One-Pot Synthesis of 3-Carboxycoumarins via Consecutive Knoevenagel and Pinner Reactions in Water

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Abstract: Chloro-, hydroxy-, methoxy-, and *tert*-butyl-substituted 3-carboxycoumarins have been prepared by one-pot procedure by reaction of suitably substituted salicylaldehydes with malononitrile in water. The over-all yields are high and the protocol does not require organic solvents.

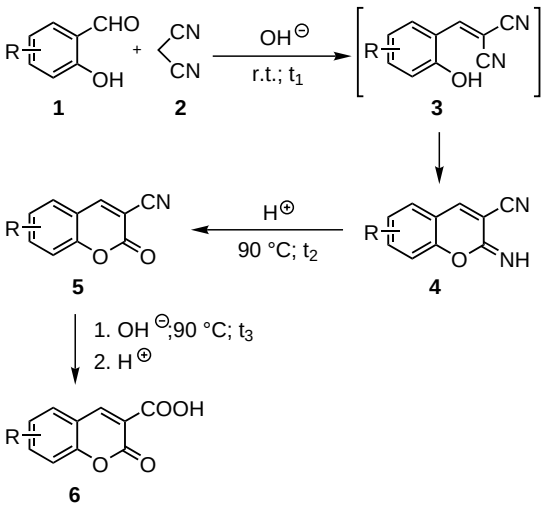
Key words: aldol reactions, cyclizations, hydrolyses, 3-carboxycoumarins, water

Coumarins are an important class of natural and synthetic compounds which display a wide variety of properties.[1] They are active as drugs,[2a–e] found in perfumes and cosmetics,[2f] and used in laser dyes,[2g] insecticides,[2h] photographic sensitizers and solar collectors,[2i–k] and are employed as fluorescent markers in biochemistry.[2l,m] Coumarins are also exploited as intermediates and building blocks in organic synthesis.[2n,o]

Recently, there has been great interest in 3-carboxycoumarins that have been used to synthesize modified cephalosporins,[3] penicillins,[4] oxygen-bridged tetrahydropyridones,[5] isoureas,[6] esters and amides which exhibit specific inhibitors of α-chymotripsin and human leukocyte elastase,[2d,e] and polymeric compounds.[7] Consequently, syntheses specifically aimed at 3-carboxycoumarins have appeared in the literature. Most of them are based on a Knoevenagel reaction between a suitably substituted salicylaldehyde and Meldrum's acid carried out under various reaction conditions.[8] Alternative procedures include a solid-phase synthesis between diethyl malonate bound to the Wang resin[9] and the condensation of salicylaldehydes with malonic acid in the presence of clay KFS.[10] These procedures are easy, and, in some cases, environmentally friendly.[8c–f,11] The 3-carboxycoumarins are usually prepared in water, in good yields, but, when highly hydrophobic substituents, such as one or two *tert*-butyl groups are present in the aromatic ring of the molecule, the reaction does not work in aqueous medium.[8f]

Continuing our work in organic synthesis performed in water,[12] we decided to investigate the use of coumarins as building blocks. Recently, we reported a one-pot synthesis under neat conditions and in aqueous medium of chromene derivatives starting from 3-nitrocoumarins.[2o] Here we report a new approach for synthesizing 3-carboxycoumarins in water that is also operative when highly hydrophobic groups such as *tert*-butyl groups are present in the aromatic moiety.

Salicylaldehydes **1** reacted with malononitrile (**2**) at room temperature in aqueous basic heterogeneous medium (pH 8.3–13.3) to give the cyanoimino ethers **4** via Knoevenagel (**1** + **2** → **3**) and Pinner (**3** → **4**) reactions (Scheme 1). Acid hydrolysis in situ of **4** at 90 °C produced the 3-cyanocoumarins **5** in high yields. These compounds could then be isolated by simple filtration or, without interruption, hydrolyzed at 90 °C under basic conditions. Final acidification of the reaction mixture allowed the isolation of 3-carboxycoumarins **6** by filtration in excellent over-all yields without using an organic solvent.



a: R = H; **b:** R = 6-Cl; **c:** R = 6-OH; **d:** R = 7-OH; **e:** R = 7-OMe; **f :** R = 8-OH; **g:** R = 8-*t*-Bu; **h:** R = 5,7-$(OMe)_2$; **i :** R = 6.8-(*t*-Bu)

Scheme 1

The results are illustrated in Table 1. If the process is stopped after the Knoevenagel and Pinner reactions, the iminoethers **4** can be isolated by filtration. As an example we report the isolation of 3-cyano-7-hydroxy-2-iminocoumarin (**4d**) (see the experimental section).

This process works well for preparing chloro- (**6b**), hydroxy- (**6c**, **6d**, **6f**), methoxy- (**6e**, **6h**) substituted 3-carboxycoumarins and is very important for synthesizing hydrophobic 3-carboxycoumarins, such as the 8- and 6,8-*tert*-butyl derivatives **6g** and **6i**. The procedure is clean, environmentally friendly and takes advantage of two as-

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Table 1 Synthesis of 3-Cyano- and 3-Carboxycoumarins in Water

Entry	Aldehyde **1**	3-Cyanocoumarin **5**			3-Carboxycoumarin **6**	
	R	t_1 (h)[a]	t_2 (h)[b]	Yield (%)[c]	t_3 (h)[d]	Yield (%)[e]
a	H	2	2.5	90	2	90
b	6-Cl	4[f]	2	95	2	85
c	6-OH	4	1	85	3	80
d	7-OH	5	2	85	2	85
e	7-OMe	3	2	95	5	95
f	8-OH	2.5	2	85	2.5	85
g	8-*t*-Bu	1[g]	1.5	84	4	60
h	5,7-$(OMe)_2$	4[f]	2	90	1[g]	90
i	6,8-$(t\text{-Bu})_2$	6[h]	1.5	95	8[i]	89

[a] At r.t. and pH 8.3.
[b] At 90 °C and under acid conditions.
[c] Yield of isolated compound.
[d] At 90 °C and pH 8.3 followed by acidification.
[e] Overall yield of isolated compound.
[f] At pH 12.4.
[g] At pH 13.3.
[h] At pH 13.3 and in H_2O–MeOH (9:1).
[i] At pH 9.0.

pects of using aqueous medium: (i) several reactions can be performed in sequence by simply changing the pH of the reaction medium and (ii) the desired products **4**, **5** and **6** can be isolated by filtration without having to use any organic solvent.

All of the compounds prepared were characterized by ^{1}H NMR, IR and GC-MS analyses and are described in the experimental section.

The coumarins **5g**, **6g**, **5i** and **6i** and the iminocoumarin **4d** are new compounds. The 3-cyanocoumarins **5a**,[11] **5b**,[13] **5c**,[14] **5d**,[11] **5e**,[11] **5f**,[11] and **5h**[11] and the 3-carboxycoumarins **6a**,[15] **6b**,[16] **6c**,[17] **6d**,[18] **6e**,[16] **6f**,[19] and **6h**[16] are known compounds, but since their spectroscopic data are often missing, all of the coumarins prepared are described here. The IR spectra were recorded with a FT Perkin-Elmer RXI spectrometer in KBr and with a FT Bruker IFS 113V spectrometer as CsI pellets. NMR spectra were recorded on FT Bruker AC 200 and FT Bruker DRX 400 instruments in DMSO-d_6 and acetone-d_6 solution. GC-MS analyses were performed with an HP 6890 GC System–HP 5973 Mass Selective Detector. All starting materials are commercially available.

3-Carboxycoumarins 6 and Their Precursors 4 and 5

A suitable salicylaldehyde **1** (10 mmol), malononitrile (**2**) (0.80 g, 12.5 mmol) and 0.05 M aq $NaHCO_3$ solution (pH 8.3, 50 mL) or 0.025 M aq NaOH solution (pH 12.4, 50 mL) or 0.2 M aq NaOH solution (pH 13.3, 50 mL) were vigorously stirred at r.t. in a 100 mL round-bottom flask fitted with a mechanical or magnetic stirrer and reflux condenser for the time (t_1) reported in Table 1. 3-Cyano-2-iminocoumarins **4** were separated by vacuum filtration or conc. HCl (1.25–2.0 mL) was added and the heterogeneous mixture was heated at 90 °C under stirring for 1–2.5 h (t_2 of Table 1). After cooling, 3-cyanocoumarins **5** were separated by vacuum filtration or 1 M aq $NaHCO_3$ solution (20 mL) or 1.5 M aq NaOH solution (20 mL) was added and the mixture was heated at 90 °C under stirring for the time (t_3) reported in Table 1. The sodium salts of 3-carboxycoumarins are soluble in H_2O. The final solution, cooled to r.t., was acidified with concd HCl to pH ≤2 under stirring and refrigerated at 0–5 °C. 3-Carboxycoumarins **6** were separated from the aqueous medium by vacuum-filtration using a Büchner funnel under reduced pressure and then dried (yield 60–95%), The crude coumarins had a purity higher than 98% which could be further purified by recrystallization.

3-Cyanocoumarin (5a)[11]
Mp 180-182 °C (EtOH).

IR (KBr): 2220 (C≡N), 1730 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 400 MHz (DMSO-d_6): δ = 7.46 (apparent t, 1 H, H-6, *J* = 7.6 Hz), 7.50 (d, 1 H, H-8, *J* = 8.0 Hz), 7.76–7.84 (m, 2 H, H-5, 7), 8.94 (s, 1 H, H-4).

MS: *m*/*z* (%) = 51 (5), 63 (8), 88 (14), 143 (100) 171 (M^+, 97).

3-Carboxycoumarin (6a)[15]
Mp 186–188 °C (EtOAc).

IR (KBr): 1750 (C=O), 1690 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 400 MHz (DMSO-d_6): δ = 7.39 (apparent t, 1 H, H-6, *J* = 7.5 Hz), 7.43 (d, 1 H, H-8, *J* = 8.2 Hz), 7.72 (ddd, 1 H, H-7, *J* = 8.2, 7.5, 1.5 Hz), 7.90 (dd, 1 H, H-5, *J* = 7.7, 1.5 Hz), 8.74 (s, 1 H, H-4).

MS: *m*/*z* (%) = 45 (9), 62 (9), 63 (17), 89 (34), 90 (20), 145 (20), 146 (100), 190 (M^+, 29).

6-Chloro-3-cyanocoumarin (5b)[14]
Mp 191–192 °C (EtOH).

IR (KBr): 2242 (C≡N), 1735 (C=O), 1614 cm^{-1} (C=C).

^{1}H NMR 200 MHz (acetone-d_6): δ = 7.49 (d, 1 H, H-8, *J* = 8.9 Hz), 7.81 (dd, 1 H, H-7, *J* = 8.9, 2.6 Hz), 7.92 (d, 1 H, H-5, *J* = 2.6 Hz), 8.75 (s, 1 H, H-4).

MS: *m*/*z* (%) = 63 (8), 75 (5), 87 (10), 114 (51), 149 (10), 177 (76), 179 (26), 205 (^{35}Cl – M^+, 100), 207 (^{37}Cl – M^+, 34).

3-Carboxy-6-chlorocoumarin (6b)[17]
Mp 240 °C (dec.).

IR (KBr): 3189 (OH), 1743 (C=O), 1678 (C=O), 1620 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 7.44 (d, 1 H, H-8, *J* = 8.9 Hz), 7.74 (dd, 1 H, H-7, *J* = 8.9, 2.6 Hz), 8.02 (d, 1 H, H-5, *J* = 2.6 Hz), 8.66 (s, 1 H, H-4).

3-Cyano-6-hydroxycoumarin (5c)[13]
Mp 237–238 °C (H_2O–EtOH).

IR (KBr): 3213 (OH), 2236 (C≡N), 1719 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 7.15–7.35 (m, 3 H, H-5, 7, 8), 8.65 (s, 1 H, H-4), 9.07 (OH).

3-Carboxy-6-hydroxycoumarin (6c)[16]
Mp 283 °C (EtOH).

IR (KBr): 3149 (OH), 1728 (C=O), 1650 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 7.15–7.33 (m, 3 H, H-5, 7, 8), 8.65 (s, 1 H, H-4).

3-Cyano-7-hydroxy-2-iminocoumarin (4d)
Mp 250 °C (dec.) (DMF–H_2O, 9:1).

IR (CsI pellet): 3261 (NH), 3094 (OH), 3049 (C=C–H), 2230 (C≡N), 1660 (C=NH), 1619, 1560 (C=C), 1252 cm^{-1} (C–O).

^{1}H NMR 400 MHz (DMSO-d_6): δ = 6.51 (d, 1 H, H-8, *J* = 2.1 Hz), 6.67 (dd, 1 H, H-6, *J* = 8.5, 2.1 Hz), 7.40 (d, 1 H, H-5, *J* = 8.5 Hz), 8.20 (s, 1 H, H-4); 8.57 (br s, 1 H, NH), 10.86 (br s, 1 H, OH).

^{13}C NMR 400 MHz (DMSO-d_6): δ = 102.0, 109.7, 112.7, 115.8, 131.1, 146.1, 146.9, 155.1, 155.8, 163.6.

3-Cyano-7-hydroxycoumarin (5d)[11]
Mp 273–275 °C (H_2O–AcOH, 9:1).

IR (CsI pellet): 3237 (OH), 3042 (C=C–H), 2236 (C≡N), 1704 (C=O), 1618, 1610, 1565 (C=C), 1274 cm^{-1} (C–O).

^{1}H NMR 400 MHz (DMSO-d_6): δ = 6.77 (d, 1 H, H-8, *J* = 2.2 Hz), 6.88 (dd, 1 H, H-6, *J* = 8.6, 2.2 Hz), 7.63 (d, 1 H, H-5, *J* = 8.6 Hz), 8.77 (s, 1 H, H-4), 11.31 (br s, 1 H, OH).

^{13}C NMR 400 MHz (DMSO-d_6): δ = 96.1, 102.5, 110.3, 114.6, 115.2, 131.8, 153.3, 156.6, 157.5, 164.8.

3-Carboxy-7-hydroxycoumarin (6d)[18]
Mp 248–250 °C (dec.) (H_2O–AcOH, 8:2).

IR (CsI pellet): 3178 (OH, COOH), 3059 (C=C–H), 1720 (C=O), 1685 (C=O), 1617, 1560 (C=C), 1217 cm^{-1} (C–O).

^{1}H NMR 400 MHz (DMSO-d_6): δ = 6.72 (d, 1 H, H-8, *J* = 2.2 Hz), 6.83 (dd, 1 H, H-6, *J* = 8.6, 2.2 Hz), 7.73 (d, 1 H, H-5, *J* = 8.6 Hz), 8.67 (s, 1 H, H-4), 11.15 (br s, 1 H, OH), 12.70 (br s, 1 H, CO_2H).

^{13}C NMR 400 MHz (DMSO-d_6): δ = 101.8, 110.7, 112.5, 114.1, 132.0, 149.4, 157.0, 157.7, 164.0, 164.3.

3-Cyano-7-methoxycoumarin (5e)[11]
Mp 217–218 °C (EtOH–acetone).

IR (KBr): 2220 (C≡N), 1730 (C=O), 1605 cm^{-1} (C=C).

^{1}H NMR 200 MHz (acetone-d_6): δ = 4.00 (s, 3 H, OCH_3), 6.95–7.15 (m, 2 H, H-6, 8), 7.75 (br d, 1 H, H-5, *J* = 8.6 Hz), 8.63 (s, 1 H, H-4).

MS: *m*/*z* (%) = 51 (5), 75 (8), 88 (5), 102 (17), 130 (15), 158 (66), 173 (69) 201 (M^+, 100).

3-Carboxy-7-methoxycoumarin (6e)[16]
Mp 192–193 °C (EtOH)

IR (KBr): 3320 (OH), 1740 (C=O), 1700 (C=O), 1620 cm^{-1} (C=C).

^{1}H NMR 200 MHz (acetone-d_6): δ = 4.01 (s, 3 H, OCH_3), 7.06–7.16 (m, 2 H, H-6, 8), 7.94 (br d, 1 H, H-5, *J* = 8.6 Hz), 8.88 (s, 1 H, H-4).

MS: *m*/*z* (%) = 50 (30), 77 (37), 133 (100), 176 (95), 220 (M^+, 51).

3-Cyano-8-hydroxycoumarin (5f)[11]
Mp 244–245 °C (H_2O–EtOH).

IR (KBr): 3216 (OH), 2230 (C≡N), 1716 (C=O), 1610 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 7.23 (m, 3 H, H-5, 6, 7), 8.84 (s, 1 H, H-4), 10.40 (OH).

3-Carboxy-8-hydroxycoumarin (6f)[19]
Mp 282–284 °C (BuOH).

IR (KBr): 3150 (OH), 1730 (C=O), 1650 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 7.1–7.4 (m, 3 H, H-5, 6, 7), 8.65 (s, 1 H, H-4).

8-*tert*-Butyl-3-cyanocoumarin (5g)
Mp 145–147 °C (EtOH).

IR (KBr): 2238 (C≡N), 1740 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 200 MHz (acetone-d_6): δ = 1.49 (s, 9 H, *t*-C_4H_9), 7.41 (t, 1 H, H-6, *J* = 7.8 Hz), 7.71 (dd, 1 H, H-5, *J* = 7.8, 1.6 Hz), 7.79 (d, 1 H, H-7, *J* = 7.8, 1.6 Hz), 8.77 (s, 1 H, H-4).

^{13}C NMR 200 MHz (acetone-d_6): δ = 29.9, 35.4, 102.6, 114.8, 118.9, 125.9, 129.1, 133.6, 138.5, 154.1, 154.4, 157.0.

MS: *m*/*z* (%) = 63 (3), 77 (4), 91 (3), 101 (2), 115 (4), 128 (7), 140 (6), 156 (8), 172 (4), 184 (90), 185 (13), 212 (100), 213 (18), 227 (M^+, 30).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.90; H, 5.79; N, 6.17.

8-*tert*-Butyl-3-carboxycoumarin (6g)
Mp 180–181 °C (EtOH–H_2O).

IR (KBr): 3174 (OH), 1761 (C=O), 1735 (C=O), 1618 cm^{-1} (C=C).

^{1}H NMR 200 MHz (acetone-d_6): δ = 1.51 (s, 9 H, *t*-C_4H_9), 7.46 (t, 1 H, H-6, *J* = 7.8 Hz), 7.82 (dd, 1 H, H-5, *J* = 7.8, 1.6 Hz), 7.88 (d, 1 H, H-7, *J* = 7.8, 1.6 Hz), 8.92 (s, 1 H, H-4).

^{13}C NMR 200 MHz (DMSO-d_6): δ = 29.4, 34.5, 117.4, 118.4, 124.4, 128.7, 131.5, 136.5, 149.3, 153.1, 156.3, 163.9.

MS: *m*/*z* (%) = 63 (3), 77 (4), 91 (5), 115 (14), 128 (11), 159 (18), 187 (4), 203 (12), 213 (59), 231 (100), 232 (16), 246 (M^+, 30).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.31; H, 5.76.

3-Cyano-5,7-dimethoxycoumarin (5h)[11]
Mp 233–235 °C (acetone).

IR (KBr): 2220 (C≡N), 1710 (C=O), 1610 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 3.09 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.57 (d, 1 H, H-8, *J* = 2.0 Hz), 6.68 (d, 1 H, H-6, *J* = 2.0 Hz), 8.68 (s, 1 H, H-4).

3-Carboxy-5,7-dimethoxycoumarin (6h)[16]
Mp 238–240 °C (EtOH).

IR (KBr): 3350 (OH), 1740 (C=O), 1690 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 3.88 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.51 (d, 1 H, H-8, *J* = 2.0 Hz), 6.60 (d, 1 H, H-6, *J* = 2.0 Hz), 8.68 (s, 1 H, H-4).

6,8-Di-*tert*-Butyl-3-cyanocoumarin (5i)
Mp 143–144 °C (EtOH).

IR (KBr): 2233 (C≡N), 1744 (C=O), 1615 cm^{-1} (C=C).

^{1}H NMR 200 MHz (acetone-d_6): δ = 1.37 (s, 9 H, *t*-C_4H_9), 1.50 (s, 9 H, *t*-C_4H_9), 7.72 (d, 1 H, H-5, *J* = 2.4 Hz), 7.84 (d, 1 H, H-7, *J* = 2.4 Hz), 8.74 (s, 1 H, H-4).

^{13}C NMR 200 MHz (acetone-d_6): δ = 30.0, 31.4, 35.3, 35.7, 102.4, 114.9, 118.6, 125.3, 131.4, 138.0, 148.5, 152.3, 154.8, 157.2.

MS: *m*/*z* (%) = 57 (12), 77 (1), 91 (1), 112 (3), 127 (3), 212 (12), 224 (2), 240 (23), 268 (100), 269 (29), 283 (M^+, 24).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.35; H, 7.46; N, 4.96.

6,8-Di-*tert*-butyl-3-carboxycoumarin (6i)
Mp 268–270 °C (dec.).

IR (KBr): 3418 (OH), 1734 (C=O), 1710 (C=O), 1620 cm^{-1} (C=C).

^{1}H NMR 200 MHz (DMSO-d_6): δ = 1.30 (s, 9 H, *t*-C_4H_9), 1.44 (s, 9 H, *t*-C_4H_9), 7.50 (d, 1 H, H-5, *J* = 2.3 Hz), 7.63 (d, 1 H, H-7, *J* = 2.3 Hz), 8.24 (s, 1 H, H-4)

^{13}C NMR 200 MHz (DMSO-d_6): δ = 29.4, 31.0, 38.9, 40.1, 118.5, 120.2, 124.3, 127.6, 135.7, 146.2, 147.0, 150.8, 157.8, 165.0.

MS: *m*/*z* (%) = 57 (7), 77 (1), 91 (1), 115 (3), 128 (4), 187 (3), 213 (9), 243 (4), 258 (3), 269 (12), 287 (100), 288 (20), 302 (M^+, 20).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.58; H, 7.29.

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References

(1) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins*; Wiley: New York, **1982**.

(2) (a) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, **1997**. (b) Burger, A.In *Burger's Medicinal Chemistry*, Vol. 1; Wolff, M. E., Ed.; Wiley: New York, **1995**, 3-8. (c) Orita, M.; Yamamoto, S.; Katayama, N.; Aoki, M.; Takayama, K.; Yamagiwa, Y.; Seki, N.; Suzuki, H.; Kurihara, H.; Sakashita, H.; Takeuchi, M.; Fujita, S.; Yamada, T.; Tanaka, A. *J. Med. Chem.* **2001**, *44*, 540. (d) Doucet, C.; Pochet, L.; Thierry, N.; Pirotte, B.; Delarge, J.; Reboud-Rovaux, M. *J. Med. Chem.* **1999**, *42*, 4161. (e) Pochet, L.; Doucet, C.; Schynts, M.; Therry, N.; Boggeto, N.; Pirotte, B. *J. Med. Chem.* **1996**, *39*, 2579. (f) *Kirk-Othmer Encyclopaedia of Chemical Technology*, 3rd ed., Vol. 7; Wiley: New York, **1997**, 196–906. (g) *Kirk-Othmer Encycopaedia of Chemical Technology*, 3rd ed., Vol. 16; Wiley: New York, **1997**, 951–955. (h) *Dye Laser*; Drexhage, K., Ed.; Mir Pub.: Moscow, **1976**. (i) Mali, R. S.; Yeola, S. N.; Kulkarni, B. K. *Indian J. Chem., Sect. B* **1983**, *22*, 352. (j) Loew, P. Ciba-Geigy AG, German Patent 2710285, **1976**; *Chem Abstr.* **1997**, *87*, 186083. (k) Hagen, H.; Kohler, R. D. BASF AG, German Patent 2950291, **1981**; *Chem Abstr.* **1981**, *95*, 187261. (l) Rane, R.; Harnish, H.; Drexhage, K. H. *Heterocycles* **1984**, *21*, 167. (m) Zimmerman, M.; Yurewicz, E.; Patel, G. *Anal. Biochem.* **1976**, *70*, 258. (n) Bissel, E. R.; Mitchell, A. R.; Smith, R. E. *J. Org. Chem.* **1980**, *45*, 2283. (o) Versleijen, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803. (p) Amantini, D.; Fringuelli, F.; Pizzo, F. *J. Org. Chem.* **2002**, *67*, 7238.

(3) Bonsignore, L.; Cottiglia, F.; Elkhaili, H.; Jehl, F.; Lavagna, S. M.; Loy, G.; Manna, F.; Monteil, H.; Pompei, D.; Secci, D. *Farmaco* **1998**, *53*, 425.

(4) Bonsignore, L.; De Logu, A.; Loy, G.; Lavagna, S. M.; Secci, D. *Eur. J. Med. Chem.* **1994**, *29*, 479.

(5) Jönsson, D.; Erlandsson, M.; Undén, A. *Tetrahedron Lett.* **2001**, *42*, 6953.

(6) Bonsignore, L.; Cottiglia, F.; Lavagna, S. M.; Loy, G.; Secci, D. *Heterocycles* **1999**, *50*, 469.

(7) Fomine, S.; Rivera, E.; Fomina, L.; Ortiz, A.; Ogawa, T. *Polymer* **1998**, *39*, 3551.

(8) (a) Neat, ZnO catal., 80 °C, H^+: Rouessac, F.; Lecler, A. *Synth. Commun.* **1993**, *23*, 1147. (b) In DMF, r.t., H^+: Amstrong, V.; Soto, O.; Valderrama, J. A.; Tapia, R. *Synth. Commun.* **1998**, *18*, 717. (c) Neat, EPZG/EPZ10 catal., MW: Bandgar, B. P.; Uppalla, L. S.; Curule, D. S. *Green Chem.* **1999**, *1*, 243. (d) Neat NH_4OAc, r.t. or in H_2O, NH_4OAc, r.t.: Scott, J. L.; Raston, C. L. *Green Chem.* **2000**, *2*, 245. (e) Neat, $LiClO_4$ or LiBr, MW: Bandgar, B. P.; Uppalla, L. S.; Sadavarte, V. S. *J. Chem. Res., Synop.* **2002**, 40. (f) In H_2O, reflux: Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Sartori, G. *Green Chem.* **2001**, *3*, 173.

(9) Watson, B. T.; Christiansen, G. E. *Tetrahedron Lett.* **1998**, *39*, 6087.

(10) Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 1033.

(11) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257.

(12) For recent work: (a) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* **2001**, *42*, 1131. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229. (c) Attanasi, O.; De Crescentini, L.; Filippone, P.; Fringuelli, F.; Mantellini, F.; Matteucci, M.; Piermatti, O.; Pizzo, F. *Helv. Chim. Acta* **2001**, *84*, 513. (d) Fringuelli, F.; Matteucci, M.; Piermatti, O.; Pizzo, F.; Burla, M. C. *J. Org. Chem.* **2001**, *66*, 4661. (e) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 3554. (f) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4719. (g) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 6734. (h) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439. (i) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Adv. Synth. Catal.* **2002**, *344*, 379.

(13) Chen, J.; Zhang, Y. *J. Chem. Res., Synop.* **2001**, 394.

(14) Bruce, J. M.; Creed, D.; Daves, K. *J. Chem. Soc., C* **1971**, 3749.

(15) Hormi, O. E. O.; Peltonen, C.; Bergström, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 219.

(16) Bonsignore, L.; Cottiglia, F.; Maccioni, A. M.; Secci, D. *J. Heterocycl. Chem.* **1995**, *32*, 573.

(17) (a) Ichikawa, M.; Ichigase, H. *Yakugaku Zasshi* **1960**, *80*, 1354; *Chem. Abstr.* **1961**, *55*, 5482b. (b) Cramer, F. D.; Windel, H. *Chem. Ber.* **1956**, *89*, 354.

(18) Lokhande, S. B.; Rangnekar, D. W. *Indian J. Chem., Sect. B* **1986**, *25*, 638.

(19) Ichikawa, M.; Takaki, Y.; Ichigase, H. *Yakugaku Zasshi* **1961**, *81*, 768; *Chem. Abstr.* **1961**, *55*, 23514a.