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Coumarin Synthesis *via* Pechmann Condensation on Silica-Supported Sulfuric Acid Under Microwave Irradiation

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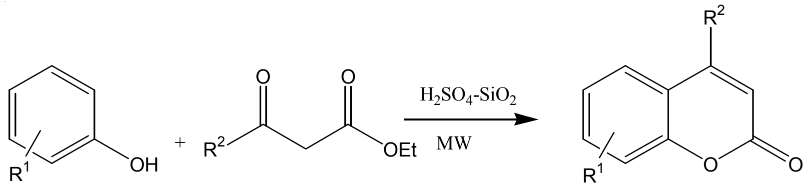
4-Methyl coumarin derivatives were synthesized from substituted phenols and ethyl acetoacetate *via* pechmann condensation under microwave and solvent-free conditions using silica-supported sulfuric acid as the catalyst.

Key Words: Pechmann condensation, Coumarin, H_2SO_4-SiO_2, Solvent-free, Microwave.

INTRODUCTION

Coumarin scaffold constitutes the main core of many natural and synthetic products which show a wide range of bioactivities, such as anticoagulant[1,2], antibacterial[3], anticancer[4], inhibitory of steroid 5α-reductase[5] and inhibitory of HIV-1 protease[6]. They are also used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals[7] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers[8]. In addition, coumarins have been used as precursors in the synthesis of chromenes, coumarones and fused coumarin heterocycles[9]. Due to these interesting features, several routes to the synthesis of coumarins have been developed employing Pechmann[10], Perkin[11], Knoevenagel[12,13], Reformatsky[14], Wittig[15] reactions and flash vacuum pyrolysis[16]. Among these reactions the Pechmann process is one of the most productive and simple methods which has been frequently used and studied. This process consists of the condensation of substituted phenols with β-ketoesters which is believed to proceed through two consecutive steps of addition of the phenol onto ketoester carbonyl groups and a dehydration step. All of these steps are acid-catalyst demanding reactions. Therefore, several acid-catalysts have been used to facilitate the reaction ranging of strong Bronsted acids, dehydrating reagents, heteropolyacids, ionic liquids, solid acids and solid supported reagents[17-22]. Concentrated sulfuric acid is the conventional and also the first catalyst which was used by Pechmann, himself, in the synthesis of coumarin derivatives[10]. However, use of sulfuric acid in this reaction suffers from formation of by-products, needs long reaction time and introduces corrosion as well as waste acid pollution problems. Consequently, there is scope for development of mild reaction conditions, using green and reusable catalysts. In recent years, heterogeneous catalysts are gaining more importance due to their environmental and economical aspects. The solid supported catalysts are generally of low cost, reduced equipment corrosion and can be easily handled or separated from organic components.



1a-g **2a-b** **3a-j**

R^2 = Me, Ph

Scheme

EXPERIMENTAL

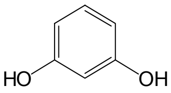
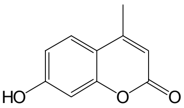
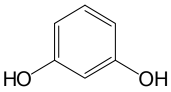
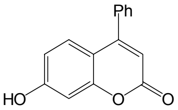
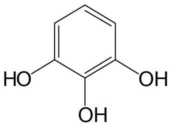
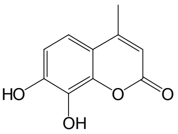
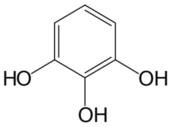
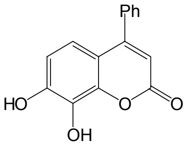
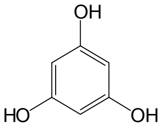
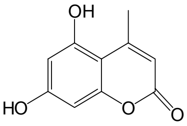
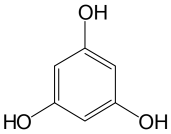
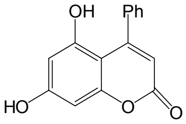
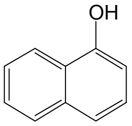
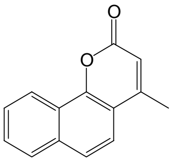
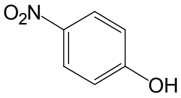
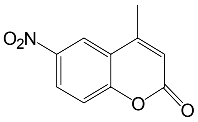
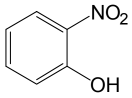
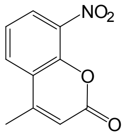
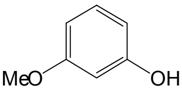
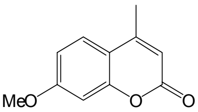
Melting points are uncorrected. The catalyst is prepared by mixing chromatographic grade silica (Merck, Kiesel gel, 60, 70-230 mesh) with 3 % of its weight of sulfuric acid (98 %) dissolved in acetone following a reported method[23]. Microwave irradiations were carried out in a domestic oven at 2450 MHz. Chemicals were obtained from Merck and were used without further purification.

General procedure: A mixture of phenol (**1a-g**) (0.002 mol), ethyl acetoacetate (**2a)** or ethyl benzoylacetate (**2b)** (0.0022 mol in each case) and 0.2 g of finely ground silica supported sulfuric acid was placed in a 50 mL beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for appropriate time (Table-1) with a power of 180 W. After completion of the reaction (monitored by TLC using ethyl acetate: hexane, 1:1), the residue was washed with ethyl acetate or acetone. The solvent of combined extraction solution was evaporated and the crude product thus obtained was recrystallized from aqueous ethanol. The catalyst could be washed with acetone and reused.

RESULTS AND DISCUSSION

As part of current ongoing researches on the use of silica supported sulfuric acid, H_2SO_4-SiO_2, in the synthesis of important heterocycles[24], herein, the microwave-assisted cyclocondensation of substituted phenols, is reported, with ethyl acetoacetate or ethyl benzoylacetate on H_2SO_4-SiO_2 gives the substituted 4-methyl coumarins (**3a-j**) in fairly high yields. To our best of the knowledge, no report on the use of sulfuric acid adsorbed on silica gel as a solid catalyst in the synthesis of coumarins has ben reported yet. Thus, ethyl acetoacetate (or ethyl benzoylacetate) reacted with an

TABLE-1
SYNTHESIS OF COUMARINS USING H_2SO_4-SiO_2
UNDER SOLVENT-FREE CONDITIONS

Phenol	Product	Time (min)	Yield[a] (%)	m.p. (°C)	m.p. [Lit.]
		3 min	91	184-187	185 [25]
		5 min	80	254-257	256-257 [26]
		4 min	88	237-240	236-238 [25]
		7 min	84	194-196	195-197 [26]
		10 min	93	280-283	282-284 [25]
		12 min	80	245-248	243-246 [26]
		6 min	92	151-153	152 [26]
		15 min	60	151-153	150-151 [27]
		20 min	55	185-188	184-186 [27]
		8 min	89	154-157	156-158 [28]

[a]Yields based on the phenols.

appropriate phenol (**1a-g**) with the aide of H_2SO_4-SiO_2 and submission to microwave irradiation to provide fairly high yields of substituted coumarins (**3a-j**) in a few minutes (Table-1). In contrast to the liquid H_2SO_4, which is difficult to recovery and takes some effort in work-up, the silica-supported H_2SO_4 can be easily separated, rinsed with acetone and recycled without considerable loss of activity for three times. As is apparent in the Table-1, 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. On the other hand, 4- or 2-nitrophenols because of their low nucleophilic character (**3h-i**) and 1-naphthol (**3g**) due to presence of another phenyl moiety required long reaction times.

All of the products are known and their MP's, IR and ^{1}H NMR spectral data are in good agreement with those of literatures, as well as the authentic samples prepared from the previously reported methods.

In conclusion, an alternative and simple procedure is introduced for the preparation of substituted coumarins *via* Pechmann condensations using H_2SO_4-SiO_2 catalyst under solvent-free and microwave condition. Low cost of the catalyst, solvent-free condition, low toxicity of the catalyst, relatively short reaction times, simple experimental procedure, recyclablity of the catalyst and high yields of the products are some advantages of this protocol.

REFERENCES

1. A.K. Mitra, A. De, N. Karchaudhuri, S.K. Misra and A.K. Mukopadhyay, *J. Indian Chem. Soc.*, **75**, 666 (1998).
2. G. Cravettos, G.M. Nano, G. Palmisano and S. Tagliapietra, *Tetrahedron: Asymmetry*, **12**, 707 (2001).
3. O. Kayser and H. Kolodziej, *Planta Med.*, **63**, 508 (1997).
4. C.J. Wang, Y.J. Hsieh, C.Y. Chu, Y.L. Lin and T.H. Tseng, *Cancer Lett.*, **183**, 163 (2002).
5. G.J. Fan, W. Mar, M.K. Park, E.W. Choi, K. Kim and S. Kim, *Bioorg. Med. Chem. Lett.*, **11**, 2361 (2001).
6. S. Kirkiacharian, D.T. Thuy, S. Sicsic, R. Bakhchinian, R. Kurkjian and T. Tonnaire, *IL Farmaco*, **57**, 703 (2002).
7. R.O. Kennedy and R.D. Thornes, Coumarins: Biology, Applications and Mode of Action, John Wiley and Sons, Chichester (1997).
8. M. Maeda, Laser Dyes, Academic Press, New York (1984).
9. S.M. Sethna and N.M. Shah, *Chem. Rev.*, **36**, 1 (1945).
10. H. von Pechmann and C. Duisberg, *Chem. Ber.*, **17**, 929 (1884).
11. J.R. Johnson, *Org. React.*, **1**, 210 (1942).
12. G. Jones, *Org. React.*, **15**, 204 (1967).
13. G. Brufola, F. Fringuelli, O. Piermatti and F. Pizzo, *Heterocycles*, **43**, 1257 (1996).
14. R.L. Shriner, *Org. React.*, **1**, 1 (1942).
15. I. Yavari, R. Hekmat-Shoar and A. Zonouzi, *Tetrahedron Lett.*, **39**, 2391 (1998).
16. G.A. Cartwright and H. McNab, *J. Chem. Res. (S)*, 296 (1997).
17. V.M. Alexander, R.P. Bhat and S.D. Samant, *Tetrahedron Lett.*, **46**, 6957 (2005).
18. D.S. Bose, A.P. Rudradas and M.H. Babu, *Tetrahedron Lett.*, **43**, 9195 (2002).

19. B.M. Reddy, M.K. Patil and P. Lakshmanan, *J. Mol. Catal. A: Chem.*, **256**, 290 (2006).
20. S. Sethna and R. Phadke, *Org. React.*, **7**, 1 (1953).
21. M.C. Laufer, H. Hausmann and W.F. Hölderich, *J. Catal.*, **218**, 315 (2003).
22. A.C. Khandekar and B.M. Khadikar, *Synlett*, 152 (2002) and their references cited in.
23. F. Charez and R. Codinez, *Synth. Commun.*, **22**, 159 (1992).
24. N. Montazeri and K. Rad-Moghadam, *Phosphorus, Sulfur, Silicon Rel. Elem.*, **179**, 2533 (2004).
25. L. Wang, J. Xia, H. Tian, C. Qian and Y. Ma, *Indian J. Chem.*, **45B**, 2097 (2003).
26. L.L. Woods and J. Sapp, *J. Org. Chem.*, **27**, 3703 (1992).
27. A. de la Hoz, A. Moreno and E. Vazquez, *Synlett*, 608 (1999).
28. H. Valizadeh and A. Shokravi, *Tetrahedron Lett.*, **46**, 3501 (2005).

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