Solvent-free synthesis of new heteryl β-ketosulfones

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A novel efficient method for the coupling of sulfinic acid salts and α-halo ketones is described. A variety of heteryl β-ketosulfones have been formed in an excellent yields at room temperature under solvent-free conditions.

Keywords: 3-(2-bromoacetyl)coumarin, sodiumarenesulfinate, β-ketosulfones, solvent-free synthesis

β-Ketosulfones are an important class of compounds in organic synthesis.[1] Several useful compounds are prepared via the intermediacy of β-ketosulfones, such as olefins,[2-4] disubstituted acetylenes,[2-4] vinyl sulfones,[5] allenes,[6] and polyfunctionalised 4H-pyrans.[7,8] Facile reductive elimination of β-ketosulfones leads to the formation of ketones.[9-12] Additionally, β-ketosulfones are precursors for optically active β-hydroxy sulfones.[13-15] Some of the β-ketosulfones possess fungicidal activity.[16]

The coumarins are heterocyclic compounds, also known as 2*H*-1-benzopyran derivatives, and constitute an important group of natural products that are well known for their biological activity and therapeutic activites.[17-20] These can also be considered as versatile building blocks and intermediates for the synthesis of various interesting heterocyclic systems.[21-23]

In the literature the common routes for the synthesis of β-ketosulfones involve oxidation of β-ketosulfides,[24,25] reactions of sulfonylchlorides with silylenol ethers,[26] reactions of diazosulfones with aldehydes,[27] alkylation of arene sulfinatesalts with α-haloketones,[28,29] acylation of alkyl sulfones, reaction of alkyl sulfones with *N*-acylbenzotriazoles,[30] and a more recent approach involving the reaction of sulfonyl chloride with arylacetylenes.[31] Very recently Suryakiran *et al.*[32] reported the preparation of β-ketosulfones in ionic liquid and in PEG-400[33] as solvent. These methods require toxic substrates, multi-step synthesis and prolonged reaction time, costly reagents and yields of the products are moderate, Consequently, there is a need for an alternative procedure involving milder reaction conditions. We report here the synthesis of some novel heteryl β-ketosulfones, we believe that these compounds may be useful intermediates in the synthesis of biological active compounds.

Results and discussion

We chose the coupling of 3-(2-bromoacetyl)coumarin with sodium arenesulfinate as the model for exploring the optimised reaction condition. It was found that if absolute ethanol was used alone the reaction requires reflux temperature with prolonged time *i.e.* eight hours to get the coupling product in only 52% yield. This is due to low solubility of sulfinate salts in organic solvents. Note that the addition of a small amount of water (10 : 2) could improve the reaction efficiency. This is presumably due to the increased water solubility of sodium arenesulfinate, hence the reaction yield increased to 64%. In addition to this when the same reaction was performed under DMF as solvent, for eight hours the reaction yield was 60% only. The addition of a small amount of water (10 : 2) improved the reaction efficiency, and the reaction yield increased to 68%.

The best results were obtained when the reaction was carried out in the solid state with 1 equiv. 3-(2-bromoacetyl)coumarin and 1.25 equiv. of arenesulfinate with few drops of DMF for 20 minutes. We observed rapid formation of β-keto sulfones in 92% yield. On the other hand when the same reaction was performed with 1 equiv. of 3-(2-bromoacetyl)coumarin and 1.25 equiv. of arenesulfinates and 1 equiv. of K_2CO_3 as base under solid state for 20 minutes gave the condensed product 88%. Based on the above result, we concluded that using solid state reaction involving few drops of DMF as the catalytic system are optimised combination of the coupling reaction. The scope of this protocol was further extended for the synthesis of variety of substituted heteryl-β-ketosulfones. It was observed that all the products formed in relatively excellent yields using solid state method.

In conclusion we have disclosed a mild, inexpensive, fast and efficient synthesis of β-ketosulfones under solvent-free conditions at room temperature.

Experimental

All the reagents and solvents were pure, purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromoacetyl) coumarin[34,35] were prepared by literature procedures. 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 β*-keto sulfones*

A mixture of the sodium arenesulfinate (1.25 mmol) and the 3-(2-bromoacetyl)coumarin (1 mmol) was taken in mortar and ground at room temperature for the appropriate time (see Table 2). After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and stirred for 10 minutes then filtered, dried and the crude product purified by column chromatography (ethyl acetate/hexane, 2 : 8) or recrystallised from acetone. All the other compounds were prepared similarly.

*3-(2-(Phenylsulfonyl)acetyl)-2*H*-chromen-2-one* **(3a):** M.p. 138–140 °C. IR (KBr, γ_{max} cm^{-1}): 1144, 1308(SO_2), 1689 (C=O), 1727 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 5.12 (s, 2H CH_2), 7.34–7.36(m, 2H, ArH), 7.54–7.56(m, 2H, ArH), 7.66–7.69(m, 3H, ArH), 7.92–7.95(m, 2H, ArH), 8.50(s, 1H, C_4 of coumarin proton). ^{13}C NMR ($CDCl_3$ δ ppm), 65.9, 117.2, 118.4, 123.7, 125.8, 128.8, 129.6, 131.1, 134.6, 135.8, 139.8, 149.6, 155.8, 159.6, 186.1. EI-MS 329 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{12}O_5S$: C, 62.19; H, 3.68; S, 9.77. Found: C, 62.00; H, 3.63; S, 9.72%.

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

Entry	Solvent	Time/h	Isolated yield/%[a]
1	Absolute ethanol	8	52
2	Aqueous ethanol	8	64
3	DMF	8	60
4	Aqueous DMF	8	68
5	Solid state (few drops of DMF)	0.20	92[b]
6	Solid state (1 equiv. of K_2CO_3)	0.20	88[b]

[a]Reagents and conditions: 3-(2-bromoacetyl)coumarin (1 mmol), sodium arenesulfinate (1.25 mmol), reflux temperature in given solvent.
[b]Reaction was carried out at room temperature.

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Table 2 Synthesis of β-ketosulfones by using solid state method at room temperature

Entry	Time/min	Yield/%
3a	20	92
3b	25	89
3c	25	87
3d	23	90
3e	25	90
3f	30	86
3g	20	93
3h	22	89
3i	24	87
3j	25	90
3k	25	90
3l	30	82

*6-Bromo-3-(2-(phenylsulfonyl)acetyl)-2*H*-chromen-2-one* **(3b):** M.p. 188–190 °C. IR (KBr, γ_{max} cm^{-1}): 1163, 1357(SO_2), 1683 (C=O), 1733 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.7 (s, 2H, CH_2), 7.12–7.25(m, 8H, ArH), 8.4 (s, 1H, C_4 coumarin proton). Anal. Calcd for $C_{17}H_{11}BrO_5S$: C, 50.14; H, 2.71; S, 7.87. Found: C, 50.08; H, 2.79; S, 7.81%.

*6,8-Dibromo-3-(2-(phenylsulfonyl)acetyl)-2*H*-chromen-2-one* **(3c):** M.p. 210–212 °C. IR (KBr, γ_{max} cm^{-1}): 1162, 1357(SO_2), 1686 (C=O), 1747 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.7 (s, 2H, CH_2), 7.25–7.45(m, 2H, ArH), 7.65–7.82(m, 5H, ArH), 8.4(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{17}H_{10}Br_2O_5S$: C, 42.00; H, 2.07; S, 6.60. Found: C, 42.03; H, 2.00; S, 6.67%.

*6-Chloro-3-(2-(phenylsulfonyl)acetyl)-2*H*-chromen-2-one* **(3d):** M.p. 210–212 °C. IR (KBr, γ_{max} cm^{-1}): 1143, 1348(SO_2), 1683 (C=O), 1735(C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.6 (s, 2H, CH_2), 7.25–7.45(m, 2H, ArH), 7.62–7.75(m, 5H, Ar–H), 8.5(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{17}H_{11}ClO_5S$: C, 56.28; H, 3.06; S, 8.84. Found: C, 56.34; H, 3.00; S, 8.90%.

*6,8-Dichloro-3-(2-(phenylsulfonyl)acetyl)-2*H*-chromen-2-one* **(3e):** M.p. 174–175 °C. IR (KBr, γ_{max} cm^{-1}): 1153, 1358(SO_2), 1689 (C=O), 1741(C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 4.7 (s, 2H, CH_2), 7.3–7.45(m, 2H, ArH), 7.60–7.80(m, 5H, ArH), 8.6(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{17}H_{10}Cl_2O_5S$: C, 51.40; H, 2.54; S, 8.07. Found: C, 51.48; H, 2.51; S, 8.0%.

*3-(2-(Phenylsulfonyl)acetyl)-2*H*-benzo[h]chromen-2-one* **(3f):** M.p. 182–184 °C. IR (KBr, γ_{max} cm^{-1}): 1152, 1357(SO_2), 1682 (C=O), 1734 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 5.1(s, 2H, CH_2), 7.10–7.45(m, 5H, ArH), 7.60–7.75(m, 5H, ArH), 8.0(d, 1H, J = 6 Hz, ArH), 8.5 (s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{21}H_{14}O_5S$: C, 66.66; H, 3.73; S, 8.47. Found: C, 66.61; H, 3.78; S, 8.40%.

*3-[2-(4-Methylphenylsulfonyl)acetyl]-2*H*-chromen-2-one* **(3g):** M.p. 152–154 °C. IR (KBr, γ_{max} cm^{-1}): 1146, 1320(SO_2), 1684 (C=O), 1733 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.39 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 7.30–7.37 (m, 4H, ArH), 7.65–7.69 (m, 2H, ArH), 7.79–7.81 (m, 2H, ArH), 8.47 (s, 1H, C_4 of coumarin proton), ^{13}C NMR ($CDCl_3$ δ ppm), 21.4, 65.3, 116.5, 117.8, 123.2, 125.2, 128.3, 129.6, 130.3, 130.5, 135.1, 136.2, 145.1, 148.8, 155.1, 158.9, 185.6, EI-MS 343 $[M + H]^+$. Anal. Calcd for $C_{18}H_{14}O_5S$: C, 63.15; H, 4.12; S, 9.37. Found: C, 63.10; H, 4.10; S, 9.32%.

*6-Bromo-3-[2-(4-methylphenylsulfonyl)acetyl]-2*H*-chromen-2-one* **(3h):** M.p. 168–170 °C. IR (KBr, γ_{max} cm^{-1}): 1135, 1351(SO_2), 1692 (C=O), 1740 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.45 (s, 3H, CH_3), 5.0 (s, 2H, CH_2), 7.30–7.40(m, 4H, ArH), 7.60–7.70(m, 2H, ArH), 7.85 (d, 1H, J = 8 Hz, ArH), 8.35 (s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{18}H_{13}BrO_5S$: C, 51.32; H, 3.11; S, 7.61. Found: C, 51.30; H, 3.15; S, 7.69%.

*6,8-Dibromo-3-[2-(4-methylphenylsulfonyl)acetyl]-2*H*-chromen-2-one* **(3i):** M.p. 208–210 °C. IR (KBr, γ_{max} cm^{-1}): 1165, 1344(SO_2), 1683 (C=O), 1728 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.5 (s, 3H, CH_3), 5.05 (s, 2H, CH_2), 7.30–7.45(m, 5H, ArH), 7.60–7.70 (m, 2H, ArH), 7.85(d, 1H, ArH), 8.35(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{18}H_{12}Br_2O_5S$: C, 43.22; H, 2.42; S, 6.41. Found: C, 43.19; H, 2.38; S, 6.36%.

*6-Chloro-3-[2-(4-methylphenylsulfonyl)acetyl]-2*H*-chromen-2-one* **(3j):** M.p. 174–176 °C. IR (KBr, γ_{max} cm^{-1}): 1135, 1358(SO_2), 1692 (C=O), 1734 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.7 (s, 3H, CH_3), 5.1 (s, 2H, CH_2), 7.10–7.30(m, 5H, ArH), 7.6–7.7(m, 2H, ArH), 7.95(d, 1H, ArH), 8.4(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{18}H_{13}ClO_5S$: C, 57.37; H, 3.48; S, 8.51. Found: C, 57.32; H, 3.42; S, 8.48%.

*6,8-Dichloro-3-[2-(4-methylphenylsulfonyl)acetyl]-2*H*-chromen-2-one* **(3k):** M.p. 204–205 °C. IR (KBr, γ_{max} cm^{-1}): 1143, 1321(SO_2), 1683 (C=O), 1734 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.4 (s, 3H, CH_3), 4.8 (s, 2H, CH_2), 7.10–8.1(m, 6H, ArH), 8.3(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{18}H_{12}Cl_2O_5S$: C, .52.57; H, 2.94; S, 7.80. Found: C, 52.51; H, 2.90; S, 7.74%.

*3-[2-(4-Methylphenylsulfonyl)acetyl]-2*H*-benzo[h]chromen-2-one* **(3l):** M.p. 240–242 °C. IR (KBr, γ_{max} cm^{-1}): 1134, 1318(SO_2), 1703 (C=O), 1724 (C=O of lactone), ^{1}H NMR ($CDCl_3$, δ ppm): 2.7 (s, 3H, CH_3), 5.1 (s, 2H, CH_2), 7.2–7.30(m, 7H, ArH), 7.55–7.7(m, 2H, ArH), 7.95(d, 1H, ArH), 8.45(s, 1H, C_4 of coumarin proton). Anal. Calcd for $C_{22}H_{16}O_5S$: C, 67.33; H, 4.11; S, 8.17. Found: C, 67.30; H, 4.16; S, 8.20%.

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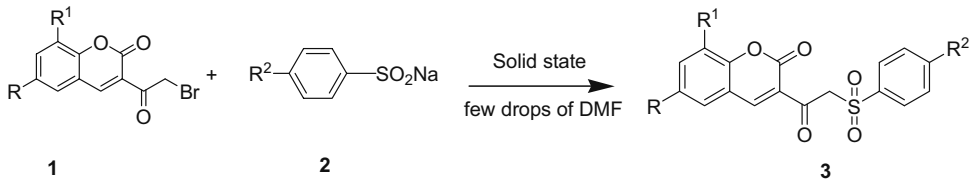

1 **2** **3**

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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