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Efficient synthesis of a new class of sulfonamide-substituted coumarins

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ABSTRACT

A convenient synthesis of new sulfonamide-substituted coumarins is reported. *N*-Sulfonyl aldimines are synthesized from the reaction of arylaldehydes and *p*-toluenesulfonamide. Next, the prepared *N*-sulfonyl aldimines are reacted with 5,7-dihydroxy-4-methylcoumarin using 40 mol % of NaOH to produce sulfonamide-substituted coumarin derivatives in good to excellent yields.

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Coumarin, as a simple oxygen-containing heterocycle, has received significant attention in the literature because of its exciting biological properties.[1–3] Coumarin and its derivatives have been shown to be useful precursors for the synthesis of a variety of medicinal agents.[4] For example, heterocycles derived from coumarin have been used as anti-HIV, anti-inflammatory, anticonvulsant, antioxidant, antibacterial, antifungal, and antihistamine agents.[5–7] Furthermore, coumarin itself is found in plants such as cinnamon, lavender, and peppermint.[8] Coumarins can be employed as useful intermediates in synthetic organic chemistry.[9] Also, they demonstrate fluorescence in the visible light range, large Stoke's shifts, high photoluminescence quantum yields and reasonable solubilities.[10] For these reasons, a large number of methods have been reported for the preparation of coumarin derivatives.[11–13]

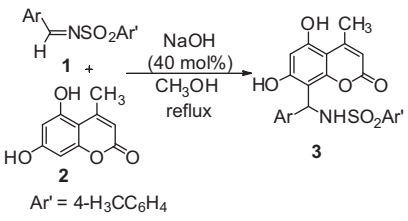
Sulfonamide-based compounds are important structural classes of medicinal molecules.[14] Examples of recently approved drugs with a sulfonamide structure include antitumor, hypoglycemic, antithyroid, anticarbonic anhydrase, anti-inflammatory, diuretic, and anti-impotence medications.[15–18] Additionally, antibacterial agents with a sulfonamide moiety have been used for many decades.[19] Numerous sulfonamide derivatives have gone on to preclinical development.[20] These compounds have also been applied as azo dyes for achieving improved light stability, water solubility, and fixation of fibers.[21]

As a result of the many chemical, biological, and pharmaceutical applications of sulfonamide and coumarin derivatives, herein we report a new approach for the synthesis of a novel class of sulfonamide-substituted coumarins.

Initially, according to the reported procedure,[22] the sulfonyl aldimines **1** were synthesized from the reaction of aromatic aldehydes and *p*-toluenesulfonamide in the presence of $AlCl_3$. Next, 5,7-dihydroxy-4-methylcoumarin (**2**) was synthesized via the $ZrOCl_2/SiO_2$-catalyzed condensation of phloroglucinol and ethyl acetoacetate.[23]

Subsequently, we synthesized sulfonamide-substituted coumarin derivatives **3** from the reaction of *N*-sulfonyl aldimines **1** and 5,7-dihydroxy-4-methylcoumarin (**2**) (Scheme 1).

In order to optimize the conditions, the reaction between *N*-sulfonyl aldimine **1a** and coumarin **2** was selected as a model system. The desired product was not produced in the absence of a catalyst, even after a long reaction time. We found that the desired reaction



Scheme 1. Synthesis of sulfonamide-substituted coumarins **3**.

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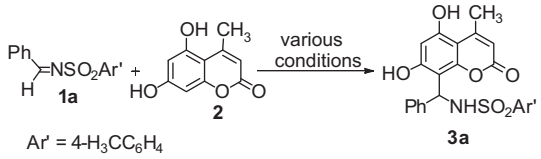
Table 1
Optimization of the conditions for the model reaction



Entry	Catalyst (mol %)	Solvent/temp (°C)	Time (h)	Yield[a] (%)
1	None	None/50	12	0
2	None	None/80–100	12	0
3	None	MeOH/80	12	0
4	NaOH (5)	MeOH/80	6	40
5	NaOH (10)	MeOH/80	6	45
6	NaOH (20)	MeOH/80	5.5	48
7	NaOH (30)	MeOH/80	5	63
8	NaOH (40)	MeOH/80	3.5	80
9	NaOH (40)	H_2O/80	12	45
10	NaOH (40)	$CHCl_3$/70	7	52
11	$ZrOCl_2{\cdot}8H_2O$ (10)	MeOH/80	12	10
12	$Y(NO_3)_3{\cdot}6H_2O$ (10)	MeOH/80	12	15

[a] Isolated yield.

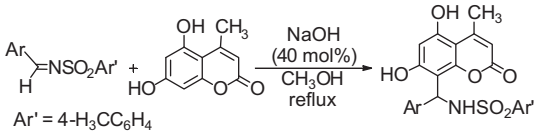
took place in the presence of NaOH (40 mol %) in refluxing methanol (Table 1).

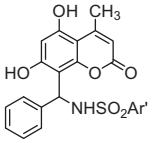
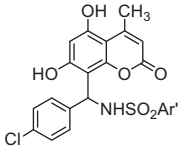
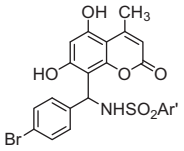
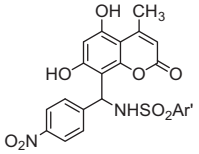
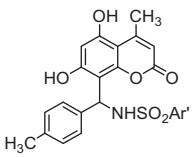
To test the generality of this procedure, the optimized reaction conditions (Table 1, entry 8) were employed with different substrates (Table 2).[24,25] It was found that both electron rich and electron poor *N*-sulfonyl aldimines reacted well, in this, process to afford the corresponding products in good to excellent yields. Data obtained from elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry confirmed the structures of the products.

A plausible mechanism for the formation of product **3** is outlined in Scheme 2. It is reasonable to assume that C-8 of coumarin **2**, in the presence of NaOH, attacks the *N*-sulfonyl aldimine **1** to give intermediate **4**, which rearranges into product **3**. As can be seen, these reactions are regioselective and only C-8 of coumarin **2** attacks the imine **1**. Although the hydroxyl groups at the C-5 and C-7 positions are expected to direct attack by positions C-8 and C-6 of the coumarin, because of the existing steric effect at C-6, position C-8 is more active. This character is similar to that observed in resorcinol and β-naphthol.

In conclusion, a new method has been developed for the synthesis of novel sulfonamide-substituted coumarins as potentially beneficial heterocyclic compounds with possible biological activity. These new compounds were synthesized from the reaction of *N*-sulfonyl aldimines and 5,7-dihydroxy-4-methyl coumarin. The advantages of this method are the simple experimental procedure,

Table 2
Synthesis of sulfonamide-substituted coumarins **3**



Entry	Ar	Product[a]	Time (h)	Yield[b] (%)	Mp (°C)
3a	C_6H_5		3.5	80	260–261
3b	4-Cl-C_6H_4		3	85	210–211
3c	4-Br-C_6H_4		3.5	77	268–269
3d	4-O_2N-C_6H_4		2.5	83	220–221
3e	4-H_3C-C_6H_4		5	70	255–256

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