SIMPLE AND EFFICIENT ONE-POT PREPARATION OF 3-SUBSTITUTED COUMARINS IN WATER

Gianluca Brufola, Francesco Fringuelli*, Oriana Piermatti, and Ferdinando Pizzo*

Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto, 8 06100 Perugia, Italy

Abstract — 3-Cyanocoumarin and seven derivatives [4-Me; 6-NO_2; 7-OH; 7-OMe; 8-OH; 5,7-OMe; 6,7-(-CH=CH-)-$_2$] and eight coumarins substituted at C-3 (CO_2Et; NO_2; Ph; *p*-NO_2-C_6H_4; Ph-SO_2; 2-pyridyl; 2-thienyl; 2-benzothiazolyl) were prepared, on multigram scale by a one-pot procedure in water alone, by the Knoevenagel reaction of *o*-hydroxyaryl aldehydes and *o*-hydroxyacetophenone with acetonitriles. The yields are high and the procedure does not require organic solvents. The reactions carried out in heterogeneous aqueous phase, sometimes in the presence of a surfactant, always have higher yields than the same reactions executed in homogeneous ethanolic medium.

During the last decade it has been discovered that the reactivity and selectivity of many organic reactions can be significantly improved by using an aqueous medium.[1-3] The thoughts that the low solubility of the reagents would be an obstacle to the reactivity [4] and that water must always be rigorously excluded when organometallic reagents are used,[7] have been overcome.

Breslow [8] and Lubineau [9] attribute the increased reactivity and selectivity of the reactions in aqueous medium to the hydrophobic effect.[10] According to Blokzijl and Engberts,[12] the water effect is not mainly due to hydrophobic packing of the reactants but is the result of a combination of enforced hydrophobic interactions and hydrogen bonding.

It has also been emphasized that an aqueous medium is particularly effective when the activation volume of the reaction is negative and this has been attributed to the high cohesive energy of water that could act as an external pressure.[9,13]

We have studied the use of water as reaction medium in the following reactions: the epoxidation of

alkenes [14] and allylic alcohols,[15] the Baeyer-Villiger oxidation,[16a] the selective oxidation of sulfides, [16b] the chemoselective oxidation of functional groups [17] and the aldol-like condensation reactions.[6]

One of the advantages of an aqueous medium is that the pH of the reaction mixture can be controlled and we have investigated the possibility of carrying out a one-pot multi-step synthesis in water by simply changing the pH of the aqueous medium.

The reaction selected for this study was the Knoevenagel condensation for synthesizing coumarins because (i) the reaction is pH-controlled,[18] (ii) the aldol-like condensation reactions have a negative volume of activation [13] and (iii) the coumarins are an interesting class of compounds, well-known for their chemical and biological properties.[19]

We report here a simple and efficient one-pot synthesis, in only water, of 3-substituted coumarins starting from some readily available commercial compounds such as salicyl aldehydes, *o*-hydroxyacetophenone, 2-hydroxy-1-naphthaldehyde and acetonitriles.[20] Derivatives of acetonitrile have rarely been used to synthesize coumarins.

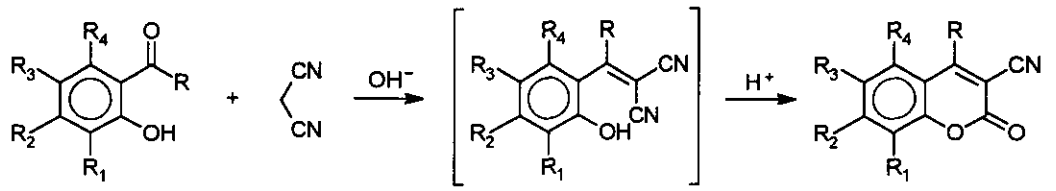
Coumarins substituted at C-3 occupy a special place in the realm of natural and synthetic coumarins because of their wide range of activities. 3-Methylcoumarins have anthelmintic, hypnotic and insecticidal properties;[22] 3-phenylcoumarins are anticoagulant, coronary constricting agents and fluorescent brighteners;[23] 3-(2-benzothyazolyl)coumarins are used as photographic sensitizers, fluorescent dyes, intermediates for pesticides and pharmaceuticals and as an active medium in laser and in light and solar collectors.[24] 3-Ethoxycarbonylcoumarins are key intermediates in the synthesis of many other coumarins.[25]

Many methods of synthesis of 3-substituted coumarins are known [26] including the Perkin, [27] Knoevenagel,[18] Reformatsky,[28] Pechman [29] and Wittig reactions [23] but the search for new and more convenient methodologies continues.

We prepared 3-cyanocoumarins by one-pot procedure by the reaction, at room temperature, of salicyl aldehydes (**1a-f**) with malononitrile (**2**) in heterogeneous alkaline aqueous medium with a subsequent acid treatment of the reaction mixture [30] (Scheme I). The coumarins (**4a-f**) were isolated in pure forms by simple filtration.

The intermediate *o*-hydroxybenzylidenemalononitriles (**3a-f**) were not isolated; their conversion to corresponding 3-cyanocoumarins generally required heating. Extension of this procedure to *o*-hydroxyacetophenone (**1g**) and 2-hydroxy-1-naphthaldehyde (**1h**) gave the corresponding coumarins

Scheme I



1 **2** **3** **4**

	R	R_1	R_2	R_3	R_4
a	H	H	H	H	H
b	H	H	OH	H	H
c	H	H	OMe	H	H
d	H	H	OMe	H	OMe

	R	R_1	R_2	R_3	R_4
e	H	OH	H	H	H
f	H	H	H	NO_2	H
g	Me	H	H	H	H
h	H	H	H	-CH=CH-$_2$	

(**4g** and **4h**). The results are reported in Table I.

The reaction yields are excellent and the process does not require an organic solvent, which is important from an environmental point of view because pollution is prevented at the source.

It should be noted that the volume of water, the pH of the condensation reaction and stirring significantly influence the yield and the rate of the reaction. If, for example, the condensation of **1a** with **2** is carried out at pH = 12.4 the yield of coumarin (**4a**) is only 60% and if stirring is not efficient, the reaction time is longer.

The methodology has been extended to the preparation of a variety of 3-substituted coumarins by using salicyl aldehyde (**1a**) and substituted acetonitriles (**5**) (Scheme II).[32] The reaction conditions and the results are reported in Table II.

Table I. Reactions of *o*-Hydroxyarylcarbonyl Compounds (**1**) with Malononitrile (**2**) in Water.

Substrate	pH[a]	Temp. (°C)[b]	Time (h)[b]	Coumarin	Yield (%)[c]
1a	8.3	20-90	2-2.5	**4a**	90
1b	8.3	20-90	4-2	**4b**	75
1c	8.3	20-90	14-2	**4c**	92
1d	12.4	20-90	5-2	**4d**	90
1e	8.3	20-90	4-1	**4e**	85
1f[d]	8.3	20-90	1-1	**4f**	80
1g[e]	8.3	20-90	3-1	**4g**	95
1h	12.4	20-20	2-2	**4h**	80

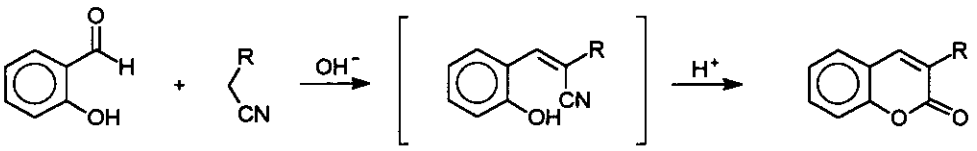
[a] The value refers to the condensation reaction. The cyclization reaction was carried out under acidic conditions (see experimental section). [b] The first value refers to the condensation step and the second to the cyclization one. [c] Yield of isolated and purified coumarin. [d] A molar ratio **1f/2** = 0.5 was used. [e] A molar ratio **1g/2** = 2 was used.[33]

With phenylacetonitrile (**5c**) and 2-pyridylacetonitrile (**5f**), the whole process occurs under alkaline conditions and with highly hydrophobic acetonitriles (**5c**, **5d**, **5e**, **5g** and **5h**) it is necessary to use catalytic amounts of cetyltrimethylammonium bromide (CTABr).[34]

The synthesis of 3-(2-benzothiazolyl)coumarin (**7h**) is significant because the preparation of **5h** and the subsequent condensation with **1a** were executed in aqueous medium in the same pot and because the benzothiazolyl group is a masked formyl group which allows the synthesis of the difficultly accessible 3-formylcoumarins.

To evaluate the effect of aqueous medium, we carried out the synthesis of 3-substituted coumarins in homogeneous ethanolic solution. The results are reported in Table III. The heterogeneous aqueous medium always gave better yields than the homogeneous alcoholic one and the more hydrophobic the substituted acetonitrile is, the higher is the advantage to carry out the reaction in water.

Scheme II



1a **5** **6** **7**

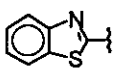
R	CO_2Et	NO_2	Ph	pNO_2-C_6H_4	Ph—S(=O)(=O)—			
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**

Table II. Reactions of Salicyl Aldehyde (**1a**) with Monosubstituted Acetonitriles (**5**) in Water.

Nitrile	pH[a]	Temp. (°C)[b]	Time (h)[b]	Coumarin	Yield (%)[c]
5a	8.3	20-70	3-2	**7a**	87
5b	8.3	20-90	1-1	**7b**	66[d]
5c [e,f,g]	12.4	90	11	**7c**	90
5d [e]	8.3	20-90	20-4	**7d**	96
5e [e]	8.3	20-90	20-4	**7e**	85
5f [f]	12.4	90	3	**7f**	98
5g [e]	12.4	90-90	6-1	**7g**	95
5h [e]	13.0	20-90	8-0.5	**7h**	93

For explanation of *a*, *b*, *c* see Table I. [d] The remainder is unreacted salicyl aldehyde. [e] In the presence of 0.1 mol/equiv. of CTABr. [f] The cyclization reaction also occurs under basic conditions. [g] A molar ratio **1a**/**5c** = 0.5 was used.

Table III. Synthesis of 3-Substituted Coumarins by Knoevenagel Reaction in Water and in Ethanol.

Reactants	Coumarin	Water [a] Yield (%)	Ethanol [a] Yield (%)
1a + **2**	**4a**	90	70 [b]
1a + **5a**	**7a**	87	80
1a + **5b**	**7b**	66	35 [c]
1a + **5c**	**7c**	90	traces
1a + **5f**	**7f**	98	55
1a + **5g**	**7g**	95	20

[a] Under the experimental conditions described in Tables I and II. For the preparation of **7a** in ethanolic solution, the condensation step was catalyzed by piperidine 0.05 N because of the low solubility of $NaHCO_3$ in ethanol. [b] Ref. 30. [c] Ref. 35.

In conclusion, the synthesis of 3-substituted coumarins by the Knoevenagel condensation can be carried out in water alone by a one-pot procedure. The synthesis of 16 simple 3-substituted coumarins has been reported but the procedure may be useful in the preparation of more complex aryl lactonic structures.

EXPERIMENTAL

The coumarins (**4a** [31], **4b** [36], **4c** [31], **4g** [37], **4h** [38], **7a** [39], **7b** [40], **7c** [41], **7d** [42], **7e** [43], **7f** [44], **7g** [39], **7h** [45] are known in the literature. The mp of all known compounds were consistent with those reported in the literature except for **4b** (mp 274-275 °C after recrystallization from H_2O-AcOH; lit., [36] 262 °C). The structures of all the coumarins were consistent with ir (Perkin Elmer mod. 983 instrument), ^{1}H-nmr in $(CD_3)_2SO$ (FT Bruker AC 80 spectrometer) and GC-ms (HP 5890 MSD instrument) analyses. All starting materials were commercial with the exception of nitroacetonitrile [46] and 2-benzothiazolylacetonitrile.[47]

General Procedure: *o*-Hydroxycarbonyl compound (**1**) (100 mmol), nitrile (**2**) or (**5**) (100 mmol) and

cetyltrimethylammonium bromide (3.64 g, 10 mmol), when necessary (Table II) were added to an aqueous solution of $NaHCO_3$ (500 ml, 0.05 M) or to an aqueous solution of NaOH (500 ml, 0.025 N or 0.05 N; Table I and II). The mixture was vigorously stirred at room temperature for the times reported in Tables I and II. The heterogeneous mixture was acidified with conc. HCl (12.5 ml) and then heated at 90 °C or left at room temperature under stirring for 1-4 h (see Tables I and II). After cooling the solid was filtered, washed with cold water and dried. The crude coumarin has a purity higher than 98% and can be purified further on by recrystallization from EtOH, AcOH, Me_2CO or mixtures H_2O-AcOH and EtOH-EtOAc. The yields of purified coumarins are reported in Tables I and II.

3-Cyano-5,7-dimethoxycoumarin (4d)

mp 233-235 °C from Me_2CO. ^{1}H-Nmr δ: 8.68 (s, 1H, H-4), 6.68 (d, 1H, H-6, J = 2.0 Hz), 6.57 (d, 1H, H-8, J = 2.0 Hz), 3.92 (s, 3H, OMe), 3.90 (s, 3H, OMe); ms m/z : 63 (16), 69 (27), 89 (14), 117 (18), 188 (31), 203 (38), 231 (100). Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.15; H, 3.90; N, 6.0.

3-Cyano-8-hydroxycoumarin (4e)

mp 244-245 °C from EtOH-EtOAc. ^{1}H-Nmr δ: 10.4 (br s, 1H, OH), 8.84 (s, 1H, H-4), 7.23 (m, 3H, H-5, H-6, H-7); ms m/z : 50 (42), 75(43), 76 (76), 103 (47), 131 (23), 159 (76), 187 (100). Anal. Calcd for $C_{10}H_5NO_3$: C, 64.19; H, 2.69; N, 7.48. Found: C, 64.10; H, 2.60; N,7.40.

3-Cyano-6-nitrocoumarin (4f)

mp 184-185 °C from EtOH-EtOAc. ^{1}H-Nmr δ: 9.03 (s, 1H, H-4), 8.77 (d, 1H, H-5, J = 2.8 Hz), 8.56 (dd, 1H, H-7, J = 9.5, 2.8 Hz), 7.73 (d, 1H, H-8, J = 9.5 Hz); ms m/z : 62 (31), 63 (31), 87 (41), 88 (46), 142 (29), 158 (47), 186 (57), 216 (100). Anal. Calcd for $C_{10}H_4N_2O_4$: C, 55.57; H, 1.87; N, 12.96. Found: C, 55.52; H, 1.98; N, 12.98.

3-(2-Benzothiazolyl)coumarin (7h)

A mixture of 2-aminothiophenol (12.5 g, 100 mmol), malononitrile (6.6 g, 100 mmol), acetic acid (5.7 ml, 100 mmol) and cetyltrimethylammonium bromide (3.64 g, 10 mmol) in water (150 ml) was stirred at room temperature for 12 h. Water (350 ml), salicyl aldehyde (**1a**) (12.2 g, 100 mmol) and NaOH (6 g, 150

mmol) were added and the mixture left at room temperature for 8 h under stirring. The mixture was then acidified with conc. HCl (28 ml) and heated at 90 °C for 30 min. After cooling the solid was filtered, washed with cold water and dried. Yields 93%, mp 216-217 °C from EtOH-AcOEt (lit., [45] 217-218 °C).

ACKNOWLEDGEMENTS

The Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Consiglio Nazionale delle Ricerche (CNR, Rome) are thanked for financial support.

REFERENCES AND NOTES

1. F. Fringuelli and F. Pizzo, *Seminars in Organic Synthesis. 17th Summer School A. Corbella,* 1992, 269.
2. C.J. Li, *Chem. Rev.*, 1993, **93**, 2023.
3. A. Lubineau, J. Augé, and Y. Queneau, *Synthesis,* 1994, 741.
4. Reactions between compounds which are highly insoluble in water do not occur in aqueous medium.[5] The problem can be generally overcome by adding a surfactant.[6]
5. T. Dunans, W. Hockstra, M. Pentaleri, and S. Liotta, *Tetrahedron Lett.*, 1988, **29**, 3745.
6. F. Fringuelli, G. Pani, O. Piermatti, and F. Pizzo, *Tetrahedron,* 1994, **50**, 11499.
7. a) T.H. Chan, C.J. Li, M.C. Lee, and Z.Y. Wei, *Canad. J. Chem.*, 1994, **72**, 1181. b) S. Kobayashi, *Synlett,* 1994, 689.
8. a) D.C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816. b) R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159 and references cited therein.
9. A. Lubineau, H. Bienaymè, Y. Queneau, and M.C. Scherrmann, *New. J. Chem.*, 1994, **18**, 279 and references cited therein.
10. The expression hydrophobic interaction is sometimes preferred to hydrophobic effect to indicate the tendency of apolar molecules or apolar groups to aggregate in water.[11] The expression hydrophobic effect is used to indicate the solute-solvent interactions and experimentally refers to the relative insolubility of apolar organic compounds in water as compared to their solubility in nonaqueous solvent.[11]
11. C. Reichardt, *Solvents and Solvent Effect in Organic Chemistry,* 2nd Ed., VCH, 1988.
12. a) W. Blokzijl and J.B.F.N. Engberts, *Angew Chem., Int. Ed. Engl.*, 1993, **32**, 1545. b) S. Otto, W.

Blokzijl, and J.B.F.N. Engberts, *J. Org. Chem.*, 1994, **59**, 5372.

13. J. Augé, N. Lubin, and A. Lubineau, *Tetrahedron Lett.*, 1994, **35**, 7947.
14. a) F. Fringuelli, R. Germani, F. Pizzo, and G. Savelli, *Tetrahedron Lett.*, 1989, **30**, 14272. b) F. Fringuelli, F. Pizzo, R. Germani, and G. Savelli, *Org. Prep. Proc. Int.*, 1989, **29**, 756.
15. a) F. Fringuelli, F. Pizzo, and R. Germani, *Synlett*, 1991, 475. b) F. Fringuelli, R. Germani, F. Pizzo, F. Santinelli, and G. Savelli, *J. Org. Chem.*, 1992, **57**, 1198.
16. a) F. Fringuelli, R. Germani, F. Pizzo, and G. Savelli, *Gazz. Chim. Ital.*, 1989, **119**, 249. b) F. Fringuelli, R. Pellegrino, and F. Pizzo, *Synthetic Commun.*, 1993, **23**, 3157.
17. F. Fringuelli, R. Pellegrino, O. Piermatti, and F. Pizzo, *Synthetic Commun.*, 1994, **24**, 2665.
18. a) E. Knoevenagel, *Ber.*, 1904, **37**, 4461. b) T. Boehm and E. Profft, *Arch. Pharm.*, 1931, **25**, 269. c) G. Jones, *Org. React.*, 1967, **15**, 204.
19. a) F.M. Dean, *Progress in Chemistry of Organic Natural Products*, ed. by L. Zechmeister, Verlag Chemie, Weinheim, 1952, Vol. 9, p. 235. b) R.D.H. Murnay, J. Mendez, and S.A. Brown, *The Natural Coumarins*, J. Wiley and Sons, N.Y., 1982, 227. c) D. Lednicer and L.A. Mitscher, *Organic Chemistry of Drug Synthesis*, J. Wiley , N.Y., 1977, **1**, 330.
20. To our knowledge, the only example of a one-pot synthesis in water of a coumarinic system is the reaction between the 6-hydroxy-7-methoxy-5-benzofurancarboxaldehyde with ethyl cyanoacetate during the synthesis of methoxsalen.[21]
21. Y.Y. Liu, E. Thom, and A. Liebman, *J. Heterocycl. Chem.*, 1979, **16**, 799.
22. R.S. Mali, S.N. Yeola, and B.K. Kulkarni, *Indian J. Chem.*, 1983, **22B**, 352.
23. N.S. Narasimhan, R.S. Mali, and M.V. Barve, *Synthesis*, 1979, 906.
24. a) J.D. Kendal, H.R.J. Waddington, and G.F. Duffin, *Chem. Abstr.*, 1961, **55**, 21927. b) P. Loew, (Ciba-Geigh A.-G.), *Chem. Abstr.*, 1977, **87**, 186083. c) H. Hagen and R.D. Kohler, (BASF A.-G.), *Chem. Abstr.*, 1981, **95**, 187261. d) R. Rane, H. Harnish, and K.H. Drexhage, *Heterocycles*, 1984, **21**, 167.
25. a) H. Haeserman and J. Voltz, *Chem. Abstr.*, 1962, **56**, 10158. b) A.M. El-Naggar, M.H.A. El-Gamal, B.H.A. El-Tawil, and F.S.M. Ahmed, *Acta Chim. Acad. Sci. Hung.*, 1976, **89**, 279.
26. A selection of references in this area is the following: a) K.D. Kaufman and R.C. Kelly, *J. Heterocycl. Chem.*, 1965, **2**, 91. b) G.A. Krans and J.O.Pezzenite, *J. Org. Chem.*, 1979, **44**, 2481. c) E.R. Bissel, *Synthesis*, 1982, 846. d) J.A. Panetta and H. Rapoport, *J. Org. Chem.*, 1982, **47**, 946.

e) R.G. Harvey, C. Cortez, T.P. Ananthenarayan, and S. Schmolka, *J. Org. Chem.*, 1988, **53**, 3936.

f) O.E. Hormi, C. Peltonen, and R. Bergström, *J. Chem. Soc., Perkin Trans. 1*, 1991, 219.

27. a) E. Späth, *Ber.*, 1973, **70**, 83. b) H. Janagisawa and H. Kondo, *Yakugaku Zasshi*, 1921, **472**, 498.
28. R.L. Shirner, *Org React.*, 1942, **1**, 1.
29. S. Sethna and R. Padke, *Org. React.*, 1953, **7**, 1.
30. The conversions of compounds **3** to **4** were carried out under less acidic conditions than those reported for the two-step preparation of 3-cyanocoumarin.[31]
31. W. Baker and C.S. Howes, *J. Chem. Soc.*, 1953, 119.
32. Some *o*-hydroxybenzylidenes (**6**) were prepared in ethanol in the presence of heterocyclic bases.[31] These condensation adducts usually have the cyano group and the benzene ring in *cis* configuration but *cis-trans* mixture has been observed.[18] The yields of coumarins obtained in aqueous medium show that the Knoevenagel reaction in water is highly diastereoselective.
33. A quantitative conversion of **1g** to **4g** is obtained only by using two equivalents of **1g**. By using stoichiometric quantities, a competitive condensation reaction occurs.
34. Tetrabuthylammonium bromide is a less effective catalyst than CTABr. The greater catalytic effect of CTABr is ascribable to its greater ability to stabilize the carbon anion.
35. F.M. Dean and B.K. Park, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1260.
36. Balaiah, *Proc. Indian Acad.[A]*, 1942, **16**, 68.
37. P.C.H. Schroeder and K.P. Link, *J. Am. Chem. Soc.*, 1953, **75**, 1886.
38. Trivedi, *J. Scient. Indian Res. India*, 1959, **18B**, 308.
39. J. Gallastegni, J.M. Lago, and C. Palomo, *J. Chem. Res.*, 1984, 170.
40. D. Danzonne and R. Royer, *Synthesis*, 1983, 836.
41. P. Pulla Rao and G. Srimannarayana, *Synthesis*, 1981, 887.
42. W.E. Soldar and M. Green, *J. Org. Chem.*, 1958, **23**, 103.
43. J.R. Merchant and P.J. Shah, *J. Heterocycl. Chem.*, 1981, **18**, 441.
44. D.R. Bragg and D.G. Wibberleg, *J. Chem. Soc.*, 1961, 5074.
45. V. Dryanska, *Synthetic Commun.*, 1987, **17**, 203.
46. W. Reid and E. Köhler, *Ann.*, 1956, **598**, 145.
47. K. Saito, S. Kamble, Y. Mekano, A. Sakurai, and H. Midorikawa, *Synthesis*, 1983, 210.

Received, 29th February, 1996