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

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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 anticancer¹⁻⁵ 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 reactions²⁰⁻²² 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 K₂CO₃ 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, $2^{3,24}$ styrene β -sulfonylchlorides²⁵ and sodium (*E*)-stryrenesulfinates²⁶ were prepared by literature procedure. 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 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–1)

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 (SO₂), 1606 (C=C), 1691 (C=O), 1733 (C=O of lactone), ¹H NMR (CDCl₃ δ ppm): 5.08 (s, 2H, −CH₂), 7.08 (d, 1H, J = 15 Hz, SO₂ <u>H</u>C=CH), 7.3–7.6 (m, 10H, ArH and SO₂HC=CH), 8.58 (s, 1H, C₄ of coumarin proton), ¹³C NMR (CDCl₃ 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 C₁₉H₁₄O₅S: C, 64.40; H, 3.98; S, 9.05. Found: C, 64.47; H, 3.96; S, 9.00%.

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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 (SO₂), 1623 (C=C), 1689 (C=O), 1733 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 5.15 (s, 2H, -CH₂), 7.24(d, 1H, SO₂ <u>H</u>C=CH), 7.35–7.97 (m, 9H, ArH and SO₂HC=C<u>H</u>), 8.84 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₁9H₁₃ BrO₅S: 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 (SO₂), 1601 (C=C), 1692 (C=O), 1740(C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 4.98 (s, 2H, -CH₂), 6.95(d, 1H, J = 16 Hz SO₂ <u>H</u>C=CH), 7.2–7.6 (m, 8H, ArH and SO₂HC=C<u>H</u>), 8.4 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₁₉H₁₂ Br₂O₅S: 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 (SO₂), 1607 (C=C), 1692 (C=O), 1734 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 4.89 (s, 2H, -CH₂), 7.49– 7.56 (m, 6H, ArH and SO₂<u>H</u>C=CH), 7.79–7.83 (m, 2H, ArH and SO₂HC=C<u>H</u>), 8.07–8.12 (m, 2H, ArH) 8.78 (s, 1H, C₄ of coumarin proton.) Anal. Calcd for C₁₉H₁₃ ClO₅S: 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 (SO₂), 1623 (C=C), 1608 (C=O), 1734 (C=O of alctone), ¹H NMR (CDCl₃, δ ppm): 4.69 (s, 2H, -CH₂), 7.49–7.53 (m, 5H, ArH and SO₂<u>H</u>C=CH), 7.75–7.79 (m, 2H, ArH and SO₂<u>H</u>C=C<u>H</u>), 8.08–8.12 (m, 2H, ArH), 8.61 (s, 1H, C₄ of coumarin proton). Anal. Calcd for C₁₉H₁₂Cl₂O₅S: 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 (SO₂), 1609 (C=C), 1623 (C=O), 1716 (C=O of lactone) ¹H NMR (CDCl₃, δ ppm): 4.76 (s, 2H, –CH₂), 7.62–7.68 (m, 6H, ArH and SO₂<u>H</u>C=CH), 8.07 (d, 1H, *J* = 15 Hz, SO₂<u>H</u>C=C<u>H</u>), 8.30 (m, 6H, ArH), 8.6 (s, 1H, C₄ coumarin proton). Anal. Calcd for C₂₃H₁₆O₅S: 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	lsolated 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 ₂ CO ₃)	0.15	70 ^b
7	PEG-400	0.12	94°

aReagents and conditions: α -halo ketone (1 mmol) sodium E-styrenesulfinate (1.25 mmol), reflux temperature in given solvent.

^bReaction was carried out at solid state.

^cReaction 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 (SO₂), 1606 (C=C), 1692 (C=O), 1725 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 2.38 (s, 3H, CH₃), 5.07 (s, 2H, -CH₂), 7.01 ³ (d, 1H, J = 15 Hz, SO₂<u>H</u>C=CH), 7.54 (d, 1H, J = 15 Hz, SO₂HC=C<u>H</u>), 7.18–7.68 (m, 8H, ArH), 8.57 (s, 1H, C₄ of coumarin proton), ¹³C NMR (CDCl₃ δ ppm), 21.5, 65.0, 116.8, 118.0, 123.3, 125.4, 159.2, 186.2, EI-MS 367 [M-H]·Anal. Calcd for C₂₀H₁Go₅S: 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-2one (**3h**): Time: 18 min, pale yellow solid, yield 92%, m.p. 176– 178°C. IR (KBr, γ_{max} cm⁻¹): 1137, 1357 (SO₂), 1606 (C=C), 1683 (C=O), 1736 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 2.9(s, 3H, CH₃), 5.15 (s, 2H, -CH₂), 7.25 (d, 1H, *J* = 15 Hz, SO₂ <u>H</u>C=CH), 7.30–7.80 (m, 8H, ArH and SO₂HC=C<u>H</u>), 8.79 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₂₀H₁₅BrO₅S: 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 (SO₂), 1603 (C=C), 1691 (C=O), 1740 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 2.4 (s, 3H, CH₃), 4.9 (s, 2H, -CH₂), 7.15 (d, 1H, *J* = 15 Hz, SO₂ <u>H</u>C=CH), 7.3–7.5(m, 7H, ArH and SO₂HC=C<u>H</u>), 8.4 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₂₀H₄Br₂O₅S: 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 (SO₂), 1609 (C=C), 1690 (C=O), 1735 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 2.4 (s, 3H, CH₃), 5.0 (s, 2H, -CH₂), 6.95(d, 1H, J = 15 Hz, SO₂ <u>H</u>C=CH) 7.2–7.7 (m, 8H, ArH and SO₂HC=C<u>H</u>), 8.4 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₂₀H₁₅ClO₅S: 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 (SO₂), 1609 (C=C), 1685 (C=O), 1738 (C=O of lactone) ¹H NMR (CDCl₃, δ ppm): 2.38 (s, 3H, CH₃), 4.85 (s, 2H, -CH₂), 7.20–7.4 (m, 8H, ArH and ethylene protons), 8.2 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₂₀H₁₄Cl₂O₅S: 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 (3): Time: 27 min, yellow solid, yield 88%, m.p. 214°C. IR (KBr, γ_{max} cm⁻¹): 1130, 1313 (SO₂), 1620 (C=C), 1673 (C=O), 1721 (C=O of lactone), ¹H NMR (CDCl₃, δ ppm): 2.40 (s, 3H, CH₃), 4.9 (s, 2H, -CH₂), 7.17 (d, 1H, J = 15 Hz, SO₂ <u>H</u>C=CH), 7.25–7.7 (m, 11H, ArH and SO₂HC=C<u>H</u>), 8.4 (s, 1H, C₄ of coumarin proton), Anal. Calcd for C₂₄H₁₈O₅S: C, 68.88; H, 4.34; S, 7.66. Found: C, 68.82; H, 4.30; S, 7.61%.

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