Facile polyethylene glycol (PEG-400) promoted synthesis of some new heteryl (*E*)-styryl sulfones

Nalajam Guravaiah and Vedula Rajeswar Rao*

Department of Chemistry, National Institute of Technology, Warangal (AP) -506 004, India

An efficient and convenient synthesis of heteryl (*E*)-styryl sulfones is described. Reaction of an 3-(2-bromoacetyl)coumarin with sodium (*E*)-styrenesulfinates yields the corresponding styryl sulfones promoted by polyethylene glycol (PEG-400) as an efficient reaction medium at room temperature

Keywords: 3-(2-bromoacetyl)coumarin, sodium (*E*)-styrenesulfinate, PEG-400 and styryl sulfones

The styryl sulfone moiety has been found in numerous biologically interesting compounds. These compounds include anticancer[1-5] and inhibitors for several enzymes such as cyclooxygenase-2 (COX-2).[6] The traditional procedures for assembling these compounds were reported from the Knoevenagel condensation of arylsulfonylacetic acid with araldehydes, [1, 7-11] coupling of mercapto compounds with haloketones or arylhalides followed by sulfonation, reduction and finally dehydration to get styryl sulfones.[1, 12]

Although the above methods are quite useful, they have some limitations such as the isolation of intermediates, harsh reaction conditions, longer reaction times and overall yields are less. None of these methods are simple, nor can they be usefully applied for the generation of functionally substituted styryl sulfones. We need to overcome these drawbacks to explore an alternative method. Among emerging strategies, direct coupling of α-haloketones and sulfinic acid salts in solvents like absolute ethanol, aqueous ethanol, DMF, aqueous DMF, phase transfer catalyst conditions were therefore suitable for the preparation of unsaturated sulfone moiety.

2*H*-1-Benzopyran-2-ones are important molecules that are well known for their biological activity and therapeutic activities.[13-16] These can also be considered as versatile building blocks and intermediates for the synthesis of various interesting heterocyclic systems.[17-19] In view of the wide range of biological activities exhibited by 2*H*-1-benzopyran-2-ones and styryl sulfones, we became interested to synthesise these moieties in one molecule, which are expected to enhance the biological activity compared to simple styryl sulfones. Based on the above observations, we now report the synthesis of some novel heteryl styryl sulfones.

Polyethylene glycol promoted reactions[20-22] have attracted the attention of organic chemists due to their ease of work up, the ability to act as phase transfer catalysts and their inexpensive and eco-friendly nature. In this connection, we report a synthesis of some new heteryl styryl sulfones in the presence of polyethylene glycol (PEG-400) as an efficient reaction medium.

Results and discussion

We chose the coupling of 3-(2-bromoacetyl)coumarin with sodium (*E*)-stryrenesulfinate as model for exploring the optimised reaction condition. It was found that if absolute ethanol was used alone, the reaction requires reflux temperature for a period of eight hours to get the coupling product in only 42% yield. This is due to the low solubility of sulfinate salts in organic solvents. It is worth noting that the addition of a small amount of water (10:2 mL) could improve the reaction efficiency this is presumably due to the increased water solubility of sodium (*E*)-strylsulfinate, hence the reaction yield increased to 58%. In addition to this when the same reaction was performed under DMF as solvent, for 8 hours at refluxed temperature the reaction yield was 66% only. The addition of a small amount of water (10:2 mL) could improve the reaction efficiency, hence the reaction yield increased to 70%.

When we carried out the reaction in polyethylene glycol (PEG-400), the formation of product was complete in 12 min in 94% yield. This is due to high polarity of solvent and probably also the solubility of the sulfinate salt in this solvent is high. In addition to this when the same reaction has been carried out in solid sate with a few drops of DMF as organic base and one equivalent K_2CO_3 as inorganic base the coupling product afforded was 86% and 70% respectively. Among the solvents tested, PEG-400 gave best result, with the alternative solvents (entries **1**–**4**) and solid state (entries **5**–**6**) methods failing to improve the yield of products. These promising results encouraged us to explore the generality of this reaction. It was found that a variety of α-haloketones and sulfinates were suitable for this reaction, giving the desired products in good yields.In conclusion, we have developed a mild, inexpensive, fast and efficient synthesis of styryl sulfones using polyethylene glycol 400 as the reaction medium.

Experimental

All the reagents and solvents were pure, purchased from commercial sources and were used with out further purification unless otherwise stated. 3-(2-Bromoacetyl)coumarins, [23-24] styrene-β-sulfonylchlorides[25] and sodium (*E*)-stryrenesulfinates[26] were prepared by literature procedure. 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 (577 model). ^{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 styryl sulfones (**3a–l**)
A mixture of the sodium (*E*)-styrenesulfinate (1.25 mmol) and 3-(2-bromoacetyl)coumarin (1 mmol) was taken in 10 mL of polyethyleneglycol, and stirred at room temperture for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and extracted into ethyl acetate. The organic layer was removed under reduced pressure, and the crude product was recrystallised from acetone. The PEG was recovered from the aqueous layer and reused without loss of activity. All the other compounds were prepared similarly.

Spectral data for styryl sulfones
3-(2-(Styrenesulfonyl)acetyl)-2H-chromen-2-one (**3a**): Reaction time: 12 min, pale yellow solid, yield 94%, m.p. 130–132 °C. IR (KBr, γ_{max} cm^{-1}): 1123, 1316 (SO_2), 1606 (C=C), 1691 (C=O), 1733 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 5.08 (s, 2H, $-CH_2$), 7.08 (d, 1H, J = 15 Hz, SO_2 HC=CH), 7.3–7.6 (m, 10H, ArH and SO_2HC=CH), 8.58 (s, 1H, C_4 of coumarin proton), ^{13}C NMR ($CDCl_3$ δ ppm), 64.9, 116.8, 118.0, 123.1, 125.3, 125.4, 128.7, 129.0, 130.6, 131.5, 131.9, 135.4, 145.3, 149.3, 155.4, 159.2, 186.2. EI-MS 355[M + H]$^+$. Anal. Calcd for $C_{19}H_{14}O_5S$: C, 64.40; H, 3.98; S, 9.05. Found: C, 64.47; H, 3.96; S, 9.00%.

* Correspondent. E-mail: vrajesw@yahoo.com

6-Bromo-3-(2-(styrenesulfonyl)acetyl)-2H-chromen-2-one **(3b)**: Time: 18 min, pale yellow solid, yield 91%, m.p. 172–74 °C. IR (KBr, γ_{max} cm^{-1}): 1137, 1357 (SO_2), 1623 (C=C), 1689 (C=O), 1733 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 5.15 (s, 2H, –CH_2), 7.24(d, 1H, SO_2 HC=CH), 7.35–7.97 (m, 9H, ArH and SO_2HC=CH), 8.84 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{19}H_{13}BrO_5S$: C, 52.67; H, 3.02; S, 7.40. Found: C, 52.61; H, 3.00; S, 7.44%.

6, 8-Dibromo-3-(2-(styrenesulfonyl)acetyl)-2H-chromen-2-one **(3c)**: Time: 22 min, pale yellow solid, yield 90%, m.p. 180 °C. IR (KBr, γ_{max} cm^{-1}): 1135, 1351 (SO_2), 1601 (C=C), 1692 (C=O), 1740(C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.98 (s, 2H, –CH_2), 6.95(d, 1H, J = 16 Hz SO_2 HC=CH), 7.2–7.6 (m, 8H, ArH and SO_2HC=CH), 8.4 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{19}H_{12}Br_2O_5S$: C, 44.56; H, 2.36; S, 6.26. Found: C, 44.52; H, 2.32; S, 6.30%.

6-Chloro-3-(2-(styrenesulfonyl)acetyl)-2H-chromen-2-one **(3d)**: Time: 19 min, pale yellow solid, yield 93%, m.p. 152 °C. IR (KBr, γ_{max} cm^{-1}): 1128, 1322 (SO_2), 1607 (C=C), 1692 (C=O), 1734 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.89 (s, 2H, –CH_2), 7.49–7.56 (m, 6H, ArH and SO_2HC=CH), 7.79–7.83 (m, 2H, ArH and SO_2HC=CH), 8.07–8.12 (m, 2H, ArH) 8.78 (s, 1H, C_4 of coumarin proton.) Anal. Calcd for $C_{19}H_{13}ClO_5S$: C, 58.69; H, 3.37; S, 8.25. Found: C, 58.64; H, 3.31; S, 8.20%.

6, 8-Dichloro-3-(2-(styrenesulfonyl)acetyl)-2H-chromen-2-one **(3e)**: Time: 21 min, pale yellow solid, yield 90%, m.p. 168–170 °C. IR (KBr, γ_{max} cm^{-1}): 1135, 1325 (SO_2), 1623 (C=C), 1608 (C=O), 1734 (C=O of alctone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.69 (s, 2H, –CH_2), 7.49–7.53 (m, 5H, ArH and SO_2HC=CH), 7.75–7.79 (m, 2H, ArH and SO_2HC=CH), 8.08–8.12 (m, 2H, ArH), 8.61 (s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{19}H_{12}Cl_2O_5S$: C, 53.91; H, 2.86; S, 7.58. Found: C, 53.86; H, 2.81; S, 7.54%.

3-(2-(Styrenesulfonyl)acetyl)-2H-benzo[h]chromen-2-one **(3f)**: Time: 24 min, Yellow solid, yield 89%, m.p. 206–208 °C. IR (KBr, γ_{max} cm^{-1}): 1127, 1343 (SO_2), 1609 (C=C), 1623 (C=O), 1716 (C=O of lactone) ^{1}H NMR ($CDCl_3$, δ ppm): 4.76 (s, 2H, –CH_2), 7.62–7.68 (m, 6H, ArH and SO_2HC=CH), 8.07 (d, 1H, J = 15 Hz, SO_2HC=CH), 8.30–8.33 (m, 6H, ArH), 8.6 (s, 1H, C_4 coumarin proton). Anal. Calcd for $C_{23}H_{16}O_5S$: C, 68.30; H, 3.99; S, 7.93. Found: C, 68.24; H, 3.91; S, 7.89%.

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

Entry	Solvent	Time/h	Isolated yield/%[a]
1	Absolute ethanol	8	42
2	Aqueous ethanol	8	58
3	DMF	8	66
4	Aqueous DMF	8	70
5	Solid state (few drops of DMF)	0.15	86[b]
6	Solid state (1 equiv of K_2CO_3)	0.15	70[b]
7	PEG-400	0.12	94[c]

[a]Reagents and conditions: α-halo ketone (1 mmol) sodium E-styrenesulfinate (1.25 mmol), reflux temperature in given solvent.
[b]Reaction was carried out at solid state.
[c]Reaction was carried out at room temperture.

3-(2-(p-Methylstyrenesulfonyl)acetyl)-2H-chromen-2-one **(3g):** Time: 14 min, pale yellow solid, yield 93%, m.p. 132–144 °C. IR (KBr, γ_{max} cm^{-1}): 1119, 1307 (SO_2), 1606 (C=C), 1692 (C=O), 1725 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.38 (s, 3H, CH_3), 5.07 (s, 2H, –CH_2), 7.01 ^{3}(d, 1H, J = 15 Hz, SO_2 HC=CH), 7.54 (d, 1H, J = 15 Hz, SO_2HC=CH), 7.18–7.68 (m, 8H, ArH), 8.57 (s, 1H, C_4 of coumarin proton), ^{13}C NMR ($CDCl_3$ δ ppm), 21.5, 65.0, 116.8, 118.0, 123.3, 124.3, 125.3, 128.7, 129.2, 129.8, 130.6, 135.2, 142.2, 145.3, 149.2, 155.4, 159.2, 186.2, EI-MS 367 $[M-H]^-$.Anal. Calcd for $C_{20}H_{16}O_5S$: C, 65.20; H, 4.38; S, 8.70. Found: C, 65.10; H, 4.30; S, 8.64%.

6-Bromo-3-(2-(p-methylstyrenesulfonyl)acetyl)-2H-chromen-2-one **(3h):** Time: 18 min, pale yellow solid, yield 92%, m.p. 176–178 °C. IR (KBr, γ_{max} cm^{-1}): 1137, 1357 (SO_2), 1606 (C=C), 1683 (C=O), 1736 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.9(s, 3H, CH_3), 5.15 (s, 2H, –CH_2), 7.25 (d, 1H, J = 15 Hz, SO_2 HC=CH), 7.30–7.80 (m, 8H, ArH and SO_2HC=CH), 8.79 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{20}H_{15}BrO_5S$: C, 53.70; H, 3.38; S, 7.17. Found: C, 53.78; H, 3.32; S, 7.10%.

6, 8-Dibromo 3-(2-(p-methylstyrenesulfonyl)acetyl)-2H-chromen-2-one **(3i):** Time: 24 min, pale yellow solid, yield 90%, m.p. 168–170 °C. IR (KBr, γ_{max} cm^{-1}): 1127, 1317 (SO_2), 1603 (C=C), 1691 (C=O), 1740 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.4 (s, 3H, CH_3), 4.9 (s, 2H, –CH_2), 7.15 (d, 1H, J = 15 Hz, SO_2 HC=CH), 7.3–7.5(m, 7H, ArH and SO_2HC=CH), 8.4 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{20}H_{14}Br_2O_5S$: C, 45.65; H, 2.68; S, 6.09. Found: C, 45.60; H, 2.72; S, 6.12%.

6-Chloro-3-(2-(p-methylstyrenesulfonyl)acetyl)-2H-chromen-2-one **(3j):** Time: 17 min, pale yellow solid, yield 92%, m.p. 156–157 °C. IR (KBr, γ_{max} cm^{-1}): 1128, 1315 (SO_2), 1609 (C=C), 1690 (C=O), 1735 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.4 (s, 3H, CH_3), 5.0 (s, 2H, –CH_2), 6.95(d, 1H, J = 15 Hz, SO_2 HC=CH) 7.2–7.7 (m, 8H, ArH and SO_2HC=CH), 8.4 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{20}H_{15}ClO_5S$: C, 59.63; H, 3.75; S, 7.96. Found: C, 59.72; H, 3.79; S, 7.93%.

6, 8-Dichloro-3-(2-(p-methylstyrenesulfonyl)acetyl)-2H-chromen-2-one **(3k):** Time: 22 min, pale yellow solid, yield 90%, m.p. 162–164 °C. IR (KBr, γ_{max} cm^{-1}): 1127, 1317 (SO_2), 1609 (C=C), 1685 (C=O), 1738 (C=O of lactone) ^{1}H NMR ($CDCl_3$, δ ppm): 2.38 (s, 3H, CH_3), 4.85 (s, 2H, –CH_2), 7.20–7.4 (m, 8H, ArH and ethylene protons), 8.2 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{20}H_{14}Cl_2O_5S$: C, 54.93; H, 3.23; S, 7.33. Found: C, 54.90; H, 3.29; S, 7.38%.

3-(2-(p-Methylstyrenesulfonyl)acetyl)-2H-benzo[h]chromen-2-one **(3l):** Time: 27 min, yellow solid, yield 88%, m.p. 214 °C. IR (KBr, γ_{max} cm^{-1}): 1130, 1313 (SO_2), 1620 (C=C), 1673 (C=O), 1721 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.40 (s, 3H, CH_3), 4.9 (s, 2H, –CH_2), 7.17 (d, 1H, J = 15 Hz, SO_2 HC=CH), 7.25–7.7 (m, 11H, ArH and SO_2HC=CH), 8.4 (s, 1H, C_4 of coumarin proton), Anal. Calcd for $C_{24}H_{18}O_5S$: C, 68.88; H, 4.34; S, 7.66. Found: C, 68.82; H, 4.30; S, 7.61%.

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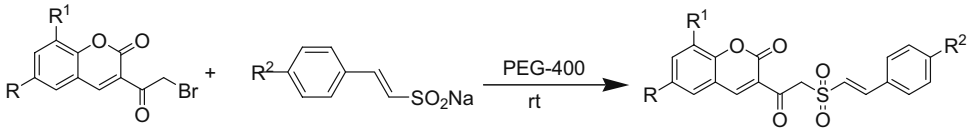

1 **2** **3**

(a) R= R^1= R^2= H
(b) R=Br, R^1=R^2=H
(c) R=R^1=Br, R^2=H
(d) R=Cl, R^1=R^2=H
(e) R=R^1=Cl, R^2=H
(f) 7,8 benzo, R^2=H
(g) R= R^1=H, R^2=CH_3
(h) R=Br, R^1=H,R^2=CH_3
(i) R=R^1=Br, R^2=CH_3
(j) R=Cl, R^1=R^2=CH_3
(k) R=R^1=Cl, R^2=CH_3
(l) 7,8 benzo, R^2=CH_3

Scheme 1

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