# Synthesis of aroyl[bis(4-hydroxycoumarin-3-yl)]methane using tungstate sulfuric acid in water

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An efficient synthesis of some new aroyl[bis(4-hydroxycoumarin-3-yl)]methanes (dicoumarols) based on the reaction of 4-hydroxycoumarin with arylglyoxals is described. The reactions were efficiently catalysed by tungstate sulfuric acid to afford the product in moderate to good yields (up to 65%).

**Keywords:** dicoumarols, tungstate sulfuric acid, arylglyoxal, 4-hydroxycoumarin

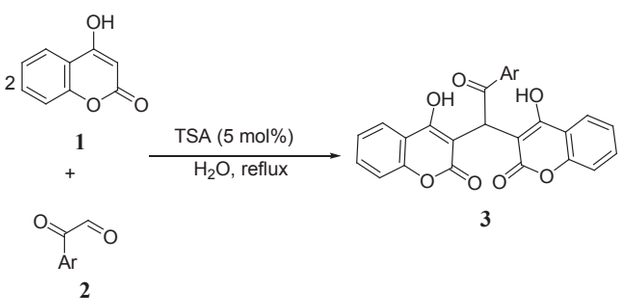
Recently, coumarin derivatives have received attention because of their biological activities.[1–3] Dicoumarol is a naturally occurring anticoagulant which functions like vitamin K.[4] This compound is an agent for the prevention or treatment of thrombosis.[5] Due to their biological significance, there has been considerable interest in developing synthetic strategies for the preparation of dicoumarol derivatives. For example, a total synthesis starting from salicylaldehyde and formaldehyde,[6] biosynthesis using micro-organisms such as *Penicillium jenseni*,[7] and Knoevenagel condensation of 4-hydroxycoumarins with carbonyls in the presence of several catalysts have been reported.[8–10] We now describe a green method for the synthesis of some new and known dicoumarols containing an aroyl group.

## Results and discussion

In continuation of our previous studies on catalysed organic reactions, we found that the condensation reaction of 4-hydroxycoumarin (**1**) and arylglyoxals **2** in the presence of catalytic amounts of tungstate sulfuric acid (TSA, disulfurotungstate acid) leads to dicoumarol derivatives **3** (Scheme 1).

Initially, we used 4-hydroxycoumarin (**1**) and phenylglyoxal as the model reaction system to investigate the reaction conditions. As can be seen in Table 1, the reaction proceeded slowly in the absence of catalyst. Increasing the catalyst amount did not affect the progress of the reaction markedly. It was observed that the condensation reaction can be successful in the presence of 5 mol% of the catalyst.

The effects of several solvents on the reaction progress were investigated as shown in Table 2.




**Scheme 1** Synthesis of dicoumarol derivatives catalysed by TSA.

It can be concluded that the solvents such as EtOH, MeOH, and $H_2O$ accelerate the condensation reaction. The use of water is cheaper and safer than using organic solvents.[11] Under the optimised conditions, a variety arylglyoxals **2** were used for the synthesis of dicoumarol derivatives (Table 3). Arylglyoxals possessing either electron-withdrawing or electron-donating groups were successfully employed in this reaction.

Recently, organic synthesis in water was reviewed by Fokin and co-workers.[12] Spectroscopically, the $^1$H NMR spectrum of compound **3h** shows a sharp singlet at 11.24 ppm as OH protons. The aromatic protons also appeared at 8.27–7.18 ppm. A sharp singlet signal at 6.19 ppm corresponds to the methine proton which has been deshielded because of joining to $sp^2$ carbons such as C=O and two C=C.

Based on the common mechanistic pathway of the Knoevenagel and Michael addition reaction, a mechanism for the acid-catalysed reaction of **1** with **2** is proposed (Scheme 2).

**Table 1** The effect of TSA amount in the synthesis of **3a** in $H_2O$ under reflux

| Entry | Catalyst/mol% | Time/min | Yield/% |
|---|---|---|---|
| 1 | – | 180 | 30 |
| 2 | 3 | 180 | 65 |
| 3 | 5 | 55 | 75 |
| 4 | 10 | 50 | 75 |

**Table 2** The effect of several solvents for the synthesis of **3a** using TSA under reflux

| Entry | Solvent | Time/min | Yield/% |
|---|---|---|---|
| 1 | MeOH | 40 | 73 |
| 2 | EtOH | 35 | 75 |
| 3 | THF | 60 | 70 |
| 4 | $CH_2Cl_2$ | 120 | 50 |
| 5 | EtOH/$H_2O$ (1/1) | 55 | 75 |
| 6 | $H_2O$ | 55 | 75 |

**Table 3** Synthesis of dicoumarols using TSA (5 mol%) under reflux in $H_2O$

| Entry | Ar | Time/min | Yield/%[a] | M.p. [Lit.]/°C |
|---|---|---|---|---|
| **3a** | $C_6H_5$ | 70 | 80 | 193–195[9] [200–202][9] |
| **3b** | 4-F–$C_6H_4$ | 65 | 75 | 233–235 |
| **3c** | 4-Br–$C_6H_4$ | 70 | 70 | 240–242 [236–238][9] |
| **3d** | 4-$NO_2$–$C_6H_4$ | 60 | 75 | 244–246 [240–242][9] |
| **3e** | 4-MeO–$C_6H_4$ | 55 | 70 | 261–263 |
| **3f** | 3-MeO–$C_6H_4$ | 75 | 65 | 205–207 |
| **3g** | 4-Cl–$C_6H_4$ | 70 | 68 | 250–252 |
| **3h** | 2-Naphthyl | 60 | 82 | 255–257 |

[a]Isolated yields.

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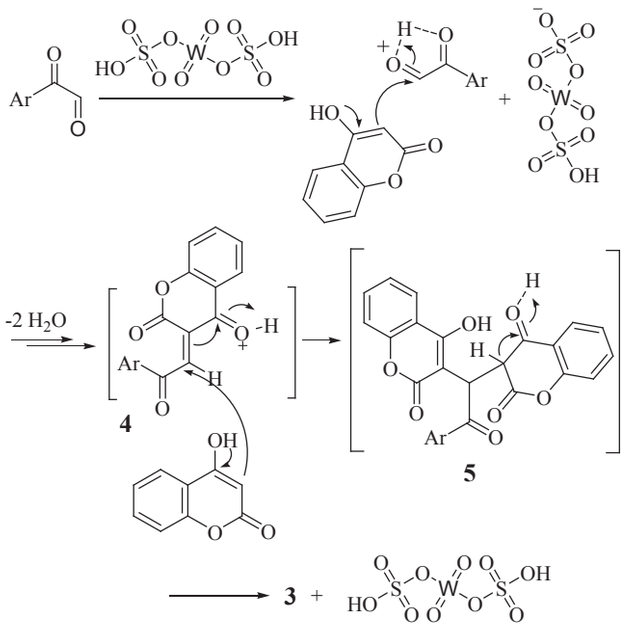

**Scheme 2** Plausible mechanism for the TSA-catalysed reaction of 4-hydroxycoumarin with arylglyoxal.

## Conclusions

In summary, a highly efficient coupling reaction of 4-hydroxycoumarin and arylglyoxals has been developed. The method is simple and generates a diverse range of new and known dicoumarols in good yields. Note that the presence of transformable functionalities in the products makes them potentially valuable for further synthetic manipulations.

## Experimental

All chemicals were purchased from Merck Aldrich. Arylglyoxals and TSA were prepared as described previously.[13,14] The reactions were monitored by TLC (silica-gel 60 $F_{254}$, hexane: ethyl acetate). IR spectra were recorded on a FT-IR JASCO-680 and the $^1$H NMR spectra were obtained on a Bruker DPX-400 or 300 MHz Avance 2 instrument. The vario El CHNS was used for elemental analysis. The structure of new compounds was completely deduced from their spectral data and elemental analysis. The known compounds **3a**, **3c** and **3d** have been characterised by FT-IR, melting points and comparison with previous reports.[9]

*Synthesis of aryloyl[bis(4-hydroxycoumarin-3-yl)]methanes*

A mixture of 4-hydroxycoumarin **1** (2 mmol), arylglyoxal **2** (1 mmol) and TSA (5 mol%) in $H_2O$ (10 mL) was refluxed for an appropriate time (Table 3). The progress of the reaction was monitored by TLC (EtOAc/hexane, 1 : 1). After completion, the mixture was poured on ice and the resulting precipitate filtered. The product **3** was obtained after recrystallisation from EtOH/THF (2 : 1). In some cases, the column chromatography is needed (EtOAc/hexane, 1 : 1).

*4-Flurobenzoyl[bis(4-hydroxycoumarin-3-yl)]methane* (**3b**): M.p. 235–237 °C. Anal. calcd for $C_{26}H_{15}FO_7$: C, 68.12; H, 3.30; found: C, 68.30; H, 3.22%. IR (KBr, cm$^{-1}$): 3500–3300, 3066.26, 2887, 1695, 1650, 1619, 1600, 1567, 1271, 1225, 1107 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, $\delta$/ppm): 11.15 (s, 2H), 7.89 (dd, 2H, $J_1$=8.2, $J_2$=1.6 Hz), 7.79–7.75 (m, 2H), 7.56–7.50 (m, 2H), 7.33–7.24 (m, 4H), 6.94 (t, 2H, $J$=8.6 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): 192.9, 165.4, 152.4, 133.2, 132.0, 130.7, 130.6, 125.0, 124.5, 116.7, 116.3, 115.9, 115.6, 42.8.

*4-Methoxy-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane* (**3e**): M.p. 265–267 °C. Anal. calcd for $C_{27}H_{18}O_8$: C, 68.94; H, 3.86; found: C, 69.10; H, 3.69%. IR (KBr, cm$^{-1}$): 3500–3300, 3076, 2978, 1684, 1650, 1620, 1601, 1571, 1263 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$=11.22 (s, 2H), 8.00 (dd, 2H, $J$=8.2, 1.6 Hz), 7.77–7.72 (m, 2H), 7.55–7.49 (m, 2H), 7.32–7.24 (m, 4H), 6.77–6.72 (m, 2H), 6.00 (s, 1H), 3.71 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 193.1, 165.2, 163.5, 152.4, 133.0, 130.4, 128.3, 124.9, 124.5, 116.6, 116.4, 113.8, 55.4, 42.6.

*3-Methoxy-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane* (**3f**): M.p. 205–207 °C. Anal. calcd for $C_{27}H_{18}O_8$: C, 68.94; H, 3.86; found: C, 69.06; H, 3.65%. IR (KBr, cm$^{-1}$): 3500–3300, 1693, 1655, 1619, 1602, 1567, 1273, 1427 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 11.16 (s, 1H), 8.00 (dd, 2H, $J$=8.2, 1.6 Hz), 7.55–7.49 (m, 2H), 7.34–7.24 (m, 6H), 7.12 (t, 1H, $J$=8.2 Hz), 6.94–6.90 (m, 1H), 6.00 (s, 1H), 3.69 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 194.2, 165.2, 159.7, 152.4, 136.9, 133.1, 129.4, 125.0, 124.5, 120.2, 120.1, 116.7, 116.4, 112.4, 42.9.

*4-Chloro-benzoyl[bis(4-hydroxycoumarin-3-yl)]methane* (**3g**): M.p. 250–252 °C. Anal. calcd for $C_{26}H_{15}ClO_7$: C, 65.76; H, 3.18; found: C, 65.91; H, 3.03%. IR (KBr, cm$^{-1}$): 3500–3300, 3080, 2884, 1713, 1665, 1650, 1614, 1564, 1266, 1090, 767 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 11.10 (s, 2H), 7.85 (d, 2H, $J$=6.0 Hz), 7.72 (d, 2H, $J$=5.2 Hz), 7.62–7.52 (m, 4H), 7.31–7.25 (m, 4H), 6.28 (s, 1H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): $\delta$ 196.1, 165.9, 163.3, 152.2, 135.9, 131.6, 131.2, 129.3, 125.9, 123.8, 123.4, 118.0, 115.8, 101.6, 42.9.

*2-Naphthoyl[bis(4-hydroxycoumarin-3-yl)]methane* (**3h**): M.p. 255–257 °C. Anal. calcd for $C_{30}H_{18}O_7$: C, 73.47; H, 3.70; found: C, 73.68; H, 3.75%. IR (KBr, cm$^{-1}$): 3550–3300, 1694, 1653, 1617, 1565, 1454, 1280 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 11.24 (s, 2H), 8.27 (s, 1H), 8.01 (dd, 2H, $J_1$=8.2, $J_2$=1.6 Hz), 7.83–7.72 (m, 4H), 7.54–7.43 (m, 4H), 7.33–7.23 (m, 4H), 6.19 (s, 1H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 177.3, 166.6, 163.6, 152.3, 134.4, 134.3, 131.8, 131.5, 129.1, 127.9, 127.5, 126.7, 124.1, 123.9, 123.3, 118.5, 115.7, 101.6, 43.1.

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