

Montmorillonite KSF as an Inorganic, Water Stable, and Reusable Catalyst for the Knoevenagel Synthesis of Coumarin-3-carboxylic Acids

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Introduction

The increasing demands of environmental legislation have been prompting the chemical industry to minimize or, preferably, eliminate waste production in chemical manufacture. Environmentally benign processes are requested for primary prevention of pollution, and environmental factors will become the driving force behind new products and processes.¹

The use of heterogeneous catalysts, in particular zeolites and clays, has reached great development in different areas of organic synthesis due to their environmental compatibility combined with the good yields and selectivities that can be achieved.²

Coumarin (2H-1-benzopyran-2-one) and coumarin derivatives are natural compounds³ and are important chemicals in the perfume, cosmetic, and pharmaceutical industrial production.⁴

The Knoevenagel reaction,⁵ a century old reaction, is one of the most common synthetic methods to produce coumarins. The process consists of the condensation of salicylic aldehydes with malonic acid or esters giving the coumarin-3-carboxylic acids or esters that successively undergo decarboxylation. The reaction is catalyzed by weak bases⁵ or by suitable combinations of amines and carboxylic⁶ or Lewis⁷ acids under homogeneous conditions. A solid-phase synthesis has just been published.⁸

In recent years many efforts have been made to prepare olefinic compounds via Knoevenagel condensation under heterogeneous catalysis: in particular aluminum oxide,⁹ Xonotlite/*tert*-butoxide,¹⁰ cation-exchanged zeolites,¹¹ alkali-containing MCM-41,¹² and bentonitic clay¹³ were employed.

As part of our research program concerning the use of solid acids in fine chemicals preparation,¹⁴ we have investigated the Knoevenagel synthesis of coumarin derivatives under montmorillonitic clay catalysis.

Results and Discussion

To study this process, we have examined the model reaction of salicylaldehyde (**1a**) (10 mmol) with diethyl malonate (**2x**) (15 mmol) in the presence of 1 g of catalyst. We observed that montmorillonite KSF^{15a} and K10^{15b} promoted the process affording the expected heterocyclic product **3**, KSF being the more efficient promoter of the reaction (Table 1).

These results suggest that the clay behaves as a ditopic catalyst containing both acid and basic sites. The basic sites, ascribable to the negative charges dispersed over entire sheets of oxygen atoms,¹⁶ activate the Knoevenagel condensation. Further, the acid sites, which are mainly due to the polarized interlayer water molecules, promote the α -pyrone ring formation by intramolecular transesterification.¹⁷

To reduce the employment of ecologically suspected solvents, we have chosen to carry out the reactions in the absence of solvent or in water. Indeed water is

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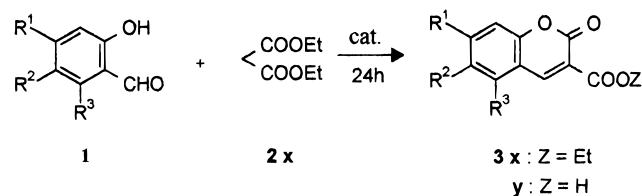
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(15) (a) KSF is a commercial (Fluka) montmorillonite with surface area 15 ± 10 m²/g, acidity 0.85 mequiv H⁺/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH₃-TPD)], and with the following chemical composition (average value): SiO₂ (54.0%), Al₂O₃ (17.0%), Fe₂O₃ (5.2%), CaO (1.5%), MgO (2.5%), Na₂O (0.4%), K₂O (1.5%). (b) K10 is a commercial (Fluka) montmorillonite with surface area 200 ± 10 m²/g, acidity 0.70 mequiv H⁺/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH₃-TPD)], and with the following chemical composition (average value): SiO₂ (73.0%), Al₂O₃ (14.0%), Fe₂O₃ (2.7%), CaO (0.2%), MgO (1.1%), Na₂O (0.6%), K₂O (1.9%).

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Table 1. Reaction of Salicylic Aldehydes with Diethyl Malonate

entry	catalyst	solvent	temp (°C)	R ¹	R ²	R ³	Z	product	yield ^a (%)
1	K10		160	H	H	H	Et	3ax	25 ^b
2	KSF		160	H	H	H	Et	3ax	44 ^b
3	K10	H ₂ O	100	H	H	H	H	3ay	30
4	KSF	H ₂ O	100	H	H	H	H	3ay	48
5	KSF		100	H	H	H	Et	3ax	21 ^b
6	KSF		160	H	-(CH=CH) ₂		Et	3bx	44 ^b
7	KSF		160	OH	H	H	Et	3cx	46 ^b

^a Isolated yield. ^b Some amount of the corresponding acid product **3y** was observed (~5%).

recognized as an attractive medium for many organic reactions.¹⁸

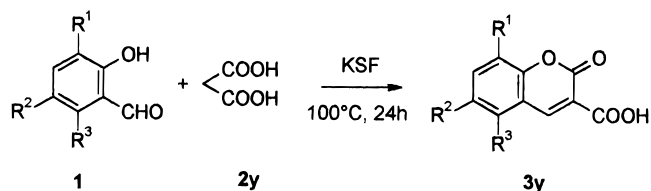
Despite the Knoevenagel condensation being a net dehydration, the reaction was surprisingly favored in aqueous medium (Table 1, entries 3, 4). However, similar unexpected solvent effects in the Knoevenagel reaction have been found by other authors.^{10b,12,19} Moreover, it is known that the Knoevenagel reaction is strongly solvent-dependent under both homogeneous^{5c} and heterogeneous conditions.²⁰ An additional advantage is that the aqueous medium caused the hydrolysis of the carboxylic ester functional group.

The simplest interpretation of these results is that water brings the active methylene compound in close proximity to the negatively charged surface of the catalyst, thus favoring the ionization into carbanion donor.

To verify the role played by the catalyst surface, we performed a comparative experiment using the acid water obtained from a stirred suspension of KSF after filtration of the catalyst. Only traces of compound **3** were detected, confirming that acid water is not sufficient to promote the process and showing that a hydrophobic effect,²¹ if involved, does not play a crucial role.

Further experiments were performed with an excess of the less expensive reagent **2x** to increase the yield. Unlike the homogeneous reaction, favored by an excess of one reagent, in this heterogeneous process a yield decrease was observed from 48% to 31% varying the malonate amount from 1.5 to 5.0 equiv. Probably the active sites become less accessible to both the reactants, which must be activated by the catalyst.

Thus the coumarin-3-carboxylic acids **3y** or their ethyl esters **3x** were accessible simply by choosing to carry out the reaction in water or without solvent. The solventless reactions were run at 160 °C, giving the products **3ax–cx** in moderate yields but with high selectivities (>90%) (Table 1, entries 2, 6, 7).

Table 2. Synthesis of Some Coumarin-3-carboxylic Acids 3y

entry	R ¹	R ²	R ³	product	yield ^a (%)	selec (%)
1	H	H	H	3ay	92	93
2	H	OCH ₃	H	3dy	89	94
3	OCH ₃	H	H	3ey	92	95
4	H	CH ₃	H	3fy	91	93
5	H	-(CH=CH) ₂ -		3by	50	95

^a Isolated yield.

With the aim at obtaining a process with better yields and higher atom efficiency¹ we employed the malonic acid **2y** instead of ethyl malonate.²² Thus, reacting **1a** and **2y** in H₂O at reflux for 24 h, coumarin-3-carboxylic acid **3ay** was obtained in excellent yield (92%) and selectivity (93%), under conditions milder than those previously reported.²³

To investigate the generality of this process, various salicylic aldehydes **1a–f** were reacted under similar conditions, allowing the easy synthesis of coumarin-3-carboxylic acids **3ay–fy** (Table 2).

The low reactivity of 2-hydroxy-1-naphthaldehyde (Table 2, entry 5) could be due to a difficulty for this substrate to interact with the active sites on the lamellar catalyst, as we have already observed.^{14a}

Finally we faced the problem of catalyst recycling. Montmorillonite KSF, simply recovered by Büchner filtration, washed with methanol, and air-dried, was reused five times to prepare **3ay** without significant loss of activity.

In conclusion we have found that coumarin-3-carboxylic acids could be synthesized in high yields and selectivities from salicylic aldehydes and malonic acid in the presence of the cheap commercially available clay KSF. Our results, according to what was stated by other authors^{11a,12} on the acid–base properties of solid cata-

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lysts, allowed us to conclude that the catalyst KSF contains both acid centers and basic sites able to abstract a proton from a methylene active compound having a $pK_a \sim 13$. Moreover, the aqueous medium used as solvent is less expensive and less dangerous than organic solvents and environmentally friendly.

Experimental Section

General Procedures. Melting and boiling points are uncorrected. ^1H NMR spectra were recorded at 400 and 300 MHz. Mass spectra were obtained in CI mode. TLC analyses were performed on Merck 60 PF₂₅₄ silica gel plates using mixtures of hexane–ethyl acetate (20–40%) or ethanol/toluene/ammonia (57/28/14%). Montmorillonite KSF and K10 (Fluka) were utilized without any previous treatment. All the reagents were of commercial quality from freshly opened containers. 2,4-Dihydroxybenzaldehyde **1c**,²⁴ 2-hydroxy-5-methoxybenzaldehyde **1d**,²⁵ and 2-hydroxy-5-methylbenzaldehyde **1f**²⁵ were prepared according to methods reported in the literature.

Synthesis of 2-oxo-2H-1-benzopyran-3-carboxylic Acids (Coumarin-3-carboxylic acids) 3y. General Procedure. The selected 2-hydroxybenzaldehyde **1** (10 mmol), malonic acid **2y** (15 mmol), and KSF (1 g) in water (3.3 mL) were heated at reflux for 24 h. After cooling to room temperature, the water was removed by Büchner filtration and the solid was heated in methanol (60 mL) for 5 min. The catalyst was removed by Büchner filtration and washed with methanol (10 mL). The solvent was distilled off, and the crude product **3y** was purified, if necessary, by crystallization from ethyl acetate or methanol. In the case of compound **3by** the unreacted aldehyde was removed with warm hexane.

2-Oxo-2H-1-benzopyran-3-carboxylic Acid (3ay): yield 1.75 g (92%), off-white crystals from methanol, mp 190–191 °C (lit.^{23b} mp: 190–191 °C).

6-Methoxy-2-oxo-2H-1-benzopyran-3-carboxylic Acid (3dy): yield 1.89 g (86%), yellow needles from ethyl acetate, mp 206–207 °C (lit.²⁶ mp: 194–196 °C).

8-Methoxy-2-oxo-2H-1-benzopyran-3-carboxylic Acid (3ey): yield 2.02 g (92%), yellow needles from ethyl acetate, mp 218–219 °C (lit. mp: 194–195 °C²⁶ or 218 °C²⁷).

6-Methyl-2-oxo-2H-1-benzopyran-3-carboxylic Acid (3fy): yield 1.86 g (91%), colorless needles from methanol, mp 166–167 °C (lit.²⁸ mp: 166 °C).

5,6-Benzo-2-oxo-2H-1-benzopyran-3-carboxylic Acid (3by): yield 1.20 g (50%), yellow woolly needles from ethyl acetate, mp 236.5–237 °C (lit.²⁹ mp: 236–237 °C).

Synthesis of 2-Oxo-2H-1-benzopyran-3-carboxylic Acid Ethyl Esters (Coumarin-3-carboxylic Acid Ethyl Esters) 3x. General Procedure. The selected 2-hydroxybenzaldehyde **1** (10 mmol), diethyl malonate **2x** (15 mmol), and clay KSF (1 g) were heated under stirring at 160 °C for 24 h. After cooling to room temperature, methanol was added (50 mL) and heated for 5 min. The catalyst was removed by filtration and the organic phase, concentrated under vacuum, was chromatographed on silica gel using a mixture of hexane–ethyl acetate as eluant.

2-Oxo-2H-1-benzopyran-3-carboxylic Acid Ethyl Ester (3ax): yield 0.97 g (44%), mp 93–94 °C (lit.³¹ mp: 94 °C).

5,6-Benzo-2-oxo-2H-1-benzopyran-3-carboxylic Acid Ethyl Ester (3bx): yield 1.19 g (44%), mp 112–114 °C (lit.³⁰ mp: 114 °C).

7-Hydroxy-2-oxo-2H-1-benzopyran-3-carboxylic Acid Ethyl Ester (3cx): yield 1.08 g (46%), mp 166–167 °C (lit.³¹ mp: 168 °C, EtOH).

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