$ZrCl_4$ catalysed solvent free synthesis of coumarins

B. Gangadasu, P. Narender, B. China Raju* and V. Jayathirtha Rao

Organic Chemistry Division-II, Uppal Road, Tarnaka, Indian Institute of Chemical Technology, Hyderabad – 500 007, India

$ZrCl_4$ is an efficient catalyst in the Pechmann condensation of phenols with ethyl acetoacetate and propynoic acid under solvent free conditions leading to formation of coumarins in very good yields.

Keywords: synthesis, coumarins, Pechmann reaction, solvent free conditions, zirconium tetrachloride

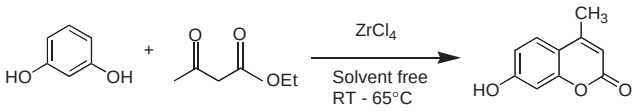
Coumarins are an important class of compounds in the field of agrochemicals and pharmaceuticals. The applications of coumarins are many as they are additives in food, cosmetics,[1] anticoagulants,[2] optical brightners,[3] dispersed fluorescent and laser dyes.[4] Several methods have been reported for the synthesis of coumarins including Pechmann,[5a] Perkin,[5b] Knoevengal,[5c] Reformatsky[5d] and Wittig[6] reactions. Among these the Pechmann reaction is the most widely used method for the preparation of coumarins, as it involves the simple condensation of phenols with β-keto esters. Several acid catalysts[7] like protic acids and Lewis acids are reported to effect this condensation. However, many of these catalysts have to be used in excess (4–12 fold excess) as a result this generates a lot of acid waste and leads to severe environmental pollution. Recently $InCl_3$,[8] Zn/I_2,[9] and Ionic liquids[10] were also reported to effect these condensation reactions.

Conventional methods are also reported for the synthesis of coumarins using solid acid catalysts[11] and microwave irradiation.[12] Still there is scope to develop environmentally benign and catalytic methods to effect this reaction. Zirconium is highly abundant in the earth, zirconium (IV) compounds are of low cost, less toxic and ideal for catalytic applications.[13] $ZrCl_4$ has been used in various chemical transformations such as deprotection of ethers and esters, [14a,b] and preparation of 3,4-dihydropyrimidin-2(1*H*)-ones.[14c]

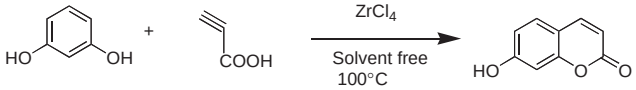
Herein we[15] report a simple, efficient and solvent free method for the synthesis of 4-methylcoumarins via Pechmann condensation in very good yields (Scheme 1).

In a typical experimental procedure which involves the condensation of a variety of phenols with ethyl acetoacetate in the presence of a catalytic amount of $ZrCl_4$ (10 mol %) for a short period of time as required to complete the reaction (TLC).[19] The Pechmann condensation was performed on a variety of phenols to study the substituent effect on the reactivity and the results are summarised in Table 1. Substrates having electron-donating (entries 1–5) groups attached to the aromatic ring undergo a very smooth condensation to give maximum yields at room temperature with shorter reaction times. Naphthols (entries 6 and 7) require higher temperatures.

Resacetophenone (entry 8) was reported not to react to give a coumarin derivative in the presence of sulfuric acid, but the reaction was observed using $AlCl_3$, [7e] but a temperature of 130°C was required in nitrobenzene. In contrast $ZrCl_4$ furnished moderate yield at 65°C with out any solvent. Under similar conditions phenol failed to yield the coumarin product (entry 9). We extended this method to prepare coumarins, which are key intermediates for xanthyletin, xanthoxyletin, dihydroxanthyletin, luvangetin and dihydroluvangetin[16] in the presence of $ZrCl_4$. Resorcinol when reacted with propynoic acid in the presence of $ZrCl_4$ (10 mol %) gave 7-hydroxy coumarin[17] in very good yield (Scheme 2).

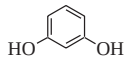
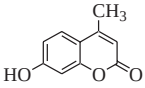
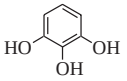
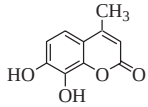
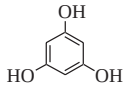
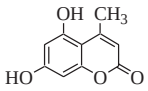
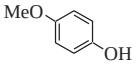
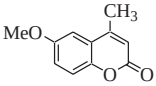
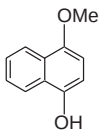
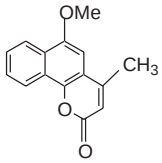
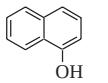
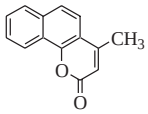
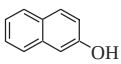
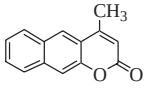
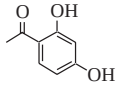
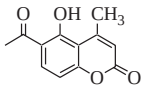
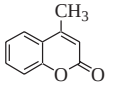


Scheme 1



Scheme 2

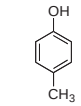
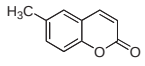
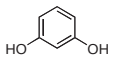
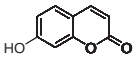
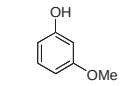
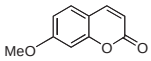
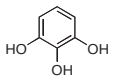
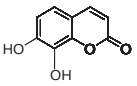
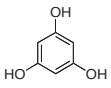
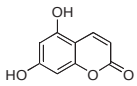
Table 1 Synthesis of coumarins catalysed by $ZrCl_4$

Entry	Substrate	Product[a]	Time/ min	Temp/ °C	Yield/ %[b]
1			20	RT	98
2			20	RT	94
3			20	RT	96
4			30	RT	94
5			30	RT	94
6			60	65	86
7			60	65	88
8			90	65	50
9			90	65	–

[a]All the products were well characterised by IR, ^{1}H NMR; and mass and compared with those of authentic compounds[8]. [b]Isolated yields.

* Correspondence. E-mail: chinaraju@iict.res.in

Table 2 $ZrCl_4$ catalysed synthesis of coumarins

S.No	Substrate	Time/min	Product	Yield/%
11		60		62
12		45		68
13		60		58
14		45		66
15		45		72

All the products were characterised by spectroscopic data and compared by authentic samples.[18]

The reaction proceeded with equimolar amounts of phenols and propynoic acid in the presence of 10mol% $ZrCl_4$. Various phenols reacted under these reaction conditions to give the corresponding coumarins and the results were tabulated in Table 2.

In summary, we have achieved the synthesis of 4-methylcoumarins via Pechmann condensation and coumarins by using $ZrCl_4$ in catalytic amount. The shorter reaction times, environmental compatibility and operational simplicity make this procedure an attractive alternative to the currently available methods.

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19 *Typical experimental procedure for compounds*: A mixture of 4-methoxynaphthol (10 mmol) and ethyl acetoacetate (10 mmol) was stirred at room temperature in the presence of $ZrCl_4$ (10 mol%) for 20 min with a guard tube. After completion of the reaction (TLC), the crude product was subjected to column chromatography to give 6-methoxy-4-methyl-2*H*-benzo [h] chromene-2-one (**5**) in 98% yield as colourless crystals, m.p. 134–136°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.52 (s, 3H, CH_3), 4.06 (s, 3H, OCH_3), 6.36 (s, 1H), 6.74 (s, 1H, aromatic), 7.58–7.68 (m, 2H, aromatic), 8.20–8.22 (m, 1H, aromatic), 8.52–8.58 (m, 1H, aromatic). Mass (*m/z*): 240 (M^+), 226, 198, 142, 115, 76 and 39. The other compounds were prepared in a similar manner.