_2), 6.68 (d, 1H, *J* = 15 Hz, styryl), 7.38–7.45 (m, 11H, ArH). Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; Found: C, 69.70; H, 5.50%.

4-Nitro-[(E)-2-(benzylsulfonyl)vinyl]benzene (**7b**): Time: 8 h, yield 90%, m.p. 170–172 °C. IR (KBr, γ_{max} cm^{-1}): 1119, 1345 (SO_2), 1608 (C=C). ^{1}H NMR ($CDCl_3$, δ ppm): 4.41 (s, 2H, –CH_2), 6.73 (d, 1H, *J* = 15 Hz, styryl), 7.44–7.60 (m, 10H, ArH), ^{13}C NMR ($CDCl_3$ δ ppm), 61.1, 123.4,123.9, 128.6, 129.2, 131.7, 131.8, 131.9, 135.1, 146.6, 148.2. EI-MS 304[M+H]$^+$. Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62 Found: C, 59.48 ; H,4.38; N, 4.67%.

1-[(E)-2-(Benzylsulfonyl)vinyl]-4-methylbenzene (**7c**): Time: 8 h, yield 88%, m.p. 148–150 °C. IR (KBr, γ_{max} cm^{-1}): 1126, 1300 (SO_2), 1616 (C=C). ^{1}H NMR ($CDCl_3$, δ ppm): 2.39 (s, 3H, methyl), 4.31 (s, 2H, –CH_2), 6.62 (d, 1H, *J* = 15 Hz, styryl), 7.21–7.37 (m, 10H, ArH). Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; Found: C, 70.59; H, 5.98%.

1-[(E)-2-(4-Nitrobenzylsulfonyl)vinyl]-4-methylbenzene (**7d**): Time: 9 h, yield 86%, m.p. 186–188 °C. IR (KBr, γ_{max} cm^{-1}): 117, 1309 (SO_2), 1607 (C=C). ^{1}H NMR ($CDCl_3$, δ ppm): 2.31 (s, 3H, methyl), 4.41 (s, 2H, –CH_2), 6.73 (d, 1H, *J* = 16 Hz, styryl), 7.43–7.59 (m, 9H, ArH). Anal. Calcd for $C_{16}H_{15}NO_4S$: C, 60.55; H, 4.76; N, 4.41; Found: C, 60.70; H,4.61; N, 4.45%.

Conclusions

In conclusion, we have developed a simple, mild, inexpensive, fast and efficient synthesis of styryl sulfones without using any catalyst. The biological activity of these new styryl sulfones is in progress and published elsewhere.

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