Use of Microwave Irradiation and Solid Acid Catalysts in an Enhanced and Environmentally Friendly Synthesis of Coumarin Derivatives

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Abstract: Condensation of phenol, 1,3-dihydroxybenzene and 1,3,5-trihydroxybenzene with propynoic and propenoic acids and ethyl acetoacetate using solid acid catalysts and microwave irradiation produces coumarins in excellent yields. The use of heterogeneous catalysts eliminates the production of acidic waste streams associated with conventional (Lewis) acid catalysts. This quick, efficient and environmentally friendly procedure permits the synthesis of substituted coumarins as well as coumarins without 4-alkyl substituents, which are the most difficult to synthesize.

Key words: phenols, α,β-unsaturated carboxylic acids, solid acid catalyst, microwave, coumarin derivatives.

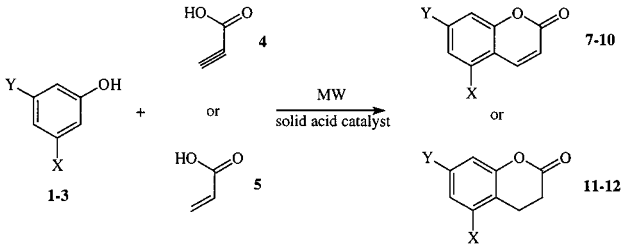
Coumarin and its derivatives find their main application as fragrances, pharmaceuticals and agrochemicals.[1,2] There have been many synthetic routes to coumarins, including the Pechmann,[3] Perkin,[4] Knoevenagel,[5] Reformatsky[6] and Wittig[7] reactions. However, the Pechmann reaction has been the most widely applied method for preparing coumarins since it proceeds from very simple starting materials and gives good yields of 4-substituted coumarins.[8] Various procedures have been developed, and in all of these methods mixtures of the reagents are allowed to stand overnight or for a number of days, depending on their reactivity, or were heated above 150 ºC. Usually these reactions occur by electrophilic aromatic substitutions and generally employ non-regenerable catalysts such as metal chlorides and mineral acids. However, these conventional catalysts have to be used in excess and they lead to increasing environmental pollution.

On the other hand, a modification of the Pechmann reaction involves the use of an α,β-unsaturated carboxylic acid and this permits the synthesis of coumarins substituted in either the pyrone, the benzene ring or both.[9] However, it is one of the few ways to prepare coumarins that do not bear a 4-alkyl substituent, compounds that are impossible to obtain by a normal Pechmann reaction approach. The reaction was shown to proceed through esterification followed by ring closure, both of which are proton-catalysed.[10]

Consequently, there is a need for efficient and heterogeneous catalytic methods for this reaction using inexpensive, easily handled and non-polluting catalysts. Replacement of mineral acids by solid acid catalysts[11] such as zeolites,[12] clays[13] and sulfonic acid resins[14] would result in simplified product recovery and a reduction in undesirable waste streams. However, such catalysts require high temperatures, longer reaction times and, in some cases, give lower yields.

Microwave irradiation in solvent-free conditions has well demonstrated its utility as a convenient energy source in many processes.[15] The rapid heating induced by the radiation leads to the formation of products under mild reaction conditions with short reactions times, thus avoiding decomposition or side-reactions and, in many cases, increasing the yields. Recently, the use of H_2SO_4 under microwave irradiation has played an important role in rate enhancement in the Pechmann reaction[16] and in the synthesis of some 3,4-dihydro-4-phenylcoumarins and 4-phenylcoumarins when montmorillonite K-10 clay is used as a catalyst.[17]

In this paper we report on the solid acid-catalysed reaction of phenols with carboxylic acids possessing either none, one or two additional functions that are able to alkylate the benzene nucleus. We examine the condensation of phenol (**1**), 1,3-dihydroxybenzene (**2**) and 1,3,5-trihydroxybenzene (**3**) with propynoic acid (**4**), propenoic acid (**5**) and ethyl acetoacetate (**6**) using solid acid catalysts and microwave irradiation as a quick, simple and environmentally friendly preparation of coumarin or substituted coumarins (Scheme 1). All the reactions were carried out at atmospheric pressure in a focused microwave reactor with measurement and control of power and temperature. Condensations were performed in the absence of solvent and reaction conditions were optimised to obtain the best yield.[18]



1: X=Y= H; **2**: X= H, Y= OH; **3**: X=Y= OH , for compounds **7-12** see Table 1.

Scheme 1

The results of a comparative study of the synthesis of coumarins by classical heating using solid acid catalysts, both with and without solvent, and microwave irradiation are shown in Table 1. From these results it is clear that the re-

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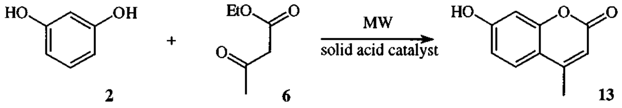
action time is reduced from several hours to only a few minutes on using microwave irradiation, indicating that microwaves play an important role in rate enhancement in these reactions. The products are also obtained in excellent yields with the exception of the reaction of phenol (entry 1), and this is due to the lower activation of the benzene ring. However, a similar reaction between phenol and propenoic acid catalysed by Zeolite H-Beta in toluene at 111 °C after 24 h gave the corresponding coumarin in only 6% yield.[10]

Open-chain products were not detected in any of the above cases.

On the other hand, on employing microwave irradiation in the reaction of 1,3-dihydroxybenzene and propynoic acid (entries 3–6) we selectively obtained coumarins **8** and **9** with an improvement in the yield in the synthesis of 7-hydroxycoumarin (**8**).

Moreover, under microwave conditions (entry 9) we were able to avoid the formation of 3,4,6,7-tetrahydrobenzo[1,2-b:5,4-b']-dipyran-2,8-dione, a compound that is formed by two consecutive reactions when a solvent is used in the reaction (entry 11).[9]

In order to assess the efficiency of our procedure, ethyl acetoacetate was allowed to react with 1,3-dihydroxybenzene (Pechmann reaction) as an approach to 4-substituted 7-hydroxycoumarins. In this case three steps, i.e. transesterification, hydroxyalkylation and dehydration, are involved. It is well know that both transesterification and hydroxyalkylation reactions can be proton-catalysed.[19] 7-Hydroxy-4-methylcoumarin, which is a useful starting material in the synthesis of an insecticide (Hymerocromone), is obtained in this reaction in *quasi* quantitative yield (97%) by employing Amberlyst-15 under microwave irradiation.



Scheme 2

Table 2: Synthesis of 7-hydroxy-4-methylcoumarin catalysed by solid acid catalysts using microwave irradiation or classical methods.

Entry	Catalyst	Reaction conditions[a] *Microwave irradiation*	*Thermal Heating*	Yield %
1	Amberlyst	5 min 60W 90 °C[b]		97
2	sulfuric acid [16]	2 min Unknown temp		72
3	Amberlyst [9]		4 h toluene reflux	81
4	Mont. K10[13]		4 h 150 °C	96

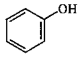
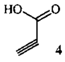
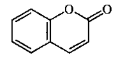
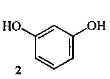
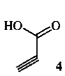
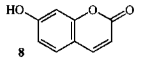
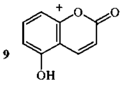
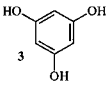
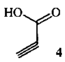
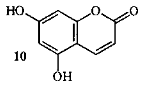
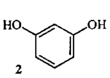
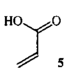
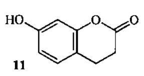
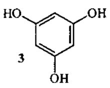
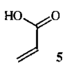
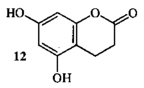
[a] molar ratio 1,3-dihydroxybenzene:ethyl acetoacetate (1:1)

[b] Temperature determined at the end of the reaction

As can be seen in Table 2, the reaction time was lower in comparison to classical conditions (entries 1 *vs.* 3 and 4) while yields were improved in relation to previously reported microwave conditions using mineral acids (entries 1 *vs.* 2). These facts demonstrate the utility of using solid acids. Moreover, under our reaction conditions the hydrolysis of the β-keto ester is avoided, whereas this reaction is produced to a significant extent (entry 3) when cation exchange resins are used.[8b]

In conclusion, the synthesis of a range of coumarin derivatives has been achieved using heterogeneous catalysts under microwave irradiation. Two types of reaction, i.e. the reaction of phenols with α,β-unsaturated carboxylic

Table1: Synthesis of coumarin derivatives without 4-substituents, catalysed by solid acid catalysts using microwave irradiation or classical methods.

Entry	Substrate	Reactant	Ratio[a]	Catalyst	Reaction conditions *Microwave irradiation*[b]	*Thermal Heating*	Product	Yield %
1	 1	 4	1:1.2	Dowex 50X2-200	15 min 180W 120 °C		 7	41
2			1:1.2	Dowex 50X2-200		15 min 120 °C		0
3	 2	 4	1:1.5	Dowex 50X2-200	10 min 30W 120 °C		 8 +  9	**8**: 69 + **9**: 31
4			1:1.5	Dowex 50X2-200	4 min 30W 84 °C			**8**: 56
5			1:1.5	Dowex 50X2-200		10 min 120 °C		**8**: <1
6			1:1	Amberlyst [14]		20 h. p-$ClC_6H_4CH_3$ 150 °C		**8**: 40
7	 3	 4	1:1.5	Dowex 50X2-200	11 min 30W 80 °C		 10	98
8			1:1.5	Dowex 50X2-200		11 min 80 °C		47
9	 2	 5	1:2	Mont. KSF	10 min 30W 95 °C		 11	72
10			1:2	Mont. KSF		10 min 95 °C		0
11			1:1	Amberlyst[14]		4 h toluene reflux		73[c]
12	 3	 5	1:2	Mont. KSF	10 min 180W 110 °C		 12	84
13			1:2	Mont. KSF		10 min 110°C		22

[a] molar ratio phenol derivative:carboxylic acids

[b] Temperature determined at the end of the reaction

[c] In addition to this product trace amounts of 3,4,6,7-tetrahydrobenzo[1,2-b:5,4-b']dipyran-2,8-dione were detected.

acids and the Pechmann reaction, are readily catalysed by cation-exchange resins such as Dowex or Amberlyst and Montmorillonite. By choosing the appropriate reactants a variety of coumarin derivatives can be synthesized.

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(18) Typical experimental procedure: A mixture of phenol (**1–3**) (10 mmol) and α,β-unsaturated carboxylic acid derivative (**4** or **5**) or ethyl acetoacetate (**6**) (15–20 mmol) supported on 1 g of solid acid support (by dissolving the mixture in 5 mL of diethyl ether followed by evaporation of the solvent) was exposed to microwave irradiation in a focused microwave reactor (Prolabo MX350) for the time and power indicated in Tables 1 and 2. For isolation of the compounds, the solid support was removed by extraction with ethanol (for reactants **4** and **6**) or acetonitrile (reactions of **5**). After solvent evaporation, the products were purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1). All compounds were characterised by analytical methods and ^{1}H- and ^{13}C NMR spectroscopy, using mono and two-dimensional techniques.

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