

## Synthesis of coumarins via Pechmann condensation using inorganic ion exchangers as solid acid catalysts

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This study involves synthesis and characterization of amorphous and crystalline M(IV) phosphates and tungstates, which are inorganic ion exchangers of the class of tetravalent metal acid (tma) salts. Presence of protons contained in structural hydroxyl groups indicates good potential for application in solid acid catalysis. Catalytic activity of materials has been explored by studying Pechmann condensation as a model reaction, wherein phenols (resorcinol, pyrogallol and phloroglucinol) have been treated with methyl acetoacetate to give coumarins, under solvent free conditions. Catalytic activity has been compared and correlated with surface properties of materials.

**Keywords:** Coumarin derivatives, Inorganic ion exchangers, M(IV) phosphates and tungstates, Pechman condensation, Solid acid catalysts, Tetravalent metal acid salts

### Introduction

Coumarins are used as additives in food and cosmetics, optical brightening agents and dispersed fluorescent and laser dyes<sup>1</sup>, exhibit useful and diverse biological activity and serve as anticoagulant agents<sup>2</sup>. Synthetic routes to coumarins include Pechmann, Perkin Knoevenagel and Reformatsky reactions<sup>3</sup>. Pechmann reaction is most widely applied method for coumarin synthesis, since it proceeds from simple starting materials (phenols and a  $\beta$  keto ester) and gives good yields of coumarins with substitution in either pyrone or benzene ring or both. Coumarins can be obtained in high yields upon reaction of ethyl acetoacetate with 1,3 dihydroxybenzene (resorcinol) with sulphuric acid as solvent and condensing agent<sup>4</sup>. Aluminium chloride and trifluoroacetic acid also act as condensing agent for synthesis of coumarins<sup>4</sup>. Conventional process requires long reaction times, corrodes reactor and creates by-products and salt waste due to acid neutralization. Use of heterogeneous acid catalysts provides safer operating conditions, ease of product work up, reduced equipment corrosion, and minimized waste stream, combined with reusability of catalyst. Among heterogeneous catalysts, cation exchangers are emerging as attractive solid acid

catalysts for Pechmann condensation of phenols<sup>5,6</sup>. However, these resins being polymers with organic framework exhibit limitation of thermal stability.

Inorganic ion exchangers of the class of tetravalent metal acid (Tma) salts indicate good potential for application as solid acid catalysts, due to presence of surface acid sites, combined with thermal stability. These materials possess general formula M (IV) (HXO<sub>4</sub>)<sub>2</sub> nH<sub>2</sub>O, where M(IV) = Zr, Ti, Sn, Th, Ce etc. and X=P, W, Mo, As, Sb etc. Tma salts behave as cation exchangers due to the presence of exchangeable protons contained in structural hydroxyl groups. With increasing crystallinity of Tma salts, surface area decreases<sup>7</sup>. Use of tma salts as solid acid catalysts has been explored for esterification<sup>8,9</sup>, cyclodehydration<sup>10</sup>, ketalisation of ketones<sup>11</sup>, hydration of nitriles<sup>12</sup> and cyclodehydration of 1,n diols<sup>13</sup>.

This study reports potential use of M(IV) phosphates and tungstates, where M(IV)=Zr,Sn,Ti; of the class of Tma salts, as solid acid catalysts by studying Pechmann condensation of resorcinol (R), pyrogallol (Py) and phloroglucinol (Ph) with methyl acetoacetate (MA) as a model reaction, wherein coumarin derivatives (4 methyl 7 hydroxy coumarin, 4 methyl 7,8 dihydroxy coumarin and 4 methyl 5,7 dihydroxy coumarin) have been synthesized under solvent free conditions. Amorphous M(IV) phosphates and tungstates of tetravalent Zr, Ti and Sn abbreviated as ZrP, TiP, SnP and ZrW, TiW, SnW respectively have been synthesized by sol gel method.

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Further, in order to see the effect of crystallinity on catalytic performance, crystalline phosphates abbreviated as ZrPcry, TiPcry and SnPcry have been synthesized by reflux method.

## Materials and Methods

### Synthesis of Catalysts M (IV) Phosphates and Tungstates

M (IV) phosphates and tungstates were prepared by sol-gel method. Aqueous solution (0.2 M, 100 ml) of sodium dihydrogen phosphate or sodium tungstate was added drop wise to an aqueous solution (0.1 M, 100 ml) of zirconium oxychloride or titanium tetrachloride or stannic tetrachloride with continuous stirring, maintaining resultant solution temperature at 70°C and pH 2. A gel was formed and solution along with gel was further stirred for 1 h. Gel was filtered, washed with conductivity water till free of chloride ions (step 1) and dried at room temperature. Resultant material (5 g) was taken and treated with 1M HNO<sub>3</sub> (50 ml) for 30 min with occasional shaking. Sample was then separated from acid by decantation and treated with conductivity water for removal of adhering acid. This process (acid treatment) was repeated at least 5 times. After final washing, material was dried at room temperature and used for all studies. To synthesize crystalline material, gel (obtained in step 1) was refluxed in 10 M H<sub>3</sub>PO<sub>4</sub> solution for 4 h and then filtered, washed to remove adhering ions and dried at room temperature and used for all studies.

### Characterisation

Elemental analysis was carried out by ICP-AES (Labtam, 8440 Plasmalab). Thermogravimetric analysis (TGA) of materials was performed on a Shimadzu DT-30 thermal analyzer at a heating rate of 10 °C/min. FTIR spectra of sample were performed using KBr wafer on a Bomem MB series with Epson Hi 80 printer/plotter. X-ray diffractograms (2θ=5-90°) were obtained on X-ray diffractometer (Rigaku-Dmax-30) with Cu-Kα radiation and nickel filter. Surface area measurement (BET method) was carried out on Micromeritics Gemini at -196°C using nitrogen adsorption isotherms. Surface acidity was determined on Micromeritics Chemisorb 2720, by a temperature programmed desorption of ammonia. Ammonia was chemisorbed at 120°C and then desorption was carried out up to 700°C at a heating rate of 10°C/min.

### Pechmann Condensation

In a typical reaction, MA (substrate as well as solvent) and R or Py or Ph (5 mmol each) was stirred with catalyst

(0.25 g for R, 0.1 g for Py and Ph) in a 50 ml two necked round bottom flask at 130°C for 6-8 h. Reaction mixture was poured in ice water when white colored 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 were optimized using ZrP. Using optimized conditions, activity of other catalysts was explored.

## Results and Discussion

### Catalyst Characterisation

Data on catalyst characterization (Table 1) indicated that the ratio of M (IV) to P or W is 1:2 in all materials. Absence of sharp peaks in X-ray diffractogram reveals amorphous nature of samples prepared by direct precipitation. Phosphates prepared by reflux method were, however, crystalline and compared with powder diffraction file. Surface area has been observed<sup>19</sup> higher for amorphous materials (75-105 m<sup>2</sup>/g) compared to crystalline materials (25-35 m<sup>2</sup>/g). Amorphous materials exhibit broad desorption peak compared to crystalline ones (Fig. 1). Though crystalline materials show sharper peaks indicating less number of acid sites, desorption temperatures of NH<sub>3</sub> are high indicating strong acid sites. However, TiW, though being amorphous, exhibits sharp desorption peak at ~435°C indicating presence of strong acid sites (Fig. 2). Acidity of a cation and hence surface acidity depends on size and charge of cation. Among Zr, Ti and Sn, all being tetravalent as well as bearing a common anion phosphate/tungstate, size of cation [Ti<sup>4+</sup>(0.745 Å), Zr<sup>4+</sup>(0.86 Å), Sn<sup>4+</sup>(0.83 Å)] seems to play a dominant role<sup>14</sup>. FTIR spectra show broad bands in the region ~3400 cm<sup>-1</sup> attributed to asymmetric and symmetric -OH stretching. A medium band around ~1620 cm<sup>-1</sup> is attributed to aquo H-O-H bending indicating presence of structural -OH protons in these materials. For M (IV) phosphates, a band in the region ~1035 cm<sup>-1</sup> is attributed to the presence of P=O stretching. A medium intensity band at 1400 cm<sup>-1</sup> is attributed to the presence of δ(P-OH). TGA indicates ~15% weight loss between 100-180°C corresponding to loss of water molecules, after which a gradual weight loss is observed till 600°C, attributed to condensation of structural -OH groups. Thus, materials possess structural hydroxyl groups (H of the OH being acid sites) indicating potential utility of these materials as solid acid catalysts.

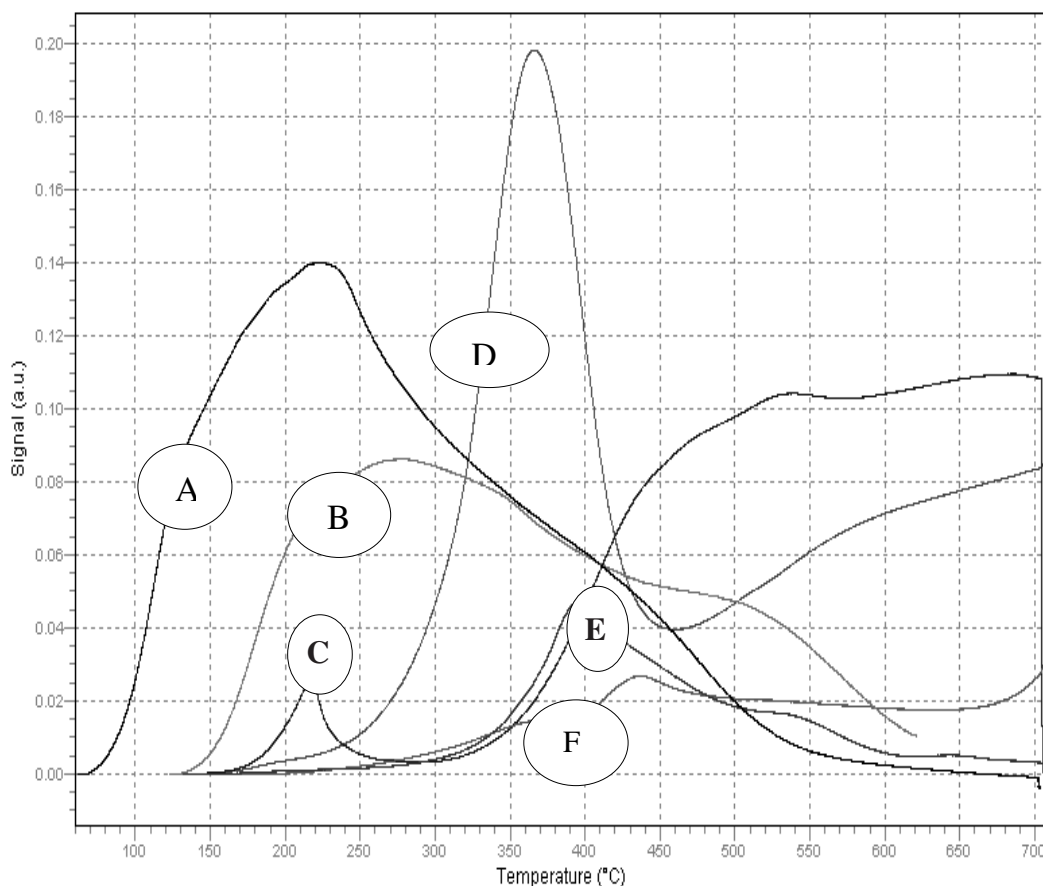
### Pechmann Condensation

Yield increases with reaction time until equilibrium is reached within 8 h (Table 2). For same reaction time, yield increases with catalyst (ZrP) amount, since number

Table 1—Characterization of catalysts [elemental analysis (M: P/W, 1:2)]

Catalyst	ZrP	TiP	SnP	ZrPcry	TiPcry	SnPcry	ZrW	SnW	TiW
Surface area, m <sup>2</sup> /g	81.9	75.45	98.55	36.75	28.00	25.00	73.11	87.33	107.75
Surface acidity, mmoles	2.34	0.59	1.81	1.75	1.5	0.66	0.64	0.77	0.89
XRD	*Am	Am	Am	JCPDS card no.			Am	Am	Am
				33-1482	44-0382	39-0513			

\*Am, amorphous

Fig 1—NH<sub>3</sub> TPD patterns of ZrP, TiP, SnP, ZrPcry, TiPcry and SnPcry (A=ZrP, B=SnP, C=TiPcry, D=ZrPcry, E=TiP, F=SnP)

of active sites per g of substrate increases. The weight percentage of catalyst is kept at an optimum level (25%) for R. A maximum product yield is obtained with reaction temperature up to 130°C, beyond which product degradation is observed. In the case of Py and Ph, equilibrium is attained within 6 h using catalyst (0.1 g). Substitution of an additional hydroxyl group in phenyl ring in case of these two isomers make them more active

compounds compared to R for Pechmann condensation with MA. The +E effect of electron-donating substituents in position meta to phenol hydroxyl group promotes condensation, by favouring formation of reactive polarised carbocation at ortho position. In general, turn over numbers are higher for Py and Ph compared to R, attributed to higher amount of catalyst used for R (Table 3).

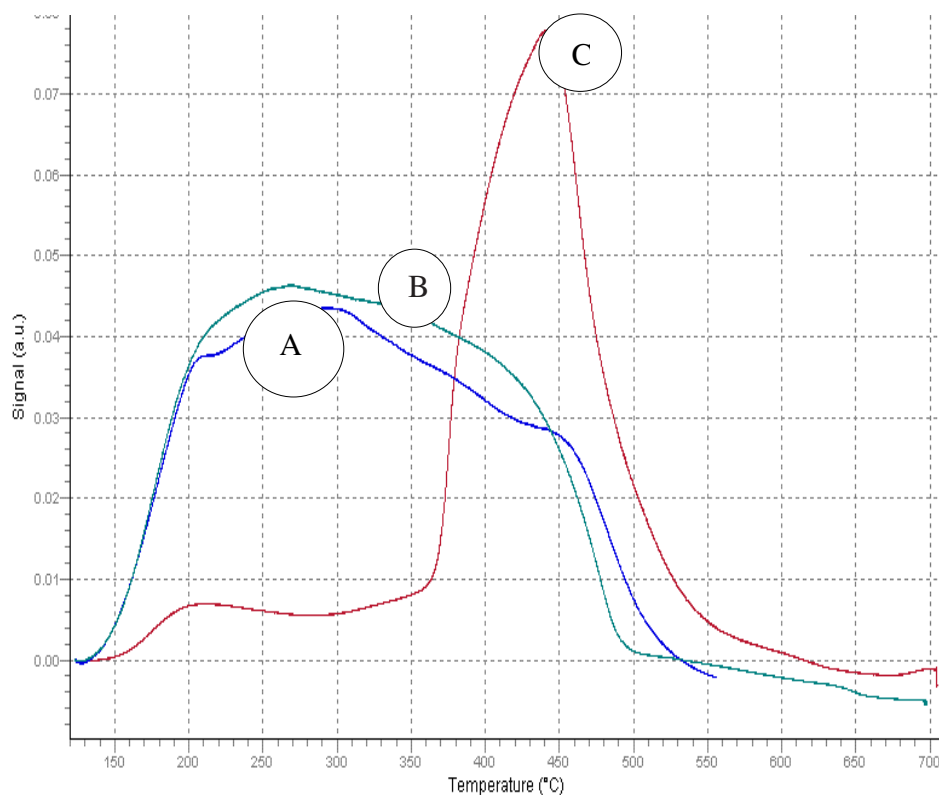


Fig 2—NH<sub>3</sub> TPD patterns of ZrW, TiW and SnW (A=ZrW, B=SnW, C=TiW)

Table 2—Optimization of reaction parameters using ZrP catalyst for Pechmann condensation of phenols

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

R+MA (resorcinol+ methyl acetoacetate), A=catalyst amount (g), B=reaction time (h), C=reaction temperature (°C)

Pechmann condensation proceeds through acid-catalyzed reactions, transesterification, intramolecular hydroxyalkylation, followed by dehydration<sup>4,15,16</sup>. Therefore, Pechmann reaction, depends strongly on acidity of catalysts<sup>15,16</sup>. Number and nature of surface acid sites play a predominant role in evaluating and correlating catalytic activity.

Amongst amorphous M (IV) Phosphates, though surface acidity values are lower for TiP and SnP compared to ZrP, catalytic activity however is slightly higher when Py and Ph are used as substrates. This could be explained on the basis of NH<sub>3</sub> TPD patterns, which indicate less acidity for TiP and SnP, but higher desorption temperature, indicating presence of very strong acid sites. Amongst tungstates, catalytic activity is highest for TiW, whereas SnW and ZrW show poor catalytic activity, attributed to lower surface acidity and surface area values of SnW and ZrW. TiW (Table 1) possesses both higher surface area as well as strong acid sites.

In case of crystalline materials, though surface area is less, there is no decrease in catalytic activity, attributed to the fact that though number of surface acid sites are less for crystalline materials, desorption temperatures are higher (Fig. 1) indicating presence of strong acidity/active sites enhancing catalytic activity. Amongst

Table 3—Pechmann condensation of phenols using TMA salts at optimized conditions (temp., 130 OC)

Substrates (Mole ratio)	A	B	Catalyst	Yield %	Turn over number
R+MA (1:1)	0.25	10	ZrP	61.1	2.76
R+MA (1:1)	0.25	10	TiP	51.4	2.33
R+MA (1:1)	0.25	10	SnP	52.9	2.39
R+MA (1:1)	0.25	10	ZrPcry	54.0	2.44
R+MA (1:1)	0.25	10	TiPcry	51.1	2.31
R+MA (1:1)	0.25	10	SnPcry	52.0	2.35
R+MA (1:1)	0.25	10	ZrW	15.2	0.69
R+MA (1:1)	0.25	10	TiW	54.9	2.66
R+MA (1:1)	0.25	10	SnW	16.2	0.73
Py+MA(1:1.5)	0.10	6	ZrP	61.1	7.40
Py+MA(1:1.5)	0.10	6	TiP	76.0	9.20
Py+MA(1:1.5)	0.10	6	SnP	76.3	9.24
Py+MA(1:1.5)	0.10	6	ZrPcry	60.0	7.27
Py+MA(1:1.5)	0.10	6	TiPcry	75.0	9.08
Py+MA(1:1.5)	0.10	6	SnPcry	75.0	9.08
Py+MA(1:1.5)	0.10	6	ZrW	8.64	1.05
Py+MA(1:1.5)	0.10	6	TiW	68.23	8.26
Py+MA(1:1.5)	0.10	6	SnW	34.6	4.19
Ph+MA(1:1.5)	0.10	6	ZrP	72.9	8.83
Ph+MA(1:1.5)	0.10	6	TiP	75.0	9.08
Ph+MA(1:1.5)	0.10	6	SnP	75.4	9.13
Ph+MA(1:1.5)	0.10	6	ZrPcry	72.5	8.78
Ph+MA(1:1.5)	0.10	6	TiPcry	73.9	8.95
Ph+MA(1:1.5)	0.10	6	SnPcry	74.0	8.96
Ph+MA(1:1.5)	0.10	6	ZrW	15.2	1.84
Ph+MA(1:1.5)	0.10	6	TiW	54.9	6.65
Ph+MA(1:1.5)	0.10	6	SnW	16.2	1.96

R+MA(resorcinol+ methyl acetoacetate), Py+MA(pyrogallol+ methyl acetoacetate), Ph+MA (phloroglucinol+methyl acetoacetate), A=catalyst amount (g), B=reaction time(h)

crystalline M(IV) phosphates, SnPcry exhibits lowest acidity. However, desorption temperature is higher indicating strong acid sites.

Catalyst turns dark brown after each catalytic run, because during course of reaction, molecules come onto surface of catalyst. Some molecules enter into reaction to give the product while a few of them get adsorbed on surface, which is marked by change in colour of catalyst. Reactant molecules are weakly adsorbed is evident from catalyst regaining original colour, when treated with ethanol. The possibility of molecules entering interstices cannot be ruled out, since yields go down by 10% after every regeneration, leading to deactivation of catalyst.

Pechmann condensation of phenols has been reported using Montmorillonite K10 and KSF as solid acid catalyst and toluene as solvent<sup>2</sup>. R.Sabou *et al*<sup>15</sup> have reported synthesis of 7-hydroxy 4 methyl coumarin by ion exchange resin Amberlyst and toluene as solvent. Reddy

*et al*<sup>3</sup> reported solvent free synthesis of hydroxy and dihydroxy coumarins by sulfated ceria zirconia catalyst. In all these cases, yields are >90%. 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 present study eliminates use of sulphuric acid, as well as solvent free synthesis of coumarins, wherein MA acts as reactant as well as solvent media for this reaction. Catalytic activity in present work is lower for a solvent free Pechmann condensation compared to earlier reports<sup>2,3,5</sup>, however with the use of a solvent.

### Conclusions

This study indicates promising use of phosphates and tungstates as solid acid catalysts for synthesis of coumarins. However, to obtain better yields, TMA salts with higher surface acidity/surface area should be synthesized using modified sol-gel routes.

### Acknowledgement

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