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Chlorosulfonic acid-catalysed one-pot synthesis of coumarin

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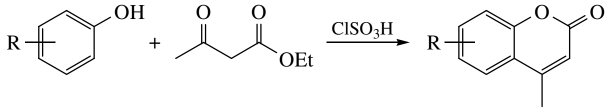
Chlorosulfonic acid is used as an alternative to conventional acid catalysts in the von Pechmann condensation of phenol with β-ketoester leading to the formation of substituted coumarin.

Coumarins occupy an important place in organic chemistry. Coumarin compounds are used for the synthesis of fluorocoumarins, chromones, coumarones, 2-acyl resorcinol, food additives and cosmetics[1] and possess anthelminthic, hypnotic, insecticidal and anticoagulant biological activities.[2] Coumarin was synthesised by von Pechmann,[3] Perkin,[4] Knövenagel,[5,6] Reformatsky[7] and Wittig[8,9] reactions.

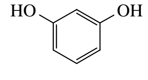
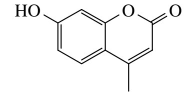
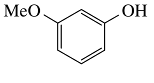
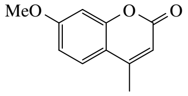
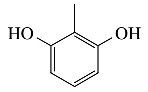
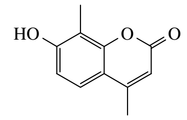
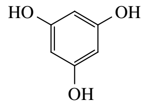
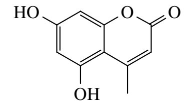
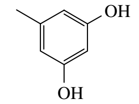
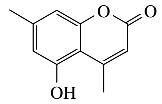
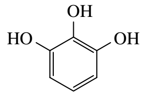
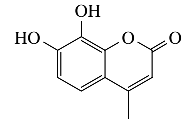
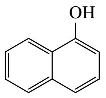
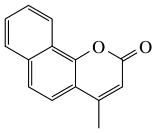
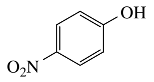
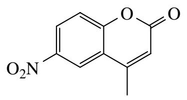
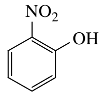
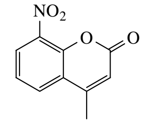
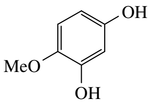
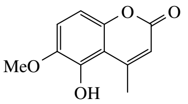
The Pechmann reaction is the most widely used method for synthesising coumarins as it involves the condensation of phenol with β-ketonic esters in the presence of a variety of acidic condensing agents and gives good yields of 4-substituted coumarins.[10,11] Acid catalysts have been used in the Pechmann reaction,[3] including sulfuric acid,[3] phosphorus pentoxide,[12,13] aluminium chloride[14] and trifluoroacetic acid.[15] However, these catalysts have to be used in an excess, for example, 10–12 equiv. of sulfuric acid or 3–4 equiv. of trifluoroacetic acid. Phosphorus pentoxide is required in a five-fold excess. Recently, the Pechmann reaction has been carried out successfully using microwave irradiation[16,17] and ionic liquids.[18]



Scheme 1

Chlorosulfonic acid has found applications in reactions such as alkylation, halogenation, rearrangement, cyclization and polymerization, usually operating as a strong acid catalyst and an efficient halogenating and dehydrating agent.[19]

Table 1 Synthesis of coumarins *via* von Pechmann condensation of phenol with β-ketoesters catalysed by chlorosulfonic acid.

Substrate	Product	Time/min Exp. (Lit.)	Temperature/°C Exp. (Lit.)	Yield (%)
		10 (60)[20]	10 (75)[20]	98
		10 (60)[20]	10 (75)[20]	94
		10 (30)[21]	10 (80)[21]	90
		10 (60)[20]	10 (75)[20]	95
		10 (40)[22]	10 (80)[22]	89
		10 (20)[20]	10 (80)[20]	91
		25 (120)[20]	10 (110)[20]	88
		22 (20)[20]	10 (80)[20]	78
		20 (35)[21]	10 (80)[21]	75
		15 (40)[20]	10 (80)[20]	50

We report the Pechmann condensation using chlorosulfonic acid as a catalyst under solvent-free conditions (Scheme 1).† In the presence of chlorosulfonic acid, the reaction of ethyl acetoacetate and resorcinol was carried out under solvent-free conditions at 10 °C and resulted in the formation of 7-hydroxy-4-methylcoumarin in 98% yield. We investigated the reactions of a series of monohydric and polyhydric phenols with β-ketoesters to obtain the corresponding coumarins (Table 1). In general, we observed that the reaction proceeded faster than conventional ones and the yields were comparable.

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† *Typical experimental procedure.* A mixture of resorcinol (1.1 g, 10 mmol) and ethyl acetoacetate (1.3 g, 10 mmol) was cooled in an ice bath. Chlorosulfonic acid (0.2 ml) was added dropwise with constant stirring at appropriate time (Table 1). The reaction mixture, after being cooled to room temperature, was poured into crushed ice (40 g) and stirred for 5–10 min. The crystalline products were collected by filtration under suction (water aspirator) washed with ice-cold water and then recrystallised from methanol to afford pure 7-hydroxy-4-methylcoumarin as yellowish prisms (1.74 g, 98%), mp 184–186 °C. ^{1}H NMR ($CDCl_3$) δ: 2.2 (s, 3H, Me), 6.1 (s, 1H), 6.83 (d, 1H, J 2.4 Hz), 6.97 (dd, 1H, J 8.7 and 2.4 Hz), 7.5 (d, 1H, J 8.7 Hz). IR (KBr, ν/cm^{-1}): 2985, 1740, 1625. ES/MS, m/z: 175 (M – H).

This procedure was followed for the preparation of all of the substituted coumarins listed in Table 1. All compounds were identified by comparison of analytical data (IR, ^{1}H NMR and mass spectra) and melting ponts with published data.