

Microwave initiated reactions: Pechmann coumarin synthesis, Biginelli reaction, and acylation

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Abstract—An energy-efficient protocol has been developed for solvent-free reactions that are mildly exothermic but not spontaneous. The exothermic reaction mixture—on several g-scale—is exposed for about 30 s to low power (about 200 W) microwaves and then the microwave oven is switched off. After this short burst of energy, the exothermic reaction gets initiated and proceeds on its own to completion. A number of coumarins were synthesized by the Pechmann reaction using this strategy.
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In 1883, Pechmann described an efficient synthesis of coumarins (**3**) that involved the condensation of phenols (**1**) with β -keto esters (**2**) (Scheme 1).^{1,2}

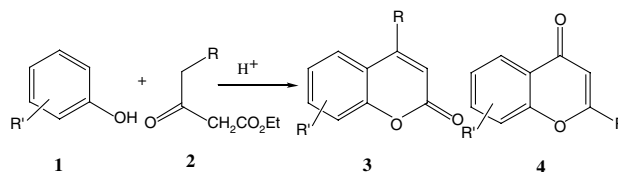
The Pechmann reaction is versatile: a wide variety of substituted phenols and β -keto esters can generate coumarins in good yield with substituents in the phenolic nucleus and/or in the heterocyclic ring. Various condensing agents have been used including metal chlorides and phosphorus oxychloride. Solvents such as alcohol, ether, and benzene have been favored. Under some conditions, chromones (**4**) may also be formed.

In an earlier publication, we described the ‘Grindstone Chemistry’ method for conducting exothermic reactions in the solvent-free mode.³ When this protocol was applied to the Pechmann synthesis on a multi-molar scale, the expected coumarins were obtained in a few minutes as pure products in high yield by solvent-free grinding. Since this reaction proved to be exothermic, we tested energy-saving procedures developed in our laboratory.

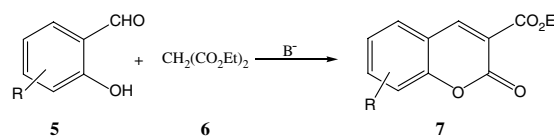
For a larger scale exothermic reaction, an efficient method that we⁴ have developed uses a ‘water-based biphasic’ reaction medium. This method consists of adding

the reactants for an exothermic reaction (and a catalyst, if required) to a large volume of water with efficient stirring. The exothermic reaction starts in a few minutes and proceeds to completion. The insoluble reaction product crystallizes out in a nearly pure form and in high yield. Thus, the condensation of salicylaldehydes (**5**) and malonic esters (**6**) by this protocol produces coumarins (**7**) in high yield (Scheme 2).

It was observed that the Pechmann reaction for coumarins (e.g., involving the interaction of resorcinol, ethyl



Scheme 1.

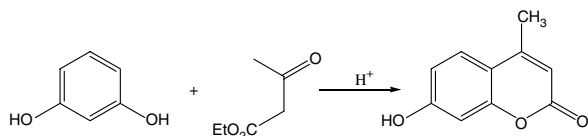


Scheme 2.

Keywords: Microwave chemistry; Coumarins; Energy-efficient reaction; Solvent-free reaction.

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acetoacetate, and *p*-toluenesulfonic acid) under the water-based biphasic reaction conditions failed to produce any coumarin (Scheme 3). A different procedure developed in our laboratory for exothermic reactions was then tested.



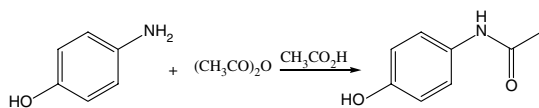
Scheme 3.

In the course of our recent studies on solvent-free reaction mixtures, it had been noticed that not all exothermic reactions are spontaneous; many of them require a short burst of energy for the initiation of the reaction. After such initiation, the exothermic reaction proceeds on its own to completion—without additional energy input.

We conducted a test: a solvent-free Pechmann reaction mixture was irradiated with microwaves of low power (200 W). The temperature of the reaction mixture started to rise. After 30 s of irradiation, the microwave oven was switched off. The reaction mixture continued to rise in temperature; the reaction was completed in less than 20 min (monitored by TLC). The target coumarin

Table 1. Synthesis of coumarins by our microwave procedure

	Phenols	β -Keto esters	Products	Yield (%)
1				94
2				81
3				96
4				92
5				86
6				90
7				82
8				80



Scheme 4.

was isolated in high yield. This new energy-saving procedure was found to be useful for the efficient preparation of several coumarins (Table 1).

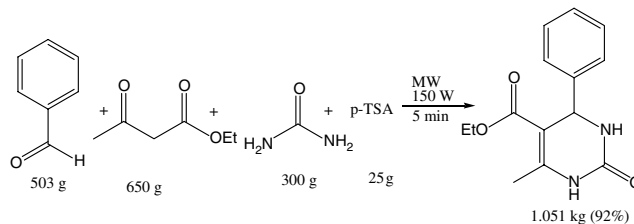
Various β -keto esters were used successfully for the Pechmann reaction (catalyzed by *p*-TSA) with resorcinol, pyrogallol and other phenols. A wide variety of coumarins were obtained by this method in about 20 min, under solvent-free, green reaction conditions.

The efficacy of our method was examined by conducting other synthetic reactions. For example, a mixture on several grams scale of *p*-aminophenol (4-hydroxyaniline), acetic anhydride and acetic acid at room temperature was placed in a domestic microwave oven (800 W) and the acetylation reaction was initiated by irradiating for 30 s at a 50% power level. After irradiation, the temperature of the mixture was 56 °C. The reaction mixture was then placed outside the oven. The temperature of the reaction mixture continued to rise and reached 121 °C in 2 min. For the next 3 min the temperature dropped slowly and then rose sharply to 150 °C and crystals appeared. After filtering, washing with cold water and drying, the crystalline product was found to be pure *p*-acetaminophenol (Tylenol) in 86% yield (Scheme 4).

This microwave protocol was then applied to the century old Biginelli reaction involving the interaction of an aldehyde, an acetoacetate, urea (or thiourea), and an acid catalyst (such as *p*-toluenesulfonic acid).^{4,5} The test was successful with this multi-component reaction mixture on a near kg scale with 92% yield of the desired product as shown in Scheme 5.

In summary, this microwave procedure is an energy-saving method for initiating exothermic reactions. Some chemical syntheses using this technique are suitable for teaching laboratories also.⁶

It is customary now to use a computerized, expensive microwave lab station that controls the temperature,



Scheme 5.

records it and can duplicate it for future repeat runs. Since only a very short burst of low level microwave energy is needed, *it is quite sufficient and convenient to use an inexpensive domestic microwave oven for the present work.*

Acknowledgements

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References and notes

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- Typical procedure for the preparation of coumarin by our microwave protocol: To a mixture of resorcinol (2.2 g, 20 mmol) and ethyl acetoacetate (2.6 g, 20 mmol) was added *p*-TSA (0.18 g, 1.0 mmol) in a 50 mL Erlenmeyer flask. This reaction mixture was placed in a microwave oven and irradiated for 30 s at 400 W power and the temp. of the reaction mixture rose to 85 °C. After removing from the microwave oven, the reaction mixture was allowed to cool down to room temp. (20 °C). Water was added to the mixture and the crystalline material that separated was collected by filtration to give 7-hydroxy-4-methylcoumarin. The crude crystals obtained were recrystallized from methanol, mp 186–187 °C; yield 94%.