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MICROWAVE ASSISTED SYNTHESIS OF COUMARINS BY PECHMANN REACTION USING HPA MODIFIED CLAYS AS CATALYSTS

Chemistry

KEYWORDS: Pechmann reaction; Solid acid catalyst; Heteropoly acid; Coumarin derivatives; microwave irradiation.

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ABSTRACT

Synthesis of coumarins by the reaction of phenols with ethyl acetoacetate (Pechmann reaction) in presence of different Heteropoly acids (HPA) modified Bentonite (STA-Ben, PTA-Ben) as catalysts with high yields, under mild reaction conditions in short reaction time have been reported. HPA-Ben have been synthesized and characterized by various analytical techniques. It has been found to be an efficient and reusable catalyst for the synthesis of coumarin derivatives in excellent yields. Other solid acid catalysts were tested for comparison reasons. The reaction conditions (time and amount of catalyst) have been optimized using various catalysts.

INTRODUCTION

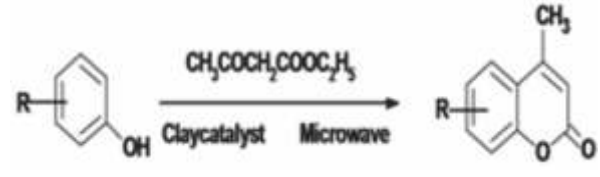
Coumarins (2H-1-benzopyran-2-ones, Figure 1) have evoked a great deal of interest due to their biological properties and characteristic conjugated molecular structure. Many of them display important pharmacological effects, including analgesic [1], anti-arthritis [2], anti-inflammatory [3], anti-pyretic [4], anti-bacterial [5], anti-viral [6], and anti-cancer [7] properties. Coumarins and its hydroxy derivatives have been effectively used as anticoagulants for the treatment of disorders in which there is excessive or undesirable clotting, such as thrombophlebitis [8], pulmonary embolism [9], and certain cardiac conditions [10]. Coumarin derivatives are typically synthesized by chemical modification of the coumarin ring. The chemical synthesis, structural modification, and a wide variety of biological activities of coumarins have been reported in many papers [11-13].

Various methods are known for the synthesis of substituted coumarins in the literature including the Pechmann [14a], Perkin [14b], Knoevenagel [14c], Claisen [14d], Reformatsky [14e] and Wittig reactions [14f]. The main disadvantage of almost all existing methods for coumarin synthesis is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, there is further scope to explore mild and efficient methods for coumarin synthesis.

A very feasable method for the synthesis of coumarins is the Pechmann reaction, which starts from phenols. In the conventional production of coumarins by Pechmann reaction, concentrated sulfuric acid is used as the catalyst [15]. This process causes formation of by-products, needs long reaction time, and introduces corrosion problems. For these reasons, there have been some attempts to find alternative environmentally benign and heterogeneously catalyzed synthesis routes. The use of heterogeneous solid acid catalysts assumes advantages like ease of operation conditions, reduced equipment corrosion, and minimized contamination of the waste streams combined with reusability of the catalyst. Nafion-H [16], zeolite H-BEA, Amberlyst 15 [17], and other solid acids [18,19] have been employed for this purpose in the Pechmann reaction.

Among the solid acids, heteropoly acids (HPAs) have been extensively studied as acid catalysts for many reactions and found industrial applications in several processes [20]. They are more active than the conventional catalysts, such as mineral acids, ion-exchange resins, zeolites, SiO_2/Al_2O_3 and H_3PO_4/SiO_2 [21- 23]. HPAs have several advantages over liquid acid catalysts, including being non-corrosive and environmentally benign. In the present work silicotungstic acid (STA) and phosphotungstic acid (PTA) modified bentonite have been synthesized to explore the properties of both clay and heteropoly acids. This makes it possible to carry out the catalytic process at a lower catalyst concentration and/or at a lower temperature.

The method presented herein involves the condensation of phenols with **β-ketoesters in the p**resence of heteropoly acids modified clay, which acts as a solid acid catalyst for the synthesis of coumarins (Scheme 1) [24, 25]. The developed HPA's modified clays have opened up a large number of applications due to their increased catalytic activity and selectivity.



Scheme 1: HPA-clay catalyzed Pechmann reaction.

EXPERIMENTAL:

Bentonite (Ben) clay purchased from Sigma Aldrich chemical company, USA. Heteropoly acids (STA and PTA purchased from Sisco Research laboratory Pvt. Ltd., Mumbai, India). Phenols and other chemicals of AR grade were purchased from E. Merck Ltd., Mumbai, India).

2.1 Typical Procedures for the catalysts preparation

Acid-activated Bentonite (H^+-Ben):

5.0 g of Na- Ben (Ben) was taken in a 250 ml conical flask containing 50 ml of 3N H_2SO_4. The mixture was exposed to microwave radiation for 30 min in a microwave oven. The suspension was then centrifuged and the residue was washed several times with double distilled water. The residue was then dried in an oven at 150°C. The resulting residue was acid activated bentonite (Ben_2) and this was further used for pillaring [26].

Pillared acid activated Bentonite ($PAA\text{-}Ben_2$)

HPA solution was prepared by dissolving 100 mg of heteropoly acid in minimum amount of double distilled water. This solution was then slowly added to 1.0 g Ben_2 suspension. This suspension was subjected to vigorous stirring (at 2000 rpm) for 16 hrs at room temperature. The suspension was centrifuged and the residue was washed several times with double distilled water to remove excess of HPA. The residue thus obtained was dried in an oven at 150°C, till constant weight was attained. The resulting residue was referred as Pillared acid activated bentonite ($PAA\text{-}Ben_2$).

HPA Modified Bentonite (HPA-Ben)

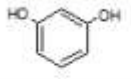
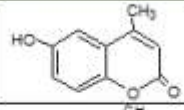
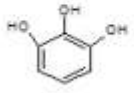
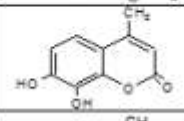
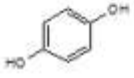
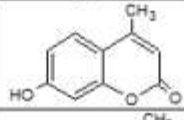
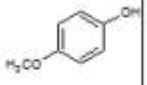
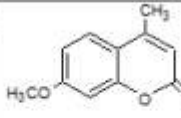
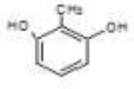
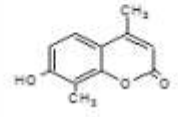
HPA solution was prepared by dissolving 100 mg of heteropoly acid in minimum amount of double distilled water. This solution was then slowly added to suspension of 1.0 g Mmt in 100 ml of double distilled water. This suspension was subjected to vigorous stirring (at 2000 rpm) for 16 hrs at room temperature. The suspension was then centrifuged and the residue was washed several times with double

distilled water, till the pH of the filtrate was found to be neutral. The residue thus obtained was dried in an oven at 150 ^{0}C.

2.2 Typical Procedure for the Synthesis of Coumarins

A mixture of phenol (1 mmol), ethyl acetoacetate (1 mmol), and HPA-clay (0.05 g) was ground in an open Pyrex beaker and the homogenized mixture was heated by microwave irradiation for about 10 min, (Scheme 1). The progress of the reaction was monitored by using TLC (ethyl acetate/*n*-hexane: 1/2). After complete conversion as indicated by TLC, the mixture was extracted with petroleum ether(3 × 30 mL) and washed with water (3 × 30 mL). The crude products were purified by recrystallization from ethanol (95%) to afford pure products (Table 1).

TABLE – 1
HPA-CLAY CATALYZED COUMARINS

S. No	Reactant	Product	Time Sec.	% Yield
01			120	99
02			150	86
03			90	90
04			240	84
05			180	78

Optimization of Reaction Conditions

For the optimization of reaction conditions resorsinol (1 mmol) and ethyl acetoacetate (1 mmol) have been selected as reactants (Table 1, Entry 1).

Optimization of the Catalysts Amount

Reactions have been performed using varying amount of different catalysts under uniform conditions (Table 2).

TABLE – 2
OPTIMIZATION OF CATALYTIC ACTIVITY OF CATALYSTS

S. No	Catalyst mg	Time, Sec.	% Yield of 4-methyl-6-hydroxy coumarin with various catalysts				
			Ben	H^+-Ben	PAA-Ben	PTA	PTA-Ben
1	20	120	33	50	55	56	72
2	30	120	40	57	62	64	80
3	40	120	50	67	72	74	90
4	50	120	58	74	78	80	99
5	60	120	58	74	78	80	99

Optimization of Time

The reaction time has been optimized by performing reactions at regular intervals. After a certain time period there is not much increase in the yield. That time has been selected as optimum time (Table 3).

After optimization of time and amount of catalyst a number of coumarin derivatives have been synthesized (Table 1).

TABLE – 3
OPTIMIZATION OF TIME

S. No.	Time, Sec.	% Yield
01	30	65
02	60	80
3	90	90
04	120	99
05	150	99

RESULT AND DISSCUSION

Characterization of Catalysts

X-Ray Diffraction

In case of HPA treated Ben (HPA-Ben), increase in d-spacing for PTA and STA modified clay confirms the intercalation of HPA molecules into the inter-layer region of Ben (Figure 1 (d), (e)).

The X-ray diffraction pattern of Ben_2 indicates a shift in the peak, 2 = 6.08, corresponding to a d-spacing of 14.5Å (0.36Å decrease in d-spacing w.r.t Ben). The intensity of this peak (**2θ = 6.08**) decreased substantially w.r.t Ben, while the other peaks resulting from amorphous silica showed enhanced intensity between **2θ = 18-30**, indicates successful exchange of Na^+ with H^+.(Figure 1 (g), (h)).

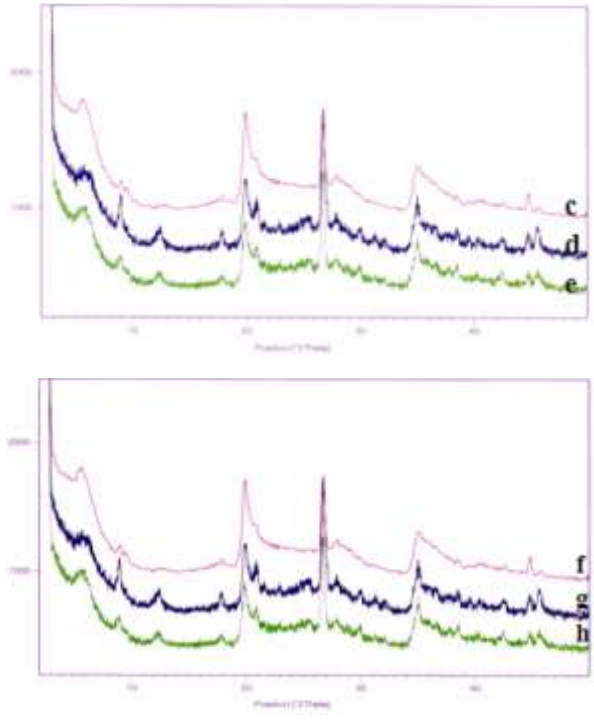


Figure 1: XRD spectra (d) PTA-Ben_1, (e) STA-Ben_1, (g) PTA-Ben_2, (h) STA-Ben_2

FT-IR Spectroscopy

In the FT-IR spectra of Ben, absorption bands in the similar region has been observed as Ca-Bentonite, except small shifting of band for O-H stretching vibrations and a low intensity peak at 796 cm^{-1} has been observed, which may be due to Si–O, Si–O–Al, (Al, Mg)-O–H and Si–O–(Mg, Al) stretching vibration [27, 28].

In the FT-IR spectra of STA-Ben and PTA-Ben, absorption bands appear in the similar regions as Ben. In addition to the above mentioned bands, two additional bands around 3630 cm^{-1} and 795

cm^{-1} have also been observed. The broad band around 3600 cm^{-1} has been assigned to the O-H stretching vibrations, which may be due to O-H groups of intercalated heteropoly acids, the band around 795 cm^{-1} is due to the M-O_e-M stretching vibrations of edge sharing Oxygen atoms [where M= W for (PTA & STA)], which is a characteristic of the Keggin unit (Figure 2 (d), (e)).

In case of Ben_2, broadening of band around 1050 cm^{-1} and disappearance of shoulder near 914 cm^{-1} region have been observed, which indicates exchange of cations for H^+ in the layers of Ben [Fig.4.2.2:b, Table 4.2.4]. In the FT-IR spectra of, STA-Ben_2 and PTA-Ben_2, same types of patterns have been observed with the disappearance of shoulder at 914 cm^{-1} (Figure 2 (g), (h)).

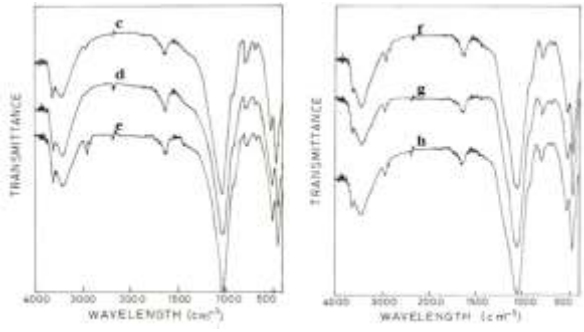


Figure 2: FT-IR spectra of (d) PTA-Ben_1, (e) STA-Ben_1, (g) PTA-Ben_2, (h) STA-Ben_2

In this research, we have synthesized some coumarin derivatives using phenols and ethyl acetoacetate in the presence of acid activated and intercalated clay as a catalyst (Scheme 1). The synthesis of compound **1** was selected as the model to optimize the reaction conditions. The corresponding results are summarized in Table 2. It can be seen from the results presented in this table, both acid activated and intercalated clay acts as an effective catalyst, significantly increasing the reaction rate and % yield of the product (Table 2). All the reactions were monitored by using thin layer chromatography (TLC) and carried forward to maximum atom utilization.

The different reaction conditions obtained by varying the amount of catalyst and the corresponding results are summarized in Table 2. It could be observed that the product yield is strongly affected by the amount of catalyst used in the reaction. Best results were obtained with microwave irradiation (Entry 1) using 0.05 g of catalyst.

The catalyst was easily recovered by simple filtration after dilution of the reaction mixture with ethyl acetate and was reused after being vacuum dried. HPA-clay was reused for four runs without significant loss of activity.

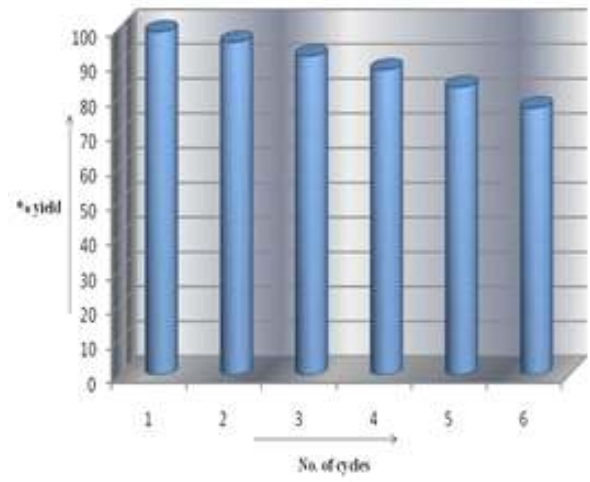


Figure 4: Reusability of modified clay catalysts upto 6 repeated cycles.

REUSABILITY OF HPA-BEN

The reusability of HPA-Ben has been investigated up to six repeated cycles using synthesis of Coumarin derivatives. The catalyst, HPA-Ben, was washed with MeOH and the dried in vacuum after every cycle. No noticeable changes in catalysts were observed even after six cycles, which indicates the stability of the catalyst. The product/s, after separation and isolation, was characterized and the yield in each case was calculated (Figure 4). The variation in the yield was found to be in the range of 82% to 62%.

CONCLUSIONS

In summary, we have demonstrated a novel methodology based on the Pechmann condensation for the synthesis of substituted coumarins under microwave irradiation conditions, catalyzed by HPAs modified clays as a highly efficient, reusable and environmental benign catalyst. Moderate to high yields of the corresponding coumarins were obtained. The unique advantages of this method include a one-pot synthesis strategy, experimental simplicity with microwave irradiation, high yields obtained under short reaction times, easy and quick isolation of the products.

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