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ARTICLE

Novel synthesis of coumarin-containing secondary benzamide derivatives using tungstate sulfuric acid

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An efficient synthesis of a novel class of coumarin-containing secondary benzamide derivatives has been developed via a one-pot condensation of 5,7-dihydroxy coumarins, aryl aldehydes and benzamide using tungstate sulfuric acid. Due to the using a reusable heterogeneous catalyst and solvent-free conditions, this procedure has been established based on green chemistry principles.

Introduction

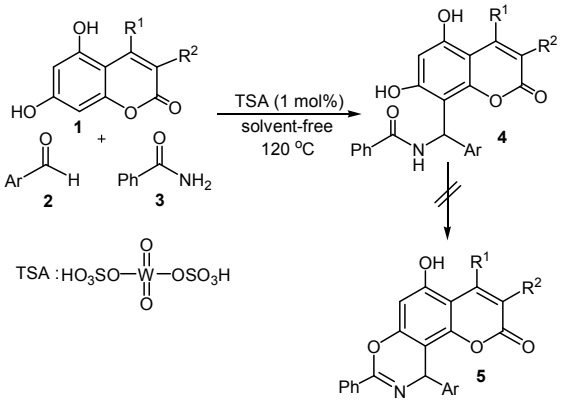
Coumarins as a main class of natural and synthetic products, display a variety of pharmacological and biological activities.[1-3] Also, there is a growing interest to coumarins and its derivatives due to their anti-HIV,[4] anti-oxidant,[5] anti-fungal,[6] antihelmintic[7], and antibacterial[8] properties. Coumarin derivatives are used in food and cosmetic industries as additives.[9,10] They have also found applications as insecticides, optical bright, fluorescent and laser dyes.[11-13] These high profile applications have promoted extensive studies for the synthesis of coumarin derivatives.[14-16]

Nowadays, the use of heterogeneous solid acid catalysts has attracted significant attention. These catalysts have some advantages such as ease of product work-up, recyclability, strong safety and tolerance for a wide range of temperature and pressure.[17-21] Therefore, there is a tendency to replace the classic acid homogeneous catalysts by heterogeneous solid acid catalysts. Tungstate sulfuric acid (TSA) as a reusable alternative to sulfuric acid was synthesized by the reaction of anhydrous sodium tungstate with chlorosulfonic acid. This safe, inexpensive, and environmentally benign solid acid has been applied as an efficient catalyst in a variety of organic transformations.[22,23]

Multi-component reaction (MCRs), as one-pot reactions in which at least three functional groups join through covalent bonds, offer significant advantages over conventional linear-type syntheses. These reactions represent a very useful tool for the synthesis of complex molecules with potential biological properties because of their effective atom economy, convergent nature, time saving, and straightforward experimental procedures.[24,25]

In a continuation of our investigations into the synthesis of novel substituted coumarins with biological activity,[26-29] and due to several advantages of heterogeneous catalysts, here we report a new approach for the synthesis of coumarin-containing secondary benzamide derivatives using TSA as a superior solid acid catalyst.

According to our designed synthetic strategy, initially, 5,7-dihydroxy coumarins **1** were prepared from the $ZrOCl_2.SiO_2$-catalyzed condensation of phloroglucinol and 1,3-dicarbonyl compounds.[30] Then, we planned to functionalize the prepared coumarins **1** to synthesize a new series of these important heterocycles. For this purpose, 5,7-dihydroxy coumarins **1** were reacted with aryl aldehydes **2** and benzamide **3** in the presence of tungstate sulfuric acid to produce coumarins **4** (Scheme 1). We originally thought that the products **5** would be formed via an intramolecular cyclization of compound **4**. However, after characterization by IR and NMR spectroscopy, we found that only compound **4** was actually formed and no trace was found of the possible product **5**.



Scheme 1 TSA-catalyzed synthesis of coumarin-containing secondary benzamides **4**

Experimental

Methods and materials

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X-Ray Diffraction (XRD) pattern was obtained by Philips X Pert Pro X diffractometer operated with a Ni-filtered Cu Kα radiation source. X-Ray Fluorescence (XRF) spectroscopy was recorded by X-Ray Fluorescence Analyzer, Bruker, S_4 PIONEER. Chemicals were purchased from Aldrich and Merck chemical companies and freshly used without purification (>99% purity). IR spectra were recorded on FT-IR JASCO-680 using KBr disks. The NMR spectra were recorded on a Brucker instrument 400 MHz ultra-shield model as DMSO solutions. The varioEl CHNS Isfahan Industrial University was used for elemental analysis.

General procedure for the preparation of tungstate sulfuric acid (TSA)

Anhydrous sodium tungstate (2 mmol, 0.5876 g) was added to dry *n*-hexane (25 mL) in a 100 mL round bottom flask, equipped with ice bath and overhead stirrer. Chlorosulfonic acid (4 mmol, 0.266 mL) was then added dropwise to the flask during 30 min and stirred for 1.5 h. Afterwards the reaction mixture was gradually poured into 25 mL of chilled distilled water with agitation. TSA was separated as a yellowish solid by filtration, washed with distilled water five times until the filtrate showed negative test for chloride ions, and dried at 120 °C for 5 h. The yield of obtained yellowish catalyst was obtained 98% that it was decomposed at 285 °C.[22]

General procedure for the synthesis of 4

TSA (1 mol%) was added to a mixture of 5,7-dihydroxy coumarin (1 mmol), aryl aldehyde (1 mmol) and benzamide (1 mmol). The reaction was heated at 120 °C for the appropriate time (Table 3). After completion of reaction, the obtained gummy mixture was diluted with chloroform (10 mL) and the catalyst was separated by filtration. Further purification was achieved by recrystallized from ethanol.

Spectral data

Compound 4a. IR (KBr) ν_{max} = 3423, 3312, 1697, 1647 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.50 (s, 3H), 5.91 (s, 1H), 6.45 (s, 1H), 6.91 (d, 1H, *J* = 8.52 Hz), 7.18-7.32 (m, 5H), 7.48-7.59 (m, 3H), 7.86 (d, 2H, *J* = 7.92 Hz), 8.60 (d, 1H, *J* = 8.6 Hz), 10.63 (s, 1H), 10.94 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.66, 47.19, 99.12, 102.31, 106.21, 108.91, 126.48, 127.01, 128.10, 128.53, 131.47, 134.21, 142.00, 153.68, 155.25, 156.72, 156.92, 158.66, 159.48, 165.37 ppm; . Anal. Calcd. for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.75; H, 4.81; N, 3.55.

Compound 4b. IR (KBr) ν_{max} = 3423, 3131, 1683, 1643 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.37 (s, 3H), 5.82 (s, 1H), 6.38 (d, 1H, *J* = 2.4 Hz), 6.86 (s, 1H), 7.22-7.54 (m, 7H), 7.88 (s, 2H), 8.69 (s, 1H), 10.56 (d, 1H, *J* = 2.4 Hz), 10.64 (d, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.17, 46.92, 99.31, 102.6, 104.9, 109.2, 126.6, 128.0, 128.6, 129.5, 130.3, 131.7, 132.7, 134.6, 139.2, 155.1, 155.5, 157.5, 159.9, 159.9, 165.9; . Anal. Calcd. for $C_{24}H_{18}ClNO_5$: C, 66.14; H, 4.16; N, 3.21. Found: C, 66.19; H, 4.12; N, 3.23.

Compound 4c. IR (KBr) ν_{max} = 3421, 3339, 1690, 1644 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.45 (s, 3H), 5.8 (s, 1H), 6.39 (s, 1H), 6.8 (s, 1H), 7.82 (s, 2H), 8.6 (s, 1H), 7.06-7.51 (m, 7H), 10.7 (s, 1H), 11.0 (s, 1H); Anal. Calcd. for $C_{24}H_{18}FNO_5$: C, 68.73; H, 4.33; N, 3.34. Found: C, 68.79; H, 4.40; N, 3.30.

Compound 4h. IR (KBr) ν_{max} = 3428, 3340, 1688, 1646 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.95-2.02 (m, 2H), 2.50 (t, 2H, *J* = 5.2 Hz), 2.61 (t, 2H, *J* = 8.8 Hz), 6.44 (s, 1H), 6.89 (d, 1H, *J* = 7.6 Hz), 7.00-7.13 (m, 3H), 7.29-7.35 (m, 1H), 7.47-7.58 (m, 3H), 7.87-7.89 (m, 2H), 8.67 (d, 1H, *J* = 8.4 Hz), 10.57 (s, 1H), 10.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.27, 28.85, 35.77, 46.96, 98.43, 101.62, 105.44, 112.60, 112.82, 113.14, 113.35, 120.34, 122.13, 127.14, 128.49, 129.99, 130.08, 131.55, 133.94, 133.98, 145.15, 145.21, 163.29, 165.68; . Anal. Calcd. for $C_{26}H_{20}FNO_5$: C, 70.11; H, 4.53; N, 3.14. Found: C, 70.08; H, 4.50; N, 3.16.

Results and discussion

TSA was prepared via the previously reported procedureas described in the Experimental section.[22] TSA was characterized by X-ray fluorescence (XRF), X-ray diffraction (XRD), FT-IR spectra, and titration with NaOH (0.1 N). Fig. 1a shows the X-Ray Diffraction Analysis (XRD) patterns of tungstate sulfuric acid (TSA). The XRD confirms the existing of WO_3 in the structure of TSA. It was reported that high degree of mixing of W–S in chlorosulfonic acid often led to the absence of X-Ray Diffraction Analysis (XRD) pattern for anhydrous sodium tungstate. The broad peak around 25.7° (2θ) (θ is the Bragg's angle) from the smaller inset could be attributed to the linking of WO_3 into the chlorosulfonic acid.[31]

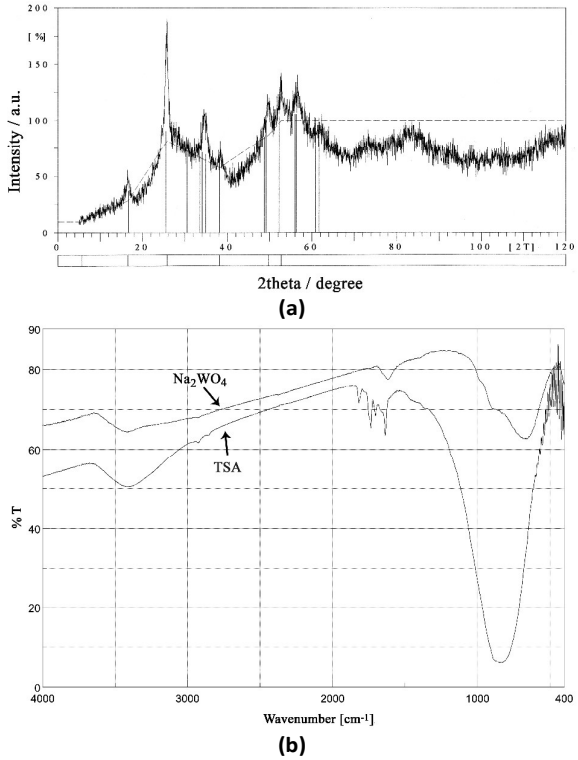


Fig. 1. (a) The powder X-Ray Diffraction pattern of the TSA; (b) FT-IR spectra of anhydrous sodium tungstate and TSA

The FT-IR spectra of anhydrous sodium tungstate and tungstate sulfuric acid (TSA) are shown in Fig. 1b. The spectrum of tungstate sulfuric acid shows the characteristic bonds of anhydrous sodium tungstate and chlorosulfonic acid. The wave numbers in 3406, 1820, 1725, 1702, 1620, 1290, 1060, 1005 and 860 cm^{-1} in catalyst spectra reveal both bonds in anhydrous sodium tungstate and $–OSO_3H$ group. Hence titration of catalyst with NaOH (0.1 N) was done. Firstly, 1 mmol of catalyst dissolved in 100 mL of water. Therefore, in the presence of phenolphthalein as an indicator with NaOH (0.1 N) titrated. At the endpoint of titration 4 mmol of titrant was consumed. The result of catalyst titration is shown four acidic valences, because of hydrolysis in aqueous solvent. The XRF data of tungstate sulfuric acid (TSA) indicates the presence of WO_4 and SO_3 in this catalyst (Table 1).

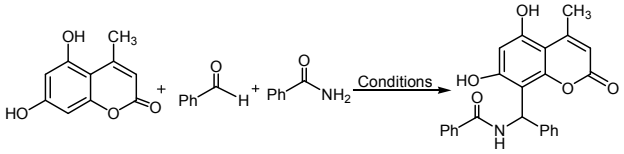
Table 1 XRF data of TSA

Compound	Concentration (%W/W)
WO_4	19.49
SO_3	0.317
Na_2O	0.190
Cl	0.056
CuO	0.023
Fe_2O_3	0.015
CaO	0.014
LOI*	79.82
Total	99.93

*Loss on Ignition

As part of an ongoing research program aiming to find novel methods within organic chemistry, after synthesis and characterization of TSA, we decided to use this catalyst TSA for the synthesis of some coumarin derivatives via the three-component reaction of 5,7-dihydroxy coumarins, aryl aldehydes and benzamide under solvent-free conditions (Scheme 1). A solvent-free or solid state reaction obviously reduce pollution, and bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour.[32,33] To optimize the conditions, a reaction between 5,7-dihydroxy-4-methylcoumarin, benzaldehyde and benzamide was chosen as a model reaction. The model reaction was screened under various conditions. After several experiments, we found that the desired reaction took place efficiently using 1 mol% of tungstate sulfuric acid (TSA) at 120 °C under solvent-free conditions (Table 2).

Table 2 Screening for the model reaction

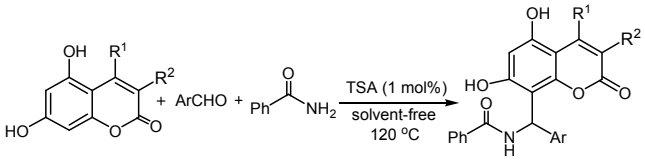


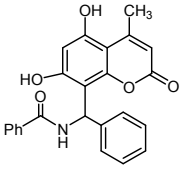
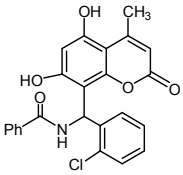
Entry	Catalyst (mol%)	Solvent/Temp (°C)	Time (h)	Yield[a] (%)
1	None	None/25	7	-
2	None	None/80	7	8
3	None	MeOH/80	7	5
4	None	H_2O/100	7	5
5	$ZnCl_2$ (5)	None/80	5	30
6	H_2SO_4 (5)	None/80	5	40
7	$ZrOCl_2.8H_2O$ (5)	None/80	5	45
8	$MgBr_2$ (5)	None/80	5	35
9	TSA (5)	None/80	4.5	50
10	TSA (5)	None/100	4.5	63
11	TSA (5)	None/120	4.5	75
12	TSA (10)	None/120	5	75
13	TSA (3)	None/120	4	80
14	TSA (1)	None/120	3.5	80
15	TSA (1)	MeOH/80	6	55
16	TSA (1)	H_2O/100	8	45
17	TSA (1)	CH_3CN/80	7	50

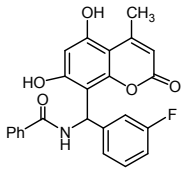
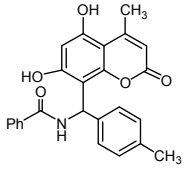
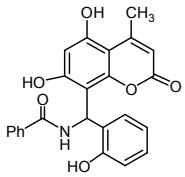
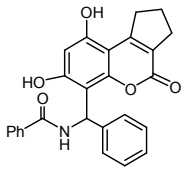
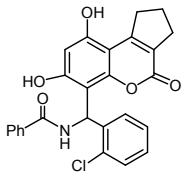
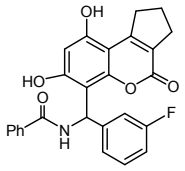
[a] Isolated yields.

To synthesize different target compounds, various substrates were treated under optimized reaction conditions (Table 3). In most cases, the reactions proceeded cleanly and the desired coumarin-containing secondary benzamide derivatives were obtained in good to excellent yields. The data obtained from elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy confirmed the structures of the products.

Table 3 TSA-catalyzed synthesis of coumarin-containing secondary benzamides **4a-h**

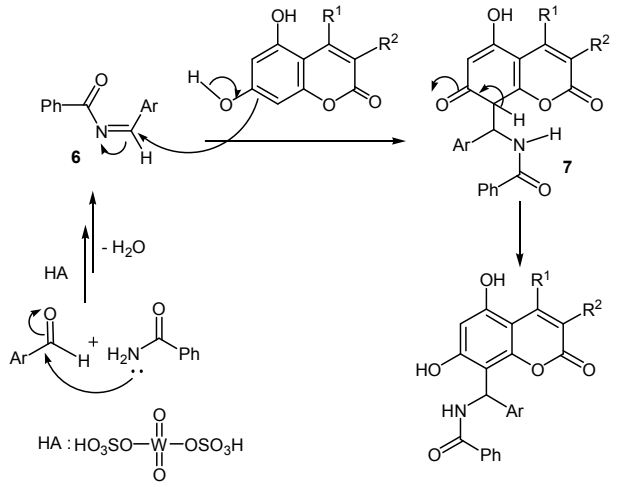


Entry	Product	Time (h)	Yield[a] (%)	Mp (°C)
4a		3.5	80	260-261
4b		3	85	210-211

4c		3.5	77	268-269
4d		5	70	255-256
4e		5	65	297-298
4f		3.5	85	270-271
4g		3	87	230-231
4h		4	60	226-227

[a] Isolated yields.

The assumed mechanism of formation of products **4** is shown in Scheme 2. According to the proposed mechanism, adduct **6** formed by the condensation of aryl aldehyde and benzamide in the presence of TSA as an efficient proton source. It is logical that C-8 of coumarin attacks to **6** and gives intermediate **7**. Finally, by a tautomerization desired product can be created (Scheme 2).



Scheme 2 Suggested mechanism for the synthesis of compound **4**

The ecological and economic profile is further improved if the catalyst is recyclable. Therefore, the recovery and reusability of TSA was investigated in this process. TSA was successfully regenerated from the model reaction by washing with EtOH and drying at 100 °C. Using the recycled catalyst for four consecutive times in the model reaction gave the product with a gradual decreasing of reaction yield (Fig. 2).

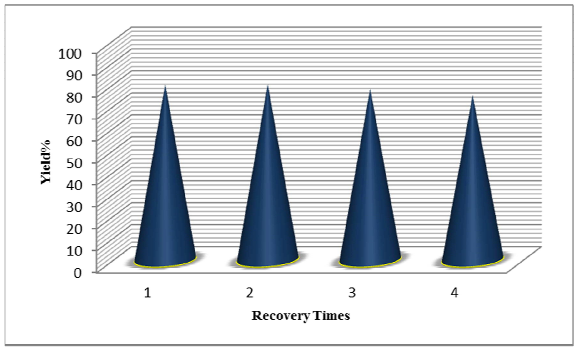


Fig. 2 Reusability study of TSA in the synthesis of **4a** at 120 °C under solvent-free conditions

Conclusions

In conclusion, a new strategy has been developed for the convenient synthesis of novel coumarin-containing secondary benzamide derivatives. These products were synthesized from the three-component reaction of 5,7-dihydroxy coumarins, aryl aldehydes and benzamide in the presence of catalytic amount of tungstate sulfuric acid. The use of tungstate sulfuric acid as a reusable heterogeneous catalyst makes this procedure mild, convenient and environmentally benign. The benefits of this method are simplicity of procedure, use of safe and recyclable catalyst, high yields and short reaction time.

Acknowledgements

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Table of Content (TOC)

Novel one-pot synthesis of coumarin-containing secondary benzamide derivatives is described using tungstate sulfuric acid as a reusable heterogeneous catalyst