

HETEROCYCLES, Vol. 71, No. 3, 2007, pp. 677 - 682. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd November, 2006, Accepted, 29th January, 2007, Published online, 30th January, 2007. COM-06-10956

SILICA SULFURIC ACID AS AN EFFICIENT AND REUSABLE CATALYST FOR THE PECHMANN SYNTHESIS OF COUMARINS UNDER SOLVENT-FREE CONDITIONS

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Abstract – Silica sulfuric acid is used as an efficient catalyst in the Pechmann condensation of phenols with β -keto-esters leading to the formation of coumarin derivatives in excellent yields under solvent-free conditions. It was found that the catalyst could be recycled and reused for several runs.

INTRODUCTION

Coumarin and its derivatives are widely used as additives in food, perfumes, cosmetics, pharmaceuticals, and agrochemicals.^{1,2} A wide range of biologically active coumarins is also reported in literature which for example posses antiprotozoal, cytotoxic,³ and antiplasmodial activity⁴ and inhibitory of acetylcholinesterase and monoamine oxidase,⁵ and HIV integrase.⁶

Due to importance of coumarin, synthesis of its nucleus is a topic of current interest.⁷ There have been many synthetic routes to coumarins, including Pechmann,⁸ Perkin,⁹ Knoevenagel,¹⁰ Reformatsky,¹¹ and Wittig reactions.¹² However, the Pechmann reaction has been the most widely applied for the synthesis of coumarins as it proceeds from very simple starting materials and gives good yields. Several acidic reagents have been used in the Pechmann reaction such as sulfuric acid,⁸ aluminum chloride,¹³ phosphorus pentoxide,¹⁴ trifluoroacetic acid,¹⁵ and etc. However, these reagents have to be used in excess amounts and in all cases mixtures of the reagents were allowed to stand for a long time, depending on their reactivity, or

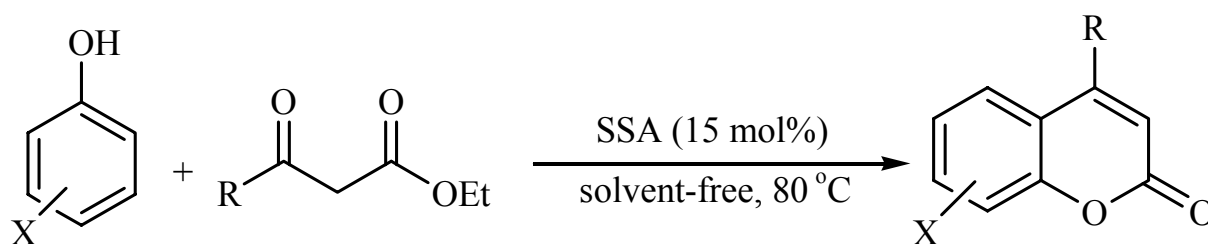
were heated above 150 °C, that caused the formation of unwanted side products. As a result, the disposal of excess acid waste leads to increasing environmental pollution. Therefore it is important to investigate a new method using less hazardous reagents and catalysts or without harmful organic solvents. To overcome these problems some environmentally benign procedures have been reported such as using solid supports,¹⁶ ionic liquids,¹⁷ and solid Lewis acids.¹⁸

It is an established fact in the literature that Pechmann reaction proceeds through transesterification and intramolecular hydroxyalkylation, followed by dehydration.¹⁹ These three steps are all typical acid-catalyzed reactions. Therefore, the outcome of the Pechmann reaction depends very much on the acidity of the catalysts.²⁰

RESULTS AND DISCUSSION

In continuation of our interest in using solid supports in organic reactions,²¹ and specially silica sulfuric acid (SSA),²² here we wish to report an efficient and environmentally benign procedure for the synthesis of coumarins via Pechmann condensation in the presence of SSA as a solid and reusable catalyst.

For optimizing the reaction conditions, the reaction of resorcinol with ethyl acetoacetate in the presence of SSA at different temperatures was investigated. The best results obtained with 15 mol% of SSA at 80 °C. Encouraged by the above results, other coumarin derivatives were synthesised under the same conditions (Scheme 1).



Scheme 1

Several types of phenolic substrates and β -keto-esters with different functionalities were used in the reaction. As could be seen in Table 1, the reaction was found to be adaptable to a variety of substrates and the yields, in general, were very high. It is worth noting that with simple phenol as a substrate also good result was obtained (Table 1, entry 13), but *ortho*- and *para*-dihydroxybenzene afforded mixture of products. The experimental procedure is very simple and work up includes the addition of ethanol followed by filtration for separation of the catalyst. Hence there will not be any unnecessary acidic waste stream to create environmentally hazardous pollution.

In order to find the possibility of recycling the catalyst, an investigation was made on the reaction of resorcinol and ethyl acetoacetate in the presence of 15 mol% of SSA. After completion of the reaction,

ethanol was added and the mixture was filtered to separate the catalyst. The recycled catalyst was used for further runs. No decrease in catalytic activity of SSA was observed even after five runs (Table 1, entry 1).

Table 1. Synthesis of coumarins by the reaction of phenols with β -keto-esters in the presence of 15 mol% of SSA

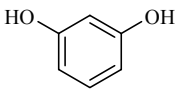
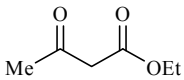
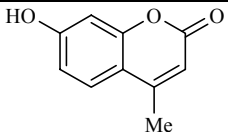
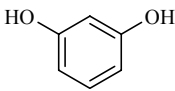
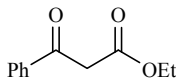
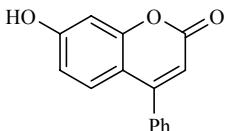
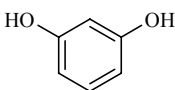
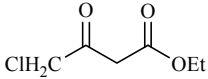
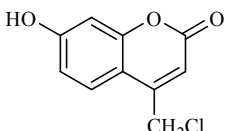
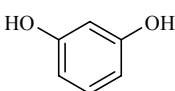
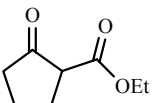
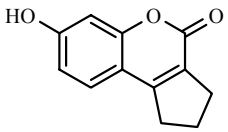
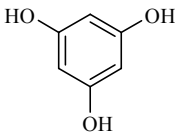
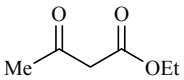
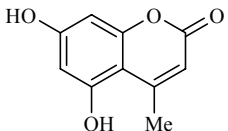
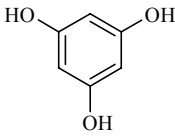
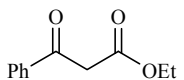
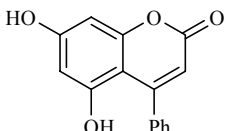
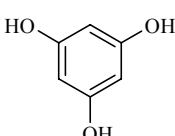
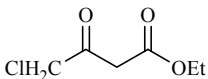
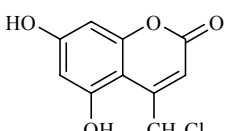
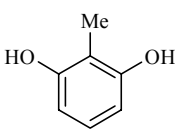
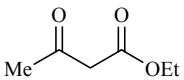
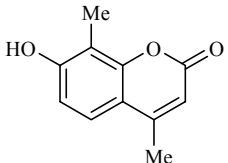
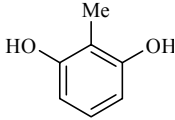
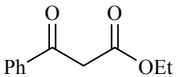
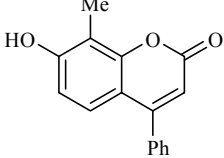
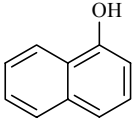
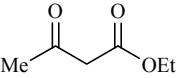
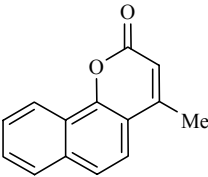
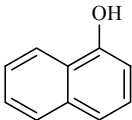
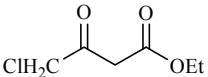
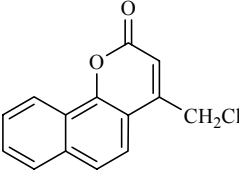
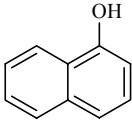
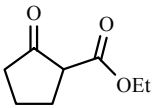
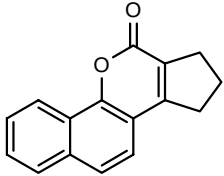
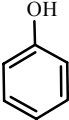
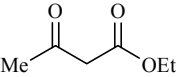
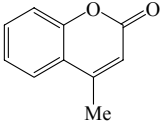
Entry	Phenol	β -Keto-ester	Product ^a	Time (h)	Yield (%)	Mp (°C)	
						Found	Reported
1				0.5	93, 92, 91, 94, 89 ^b	187-188	186-189 ^{18a}
2				0.5	95	255-257	256-257 ^{18c}
3				1	90	192-193	190-191 ^{18a}
4				1	90	246-248	244-246 ^{17a}
5				0.5	92	285-287	289-290 ^{18a}
6				0.75	92	241-242	243-246 ^{18c}
7				1	90	245-246	246-248 ^{18a}
8				0.5	94	264-266	263-265 ^{18c}

Table 1. Synthesis of coumarins by the reaction of phenols with β -keto-esters in the presence of 15 mol% of SSA (Continued)

Entry	Phenol	β -Keto-ester	Product ^a	Time (h)	Yield (%)	Mp (°C)	
						Found	Reported
9				0.5	97	282-284	284-285 ^{18c}
10				1	93	152-153	153-155 ^{18c}
11				1	96	166-169	165-167 ^{18c}
12				1	85	213-214	215-217 ^{17a}
13				2	70	80-81	78-80 ^{18d}

^a The products were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures.

^b The catalyst was used for five runs.

In conclusion, we have demonstrated an efficient and simple alternative for the preparation of substituted coumarins via the SSA catalyzed Pechmann reaction under solvent-free conditions. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times and an easy work-up procedure. The catalyst is also reusable and can be recycled for several runs.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ¹H and ¹³C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. All the products are known compounds,

which were characterized by melting point, IR, ^1H NMR and ^{13}C NMR spectral data and mass spectroscopy.

General Procedure

Phenolic substrate (1mmol), β -keto ester (1mmol) and SSA (0.06 g equal to 0.15 mmol H^+) were mixed together in a round bottom flask. The mixture was stirred at 80 $^\circ\text{C}$ for the appropriate time (see Table 1). After completion of the reaction indicated by TLC (eluent: *n*-hexane/EtOAc: 3/1), hot EtOH was added and filtered. EtOH was evaporated under reduced pressure and crude product was recrystallized from EtOH.

ACKNOWLEDGEMENTS

Financial support by the Research Council of Shahid Beheshti University is gratefully acknowledged.

REFERENCES

1. R. O'Kennedy and R. D. Thornes, 'Coumarins: Biology, Applications and Mode of Action, Wiley, Chichester, 1997.
2. R. D. H. Murray, J. Mendez, and S. A. Brown, 'The Natural Coumarins: Occurrence, Chemistry and Biochemistry, Wiley, New York, 1982.
3. (a) M. R. Camacho, J. D. Phillipson, S. L. Croft, V. Yardley, and P. N. Solis, *Planta Med.*, 2004, **70**, 70. (b) L. L. Yang, M. C. Wang, L. G. Chen, and C. C. Wang, *Planta Med.*, 2003, **69**, 1091.
4. C. Yenjai, S. Sripontan, P. Sriprajun, P. Kittakoo, A. Jintasirikul, M. Tanticharoen, and Y. Thebtaranonth, *Planta Med.*, 2000, **66**, 277.
5. C. Bruhlmann, F. Ooms, P. A. Carrupt, B. Testa, M. Catto, F. Leonetti, C. Altomare, and A. Carotti, *J. Med. Chem.*, 2001, **44**, 3195.
6. H. Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G. W. A. Milne, Y. Pommier, and J. T. R. Burke, *J. Med. Chem.*, 1997, **40**, 242.
7. R. D. H. Murray, *Nat. Prod. Rep.*, 1995, 477.
8. (a) H. von Pechmann and C. Duisberg, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 929. (b) L. Kurti and B. Czako, 'Strategic Applications of Named Reactions in Organic Synthesis, p. 472, Elsevier Science & Technology Books, 2005.
9. W. H. Perkin and W. S. Henry, *J. Chem. Soc.*, 1875, **28**, 10.
10. G. Brufola, F. Fringuelli, O. Piermatti, and F. Pizzo, *Heterocycles*, 1996, **43**, 1257.
11. R. L. Shirner, *Org. React.*, 1942, **1**, 15.
12. I. Yavari, R. Hekmat-Shoar, and A. Zonouzi, *Tetrahedron Lett.*, 1998, **39**, 2391.
13. S. M. Sethna, N. M. Shah, and R. C. Shah, *J. Chem. Soc.*, 1938, 228.

14. A. Robertson, W. F. Sandroock, and C. B. Henry, *J. Chem. Soc.*, 1931, 2426.
15. L. L. Woods and J. Sapp, *J. Org. Chem.*, 1962, **27**, 3703.
16. (a) B. M. Reddy, M. K. Patil, and P. Lakshmanan, *J. Mol. Catal. A Chem.*, 2006, **256**, 290. (b) J. C. Rodriguez-Dominguez and G. Kirsch, *Tetrahedron Lett.*, 2006, **47**, 3279. (c) M. Maheswara, V. Siddaiah, G. L. V. Damu, Y. K. Rao, and C. V. Rao, *J. Mol. Catal. A Chem.*, 2006, **255**, 49.
17. (a) A. C. Khandekar and B. M. Khadilkar, *Synlett*, 2002, 152. (b) M. K. Potdar, M. S. Rasalkar, S. S. Mohile, and M. M. Salunkhe, *J. Mol. Catal. A Chem.*, 2005, **235**, 249.
18. (a) J. C. Rodriguez-Dominguez and G. Kirsch, *Synthesis*, 2006, 1895. (b) H. Valizadeh and A. Shockravi, *Tetrahedron Lett.*, 2005, **46**, 3501. (c) S. K. De and R. A. Gibbs, *Synthesis*, 2005, 1231. (d) G. V. M. Sharma, J. J. Reddy, P. S. Lakshmi, and P. R. Krishna, *Tetrahedron Lett.*, 2005, **46**, 6119. (e) S. S. Bahekar and D. B. Shinde, *Tetrahedron Lett.*, 2004, **45**, 7999.
19. (a) E. A. Gunnewegh, A. J. Hoefnagel, and H. van Bekkum, *J. Mol. Catal. A Chem.*, 1995, **100**, 87. (b) J. Oyamada, C. Jia, Y. Fujiwara, and T. Kitamura, *Chem. Lett.*, 2002, **31**, 380.
20. M. C. Laufer, H. Hausmann, and W. F. Holderich, *J. Catal.*, 2003, **218**, 315.
21. (a) M. Dabiri, P. Salehi, A. A. Mohammadi, and M. Baghbanzadeh, *Synth. Commun.*, 2005, **35**, 279. (b) P. Salehi, M. Dabiri, M. Baghbanzadeh, and M. Bahramnejad, *Synth. Commun.*, 2006, **36**, 2287. (c) M. Dabiri, P. Salehi, A. A. Mohammadi, M. Baghbanzadeh, and G. Kozehgiry, *J. Chem. Res.*, (S) 2004, 570. (d) M. Dabiri, P. Salehi, M. S. Khajavi, and A. A. Mohammadi, *Heterocycles*, 2004, **63**, 1417. (e) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh, *Heterocycles*, 2005, **65**, 1177. (f) P. Salehi, M. Dabiri, A. R. Khosropour, and P. Roozbehniya, *J. Iran. Chem. Soc.*, 2006, **3**, 98.
22. (a) P. Salehi, M. A. Zolfigol, F. Shirini, and M. Baghbanzadeh, *Curr. Org. Chem.*, 2006, **10**, 2171. (b) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. A. Bodaghi Fard, *Tetrahedron Lett.*, 2003, **44**, 2889. (c) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh, *Synlett*, 2005, 1155. (d) M. A. Zolfigol, *Tetrahedron*, 2001, **57**, 9509. (e) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. A. Bodaghi Fard, *Heterocycles*, 2003, **60**, 2435. (f) P. Salehi, M. Dabiri, M. A. Zolfigol, and M. Baghbanzadeh, *Tetrahedron Lett.*, 2005, **46**, 7051. (g) P. Salehi, M. Dabiri, M. A. Zolfigol, S. Otokesh, and M. Baghbanzadeh, *Tetrahedron Lett.*, 2006, **47**, 2557.