Solvent-Free Coumarin Synthesis

Teizo Sugino and Koichi Tanaka*
Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Ehime 790-8577

(Received November 20, 2000; CL-001048)

The synthesis of coumarins via Pechmann and Knoevenagel condensation reactions under solvent-free conditions is reported, in which waste minimization, simple operation and easier product work-up can be achieved.

Coumarin derivatives are important chemicals in the perfume, cosmetic, agricultural and pharmaceutical industries.[1] However, the conventional methods for coumarin synthesis require drastic conditions. For example, 4-methyl-7-hydroxycoumarin has been prepared by stirring a mixture of resorcinol and ethyl acetoacetate in concd H_2SO_4 for 12–24 h.[2] The development of alternative environmentally friendly synthetic methods of coumarins is strongly requested. Recently, synthesis of 7-hydroxycoumarin derivatives via the Pechmann reaction catalyzed by solid acid catalysts (e.g., zeolite H-beta) in refluxing toluene has been reported.[3] The solid base catalyzed synthesis of coumarin-3-carboxylic acids derivatives by Knoevenagel reaction in refluxing toluene has also been reported.[4] Here, we report a simple and efficient synthesis of coumarins via the Pechmann and Knoevenagel condensation reactions under solvent-free conditions.

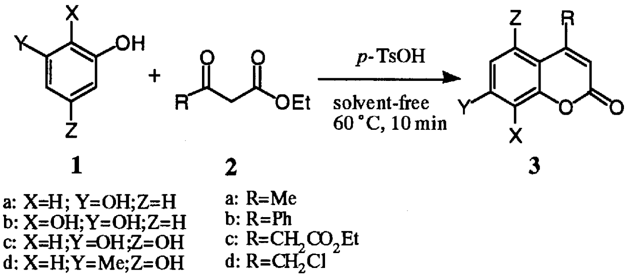
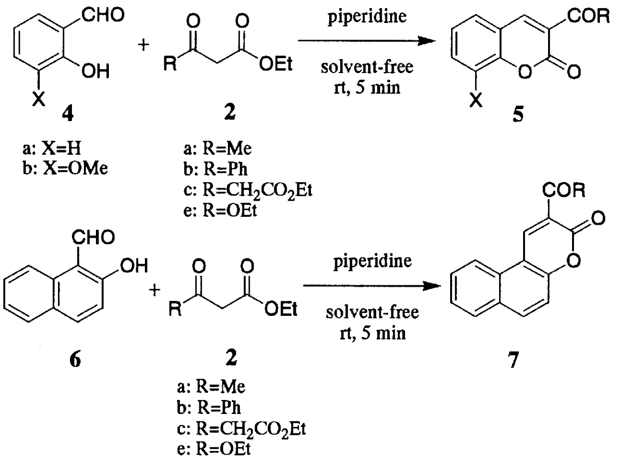


Table 1. Solvent-free Pechmann reactions of phenols (**1**) and β-keto esters (**2**)

3	X	Y	Z	R	Yield / % solvent-free	Yield / % in H_2SO_4[a]
a	H	OH	H	Me	98	82-90
b	H	OH	H	Ph	92	0
c	H	OH	H	CH_2CO_2Et	79	40
d	H	OH	H	CH_2Cl	0	0
e	OH	OH	H	Me	69	0
f	H	OH	OH	Me	81	0
g	H	Me	OH	Me	66	68

[a] Ref. 2 and 5.

To an equivalent mixture of resorcinol (**1a**, 1.1 g, 10.0 mmol) and ethyl acetoacetate (**2a**, 1.3 g, 10.0 mmol) was added TsOH (0.09 g, 0.5 mmol) in a mortar and ground well with a pestle at room temperature. The mixture was heated at 60 °C for 10 min under atmosphere. After cooling, water was added to the reaction mixture and the crystalline products were collected by filtration to give 7-hydroxy-4-methylcoumarin (**3a**, 1.73 g) in 98% yield. The crude crystals thus obtained were recrystallized from EtOH to give pure **3a** as colorless prisms (mp 185–187 °C). Similarly, solvent-free Pechmann reactions of **1** and **2** afforded **3b**, **3c**, **3e**, **3f**, and **3g** in 92, 79, 69, 81, and 66% yields, respectively (Table 1). This method is very useful because **3b**, **3d**, **3e** and **3f** have not hitherto been obtained from the reaction in H_2SO_4;[5] however **3d** was not formed either in H_2SO_4 or in the absence of a solvent.



Solvent-free Knoevenagel reactions of salicylaldehydes (**4**) and β-keto esters (**2**) were also found to proceed efficiently and under milder reaction conditions than in EtOH solution.[6] For example, a mixture of salicylaldehyde (**4a**, 1.22 g, 10.0 mmol), diethyl malonate (**2e**, 1.60 g, 10.0 mmol) and a few drops of piperidine was mixed and ground well for 5 min at room temperature. The reaction mixture was neutralized with dil HCl and then the crystalline product was isolated by filtration to give 3-ethoxycarbonylcoumarin (**5c**, 2.07 g) in 95% yield. The crude crystals thus obtained were recrystallized from EtOH to give pure **5c** as colorless prisms (mp 94–95 °C). Similarly, substituted coumarin derivatives were obtained in high yields (Table 2). When 2-hydroxy-1-naphthaldehyde (**6**) reacted with β-keto esters (**2**) under the same reaction conditions in the absence of a solvent, benzocoumarin derivatives (**7**) were obtained in high yields (Table 3). Recently, montmorillonite KSF catalyzed Knoevenagel reaction of salicylaldehyde (**4a**) and diethyl malonate (**2e**) in the absence of solvent at 160 °C was found to give **5c** in 44% yield.[7]

It has been reported that the Knoevenagel reaction of 2-

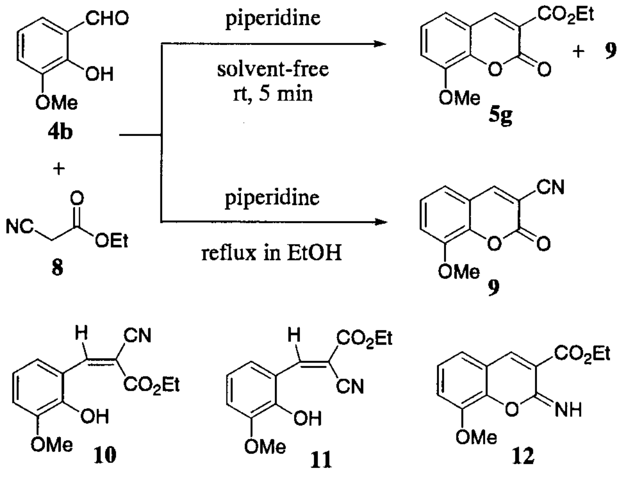
Table 2. Solvent-free Knoevenagel reactions of salicylaldehyde (**4**) and β-keto esters (**2**)

5	X	R	Yield / %
a	H	Me	99
b	H	Ph	97
c	H	OEt	95
d	H	CH_2CO_2Et	73
e	OMe	Me	99
f	OMe	Ph	99
g	OMe	OEt	97
h	OMe	CH_2CO_2Et	91

Table 3. Solvent-free Knoevenagel reactions of 2-hydroxy-1-naphthaldehyde (**6**) and β-keto esters (**2**)

7	R	Yield / %
a	Me	92
b	Ph	93
c	CH_2CO_2Et	98
d	OEt	97

hydroxy-3-methoxybenzaldehyde (**4b**) and ethyl cyanoacetate (**8**) affords 8-methoxy-2-oxo-2*H*-chromene-3-carbonitrile (**9**) via intramolecular cyclization of *Z*-**10** in 35% yield under reflux in EtOH.[8] Very interestingly, however, the condensation reaction of **4b** and **8** in the absence of a solvent gave 8-methoxy-2-oxo-2*H*-chromene-3-carboxylic acid ethyl ester (**5g**) in 65% yield along with small amount of **9** (11% yield). Compound **5g** might be obtained via hydrolysis of iminolactone **12** formed by intramolecular cyclization of *E*-**11**.



In conclusion, this simple solvent-free technique[9] affords various kinds of coumarin derivatives in excellent yields without forming environmentally harmful waste.

References and Notes

1 W. C. Meuly, "Kirk–Othmer Encyclopedia of Chemical Technology," 3rd ed., John Wiley & Sons, New York (1979).
2 E. C. Horning, "Organic Syntheses, Coll. Vol. III," John Wiley & Sons, New York (1955), p. 281.
3 A. J. Hoefnagel, E. A. Gunnewegh, R. S. Downing, and H. van Bekkum, *J. Chem. Soc., Chem. Commun.*, **1995**, 225.
4 A. Ramani, B. M. Chandra, S. Velu, and S. Sivasanker, *Green Chem.*, **1**, 163 (1999).
5 S. Sethna and R. Phadke, *Org. React.*, **7**, 1 (1953).
6 G. Jones, *Org. React.*, **15**, 204 (1967).
7 F. Bigi, L. Chesini, R. Maggi, and G. Sartori, *J. Org. Chem.*, **64**, 1033 (1999).
8 E. C. Horning and M.G. Horning, *J. Am. Chem. Soc.*, **69**, 968 (1947).
9 K. Tanaka and F. Toda, *Chem. Rev.*, **100**, 1025 (2000).