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One-pot catalyst-free synthesis of 3-heterocyclic coumarins

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Abstract 3-Heterocyclic coumarins were prepared in one-pot three-component reaction without catalyst. The mixture of salicylaldehydes, ethyl cyanoacetate, and *o*-aminophenols or *o*-phenylenediamines in refluxing *n*-butanol gave title compounds with good yields and high purity. Short reaction time, mild reaction condition, simple workup, and less waste are significant advantages of the presented method.

Keywords 3-Heterocyclic coumarin · Catalyst free · One-pot synthesis · Salicylaldehyde

Introduction

Coumarins, an important class of organic heterocycles, are applicable in different fields of science and technology. They possess versatile biological activities and can be found in many natural or synthetic drug molecules [1–6]. Moreover, coumarin derivatives are characterized by sufficient fluorescence in the visible light range, large Stokes shift, high quantum yield of photoluminescence, and reasonable solubility, making them some of the most extensively investigated and commercially significant organic fluorescent materials [7–11]. Coumarin dyes are fluorescent in the blue–green spectral region and widely used in fluorescent probes, coloration of synthetic fibers such as polyester, daylight fluorescent pigments, and other functional applications such as tunable dye lasers, solar energy collectors, and

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organic light-emitting diodes (LEDs) [12–18]. 3-Heterocyclic coumarins are a well-known strong intramolecular charge-transfer chromophoric system in which the coumarin ring acts as a donor while the heterocycle moiety acts as an acceptor, which gives good fluorescent properties (Fig. 1). These typical coumarin fluorescent dyes generally contain electron donors at the 7-position and electron acceptors benzothiazole, benzimidazole or benzoxazole at the 3-position.

Two main methods commonly used for preparation of 3-heterocyclic coumarins are: (1) condensation of 2-cyanomethylbenzoxazole, obtained from the reaction of *o*-aminophenol (or *o*-aminothiophenol, *o*-phenylenediamine) with malononitrile or ethyl cyanoacetate, and salicylaldehyde to give 3-heterocyclic coumarin [19–21]; (2) condensation of a coumarin and *o*-aminophenol (or *o*-aminothiophenol, *o*-phenylenediamine) to construct the heterocyclic structure [22, 23]. However, these syntheses often suffer from corrosive catalysts such as H_2SO_4, PPA (polyphosphoric acid), laborious multistep procedures, long reaction time, high reaction temperature, and waste problems. Although there are many reports about improved methods for synthesis of coumarins or benzoheterocycles [24–27], fewer have been reported for 3-heterocyclic coumarins. Herein, we report a three-component reaction among salicylaldehydes, ethyl cyanoacetate, and *o*-aminophenols or *o*-benzenediamines to afford 3-heterocyclic coumarins in 50–80 % yields under catalyst-free conditions (Scheme 1).

Experimental

General information

All reactants were commercially available and used without further purification. All melting points were uncorrected. Nuclear magnetic resonance spectra were recorded on Bruker Avance III 500 MHz, and chemical shifts are expressed in ppm using tetramethylsilane (TMS) as internal standard. Mass spectra were measured using a Thermo Finnigan LCQ Series, Agilent 6210 Series time-of-flight mass spectrometer (ESI/APCI), Thermo Scientific ITQ 1100, and Waters GCT Premier mass spectrometer (EI/CI).

General procedure for synthesis of 3-heterocyclic coumarins

Salicylaldehyde (2 mmol), ethyl cyanoacetate (2 mmol), and *o*-aminophenol (2 mmol) were mixed in *n*-BuOH (20 mL), and the solution was refluxed for 7 h. The solvent was removed, and the residue was suspended in EtOH (10 mL) and

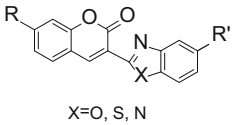
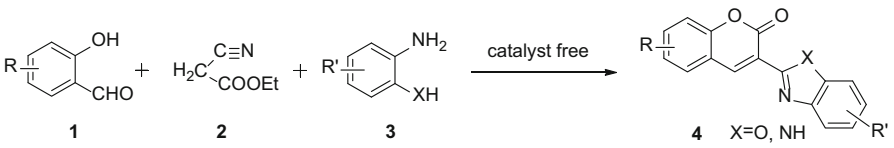


Fig. 1 Typical coumarin fluorescent dyes



Scheme 1 One-pot catalyst-free synthesis of 3-heterocyclic coumarins

stirred with 1 % NaOH (10 mL) for 30 min. After filtration and washing with water, the product was obtained as yellow solid.

3-(2′-Benzoxazole)-2*H*-1-benzopyran-2-one (**4a**): yellow solid. M.p. 186–189 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.78 (s, 1H, 4-H), 7.87 (1H, d, $J = 7.38$ Hz, 5-H), 7.69–7.63 (3H, m, 7-H, 5′-H, 6′-H), 7.43–7.37 (4H, m, 6-H, 8-H, 4′-H, 7′-H). ESI–MS: 264.4 $[M + H]^+$. HR-ESI–MS for $C_{16}H_{10}NO_3$: Found 264.0656, Calcd. 264.0661.

3-(5′-Methyl-2′-benzoxazole)-2*H*-1-benzopyran-2-one (**4b**): yellow solid. M.p. 161–163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (1H, s, 4-H), 7.68–7.64 (3H, m, 5-H, 7-H, 7′-H), 7.49 (1H, d, $J = 8.33$ Hz, 8-H), 7.41 (1H, d, $J = 8.26$ Hz, 6-H), 7.37 (1H, t, $J = 7.12$ Hz, 4′-H), 7.20 (1H, d, $J = 8.55$ Hz, 6′-H), 2.49 (3H, s, Ar-CH_3). ESI–MS: 278.4 $[M + H]^+$. HR-ESI–MS for $C_{17}H_{12}NO_3$: Found 278.0814, Calcd. 278.0817.

3-(5′-Chloro-2′-benzoxazole)-2*H*-1-benzopyran-2-one (**4c**): yellow solid. M.p. 259–260 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.79 (1H, s, 4-H), 7.82 (1H, s, 5-H), 7.70–7.67 (2H, m, 4′-H, 7′-H), 7.55 (1H, d, $J = 8.66$ Hz, 7-H), 7.43 (1H, d, $J = 8.27$ Hz, 8-H), 7.41–7.37 (2H, m, 6′-H, 6-H). ESI–MS: 320 $[M + Na]^+$. HR-ESI–MS for $C_{16}H_8ClNNaO_3$: Found 320.0079, Calcd. 320.0090.

3-(5′-Nitro-2′-benzoxazole)-2*H*-1-benzopyran-2-one (**4d**): yellow solid. M.p. 295–297 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.87 (1H, s, 4′-H), 8.74 (1H, s, 4-H), 8.39 (1H, d, $J = 8.64$ Hz, 6′-H), 7.78–7.72 (3H, m, 5-H, 7-H, 7′-H), 7.47–7.41 (2H, m, 6-H, 8-H); ESI–MS: 331 $[M + Na]^+$. HR-ESI–MS for $C_{16}H_8N_2NaO_5$: Found 331.0343, Calcd. 331.0331.

3-(2′-Benzoxazole)-7-methoxy-2*H*-1-benzopyran-2-one (**4e**): yellow solid. M.p. 191–193 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.71 (1H, s, 4-H), 7.85–7.83 (1H, m, 6′-H), 7.62–7.59 (1H, m, 5′-H), 7.56 (1H, d, $J = 8.67$ Hz, 5-H), 7.40–7.35 (2H, m, 4′-H, 7′-H), 6.93 (1H, dd, $J = 8.66$, 2.32 Hz, 6-H), 6.88 (1H, s, 8-H), 3.92 (3H, s, OCH_3). ESI–MS: 294.4 $[M + H]^+$. HR-ESI–MS for $C_{17}H_{12}NO_4$: Found 294.0761, Calcd. 294.0766.

3-(5′-Methyl-2′-benzoxazole)-7-methoxy-2*H*-1-benzopyran-2-one (**4f**): yellow solid. M.p. 197–199 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.69 (1H, s, 4-H), 7.60 (1H, s, 5-H), 7.55 (1H, d, $J = 8.68$ Hz, 7′-H), 7.47 (1H, d, $J = 8.31$ Hz, 4′-H), 7.18 (1H, d, $J = 9.43$ Hz, 6′-H), 6.92 (1H, dd, $J = 8.64$, 2.47 Hz, 6-H), 6.87 (1H, s, 8-H), 3.91 (3H, s, Ar-OCH_3), 2.48 (3H, s, Ar-CH_3). ^{13}C NMR (pyridine): 165.4, 157.7, 157.3, 153.21, 147.3, 143.2, 135.3, 131.3, 131.4, 127.5, 120.9, 114.8, 114.2, 111.1, 101.8, 101.3, 56.5, 21.8. ESI–MS: 308.3 $[M + H]^+$. HR-ESI–MS for $C_{18}H_{14}NO_4$: Found 308.0915, Calcd. 308.0923.

3-(5′-Chloro-2′-benzoxazole)-7-methoxy-2*H*-1-benzopyran-2-one (**4g**): yellow solid. M.p. 234–236 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.71 (1H, s, 4-H), 7.79 (1H, d, $J = 1.96$ Hz, 4′-H), 7.57 (1H, d, $J = 8.68$ Hz, 7′-H), 7.53 (1H, d, $J = 8.64$ Hz, 5-H), 7.34 (1H, dd, $J = 8.57$, 2.04 Hz, 6′-H), 6.94 (1H, dd, $J = 8.63$, 2.40 Hz, 6-H), 6.88 (1H, s, 8-H), 3.93 (3H, s, Ar-CH_3). ESI–MS: 350 $[M + Na]^+$. HR-ESI–MS for $C_{17}H_{10}ClNNaO_4$: Found 350.0211, Calcd. 350.0196.

3-(5′-Sulfonylamine-2′-benzoxazole)-7-methoxy-2*H*-1-benzopyran-2-one (**4h**): yellow solid. M.p. 285–287 °C. ^{1}H NMR (500 MHz, pyridine) δ: 9.22 (2H, s, SO_2NH_2), 8.84 (2H, d, $J = 9.55$ Hz, 4-H, 4′-H), 8.35 (1H, d, $J = 8.54$ Hz, 6′-H), 7.75 (1H, d, $J = 8.51$ Hz, 5-H), 7.66 (1H, d, $J = 8.21$ Hz, 7′-H), 6.98 (2H, d, $J = 8.12$ Hz, 6-H, 8-H), 3.79 (3H, s, OCH_3); ^{13}C NMR (pyridine) δ: 165.7, 162.1, 157.9, 157.1, 153.0, 147.3, 143.1, 142.8, 131.6, 124.7, 119.3, 114.3, 113.0, 112.0, 111.4, 101.3, 56.6; ESI–MS: 373.0 $[M + H]^+$. HR-ESI–MS for $C_{17}H_{13}N_2O_6S$: Found 373.0481, Calcd. 373.0494.

3-(2′-Benzoxazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**4i**): yellow solid. M.p. 189–191 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.60 (1H, s, 4-H), 7.81–7.79 (1H, m, 6′-H), 7.59–7.58 (1H, m, 5′-H), 7.41 (1H, d, $J = 8.93$ Hz, 5-H), 7.35–7.31 (2H, m, 4′-H, 7′-H), 6.64 (1H, dd, $J = 8.93$, 2.38 Hz, 6-H), 6.53 (1H, d, $J = 2.26$ Hz, 8-H), 3.45 (4H, q, $J = 7.15$ Hz, $N(C\underline{H}_2CH_3)_2$), 1.24 (6H, t, $J = 7.10$ Hz, $N(CH_2C\underline{H}_3)_2$); ESI–MS: 357.1 $[M + Na]^+$. HR-ESI–MS for $C_{20}H_{18}N_2NaO_3$: Found 357.1199, Calcd. 357.1215.

3-(5′-Methyl-2′-benzoxazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**4j**): yellow solid. M.p. 205–208 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.61 (1H, s, 4-H), 7.58 (1H, s, 4′-H), 7.45 (1H, d, $J = 8.17$ Hz, 7′-H), 7.41 (1H, d, $J = 8.85$ Hz, 5-H), 7.14 (1H, d, $J = 8.26$ Hz, 6′-H), 6.64 (1H, d, $J = 7.18$ Hz, 6-H), 6.54 (1H, s, 8-H), 3.46 (4H, q, $J = 7.1$ Hz, $N(C\underline{H}_2CH_3)_2$), 2.48 (3H, s, $ArCH_3$), 1.25 (6H, t, $J = 7.0$ Hz, $N(CH_2C\underline{H}_3)_2$); ESI–MS: 371.1 $[M + Na]^+$. HR-ESI–MS for $C_{21}H_{20}N_2NaO_3$: Found 371.1359, Calcd. 371.1372.

3-(5′-Chloro-2′-benzoxazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**4k**): yellow solid. M.p. 205–207 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.58 (1H, s, 4-H), 7.74 (1H, s, 4′-H), 7.49 (1H, d, $J = 8.59$ Hz, 7′-H), 7.41 (1H, d, $J = 8.96$ Hz, 5-H), 7.28 (1H, d, $J = 8.65$ Hz, 6′-H), 6.64 (1H, d, $J = 8.92$ Hz, 6-H), 6.52 (1H, s, 8-H), 3.46 (4H, q, $J = 7.14$ Hz, $N(C\underline{H}_2CH_3)_2$), 1.25 (6H, t, $J = 7.13$ Hz, $N(CH_2C\underline{H}_3)_2$); ESI–MS: 391.1 $[M + Na]^+$. HR-ESI–MS for $C_{20}H_{17}ClN_2NaO_3$: Found 391.0817, Calcd. 391.0825.

3-(5′-Nitro-2′-benzoxazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**4l**): yellow solid. M.p. 263–265 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.62–8.61 (2H, m, 4′-H, 4-H), 8.27 (1H, dd, $J = 8.90$, 2.19 Hz, 6′-H), 7.66 (1H, d, $J = 8.89$ Hz, 7′-H), 7.43 (1H, d, $J = 8.93$ Hz, 5-H), 6.66 (1H, d, $J = 8.95$ Hz, 6-H), 6.51 (1H, s, 8-H), 3.48 (4H, q, $J = 7.16$ Hz, $N(C\underline{H}_2CH_3)_2$), 1.27 (6H, t, $J = 7.10$ Hz, $N(CH_2C\underline{H}_3)_2$); ESI–MS: 402.1 $[M + Na]^+$. HR-ESI–MS for $C_{20}H_{17}N_3NaO_5$: Found 402.1061, Calcd. 402.1066.

3-(5′-Sulfonylamine-2′-benzoxazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**4m**): yellow solid. M.p. >300 °C. ^{1}H NMR (500 MHz, DMSO) δ: 8.83 (1H, s, 4-H), 8.15 (1H, s, 4′-H), 7.93 (1H, d, $J = 8.51$ Hz, 6′-H), 7.88 (1H, d, $J = 8.58$ Hz, 7′-H), 7.70 (1H, d, $J = 9.03$ Hz, 5-H), 7.48 (2H, s, SO_2NH_2), 6.80

(1H, dd, $J = 9.04$, 2.34 Hz, 6-H), 6.59 (1H, s, 8-H), 3.49 (4H, q, $J = 7.07$ Hz, $N(C\underline{H}_2CH_3)_2$), 1.16 (6H, t, $J = 7.02$ Hz, $N(CH_2C\underline{H}_3)_2$); ESI–MS: 436.1 $[M + Na]^+$. HR-ESI–MS for $C_{20}H_{19}N_3NaO_5S$: Found 436.0942, Calcd. 436.0943.

3-(2′-Benzoxazole)-6-chloro-2*H*-1-benzopyran-2-one (**4n**): yellow solid. M.p. 237–239 °C. ^{1}H NMR (500 MHz, DMSO) δ: 8.70 (1H, s, 4-H), 7.88 (1H, d, $J = 6.50$ Hz, 5-H), 7.65–7.63 (2H, m, 5′-H, 6′-H), 7.61 (1H, dd, $J = 8.76$, 2.35 Hz, 7-H), 7.45–7.37 (3H, m, 8-H, 4′-H, 7′-H). ESI–MS: 320 $[M + Na]^+$. HR-ESI–MS for $C_{16}H_8ClNNaO_3$: Found 320.0086, Calcd. 320.009.

3-(5′-Methyl-2′-benzoxazole)-6-chloro-2*H*-1-benzopyran-2-one (**4o**): yellow solid. M.p. 225–227 °C. ^{1}H NMR (500 MHz, DMSO) δ: 8.67 (1H, s, 4-H), 7.63 (2H, bs, 5-H,7′-H), 7.59 (1H, dd, $J = 8.76$, 2.36 Hz, 7-H), 7.50 (1H, d, $J = 8.29$ Hz, 8-H), 7.36 (1H, d, $J = 8.77$ Hz, 4′-H), 7.22 (1H, d, $J = 8.23$ Hz, 6′-H), 2.50 (3H, s, Ar-CH_3). ^{13}C NMR (DMSO) δ: 158.0, 155.4, 152.6, 148.3, 144.6, 141.2, 134.6, 133.3, 128.7, 128.6, 127.3, 119.8, 119.7, 118.2, 115.4, 110.4, 21.0; ESI–MS: 334 $[M + Na]^+$. HR-ESI–MS for $C_{17}H_{10}ClNNaO_3$: Found 334.0273, Calcd. 334.0247.

3-(2′-Benzoxazole)-6-bromo-2*H*-1-benzopyran-2-one (**4p**): yellow solid. M.p. 229–231 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.70 (1H, s, 4-H), 7.88 (1H, d, $J = 7.29$ Hz, 5-H), 7.81 (1H, d, $J = 2.28$ Hz, 6′-H), 7.74 (1H, dd, $J = 8.79$, 2.29 Hz, 5′-H), 7.64 (1H, d, $J = 7.38$ Hz, 7-H), 7.45–7.39 (2H, m, 4′-H, 7′-H), 7.32 (1H, d, $J = 8.77$ Hz, 8-H). ESI–MS: 364, 366 $[M + Na]^+$. HR-ESI–MS for $C_{16}H_8BrNNaO_3$: Found 363.9608; 365.9588, Calcd. 363.9585; 365.9585.

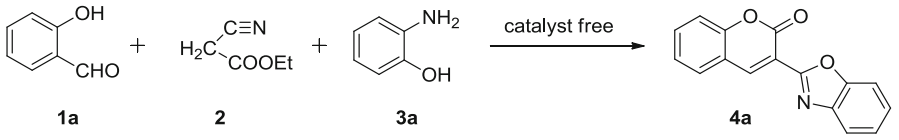
3-(5′-Methyl-2′-benzoxazole)-6-bromo-2*H*-1-benzopyran-2-one (**4q**): yellow solid. M.p. 248–251 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.67 (1H, s, 4-H), 7.78 (1H, d, $J = 2.27$ Hz, 5-H), 7.72 (1H, dd, $J = 8.79$, 2.29 Hz, 7-H), 7.64 (1H, s, 7′-H), 7.50 (1H, d, $J = 8.34$ Hz, 4′-H), 7.30 (1H, d, $J = 8.81$ Hz, 8-H), 7.22 (1H, d, $J = 8.45$ Hz, 6′-H), 2.50 (3H, s, Ar-CH_3). ESI–MS: 356.3, 358.3 $[M + 2H]^+$. HR-ESI–MS for $C_{17}H_{10}BrNNaO_3$: Found 377.9762; 379.9744, Calcd. 377.9742; 379.9742.

3-(5′-Chloro-2′-benzoxazole)-6-bromo-2*H*-1-benzopyran-2-one (**4r**): Yellow solid. M.p. 274–276 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.70 (1H, s, 4-H), 7.84 (1H, d, $J = 2.00$ Hz, 5-H), 7.82 (1H, d, $J = 2.23$ Hz, 4′-H), 7.76 (1H, dd, $J = 8.76$, 2.24 Hz, 7′-H), 7.57 (1H, d, $J = 8.68$ Hz, 7-H), 7.41 (1H, dd, $J = 8.68$, 1.93 Hz, 6′-H), 7.32 (1H, d, $J = 8.79$ Hz, 8-H). ESI–MS: 376.3, 378.3 $[M + 2H]^+$. HR-ESI–MS for $C_{16}H_7BrClNNaO_3$: Found 397.9215; 399.9195, Calcd. 397.9196; 399.9196.

3-(5′-Sulfonylamine-2′-benzoxazole)-6-bromo-2*H*-1-benzopyran-2-one (**4s**): yellow solid. M.p. > 300 °C. ^{1}H NMR (500 MHz, DMSO) δ: 9.09 (1H, s, 4′-H), 8.28-8.26 (2H, m, 6′-H, 5-H), 8.05 (1H, d, $J = 8.63$ Hz, 4-H), 7.97 (1H, d, $J = 8.59$ Hz, 7-H), 7.91 (1H, d, $J = 8.52$ Hz, 7′-H), 7.53–7.48 (1H, m, 8-H). ^{13}C NMR(DMSO) δ: 160.6, 155.3, 153.2, 151.6, 145.7, 141.4, 140.9, 136.6, 131.9, 124.1, 120.1, 118.5, 117.8, 116.5, 114.9, 111.7; ESI–MS: 420.9, 422.9 $[M + H]^+$. HR-ESI–MS for $C_{16}H_{10}BrN_2O_5S$: Found 420.9486; 422.9486, Calcd. 420.9494; 422.9494.

3-(2′-Benzimidazole)-2*H*-1-benzopyran-2-one (**6a**): yellow solid. M.p. 257–259 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.32 (bs, 1H, NH), 9.13 (1H, s, 4-H), 7.82 (1H, s, 5-H), 7.72 (1H, d, $J = 7.75$ Hz, 7-H), 7.64 (1H, t, $J = 7.16$ Hz, 4′-H), 7.56 (1H, s, 7′-H), 7.46 (1H, d, $J = 8.33$ Hz, 8-H), 7.41 (1H, t, $J = 8.41$ Hz, 6-H), 7.35–7.31 (2H, m,

Table 1 Catalyst-free synthesis of 3-(2-benzoxazole)-2*H*-1-benzopyran-2-one **4a**



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

Entry	Solvent	Reactant ratio[a]	Yield of **4a** (%)[b]
1	MeOH	1:1:1	31
2	EtOH	1:1:1	31
3	BuOH	1:1:1	61
4	Amyl alcohol	1:1:1	50
5	BuOH[c]	1:1:1	61
6	BuOH	1:1.5:1	62
7	BuOH	1:2:1	65
8	BuOH	1:1.5:1.5	66

General conditions: salicylaldehydes (2 mmol), solvent (20 mL), reaction time (7 h) at reflux

[a] Reactant ratio: **1a**:**2**:**3a**

[b] Isolated yield of **4a**

[c] N_2 protection

5′-H, 6′-H); ESI–MS: 263.1 $[M + H]^+$. HR-ESI–MS for $C_{16}H_{11}N_2O_2$: Found 263.0832; Calcd. 263.0821.

3-(2′-Benzimidazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**6b**): yellow solid. M.p. 241–243 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.27 (1H, s, NH), 8.90 (1H, s, 4-H), 7.76 (1H, d, $J = 7.42$ Hz, 4′-H), 7.50 (1H, d, $J = 7.26$ Hz, 7′-H), 7.44 (1H, d, $J = 8.86$ Hz, 5-H), 7.29–7.24 (2H, m, 5′-H, 6′-H), 6.65 (1H, d, $J = 8.88$ Hz, 6-H), 6.54 (1H, s, 8-H), 3.43 (4H, q, $J = 7.03$ Hz, $N(C\underline{H}_2CH_3)_2$), 1.23 (6H, t, $J = 7.07$ Hz, $N(CH_2C\underline{H}_3)_2$); ESI–MS: 334.2 $[M + H]^+$; HR-ESI–MS for $C_{20}H_{20}N_3O_2$: Found: 334.1566, Calcd.: 334.1556.

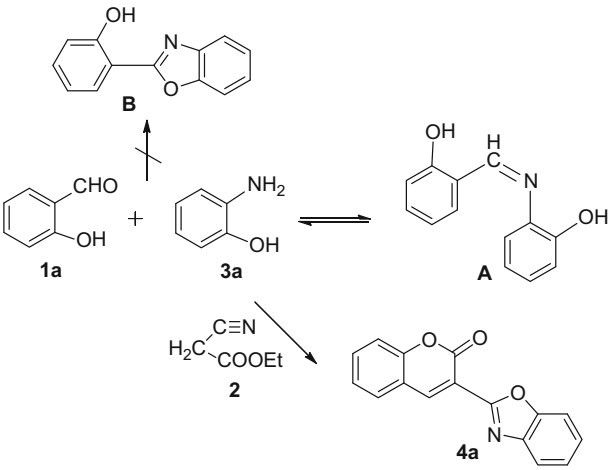
3-(5′-Methyl-2′-benzimidazole)-7-diethylamino-2*H*-1-benzopyran-2-one (**6c**): yellow solid. M.p. 205–207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.13 (1H, s, NH), 8.91 (1H, s, 4-H), 7.65–7.55 (1H, m, 6′-H), 7.45 (1H, d, $J = 8.90$ Hz, 5-H), 7.30 (1H, s, 4′-H), 7.10 (1H, d, $J = 8.05$ Hz, 7′-H), 6.67 (1H, d, $J = 8.88$ Hz, 6-H), 6.56 (1H, s, 8-H), 3.46 (4H, q, $J = 7.14$ Hz, $N(C\underline{H}_2CH_3)_2$), 2.50 (3H, s, CH_3), 1.24 (6H, t, $J = 7.09$ Hz, $N(CH_2C\underline{H}_3)_2$); ^{13}C NMR($CDCl_3$): 162.0, 158.5, 157.8, 156.6, 153.2, 151.7, 150.4, 142.2, 130.5, 130.2, 124.1, 109.9, 108.7, 108.1, 107.1, 96.8, 45.0, 21.7, 12.4; ESI–MS: 348.2 $[M + H]^+$; HR-ESI–MS for $C_{21}H_{22}N_3O_2$: Found: 348.1725, Calcd.: 348.1712.

2-Benzothiazolyl phenol: pale-yellow solid. M.p. 132–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.50 (1H, s, ArOH), 7.97 (1H, d, $J = 8.22$ Hz, 7′-H), 7.88 (1H, d, $J = 8.61$ Hz, 4′-H), 7.68 (1H, d, $J = 7.84$ Hz, 6′-H), 7.50 (1H, t, $J = 7.24$ Hz, 5′-H), 7.41–7.36 (2H, m, 3-H, 5-H), 7.10 (1H, d, $J = 8.30$ Hz, 4-H), 6.95 (1H, t, $J = 7.33$ Hz, 6-H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 169.4, 158.0, 151.9, 132.7, 132.6, 128.4, 126.7, 125.5, 122.2, 121.5, 119.5, 117.9, 116.8; ESI–MS: 228.0 $[M + H]^+$.

Results and discussion

For a model experiment, we first estimated the reactivity of salicylaldehyde (2 mmol), ethyl cyanoacetate (2 mmol), and *o*-aminophenol (2 mmol) by refluxing the mixture in MeOH for 7 h; the corresponding 3-(2-benzoxazole)-2*H*-1-benzopyran-2-one **4a** was obtained in 31 % yield (Table 1, entry 1). Considering the formation of benzoxazole ring accompanied with NH_3 release, MeOH was replaced with other alcohol solvents with higher boiling point to help free NH_3 and improve the yield. EtOH did not improve the result, which may be due to the similar boiling point to MeOH (Table 1, entry 2). When the reaction temperature was increased greatly, the yield of **4a** was improved to 61 % in *n*-BuOH from 31 % in MeOH (Table 1, entry 3). Further replacement of *n*-BuOH with *n*-amyl alcohol led to decreased yield of **4a** (Table 1, entry 4). To avoid oxidation of salicylaldehyde and *o*-aminophenol at high temperature, one-pot reaction with N_2 protection was attempted but did not give a better result (Table 1, entry 5). In addition, the reactant ratio was examined and the amount of ethyl cyanoacetate and *o*-aminophenol were increased to improve the yield (Table 1, entry 6–8). However, similar results were afforded as when using the conditions shown in entry 3 (Table 1).

In this one-pot synthesis involving three components, there are two main possible side reactions. One is the formation of imine **A** (Scheme 2) from the reaction of salicylaldehyde and *o*-aminophenol. In fact, the imine was formed as a red solid quickly when salicylaldehyde was mixed with *o*-aminophenol at room temperature. Without heating, when three components were stirred for 3 h, imine precipitation was obtained with yield of 26.8 % and no **4a** was found (Table 2, entry 1). After heating, the red imine gradually dissolved with the increased temperature and the reactant solution turned clear. However, with the formation of **4a**, the reactant solution became turbid again. When the reaction finished, high-performance liquid chromatography (HPLC) estimation indicated that the amount of imine dropped to 8.7 % (Table 2, entry 2). Since imine formation between *o*-aminophenol and



Scheme 2 Possible side reaction of one-pot catalyst-free synthesis of 3-benzoxazole

Table 2 Solvent effect on yield of **4a** and imine byproduct

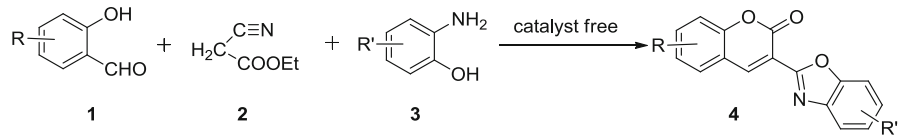
Entry	Solvent	Yield of **4a** (%)	Yield of imine (%)
1	BuOH[a]	None	26.8
2	BuOH	61	8.7
3	CH_3CN	19	22.4
4	THF	Trace	87.6
5	Toluene	9	64.1
6	DMF	11	3.7
7	H_2O	Trace	Trace

General conditions: salicylaldehydes (2 mmol), **1a/2/3a** = 1:1:1, solvent (20 mL), reaction time (7 h) at reflux

HPLC yield

[a] Reaction condition: 3 h at room temperature

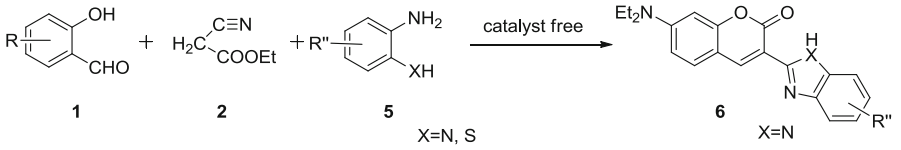
Table 3 Scope of one-pot catalyst-free synthesis of 3-benzoxazole coumarins

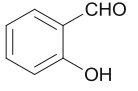
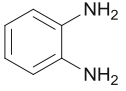
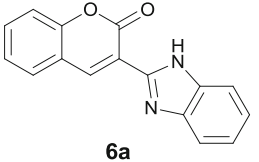
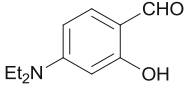
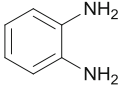
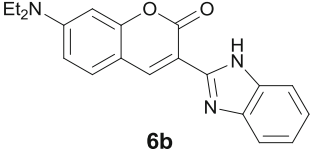
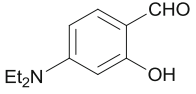
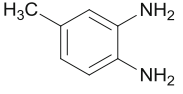
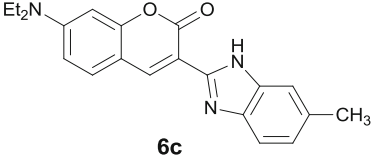
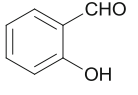
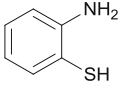
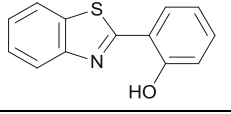


1 2 3 4

Compd.	R	R'	Yield (%)
4a	H	H	61
4b	H	5′-CH_3	51
4c	H	5′-Cl	79
4d	H	5′-NO_2	67
4e	7-CH_3O	H	67
4f	7-CH_3O	5′-CH_3	70
4g	7-CH_3O	5′-Cl	65
4h	7-CH_3O	5′-SO_2NH_2	58
4i	7-NEt_2	H	72
4j	7-NEt_2	5′-CH_3	56
4k	7-NEt_2	5′-Cl	73
4l	7-NEt_2	5′-NO_2	64
4m	7-NEt_2	5′-SO_2NH_2	68
4n	6-Cl	H	55
4o	6-Cl	5′-CH_3	40
4p	6-Br	H	71
4q	6-Br	5′-CH_3	47
4r	6-Br	5′-Cl	50
4s	6-Br	5′-SO_2NH_2	68

Table 4 Scope of aryl amine in one-pot catalyst-free reaction



Entry	Salicylaldehyde	Aryl amine	Product	Yield (%)
1			 **6a**	67
2			 **6b**	60
3			 **6c**	50
4				65

salicylaldehyde is a reversible reaction, we presumed that during one-pot reaction the imine byproduct firstly formed will decompose to the reactants to take part in the preparation of the stable target molecule (Scheme 2). Therefore, the addition sequence of reactants has little effect on the product yield (data not given). Another byproduct was 2-(benzoxazolyl)-phenol **B** (Scheme 2) whose formation was irreversible and would reduce the yield of **4a** greatly, just as in the case of benzoic acid-catalyzed synthesis of 3-(2′-benzothiazolyl)coumarins [28]. Fortunately, no 2-(benzoxazolyl)phenol was found in this catalyst-free one-pot synthesis.

Besides alcohol solvents, other solvents were tried. Unfortunately, none of them was an effective solvent for this one-pot catalyst-free synthesis. Compound **4a** was synthesized in 19 % yield in CH_3CN, which was lower than the yield of imine (Table 2, entry 3). Toluene and THF gave the imine as the main product and **4a** in trace (Table 2, entry 4, 5). DMF and H_2O were not good solvents for preparation of either compound **4a** or imine (Table 2, entry 6, 7). Therefore, optimized conditions involved reaction of salicylaldehyde, ethyl cyanoacetate (1 equiv), and *o*-aminophenol (1 equiv) in BuOH at reflux for 7 h, giving **4a** in 61 % yield (Table 1, entry 3).

To investigate the scope of this one-pot synthesis, different salicylaldehydes and *o*-aminophenols were reacted with ethyl cyanoacetate; the results are listed in Table 3. The reaction proceeded smoothly giving 40–80 % yields with salicylaldehydes and *o*-aminophenols bearing different substituents. Salicylaldehydes with electron-donating group reacted well with all *o*-aminophenols; however, chloro-substituted or bromo-substituted salicylaldehydes sometimes gave low yields, especially when reacting with methyl-substituted *o*-aminophenols; For example, compounds **4o** and **4q** were obtained in yields below 50 %.

Moreover, the scope of aryl amines was finally surveyed; the results are shown in Table 4. *o*-Phenylenediamines were readily transformed into the corresponding 3-benzimidazolyl coumarins in fair yields (Table 4, entry 1–3). However, *o*-aminobenzenethiol proved to be an unwilling substrate for this catalyst-free one-pot synthesis and gave the main byproduct 2-(benzothiazolyl)phenol (Table 4, entry 4), similar to the case of benzoic acid catalysis [28].

Conclusions

We have demonstrated a convenient and efficient method for preparation of the important class of 3-(2′-benzoxazolyl)coumarins and 3-(2′-benzimidazolyl)coumarin with salicylaldehydes, ethyl cyanoacetate, and *o*-aminobenzenethiols or *o*-phenylenediamines. This one-pot catalyst-free synthesis has wide substrate scope, and different salicylaldehydes and aryl amines bearing electron-donating and electron-withdrawing groups react smoothly giving yields of 50–80 %. Short reaction time, mild reaction condition, simple workup, and less waste are significant advantages of the presented method.

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