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# Direct sulfanylation of 4-hydroxycoumarins with thiols in water

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ABSTRACT

The direct sulfanylation of 4-hydroxycoumarins with thiols via C–OH bond activation in water under mild conditions is described, which afforded the corresponding 4-sulfanylcoumarins in good yields.



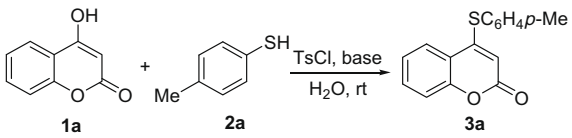
As a privileged scaffold, coumarin shows interesting biological properties.[1] The prominence of coumarin in natural products and biologically active molecules has promoted considerable efforts toward their synthesis.[2] Recently, it was found that 4-sulfanylcoumarins showed promising *anti*-HCV activity.[3] The discovery of promising lead antivirus compounds and their moderate activity warranted the development of efficient and rapid syntheses and evaluations of analogous structures in the search for better inhibitors. Although 4-sulfanylcoumarins have been synthesized either for biological evaluation or as key intermediates in generation of complex molecules, their syntheses usually suffer from multiple synthetic steps, harsh reaction conditions (such as utilizing toxic reagents often under high temperatures), and poor substituent tolerance.[4] Thus, it is highly desired to develop general and efficient methods for the synthesis of 4-sulfanylcoumarins, especially in a green process.

Recently, palladium-catalyzed cross-coupling reactions via C–OH bond activation of tautomerizable heterocycles with arylboronic acids using phosphonium salts as activation reagent were disclosed. In this Letter, Kang et al. described that phosphonium salts enabled an in situ activation of tautomerizable heterocycles, as well as their subsequent palladium-catalyzed cross-coupling reactions of arylboronic acids.[5] Subsequently, Ackermann reported that phenols could be employed as proelectrophiles in ruthenium-catalyzed dehydrative direct arylations, and *p*-toluenesulfonyl chloride was utilized for the C–OH bond activation.[6] Prompted by the results, we envisioned that 4-hydroxycoumarin might be utilized as starting material for synthesis of 4-sulfanylcoumarins in the presence of *p*-toluenesulfonyl chloride as C–OH bond activator. Meanwhile, considering the green process, it is of importance to perform this reaction in water since water is environmentally benign and potential advantages of using water as a solvent are its low cost, safety, and ease of use. Thus, to verify the practicability of this projected route, we started to investigate the possibility of this transformation.

Initially, a set of experiments were carried out using 4-hydroxycoumarin **1a** and 4-methylbenzenethiol **2a** as model substrates. We conceived that the presence of arenesulfonyl chloride would enable an in situ activation of 4-hydroxycoumarin substrates.[7] Thus, the reactions were performed in water at room temperature in the presence of different bases and *p*-toluenesulfonyl chloride (Scheme 1). Gratifyingly, we observed the formation of the desired product **3a** (30% yield) when the reaction occurred in the presence of sodium bicarbonate. Further screening of bases (including inorganic and organic bases) revealed that triethylamine was the best choice. Under this condition, the desired 4-sulfanylcoumarin **3a** was isolated in 76% yield. Similar yield was generated while adding surfactant in the reaction. No product was detected without addition of base. The reaction could not proceed in the absence of *p*-toluenesulfonyl chloride. It is also noteworthy that this reaction could be carried out under air atmosphere without loss of yield.

The scope of this reaction was then investigated under this preliminary optimized conditions (TsCl, $Et_3N$, $H_2O$, rt, air), and the results are summarized in Table 1. For all cases, 4-hydroxycoumarin **1** reacted with thiols **2** leading to the corresponding products **3** in good yields. For instance, reaction of 4-hydroxycoumarin **1a** with benzenethiol **2b** under the standard conditions gave rise to the desired product **3b** in 80% yield (Table 1, entry 2). Similar yield was obtained when 4-fluorobenzenethiol **2c** was utilized as the reaction partner (Table 1, entry 3, 83% yield).

Reactions of 4-hydroxycoumarin **1a** and benzenethiols with electron-withdrawing group attached on the aromatic ring proceeded well to afford the desired products **3** in good yield (Table 1, entries 3–5). It seems that the groups attached on the aromatic




**Scheme 1.** Screening conditions for reaction of 4-hydroxycoumarin **1a** with 4-methylbenzenethiol **2a**.

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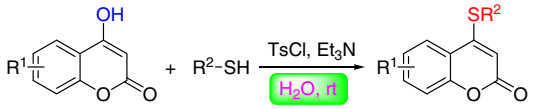
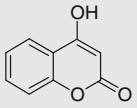
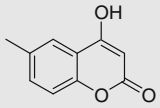
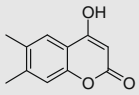
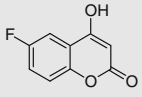
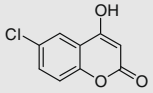
**Table 1**
Direct sulfanylation of 4-hydroxycoumarin **1** with thiol **2** in water




| Entry | R | $R^2$ | Product | $Y^a$ (%) |
|---|---|---|---|---|
| 1 |  **1a** | 4-$MeC_6H_4$ (**2a**) | **3a** | 76 |
| 2 | **1a** | $C_6H$ (**2b**) | **3b** | 80 |
| 3 | **1a** | 4-$FC_6H_5$ (**2c**) | **3c** | 83 |
| 4 | **1a** | 2-$ClC_6H_5$ (**2d**) | **3d** | 70 |
| 5 | **1a** | 4-$ClC_6H_5$ (**2e**) | **3e** | 80 |
| 6 | **1a** | $C_6H_5CH_2$ (**2f**) | **3f** | 65 |
| 7 | **1a** | $CH_3CH_2CH_2$(**2g**) | **3g** | 63 |
| 8 | **1a** | $HOCH_2CH_2$ (**2h**) | **3h** | 64 |
| 9 |  **1b** | 4-$MeC_6H_4$ (**2a**) | **3i** | 71 |
| 10 |  **1c** | 4-$MeC_6H_4$ (**2a**) | **3j** | 72 |
| 11 | **1c** | $C_6H$ (**2b**) | **3k** | 73 |
| 12 | **1c** | 4-$FC_6H_5$ (**2c**) | **3l** | 76 |
| 13 |  **1d** | 4-$MeC_6H_4$ (**2a**) | **3m** | 77 |
| 14 | **1d** | $C_6H$ (**2b**) | **3n** | 75 |
| 15 | **1d** | 4-$FC_6H_5$ (**2c**) | **3o** | 71 |
| 16 |  | 4-$MeC_6H_4$ (**2a**) | **3p** | 76 |
| 17 | **1e** | $C_6H$ (**2b**) | **3q** | 78 |
| 18 | **1e** | 4-$FC_6H_5$ (**2c**) | **3r** | 80 |

[a] Isolated yields based on 4-hydroxycoumarin.

ring of benzenethiol **2** do not effect the reaction markedly. The aliphatic thiol (such as benzyl thiol and *n*-propyl thiol) employed in the reaction also worked well although the yield was lower (Table 1, entries 6 and 7). It is noteworthy that the hydroxy group in the thiol is also tolerated under the conditions (Table 1, entry 8). Other 4-hydroxycoumarins were also examined. 4-Hydroxy-6-methylcoumarin **1b** reacted with 4-methylbenzenethiol **2a** leading to the desired product **3i** in 71% yield (Table 1, entry 9). 72% yield of 4-sulfanylcoumarin **3j** was generated when 6,7-dimethyl-4-hydroxycoumarin **1c** was utilized as substrate in the reaction of 4-methylbenzenethiol **2a** (Table 1, entry 10). Reaction of 6,7-dimethyl-4-hydroxycoumarin **1c** with benzenethiol **2b** or **2c** also proceeded well to give rise to the corresponding product **3k** or **3l** in good yields (Table 1, entries 11–12). 6-Fluoro-4-hydroxycoumarin **1d** and 6-chloro-4-hydroxycoumarin **1e** were good substrates in this kind of transformation, and the corresponding products were generated as expected with good yields (Table 1, entries 13–18). In this transformation the conditions are extremely mild, since the reactions are performed using water as the solvent at room temperature. For the mechanism of this reaction, we reasoned that the presence of *p*-toluenesulfonyl chloride enabled an in situ activation of 4-hydroxycoumarin. The generated intermediate enol tosylate in α,β-conjugated system subsequently reacted with thiol via 1,4-addition and elimination[8] to afford the expected 4-sulfanylcoumarin. We believed the results presented here not only represented a green process but also provided a facile and novel route for the synthesis of 4-sulfanylcoumarins.

In conclusion, we have described a green, efficient, and novel route for the synthesis of 4-sulfanylcoumarins via direct sulfanylation of 4-hydroxycoumarins with thiols. This transformation is highly effective which is performed in water at room temperature under air atmosphere. The efficiency of this method combined with the operational simplicity of the present green process makes it potential attractive for library construction.

## Acknowledgment

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7. *General procedure for direct sulfanylation of 4-hydroxycoumarins with thiols*: A mixture of 4-hydroxycoumarin **1** (0.2 mmol) and triethylamine (0.6 mmol) in water (1 ml) was stirred for several minutes. Then, 4-methylbenzenesulfonyl chloride (0.3 mmol) was added to the mixture. The mixture was stirred at room temperature for 1–2 h. After completion of the reaction as indicated by TLC, thiophenol **2** (0.34 mmol) was added to the mixture. The mixture was stirred at room temperature for 16–30 h. After completion of the reaction as indicated by TLC, the reaction mixture extracted with EtOAc (3 × 10 mL), washed with saturated aqueous NaCl (10 mL), dried ($Na_2SO_4$), and filtered. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**. Selected example: 4-(*p*-tolylthio)coumarin, 76% yield. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 2.44 (s, 3H), 5.63 (s, 1H), 7.30–7.35 (m, 4H), 7.46 (d, $J$ = 8.0 Hz, 2H), 7.57 (s, 1H), 7.85 (dd, $J$ = 1.2, 8.0, Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 21.4, 108.2, 117.1, 117.9, 122.6, 123.7, 124.1, 131.2, 132.2, 136.0, 141.4, 152.3, 158.4, 159.6.
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