Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters

Tetrahedron Letters 46 (2005) 6119–6121

# An efficient $ZrCl_4$ catalyzed one-pot solvent free protocol for the synthesis of 4-substituted coumarins[☆]

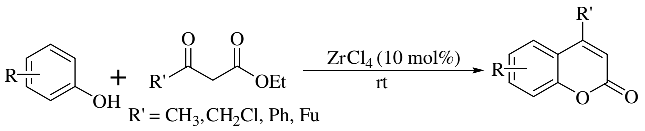
G. V. M. Sharma,* J. Janardhan Reddy, P. Sree Lakshmi and P. Radha Krishna

*D-211, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

Received 15 April 2005; revised 22 June 2005; accepted 29 June 2005
Available online 25 July 2005

**Abstract**—A versatile and efficient route to 4-substituted coumarins via a Pechmann reaction using $ZrCl_4$ as the catalyst (10 mol %) is described. This method provides several advantages over alternative procedures such as mild, solvent-free conditions at ambient temperature, and direct isolation of the products in high yields.

Coumarins are structural units of several natural products,[1] and feature widely in pharmacologically and biologically active compounds.[2] Besides functionalized coumarins,[3–7] polycyclic coumarins such as calanolides,[8] isolated from *Calophyllum* genus, and others have shown potent anti-HIV (NNRTI) activity. A variety of methods viz., Pechmann,[9a] Perkin,[9b] Claisen,[9c] Knoevenagel,[9d] Reformatsky[9e] and Wittig,[9f,g] have been developed to synthesize coumarins. The Pechmann reaction,[9h] a two component (phenol and β-keto ester) coupling under acid catalysis,[10–13] is a very well established protocol for coumarin ring synthesis. It may also utilize heterogenous catalysis,[14] transition metal catalysis,[15] ionic liquids[16] and microwave irradiation.[17] However, most of these procedures suffer from disadvantages such as elevated temperatures, longer reaction times and poor yields. In our earlier work on the synthesis of dihydrocalanolides,[18] the coumarin ring was constructed in poor yields, using $CF_3COOH$ as the solvent at reflux, for the Pechmann reaction. In connection with our research on drug discovery, an improved procedure for the one-pot construction of coumarin ring systems on large scale was investigated. Based on our past experience with $ZrCl_4$ as an efficient acid catalyst,[19] we report the studies on a $ZrCl_4$ catalyzed solvent-free one-pot protocol at room temperature for the synthesis of coumarins (Eq. 1).



(1)

To establish the reaction conditions, equimolar quantities of resorcinol **1** (Table 1, entry 1) and ethyl acetoacetate were treated with $ZrCl_4$ (10 mol %) at room temperature for 5 min to give the corresponding coumarin **1a** in 92% yield, mp 184–185 °C (lit.[12c] 185 °C). Coumarin **1a** was characterized by IR, NMR and other spectral data and treated with AcCl in pyridine to afford its corresponding acetate, whose structure was established from spectral data. Similarly, resorcinol **1** was treated with a variety of β-ketoesters viz., ethyl 4-chloroacetoacetate, ethyl benzoylacetate and ethyl furoacetate (Table 1, entries 2–4) to furnish coumarins **1b**, **1c** and **1d**, respectively, in 90–95% yields within 5–10 min. Compounds **1b**, **1c** and **1d** had mp's corresponding to reported values.[20a,10]

Encouraged by the above results, other phenolic substrates were subjected to the Pechmann reaction using $ZrCl_4$. Pyrogallol **2**, phloroglucinol **3**, 2-methylresorcinol **4** and α-naphthol **5** were subjected to the reaction with different β-ketoesters as shown in Table 1 to give the corresponding coumarins. The reaction was found to be adaptable to a variety of substrates and the yields, in general, were very high (90–98%). Short reaction times were observed (5–10 min) regardless of structural variations in the phenols or β-ketoesters. Most of these

---

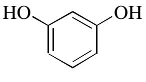
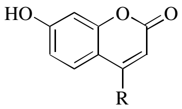
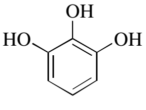
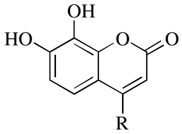
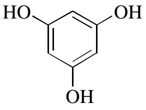
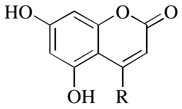
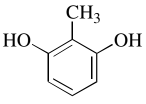
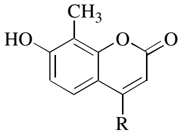
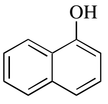
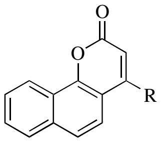
*Keywords*: Coumarins; Phenols; β-Ketoesters; Pechmann reaction and $ZrCl_4$.

[☆] IICT Communication No. 041103.

[*] Corresponding author. Fax: +91 40 2716 0387; e-mail: esmvee@iict.res.in

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.06.166

**Table 1.** $ZrCl_4$ (10 mol %) catalyzed synthesis of coumarins

| Entry | Phenol | β-Keto ester | Product | Time (min) | Yield (%) | Mp, °C$^{\text{ref}}$ |
|---|---|---|---|---|---|---|
| 1 | <br>**1** | $RCOCH_2CO_2Et$ |  | | | |
| | | $R = CH_3$ | **1a** $R = CH_3$ | 5 | 92 | 184–185[12c] |
| | | $R = CH_2Cl$ | **1b** $R = CH_2Cl$ | 5 | 95 | 180–181[20a] |
| | | R = Ph | **1c** R = Ph | 10 | 91 | 256–257[10] |
| | | R = Furyl | **1d** R = Furyl | 10 | 90 | 210–212[20d] |
| 2 | <br>**2** | $RCOCH_2CO_2Et$ |  | | | |
| | | $R = CH_3$ | **2a** $R = CH_3$ | 5 | 96 | 241–243[12c] |
| | | $R = CH_2Cl$ | **2b** $R = CH_2Cl$ | 5 | 98 | 133–135[20b] |
| | | R = Ph | **2c** R = Ph | 10 | 94 | 195–197[10] |
| | | R = Furyl | **2d** R = Furyl | 10 | 90 | 190 decom[20c] |
| 3 | <br>**3** | $RCOCH_2CO_2Et$ |  | | | |
| | | $R = CH_3$ | **3a** $R = CH_3$ | 5 | 93 | 280–281[12c] |
| | | $R = CH_2Cl$ | **3b** $R = CH_2Cl$ | 5 | 97 | 187–189[20b] |
| | | R = Ph | **3c** R = Ph | 10 | 94 | 243–246[10] |
| 4 | <br>**4** | $RCOCH_2CO_2Et$ |  | | | |
| | | $R = CH_3$ | **4a** $R = CH_3$ | 5 | 95 | 263–265[10] |
| | | $R = CH_2Cl$ | **4b** $R = CH_2Cl$ | 5 | 96 | 284–286[10] |
| | | R = Ph | **4c** R = Ph | 10 | 90 | 284–285[10] |
| 5 | <br>**5** | $RCOCH_2CO_2Et$ |  | | | |
| | | $R = CH_3$ | **5a** $R = CH_3$ | 10 | 92 | 153–155[10] |
| | | $R = CH_2Cl$ | **5b** $R = CH_2Cl$ | 10 | 95 | 165–167[10] |

coumarins were characterized from melting points and $M^+$ peaks in the EIMS. All the coumarins except for **1d**, **2d**, **5a** and **5b** were converted into their acetates (**1a′**–**c′**, **2a′**–**c′**, **3a′**–**c′** and **4a′**–**c′**), which were characterized by $^1H$ NMR and other spectral techniques.

*Typical experimental procedure*: To an equimolar mixture of the phenol and the β-ketoester, $ZrCl_4$ (10 mol %) was added and the mixture stirred at room temperature for a few minutes (5–10 min). After the completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water, filtered and the separated solid was washed with water and dried to furnish the coumarin.

## Acknowledgements

P.S. and J.J.R. are thankful to the CSIR, New Delhi, India for financial support.

## References and notes

1. Murray, R. D. H. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 84–316.
2. O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications and Mode of Action*; Wiley & Sons: Chichester, 1997.
3. Singer, L. A.; Long, N. P. *J. Am. Chem. Soc.* **1996**, *88*, 5213–5219.

4. Zahradnik, M. *The Production and Application of Flourescent Brightening Agents*; Wiley & Sons, 1992.
5. Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley & Sons: New York, 1982.
6. Maria, J. B.; Santos, C.; Susana, N.; Barbara, G.; Mario, N. B. S. *Tetrahedron Lett.* **2004**, *45*, 6927–6929.
7. (a) Hara, K.; Sayama, K.; Ogha, Y.; Shinpo, A.; Suga, S.; Arakawa, H. *Chem. Commun.* **2001**, 569–570; (b) Jiao, C.; Chen, L.; Shen, G.; Yu, R. *Sens. Actuators* **2003**, *94*, 176–183.
8. Kashman, Y.; Gustafson, K. R.; Fuller, R.; Cardellina, J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735–2743.
9. (a) Pechmann, V. H.; Duisberg, C. *Chem. Ber.* **1884**, *17*, 929–979; (b) Perkin, W. H.; Henry, W., Sr. *J. Chem. Soc.* **1875**, *28*, 10–11; (c) Cairns, N.; Harwood, L. M.; Astles, D. P. *J. Chem. Soc.; Perkin Trans. 1* **1994**, 3101–3107; (d) Jones, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257–1266; (e) Shriner, R. L. *Org. React.* **1942**, *1*, 15–46; (f) Mali, R. S.; Tilve, S. G. *Synth. Commun.* **1990**, *20*, 1781–1791; (g) Maercker, A. *Org. Synth.* **1934**, *14*, 270–291; (h) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1–58.
10. Woods, L. L.; Sapp, J. *J. Org. Chem.* **1962**, *27*, 3703–3705.
11. (a) Simmonis, H.; Remmert, P. *Chem. Ber.* **1914**, *47*, 2229–2233; (b) Robertson, A.; Sandrock, W. F.; Henry, C. B. *J. Chem. Soc.* **1931**, 2426–2432.
12. (a) Sethna, S. M.; Shah, N. M.; Shah, R. C. *J. Chem. Soc.* **1938**, 228–232; (b) Bose, D. S.; Rudradas, A. P.; Hari Babu, M. *Tetrahedron Lett.* **2002**, *43*, 9195–9197; (c) Wang, L.; Xia, J.; Tian, H.; Qian, C.; Ma, Y. *Indian J. Chem.* **2003**, *42B*, 2097–2099.
13. Romanelli, G. P.; Benardi, D.; Ruiz, D. M.; Baronetti, G.; Thomas, H. J.; Autino, J. C. *Tetrahedron Lett.* **2004**, *45*, 8935–8939.
14. (a) Hoefnagel, A. J.; Gunnewegh, E. A.; Downing, R. S.; Bekkum, H. V. *J. Chem. Soc., Chem. Commun.* **1995**, 225–226; (b) Reddy, B. M.; Reddy, V. R.; Giridhar, D. *Synth. Commun.* **2001**, *31*, 3603–3607.
15. (a) Nguyen Van, T.; Debenedetti, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 4199–4204; (b) Chatterjee, A. K.; Toste, F. D.; Goldberg, S. D.; Grubbs, R. H. *Pure Appl. Chem.* **2003**, *75*, 421.
16. (a) Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2001**, *42*, 9285–9287; (b) Khandekar, A. C.; Khadilkar, B. M. *Synlett* **2002**, 152–154.
17. Hoz, A. D.; Andres, M.; Vazquez, E. *Synlett* **1999**, 608–610.
18. Mahender Rao, S. Ph. D. thesis, Osmania University, Hyderabad, India, 1995.
19. (a) Sharma, G. V. M.; Govardhan Reddy, Ch.; Radhakrishna, P. *J. Org. Chem.* **2003**, *68*, 4574–4575; (b) Sharma, G. V. M.; Govardhan Reddy, Ch.; Radhakrishna, P. *Synlett* **2003**, 1728–1730; (c) Sharma, G. V. M.; Srinivas, B.; Radhakrishna, P. *Tetrahedron Lett.* **2003**, *44*, 4689–4691; (d) Sharma, G. V. M.; Janardhan Reddy, J.; Sree Lakshmi, P.; Radhakrishna, P. *Tetrahedron Lett.* **2004**, *45*, 6963–6965.
20. (a) Zagotto, G.; Gia, O.; Baccichetti, F.; Uriarte, E.; Palum, M. *Photochem. Photobiol.* **1993**, *58*, 486–491; (b) Khaikin, M. S.; Petrova, N. L.; Kukhtin, V. A. *Zh. Obshch. Khim.* **1963**, *33*, 3941–3943; (c) Khaikin, M. S.; Fedorina, L. G.; Fakhrutdinov, A.; Kukhtin, V. A. *Zh. Obshch. Khim.* **1965**, *1*, 356–358; (d) Sreenivasulu, B. S.; Murthy, V. S.; Rao, N. V. S. *Curr. Sci.* **1969**, *38*, 240–241.