# Facile synthesis of 3-benzylsulfinyl- and 3-benzylsulfonyl-7-diethylaminocoumarins

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The efficient synthesis of a 3-benzylsulfinylcoumarin and a 3-benzylsulfonylcoumarin starting from thiobenzyl alcohol using solvent-free Knoevenagel reaction as the key step is reported. Moreover, the molecular structure of 3-benzylsulfonyl-7-diethylaminocoumarin is confirmed by X-ray crystal analysis.

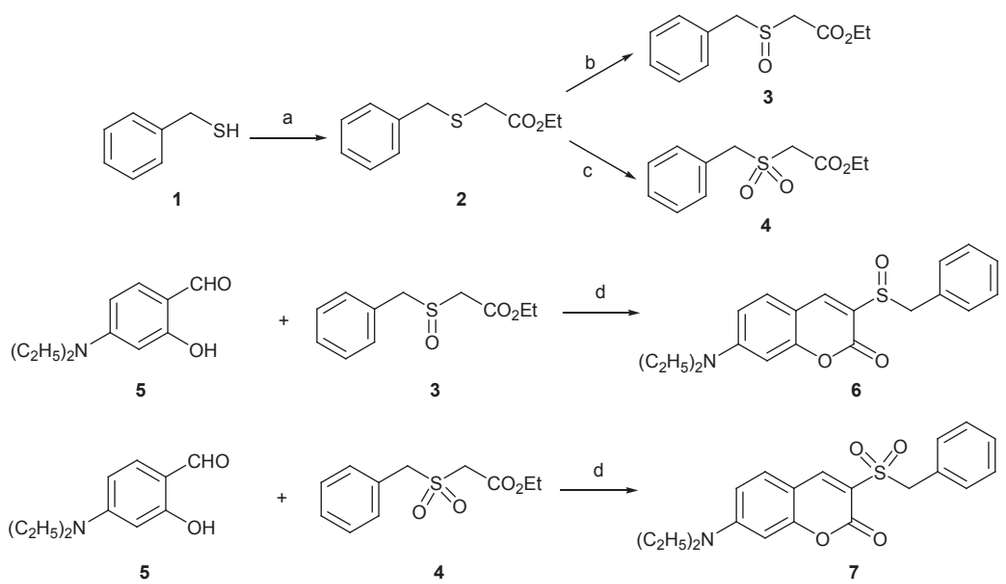
**Keywords:** coumarin, sulfide, oxidation, Knoevenagel reaction, X-ray analysis

Coumarins are important organic compounds that have been widely studied. Many of these compounds exhibit a diverse array of biological properties such as antibacterial, anti-HIV, anticancer, antioxidant and anti-inflammatory activities.[1] In addition, owing to their thermal stability and optical properties, coumarin derivatives are widely used as nonlinear optical chromophores, laser dyes, fluorescent whiteners, fluorescent probes and solar energy collectors.[2] Therefore, the design and synthesis of coumarin derivatives is a popular research topic in organic chemistry.

Traditionally, coumarins can be synthesised by various methods including the Perkin, Knoevenagel, Pechmann and Wittig reactions.[3] The Knoevenagel reaction has been one of the most popular methods in which substituted salicylaldehydes are condensed with active methylene compounds in the presence of a base to afford coumarins. Various active methylene compounds, such as β-keto esters, diethyl malonate and ethyl (2-benzthiazolyl)acetate, have been employed in this reaction.[4,5] Since we have previously applied the sulfones in the Ramberg–Bäcklund reaction,[6] we reasoned that the α-sulfinylester and α-sulfonylester derived from sulfides could react with salicylaldehyde readily to give the corresponding coumarins.

A literature survey revealed that studies on the synthesis of sulfinyl and/or sulfonyl coumarins were very limited. Merchant and Shah[7] prepared a series of 3-phenylsulfonyl coumarins by oxidising the corresponding sulfides, which were obtained *via* the condensation of salicylaldehydes and sodium *S*-phenylthioacetate. Some of the sulfides could be oxidised only to the sulfoxide stage (*i.e.* the sulfinylcoumarins) even with excess oxidising agent. Recently, Zhu and coworkers[8] achieved 3-polyfluoroalkanesulfonyl coumarins by L-proline catalysed Knoevenagel reaction of salicylaldehydes and ethyl perfluorobutylsulfonylacetate in more than 15 hours, wherein the latter substrate was generated from the reaction of methyl nonafluorobutyl sulfone and methyl chloroformate.[8] These methodologies are associated with several drawbacks such as long reaction time, high temperature and limited availability of substrates. Consequently, it is desirable to develop a practical and convenient method for the synthesis of sulfinyl and sulfonyl coumarins from readily available materials. Here we present the facile synthesis of a 3-benzylsulfinylcoumarin and a 3-benzylsulfonylcoumarin from commercially available and inexpensive thiobenzyl alcohol.

The synthesis of the target coumarins was carried out as outlined in Scheme 1. Initially, we conducted the reaction of thiobenzyl alcohol (**1**) and ethyl chloroacetate at room temperature in DMF promoted by a base in the hope of preparing the corresponding sulfide. The use of KOH proved to be unsuccessful, the reaction was sluggish and considerable




**Scheme 1** Reagents and conditions: (a) $ClCH_2CO_2Et$, NaH, DMF, room temperature, 1 h, 92%; (b) 30% aq. $H_2O_2$, AcOH, room temperature, 5 h, 86%; (c) 30% aq. $H_2O_2$, AcOH, 60 °C, 7 h, 83%; (d) piperidine, solvent-free, room temperature to 50 °C, 0.5 h, **6**: 78%, **7**: 82%.

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amounts of starting materials were recovered even after prolonged reaction time. However, when NaH was employed, the desired sulfide **2** was obtained as the sole product in 92% yield. The next synthetic challenge was the selective oxidation of the sulfide to form the corresponding sulfoxide and sulfone, respectively. It was reported that sulfides can be oxidised to sulfoxides or sulfones by *m*-chloroperbenzoic acid (MCPBA), oxone or metal oxide catalyst-$H_2O_2$ system.[9] Fortunately, in a simple and cost effective manner, sulfide **2** was smoothly oxidised to ethyl benzylsulfinylacetate (**3**) in 86% yield by 30% $H_2O_2$ without any catalyst in acetic acid at room temperature. Then, we reasoned that the sulfide **2** could be converted to the corresponding sulfone *via* oxidation at higher temperatures. However, the oxidation under reflux condition led to extensive decomposition and did not give the desired product. After systematic exploration of reaction temperature, we found that the oxidation proceeded optimally at 60 °C to produce ethyl benzylsulfonylacetate (**4**) in 83% yield. Subsequently, compounds **3** and **4** were respectively subjected to Knoevenagel reaction with 4-(diethylamino)salicylaldehyde (**5**) catalysed by piperidine under solvent-free conditions to afford the corresponding 3-benzylsulfinylcoumarin **6** and 3-benzylsulfonylcoumarin **7** in good yields (Scheme 1). We also examined the same Knoevenagel reactions in refluxing ethanol, wherein the desired products were obtained in unsatisfactory yields along with appreciable quantities of by-products.

Fortunately, suitable single crystals of **7** were obtained by recrystallisation from petroleum ether/ethyl acetate for X-ray analysis (Fig. 1), whereby the molecular structure and stereochemistry of this coumarin was unambiguously confirmed. A summary of the crystallographic data and structure refinement details is shown in Table 1, and the selected bond lengths and bond angles are listed in Table 2. Crystallographic data for **7** has been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 1009941. These data can be obtained free of charge on application to CCDC *via* www.ccdc.cam.ac.uk.

In summary, the efficient synthesis of a 3-benzylsulfinylcoumarin and a 3-benzylsulfonylcoumarin from readily available thiobenzyl alcohol has been described, in which the sulfide was oxidised to sulfoxide and sulfone by $H_2O_2$ without any catalyst and the Knoevenagel reactions were conveniently performed under solvent-free conditions. The structure of 3-benzylsulfonyl-7-diethylaminocoumarin (**7**) was further confirmed by X-ray single crystal analysis. This synthetic approach should provide a succinct route to a diverse array of sulfinyl- and sulfonylcoumarins for biological or optical studies. Further work is in progress in our laboratory.

**Table 1** Crystal data and structure refinement of **7**

| Empirical formula | $C_{20}H_{21}NO_4S$ |
|---|---|
| Formula weight | 371.44 |
| Temperature/K | 293(2) |
| Wavelength/Å | 0.71073 |
| Crystal system | Monoclinic |
| Space group | $P2_1/n$ |
| Unit cell dimensions/ Å | $a$=13.2890(7) |
| | $b$=10.5679(5) |
| | $c$=13.3597(7) |
| | α=90° |
| | β=90.606(5) ° |
| | γ=90° |
| Volume/Å$^3$ | 1876.09(17) |
| Z | 4 |
| Calculated density/Mg m$^{-3}$ | 1.315 |
| Absorption coefficient/mm$^{-1}$ | 0.197 |
| F(000) | 784 |
| Crystal size | 0.29×0.26×0.12 mm |
| 2Θ range for data collection | 6.1 to 52.04° |
| Limiting indices | $-16 \le h \le 16$ |
| | $-13 \le k \le 13$ |
| | $-15 \le l \le 16$ |
| Reflections collected/unique | 10020/3612 [R(int)=0.0644] |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 3612/25/256 |
| Goodness-of-fit on $F^2$ | 1.077 |
| Final R indices [I>2σ (I)] | $R^1$=0.0624, w$R^2$=0.1350 |
| R indices (all data) | $R^1$=0.1085, w$R^2$=0.1724 |
| Largest diff. peak and hole/e Å$^{-3}$ | 0.23 and −0.31 |

**Table 2** Selected structural parameters for compound **7**

| Bond lengths (Å) | | | |
|---|---|---|---|
| S1–O3 | 1.431(2) | O2–C7 | 1.211(4) |
| S1–O4 | 1.436(2) | C1–N1 | 1.362(4) |
| S1–C8 | 1.754(3) | C7–C8 | 1.439(4) |
| S1–C14 | 1.775(3) | C8–C9 | 1.365(4) |
| O1–C5 | 1.381(4) | C4–C9 | 1.401(4) |
| O1–C7 | 1.385(4) | C14–C15 | 1.505(4) |
| **Bond angles (°)** | | | |
| O3–S1–O4 | 117.57(17) | C15–C14–S1 | 110.0(2) |
| O3–S1–C8 | 106.62(15) | N1–C1–C2 | 120.5(3) |
| O3–S1–C14 | 108.24(17) | N1–C1–C6 | 121.9(3) |
| O4–S1–C8 | 109.57(15) | C6–C1–C2 | 117.6(3) |
| O4–S1–C14 | 108.51(17) | C6–C5–O1 | 116.2(3) |
| C8–S1–C14 | 105.69(16) | O1–C7–C8 | 116.4(3) |
| C5–O1–C7 | 122.6(2) | O2–C7–O1 | 116.3(3) |
| O1–C5–C4 | 120.1(3) | O2–C7–C8 | 127.3(3) |

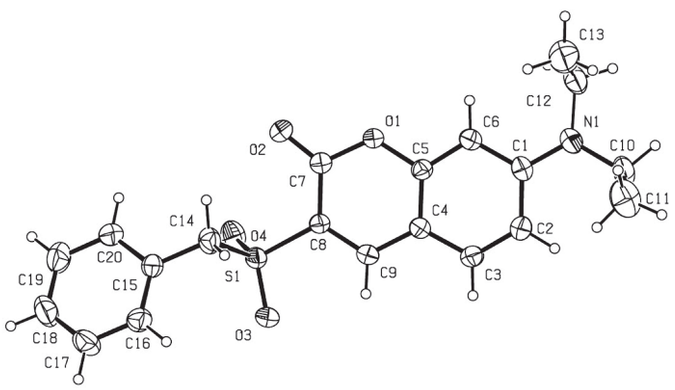


**Fig. 1** The molecular structure of compound **7**. Non-hydrogen atoms are shown at the 30% probability level.

## Experimental

Reagents and solvents were all from commercial sources and used without further purification. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Mercury Plus 400 MHz spectrometer. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) for $^1$H and $CDCl_3$ (δ 77.0 ppm) for $^{13}$C. Coupling constants (*J*) are given in Hertz (Hz). Melting points were measured on a Kofler apparatus and uncorrected. Column chromatography purifications were performed on 200–300 mesh silica gel. Analytical TLC was performed on silica gel GF254 plates. X-ray crystallographic analysis was performed on a SuperNova, Dual, Cu at zero, Eos diffractometer. The crystal was kept at 293(2) K during data collection. Using Olex2, the structure was solved with the ShelXS structure solution program using direct methods and refined with the ShelXL refinement package using least squares minimisation. High resolution mass spectra (HRMS) were determined on a Bruker Daltonics APEX II 47e spectrometer.

*Ethyl benzylsulfidylacetate* (**2**): Thiobenzyl alcohol (1.24 g, 10.0 mmol) was dissolved in dry DMF (15 mL), NaH (0.48 g, 60% in mineral oil, 12.0 mmol) was added and the resulting mixture was stirred at room temperature for 15 min. Then, ethyl chloroacetate (1.23 g, 10.0 mmol) was added and the resulting solution was stirred for 1 h at room temperature. On completion of the reaction (monitored by TLC), AcOEt (50 mL) was added to the mixture and washed with brine (3 × 50 mL). The organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 10 : 1) as eluent to afford **2** (1.93 g) as a colourless oil in 92% yield. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 2H), 3.04 (s, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.4, 137.3, 129.2, 128.5, 127.2, 61.3, 36.3, 32.2, 14.2. HRMS calcd for $C_{11}H_{15}O_2S$ $[M+H]^+$: 211.0787; found: 211.0792.

*Ethyl benzylsulfinylacetate* (**3**): Sulfide **2** (0.42 g, 2.0 mmol) was dissolved in glacial acetic acid (5 mL). Then, $H_2O_2$ (30% w/v, 2 mL) was added and the resulting solution was stirred for 5 h at room temperature. When the reaction was judged to be complete (TLC monitoring), the mixture was dissolved in ethyl acetate (50 mL). The solution was washed with brine (3 × 50 mL), dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 1 : 1) as eluent to afford **3** (0.39 g, yield 86%) as a colourless solid, m.p. 44–46 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.41–7.32 (m, 5H), 4.27–4.21 (m, 3H), 4.11 (d, *J* = 13.2 Hz, 1H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.47 (d, *J* = 14.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 165.3, 130.5, 129.2, 129.1, 128.8, 62.2, 58.1, 53.7, 14.2. HRMS calcd for $C_{11}H_{15}O_3S$ $[M+H]^+$: 227.0736; found: 227.0744.

*Ethyl benzylsulfonylacetate* (**4**): Sulfide **2** (0.42 g, 2.0 mmol) was dissolved in glacial acetic acid (5 mL). Then, $H_2O_2$ (30% w/v, 2 mL) was added and the resulting solution was stirred at 50 °C for 7 h. Upon completion of the reaction (TLC monitoring), the mixture was dissolved in ethyl acetate (50 mL) and then extracted with brine (3 × 50 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 5 : 1) as eluent to afford **4** (0.40 g) as a colourless oil in 83% yield. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.46–7.35 (m, 5H), 4.48 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 163.0, 130.8, 128.9, 128.7, 127.5, 62.3, 59.1, 54.8, 13.7. HRMS calcd for $C_{11}H_{15}O_4S$ $[M+H]^+$: 243.0686; found: 243.0693.

*3-Benzylsulfinyl-7-diethylaminocoumarin* (**6**): A mixture of 4-(diethylamino)salicylaldehyde (**5**, 0.29 g, 1.5 mmol), ethyl benzylsulfinylacetate (**3**, 0.34 g, 1.5 mmol) and piperidine (0.5 mL) in a mortar was ground well with a pestle at room temperature. The reaction was heated at 50 °C and ground for 30 min. Then, the mixture was dissolved in ethyl acetate (50 mL), neutralised with 3N HCl and extracted with brine (3 × 50 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 2 : 1) as eluent to afford **6** (0.41 g, yield 78%) as a yellow solid, m.p. 160–162 °C. IR (KBr) $cm^{-1}$: 1718, 1616, 1511, 1249, 1130, 1076, 1048, 700, 633. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.27–7.18 (m, 6H), 6.58 (dd, *J* = 8.8 and 2.0 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 12.8 Hz, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.44 (q, *J* = 7.2 Hz, 4H), 1.21 (t, *J* = 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.6, 157.2, 152.0, 143.1, 130.7, 130.1, 129.6, 128.5, 128.4, 120.6, 109.7, 108.3, 97.3, 58.0, 45.2, 12.6. HRMS calcd for $C_{20}H_{22}NO_3S$ $[M+H]^+$: 356.1315; found: 356.1316.

*3-Benzylsulfonyl-7-diethylaminocoumarin* (**7**): A mixture of 4-(diethylamino)salicylaldehyde (**5**, 0.29 g, 1.5 mmol), ethyl benzylsulfonylacetate (**4**, 0.36 g, 1.5 mmol) and piperidine (0.5 mL) in a mortar was ground well with a pestle at room temperature. The reaction was heated at 50 °C and ground for 30 min. Then, the mixture was dissolved in ethyl acetate (50 mL), neutralised with 3N HCl and extracted with brine (3 × 50 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (v/v = 2 : 1) as eluent to afford **7** (0.46 g, yield 82%) as a yellow-greenish solid, m.p. 172–173 °C. IR (KBr) $cm^{-1}$: 1717, 1620, 1509, 1352, 1131, 700, 633. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.40–7.29 (m, 6H), 6.62 (dd, *J* = 8.8 and 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 4.74 (s, 1H), 3.48 (q, *J* = 7.2 Hz, 4H), 1.26 (t, *J* = 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.5, 157.5, 153.4, 148.2, 131.6, 130.8, 128.7, 128.3, 115.4, 110.0, 106.7, 96.8, 59.3, 45.2, 12.4. HRMS calcd for $C_{20}H_{22}NO_4S$ $[M+H]^+$: 372.1264; found: 372.1272.

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