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Short communication

A solvent-free synthesis of coumarins via Pechmann condensation using heterogeneous catalyst

Muchchintala Maheswara, Vidavalur Siddaiah, Guri Lakishmi Vasantha Damu, Yerra Koteswara Rao, Chunduri Venkata Rao *

Department of Chemistry, Sri Venkateswara University, Tirupati 517502, India

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Abstract

Substituted coumarins are synthesized from phenols and ethyl acetoacetate or methyl acetoacetate via Pechmann condensation using heterogeneous recyclable catalyst ($HClO_4$·SiO_2) under solvent-free conditions. This method is simple, cost effective, requires short reaction times and benefits from the elimination of production of acidic waste streams generated with conventional acid catalyst to give good yields.

Keywords: Phenols; Ethyl acetoacetate; Methyl acetoacetate; Coumarins; $HClO_4$·SiO_2; Recyclable heterogeneous catalyst; Solvent-free conditions

The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals [1] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers [2]. They have varied bioactivities, such as, inhibitory of platelet aggregation [3], antibacterial [4], anticancer [5], inhibitory of steroid 5α-reductase [6] and inhibitory of HIV-1 protease [7]. Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [8]. Their properties turn coumarins very interesting targets to organic chemists, and several strategies for their synthesis were already developed.

Coumarins can be synthesized by various methods such as Pechmann [9], Perkin [10], Knoevenagel [11], Reformatsky [12] and Witting [13] reactions. Pechmann condensation is one of the most common procedures for the preparation of coumarin and its derivatives. This method involves the reactions between a phenol and a β-keto ester in the presence of an acidic catalyst. Simple starting materials are required here to produce various substituted coumarins in good yields. Different acid catalysts like H_2SO_4, P_2O_5, $FeCl_3$, $ZnCl_2$, $POCl_3$, $AlCl_3$, PPA, HCl, phosphoric acid and trifluoroacetic acid are known to affect this condensation [14]. However, in the current context of environmental impact, these methods are not attractive as they require catalyst in excess, for example, sulfuric acid in 10–12 equivalents [15], trifluoroacetic acid in three to four equivalents [14b] and phosphorus pentoxide in five-fold excess [16]. Further, such reactions required long reaction time and in some cases gave lower yields. Recently, cation exchange resins [17] and solid acid catalysts [18] have been tried for this reaction. These reactions have been attempted using microwave irradiation [19] for accelerated syntheses of different coumarins. In previous year a profound interest was shown in the use of ionic liquids [20] for organic synthesis and on green chemistry [21] we set out to develop a solvent-free synthesis of coumarins using an inexpensive and non-polluting catalyst. In recent years heterogeneous catalysts are gaining more importance due to enviro-economic factor. The catalyst is generally of low cost and can be easily handled or removed. Thus there will be no undesirable wastage causing environmental pollution. To the best of our knowledge, no report has been made about the use of heterogeneous catalyst for synthesis of coumarins via Pechmann condensation using the heterogeneous catalyst, silica supported perchloric acid ($HClO_4$·SiO_2).

Here in, we report as the substituted phenols and ethyl acetoacetate or methyl acetoacetate undergo condensation in the

* Corresponding author. Tel.: +91 877 2249532; fax: +91 877 2249532.
E-mail address: cvr_svu@yahoo.com (C.V. Rao).

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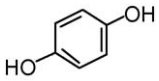
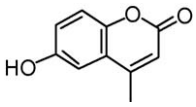
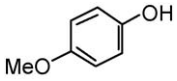
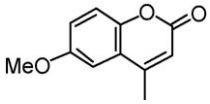
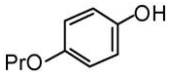
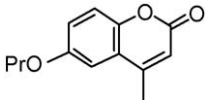
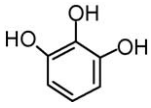
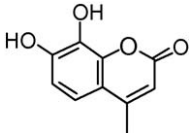
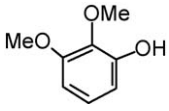
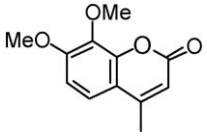
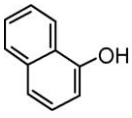
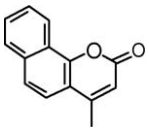
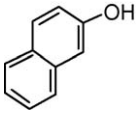
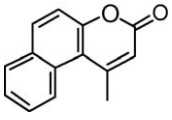
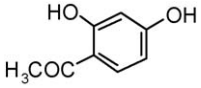
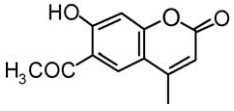
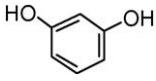
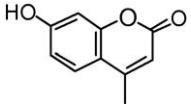
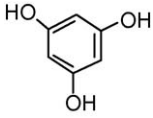
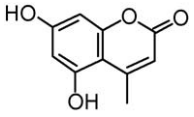
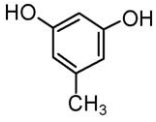
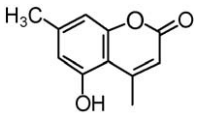
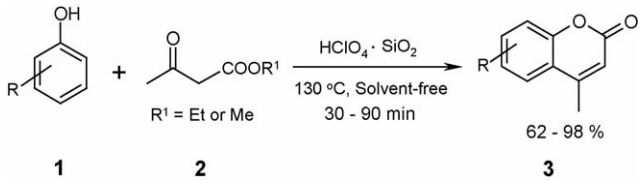
Table 1
Synthesis of coumarins using $HClO_4$ SiO_2 under solvent-free conditions[a]

Entry	Substrate	Time (min)	Product	Isolated yield (%)
3a		30		91[b], 90[c]
3b		45		82[b], 78[c]
3c		55		80[b], 80[c]
3d		75		98[b], 96[c]
3e		75		96[b], 93[c]
3f		65		89[b], 84[c]
3g		80		76[b], 77[c]
3h		90		67[b], 65[c]
3i		35		95[b], 95[c]
3j		60		97[b], 97[c]
3k		45		82[b], 78[c]

[a] The structures of the products were determined from their spectroscopic (^{1}H NMR and MS) data.
[b] Ethyl acetoacetate is used as a reactant.
[c] Methyl acetoacetate is used as a reactant.



Scheme 1.

presence of heterogeneous $HClO_4{\cdot}SiO_2$ catalyst under solvent-free conditions to produce the coumarins in excellent yields (Scheme 1).

Several coumarins were successfully synthesized (Table 1) in high yields by following the above method. The reaction mixture was stirred at 130 °C in a preheated oil-bath. We have carried out these reactions with a series of monohydric and polyhydric phenols with ethyl acetoacetate as well as with methyl acetoacetate to obtain the corresponding coumarins. The present catalyst can easily be prepared [22] from perchloric acid and silica gel. The experimental procedure with this catalyst is very simple and the catalyst can be removed easily by filtration. Hence there will not be any unnecessary acidic waste streams to create environmentally hazardous pollution. However, substrates having electron-donating groups in the *para* position to the site of electrophilic substitution gave maximum yields under reaction conditions in short periods of time. Similarly naphthols (Table 1, entries **3f** and **3g**) required long reaction times due to presence of another phenyl moiety. From Table 1, it is observed that the reactions proceeded faster than the conventional methods and the yields are comparable. Both the acetoacetic esters (ethyl and methyl) reacted almost similarly to produce coumarins. The catalyst was recovered, activated and reused for four consecutive times with only slight variation in the yields of the products. All the products were identified by comparison of analytical data (IR, NMR, and MS) of those reported for authentic samples.

In conclusion, we have developed a simple and efficient synthesis of substituted coumarins via Pechmann condensations using $HClO_4{\cdot}SiO_2$ catalyst under solvent-free conditions. Moreover the low cost of the catalyst, solvent-free condition, low toxicity of the catalyst, fast reaction times, simple experimental procedure, recyclablity of the catalyst and high yields of the products are the advantages. We believe our procedure will find important applications in the synthesis of coumarins. The method is environmentally benign.

1. Experimental

1.1. General procedure

A mixture of a phenol (1 mmol), ethyl acetoacetate or methyl acetoacetate (1.1 mmol) and $HClO_4{\cdot}SiO_2$ (50 mg) was added and the reaction mixture was stirred at 130 °C in a pre-heated oil-bath. The reaction was monitored by TLC. After completion of the reaction mixture was filtered and the residue was washed with EtOAc. The total organic portion was concentrated and subjected to purification by column chromatography. The compounds are well known and in agreement with spectral and physical data.

The spectral (IR, ^{1}H NMR and MS) and elemental data of some representative compounds are given below.

Compound **3d**: IR (Neat) (cm^{-1}) 3411, 3228, 1647, 1620, 1583, 1433, 1140, 804; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.40 (brs, 1H), 9.12 (brs, 1H), 6.99 (d, J = 7.0 Hz, 1H), 6.90 (d, J = 7.0 Hz, 1H), 5.98 (s, 1H), 2.38 (s, 3H); EIMS (*m*/*z*) 192 ($M^{\bullet+}$); Anal. Calcd for $C_{10}H_8O_4$: C, 62.5; H, 4.16%. Found: C, 62.2; H, 4.12%.

Compound **3e**: IR (Neat) (cm^{-1}) 2928, 1639, 1622, 1493, 1233, 1192, 798; ^{1}MR ($CDCl_3$, 200 MHz) δ 7.28 (d, J = 7.0 Hz, 1H), 6.87 (d, J = 7.0 Hz, 1H), 6.10 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.41 (s, 3H); EIMS (*m*/*z*) 220 ($M^{\bullet+}$); Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.45%. Found: C, 65.70; H, 5.40%.

Compound **3j**: IR (Neat) (cm^{-1}) 3473, 3199, 1660, 1618, 1533, 1416, 1160, 815; ^{1}NMR ($CDCl_3$, 200 MHz) δ 9.90 (brs, 1H), 9.70 (brs, 1H), 6.23 (d, J = 7.0 Hz, 1H), 6.17 (d, J = 7.0 Hz, 1H), 5.70 (s, 1H), 2.11 (s, 3H); EIMS (*m*/*z*) 192 ($M^{\bullet+}$); Anal. Calcd for $C_{10}H_8O_4$: C, 62.5; H, 4.16%. Found: C, 62.2; H, 4.20%.

Acknowledgement

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References

[1] R.O. Kennedy, R.D. Thornes, Coumarins: Biology, Applications and Mode of Action, John Wiley and Sons, Chichester, 1997.
[2] M. Maeda, Laser Dyes, Academic Press, New York, 1984.
[3] (a) A.K. Mitra, A. De, N. Karchaudhuri, S.K. Misra, A.K. Mukopadhyay, J. Indian Chem. Soc. 75 (1998) 666;
(b) G. Cavettos, G.M. Nano, G. Palmisano, S. Tagliapietra, Tetrahedron: Asymmetry 12 (2001) 707.
[4] O. Kayser, H. Kolodziej, Planta Med. 63 (1997) 508.
[5] C.J. Wang, Y.J. Hsieh, C.Y. Chu, Y.L. Lin, T.H. Tseng, Cancer Lett. 183 (2002) 163.
[6] G.J. Fan, W. Mar, M.K. Park, E. Wook Choi, K. Kim, S. Kim, Bioorg. Med. Chem. Lett. 11 (2001) 2361.
[7] S. Kirkiacharian, D.T. Thuy, S. Sicsic, R. Bakhchinian, R. Kurkjian, T. Tonnaire, Il Farmaco 57 (2002) 703.
[8] S.M. Sethna, N.M. Shah, Chem. Rev. 36 (1945) 1.
[9] S.M. Sethna, R. Phadke, Org. React. 7 (1953) 1.
[10] (a) B.J. Donnelly, D.M.X. Donnelly, A.M.O. Sullivan, Tetrahedron 24 (1968) 2617;
(b) J.R. Johnson, Org. React. 1 (1942) 210.
[11] (a) G. Jones, Org. React. 15 (1967) 204;
(b) F. Bigi, L. Chesini, R. Maggi, G. Sartori, J. Org. Chem. 64 (1999) 1033.
[12] R.L. Shirner, Org. React. 1 (1942) 1.
[13] I. Yavari, R. Hekmat-shoar, A. Zonuzi, Tetrahedron Lett. 39 (1998) 2391.
[14] (a) H. Appel, J. Chem. Soc. (1935) 1031;
(b) L.L. Woods, J. Sapp, J. Org. Chem. 27 (1962) 3703;
(c) Z.S. Ahmad, R.D. Desai, Proc. Indian Acad. Sci. Chem. Sci. 5A (1937) 277;
Z.S. Ahmad, R.D. Desai, Chem. Abstr. 31 (1937) 5785;
(d) R. Robinson, F. Weygand, J. Chem. Soc. (1941) 386;
(e) A.J. Nadkarni, N.A. Kudav, Ind. J. Chem., Sect. B 20 (1981) 719.

[15] A. Russell, J.R. Frye, Org. Synth. 21 (1941) 22.
[16] (a) H. Simmonis, P. Remmert, Chem. Ber. 47 (1914) 2229;
(b) A. Robertson, W.F. Sandrock, C.B. Henry, J. Chem. Soc. (1931) 2426.
[17] E.V.O. John, S.S. Israelstam, J. Org. Chem. 26 (1961) 240.
[18] A.J. Hoefnagel, E.A. Gennewagh, R.S. Downing, H. Vanbekkum, J. Chem. Soc., Chem. Commun. (1995) 225.
[19] S. Frere, V. Thiery, T. Besson, Tetrahedron Lett. 42 (2001) 2791.
[20] (a) M.K. Potdar, S.S. Mohile, M.M. Salunkhe, Tetrahedron Lett. 42 (2001) 9285;
(b) A.C. Khandekar, B.M. Khadikar, Synlett (2002) 152.
[21] K. Tanaka, F. Toda, Chem. Rev. 100 (2000) 1025 (and references cited therein).
[22] A.K. Chakrabarti, R. Gulhane, Chem. Commun. (2003) 1896.