CHAPTER 4

PECHMANN CONDENSATION

4.1 INTRODUCTION

The fusion of a pyrone ring with a benzene ring gives rise to a class of heterocyclic compounds known as benzopyrones, of which two distinct types are recognized (1) benzo-α-pyrones, commonly called coumarins, and (2) benzo-γ- pyrones, called chromones, the latter differing from the former only in the position of the carbonyl group in the heterocyclic ring.(Figure 1)

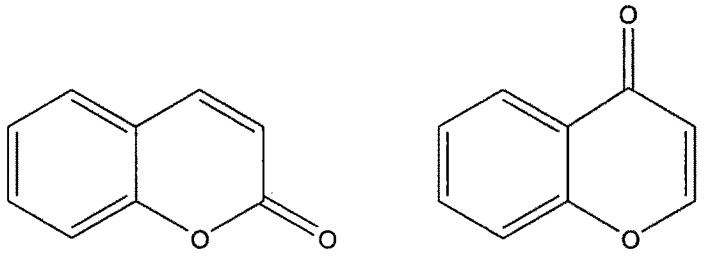


Figure1 Benzo pyrone structures

Several coumarin derivatives have been found to be widely distributed in the plant kingdom, particularly the plants belonging to the natural orders of Orchidaceae, Leguminoceae, Rutaceae, Umbelliferae, and Labiatae that are rich sources of naturally occuring coumarins. Coumarin, the parent substance of the benzo-α-pyrone group, was first isolated from tonka beans in 1820.

Coumarins are an important group of organic compounds that are used as additives in food and cosmetics, optical brightening agents and dispersed fluorescent and laser dyes [1-3]. Many products which contain this subunit, exhibit useful and diverse biological activity such as molluscacides [4] that exhibit anthelmintic, hypnotic and insecticidal properties[5] or serve as anticoagulant agents[6] or fluorescent brighteners [7].

4.2 SYNTHETIC ROUTES TO COUMARINS

Various routes to coumarin synthesis [8] include the Pechmann [9], Perkin [10], Knoevenagel [11,12] and Reformatsky [13] reactions.

Perkin reaction:

This classical method has entered into every textbook of organic chemistry. Perkin first synthesized coumarin from salicylaldehyde by heating it with acetic anhydride and anhydrous sodium acetate. This reaction occurs

with the formation of an intermediate, o-hydroxycinnamic acid derivative, which passes spontaneously into the lactone, when dissociated from its sodium salt. This synthetic route has, however, some limitations. It is rather difficult to obtain the appropriate initial o-hydroxy aldehydes in case of substituted phenols. Further, by this route, it is not possible to synthesise coumarins with substitution in pyrone ring. A schematic representation of Perkin reaction is given in Figure 2.

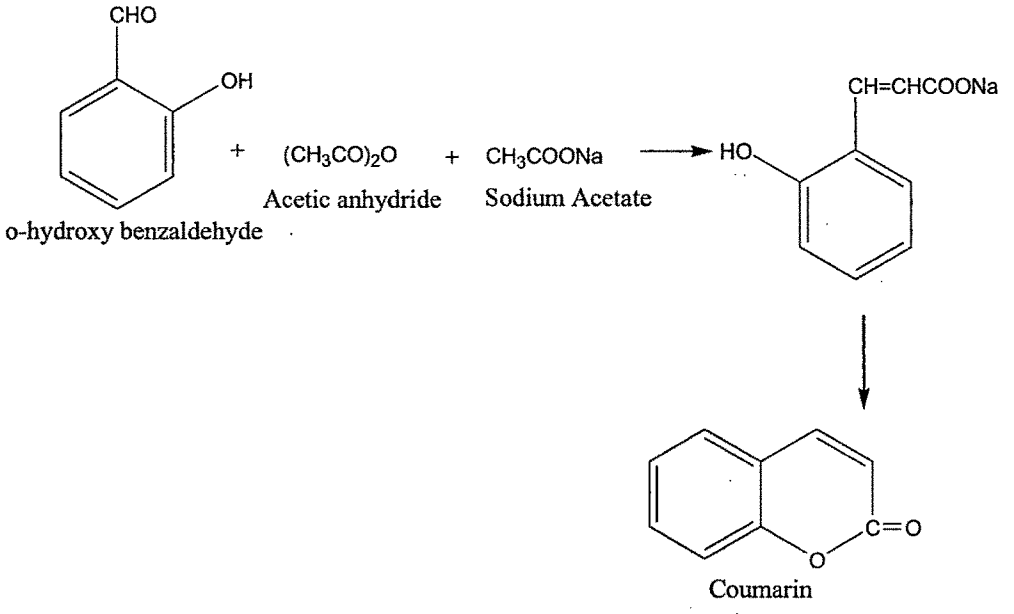


Figure 2 Perkin reaction

Knoevenagel reaction:

Knoevenagel developed a method for the synthesis of coumarin derivatives from o-hydroxyaldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, etc., in the presence of piperidine, pyridine, and other organic bases (Figure 3 & 4).

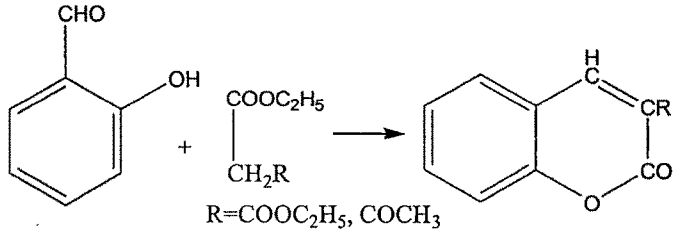


Figure 3 Knoevenagel reaction

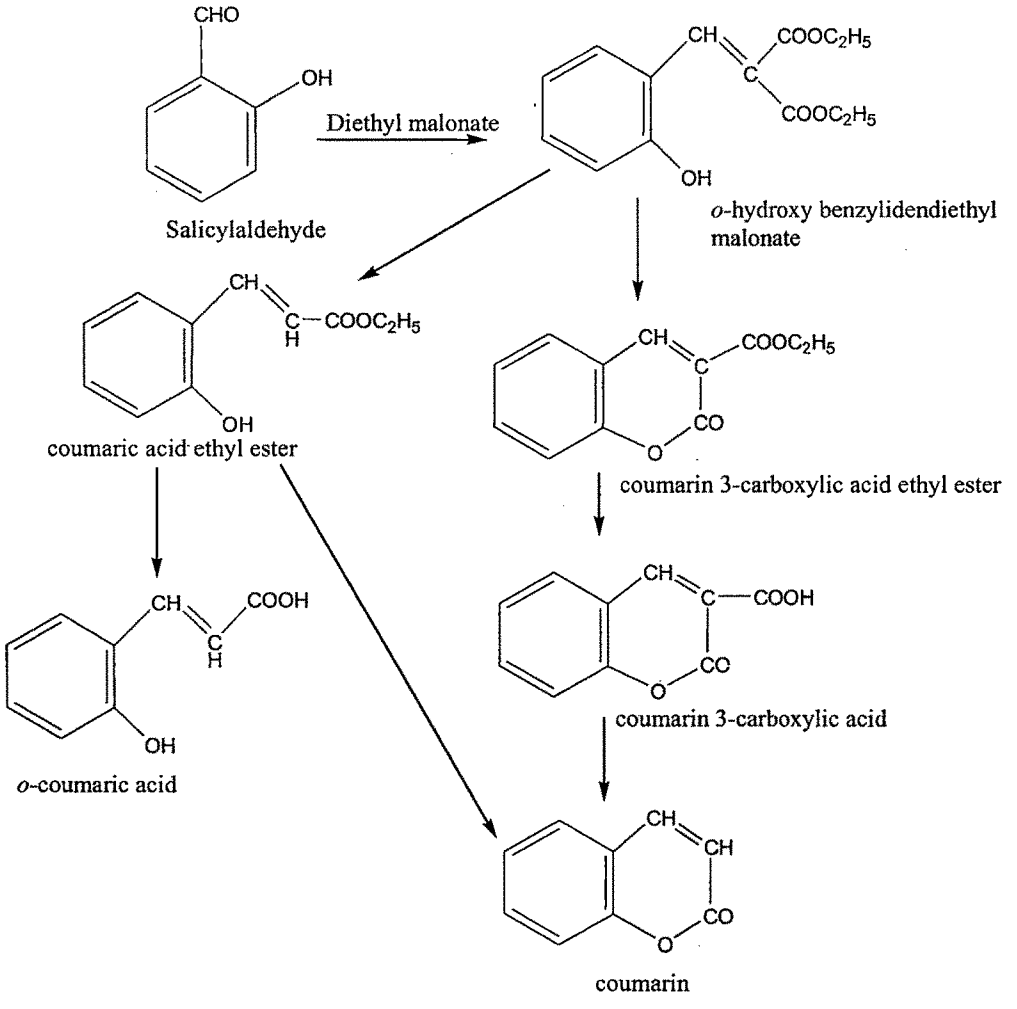


Figure 4 Reaction pathway for the synthesis of coumarin derivatives by Knoevenagel condensation [14]

Reformatsky reaction:

The Reformatsky reaction involves condensation of aldehydes(or ketones) with α-halo esters in presence of metallic zinc to form β-hydroxy-esters .It was carried out by Sergei Nikolaevich Reformatskii. The Reformatsky reaction between α-haloester and a carbonyl compound constitutes one of the most useful methods for carbon-carbon bond formation in organic synthesis. 3,4-dialkyl-substituted coumarins not synthesised by the usual methods may be synthesized using Reformatsky reaction. *o*-hydroxy aryl/ alkyl ketones, under the conditions of the Reformatsky reaction, are ultimately converted into

coumarin derivatives. A reaction scheme for synthesis of coumarin by Reformatsky reaction is presented in Figure 5.

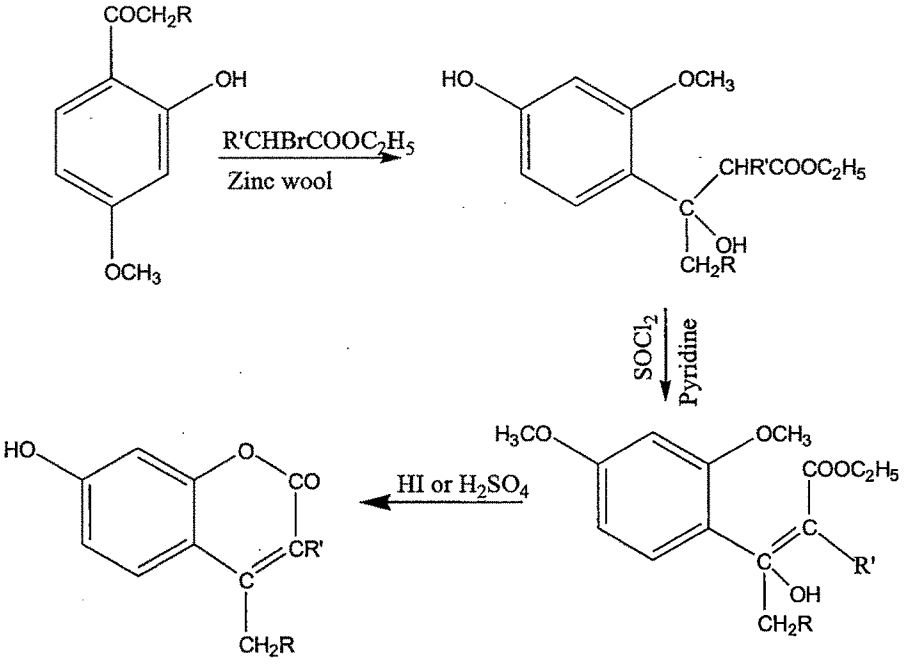


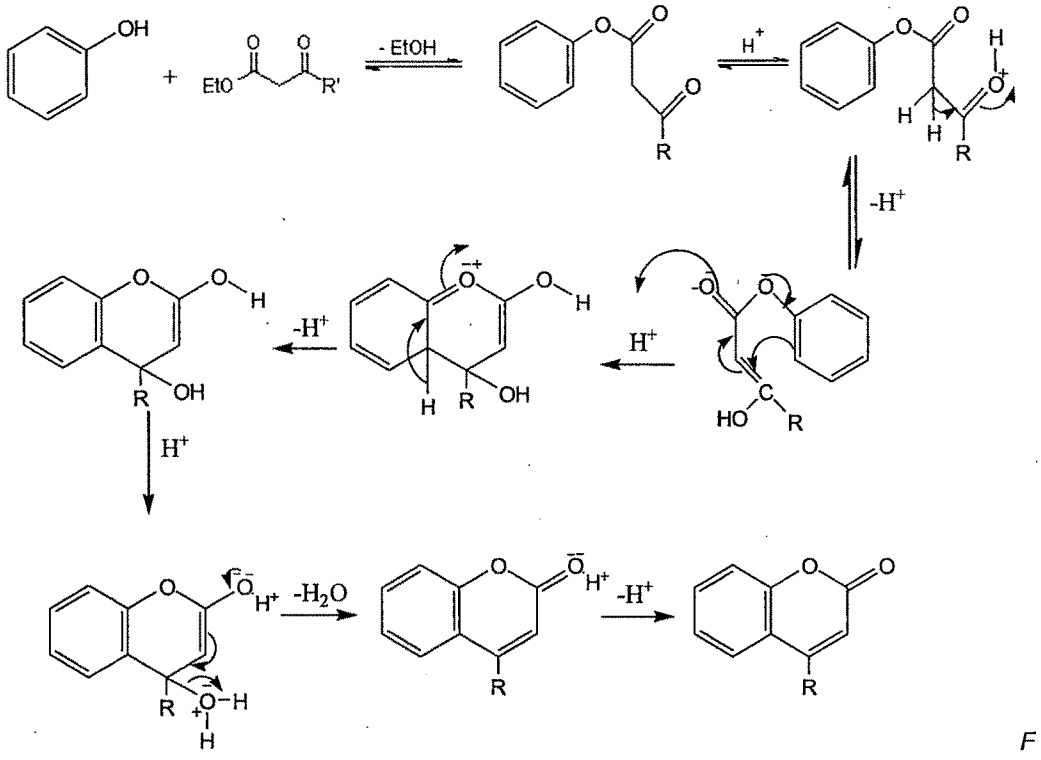
Figure 5 Reformatski Reaction

Pechmann condensation

Pechmann condensation is the most widely applied method for coumarin synthesis, since it proceeds from simple starting materials i.e phenols and a β keto ester, and gives good yields of coumarins with substitution in either the pyrone or benzene ring or in both. The course of the reaction depends on the substituents on the phenol, on the catalyst used and on the nature of the β - keto ester. Of the number of synthetic methods, there are a few which have yielded important results; there are several others whose applications are less general. All these methods center around the possibility of building up the pyrone ring on a suitable benzene derivative.

The reaction is conducted with a strong Brønsted acid such as methanesulfonic acid or a Lewis acid such as $AlCl_3$. The acid catalyses transesterification as well as keto-enol tautomerisation.

A Michael Addition leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation. Subsequent acid-induced elimination of water gives the product. A schematic of the reaction mechanism for Pechmann condensation is presented in Figure 6.



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igure 6 Mechanism for Pechmann condensation

Conventionally, coumarins say 7-hydroxy-4-methylcoumarin can be obtained in high yields upon reaction of ethyl acetoacetate with 1,3 dihydroxybenzene (resorcinol) with sulphuric acid as solvent and condensing agent[15]. Aluminium chloride [16] and trifluoroacetic acid [17] are also reported as condensing agents for synthesis of coumarins. Use of lewis acidic ionic liquid 1-butyl-3-methylimidazolium chloroaluminate is reported for coumarin syntheses via Pechmann condensation[18]. The reaction time is reduced drastically even at ambient conditions. The ionic liquid plays the dual role of solvent and Lewis acid catalyst providing a quick and efficient route to the syntheses of coumarins. Kotharkar et al [19] have reported use of

chlorosulfonic acid as an alternative to conventional acid catalysts in the Pechmann condensation.

The conventional process requires long reaction times, corrodes the reactor and creates by-products and salt waste due to neutralisation of the acid. As indicated earlier in Chapter 1, in view of the deficiencies encountered, there is a global effort to replace the conventional homogeneous liquid acids by heterogeneous solid acids. Therefore, attempts have been made to develop alternate, environmentally benign and heterogeneously catalysed synthesis routes. The use of heterogeneous acid catalysts presents advantages, such as safer operating conditions, ease of product work up, reduced equipment corrosion, and minimised waste stream, combined with reusability of the catalyst.

4.3 LITERATURE SURVEY IN THE CURRENT AREA OF STUDY:

Tyagi et al [20] have studied microwave-assisted solvent free synthesis of hydroxy derivatives of 4-methyl coumarin using nano-crystalline sulfated-zirconia catalyst. The catalyst showed good activity for activated *m*-hydroxy phenol substrates, viz., phloroglucinol and pyrogallol with ethyl acetoacetate for the synthesis of 5,7-dihydroxy 4-methyl coumarin and 7,8-dihydroxy 4-methyl coumarin, respectively, showing significant yields ranging from 78 to 85% within 5–20 min at 130 °C. However, the less activated phenol and *m*-methyl phenol was observed to be inactive for the synthesis of 4-methyl coumarin and 4,7-dimethyl coumarin, respectively, under the studied experimental conditions. Benzylsulfonic acid functionalized zirconia based transition metal oxide mesoporous molecular sieves (Zr-TMS-BSA) [21] catalyst is reported as an alternative to conventional acid catalysts in the Pechmann condensation of aromatic alcohols with ethyl acetoacetate leading to the formation of coumarin derivatives in solvent free condition at 150 °C. Reddy et al [22] have reported a novel $SO_4^{2-}/Ce_xZr_{1-x}O_2$ catalyst for Pechmann condensation of phenols under solvent-free conditions. Jin et al have reported Pechmann condensation of phenols using SO_4^{2-}/ ZrO_2 and SO_4^{2-}/ TiO_2 solid super acids[23].

Singhal et al [24] have studied Pechmann condensation of phenols using MoO_3/Al_2O_3 catalysts under solvent free conditions and reported regeneration and reusability studies of the catalyst. Pechmann condensation of phenols have been reported using Montmorillonite K10 and KSF as solid acid catalyst and toluene as solvent [25] .

Pechmann condensation is reported using a metal complex bipyridine cobalt chloride as catalyst under solvent free conditions using conventional method as well as microwave irradiation [26]. A faster reaction and higher yields compared to the conventional method and no side products were identified using microwave irradiation. Further, they have reported that, electron releasing groups on the phenol ring shows more reactivity and gives higher yields compared to simple phenol.

Patil et al [27] have reported ultrasound assisted Pechmann condensation of phenols with β-ketoesters to form coumarins, in the presence of Bismuth(III) Chloride catalyst at room temparature, with a considerable reduction of reaction time. Ultrasound was found to synergistically accelerate the condensation of phenol with β-ketoesters in the presence of $BiCl_3$. In the absence of ultrasound, under the same conditions, the reaction was found to be slow. Bahekar et al [28] have reported use of Samarium(III) nitrate hexahydrate as an alternative to conventional acid catalysts in the Pechmann condensation of phenols with ethyl acetoacetate leading to the formation of coumarin derivatives.

Maheshwara et al [29] have reported cost effective synthesis of coumarins via Pechmann condensation using heterogeneous recyclable catalyst ($HClO_4 \cdot SiO_2$) under solvent-free conditions.7-hydroxy-4-methylcoumarin, 7-methoxy-4-methylcoumarin and 7,8-benzo-4-methylcoumarin derivatives have been prepared using resorcinol, 3-methoxyphenol and 1-naphthol, respectively . The catalytic activity and the recycle studies of the catalyst in all the three reactions have been carried out and a probable mechanism for Pechmann condensation reported.

Torviso et al [30] have reported Pechmann condensation using Keggin heteropolycompounds as catalysts. The catalytic activity using several phenols such as resorcinol, 3,5-dimethoxyphenol, α-napthol and β-napthol were determined. High yield of product was obtained in the case of 4-methyl-7-hydroxycoumarin (80–95%), 4-methyl-5,7-dimethoxycoumarin (60–92%) and 4-methyl-7,8-benzocoumarin (90%). However, the 4-methyl-5,6-benzocoumarin yield was low. It was observed that the use of microwave radiation as power source, increases the reaction yield and mainly decreases the reaction time. Sudha et al [31] have reported single step synthesis of 4-methyl 7-hydroxy coumarin over Al-MCM-41 and phosphotungstic acid supported onto Al-MCM- 41 under solvent-free condition and observed that 20% heteropoly acid supported catalyst was the most active amongst all the catalysts studied.

Apart from the other heterogeneous catalysts, cation exchangers are emerging as attractive solid acid catalysts for Pechmann condensation of phenols.

Synthesis of 7-hydroxycoumarins by Pechmann reaction using Nafion resin/silica nanocomposites as catalysts has been reported by Laufer et al [32] using toluene as solvent. 7-hydroxy-4-methylcoumarin was obtained in very high yields up to 81% over SAC 40 (containing 40% Nafion on silica) and 96% yield over SAC 80 (80% of Nafion in composite) in refluxing toluene after 2 h of contact time. In contrast to the reaction conditions of the Pechmann reaction in toluene, studied by van Bekkum and co-workers [33,34], the use of the Nafion resin/silica composite materials led to 50% reduction of catalyst amount and reaction time.

The synthesis of 7-hydroxy-4-methylcoumarin via the Pechmann reaction of resorcinol and ethyl acetoacetate over various Amberlyst-type catalysts using toluene as solvent has been investigated by Sabou et al [35]. The highest yields of 7-hydroxy-4-methylcoumarin was found over dry Amberlyst-S with 95% conversion and 98% selectivity in refluxing toluene after 2 h of reaction time at 120 °C. Catalysts with fewer acid sites, showed the best

catalytic performance.However, these resins being polymers with organic framework exhibit limitation of thermal stability.

In the present endeavor, we report the potential use of M(IV) phosphates and tungstates, of the class of Tma salts, as solid acid catalysts by studying Pechmann condensation of resorcinol (R), pyrogallol (P) and phloroglucinol (Ph) with methyl aceto acetate (MA) as a model reaction wherein coumarin derivatives 4-methyl 7-hydroxy coumarin(4MHC),4-methyl 7,8-dihydroxy coumarin(4M7,8HC) and 4-methyl 5,7-dihydroxy coumarin(4M5,7HC) have been synthesized under solvent free conditions. Further, in order to see the effect of crystallinity on the catalytic performance, crystalline M(IV)phosphates have been explored for Pechmann condensation of phenols. The catalytic activity of amorphous and crystalline materials as well as M(IV)phosphates and tungstates of the class of TMA salts have been compared and correlated with surface properties of the materials.

4.4 EXPERIMENTAL

Catalyst Synthesis and Characterisation

Discussed in Chapter II.

Materials

Resorcinol, pyrogallol, phloroglucinol and methyl aceto acetate were procured from Loba chemie.

Experimental setup:

In a typical reaction, methyl acetoacetate (5 mmol) and resorcinol (5 mmol) or pyrogallol (5 mmol) or phloroglucinol(5 mmol) was stirred with the catalyst (0.25 g for resorcinol and 0.1 g for pyrogallol and phloroglucinol) in a 50 ml two necked round bottom flask at 130°C for 6-8 hours. Methyl acetoacetate works as a substrate as well as solvent for this reaction.The reaction mixture was poured in ice-water when white coloured product separated out. The product was filtered, recrystallised from ethanol, dried and weighed. Reaction parameters, mole ratio of reactants, reaction temperature, time and catalyst amount have been optimized using ZrP. Using these optimized conditions the activity of the other catalysts have been explored.

The spent catalyst was regenerated by refluxing in ethanol followed by drying at 250 °C for 30 minutes to remove organic compounds from the surface. This regenerated material was acid treated as described in Chapter 2,section 2.5.

4.5 RESULTS AND DISCUSSION

Optimization of reaction parameters using ZrP have been presented in Table 4.1. It is observed that yield increases with reaction time until an equilibrium is reached within 8h. For the same reaction time, yield increases with catalyst amount, since the number of active sites per gm of substrate increases. The weight percentage of catalyst is kept at an optimum level of 25% for resorcinol. A maximum product yield is obtained with reaction temperature up to 130 °C. Beyond this temperature, product degradation is observed.

In the case of pyrogallol and phloroglucinol, the equilibrium is attained within 6h using 0.1 g of the catalyst. Substitution of an additional hydroxyl group in the phenyl ring in case of these two isomers make them more active compounds compared to resorcinol, for Pechmann condensation with methyl acetoacetate .This can be explained on the basis of electromeric effect (+E effect) exhibited by an electron donating –OH group at meta position to the phenol hydroxyl group. Thus, electron-donating substituents in the position meta to the phenol hydroxyl group promotes condensation by favouring the formation of the reactive polarised carbocation at the *ortho* position, thereby making more facile intermediate for electrophlic substitution reaction. The *+E* effect causes displacement of electron pair away from the group, due to which negative charge in the ring system is increased and high degree of polarity is induced in the molecule.

Pechmann condensation proceeds through transesterification and intramolecular hydroxyalkylation, followed by dehydration [36,37]. All the three steps are typically acid-catalyzed reactions. Therefore, the Pechmann reaction, depends strongly on the acidity of the catalysts [36] .The number and nature of the surface acid sites play a predominant role in evaluating and correlating the catalytic activity.

Amongst amorphous M (IV) Phosphates, though surface acidity values are lower for TiP(0.59 mmol/g) and SnP(1.81 mmol/g) compared to ZrP(2.34 mmol/g), the catalytic activity/TON however is slightly higher when pyrogallol and phloroglucinol are used as substrates. This could be explained on the basis of NH_3TPD patterns which though indicates less acidity for TiP and SnP, but with a higher desorption temperature indicates presence of very strong acid sites. Acidity of a cation and hence surface acidity depends on the size and charge of the cation.In the materials under study Zr,Ti and Sn all being tetravalent as well as bearing a common anion phosphate/tungstate the size of the cation [Ti^{+4}(0.74 A°) ,Zr^{+4}(0.86 A°), Sn^{+4}(0.83 A°)] seems to play a dominant role [38]. In case of Ti^{+4} the ionic radius is small and hence the positive charge is concentrated in a small area, increasing the tendency to polarize the O–H bond in the hydroxyl group bonded to it.

Amongst tungstates, catalytic activity/TON is highest for TiW compared to SnW and ZrW. This could be explained to be due to lower surface acidity and surface area values of SnW and ZrW. TiW possesses both- a higher surface area as well as higher acidity and strong acid sites.

In case of crystalline materials, though surface area is less there is no decrease in the catalytic activity/TON. This can be attributed to the fact that though the number of surface acid sites are less for crystalline materials, the desorption temperatures are higher indicating the presence of strong acidity/ active sites enhancing the catalytic activity. Amongst the crystalline M(IV) phosphates SnPcry exhibits highest yield with the lowest acidity, which could be attributed to high desorption temperature indicating strong acid sites.

Based on the mechanism proposed earlier for Pechmann condensation of phenols using solid super acids [23], we propose the following mechanism for coumarin synthesis using TMA salts as solid acid catalysts.

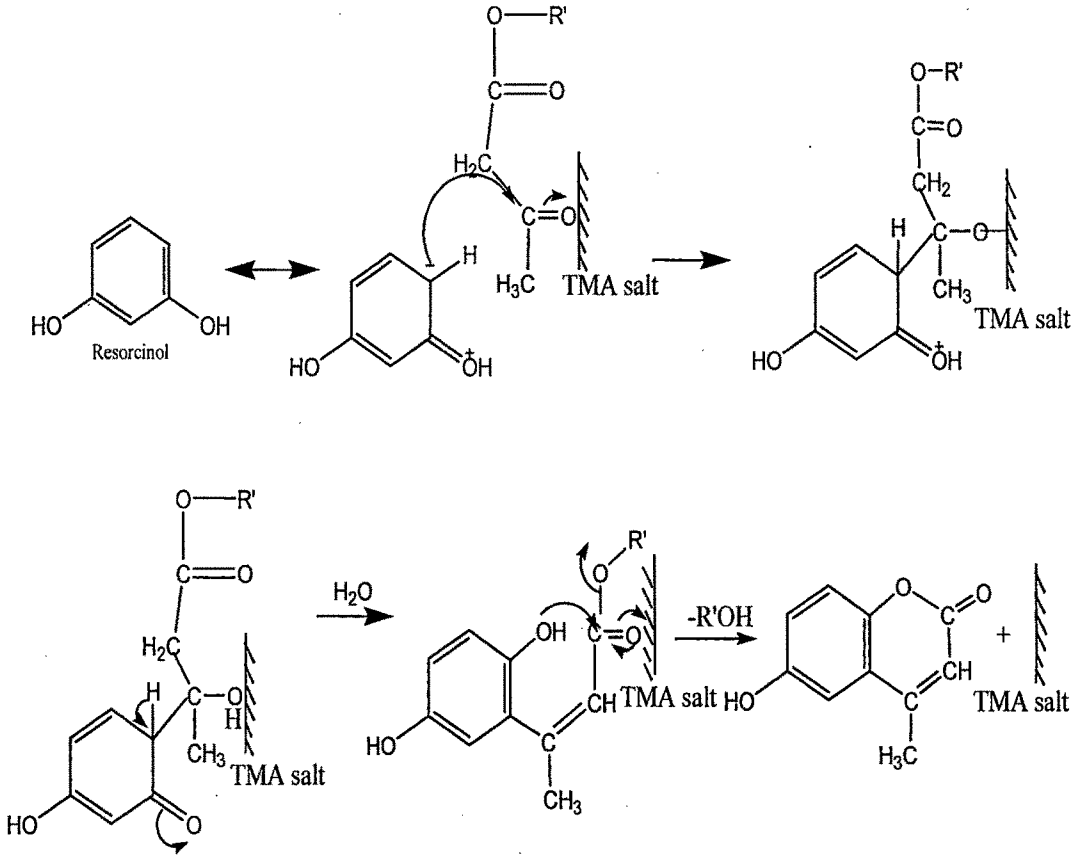

Figure 6 Proposed mechanism for Pechmann condensation using TMA salts

The conventional method for synthesis of coumarins involves use of sulphuric acid in large amount. Use of M(IV)phosphates and tungstates of the class of tma salts in the present study, eliminates use of sulphuric acid, as well as solvent free synthesis of coumarins, wherein methyl acetoacetate acts as reactant as well as solvent media for this reaction. The catalytic activity in the present work is lower for Pechmann condensation compared to earlier reports [24,30,34] however with the use of a solvent.

It is observed that in general the activity falls by ~10 % after regeneration. This could be attributed to reacting molecules entering the interstices of the catalyst which is evident from the fact that the catalyst turns dark brown after each catalytic run. However, the catalyst regains its original colour after regeneration. The study shows that M(IV) phosphates and tungstates are

insoluble during the reaction, are recoverable by filtration, and can be reused without significant loss in catalytic activity.

Table 4.1 Optimisation of reaction parameters for Pechmann Condensation of Phenols using ZrP

Substrates (Mole ratio)	A	B	C	% Yield
R+MA(1:1)	0.05	2	110	14.7
R+MA(1:1)	0.05	4	110	21.6
R+MA(1:1)	0.1	4	110	35.0
R+MA(1:1)	0.1	6	110	38.0
R+MA(1:1)	0.1	8	110	39.0
R+MA(1:1)	0.15	8	110	47.0
R+MA(1:1)	0.20	8	110	51.1
R+MA(1:1)	0.20	8	120	54.1
R+MA(1:1)	0.25	8	130	60.9
R+MA (1:1.5)	0.25	10	130	61.1
R+MA (1:2)	0.25	8	130	49.5
R+MA (1.5:1)	0.25	8	130	32.1

Table 4.2 Pechmann Condensation of resorcinol using TMA salts

Substrates (Mole ratio)	Catalyst	% Yield	TON
R+MA (1:1)	ZrP	61.1	2.76
R+MA (1:1)	TiP	51.4	2.33
R+MA (1:1)	SnP	52.9	2.39
R+MA (1:1)	ZrPcry	54.0	2.44
R+MA (1:1)	TiPcry	51.1	2.31
R+MA (1:1)	SnPcry	52.0	2.35
R+MA (1:1)	ZrW	15.2	0.69
R+MA (1:1)	TiW	54.9	2.66
R+MA (1:1)	SnW	16.2	0.73

Catalyst amount= 0.25g,reaction time=10h, reaction temperature=130^{o}C

Table 4.3 Pechmann Condensation of pyrogallol using TMA salts

Substrates (Mole ratio)	Catalyst	% Yield	TON
P+MA(1:1.5)	ZrP	61.1	7.40
P+MA(1:1.5)	TiP	76.0	9.20
P+MA(1:1.5)	SnP	76.3	9.24
P+MA(1:1.5)	ZrPcry	60	7.27
P+MA(1:1.5)	TiPcry	75	9.08
P+MA(1:1.5)	SnPcry	75	9.08
P+MA(1:1.5)	ZrW	8.64	1.05
P+MA(1:1.5)	TiW	68.23	8.26
P+MA(1:1.5)	SnW	34.6	4.19

Catalyst amount= 0.1g, reaction time=6h, reaction temperature=130°C

Table 4.4 Pechmann Condensation of phloroglucinol using TMA salts

Substrates (Mole ratio)	Catalyst	% Yield	TON
Ph+MA (1:1.5)	ZrP	72.9	8.83
Ph+MA(1:1.5)	TiP	75.0	9.08
Ph+MA(1:1.5)	SnP	75.4	9.13
Ph+MA(1:1.5)	ZrPcry	72.5	8.78
Ph+MA(1:1.5)	TiPcry	73.9	8.95
Ph+MA(1:1.5)	SnPcry	74	8.96
Ph+MA(1:1.5)	ZrW	15.2	1.84
Ph+MA(1:1.5)	TiW	54.9	6.65
Ph+MA(1:1.5)	SnW	16.2	1.96

Catalyst amount= 0.1g, reaction time=6h, reaction temperature=130°C

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