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# A solvent-free synthesis of coumarins using a Wells–Dawson heteropolyacid as catalyst

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**Abstract**—Substituted coumarins are synthesized from phenols and β-ketoesters by the Pechmann reaction, using a Wells–Dawson heteropolyacid ($H_6P_2W_{18}O_{62}\cdot 24H_2O$) as catalyst by a solvent-free procedure. This one requires low reaction times, 130 °C temperature and as little as 1 mol% of Wells–Dawson acid, obtaining good to excellent yields of coumarins. The catalyst showed to be reusable with no differences in the yields. The results are compared with those of the reactions performed in toluene solution. The presented synthetic procedure is a convenient, clean and fast alternative for synthesizing 4-substituted coumarins (17 examples).


## 1. Introduction

Coumarins and their derivatives are widely applied. They are mainly used as active components in the formulation of pesticides and additives in manufacture of pharmaceuticals, foods and cosmetics.[1] Coumarins have also been used as optical brightening agents, laser dyes and fluorescent markers for derivatize and further analyze diverse compounds, for example, alcohols, carboxylic acids[2] and type A trichothecenes.[3]

Coumarins have varied bioactivities, for example, inhibitory of platelet aggregation,[4] antibacterial,[5] anticancer,[6] inhibitory of steroid 5α-reductase[7] and inhibitory of HIV-1 protease.[8] Their properties turn coumarins in very interesting targets to organic chemists, and several strategies for their synthesis were already developed. Mention must be made of the Pechmann reaction, the Perkin reaction and the Knoevenagel condensation. However, all the reported methods have disadvantages (severe reaction conditions, low yield of products being hard to purify) turning the research on novel and efficient procedures for the synthesis of coumarins in a relevant subject.

Pechmann reaction is the most used method for preparing 4-substituted coumarins since it proceeds from very simple starting materials, phenols and β-ketoesters or α,β-unsaturated carboxylic acids.[9] The reaction involves acidic catalysis, and good yields of coumarins substituted in either or in both rings, can often be obtained. However, rough quantities of mineral acid are usually required in the classical preparations, leading to increase the environmental pollution. For example, a well-established textbook of practical organic chemistry specifies the use of 1.1 L of concentrated $H_2SO_4$ for preparing 1 mol of 4-methylumbelliferone by the Pechmann reaction.[10] Other classic procedures involve, for example, allowing to stand the reaction mixtures overnight. Or even for a number of days, or heating the reaction

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mixtures above 150 °C. Formation of undesired side-products alongside coumarins have been observed in these cases.[11]

In the previous years, a number of procedures were reported for synthesizing coumarins by sustainable catalytic methods, for example, using Nafion/silica,[11] Montmorillonite and other clays,[12] zeolites,[13] solid acid catalysts[14] and cation exchange resins (Dowex 50:2–200, Amberlyst-14).[15] Besides, $InCl_3$,[16] $W/ZrO_2$,[17] supported polyaniline acid catalyst[18] and calcined Mg–Al hydrotalcite (solid base catalyst)[19] have been employed. Reactions were also carried out in a Lewis ionic liquid[20] and with the aid of microwave irradiation, for example, over graphite–Montmorillonite K10.[21] However, to the best of our knowledge, no report has been made about the use of heteropolyacids as catalysts for synthesizing coumarins.

Heteropolyacids are useful solid catalysts because of their superacidic properties.[22] As a part of a research project to develop environmentally friendly organic reactions, we have recently applied the Wells–Dawson (WD) heteropolyacid catalyst ($H_6P_2W_{18}O_{62}{\cdot}24H_2O$) to different reactions. Among them, protection of aldehydes as acylals[23] and acetylation[24] could be mentioned.

In this letter we report the catalytic activity of a WD heteropolyacid in a sustainable, simple preparation of substituted coumarins. WD acid was tested as a bulk (non-supported) catalyst. The reaction was studied starting on substituted phenols (**1**) and ethyl acetoacetates (**2**), their structures and the obtained results are showed in Table 1. Temperature, time, concentration of the solutions and molar ratio of the WD acid to substrates were checked to optimize the reaction, using resorcinol as the substrate. The experiments were driven until the phenol was consumed, or until no changes in the composition of the reaction mixture were observed, in both the toluene solution and excluding the solvent.

When 1% (mmol) WD acid was added, the higher yield of 4-methylumbelliferone (**3a**) was attained at 270 min reaction in refluxing toluene, or at 40 min by heating to 130 °C in solventless conditions. Higher amounts of WD acid did not improve the result to any extent; shorter and longer times gave lower yields. Besides, using a 1:5 molar ratio of the reagents (**1**:**2**) and keeping unchanged other reaction conditions, yields were only 1–3% higher than the ones recorded in Table 1.

Recycling of the catalyst (performed in entries a and j, Table 1) was checked in two consecutive batches after the first use; the catalyst showed almost constant activity. Substituted phenols (**1d**–**f**), substituted resorcinols (**1a**,**b**,**g**), hydroquinone and α-naphthol gave good to excellent yields of the corresponding 4-methylcoumarins **3**. However, when pyrogallol was subjected to the reaction in the air and diffuse light as in the other examples, moderate yields were obtained, although working in nitrogen and protecting from the light cause that the yield increases by 12%. On the other hand, the reaction of **1a** with methyl acetoacetate in toluene gives in 3 h similar yield of **3a** to that obtained in the reaction with ethyl acetoacetate. But when no solvent is used, both the reaction time and the yield stay almost in the values obtained with ethyl acetoacetate.

Regarding the experiments involving ethyl α-methylacetoacetate, most of them were performed in only solvent-free conditions in view of the results obtained in the preparation of **3a**–**h**. Yields of 3,4-dimethylcoumarins from resorcinols (**1j**,**k**,**p**) or activated phenols (**1o**,**q**) were similar to that obtained from unsubstituted ethyl acetoacetate (see Table 1).

The experiments carried out in refluxing toluene involve stirring of the starting materials (in 1:1 molar ratio) in the presence of 1% of the catalyst, by the indicated time (see Table 1). The nature of the substituent in the starting phenol seems to have relevant effect on the yield (see e.g., entries a and d). The reactions performed on not very activated phenols led to poor yields of coumarins (**3d** and **3e**); methyl ether **1f** unexpectedly gave low yield of **3f**.

The experiments performed in solvent-free conditions by heating the reaction mixtures at 130 °C showed a substantial reduction of the reaction times, usually giving higher yields (see Table 1); see entries d–f and i as outstanding examples. Reduction of times becomes important in relation to classical methods.

Other phenols were also checked for the reaction: resacetophenone and *m*-aminophenol failed to give the expected coumarins. As expected, beta-naphthol was less reactive than the alpha-isomer, yielding no more than 7% 4-methylbenz[*f*]coumarin in refluxing *o*-xylene.

All the yields were calculated from crystallized products. All the products were identified by comparison of analytical data (TLC, mp, IR, NMR) with those reported or with authentic samples prepared by the conventional method, using sulfuric acid as the catalyst. The preparation from an aqueous solution of α/β $K_6P_2W_{18}O_{62}{\cdot}10H_2O$ salt, which was treated with ether and concentrated (37%) HCl solution, and the molecular structure of the WD heteropolyacid catalyst ($H_6P_2W_{18}O_{62}{\cdot}24H_2O$) was described elsewhere.[25]

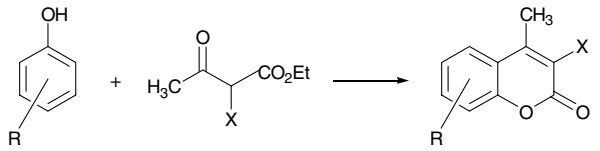
## 2. General procedures for the synthesis of coumarins[†]

### 2.1. Reaction in toluene solution

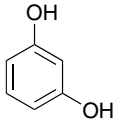
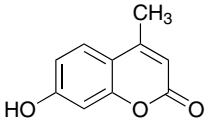
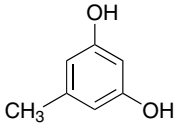
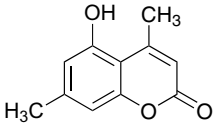
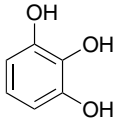
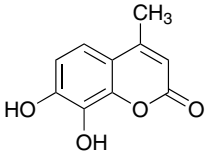
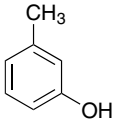
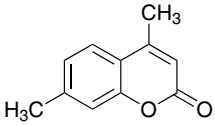
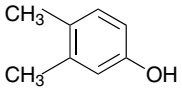
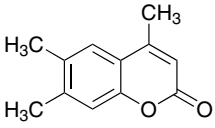
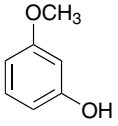
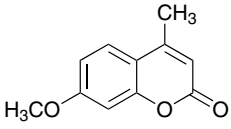
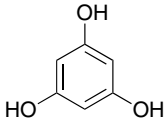
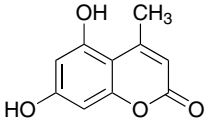
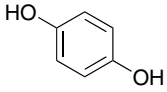
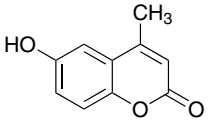
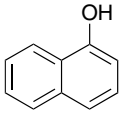
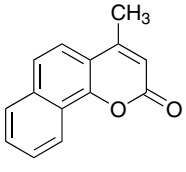
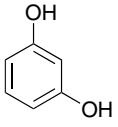
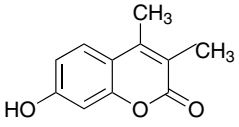
A mixture of phenol **1** (1 mmol) and ethyl acetoacetate/ethyl α-methylacetoacetate **2** (1 mmol) dissolved in 3 mL toluene, and bulk WD catalyst (1% mmol) (ca. 45 mg) was refluxed with stirring for the indicated time (see Table 1), and the mixture was filtered off while hot. The work-up was carried out essentially as stated below, yielding the pure 4-methylcoumarins **3**.

[†] Starting phenols and alkyl acetoacetates were commercial, and were used without purification.

**Table 1.** Synthesis of coumarins catalyzed with bulk Wells–Dawson heteropolyacid[a]

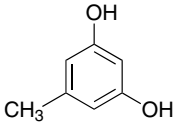
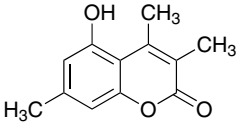
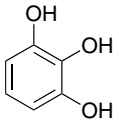
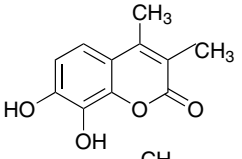
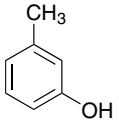
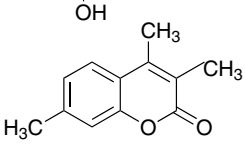
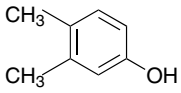
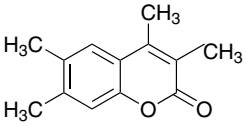
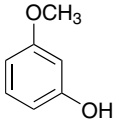
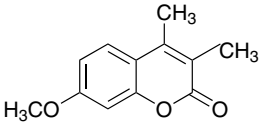
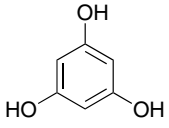
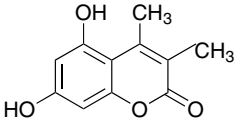
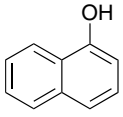
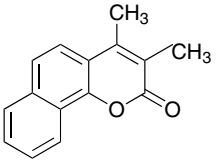



**1** **2** X: H, $CH_3$ **3**

| Entry | Phenol **1** | Coumarin **3** | Time, h (toluene) | % Yield of **3** (toluene) | Time, h (solvent free) | % Yield of **3** (solvent free) |
|---|---|---|---|---|---|---|
| a |  |  | 4.5<br>3 | 82<br>84[b] | 0.7<br>1 | 87<br>87[b] |
| b |  |  | 5 | 83 | 0.7 | 86 |
| c |  |  | 5 | 62 | 1<br>1 | 56<br>68[c] |
| d |  |  | 4.5<br>7 | 13<br>39 | 1.8 | 71 |
| e |  |  | 6.5 | 6 | 1.5 | 82 |
| f |  |  | 5 | 28 | 1 | 86 |
| g |  |  | 5<br>6.5 | 78<br>65 | 0.8 | 97 |
| h |  |  | 6.5 | 50 | 1.5 | 71 |
| i |  |  | 5 | 7 | 0.8 | 75 |
| j |  |  | 9 | 84 | 0.5 | 87 |

(*continued on next page*)

**Table 1** (*continued*)

| Entry | Phenol **1** | Coumarin **3** | Time, h (toluene) | % Yield of **3** (toluene) | Time, h (solvent free) | % Yield of **3** (solvent free) |
|---|---|---|---|---|---|---|
| k |  |  | 9 | 74 | 1.3 | 74 |
| l |  |  | | | 0.8 | 50 |
| m |  |  | | | 1 | 38 |
| n |  |  | | | 1 | 41 |
| o |  |  | | | 0.7 | 82 |
| p |  |  | | | 0.5 | 94 |
| q |  |  | | | 1.3 | 77 |

[a] Reactions were performed in the air and diffuse light. All the yields were calculated from crystallized products (see text).
[b] Results for the reaction of **1a** with methylacetoacetate.
[c] Results obtained protecting the reaction mixture from both air and light.

### 2.2. Solvent-free reaction

A mixture of phenol **1** (1 mmol) and ethyl acetoacetate/ethyl α-methylacetoacetate **2** (1 mmol) was stirred at 130 °C in the presence of bulk WD acid (1% mmol) (ca. 45 mg) for the indicated time (Table 1). The reaction mixture was extracted with hot toluene (3 × 5 mL). The solution was concentrated and the crude product was recrystallized from methanol yielding each of pure 4-methylcoumarins **3**.

## 3. Conclusions

The procedure described above provides a useful, clean and fast alternative for the preparation of 4-substituted coumarins. For nearly all the substrates, the reaction time is reduced drastically in contrast to classical methods. The time economy, along with the conservation of the catalyst activity and the high recovery of the acid catalyst, play for both low environmental impact and low cost. Other 'green' advantages of the procedure are the low formation of wastes, no requiring for the use of adsorbents; and principally, the replacement of corrosive mineral acids.

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