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Zeolite-catalyzed Pechmann synthesis of coumarins

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The Pechmann condensation of phenols with ethyl acetoacetate in the presence of a modified small pore size zeolite E4a resulting in the formation of coumarin derivatives in good yields.

KEY WORDS: coumarins; Pechmann reaction; zeolites; green chemistry.

The coumarins are important compounds in the synthetic organic and medicinal chemistry. They are widely used as additives in foods, perfumes, cosmetics, pharmaceuticals [1], and in the preparation of insecticides, optical brighteners [2] and dispersed fluorescent and laser dyes [3]. Coumarins have been synthesized by several methods including Pechmann [4], Perkin [5], Knoevenagel [6,7] Reformatsky [8] and Wittig [9,10] reactions.

The Pechmann reaction is one of the most widely applied method for synthesizing coumarins. It involves the condensation of phenols with *β*-ketoesters in the presence of a variety of acidic condensing agents. Several acid catalyst have been used in the Pechmann reaction, e.g. sulfuric acid [4], aluminum chloride [11], phosphorus pentoxide [12,13] or trifluoroacetic acid [14]. However, these catalysts have to be used in large excess, for example 10–12 equiv. sulfuric acid [15], 3–4 equiv. trifluoroacetic acid [14], and they cannot be recovered or reused. The disposal of acidic waste leads to environmental pollution. Therefore, it is important to find a simple, cheap, recoverable and/or reusable catalyst for the synthesis of coumarins. Nowadays cleaner and safer methods have been developed, using microwave irradiation [16,17], ionic liquids [18] and $InCl_3$ [19], $Sm(NO_3)_3{*}6H_2O$ [20] or $ZrCl_4$ [21] as catalysts.

Ersorb-4 (E4) is a weakly acidic clinoptylolite-type zeolite adsorbent with 4 Å pore size. It can adsorb only small molecules such as water, hydrochloric acid, ammonia, methanol. E4a is the more acidic modification of E4 (the pH of its aqueous suspension is about 3) [22,23].

Recently we reported, that E4 showed good activity in different condensation reactions such as synthesis of oxazoline derivatives from *β*-aminoalcohols and carboxylic acids [24], preparation of 2-arylimidazolines and 2-arylbenzoxazoles [25], and tetrahydropyranylation of alcohols and phenols [26]. E4a has been found to be a good catalyst in the preparation of 1-substituted tetrahydroisoquinolines *via* the Pictet–Spengler reaction [27], in the oxa-Pictet–Spengler reaction [28], in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones [29] or in the synthesis of 1,5-benzodiazepines [30].

In continuation of our work we examined the application of modified Ersorb adsorbents as catalysts in the Pechmann reaction under mild reaction conditions. The reaction of phenol and ethyl acetoacetate in the presence of E4a in hot toluene gave the appropriate 4-methylcoumarin in good yield (Scheme 1). The optimal reaction conditions were determined in this reaction. The best result was obtained using 0.5 g E4a/2 mmol phenol in toluene as solvent at 110 °C for 3 h. Longer reaction time did not result higher yield. The weaker acidic E4 adsorbent as catalyst showed no activity.

Under the optimal reaction conditions we examined the reaction of different phenol derivatives with ethyl acetoacetate. The results are summarized in Table 1.

There was no significant substituent effect observed in the reactions, in all cases the appropriate coumarins were obtained in high yield. The work-up of the reaction mixture was very simple; the catalyst was filtered out and the solvent was evaporated. The catalyst could be recycled easily without significant loss of activity after washing it with acetone following by heating at 120 °C for 4 h (Table 1, entries 1, 3, 4).

In summary, the results show that the modified zeolite-type adsorbent E4a is a suitable catalyst for the Pechmann synthesis of coumarins. The method is simple, convenient, cheap and environmentally-friendly, the catalyst can be recycled easily without any loss of activity.

1. Experimental

The commercial starting materials were purchased from Merck-Hungary Ltd. except of E4a, which is the product of Erdőkémia-ker Ltd., Hungary.

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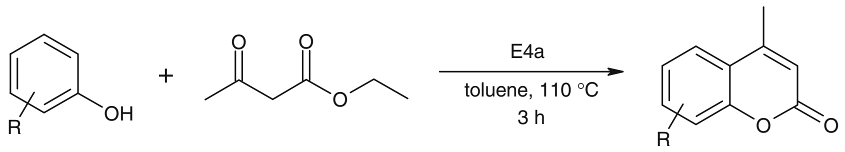


Scheme 1.

Table 1
Reaction of phenols with ethyl acetoacetate in the presence of E4a[a]

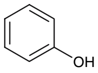
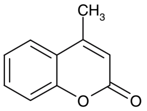
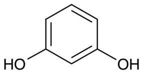
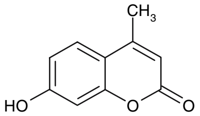
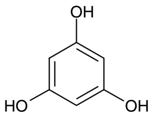
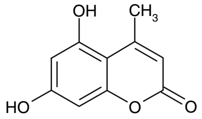
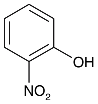
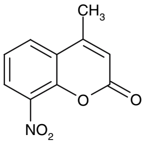
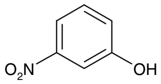
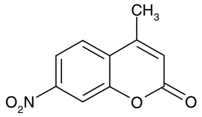
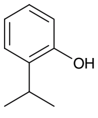
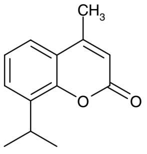
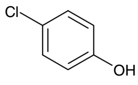
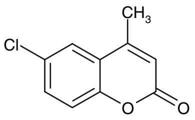
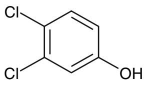
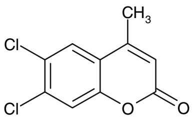
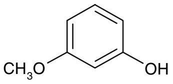
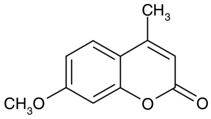
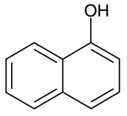
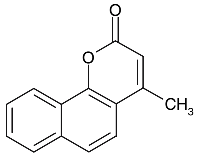
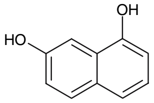
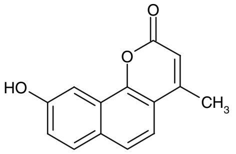
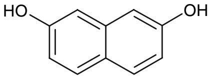
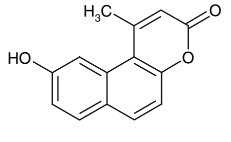
Entry	Phenol	Product	Yield[b] (%)	M.p. (L) (°C)
1			76 (76[c], 73[d])	82 (83–84) [31]
2			97	182–184 (185) [32]
3			97 (94[c])	282–284 (280–285) [32]
4			89 (89[c], 85[d])	183 (184–186) [16]
5			91	177–179
6			87	126–129
7			91	183–185
8			88	197–198
9			98	171

Table 1 Continued

Entry	Phenol	Product	Yield[b] (%)	M.p. (L) (°C)
10			85	158–159 (155) [32]
11			82	287–288 (285) [33]
12			74	278–279 (275) [34]

[a] 2 mmol phenol, 2 mmol ethyl acetoacetate, 0.5 g E4a, toluene, 110 °C, 3 h.
[b] Isolated yield.
[c] Recycled E4a.
[d] Third use of E4a.

^{1}H NMR spectra were made on Bruker Avanche 500 spectrometer in DMSO-d$_6$ using TMS as internal standard.

Pretreatment of the catalyst: Before each experiment the sample of E4a was powdered and heated at 120 °C for 2 h.

General procedure for the preparation of coumarines: A mixture of 2 mmol of phenol derivatives, 2 mmol of ethyl acetoacetate and 0.5 g of E4a in toluene (10 mL) was heated at 110 °C for 3 h. Then the solid was filtered out, the filtrate was evaporated and the residue purified by recrystallization from ethanol.

The known products were characterized by ^{1}H NMR and IR spectroscopy and by their melting points. The spectral and physical data of the known compounds were identical with those reported in the literature.

Physical and spectroscopic data of the new compounds: 7-nitro-4-methylcoumarin (Table 1, entry 5): light yellow solid; m.p.: 177–179 °C (ethanol); ^{1}H NMR (DMSO-d$_6$, 300 MHz): 2.25 (s, 3H, CH$_3$), 6.18 (s, 1H, CH), 7.08 (s, 1H, Ar CH), 7.25 (d, 1H, Ar CH), 7.38 (d, 1H, Ar CH); IR (KBr): 2981, 1745, 1625 cm^{-1}.

8-*i*-propyl-4-methylcoumarin (Table 1, entry 6): white solid; m.p.: 126–129 °C (ethanol); ^{1}H NMR (DMSO-d$_6$, 300 MHz): 1.14 (d, 6H, CH$_3$), 1.92 (m, 1H, CH), 2.18 (s, 3H, CH$_3$), 6.15 (s, 1H, CH), 7.05 (s, 1H, Ar CH), 7.26 (d, 1H, Ar CH), 7.43 (d, 1H, Ar CH); IR (KBr): 2977, 1750, 1628 cm^{-1}.

6-chloro-4-methylcoumarin (Table 1, entry 7): white solid; m.p.: 183–185 °C (ethanol); ^{1}H NMR (DMSO-d$_6$, 300 MHz): 2.21 (s, 3H, CH$_3$), 6.10 (s, 1H, CH), 7.11 (s, 1H, Ar CH), 7.17 (d, 1H, Ar CH), 7.42 (d, 1H, Ar CH); IR (KBr): 2979, 1750, 1620 cm^{-1}.

6,7-dichloro-4-methylcoumarin (Table 1, entry 8): light yellow solid; m.p.: 197–198 °C (ethanol); ^{1}H NMR (DMSO-d$_6$, 300 MHz): 2.19 (s, 3H, CH$_3$), 6.18 (s, 1H, CH), 7.21 (s, 1H, Ar CH), 7.35 (s, 1H, Ar CH); IR (KBr): 2980, 1747, 1628 cm^{-1}.

7-methoxy-4-methylcoumarin (Table 1, entry 9): white solid; m.p.: 171 °C (ethanol); ^{1}H NMR (DMSO-d$_6$, 300 MHz): 2.21 (s, 3H, CH$_3$), 3.75 (s, 3H, CH$_3$O), 6.19 (s, 1H, CH), 7.07 (s, 1H, Ar CH), 7.23 (d, 1H, Ar CH), 7.38 (d, 1H, Ar CH); IR (KBr): 2980, 1742, 1625 cm^{-1}.

Acknowledgments

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References

[1] R. O'Kennedy and R.D. Thornes, *Coumarins: Biology, Applications and Mode of Action* (John Wiley & Sons, Chichester, 1997).
[2] M. Zahradnik, *The Production and Application of Fluorescent Brightening Agents* (John Wiley & Sons, New York, 1992).
[3] R.D.H. Murray, J. Mendez and S.A. Brown, *The Natural Coumarins: Occurrence, Chemistry and Biochemistry* (John Wiley & Sons, New York, 1982).
[4] H. von Pechmann and C. Duisberg, Chem. Ber. 17 (1884) 929.
[5] J.R. Johnson, Org. React. 1 (1942) 210.

[6] G. Jones, Org. React. 15 (1967) 204.
[7] G. Brufola, F. Fringuelli, O. Piermatti and F. Pizzo, Heterocycles 43 (1996) 1257.
[8] R.L. Shriner, Org. React. 1 (1942) 1.
[9] N.S. Narasimahan, R.S. Mali and M.V. Barve, Synthesis (1979) 906.
[10] I. Yavari, R. Hekmat-Shoar and A. Zonouzi, Tetrahedron Lett. 39 (1998) 2391.
[11] S.M. Sethna, N.M. Shah and R.C. Shah, J. Chem. Soc. (1938) 228.
[12] H. Simmonis and P. Remmert, Chem. Ber. 47 (1914) 2229.
[13] A. Robertson, W.F. Sandrock and C.B. Henry, J. Chem. Soc. (1931) 2426.
[14] L.L. Woods and J. Sapp, J. Org. Chem. 27 (1962) 3703.
[15] A. Russel and J.R. Frye, Org. Synth. 21 (1941) 22.
[16] A. de la Hoz, A. Moreno and E. Vazquez, Synlett (1999) 608.
[17] S. Frere, V. Thiery and T. Besson, Tetrahedron Lett. 42 (2001) 2791.
[18] M.K. Potdar, S.S. Mohile and M.M. Salunkhe, Tetrahedron Lett. 42 (2001) 9285.
[19] D. Subhas Bose, A.P. Rudradas and M. Hari Babu, Tetrahedron Lett. 43 (2002) 9195.
[20] S.S. Bahekar and D.B. Shinde, Tetrahedron Lett. 45 (2004) 7999.
[21] G. Smitha and Ch. Sanjeeva Reddy, Synth. Commun. 34 (2004) 3997.
[22] G. Klopp, Ph.D. Theses (Budapest, 1975).
[23] The characterization of the Ersorb products was described elsewhere. See e.g. A. Hegedüs, Z. Hell and A. Potor, Catal. Lett. 105 (2005) 229.
[24] A. Cwik, Z. Hell, A. Hegedüs, Z. Finta and Z. Horváth, Tetrahedron Lett. 43 (2002) 3985.
[25] A. Hegedüs, I. Vígh and Z. Hell, Heteroatom Chem. 15 (2004) 428.
[26] A. Hegedüs, I. Vígh and Z. Hell, Synth. Commun. 32 (2004) 4145.
[27] A. Hegedüs and Z. Hell, Tetrahedron Lett. 45 (2004) 8553.
[28] A. Hegedüs and Z. Hell, Org. Biomol. Chem. 4 (2006) 1220.
[29] A. Hegedüs, Z. Hell and I. Vígh, Synth. Commun. 36 (2006) 129.
[30] A. Hegedüs, Z. Hell and A. Potor, Catal. Lett. 105 (2005) 229.
[31] T. Jin, J. Guo, Y. Yin, H. Liu and T. Li, Ind. J. Chem. 42B (2003) 2612.
[32] A.C. Khandekar and B.M. Khadilkar, Synlett (2002) 152.
[33] Ng.Ph. Buu-Hoi and D. Lavit, J. Org. Chem. 21 (1956) 1022.
[34] Z.-F. Tao, X. Qian and M. Fan, Tetrahedron 53 (1997) 13329.