Article

One-pot synthesis of coumarins unsubstituted on the pyranic nucleus catalysed by a Wells–Dawson heteropolyacid ($H_6P_2W_{18}O_{62}$)

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Abstract: The development of a method to produce coumarins unsubstituted on the pyranic nucleus catalyzed from Wells–Dawson heteropolyacid ($H_6P_2W_{18}O_{62}$), phenol derivatives and ethyl 3, 3-diethoxypropionate using Pechmann condensation under solvent-free conditions is described. This catalytic method was also applied successfully to synthesize various substituted coumarins, including the corresponding phenols and ethyl 3, 3-diethoxypropionate. This work provides a novel, cheaper and safer way to syhthesize coumarins unsubstituted on the pyranic nucleus.

Keywords: coumarin; one-pot synthesis; catalysis; Wells–Dawson heteropolyacid

1. Introduction

Coumarin is an important structural unit frequently found in many biologically important compounds and natural products [1]. Coumarins exhibit various biological properties which include antibacterial, anticoagulant, hypothermal and anti-helminthic properties, as well as having various applications, eg as food additives, insecticides, cosmetics, perfumes, optical brighteners, and dispersed fluorescent [2–9]. Coumarins are also used as intermediates for the synthesis of coumarones, chromenes, 2-acylresorcinols, and fluorocoumarins [10–13]. Coumarins can be synthesized using the Wittig reaction, Perkin reaction, Reformatsky reaction, Pechmann reaction, Claisen reaction and Knoevenagel condensation [14–17]. The most common mehotd used for their synthesis is the Pechmann condensation, where phenol is reacted with a β-ketoester or acid under strongly acidic conditions [18–20]. The products synthesized by Pechmann condensation frequently have a substituent group on the pyranic heterocyclic nucleus [21–23]. The synthesis of coumarins unsubstituted on the pyranic heterocyclic nucleus poses a challenge in chemistry [24]. Despite having a number of effective methods, the synthesis of coumarins unsubstituted on the pyranic nucleus remains under review (Figure 1) [25–34]. The current experimental procedures often require expensive reagents, long reaction times, use of expensive catalysts or strong acid, an inert atmosphere with air and moisture sensitivity.

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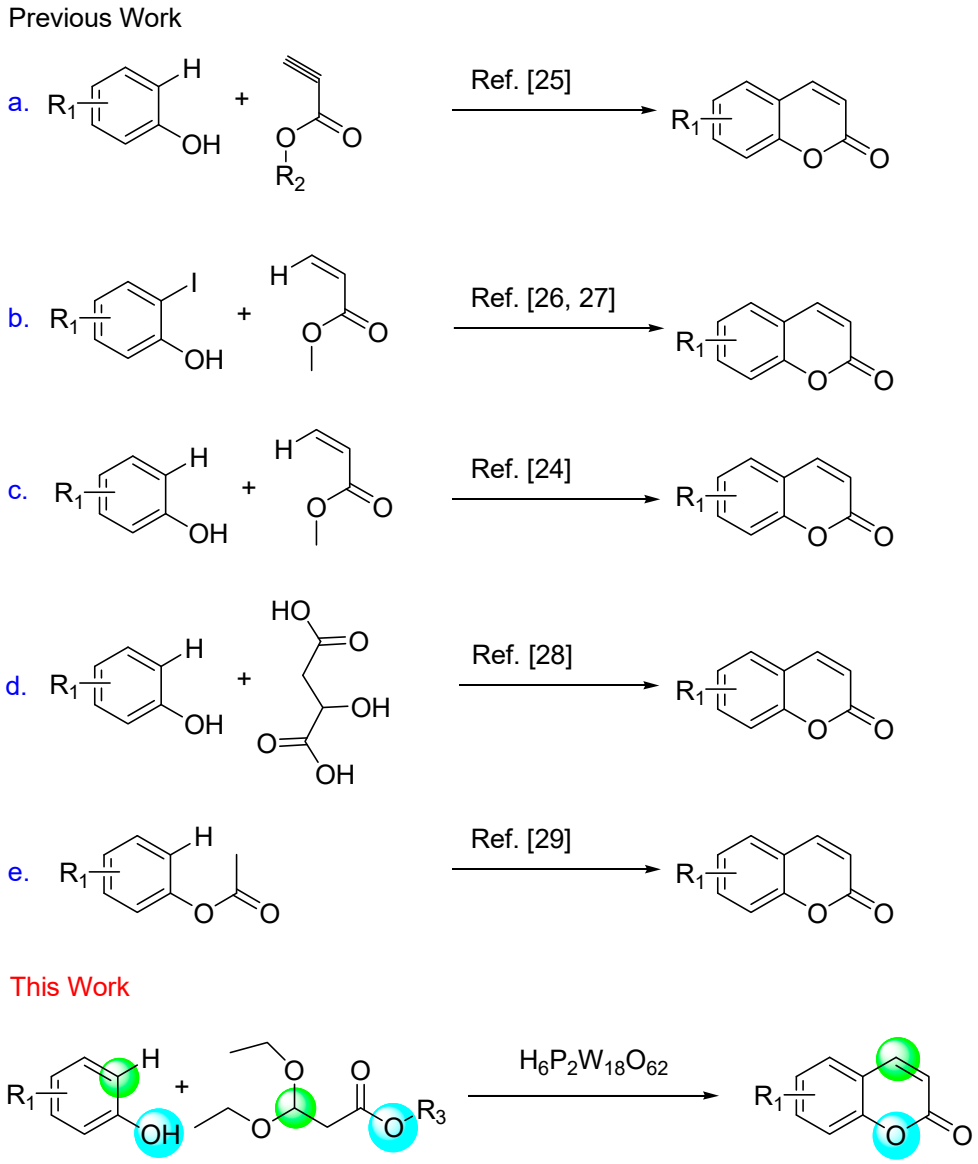

Figure 1. Synthesis of coumarins unsubstituted on the pyranic nucleus

Due to the simple and relatively inexpensive reagents, the Pechmann Condensation enables the synthesis of coumarins by condensing phenols with β-keto esters in the presence of acid catalysts (Figure S1) [35, 36].

The products coumarins have a substituent group on the pyranic heterocyclic nucleus. Several mineral acids, organic acids and Lewis acidic salts such as P_2O_5, H_2SO_4, HCl, $ZnCl_2$, $TiCl_4$, $FeCl_3$ and trifluoroacetic acid have been used as catalysts [37–39]. The coumarin product unsubstituted on the pyranic nucleus could be synthesized by condensing phenols with formylacetic esters using Pechmann condensation (Figure S2). However, formylacetic ester is not stable in the reaction and present in the form of formylacetic esters acetal or sodium salt of formylacetic esters [40–44]. Pechmann condensation was done under acidic conditions. Therefore acidic catalysts were used for synthesizing coumarins unsubstituted on the pyranic nucleus from formylacetic esters acetal (ethyl 3, 3-diethoxypropionate). Several mineral acids, such as H_2SO_4 and H_3PO_4 have been used as catalysts [45, 46]. To look for a more effective, safer and greener synthetic protocol for these scaffolds, we report Wells–Dawson heteropolyacid ($H_6P_2W_{18}O_{62}$)-catalyzed the synthesis of coumarins unsubstituted on the pyranic nucleus from phenol derivatives and ethyl 3, 3-diethoxypropionate using Pechmann condensation under solvent-free conditions.

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2. Results

The activity of catalysts was tested using the Pechmann reaction. 2-methyl-3-hydroxy-phenol and ethyl 3, 3-diethoxypropionate were selected to optimize the catalysts. The yield of product 7-hydroxy-8-methylcoumarin was between 5 and 82 % under solvent-free conditions (Table 1, entries 1–12). These results showed the significant effect of the catalyst Wells–Dawson heteropolyacid ($H_6P_2W_{18}O_{62}$) in the reaction (Table 1, entries 10). Initial studies revealed that 7-hydroxy-8-methylcoumarin can be synthesized efficiently (82%) from 2-methyl-3-hydroxy-phenol and ethyl 3, 3-diethoxypropionate by a $H_6P_2W_{18}O_{62}$ (10 mol %)-catalyzed method at 100 °C for 3 hours.

Table 1. Comparison of the efficiencies of various catalysts used in the synthesis of 7-hydroxy-8-methylcoumarin

Entry	Catalyst	Time (h)	Yield (%)
1	$MeSO_3H$ (3mmol)	3	20
2	$MeSO_3H$ (0.5 mmol)/ (0.5 mmol) basic Al_2O_3	3	30
3	$MeSO_3H$ (0.5 mmol)/ (0.5mmol) neutral Al_2O_3	3	34
4	$MeSO_3H$(0.5 mmol)/ acidic Al_2O_3(0.5 mmol)	3	80
5	acidic Al_2O_3(0.5 mmol)	3	30
6	$AlCl_3$(0.5 mmol)	2	10
7	$AlCl_3$(0.5 mmol) / $MeSO_3H$(0.5 mmol)	2	12
8	$ZnCl_3$(0.5 mmol) / $MeSO_3H$(0.5 mmol）	2	5
9	$Cu(CH_3CN)_4PF_6$ (0.5 mmol）	2	10
10	$H_6P_2W_{18}O_{62}$ (0.5 mmol)	2	82
11	$FeCl_3$ (0.5 mmol)	3	8
12	$TiCl_4$ (0.5 mmol)	3	5

* Reaction conditions: 2-methylbenzene-1, 3-diol (5 mmol), ethyl 3, 3-diethoxypropionate (5 mmol), stirred at 100 °C, under solvent-free conditions; GC yield.

Optimization of the reaction conditions for the Pechmann reaction was tested under solvent-free conditions. Firstly, the effect of the amount of catalyst on yields was thoroughly investigated (Table 2, entries 1–4). The yield of 7-hydroxy-8-methylcoumarin compared to product progressively increased from 75 to 87 % as the amount of catalyst increased (Table 2, entries 1–2). However, the product yield did not change as catalyst continued to increase above 10 mol % (Table 2, entries 3–4). Noteworthy, 0.25 mmol (5 mol %) catalyst proved to be very effective for the reaction (Table 2, entry 2). The effect of the temperature, reaction time and raw material ratio of reaction were investigated. These results indicated that the temperature, reaction time and raw material ratio all had a significant effect on the reaction (Table 2, entries 5–12). Optimum conditions were found include a raw material ratio (2-methyl-3-hydroxy-phenol/ethyl 3, 3-diethoxypropionate) of 1:1.5, addition of 5 mol % catalyst loading at 90°C for 3 hours (Table 2, entry 11).

Table 2. Optimisation of Pechmann condensation in the synthesis of 7-hydroxy-8-methylcoumarin

Entry	Cat. loading (mmol)	T (°C)	Time (h)	Raw material ratio	Yield (%)
1	0.10	100	3	1:1	75
2	0.25	100	3	1:1	87
3	0.5	100	3	1:1	86
4	1.00	100	3	1:1	84
5	0.25	80	3	1:1	74
6	0.25	90	3	1:1	90
7	0.25	90	2	1:1	72

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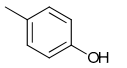
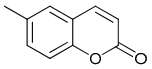
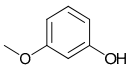
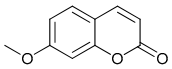
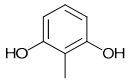
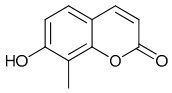
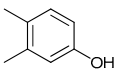
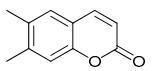
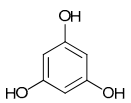
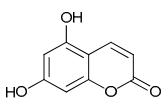
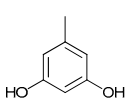
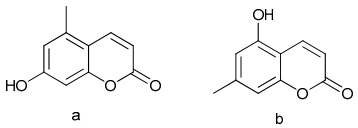
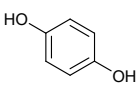
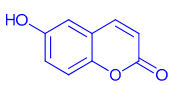
8	0.25	90	4	1:1	89
9	0.25	90	3	1:0.8	84
10	0.25	90	3	1:1.2	90
11	0.25	90	3	1:1.5	95
12	0.25	90	3	1:2	95

* Reaction conditions: 2-methylbenzene-1, 3-diol (5 mmol), ethyl 3, 3-diethoxypropionate, $H_6P_2W_{18}O_{62}$; under solvent-free conditions; Raw material ratio: 2-methyl-3-hydroxy-phenol/ethyl 3, 3-diethoxypropionate; GC yield.

These optimal reaction conditions were used to synthesize coumarin derivatives by condensing phenol derivatives and ethyl 3, 3-diethoxypropionate (Table 3). Substituents such as CH_3, OCH_3 and OH, at the meta-position on a phenol ring produced good yields of the corresponding coumarins (Table 3, entries b–f). The electron-donating substituents in the meta-position to the phenolic-OH facilitated the cyclisation. Reaction of phloroglucinol with ethyl 3, 3-diethoxypropionate gave 63% yield. However, coumarin could not be produced \ from both benzene-1, 2, 3-triol and benzene-1, 2, 4-triol (Table 3, entries i, j). The reactivity of phloroglucinol was observed to be higher than benzene-1, 2, 3-triol and benzene-1, 2, 4-triol due to the two hydroxyl groups at the metapositions compared to one hydroxyl group in benzene-1, 2, 3-triol and benzene-1, 2, 4-triol. Similarly, coumarin could not be produced from hydroquinone (Table 3, entries g) and p-cresol (no hydroxyl groups at the metapositions) (Table 3, entries a) gave a low yield of 30%. Phenols containing the electron-withdrawing functional group NO_2 (Table 3, entries h) and bulky substituents (Table 3, entries k) failed to produce corresponding coumarins. Substituting hydroxyl groups at the ortho, or para positions on a phenol ring also failed to produce the corresponding coumarins (Table 3, entries g, i, j). In the case of unsymmetrical phenols, a regioisomer corresponding to cyclisation at the sterically hydroxyl group at ortho-position of Michael addition reaction sites is favoured (Table 3, entries f). However, the regioisomer do not appear in the Pechmann Condensation of phenols with β-keto esters. This may be due to the reactivity of the formylacetic esters acetal (ethyl 3, 3-diethoxypropionate) being weaker than β-keto esters.

Table 3. Syntheses of coumarins using Pechmann condensation of phenols with ethyl 3, 3-diethoxypropionate

Entry	Phenol	product	Yield (%)
a			30
b			66
c			90
d			52
e			63
f		 a b	80(a:b=3:1)
g			<5

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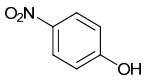
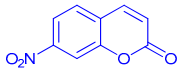
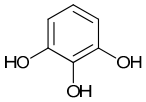
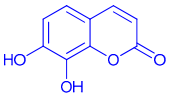
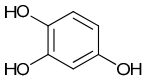
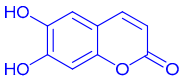
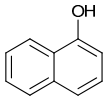
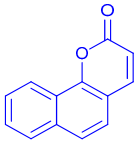
h			<5
i			<5
j			<5
k			<5

* Reaction conditions: Phenol (5 mmol), ethyl 3, 3-diethoxypropionate (7.5 mmol) stirred at 90 °C for 3 hours; Under solvent-free conditions. Isolated yield (compound a-f), GC yield (compound g-k).

The yield of coumarin produced from 5-methylbenzene-1, 3-diol increased from 74% to 88% as the reaction temperature increased from 80 °C to 90 °C. However, the yield did not change as the reaction temperature continued to increase to 100 °C. The isomer ratio (a:b) increased from 2:1 to 6.7:1 as the reaction temperature increased. It was found that high temperature was suitable to generate an isomer a ring and low temperatures were favorable to generate an isomer b ring (Table S1).

A mechanism is suggested in Figure 2. The reaction was conducted using a Lewis acid $H_6P_2W_{18}O_{62}$. The acid catalyses transesterification as well as acetal-enol tautomerisation, then a Michael addition leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation. A subsequent acid-induced elimination of ethanol gives the final product.

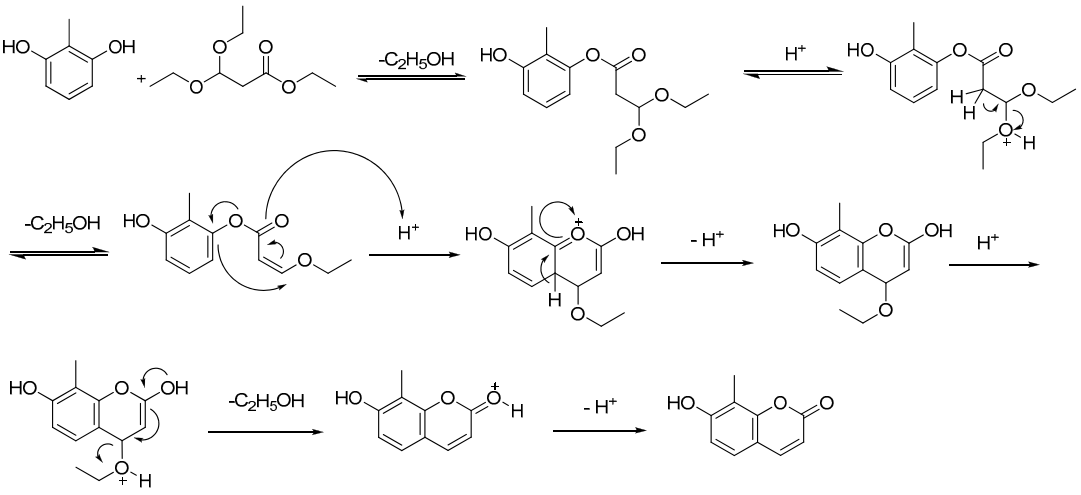


Figure 2. Suggested mechanism

3. Materials and Methods

3.1 General Procedure for Synthesis of Coumarins

To a mixture of 2-methylbenzene-1, 3-diol (5 mmol) and ethyl 3, 3-diethoxypropionate (7.5 mmol), $H_6P_2W_{18}O_{62}$ (0.25 mmol) was added at 90 °C. The mixture was stirred vigorously for 3 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, water (15.0 mL) was added to the reaction mixture, filter, The product was isolated by column chromatography on silica gel (acetone–petroleum ether: 1: 10).

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3.2 Characterization Data of Coumarins

6-methylcoumarin: white solid. 30% yield. M.p. 181-182 °C. ^{1}H NMR (300 MHz; $CDCl_3$) δ: 7.67 (1H, d, J = 9.3 Hz), 7.35 (1H, d, J = 1.5 Hz), 7.32 (1H, d, J = 1.5 Hz), 7.23(1H, d, J = 8.4 Hz), 6.40(1H, d, J = 9.3 Hz), 2.23 (3H, s, CH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 160.6, 142.9, 133.6, 132.3, 127.2, 118.0, 116.1, 20.2. IR (KBr) ν: 1170, 1261, 1490, 1575, 1620, 1709 cm^{-1}. MS major fragments m/z, (%): 51.1 (10), 77.1(25), 104.1 (26), 131.1 (90), 161.1 (100).

7-methoxycoumarin: white solid. 66% yield. M.p. 112-113 °C. ^{1}H NMR (300 MHz; $CDCl_3$) δ: 7.65(1H, d, J = 9.6 Hz), 7.37 (1H, d, J = 8.4 Hz), 6.85(1H, d, J = 2.4 Hz), 6.82(1H, d, J = 2.4 Hz), 6.25(1H, d, J = 9.3 Hz), 3.87 (3H, s, OCH_3). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 163.3, 161.9, 155.7, 144.3, 112.5, 112.4, 111.9, 100.2, 55.0. IR (KBr) ν: 1024, 1262, 1395, 1507, 1613, 1706 cm^{-1}. MS major fragments m/z, (%): 51.1 (12), 63.0 (12), 77.1(18), 89.1 (6), 105.0 (14), 119.9 (3), 133.1 (100), 148.0 (83), 160.2 (2), 176.1 (92).

7-hydroxy-8-methylcoumarin: white solid. 90% yield. M.p. 189-190 °C. ^{1}H NMR (300 MHz; MeOD) δ: 7.91(1H, d, J = 9.3 Hz), 7.36 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 8.7 Hz), 6.18(1H, d, J = 9.3 Hz), 2.14(3H, s, CH_3). ^{13}C NMR (75 MHz; MeOD) δ: 161.4, 160.9, 156.6, 142.3, 138.6, 114.8, 111.1, 110.7, 100.7, 18.5. IR (KBr) ν: 1146, 1199, 1473, 1608, 1684, 1717, 1733, 3420 cm^{-1}. MS major fragments m/z, (%): 51.1 (10), 63.0 (7), 78.1(21), 89.0 (2), 105.1 (21), 123.0 (1), 134.1 (100), 162.0 (70).

6, 7-dimethylcoumarin: white solid. 52% yield. M.p. 197-198 °C. ^{1}H NMR (300 MHz; DMSO) δ: 8.05(1H, d, J = 9.6 Hz), 6.63 (1H, s), 6.54 (1H, s), 6.19 (1H, d, J = 9.9 Hz), 2.50(3H, s, CH_3), 2.21(3H, s, CH_3). ^{13}C NMR (75 MHz; DMSO) δ: 168.0, 150.2, 137.6, 132.8, 125.9, 121.7, 117.8, 19.5, 14.6. IR (KBr) ν: 1137, 1455, 1585, 1626, 1735, 2851, 2922, 2972, 3382 cm^{-1}. MS major fragments m/z, (%): 51.1 (6), 65.1 (5), 77.0 (10), 91.0 (15), 103.1 (6), 115.1 (21), 131.1 (68), 146.1 (64), 159.0 (8), 174.1 (100) .

5, 7-dihydroxycoumarin: white solid. 63% yield. M.p. 290-292 °C. ^{1}H NMR (300 MHz; MeOD) δ: 8.07 (1H, d, J = 9.9Hz,), 6.15-6.28 (2H, m), 6.03 (1H, d, J = 9.9 Hz). ^{13}C NMR (75 MHz; MeOD) δ: 162.5, 161.2, 159.4, 156.9, 156.4, 140.0, 109.1, 102.1, 98.7, 94.5. IR (KBr) ν: 1150, 1244, 1362, 1602, 1662, 1699, 3177 cm^{-1}. MS major fragments m/z, (%): 51.1 (5), 69.0 (19), 121.0 (10), 150.1 (100), 178.0 (45).

7-hydroxy-5-methylcoumarin: white solid. 50% yield. M.p. 212-213 °C. ^{1}H NMR (300 MHz; MeOD) δ: 8.04(1H, d, J = 9.6Hz), 6.65 (1H, s), 6.55(1H, d, J = 2.1 Hz), 6.18 (1H, d, J = 9.6 Hz), 2.46 (3H, s, CH_3). ^{13}C NMR (75 MHz; MeOD) δ: 161.0, 160.6, 156.3, 141.9, 138.3, 114.5, 110.8, 110.4, 100.4, 18.2. IR (KBr) ν: 1124, 1243, 1566, 1607, 1682, 1696, 3240 cm^{-1}. MS major fragments m/z, (%): 65.1 (9), 91.1 (26), 120.1 (8), 148.1 (90), 176.0 (100) .

5-hydroxy-7-methylcoumarin: white solid. 25% yield. M.p. 181-182 °C. ^{1}H NMR (300 MHz; MeOD) δ: 8.14 (1H, d, J = 9.6 Hz), 6.63 (1H, s), 6.60 (1H, s), 6.23 (1H, d, J = 9.6 Hz), 2.35 (3H, s, CH_3). ^{13}C NMR (75 MHz; MeOD) δ: 161.6, 157.2, 154.0, 143.5, 138.9, 110.8, 109.7, 106.4, 105.7, 19.9. IR (KBr) ν: 1122, 1339, 1508, 1609, 1627, 1700, 3177 cm^{-1}. MS major fragments m/z, (%): 65.0 (10), 91.1 (31), 119.1 (7), 148.1 (81), 176.0 (100) .

4. Conclusions

In summary, an acid-catalyzed synthesis of coumarins unsubstituted on the pyranic nucleus, derived from phenol derivatives and ethyl 3, 3-diethoxypropionate using Pechmann condensation under solvent-free conditions has been described. The catalytic method was also applied successfully to synthesize various substituted coumarins, from the corresponding phenols and ethyl 3, 3-diethoxypropionate. Carrying out reactions under solvent-free conditions is an important strategy in organic synthesis as it significantly reduces production waste and precludes post-synthesis steps, such as product isolation and solvent recycling [47–49]. This method provides a novel greener and safer choice for the synthesis of coumarins unsubstituted on the pyranic nucleus. Development of this method to synthesize related heterocyclic moieties is ongoing in our laboratory.

Supplementary Materials: The Supplementary Materials are available online.

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Sample Availability: Samples of the compounds **a–f** are available from the authors.