Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 1313–1316
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Melamine–formaldehyde resin supported H^+ a mild and inexpensive reagent for synthesis of coumarins under mild conditions

Ramin Rezaei [a,*], Leila Dorosty [a], Maryam Rajabzadeh [a], Reza Khalifeh [b]

[a] Department of Chemistry, Firoozabad Branch, Islamic Azad University, P.O. Box 74715-117 Firoozabad, Iran
[b] Department of Chemistry, Faculty of Basic Sciences, Shiraz University of Technology, Shiraz 71555-313, Iran

Received 13 April 2011
Available online 30 July 2011

Abstract

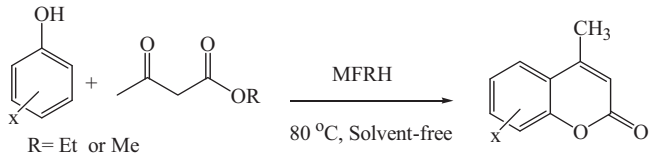
Melamine–formaldehyde resin supported H^+ is used as an efficient catalyst in the Pechmann condensation reaction of phenols with β-ketoesters, in solvent-free media leading to the formation of coumarin derivatives using conventional heating and microwave irradiation in excellent yields with good purity.

Keywords: Coumarins; Phenols; β-Ketoesters; Melamine–formaldehyde resin; Pechmann condensation; Solvent-free

Coumarins and their derivatives form an elite class of compounds, occupying an important place in the realm of natural products and synthetic organic chemistry. Their applications range from additives in food, perfumes, cosmetics, pharmaceuticals and in the preparation of insecticides [1], optical brighteners [2] and dispersed fluorescent and tunable laser dyes [3]. Also, coumarins have varied bioactivities, for example, inhibition of platelet aggregation [4], anticancer [5] and inhibition of steroid 5α-reductase [6]. These properties have made coumarins into interesting targets for organic chemists. The last decade witnessed a series of publications on the development of synthetic protocols for this important heterocyclic scaffold. Thus, it is clearly evident that the need for the development of new and flexible protocols is required, especially when they accommodate important functionalities. Coumarins have been synthesized by several routes including Pechmann [7], Perkin [8], Knoevenagel [9], Reformatsky [10] and Wittig reactions [11] and by flash vacuum pyrolysis [12]. Among these, the Pechmann reaction is the most widely used method, as the reaction involves the use of simple starting materials, that is, phenols and β-ketoesters, in the presence of a variety of acidic agents. The use of various reagents such as H_2SO_4, P_2O_5, $FeCl_3$, $ZnCl_2$, $POCl_3$, $AlCl_3$, PPA, HCl, phosphoric acid, trifluoroacetic acid, montmorillonite and other clays are all well documented in the literature [13]. Most of these methods suffer from severe drawbacks including the use of a large amount of catalysts, sometimes long reaction times and very often temperatures to the extent of 150 °C. Some of the recent achievements in the efficient construction of this nucleus include the development of cation exchange resins [14], several solid acid catalysts [15a–c] and metal nitrates [15d] supported polyaniline catalysts [16], the use of microwave irradiation [17] and recently, the use of ionic liquids as efficient catalysts [18].

* Corresponding author.
E-mail address: rezaieramin@yahoo.com (R. Rezaei).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2011.06.009



Scheme 1. Pechmann condensation using melamine–formaldehyde resin supported H^+ (MFRH).

Herein, we report an efficient method for the preparation of coumarins using melamine–formaldehyde resin supported H^+ (MFRH) as a catalyst in the pechmann reaction through a mixture of a phenol and a β-ketoester under solvent-free conditions (Scheme 1).

In a typical experimental procedure involves the condensation of phenol with ethyl acetoacetate. The reactants were heated together in the presence of a catalytic amount of MFRH (0.05 g/mmol) at 80 °C in a preheated oil-bath for a short period of time as required to complete the reaction (monitored by TLC). In order to study substituent effects on the reactivity of the phenol, the reactions were performed on a wide range of structurally diverse phenols and ethyl acetoacetate as well as with methyl acetoacetate. The reaction proceeds and the results are summarized in Table 1. The use of just 0.05 g/mmol of MFRH is sufficient to push the reaction forward. Higher amounts of MFRH did not improve the result to any extent. The yields are, in general, high regardless of the structural variations in phenols. Another important aspect of this procedure is survival of a variety of functional groups such as CH_3, OH, OCH_3 under the reaction conditions. Phenol (entry 1) required a higher reaction temperature and longer reaction duration, as no electron-donating group is present. *m*-Methoxyphenol (entry 5) showed no detectable demethylation under the reaction conditions. Similarly, 1-naphthol (entry 10) requires a slightly higher temperature and longer reaction time. Both the acetoacetic esters (ethyl and methyl) reacted almost similarly to produce coumarins. Similarly, resorcinol was treated with a variety of β-ketoesters viz., ethyl 4-chloroacetoacetae, ethyl benzoylacetate and ethyl furoacetate (Table 2, entries 1–3) to furnish corresponding 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 [13–18].

In conclusion this procedure described provides a useful, clean and fast method for the preparation of 4-substituted coumarins. For most of the substrates, the reaction time is reduced in contrast to classical methods. In conclusion other green advantages of the procedure are the low formation of wastes, no requiring for the use of adsorbents; and principally, the replacement of corrosive mineral acids.

1. Experimental

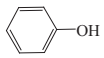
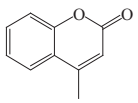
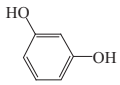
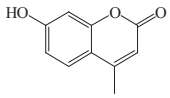
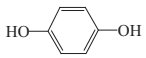
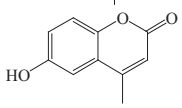
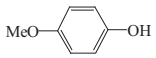
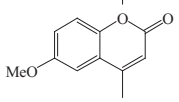
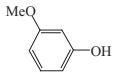
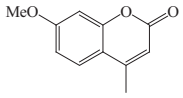
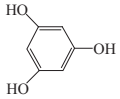
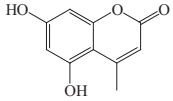
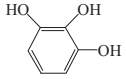
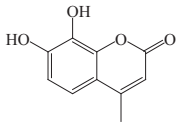
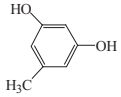
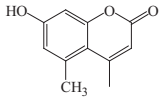
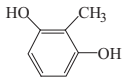
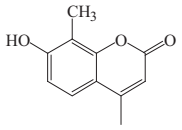
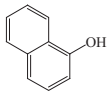
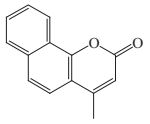
All chemicals and analytical grade solvents were purchased from Merck or Fluka chemical company. Melting points of all coumarins were determined in open glass capillaries on Mettler FP51 melting point apparatus. ^{1}H NMR spectra were recorded on an Bruker AVANCE DRX 500 spectrometer. A stars SYNTH microwave oven was used with power output of 450 W for all the experiments. The reaction was monitored by TLC using pre-coated plates (Merck).

Preparation of melamine–formaldehyde resin supported H^+ (MFRH): HCl (3.0 g, as a 36.5% aq. solution) was added to a suspension of melamine–formaldehyde resin (5 g) in Et_2O (70.0 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to furnish MFRH as a free flowing powder.

1.1. Conventional method (method A)

A mixture of a phenol (1 mmol), ethyl acetoacetate or methyl acetoacetate (1.1 mmol) and MFRH (0.05 g) was added and the reaction mixture was stirred at 80 °C in a pre-heated oil-bath. The reaction was monitored by TLC. After completion of the reaction, warm ethanol (10 mL) was added and filtered, and the remaining was washed with warm ethanol (2 × 10 mL) in order to separate catalyst. Ethanol was evaporated and crude product was recrystallized from EtOH. Products were characterized by comparison of their physical and spectral data with those of authentic samples [13–18].

Table 1
Synthesis of coumarins using MFRH under solvent-free conditions.

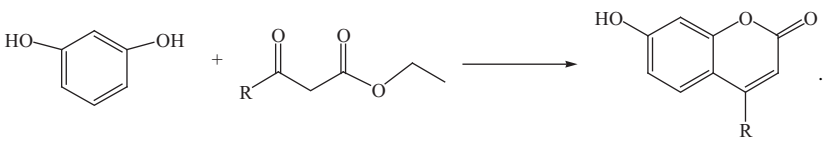
Entry	Substrate	Product	Method A			Method B			Mp (°C)	
			Time (min)	Yield (%)		Time (min)	Yield (%)		Found	Reported
1			50	65[a]	62[b]	3	70[a]	70[b]	80–82	83–84
2			15	90[a]	90[b]	1	90[a]	90[b]	180–182	183–185
3			20	80[a]	77[b]	2	80[a]	78[b]	180–182	184–186
4			25	85[a]	82[b]	2	88[a]	85[b]	160–162	164–166
5			20	88[a]	83[b]	2	90[a]	87[b]	157–159	160–161
6			15	92[a]	90[b]	1	94[a]	94[b]	279–281	280–282
7			25	80[a]	80[b]	2	85[a]	83[b]	241–243	243–244
8			20	85[a]	83[b]	2	85[a]	80[b]	245–247	246–248
9			30	70[a]	67[b]	2	80[a]	80[b]	136–137	137–139
10			20	75[a]	73[b]	2	75[a]	72[b]	150–152	153–155

[a] Ethyl acetoacetate is used as a reactant.
[b] Methyl acetoacetate is used as a reactant.

1.2. Microwave method (method B)

To a mixture of the phenolic compound (1 mmol) and ethyl acetoacetate or methyl acetoacetate (1.1 mmol), MFRH (0.05 g) was added and the mixture was placed in a microwave oven and heated at 450 W for the appropriate time (TLC). After completion of the reaction, warm ethanol (10 mL) was added and filtered, and the remaining was washed with warm ethanol (2 × 10 mL) in order to separate catalyst. Ethanol was evaporated and crude product was recrystallized from EtOH. Products were characterized by comparison of their physical and spectral data with those of corresponding samples [13–18].

Table 2
Pechmann condensation of resorcinol with β-ketoesters for the synthesis of corresponding 4-substituted coumarins.



No.	R	Method A		Method B		Mp (°C)	
		Time (min)	Yield (%)	Time (min)	Yield (%)	Found	Reported
1	R=CH_2Cl	15	85	2	80	177–179	180–181
2	R=Ph	20	80	2	77	253–255	256–257
3	R=Furyl	20	78	2	70	206–207	210–212

Spectral data for selected products: *Compound* **6**: IR (Neat) (cm^{-1}) 3473, 3199, 1660, 1618, 1533, 1416, 1160, 815; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.90 (brs, 1H), 9.70 (brs, 1H), 6.23 (d, 1H, J = 7.0 Hz), 6.17 (d, 1H, J = 7.0 Hz), 5.70 (s, 1H), 2.11 (s, 3H); EIMS (*m*/*z*) 192 (M+); Anal. Calcd. for $C_{10}H_8O_4$: C, 62.5; H, 4.16%. Found: C, 62.2; H, 4.20%.

References

[1] R.O. Kennedy, R.D. Zhorenes, Coumarins: Biology, Applications and Mode of Action, John Wiley and Sons, Chichester, 1997.
[2] M. Zabradnik, The Production and Application of Fluorescent Brightening Agents, John Wiley and Sons, New York, 1992.
[3] R.D.H. Murray, J. Mendez, S.A. Brown, The Natural Coumarins: Occurrence, Chemistry and Biochemistry, John Wiley and Sons, New York, 1982.
[4] (a) A.K. Mitra, A. De, N. Karchaudhuri, S.K. Misra, A.K. Mukopadhyay, J. Indian Chem. Soc. 75 (1998) 666;
(b) G. Cravotto, G.M. Nano, G. Palmisano, S. Tagliapietra, Tetrahedron: Asymmetry 12 (2001) 707.
[5] C.J. Wang, Y.J. Hsieh, C.Y. Chu, et al. Cancer Lett. 183 (2002) 163.
[6] G.J. Fan, W. Mar, M.K. Park, et al. Bioorg. Med. Chem. Lett. 11 (2001) 2361.
[7] H. von Pechmann, C. Duisberg, Chem. Ber. 17 (1884) 929.
[8] J.R. Johnson, Org. React. 1 (1942) 210.
[9] (a) G. Jones, Org. React. 15 (1967) 204;
(b) G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, Heterocycles 43 (1996) 1257.
[10] R.L. Shirner, Org. React. 1 (1942) 1.
[11] (a) N.S. Narasimhan, R.S. Mali, M.V. Barve, Synthesis (1979) 906;
(b) I. Yavari, R. Hekmat-Shoar, A. Zonouzi, Tetrahedron Lett. 39 (1998) 2391.
[12] G.A. Cartwright, W. McNab, J. Chem. Res. (S) (1997) 296.
[13] (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. 5A (1937) 277, Chem Abstr. 1937, 31, 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;
(f) T.S. Li, Z.H. Zhang, F. Yang, C.G. Fu, J. Chem. Res. (S) (1998) 38.
[14] E.V.O. John, S.S. Israelstam, J. Org. Chem. 26 (1961) 240.
[15] (a) A.J. Hoefnagel, E.A. Geenewagh, R.S. Downing, et al. J. Chem. Soc., Chem. Commun. (1995) 225;
(b) P.R. Singh, D.U. Singh, S.D. Samant, Synlett 11 (2004) 1909;
(c) G.P. Romanelli, D. Bennardi, D.M. Ruiz, et al. Tetrahedron Lett. 45 (2004) 8935;
(d) S.S. Bahekar, D.B. Shinde, Tetrahedron Lett. 45 (2004) 7999.
[16] S. Palaniappan, R.C. Sekhar, J. Mol. Catal. 209 (2004) 117.
[17] (a) J. Singh, J. Kaur, S. Nayyar, G.L. Kad, J. Chem. Res. (S) (1998) 280;
(b) S. Frere, V. Thiery, T. Besson, Tetrahedron Lett. 42 (2001) 2791.
[18] (a) M.K. Potdar, S.S. Mohile, M.M. Salunkhe, Tetrahedron Lett. 42 (2001) 9285;
(b) A.C. Khandekar, B.M. Khadilkar, Synlett 1 (2002) 152;
(c) V. Singh, S. Kaur, V. Sapehiyia, J. Singh, G.L. Kad, Catal. Commun. 6 (2005) 57.