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One-pot synthesis of coumarin derivatives

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Abstract

An efficient one-pot three-component cyclocondensation reaction for the synthesis of coumarin derivatives 3-(5′-substituted-2′-benzoxazolyl)-7-diethylaminocoumarins from 4-diethylaminosalicylaldehyde, ethyl cyanoacetate and 4-substituted-2-aminophenol is described. The novel procedure features short reaction time, moderate yields and simple workup.

Keywords: Coumarin derivative; One-pot synthesis; Cyclocondensation

1. Introduction

Coumarin and its derivatives are one kind of significant organic fluorescent chromophores and widely used to synthesize laser dyes, fluorescent whiteners, the organic nonlinear optical materials and so on [1–4]. It is well known that the electron-donating group substitution of coumarin will increase the intermolecular electron transferring and thus improve the fluorescence performance of coumarin derivatives. 3-Substitued 7-diethylaminocoumarins (Fig. 1) are the representative structure of the fluorescence dyes and their synthesis and molecular design attract great interest.

Classical routes to coumarins incorporate Pechmann, Knoevenagel, Perkin, Reformatsky, and Wittig condensation reactions [5–8]. To make these classical reactions efficacious, several variations in terms of catalyst and reaction conditions have been introduced [9]. However, the classic methods suffer from expensive catalyst, laborious multi-step procedures, long reaction time, high reaction temperature or waste problem. In this paper, a facile one-pot synthesis of 3-(5′-substituted-2′-benzoxazolyl)-7-diethylamino-2*H*-chromen-2-ones was reported under the acid catalysis from commercially available starting materials as shown in Scheme 1.

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2. Results and discussion

A facile three-component one-pot cyclocondensation takes place between 4-diethylaminosalicylaldehyde **2**, ethyl cyanoacetate **3** and 4-substituted-2-aminophenol **4** affording 3-(5′-substituted-2′-benzoxazolyl)-7-diethylamino-2*H*-chromen-2-ones **5**(**a**–**e**). Therefore, equimolar amounts of starting compounds **2**–**4** were reacted in alcohol with benzoic acid as catalyst to give the compounds **5** in moderate yield (Table 1).

The cyclocondensation of 4-diethylaminosalicylaldehyde **2**, ethyl cyanoacetate **3** with aminophenol **4c** to generate coumarin **5c** was investigated under a variety of conditions (solvent, reaction time etc.), as a test case, to optimize the yield. The effect of alcohol solvents was tested first. The solvent *n*-pentanol was the best choice to give 68% yield compared with ethanol (38%), isopropanol (40%), *n*-butanol (53%), *n*-octanol (50%). The reaction selectivity increased from 60.12% to 96.30% as the reaction time was increased from 5 to 12 h, while further prolongation of reaction time afforded negligible improvement. Among different acid catalysts being tested, benzoic acid was found to be the best catalyst to obtain **5c** in yield 68%. Consequently, 3-(5′-substituted-2′-benzoxazolyl)-7-diethylamino-2*H*-chromen-2-ones **5**(**a**–**e**) were prepared in *n*-pentanol at 138 °C under the catalysis of benzoic acid.

In summary, compared with the conventional methods, the novel one-pot procedure for rapid preparation of

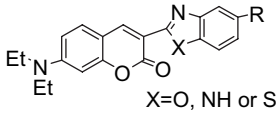

Fig. 1. Chemical structure of coumarin derivatives.

3-(5′-substituted-2′-benzoxazolyl)-7-diethylaminocoumarins affords advantages of short reaction time, moderate yields and simple workup.

3. Experimental

3.1. General procedure for the synthesis of compounds 5a–e

A mixture of 4-diethylaminosalicylaldehyde (17 mmol), 4-substituted-2-aminophenol (17 mmol) and ethyl cyanoacetate (17 mmol) in *n*-pentanol (50 mL) containing benzoic acid (5.8 mmol) was refluxed for 10–12 h till the reaction was completed (monitored by TLC). After the solvent was partly evaporated under reduced pressure, the reaction mixture was poured into water and cooled to room temperature. The solid was filtered, washed with excess water and then recrystallized from DMF to afford pure **5a–e**.

3.1.1. Compound 5a

Mp: 195–196 °C; IR (KBr): 1736, 1623, 1505, 1353, 1229, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, t, N–CH_2–CH_3), 3.47 (4H, q, N–CH_2–CH_3), 6.45 (1H, s, 8-H), 6.56 (1H, d, 6-H), 7.32 (1H, s, 6′-H), 7.44 (1H, d, 7′-H), 7.58 (1H, d, 5-H), 7.71 (1H, d, 4′-H), 8.60 (1H, s, 4-H). Anal. calcd. for $C_{20}H_{17}ClN_2O_3$: C, 65.13; N, 7.60; H, 4.61. Found: C, 65.15; N, 7.59; H, 4.62.

3.1.2. Compound 5b

Mp: 209–210 °C (Lit. [7] 204–206 °C); IR (KBr): 1740, 1618, 1588, 1508, 1451, 1421, 1310, 1234, 1134, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, t, N–CH_2–CH_3), 2.48 (3H, s, Ar–CH_3), 3.47 (4H, q, N–CH_2–CH_3), 6.56 (1H, d, 8-H), 6.68 (1H, q, 6-H), 7.16 (1H, d, 6′-H), 7.45–7.49 (2H, t, 7′-H, 5-H), 7.61 (1H, s, 4′-H), 8.77 (1H, s, 4-H). Anal. calcd. for $C_{21}H_{20}N_2O_3$: C, 72.41; N, 8.05; H, 5.75. Found: C, 72.42; N, 80.7; H, 5.74.

3.1.3. Compound 5c

Mp: 185–186 °C; IR (KBr): 1740, 1624, 1608, 1588, 1508, 1420, 1451, 772, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, t, N-–CH_2–CH_3), 3.47 (4H, q, N–CH_2–CH_3), 6.57 (1H, s, 8-H), 6.68 (1H, d, 6-H), 7.34–7.37 (2H, m, 5′-H, 6′-H), 7.45 (1H, d, 5-H), 7.60 (1H, t, 4′-H), 7.82 (1H, t, 7′-H), 8.72 (1H, s, 4-H). Anal. calcd. for $C_{20}H_{18}N_2O_3$: C, 71.86; N, 8.38; H, 5.39. Found: C, 71.87; N, 8.39; H, 5.38.

Table 1
Synthesis of compounds **5a–e** by one-pot procedure[a]

Entry	R	Product	Yield (%)[b]	Purity (%)[c]	λ_{max} (nm)[d]
1	–Cl	**5a**	65	99.49	451
2	$-CH_3$	**5b**	78	99.23	446
3	–H	**5c**	68	98.92	442
4	$-NO_2$	**5d**	64	99.20	454
5	$-SO_2NH_2$	**5e**	66	98.77	435

[a] The reaction was conducted with equimolar amounts of starting compounds **2–4** with benzoic acid as catalyst and *n*-pentanol as solvent with the oil bath temperature at 138 °C for 12 h.
[b] Isolated yield.
[c] Based on HPLC analysis after recrystallization.
[d] UV–vis spectra of **5a–e** in methanol.

3.1.4. Compound 5d

Mp: 264–265 °C; IR (KBr): 1763, 1613, 1508, 1343, 1136, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (6H, t, N–CH_2–CH_3), 3.49 (4H, q, N–CH_2–CH_3), 6.56 (1H, d, 8-H), 6.70 (1H, m, 6-H,), 7.46 (1H, d, 6′-H), 7.68 (1H, d, 7′-H), 8.31 (1H, m, 5-H), 8.64 (1H, d, 4′-H), 8.67 (1H, s, 4-H). Anal. calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; N, 11.08; H, 4.48. Found: C, 63.31; N, 11.09; H, 4.46.

3.1.5. Compound 5e

Mp: 298–299 °C; IR (KBr): 1730, 1605, 1588, 1450, 1232, 1154, 937 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$). δ: 1.14 (6H, t, N–CH_2–CH_3), 3.48 (4H, q, N–CH_2–CH_3), 6.61 (1H, s, 8-H), 6.85 (1H, d, 6-H), 7.45 (2H, s, SO_2NH_2), 7.71 (1H, d, 6′-H), 7.85 (1H, s, 7′-H), 7.91 (1H, d, 5-H), 8.12 (1H, s, 4′-H), 8.86 (1H, s, 4-H). Anal.calcd. for $C_{20}H_{19}N_3O_5S$: C, 58.11; N, 10.17; H, 4.60. Found: C, 58.12; N, 10.16; H, 4.61.

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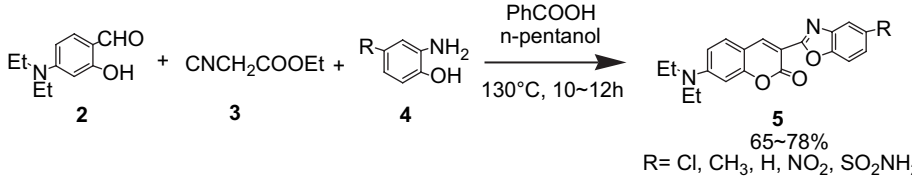

Scheme 1. Overall synthesis of compounds **5**.

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