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PHOSPHOTUNGSTICACID ($H_3PW_{12}O_{40}$) CATALYZED ECO-FRIENDLY SYNTHESIS OF SUBSTITUTED COUMARINS AND STUDY THEIR ANTI-MICROBIAL ACTIVITIES

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ABSTRACT

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 The Coumarine heterocyclic ring is common feature of various bioactive compounds such as calanolides, lipid-lowering agents. 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. Phosphotungsticacid ($H_3PW_{12}O_{40}$) 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 Phosphotungsticacid ($H_3PW_{12}O_{40}$). and also by the Knoevenagel condensation under microwave irradiation. The synthesized coumarin derivatives were screened in Vitro anti-microbial efficacy testing. In vitro anti-microbial efficacy testing was carried out by broth dilution method by broth dilution method as mentioned in "Pharmaceutical Microbiology". For anti-bacterial activity, Muller Hintonmedium was used as the nutrient media. Test bacterial species used are Escherichia coli, (ATCC 10148), Staphylococcus aureus(NCTC 3750), Pseudomonas aeruginosa (Fisher' Immunotype IV), test fungi species used are Aspergilliusniger(ATCC 16404) and Candida

albicans (ATCC 10231) in different concentrations starting from 25ppm. All the coumarin derivatives are active against the test bacteria and fungai in different concentrations. This paper focuses is to develop environment friendly reactions, simple, highly efficient and high yielding protocol for the synthesis of coumarin derivatives using Phosphotungsticacid as a catalyst.

KEYWORDS: Phosphotungsticacid, microwave irradiation, anti-microbial.

INTRODUCTION

Coumarin and its derivatives are biologically active compounds and widely occur in nature. Some Coumarin derivatives have been widely used as an important chemical in perfume, cosmetic as well as pharmaceutical industrial preparation. 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. Thus the synthesis of coumarins is of continuing interest.

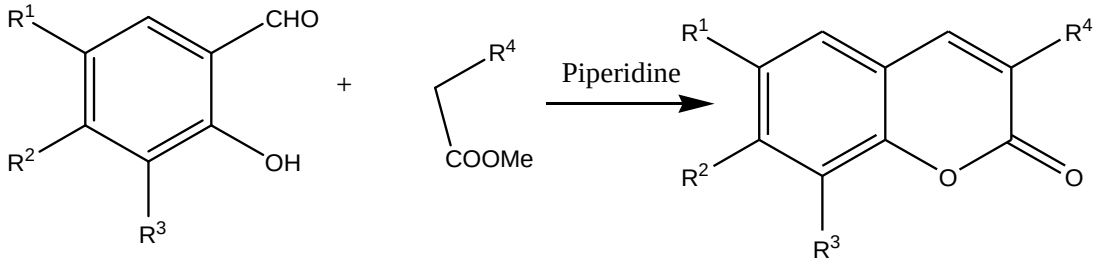
Coumarins are nowadays an important group of organic compounds that are used as additives to food and cosmetics,[1] optical brightening agents,[2] and dispersed fluorescent and laser dyes.[3] The derivatives of coumarin usually occur as secondary metabolites present in seeds, root, and leaves of many 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 synthesised by one of such methods as the Claisen rearrangement, Perkin reaction, Pechmann reaction as well as the Knoevenagel condensation.[5] It was recently shown that the Pechman reaction could be quickly achieved using microwave irradiation of the reagents in household microwave oven.[6] Since the solvent free phase-transfer catalytic reactions under microwave irradiation has prompted us to present our results of the synthesis of coumarins by the Knoevenagel condensation under such conditions.

Phosphotungsticacid ($H_3PW_{12}O_{40}$) is a heteropoly acid[7] and grayish in color commercially available environmentally benign catalyst non-toxic widely used heterogeneous catalyst. Phosphotungstic acid[20] is the strong acid of the hetero poly acid. Hetro poly anion ($PW_{12}O_{40}$-$_3$) represent the structure of HPW, which then forms a bulk structure by coordinating to acidic

proton. Hetero poly acids are stronger than the usual mineral acids such an HCI, H_2SO_4. $H_3PW_{12}O_{40}$ has been utilized for several organic transformation. This paper focuses is to develop environment friendly reactions, simple, highly efficient and high yielding protocol for the synthesis of coumarin derivatives using novel catalyst.

I. Experimental technique

General experimental procedure for (Scheme-1-A) A mixture of 5-nitro 2-hydroxy benzaldehyde (1) (1mmol), carbonyl compound (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 neutralised with ammonium chloride solution extracted with ether. Ether layer was dried with sodium sulphate and evaporated to dryness to get the product.Fig-1(Table-1&2). They are characterised by IR(KBr), NMR: ȣ (ppm).



1 2 3(a,b,c)

Figure 1: Synthesis of derivative of coumarin using Piperidine & Phosphotungsticacid as catalyst.

Table -1.

Compound	R^1	R^2	R^3	R^4
3a	NO_2	H	H	COMe
3b	NO_2	H	H	COOMe
3c	NO_2	H	H	CN

Table -2.

Compound	Colour	Melting point ^oC	Yield %	IR(KBr)	NMR: ȣ (ppm)
3a	dark brown	180	90	3082,30402923,1680,1552,1465,1260,1100,1152,999.41,793,655 cm^{-1}	2.5(,s3H),7.42(s,1H),7.76(d,1H)7.78(d,1H) 8.34(s,1H)
3b	yellow	210	96	3345,3040,2880,1750,1556,1465,1680,655 cm^{-1}	1.45(t,3H)7.30(s,1H,7.68(d,1H)7.7d,,1H) 8.42(s1H)
3c	Light brown	192	88	34333062,2209,1735,1680,1566,1465,817743 cm^{-1}	7.8(s1H),7.67(d,1H) 7.76 (d,1H),8.47 (s,1H)

II. RESULTS AND DISCUSSION: The aim of the present paper is to show that under the microwave irradiation the Knoevenagel condensation can be successfully applied to the synthesis of a number of coumarins, and the scope of the method is much broader. Here I report a very simple, fast and general procedure where the condensation of Condensation of 5-nitro 2-hydroxy benzaldehyde with derivative of ethyl acetate using Phosphotungsticacid ($H_3PW_{12}O_{40}$ (Figure-1) &Table-1) It is found that a 10 mol% amount catalyst Phosphotungsticacid ($H_3PW_{12}O_{40}$.

Could effective the reaction to complete.

III. Pharmacology analysis

In vitro anti microbial assay: The synthesized coumarin derivatives were screened in Vitro anti-microbial efficacy testing. In vitro anti-microbial efficacy testing was carried out by broth dilution method by broth dilution methods asmentioned in ―Pharmaceutical Microbiology‖. For anti-bacterial activity, Muller Hinton broth was used as the nutrient media. Test bacterial species used are Escherichia coli, (ATCC 10148), Staphylococcus aureus(NCTC 3750), Pseudomonas aeruginosa (Fisher'Immunotype IV), test fungi species used are Aspergilliusniger(ATCC 16404) and Candida albicans (ATCC 10231) in different concentrations starting from 25ppm. All the coumarin derivatives are active against the test bacteria and fungai in different concentrations. The four different concentrations of the samples 25ppm, 50ppm,100ppm, &150ppmper ml. were prepared and taken in Muller Hinton broth separately in sterile test tube and to each individual test tube 0.1 cm3 of above mentioned bacterial suspension was added (having approximately1.0 x 106 *CFU). These tubes were then kept for incubation at 37oC for 48 hours. To check the growth if any. (Yable 3, 4&5).

Table 3: Compound name 3a.

Sr. no.	Test bacterial species	Standard referencesample Ampicilline	Inhibition\ Viability of the test bacterial species after 48 hours of incubation in the concentration of 50ppm 100ppm 150ppm 200ppm			
01	Pseudomonas Aeroginosa (Fisher's immunotype-IV)	150	V	V	**N	N
02	Escherichia coli, (ATCC 10148),	100	V	V	**N**	N
03	Staphylococcus aureus(NCTC 3750),	100	V	V	N	N

04	Aspergillius niger(ATCC 16404)	150	V	V	V	N
05	Candida albicans (ATCC 10231)	100	V	V	V	N

***CFU = Colony formin ** N = No growth or bacteria was killed / inactivated MIC**= minimum inhibitory concentration expressed in ppm (parts per million in this contest) Compound labelled as' 3d,' kills /inactivates the test organism Escherichia coli, (ATCC 10148), Staphylococcus aureus(NCTC 3750), Pseudomonas aeruginosa (Fisher'Immunotype IV),in concentration 150ppm where as it does not kill the fungal species Aspergillius niger(ATCC 16404) and Candida albicans (ATCC 10231) Aspergillius niger(ATCC 16404) and Candida albicans (ATCC 10231) in the concentration of 100 ppm. But kills /inactivates in the concentration 200ppm. In other words the compound 3a have shown the anti-bacterial/antifungal activities in the concentration of 150 ppm/200ppm respectively, against the above mentioned test bacterial/fungal species.

Table 4: Compound name 3b.

Sr. no.	Test bacterial species	Standard referencesample Ampicilline	Inhibition\ Viability of the test bacterial species after 48 hours of incubation in the concentration of 25ppm 50ppm 100ppm 150ppm			
01	Pseudomonas Aeroginosa (Fisher's immunotype-IV)	150	V	V	**** N**	N
02	Escherichia coli, (ATCC 10148),	100	V	V	N	N
03	Staphylococcus aureus (NCTC 3750),	100	V	V	N	N
04	Aspergillius niger (ATCC 16404)	150	V	V	V	N
05	Candida albicans (ATCC 10231)	100	V	V	V	N

***CFU = Colony formin ** N = No growth or bacteria was killed / inactivated MIC**= minimum inhibitory concentration expressed in ppm (parts per million in this contest) Compound labelled as' 3e,' kills /inactivates the test organism Escherichia coli, (ATCC 10148), Staphylococcus aureus(NCTC 3750), Pseudomonas aeruginosa (Fisher'Immunotype IV),in concentration 100ppm where as it does not kill the fungal species Aspergillius niger(ATCC 16404) and Candida albicans (ATCC 10231) Aspergillius niger(ATCC 16404) and Candida albicans (ATCC 10231) in the concentration of 100 ppm. but kills /inactivates in the concentration 150ppm In other words the compound 3b have shown the anti-

bacterial/antifungal activities in the concentration of 100 ppm/150ppm respectively, against the above mentioned test bacterial/fungal species.

Table 5: Compound name 3c.

Sr. no	Test bacterial species	Standard referencesample Ampicilline	Inhibition\ Viability of the test bacterial species after 48 hours of incubation in the concentration of 25ppm 50ppm 100ppm 150ppm			
01	Pseudomonas Aeroginosa (Fisher's immunotype-IV)	150	V	V	** N	N
02	Escherichia coli, (ATCC 10148),	100	V	V	N	N
03	Staphylococcus aureus (NCTC 3750),	100	V	V	N	N
04	Aspergillius niger (ATCC 16404)	150	V	V	N	N
05	Candida albicans (ATCC 10231)	100	V	V	N	N

***CFU = Colony formin ** N = No growth or bacteria was killed / inactivated MIC**= minimum inhibitory concentration expressed in ppm (parts per million in this contest) Compound labeled as' 3c kills /inactivates the test organism Escherichia coli, (ATCC 10148), Staphylococcus aureus(NCTC 3750), Pseudomonas aeruginosa (Fisher'Immunotype IV), test fungai species used are Aspergillius Niger(ATCC 16404) and Candida albicans (ATCC 10231 in the concentration of 100 ppm, In other words the compound 3c has shown the anti-bacterial/antifungal activities in the concentration of 100 ppm, against the above mentioned test bacterial/fungal species . whereas Standard reference sample ampicillin/fluconazole (MIC) at 100ppm in the same condition against Escherichia coli, (ATCC 10148), and Staphylococcus aureus(NCTC 3750),but against Pseudomonas aeruginosa is150ppm. Standard reference sample fluconazole shows MIC at 100ppm against Candida albicans (ATCC 10231) but 150 ppm against Aspergillius Niger(ATCC 16404).

(III) RESULTS AND DISCUSSION

The aim of the present paper is to show that under the microwave irradiation the Knoevenagel condensation can be successfully applied to the synthesis of a number of coumarins, and the scope of the method is much broader. Here I report a very simple, fast and general procedure where the condensation of Condensation of 5-nitro 2-hydroxy benzaldehyde with derivative of ethyl acetate using Phosphotungsticacid ($H_3PW_{12}O_{40}$).

IV. Experimental protocol

All starting materials and reagents were commercially available and used without further purification. All chemical and solvents used were of A.R. grade. Further, remaining, pure reagents were purchased from S.D. chemicals. All the melting points were taken in an open capillary and are uncorrected. I.R spectra of the synthesized compounds 3a-c were recorded were recorded on Bruker, Germany Model: 3000 Hyperion Microscope with Vertex 80 FTIR System. The NMR spectra of all the synthesized compounds were recorded on Model: Mercury plus Make: Varian USA NMR AS 300 MHz (strength 9.3 Tesla) Spectrophotometer at room temperature.

V. 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 (a-c) 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 up cheapness of the reagents are the noteworthy advantages of this environment friendly protocol.
- This methodology offers significant improvements for the synthesis of derivatives of coumarins with regard to yield of products, simplicity in operation and green aspects by avoiding toxic conventional catalysts and solvents. Therefore owing the importance of phosphotugstic acid a 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.
- The compounds are found to possess good anti bacterial/anti fungal activity when compared with the standard.

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