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Preparation of α-benzylamino coumarin derivatives using oxalic acid in aqueous media

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A simple and efficient preparative approach for the synthesis of different α-benzylamino coumarins catalyzed by oxalic acid is developed which involves three-component reaction of 4-hydroxycoumarin, aromatic aldehydes and secondary amines under ambient conditions in aqueous media. The salient features of this protocol are aerobic conditions, short reaction time, and mild reaction conditions without additives.

Keywords: Oxalic acid, 3-substituted coumarin, Mannich type reaction, α-benzylamino coumarin

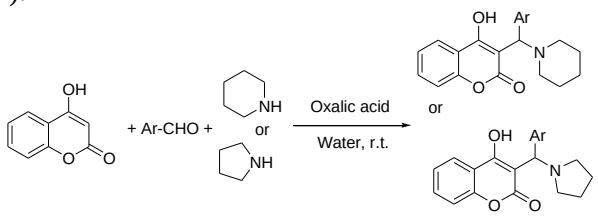
INTRODUCTION

There is a great deal of interest in finding environmentally friendly solvents for synthesis. The use of water as a solvent in organic synthesis leads to a clean and economical technology. With water as a solvent the safety is largely increased, work-up is considerably simplified and cost is reduced [1,2]. The use of water as a solvent coupled with high yields and short reaction times makes synthetic procedures very attractive. The rates of the multicomponent reactions (MCRs) can increase when carried out in water [3]. MCRs have the advantages of high atom economy, structural diversity, operational simplicity, and lack of waste products in multistep reactions. The use of efficient and eco-friendly MCRs for construction of carbon-carbon and carbon-nitrogen bonds is a continued issue in organic synthesis [4-10].

3-Benzylcoumarin and its derivatives are an important class of heterocyclic compounds that have attracted much attention because of their diverse therapeutic and pharmacological activities such as anti-HIV, anti-malarial, anticoagulant, antibacterial, insecticide, antioxidant and antiviral [14-16]. The existence of coumarin derivatives in natural products is also of interest. Some analogues of coumarin have been isolated from sweet clover, bison grass and woodruff and are used to prevent clotting of blood in the veins, lungs or heart [17-20].

Mannich reaction is one of the most important C-C bond formation methods in organic synthesis, and its products (Mannich bases) are of considerable importance in industry, natural products chemistry, and pharmacy [21]. The classical Mannich reaction has limited applications, and many attempts have been made to extend this reaction [22]. The first report of Mannich type reaction was done by Robertson and Link [23] to prepare a range of benzyl amino coumarins at the mid of the 20th century. Thereafter, numerous modifications of this reaction surfaced and several methods have been developed for the preparation of 3-(benzyl)-substituted coumarins by using various catalysts, including triton X-100 as a non-ionic surfactant [24], nano crystalline ZnO [25] and $InCl_3$ [26].

Based on the above informations and due to our interest in developiing synthetic strategies for the construction of heterocyclic compounds, herein we report a facile methodology for the multicomponent condensation reaction of 4-hydroxycoumarin, aromatic aldehydes and secondary amines (Scheme 1).



Scheme 1. Preparation of 3-(benzyl) amino coumarins.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra

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were measured in DMSO-d_6 relative to TMS (0.00 ppm). Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates.

General procedure

To a mixture of 4-hydroxycoumarin (1.0 mmol), aromatic aldehyde (1.2 mmol) and secondary amine (1.2 mmol) in water (3 mL), oxalic acid (0.28 mmol) was added as the catalyst, and the mixture was stirred for an appropriate time at room temperature. After the reaction was completed, the solid compound obtained was filtered off and the crude products were purified by recrystallization from EtOH.

Selected data

3-((4-*tert*-Butylphenyl)(piperidin-1-yl)methyl)-4-hydroxy-2*H*-chromen-2-one (g): ^{1}H-NMR (400 MHz, DMSO-d_6): 1.28 (s, 9H), 1.73-1.94 (m, 6H), 2.22-2.26 (m, 2H), 3.09-3.12 (m, 2H), 5.29 (s, 1H), 7.11-7.27 (m, 4H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.82(d, *J* = 7.7Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 19.9, 20.3, 22.8, 34.5, 35.7, 52.7, 67.9, 103.4, 115.9, 122.6, 123.9, 124.5, 128.7, 131.4, 135.9, 152.7, 153.6, 163.3, 164.7, 172.7 ppm; Found: C, 76.77; H, 7.56; N, 3.66; $C_{25}H_{29}NO_3$; requires: C, 76.70; H, 7.47; N, 3.58%.

4-Hydroxy-3-((3-nitrophenyl)(piperidin-1-yl)methyl)-2*H*-chromen-2-one (h): ^{1}H-NMR (400 MHz, DMSO-d_6): 1.70-1.93 (m, 6H), 2.21-2.25 (m, 2H), 3.12-3.14 (m, 2H), 5.59 (s, 1H), 7.10-7.16 (m, 2H), 7.43-7.48 (m, 2H), 7.49-7.53 (m, 2H), 7.82(d, *J* = 7.7Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 8.08 (s, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 20.3, 22.8, 34.5, 52.7, 103.6, 116.3, 121.6, 122.9, 123.7, 124.5, 128.9, 130.3, 133.9, 144.7, 148.3, 153.6, 166.3, 165.7, 172.3 ppm; Found: C, 66.39; H, 5.38; N, 7.44; $C_{21}H_{20}N_2O_5$; requires: C, 66.31; H, 5.30; N, 7.36%.

4-Hydroxy-3-((9-methyl-9H-carbazol-2-yl)(piperidin-1-yl)methyl)-2H-chromen-2-one (q): ^{1}H-NMR (400 MHz, DMSO-d_6): 1.66-1.91 (m, 6H), 2.35-3.71 (m, 4H), 3.79 (s, 3H, CH_3), 5.23 (s, 1H), 7.19-7.72 (m, 9H), 7.84 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 23.7, 26.3, 29.7, 50.9, 54.3, 107.8, 116.4, 116.6, 116.9, 120.7, 120.9, 121.6, 122.2, 123.7, 124.5, 126.4, 127.7, 128.0, 129.5, 131.6, 139.7, 140.3, 142.6, 153.7, 165.3, 173.1 ppm; Found: C, 76.86; H, 6.21; N, 6.54; $C_{28}H_{26}N_2O_3$; requires: C, 76.69; H, 5.98; N, 6.39%.

4-Hydroxy-3-((9-methyl-9H-carbazol-2-yl)(pyrrolidin-1-yl)methyl)-2H-chromen-2-one (r): ^{1}H-NMR (400 MHz, DMSO-d_6): 1.89-1.96 (m, 4H), 3.02-3.11 (m, 4H), 3.79 (s, 3H, CH_3), 5.25 (s, 1H), 7.20-7.71 (m, 9H), 7.84 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): 24.2, 29.9, 50.3, 54.2, 107.6, 116.3, 116.7, 116.9, 120.6, 120.9, 121.7, 122.3, 123.7, 124.4, 126.5, 127.6, 127.8, 129.5, 131.6, 139.5, 142.7, 140.4, 153.6, 165.1, 173.3 ppm; Found: C, 76.56; H, 5.84; N, 6.78; $C_{27}H_{24}N_2O_3$; requires: C, 76.39; H, 5.70; N, 6.60%.

RESULTS AND DISCUSSION

Initial investigations were carried out using benzaldehyde (1.2 mmol), 4-hydroxycoumarin (1 mmol) and piperidine (1.2 mmol) as reactants in order to assess the suitability of oxalic acid as a catalyst (Scheme 2) and to optimize the reaction conditions. The results are presented in Table 1.

Scheme 2. synthesis of 4-hydroxy-3-(phenyl(piperidin-1-yl)methyl)-2H-chromen-2-one

As shown in Table 1, a variety of polar and non-polar solvents like CH_2Cl_2, ethanol, methanol, *n*-hexane, ethyl acetate, diethyl ether and water were examined. Under solvent-free conditions the product was obtained in a low yield. It was noticed that the polar protic solvents afforded better yields than other solvents and the best catalytic activity of oxalic acid (0.56 mmol) was observed in aqueous medium (Table 1).

To find out the optimial amount of barium chloride, the reaction was carried out by varying the quantity of catalyst (Table 1, entries 7, 9-11). The maximum yield was obtained using 0.28 mmol of catalyst (Table 1, entry 10). Further increase in the amount of oxalic acid in the mentioned reaction had no significant effect on the product yield.

With the successful optimization of the synthesis of 4-hydroxy-3-(phenyl(piperidin-1-yl)methyl)-2*H*-chromen-2-one we further studied the reactions of various aromatic aldehydes, piperidine/pyrrolidine and 4-hydroxy coumarin under similar conditions (Table 2, products **a-p**). A wide range of aromatic aldehydes was investigated under the optimal conditions.

The electron-donating groups attached to the phenyl rings of aldehydes decreased the reactivity (Table 2, entries 5-7,). However, the electron withdrawing groups (Table 2, entry 8) exhibited good reactivity.

Table 1. Optimization of the reaction conditions in the synthesis of 4-hydroxy-3-(phenyl(piperidin-1-yl)methyl)-2H-chromen-2-one (Scheme 2)

Entry	Catalyst (mmol)	Temperature	Solvent (5 mL)	Yield (%)[a]
1	0.56	r.t.	*n*-Hexane	-
2	0.56	r.t.	CH_2Cl_2	-
3	0.56	r.t.	Et_2O	5
4	0.56	r.t.	EtOAc	20
5	0.56	r.t.	EtOH	40
6	0.56	r.t.	MeOH	40
7	0.56	r.t.	H_2O	80
8	0.56	r.t.	-	10
9	1	r.t.	H_2O	85
10	0.28	r.t.	H_2O	89
11	0.14	r.t.	H_2O	50

[a] Isolated yields, reaction time: 2 h

Table 2. Synthesis of α-benzylamino coumarin derivatives

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)[a]
1	Benzaldehyde	piperidine	**a**	2	89
2	2-Chlorobenzaldehyde	piperidine	**b**	3	87
3	4-Chlorobenzaldehyde	piperidine	**c**	2	74
4	2-Methylbenzaldehyde	piperidine	**d**	4	80
5	4-Methylbenzaldehyde	piperidine	**e**	3	86
6	4-Methoxybenzaldehyde	piperidine	**f**	3	77
7	4-*tert*-Butylbenzaldehyde	piperidine	**g**	3	85
8	3-Nitrobenzaldehyde	piperidine	**h**	2	95
9	2,4-Dichlorobenzaldehyde	piperidine	**i**	3	60
10	4-Bromobenzaldehyde	piperidine	**j**	2	93
11	Benzaldehyde	pyrrolidine	**k**	2	90
12	2-Chlorobenzaldehyde	pyrrolidine	**l**	2	94
13	4-Chlorobenzaldehyde	pyrrolidine	**m**	3	95
14	2-Methylbenzaldehyde	pyrrolidine	**n**	2	80
15	4-Methylbenzaldehyde	pyrrolidine	**o**	2	90
16	3-Nitrobenzaldehyde	pyrrolidine	**p**	2	92
17	9-Methyl-9H-carbazole-2-carbaldehyde	piperidine	**q**	5	85
18	9-Methyl-9H-carbazole-2-carbaldehyde	pyrrolidine	**r**	5	87

[a]Isolated yields. All products have been reported previously in the literature and were characterized by comparison of NMR spectra with authentic samples [20-22].

CONCLUSION

In conclusion, a one-pot three-component reaction of aromatic aldehydes, piperidine/ pyrrolidine and 4-hydroxycoumarin was described and an efficient procedure for the synthesis of a variety of α-benzylamino coumarins was found. Prominent among the advantages of this method are: easy workup procedure, operational simplicity and excellent yields of products in short reaction times.

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ПРИГОТВЯНЕ НА ПРОИЗВОДНИ НА α-БЕНЗИЛАМИНОКУМАРИН С ИЗПОЛЗВАНЕТО НА ОКСАЛОВА КИСЕЛИНА ВЪВ ВОДНА СРЕДА

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(Резюме)

Разработен е прост и ефикасен препаративен подход за синтезата на различни производни на α-бензиламинокумарин при катализатор оксалова киселина, който включва три-компонентна реакция на 4-хидроксикумарин, ароматни алдехиди и вторични амини във водна среда. Характерни особености на този протокол са аеробни условия, кратко реакционно време и меки условия, без добавки.