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Phototungstic Acid Catalyzed Synthesis of Benzo (h) Chromen-2-one3-methyl Carboxylate and Study its Anti-Inflammatory Property

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Abstract: ***The Coumarin heterocyclic ring is a common feature of various bioactive compounds such as Calanolides, lipid lowering agents. Coumarins, the most important classes of fluorescent molecules constitute important structural features present in a number of bioactive natural products. coumarin and its derivative are biologically activecompounds and widely occur in nature. Phosphotungstic acid ($H_3PW_{12}O_{40}$) a commercially available environmentally benign catalyst non-toxic widely used for the synthesis of the substituted coumarin. Owing to the numerous advantages associated with cheap and non-hazardous catalyst, and also realizing g the importance of coumarin herein we would like to focus the eco –friendly method for his synthesis of derivatives of coumarin using cheaper and commercially available acid catalyst Phosphotungstic acid ($H_3PW_{12}O_{40}$) and also by the Knoevenagel condensation under microwave irradiation.This derivative of the coumarin was studied its anti-inflammatory activity. Anti-inflammatory activity of the newly synthesised Coumarin has been evaluated by calculating the percentage protection or percentage inhibition which was calculated by following equation.% protection= [O.D of control – O.D of test/ O.D of control x 100Where O.D stands for optical density. This methodology offers significant improvements for the synthesis of derivative of coumarin with regard to yield of products, simplicity in operation and green aspects by avoiding toxic conventional catalysts and solvents. The coupling of microwave heating with solid phase catalysts in solvent-free conditions catalysis chemical processes with special attributes such as s enhanced reaction rate, Therefore owing the importance of Phosphotungsticacid ($H_3PW_{12}O_{40}$) a facile catalyst used for the green synthesis of derivatives of coumarin. This paper focuses is todevelop environment friendly reactions, simple, highly efficient and high yielding protocol for the synthesis of Benzo (h)chromen-2-one3-methyl carboxylate using Phosphotungsticacid ($H_3PW_{12}O_{40}$) as a catalyst. This compound is characterized by IR and NMR spectroscopy.***

Keywords: Phosphotungsticacid (H3PW12O40), microwave irradiation,anti inflammatory

1. Introduction

The Chemists all over the globe are motivated not only for the environmentally benign synthesis of new products but also to develop green synthesis for existing chemicals. This has been possible by the replacement of the organic solvents, which are hazardous by water or eliminate the use of solvent altogether. Recent studies have been revealed that coumarin and the derivatives exhibit several other medicinal applications such as anti-coagulants, antifungal, insecticidal, hypnoticsphytoalexins, HIV protease & inhibitors. Coumarins act as in intermediate for the synthesis of various biologically active molecule such as coumarones, and fluorocoumarins. Thus the synthesis of coumarins is of continuing interest.

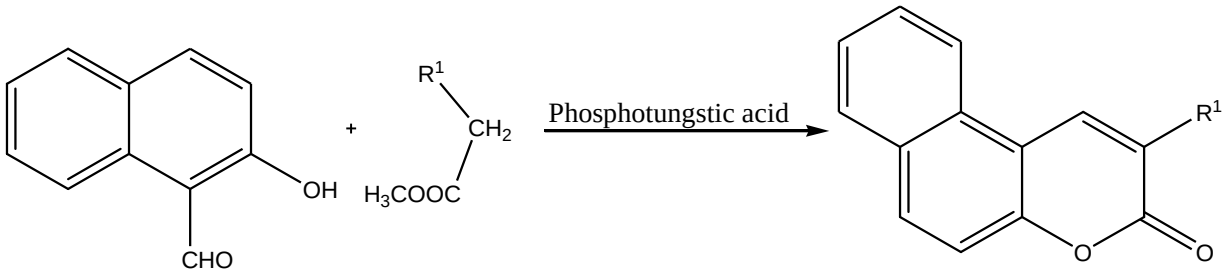
Coumarins are nowadays an important group of organic compounds that are used as additives to food and cosmetics [1] optical brightening agents[2] and dispersed fluorescent and laser dyes [3].The derivatives of coumarin usually occur as secondary metabolites present in seeds, root, and leaves of many plant species. Their function is far from clear, though suggestions include waste products, plant growth regulators, fungistats and bacteriostats[4]. It is therefore of utmost importance that the synthesis of coumarin and its derivatives should be achieved by a simple and effective method. Coumarins can be synthesized by one of such methods as the Claisen rearrangement, Perkin reaction, Pechmann reaction as well as the Knoevenagel condensation [5]. It was recently shownthat the Pechman reaction could be quickly achieved using microwave irradiation of the reagents in household microwave oven [6] .Since thesolvent free phase-transfer catalytic reactions under microwave irradiation has prompted us to present our results of the synthesis of coumarins by the Knoevenagelcondensation under such conditions.

Phosphotungsticacid ($H_3PW_{12}O_{40}$) is a heteropoly acid7 and grayish in color commercially available environmentally benign catalyst non-toxic widely used heterogeneous catalyst. Phosphotungstic acidis the strong acid of the hetero poly acid. Hetro poly anion ($H_3PW_{12}O_{40}^{-3}$) represents the structure of HPW, which then forms a bulk structure by coordinating to acidic proton. ($H_3PW_{12}O_{40}$) has been utilized for several organic transformations. This paper focuses is to develop environment friendly reactions, simple, highly efficient and high yielding protocol for the synthesis of coumarin derivative using novel catalyst.

2. Results and Discussion

I report a very simple, fast and general procedure where the Condensation of 2- hydroxynaphthaledyde with and dimethyl malonate in presence of Phosphotungstic acid (H3PW12O40) catalyst leads to the synthesis of derivatives of coumarins (Figure-1)

Scheme 1



1 2 3-k
Where R1 is COOCH3

Figure 1: Synthesis of coumarin derivatives byKnoevenagel condensation under microwave irradiation &using Phosphotungsticacid (H3PW12O40) as catalyst.

Material required: 2- hydroxyl naphthaledyde, dimethylmalonate, Phosphotungsticacid ($H_3PW_{12}O_{40}$), ethanol.

Experimental section

A mixture of 2- hydroxyl naphthaledyde (1). (1mmol), carbonylcompound (dimethyl malonate) (2) (1 mmol), and Phosphotungsticacid ($H_3PW_{12}O_{40}$) (20mol%)in ethanol (5ml)was stirred at room temperature for one hour .It is then neutralized with ammonium chloride solution extracted with ether. Ether layer was dried with sodium sulphate and evaporated to dryness to get the product.

Table 1

Compound	Melting point ^oC	Yield %	IR (KBr) ύ cm^{-1}	^{1}HNMR: δ (ppm)
Benzo (h)chromen-2-one3-methyl carboxylate (3K)	215	68	1220,1210,1720,3080,1604,1450,	3.9 (s,3H)8.12 (s,1H)7.68 (m,4H) 8.57 (d,1H)8.33 (d,1H)

Frist experiment focused to carry out the reaction in piperidine in microwave undernormal condition, in the second stage the reaction was carried out in presence of Phosphotungsticacid ($H_3PW_{12}O_{40}$) catalyst with conventional heating and in modified microwave and compared their yield with first part. Under modified microwave heating offers a convenient environmentally friendly alternative to conventional reactions. Clearly, the reaction time by microwave heating has been reduced with higher yield than conventional heating (86% versus 65 %,)

Monitoring of the reactions and analysis can be accomplished by using standard methods (thin layer chromatography, 1HNMR, FT-IR spectroscopy.). Finally, the product is isolated by crystallization. The formation of coumarin was evidenced by the absence of two peaks at 2880cm^{-1} (Ar-CHO) and 3550cm^{-1} (Ar-OH)but the appearance of two prominent peaks due to C-O-C at 1275-1210$cm^{-1}$and lactone C=Oat 1720-1700cm^{-1}, rest all the substituents peaks are shown as per literature .The detailed data is as shown in the Table -1

The proton nuclear magnetic spectral analysis (1HNMR) of the compound showed signals corresponding to the multiplicity for different types of protons were consistent with assigned structure.

Anti-inflammatory Study

General Experimental Procedure

Sample preparation

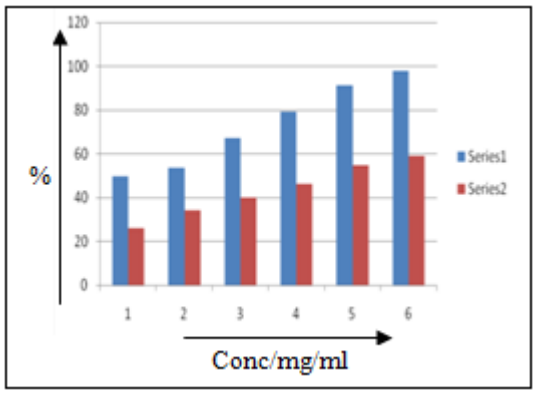
Samples were freshly prepared in DMSO and then appropriate dilutions were prepared just prior to start of study.

1) Blood was collected from healthy volunteer who was not taken any NSAIDS for two weeks prior to the experiment.
2) The collected blood was mixed with equal volume of sterilized Alsever solution (2%dextrose, 0.8% sodium citrate, 0.5% citric acid and 0.42% sodium chloride in water).
3) The blood was centrifuged at 3000 rpm and packed cell were washed with isosaline (0.85%.pH 7.2) and a 10 % (v/v) suspension was made with isosaline.
4) The assay mixture contained the drug, 1 ml of phosphate buffer (0.15M, pH 7.4), 2 ml of hyposaline (0.36%) and 0.5ml of HRBC suspension sodium diclofenac was used as reference drug.
5) Instead of hyposaline 2ml of distilled water was used in the control. All the assay mixture were incubated at 370C for 30 min and centrifuged.
6) The haemoglobin content in the supernatant solution was estimated using spectrophotometer at 560 nm.
7) The percentage protection was calculated by following equation

% protection= [O.D of control – O.D of test/ O.D of control x 10 (Table 2)

Table 2: % Inhibition of compound 3k

S. No	Conc/mg/ml	Sodium diclofenac	Percentage
1	1	49.59	28.31
2	2	53.51	33.47
3	4	67.23	37.51
4	6	79.34	46.59
5	8	91.14	54.81
6	10	97.87	59.71



Series1= sodium diclofenac
Series 2=compound 3k

3. Conclusion

- Highly practical procedure has been developed, using green chemistry principles for the synthesis of coumarin derivatives.
- A practical method for an efficient synthesis of product (3k) using an inexpensive catalyst at ambient temperature has been described. High yields along with simple reaction condition auger well for the application of this strategy for the synthesis of derivative of coumarin.
- Mild reaction conditions, short reaction time, simple experimental work upcheapness of the reagents are the noteworthy advantages of this environment friendly protocol.
- This methodology offers significant improvements for the synthesis of derivative of coumarin with regard to yield of products, simplicity in operation and green aspects by avoiding toxic conventional catalysts and solvents. Therefore owing the importance of Potassium dihydrogen phosphatea facile catalyst used for the green synthesis of new derivatives of coumarin
- Thus the development of an efficient and versatile method to synthesis of coumarin derivatives is an active ongoing research and there is a scope further improvement towards milder reaction condition and yield.
- This derivative of the coumarin was studied anti-inflammatory activity and were showing significant inhibition between 45% to 60%.. All these results were compared with the standard sodium diclofenac.

4. Acknowledgement

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