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Real-time Raman monitoring during coumarins synthesis via Pechmann condensation: A tool for controlling the preparation of pharmaceuticals

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ABSTRACT

Raman spectra provide unique fingerprints for real-time analysis and monitoring chemical reactions and processes. The model reaction studied was the synthesis of coumarins, in particular, 7-hydroxy-4-methylcoumarin, via Pechmann condensation between resorcinol and ethyl acetoacetate in acid media and solvent-free conditions. The corresponding Hymecromone, 7-hydroxy-4-methylcoumarin or 7-hydroxy-4-methyl-2H-1-benzopyran-2-one, finds applications in synthesis of pharmaceuticals and insecticides. Raman spectroscopy was used to monitor the progress of this reaction and results were compared with off-line chromatographic analyses.

1. Introduction

Coumarins and their derivatives are important compounds in the synthetic organic and medicinal chemistry and are used for the preparation of coumarino-pyrones, furocumarins, chromenes, and 2-acylresorcinols. These compounds find applications in synthesis of pharmaceuticals, fragrances, agrochemicals, and insecticides. Hymecromone, 7-hydroxy-4-methylcoumarin or 7-hydroxy-4-methyl-2H-1-benzopyran-2-one, is used commercially as laser dye, as biliary antispasmodic, and it is also the substrate material for the production of several insecticides. Pechmann reaction is an efficient and simple method to synthesize coumarins. In a classical way, the reaction consists of the condensation of phenols with β-ketoesters. This contribution reports the synthesis of coumarins, especially of 7-hydroxy-4-methylcoumarin (Hymecromone) (Scheme 1) via Pechmann condensation between resorcinol and ethyl acetoacetate in acid media [1–6].

Raman spectroscopy is highly efficient for *in situ* studies [7], which makes it particularly suited for process monitoring and real-time reaction control. The high information content of the Raman spectrum provides a unique fingerprint to identify and monitor chemical reactions and processes [8–10]; any liquid-phase reaction can be monitored, even in the presence of a solid catalyst. It offers a non-destructive, non-contact method of analysis that is suitable for both laboratory and industrial applications. The model reaction studied was the synthesis of coumarins under conventional thermal heating in dry media. Monitoring condensation reactions traditionally requires off-line analyses by chromatography; however, these are time-consuming and may not provide direct real-time analysis of reaction progress nor can they provide molecular insight into reaction mechanism and the possible formation/role of intermediates.

2. Experimental

The Pechmann reaction for the synthesis of coumarins was run in a batch reactor under thermal activation at 60 °C and under continuous stirring. Typically, 10 mmol of each reactant (resorcinol and ethyl acetoacetate) and 0.2 g of catalyst (HCl) were stirred at 60 °C for 6 h. In order to follow the evolution of the reaction; aliquots of 1 mL of the reaction mixture were sampled from the reaction mixture with a syringe and analyzed by gas chromatography (GC) (HP-5890 GC fitted to a capillary column), this procedure is described elsewhere [2].

The reaction was real-time monitored by Raman spectroscopy using a PerkinElmer Raman Station 400F fitted to a fiber optic probe with an immersion sleeve, using 100 mW laser power of 785 nm excitation and with a spectral resolution of 4 cm^{-1}; spectra consisted of 1 accumulation of 6 s acquisition. A comparison of the Raman bands intensity with off-line GC analyses allow for quantitative reaction monitoring and insight into the reaction mechanism.

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Scheme 1. Structure of 7-hydroxy-4-methylcoumarin (Hymecromone).

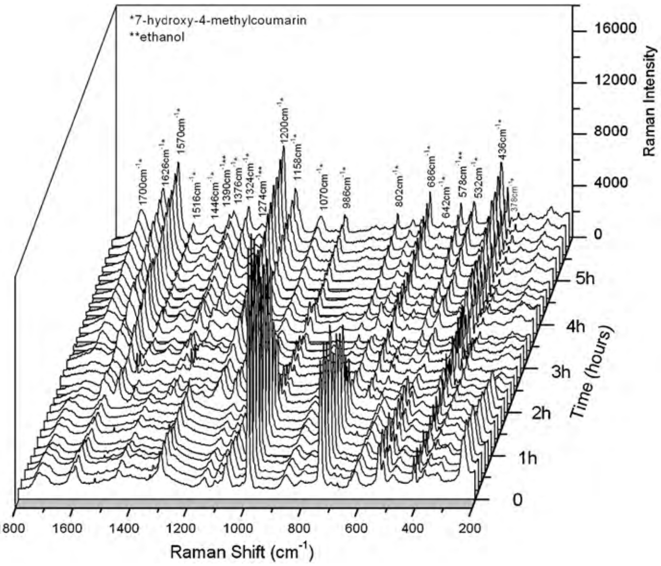


Fig. 1. Raman spectra of the Pechmann reaction between resorcinol and ethyl acetoacetate at 60 °C using HCl as catalyst for the synthesis of 7-hydroxy-4-methylcoumarin (Hymecromone).

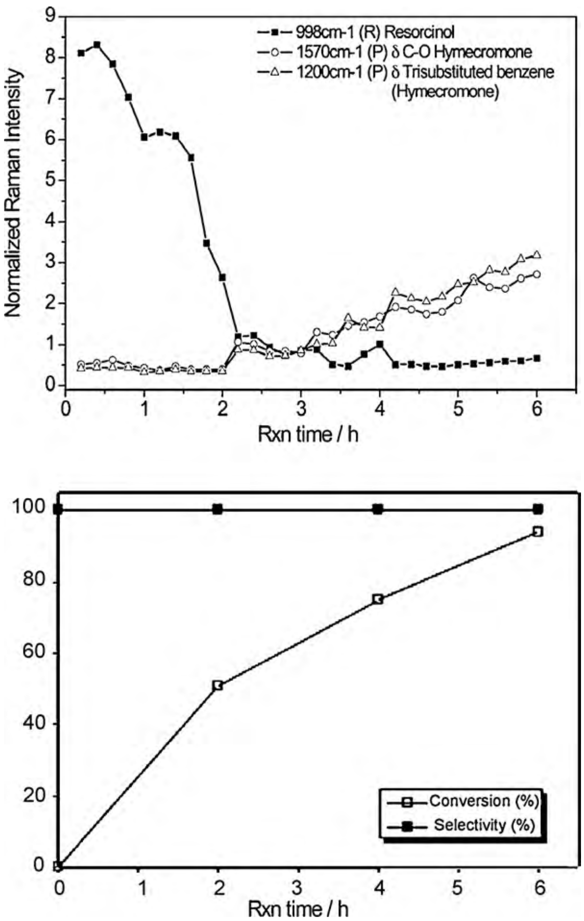
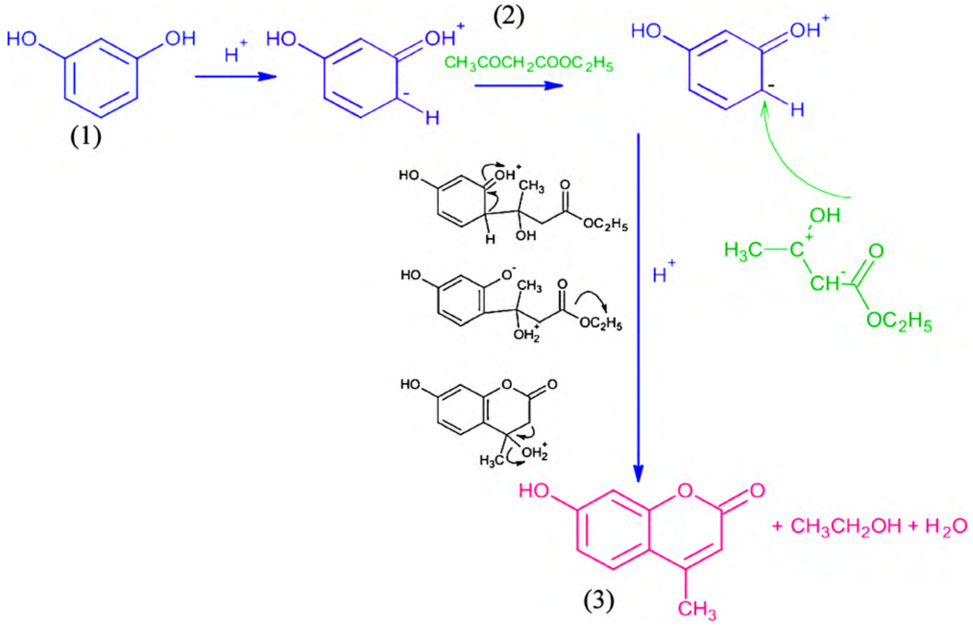


Fig. 2. Comparison of representative Raman bands intensity and gas chromatographic analyses of reaction progress. Top: reactant (R, resorcinol) Raman band at 998 cm^{-1} and product Raman bands (P, 7-hydroxy-4-methylcoumarin, Hymecromone) at 1200 and 1570 cm^{-1} (top) *vs.* reaction time. Bottom: resorcinol conversion and Hymecromone selectivity *vs.* reaction time.



Scheme 2. Mechanism of Pechmann reaction between resorcinol (1) and ethyl acetoacetate (2) for the synthesis of coumarins (3) in acid media under solvent-free conditions.

3. Results and discussion

Scheme 2 shows the mechanism for the reaction of resorcinol and ethyl acetoacetate in acid media. When resorcinol (1) reacts with the ester, ethyl acetoacetate (2), in acid media, three reactions, hydroxyalkylation, transesterification, and dehydration occur. Both reactants condense at two sites forming a heterocycle (3), which is a coumarin.

Fig. 1 illustrates representative Raman spectra acquired every 10 min during 6 h of reaction time. Resorcinol exhibits Raman vibrations characteristic of 1,3-disubstituted benzene (242, 524, 640, 744, 998, 1075, 1302, 1730 cm^{-1}). Ethyl acetoacetate exhibits Raman vibrations at 538, 862, 1112, 1156, 1632, 1734 cm^{-1} characteristic of C═O/C─O─C stretching modes. The Raman bands of these two compounds decrease with reaction time coordinate, reflecting the progressive conversion of reactants. 7-Hydroxy-4-methylcoumarin exhibits Raman bands characteristic of aromatic alcohols (986, 1070, 1158, 1200, 1324, 1516 and 1570 cm^{-1}) and of conjugated alkenes with aryl, and methyl alkenes (802, 1376, 1446 and 1626 cm^{-1}). The intensity of these Raman bands increases during reaction time. Raman spectra in Fig. 1 suggest the absence of reaction intermediates during Pechmann condensation between resorcinol and ethyl acetoacetate since no Raman bands of other species become apparent during reaction. In addition, no other reaction products are apparent to Raman spectroscopy, in line with chromatographic analyses that show 100% to the coumarin molecule. Representative bands are plotted *vs.* reaction time in Fig. 2, which illustrates the progress of the reaction. Raman intensity trends are in good agreement with GC analyses, which indicate total selectivity with a yield of 94% to coumarin. The sharp decrease of the Raman bands of resorcinol at 998 cm^{-1} should reflect the initial steps of the reaction when hydroxyalkylation and transesterification occur before dehydration. The progressive increase of the Raman bands of Hymecromone is consistent with the progressive formation of Hymecromone.

4. Conclusions

Pechmann reaction with an acid catalyst results in an efficient, mild and effective synthesis of coumarins with 100% selectivity being an alternative method for the clean production of Hymecromone and others coumarin derivatives, which are key intermediates in the production of insecticides. Raman monitoring during Pechmann condensation between resorcinol and ethyl acetoacetate at moderate reaction temperatures in dry media produce Hymecromone with 100% selectivity, based on gas chromatographic analyses. Real-time Raman spectra provide during thorough molecular information on the reaction progress and mechanism, evidencing the absence of intermediates. Raman bands intensity appear as a convenient way for a quantitative determination of reaction conversion. With the appropriate calibration, it may be used for real-time reaction monitoring, having the advantage of being non-invasive. In addition, Raman spectroscopy provides real-time analyses since spectra requires few seconds.

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