ONE-POT SYNTHESIS OF 3-(2'-BENZOXAZOLE)-2H-1-BENZOPYRAN-2-ONE DERIVATIVES WITH BENZOIC ACID CATALYSIS

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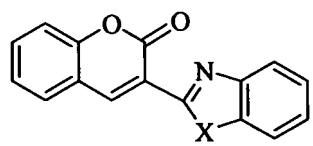
Abstract

A novel one-pot synthesis method of 3-heterocycle substitutued coumarin derivatives was reported. 3-(2'-benzoxazole)-2H-1-benzopyran-2-one derivatives were synthesized from substituted salicylaldehydes, o-aminophenols and ethyl cyanoacetate in n-butanol under the benzoic acid catalysis in one-pot reaction. This one-pot synthesis has a wide substrate scope and the salicylaldehydes with electron-donating group gave good yields. The coumarin derivatives were obtained with high purity and good yields with the simple filtration and characterized by ^{1}H NMR and MS. The possible mechanism was presumed. This reaction was characterized by mild acid catalysis, short reaction time, simple experimental procedure and high product purity.

Keywords: Coumarin, 3-(2-benzoxazole)-2H-1-benzopyran-2-ones, One-pot synthesis, Benzoic acid

Introduction

Coumarins and their analogues represent an important class of organic heterocycles, which can be found in many natural or synthetic drug molecules and possess versatile biological activities (1-5). They have been used as fragrances, pharmaceuticals, additives to food, cosmetics, agrochemicals, optical brightening agents, dispersed fluorescent, tunable dye lasers. Especially, 3-heterocycle substituted coumarin (**Fig. 1**) is the parent structure of the commercially significant organic fluorescent dyes and emits the yellow or green fluorescent light with different substituted groups in aromatic rings.



X=O, S, N

Figure 1

There are many methods to synthesize this kind of 3-heterocycle substituted coumarins, which can be summarized in two methods: the coumarin-3-carboxylic acid compounds were synthesized firstly and then reacted with different aryl amines to introduce the heterocyclic structure (6); or the heterocyclic derivatives prepared firstly reacted with substituted salicylaldehydes to give the parent coumarin (7, 8). Those methods often suffer from corrosive catalysts, long reaction time, high reaction temperature and waste problem. In our ongoing efforts to prepare coumarin fluorescent dyes, we found benzoic acid is able to catalyze the one-pot synthesis of 3-heterocycle substituted coumarin from

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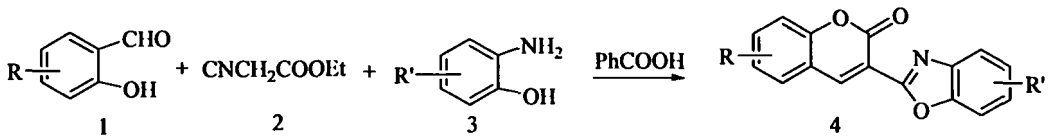
commercially available starting materials (9). The good yields and simple workup of this one-pot synthesis prompted us to explore the scope of this reaction with different salicylaldehydes and o-aminophenols and a series of 3-(2'-benzoxazole)-2H-1-benzopyran-2-one derivatives were synthesized (**Scheme 1**).



1 2 3 4

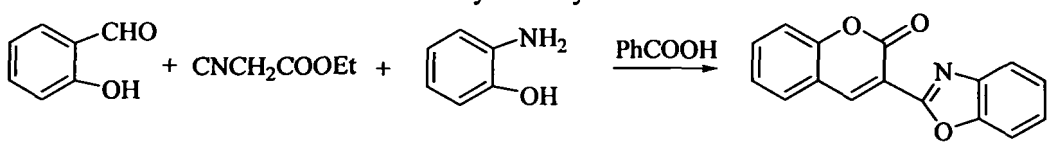
Scheme 1

Results and Discussion

O-aminophenols were reacted with ethyl cyanoacetate and salicylaldehydes under the catalysis of benzoic acid for 7-9 h in refluxing n-butanol, and then 1% NaOH was added to neutralize the reaction solution and remove the byproducts. After the simple filtration the target compounds were obtained with high purity and good yields.

The reaction of o-aminophenol, ethyl cyanoacetate and salicylaldehyde was selected as a model reaction to screen the catalysts and investigate the effects of catalyst amount and solvent (**Table 1**). The benzoic acid gave the better result than other acid catalysts (**Table 1**, Entry 1~3) and the reaction was carried out smoothly in a range of alcohol solvents (**Table 1**, Entry 3~8), and the best yield 72% was achieved in n-butanol (**Table 1**, Entry 3). The lower yield in ethanol and n-octanol may be due to the low reaction temperature and the poor solubility of the starting materials, respectively (**Table 1**, Entry 4 and Entry 8). Other solvents only gave trace product. Though the catalyst amount 0.3 equivalents was a little high, the increase or decrease of benzoic acid amount was unfavorable to the yield improvement (**Table 1**, Entry 9~14).

Table 1 Survey of catalysts and solvents



Entry	Catalyst	Catalyst amount /equiv.	Solvent	Yield /%
1	H_2SO_4	0.3	n-butanol	23
2	TsOH	0.3	n-butanol	45
3	PhCOOH	0.3	n-butanol	72
4	PhCOOH	0.3	ethanol	40
5	PhCOOH	0.3	i-butanol	56
6	PhCOOH	0.3	n-pentanol	56
7	PhCOOH	0.3	i-pentanol	65
8	PhCOOH	0.3	n-octanol	38
9	PhCOOH	0.05	n-butanol	51
10	PhCOOH	0.1	n-butanol	53
11	PhCOOH	0.2	n-butanol	48
12	PhCOOH	0.5	n-butanol	60
13	PhCOOH	0.75	n-butanol	65
14	PhCOOH	1	n-butanol	65

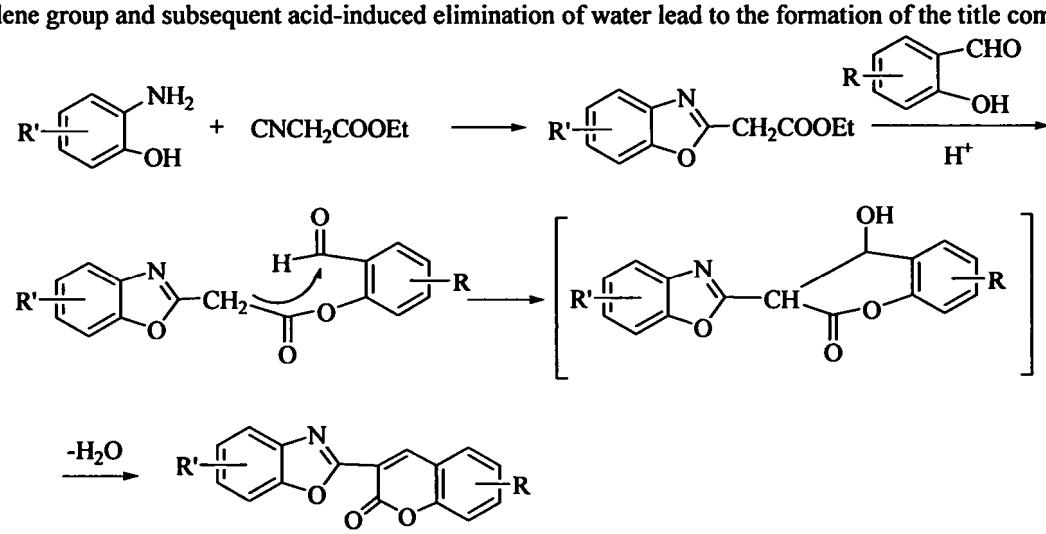
Reaction condition: o-aminophenol (2.3 mmol), cyanoacetate (1.5 equiv.), salicylaldehyde (1.5 equiv), solvent (10 mL), refluxing temperature.

A variety of substituted salicylaldehydes and o-aminophenols were found to be suitable for this one-pot synthesis of three components (**Table 2**). The results indicate that this one-pot reaction has a wide substrate scope and the salicylaldehyde with electron-donating group gave a better yield than those with electron-accepting substituent or without substituent. For example, 4-methoxysalicylaldehyde reacted with the o-aminophenol having different substituent except chloro atom affording over 87% yield(**Table 2**, Entry 11~14), while the other title compounds were obtained in below 80% yield.

Table 2 One Pot Synthesis of 3-(2-Benzoxazole)-2H-1-Benzopyran -2-One Derivatives

No.	R	R'	Product	Yield%
1	H	H	**4a**	77
2	H	CH_3	**4b**	51
3	H	Cl	**4c**	47
4	Cl	H	**4d**	69
5	Cl	CH_3	**4e**	58
6	Cl	Cl	**4f**	54
7	Cl	NO_2	**4g**	66
8	Br	H	**4h**	81
9	Br	CH_3	**4i**	67
10	Br	Cl	**4j**	57
11	OCH_3	H	**4k**	87
12	OCH_3	CH_3	**4l**	88
13	OCH_3	Cl	**4m**	61
14	OCH_3	NO_2	**4n**	89

A mechanistic rationalization for this reaction is provided in **Scheme 2**. Ethyl cyanoacetate reacts firstly with o-aminophenol to afford the ethyl 2-(benzoxazol-2-yl) acetate upon heating. The benzoic acid catalyzes transesterification between salicylaldehyde and the ester group on benzoxazole ring. The nucleophilic addition of the aldehyde group by the methylene group and subsequent acid-induced elimination of water lead to the formation of the title compounds.



Scheme 2

Conclusions

In conclusion, 3-(2'-benzoxazole)-2H-1-benzopyran-2-one derivatives were prepared from one-pot synthesis of o-aminophenols, ethyl cyanoacetate and salicylaldehydes under the benzoic acid catalysis. The product yield seemed associated with the substituent on salicylaldehyde and those with electron-donating substituent gave near 90% yields. This novel method to obtain the 3-heterocycle substituted coumarin derivatives was characterized by mild condition, simple workup process and high product purity.

Experimental Section

General.

The starting materials were all commercial chemicals and were used without further purification. m.p.: Taike X-4 melting point apparatus. ^{1}H NMR Spectra: Bruker AVANCE III 500MHz spectrometer, in $CDCl_3$ at 500 MHz; δ in ppm. ESI-MS: Therm LCQ TM Deca XP plus ion trap mass spectrometer; in m/z. HR-ESI-MS: Agilent 6210 TOF mass spectrometer; in m/z. The reaction progress is followed with TLC plates run in PE-EtOAc solvent systems. Spots were visualized by exposure to UV light (254 nm) followed by I_2 vapor.

General procedure for the preparation of compounds 4

A mixture of o-aminophenol (2.3 mmol), salicylaldehyde (3.45 mmol) and ethyl cyanoacetate (3.45 mmol) in n-butanol (10 ml) containing benzoic acid (0.69 mmol) was refluxed for 7-9 h till the reaction was completed (monitored by TLC). After the solvent was partly removed, 1% NaOH was added and the solution was stirred for 0.5 h. The solid was filtered, washed with water to afford pure compound **4**.

3-(2'-benzoxazole)-2H-1-benzopyran-2-one (**4a**). Yield: 77%. Yellow solid. m.p. 187~188 °C. ^{1}H NMR: 8.78(s, 1H, 4-H), 7.88-7.86(d, 1H, 5-H), 7.69-7.63 (m, 3H, 7-H, 5'-H, 6'-H), 7.43-7.37(m, 4H, 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)-2H-1-benzopyran-2-one (**4b**). Yield: 51%. Yellow solid. m.p. 158~160 °C. ^{1}H NMR: 8.76(s, 1H, 4-H), 7.68-7.64(m, 3H, 5-H, 7-H, 7'-H), 7.51-7.49(d, 1H, 8-H), 7.43-7.41(d, 1H, 6-H), 7.39-7.36(t, 1H, 4'-H), 7.22-7.21(d, 1H, 6'-H), 2.49(s, 3H, 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)-2H-1-benzopyran-2-one (**4c**): Yield: 47%. Yellow solid. m.p. 255~256 °C. ^{1}H NMR: 8.79(s, 1H, 4-H), 7.831-7.827(d, 1H, 5-H), 7.70-7.67(m, 2H, 4'-H, 7'-H), 7.57-7.56(d, 1H, 7-H), 7.44-7.43(d, 1H, 8-H), 7.41-7.37(m, 2H, 6'-H, 6-H). ESI-MS: 320 $[M+Na]^+$. HR-ESI-MS for $C_{16}H_8ClNNaO_3$: Found 320.0079, Calcd. 320.009.

3-(2'-benzoxazole)-6-chloro-2H-1-benzopyran-2-one (**4d**): Yield: 69%. Yellow solid. m.p. 229 °C. ^{1}H NMR: 8.70(s, 1H, 4-H), 7.88-7.87(d, 1H, 5-H), 7.65-7.63 (d, 2H, 5'-H, 6'-H), 7.61-7.59(dd, 1H, 7-H), 7.45-7.37(m, 3H, 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-2H-1-benzopyran-2-one (**4e**): Yield: 58%. Yellow solid. m.p. 227~229 °C. ^{1}H NMR: 8.67(s, 1H, 4-H), 7.643-7.638 (d, 2H, 5-H,7'-H), 7.60-7.58(dd, 1H, 7-H), 7.51-7.50(d, 1H, 8-H), 7.37-7.36(d, 1H, 4'-H), 7.24-7.22(d, 1H, 6'-H), 2.50(s, 3H, Ar-CH_3). ESI-MS: 334$[M+Na]^+$. HR-ESI-MS for $C_{17}H_{10}ClNNaO_3$: Found 334.0273, Calcd. 334.0247.

3-(5'-chloro-2'-benzoxazole)-6-chloro-2H-1-benzopyran-2-one (**4f**): Yield: 54%. Yellow solid. m.p. 258~260 °C. ^{1}H NMR: 8.70(s, 1H, 4-H), 7.838-7.834 (d, 1H, 4'-H), 7.663-7.659(d, 1H, 7'-H), 7.63-7.61(dd, 1H, 5-H), 7.58-7.56(d, 1H, 8-H), 7.41-7.37(m, 2H, 7-H, 6'-H). ESI-MS: 354 $[M+Na]^+$. HR-ESI-MS for $C_{16}H_7Cl_2NNaO_3$: Found 353.9726; 355.9702; 357.9682, Calcd. 353.9701; 355.9701; 357.9701.

3-(5'-nitro-2'-benzoxazole)-6-chloro-2H-1-benzopyran-2-one (**4g**): Yield: 66%. Yellow solid. m.p. 259 °C. ^{1}H NMR: 8.79(s, 1H, 4'-H), 8.76-8.75(d, 1H, 4-H), 8.41-8.39(dd, 1H, 6'-H), 7.79-7.77(d, 1H, 5-H), 7.71-7.70(d, 1H, 7'-H), 7.67-7.65(dd, 1H, 7-H), 7.42-7.40(d, 1H, 8-H). ESI-MS: 707$[2M+Na]^+$. HR-ESI-MS for $C_{16}H_7ClN_2NaO_5$: Found 364.9967, Calcd. 364.9941.

3-(2'-benzoxazole)-6-bromo-2H-1-benzopyran-2-one (**4h**): Yield: 81%. Yellow solid. m.p. 229~231 °C. ^{1}H NMR: 8.70(s, 1H, 4-H), 7.89-7.87(d, 1H, 5-H), 7.811-7.806(d, 1H, 6'-H), 7.75-7.73(dd, 1H, 5'-H), 7.65-7.64(d, 1H, 7-H), 7.45-7.39(m, 2H, 4'-H, 7'-H), 7.33-7.31(d, 1H, 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-2H-1-benzopyran-2-one (**4i**): Yield: 67%. Yellow solid. m.p. 248~251 °C. ^{1}H NMR: 8.67(s, 1H, 4-H), 7.798-7.793 (d, 1H, 5-H), 7.74-7.72(dd, 1H, 7-H), 7.64(s, 1H, 7'-H), 7.52-7.50(d, 1H, 5-H), 7.32-7.30(d, 1H, 4'-H), 7.24-7.22(d, 1H, 6'-H), 2.50(s, 3H, 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-2H-1-benzopyran-2-one (**4j**): Yield: 57%. Yellow solid. m.p. 271~273°C. ^{1}H NMR: 8.70(s, 1H, 4-H), 7.842-7.838(d, 1H, 5-H), 7.82-7.81(d, 1H, 4'-H), 7.77-7.74(dd, 1H, 7'-H), 7.58-7.56(d, 1H, 7-H), 7.41-7.39(dd, 1H, 6'-H), 7.33-7.31(d, 1H, 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-(2'-benzoxazole)-7-methoxy-2H-1-benzopyran-2-one (**4k**): Yield: 87%. Yellow solid. m.p. 189~192 °C. ^{1}H NMR: 8.71(s, 1H, 4-H), 7.85-7.83(m, 1H, 6'-H), 7.62-7.59(m, 1H, 5'-H), 7.57-7.55(d, 1H, 5-H), 7.40-7.35(m, 2H, 4'-H, 7'-H), 6.94-6.92(dd, 1H, 6-H), 6.877-6.873(d, 1H, 8-H), 3.92(s, 3H, 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-2H-1-benzopyran-2-one (**4l**): Yield: 88%. Yellow solid. m.p. 197~199 °C. ^{1}H NMR: 8.69(s, 1H, 4-H), 7.60(s, 1H, 5-H), 7.56-7.54(d, 1H, 7'-H), 7.48-7.47(d, 1H, 4'-H), 7.19-7.17(d, 1H, 6'-H), 6.94-6.91(dd, 1H, 6-H), 6.873-6.868(d, 1H, 8-H), 3.91(s, 3H, Ar-OCH_3), 2.48(s, 3H, Ar-CH_3). 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-2H-1-benzopyran-2-one (**4m**): Yield: 61%. Yellow solid. m.p. 234~236 °C. ^{1}H NMR: 8.71(s, 1H, 4-H), 7.791-7.787 (d, 1H, 4'-H), 7.58-7.56(d,1H, 7'-H), 7.54-7.52(d, 1H, 5-H), 7.36-7.34(dd, 1H, 6'-H), 6.95-6.93(dd, 1H, 6-H), 6.880-6.875(d, 1H, 8-H), 3.93(s, 3H, 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'-nitro-2'-benzoxazole)-7-methoxy-2H-1-benzopyran-2-one (**4n**): Yield: 89%. Yellow solid. m.p. 278~280 °C. ^{1}H NMR: 8.80(s, 1H, 4'-H), 8.70(s, 1H, 4-H),8.37-8.35(d, 1H, 6'-H), 7.74-7.72(d, 1H, 5-H), 7.62-7.60(d, 1H, 7'-H), 6.98-6.97(d, 1H, 6-H), 6.91(s, 1H, 8-H), 3.95(s, 3H, Ar-OCH_3). ESI-MS: 361$[M+Na]^+$. HR-ESI-MS for $C_{17}H_{10}N_2NaO_6$: Found 361.0455, Calcd. 361.0437.

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