$KHSO_4$ catalysed Pechmann condensation under solvent-free conditions

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$KHSO_4$ is used as an alternative to conventional acid catalysts in the Pechmann condensation of phenols with β-ketoesters leading to the formation of substituted coumarins. The method is simple, cost-effective, solvent-free and gives good isolated yields.

Keywords: potassium hydrogensulfate, Pechmann reaction, coumarins

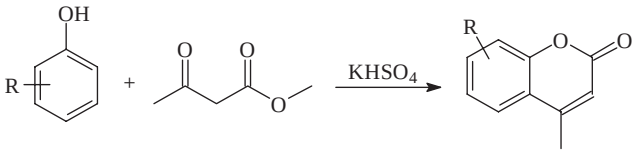
Coumarins attract interest because of their diverse biological activity.[1] They find their application as pharmaceuticals, fragrances, agrochemicals, and insecticides.[2] A valuable method for the synthesis of coumarins is the Pechmann reaction, of phenols. Using concentrated sulfuric acid as the catalyst.[3] By-products, are formed and the reaction needs a long time, and introduces corrosion problems.[4] For these reasons, there have been some attempts to find alternative environmentally benign synthetic routes. Nafion-H,[5] zeolite H-BEA, amberlyst 15,[6] montmorillonite clay,[7] and other solid acids[8] have been employed for this purpose in the Pechmann condensation. Some organic acids and metallic Lewis acids are also examined in this transformation.[9] Although these methods are suitable for certain synthetic applications many of these procedures are associated with one or more disadvantages such as expensive or corrosive reagents, long reaction time, tedious workup, and low selectivity. Large amounts of solid supports result in the generation of a large amount of toxic waste. Pechmann reactions have also been conducted in chloroaluminate ionic liquids.[10] However, in the case of chloroaluminate ionic liquid method, it requires the use of HCl for the quenching of the reaction mixture, thus making the process costly and environmentally hazardous.

Recently, hydrogensulfates have emerged as a new class of environmentally benign acidic catalysts for organic transformations.[11–18] They are inexpensive and easy to handle. Some typical acid-catalysed reactions, such as synthesis of 4(3H)-quinazolinones,[11] deprotection of TBDMS and acetonides,[12,13] biginelli condensation,[14,15] esterification[16,17] and synthesis of bis-indolylmethanes[18] have been evaluated using hydrogensulfates as catalysts. In view of the emerging importance of the hydrogensulfates as novel acidic catalysts, we wished to explore the use of potassium hydrogensulfate ($KHSO_4$) as promoters for the synthesis of coumarins by Pechmann condensation.

Results and discusions

Initially, resorcinol and methyl acetoacetate were used as substrater to test the feasibility of $KHSO_4$ as a catalyst for the Pechmann reaction. At 90 °C, better catalytic activity of $KHSO_4$ was obtained in 20 mol % of catalyst amount than in 10 mol % (Table 1, entries 1 and 2). The subsequent condition optimisation experiments revealed that both the 5 h and 90 °C was necessary to complete the reaction. When 3 h or 75 °C was used, the yields only reached 44 % and 20 %, respectively (entries 3 and 4).

Having these results in hand, other phenols have been subjected to the conditions of run 1 in Table 1, and the results are listed in Table 2. $KHSO_4$ proved to be active toward all substrates. Many activated phenols, such as resorcinol, pyrogallol, phloroglucinol, 3-methoxyphenol and 2-methylresorcinol could be converted to corresponding coumarins in excellent yields (entries 1–5). The reactivity of 3-methylphenol and 1-naphthol seems to be inferior as compared with that of the formers; 4,7-dimethylcoumarin and 4-Me-7,8-benzocoumarin were obtained in yields of 55 % and 44 %, respectively (entries 6 and 7).



Scheme 1

Experimental

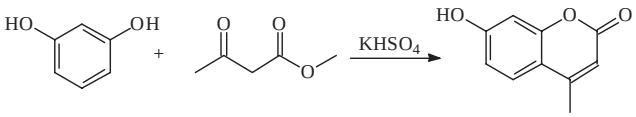
Typical procedure of Pechmann reaction: $KHSO_4$ (3.0 mmol) was dissolved into a mixture of resorcinol (15.0 mmol) and methyl acetoacetate (15.0 mmol) in a 25 ml round bottom flask equipped with a distillation condenser. The content was stirred vigorously for desired time at 90 °C. At the end of reaction, the reaction mixture was cooled to room temperature. The liquid mixture solidified at ambient temperature. Ethanol (10 ml) was added and heated at 50 °C until complete dissolution of the solid. This ethanol solution was then put into a 100 ml beaker containing a lot of water. Crystalline products were collected by filtration to give 7-hydroxy-4-methylcoumarin in 93 % yield; the crude crystals thus obtained were recrystallised from EtOH to give pure 7-hydroxy-4-methylcoumarin as colourless prisms (m.p. 183–186 °C) (lit.,[9] 158–187 °C).

Spectroscopic data for selective products

7-hydroxy-4-methylcoumarin: Colourless prisms (2.46 g, 93 %), m.p. 183–186 °C; δ_H(400; CD_3COCD_3) 2.40 (s, 3H), 6.07 (s, 1H), 6.73 (s, 1H), 6.85 (d, J = 8.4, 1H), 7.60 (d, J = 8.8, 1H), 9.50 (s, 1H); IR (KBr) 3499 (OH), 1670 (C=O) cm; MS: m/z = 176 (M^+), 148, 120, 110, 91, 74; $C_{10}H_8O_3$ (176.171): calcd. C 68.18, H 4.58; found C 68.39, H 4.56.

7,8-dihydroxy-4-methylcoumarin: White solid (2.62g, 91 %), m.p. 238–240 °C; δ_H(400; CD_3COCD_3) 2.40 (s, 3H), 6.07 (s, 1H), 6.87 (d, J = 8.8, 1H), 7.14 (d, J = 8.0, 1H), 8.62 (s, 1H), 8.74 (s, 1H); IR (KBr) 3227 (OH), 1620 (C=O) cm; MS: m/z = 192 (M^+), 176, 164, 147, 136, 118, 89, 77, 63; $C_{10}H_8O_4$ (192.171): calcd. C 62.50, H 4.20; found C 62.33, H 4.24.

Table 1 Pechmann condensation between resorcinol and methyl acetoacetate over $KHSO_4$ catalyst[a]



Entry	Amount of catalyst/mol %	Temperature/ °C	Time/h	Yield/%
1	20	90	5	93
2	10	90	5	24
3	20	90	3	44
4	20	75	5	20

[a]Resorcinol, 15 mmol; methyl acetoacetate.

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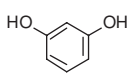
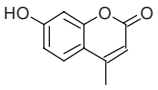
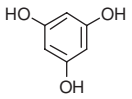
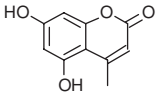
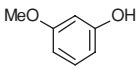
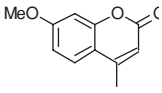
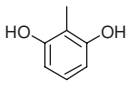
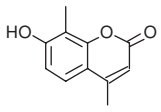
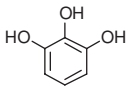
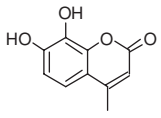
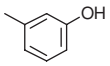
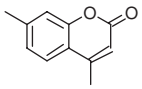
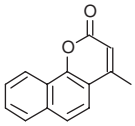
Table 2 Pechmann reactions between phenols and methyl acetoacetate over $KHSO_4$[a]

Entry	Phenols	Products	Time/h	Temperature/°C	Yields/%	M.p./°C
1			5	90	93	183–186 (185–187[9d])
2			5	90	89	180–184 (180–185[10a])
3			8	110	88	160–162 (160–162[9d])
4			4	90	92	138–139 (138–139[9d])
5			3	90	91	238–240 (236–239[9d])
6			10	110	55	131–132 (131.5–132[7b])
7			10	110	44	155–157 (154–156[9d])

[a]Reaction conditions: $KHSO_4$, 3.0 mmol; phenols, 15 mmol; methyl acetoacetate, 15 mmol; 90 °C.

5,7-dihydroxy-4-methylcoumarin: White solid (2.57g, 89 %), m.p. 180–184 °C; δ_H(400; CD_3COCD_3) 2.63 (s, 3H), 5.83 (s, 1H), 6.27 (d, *J* = 1.6, 1H), 6.36 (d, *J* = 2.4, 1H), 9.57 (s, 2H); IR (KBr) 3152 (OH), 1620 (C=O) cm; MS: *m/z* = 192 (M^+), 178, 164, 149, 135, 121, 77, 69, 43; $C_{10}H_8O_4$ (192.171): calcd. C 62.50, H 4.20; found C 62.44, H 4.25.

7-methoxy-4-methylcoumarin: colourless prisms (2.51 g, 88 %), m.p. 160–162 °C; δ_H(400; CD_3COCD_3) 2.35 (s, 3H), 3.82 (s, 3H), 6.16 (s, 1H), 6.91 (d, *J* = 8.8, 1H), 7.62 (d, *J* = 8.8, 1H); IR (KBr) 1609 (C=O) cm; MS: *m/z* = 190 (M^+), 162, 147, 138, 124, 94, 81, 65, 51; $C_{11}H_{10}O_3$ (190.198): calcd. C 69.46, H 5.30; found C 69.40, H 5.33.

Conclusion

In conclusion, we have demonstrated an efficient and simple alternative for the preparation of substituted coumarins via the Pechmann condensation using $KHSO_4$ as catalyst. Prominent among the advantages of this new method are operational simplicity, good isolated yields, solvent-free condition, very inexpensive, easily available catalyst and easy workup procedure employed.

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