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Microwave acceleration of the Pechmann reaction on graphite/montmorillonite K10: application to the preparation of 4-substituted 7-aminocoumarins

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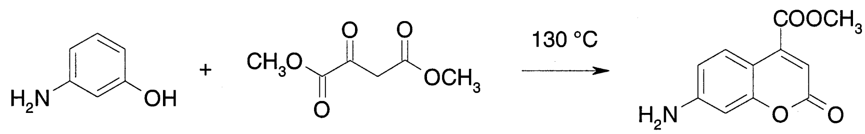
Abstract—Efficient synthesis of 7-aminocoumarins was performed via the Pechmann reaction by microwave irradiation of the reactants on solid support (graphite/montmorillonite K10). In this convenient new methodology, the strong thermal effect due to graphite/microwaves interaction is associated with the acidic catalyst role of the clay.

Coumarins are common in Nature and find their main applications as fragrances, pharmaceuticals and agrochemical.[1] In the course of our recent work on the preparation of new polyheterocyclic systems with potent pharmacological value,[2] we planned to prepare aminocoumarins which can be employed as intermediates in the synthesis of useful bioactive compounds.[3] Such molecules are usually synthesized by a Pechmann reaction, which involves condensation of phenols with β-ketonic esters in the presence of various reagents (e.g. H_2SO_4). In some methods, mixtures of substituted phenols, β-ketoesters and the acidic catalyst were allowed to stand overnight or for a number of days (depending on their reactivity) or were heated above 150°C, and undesired products such as chromones, in addition to coumarins, have also been reported. In the hope of developing convenient and reproducible methods for the preparation of the rare amino compounds, we transposed this Pechmann reaction to a focused microwave oven (open oven, monomode system S402 Prolabo)[4] especially designed for organic synthesis. There are few papers on the use of microwave activation of Pechmann reactions and all report reactions that started from resorcinols or activated alkoxyphenols;[5] however, none of them described the preparations of aminocoumarins. In this paper we report an original and environmentally friendly solvent-free procedure and study the opportunity to use solid supports and acid catalysts in such experiments.

Synthesis of aminocoumarin-4-carboxylic acid derivatives

Synthesis of the methylester of 7-aminocoumarin-4-carboxylic acid **1** usually consists of the heating of the starting *m*-aminophenol with dimethyloxalacetate, at 130°C for 2 h (Scheme 1).[6]

The amount of coumarins obtained in such conditions is variable and sometimes low (e.g. 36%, see Table 1),



Scheme 1.

Keywords: coumarins; Pechmann reaction; microwave irradiation.

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Table 1. Selected results on the preparation of the 7-aminocoumarin **1**[7,8a]

Experimental conditions[a]	Conventional heating[b]		Microwave irradiation	
	Reaction time (min)	Yield (%)	Reaction time (min)	Yield (%)
Neat (fusion)	120	36	85	39
Support: graphite	120	44	50	44
Support: graphite/K10 (2:1)[c,d,e]	66	64	30	66

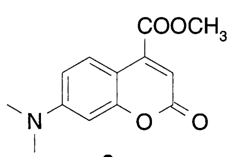
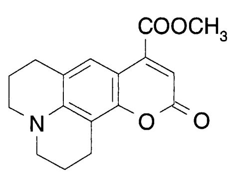
[a] Reactions performed at 130°C; lowest (110°C) or highest (150 and 170°C) temperatures involved incomplete or complex (degraded) reactions and poor yields of the attempted products.
[b] Oil bath.
[c] The ratio between the quantity of reactant and the graphite is very important; if it is too large or too small, degraded or incomplete reactions were observed.
[d] No modifications were observed when a preliminary activation (2 h at 180°C) of the clay was realized.
[e] No significant results were observed in the absence of graphite (montmorillonite K10+phenol+β-ketoester).

accompanied by complicated mixtures of carbonaceous compounds and colored impurities which are very difficult to eliminate, even by column chromatography and recrystallization. Transposition of this procedure to a focused microwave reactor (130°C, 60 W) led to a reduction of the reaction time (85 min) in a similar yield (39%). Because it is well known that the use of acid catalysts may play an important role in rate enhancement in Pechmann reaction,[3] a few drops of sulphuric acid were added to the starting mixture. Unfortunately, whatever conditions were used (thermal heating or microwave irradiation) no improvements of the reactions were observed, the yields became lower and a lot of by-products were also detected.

Graphite is one of the solids most efficiently heated by microwaves and is also known for its absorbing properties of organic molecules.[9] Inspired by a recent work on Friedel–Crafts acylation reactions with carbon graphite as support,[10] we showed that irradiation of a mixture of *m*-aminophenol and methyl oxalacetate (1 equiv.), adsorbed on graphite, led to the expected 7-aminocoumarin **1** in a yield of 44% and in a shorter time (50 min) than for the purely thermal procedures (see Table 1 and Scheme 1) (in similar experimental conditions with the same amount of starting materials and graphite, conventional heating needed 120 min to give the expected product in similar yield). Here again addition of a catalytic amount of sulphuric acid led to a very complex reaction.

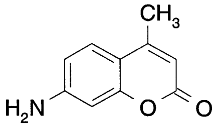
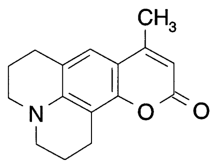
In order to avoid the use of mineral acids (e.g. H_2SO_4), we studied the opportunity to associate graphite to montmorillonite clay, which has been used as an efficient solid acidic catalyst for a variety of organic reactions.[11] Then, treatment of *m*-aminophenol with the tertiary β-ketonic ester was carried out on a mixture of graphite/montmorillonite K10 under microwave irradiation. Various parameters were studied and optimized (reaction time: 30 min, temperature: 130°C, and ratio of graphite/montmorillonite→2:1 w/w) and we also found that the optimum amount of solid support was 75% by weight of the global reactants (Table 1). An extension of this procedure to various aminophenols was per-

Table 2. Synthesis of 7-aminocoumarins derivatives **2** and **3**[7,8a]

Product[a]	Conventional heating		Microwave irradiation		Mp (°C)
	Reaction time (min)	Yield (%)	Reaction time (min)	Yield (%)	
 **2**	45	54	8	61	148–150
 **3**	56	68	8	75	156–158[b]

[a] Reactions performed at 130°C. Support: graphite/K10 (2:1).
[b] Mp lit.:[13] 156°C.

Table 3. Synthesis of 7-aminocoumarins derivatives **4** and **5**[7,8b]

Product[a]	Conventional heating		Microwave irradiation		Mp (°C)
	Reaction time (min)	Yield (%)	Reaction time (min)	Yield (%)	
 **4**	30	66	5	65	220–224[b]
 **5**	390	62	12	62	94–96

[a] Reactions performed at 130°C. Support: graphite/K10 (2:1).
[b] Mp lit.:[15] 220–224°C.

formed and results obtained (Table 2) are in accordance with data observed for the synthesis of coumarin **1**.[12]

Synthesis of 7-amino-4-methylcoumarins[7,8b] (Table 3)

In this case the starting β-ketonic ester (ethyl acetoacetate, $CH_3COCH_2COOC_2H_5$) is a liquid. Mixing aminophenols[14] and ethyl acetoacetate on graphite/K10 (2:1, w/w) led to a heterogeneous mixture and resulted in hazardous bumping in the reactor and incomplete reactions with a large amount of by-products (only 5% yield of attempted compound). The best alternative consisted of the microwave exposition of phenols and ethyl acetoacetate in the presence of concentrated sulphuric acid. Here again, the comparative study of this procedure by classical heating and microwave irradiation showed that reaction time was reduced from several hours to only a few minutes by using the latest technique. On this point, these experiments are showing the difficulties of associating liquid and solid phase in microwave reactions, but it confirms that, in favorable conditions, focused microwave irradiation is a very powerful technique for accelerating thermal organic reactions.

In conclusion, we performed the synthesis of rare aminocoumarins via the Pechmann reaction by exposition of the reactants to a microwave field, on original support (graphite/montmorillonite K10). In this efficient new methodology, the strong thermal effect due to graphite/microwaves interaction is associated with the acidic catalyst role of the clay.

In relation to our recent published results,[16] this work also demonstrated that working under focused microwave irradiation needs special attention: (a) the ratio between the quantity of the material and the support (or the solvent)[16] is very important; (b) for solid starting materials, the use of solid supports offer operational, economical and environmental benefits over conventional methods. In contrast, association of liquid/solid reactants on solid supports may involve uncontrolled reactions and are generally worse than comparative thermal reactions. In this case, simple fusion of the products or addition of an appropriate solvent may lead to more convenient mixtures or solutions for microwave applications.

Acknowledgements

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has quartz reactors, visual control, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC). The oven equipment can be completed by an external stirring system, a condenser and a dropping funnel allowing conditions close to those involved in classical methods; it is also possible to work under a dry atmosphere or in vacuo if necessary.

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8. (a) *Typical procedure for the synthesis of compounds* ***1–3****:* A mixture of the aminophenol (2 mmol), methyl oxalacetate (2 mmol) and graphite/montmorillonite K10 (2:1, w/w) (75 wt% to the phenol and β-ketoester) were placed in a quartz vial (250 ml) inside the oven and irradiated for 30 min. The irradiation was programmed to obtain a constant temperature (130°C) with a maximal power output of 90 W. After cooling, the mixture was filtered (methanol) and the crude purified by column chromatography (silica gel) with light petroleum–dichloromethane as the eluent; (b) *Typical procedure for the synthesis of compounds* ***4–5***: A mixture of aminophenols (2 mmol) and ethyl acetoacetate (2 mmol) was placed in a quartz vial (70 ml) and to it was added conc. H_2SO_4 (3 ml). The mixture was then subjected to microwave irradiation at 130°C for an optimized time (8 min) with a maximal power output of 90 W. After completion of the reaction (monitored by TLC), dichloromethane was added, the organic layer washed with water, dried over $MgSO_4$, and the crude product was purified as above.
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