ONE-POT PREPARATION OF COUMARINS BY KNOEVENAGEL CONDENSATION IN SOLVENT-FREE CONDITION UNDER MICROWAVE IRRADIATION

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Abstract

3-Substituted coumarins were prepared by the Knoevenagel reaction of 2-hydroxybenzaldehyde derivatives and 2-hydroxy-1-naphthaldehyde in the presence of ammonium aceteate on basic alumina or silica gel under microwave irradiation. High yields, low reaction times, being environmentally friendly, elimination of organic base and solvent are advantages of this method.

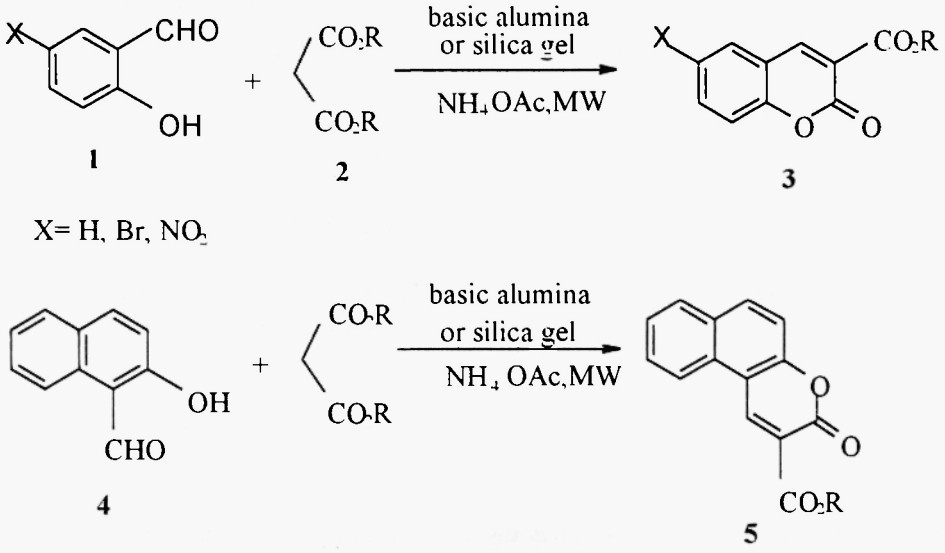
Introduction

Coumarins substituted at C-3 are an important class of organic compounds which are used in pharmaceutical chemistry as intermediates in the synthesis of pesticides and bioactive compounds (1). Coumarins have wide range of activities, i.e anthelmintic, hypnotic and insecticidal properties (2a), anticoagulant (2b), coronary and fluorescent brighthners (2c), photographical sensitizers and fluorescent dyes (3). Naphtho-[2,1-b]-pyran-3-oxo have shown antimicrobial (4a) antiinflammatory (4b) and anticancer activities (4c).

In view of the biological importance of coumarin derivatives, we have developed a new method for rapid synthesis of these compounds. There are many methods for the synthesis of coumarins (5) such as Perkin reaction (6), Pechmann reaction (7), Knoevenagel reaction (8), Reformatsky (9) and Wittig reaction (2a, 2c, 10).

Solvents are often expensive, toxic, difficult to remove from reaction mixture and are environmentally polluting agents. Solvent-free condition under microwave irradiation as an efficient method in organic synthesis (11) has several advantages i.e. cleaner reaction, shorter reaction time and ease of manipulation.

We wish to report here, ammonium acetate on basic alumina (12) or silica gel, as highly efficient catalysts for the synthesis of coumarins via Knoevenagel condensation of salicylaldehyde derivatives and 2-hydroxy-1-naphthaldehyde with ethyl and methyl malonate in solvent-free condition under microwave irradiation. Reaction conditions and yields are shown in Table 1.



Scheme 1

Table 1: Synthesis of coumarins catalyzed by ammonium acetate-basic alumina or silica gel under microwave irradiation.

Product	R	X	Time (min)		Yield%*	
			silica gel	basic alumina	silica gel	basic alumina
3a	Me	H	2	2	93	94
3b	Et	H	3	3	78	76
3c	Me	Br	8	8	65	68
3d	Et	Br	8	8	65	70
3e	Me	NO_2	15	15	55	58
3f	Et	NO_2	15	15	53	55
5a	Me	H	2	2	88	90
5b	Et	H	3	3	77	81

*Isolated yield.

Results and discussion

Recently, solid catalysts have been used for the synthesis of coumarins. Hydrotalcite as a basic surface in reflux condition in toluene under inert atmosphere catalyzed Knoevenagel condensation of various phenols with 2-substituted ethyl acetates. The uncalcined catalyst gave low yield with ethyl malonate (13). Meanwhile, natural kaolinitic clay (EPZG, EPZ10) are solid catalysts which exhibit both Bronsted and Lewis acid characteristics catalyzed Knoevenagel condensation focused microwave irradiation (14).

In the classic approach, cyclocondensation of salicylaldehyde and 2-hydroxy-1-naphthaldehyde requires many hours with heating in ethanol or other solvents in reflux condition in the presence of a base (15). In contrast, the same reaction required 2-15 minutes when carried out under microwave irradiation. Previously this reaction has been carried out under microwave irradiation in the presence of piperidine as catalyst (16) However, the method reported here, is simpler with easy work up. All compounds are known and their identity were characterized on the basis of IR, and ^{1}H-NMR spectra. The IR spectra showed absorption at 1710-1730 cm^{-1} due to the lactone moiety of the coumarin ring. In the ^{1}H-NMR spectra, the singlet at 8.20-9.20 ppm was assigned to the H-4 proton of coumarin skeleleton. Comparing the results shown in Table 1, we noted that the best yields were achieved with basic alumina (55-94%) that is comparable with classic method.

Conclusions

In conclusion we have developed a general, rapid and solvent-free protocol for the synthesis of coumarins via Knoevenagel condensation of 2-hydroxyaldehydes with methyl or ethyl malonate catalyzed by ammonium acetate. It has simple set-up and work-up and is environmentally friendly and the results are comparable to other methods. Some of these compounds have biological activity. This method offers a practical alternative to conventional bases and the process itself is environment friendly.

Experimental:

Melting points were measured on an *Electrothermal* melting point apparatus and are uncorrected. IR spectra were recorded with a *Shimadzu IR-408* spectrometer (KBr). ^{1}H-NMR spectra were determined in chloroform-d solution on a *FT-NMR Bruker AC-80* (80 MHz) and reported in ppm. We used a domestic microwave oven (*Moulinex* 2735A) at 2450 MHz (100% power 850W) under the conditions shown in Table 1.

General procedure for preparation of Coumarins (3a-3d, 5a, 5b):

2-Hydroxyaldehyde (3 mmol), ethyl or methyl malonate (3 mmol), ammonium acetate (231 mg, 3 mmol) and basic alumina or silica gel (3 g) were mixed thoroughly in a mortar. The reaction mixture was placed in a beaker and irradiated under the conditions shown in Table 1. The progress of reaction was monitored by TLC using (petroleum ether:CH_2Cl_2 = 30:70). The mixture was extracted into methylenechloride (3×30 ml) then filtered and washed with water, the organic phase was removed under reduced pressure by rotary evaporator. Further purification by column chromatography on silica gel gave the desired product. Crystallization was carried out in EtOH.

2-Oxo-2H-1-benzopyran-3-carboxylic acid methyl ester (3a):

m.p.= 116 °C [lit (17) =117 °C]; ^{1}H-NMR ($CDCl_3$, δ ppm): 3.90 (s, 3H, OCH_3), 7.28-7.80 (m, 4H, Ar), 8.50 (s, 1H, H-4); IR (KBr,cm^{-1}): 1750 (C=O), 1700 (C=O), 1610 (C=C), 1560 (C=C).

2-Oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester (3b):

m.p.= 92 °C [lit (16c) =92 °C]; ^{1}H-NMR ($CDCl_3$, δ ppm): 1.75 (t, 3H, J=7.20 Hz, CH_3), 4.20 (q, 2H, J=7.20 Hz, CH_2), 7.10-7.70 (m, 4H, Ar), 8.20 (s, 1H, H-4); IR (KBr, cm^{-1}): 1750 (C=O), 1700 (C=O), 1610(C=C), 1560(C=C).

6-Bromo-2-oxo-2H-1-benzopyran-3-carboxylic acid methyl ester (3c):

^{1}H-NMR ($CDCl_3$, δppm): 3.80 (s, 3H, OCH_3), 7.00-7.70 (m, 4H, Ar), 8.30 (s, 1H, H-4); IR (KBr, cm^{-1}): 1755 (C=O), 1700 (C=O), 1620 (C=C), 1550 (C=C).

6-Bromo-2-oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester (3d):

m.p.= 163 °C [lit(18)=166 °C]; ^{1}H-NMR ($CDCl_3$, δ ppm): 1.30 (t, 3H, J=7.20 Hz, CH_3), 4.20 (q, 2H, J=7.20 Hz, CH_2), 7.10-7.70 (m, 3H, Ar), 8.30 (s,1H, H-4); IR (KBr, cm^{-1}): 1750 (C=O), 1700 (C=O), 1610 (C=C), 1560 (C=C).

6-Nitro-2-oxo-2H-1-benzopyran-3-carboxylic acid methylester (3e):

^{1}H-NMR ($CDCl_3$, δ ppm):, 3.90 (s, 3H, OCH_3), 7.40-8.60 (m, 3H, Ar), 8.50 (s, 1H, H-4); IR (KBr, cm^{-1}): 1760 (C=O), 1700 (C=O), 1620 (C=C), 1570 (C=C), 1530, 1350 (NO_2).

6-Nitro-2-oxo-2H-1-benzopyran-3-carboxylic acid ethylester (3f):

m.p.= 190 °C [lit(19)=193 °C]; ^{1}H-NMR ($CDCl_3$, δ ppm): 1.40 (t, 3H, J=7.20 Hz, CH_3), 4.40 (q, 2H, J= 7.20 Hz, CH_2), 7.40-8.60 (m, 3H, Ar), 8.50 (s, 1H, H-4); IR (KBr, cm^{-1}): 1760 (C=O), 1700 (C=O), 1620 (C=C), 1570 (C=C), 1530, 1350 (NO_2).

3-Oxo-3H-naphto[2,1-b]pyran-2-carboxylic acid methyl ester (5a):

m.p.= 159 °C; ^{1}H-NMR ($CDCl_3$, δ ppm): 3.90 (s, 3H, OCH_3), 7.30-8.30 (m, 6H, Ar), 9.20 (s, 1H, H-4); IR (KBr, cm^{-1}): 1740 (C=O), 1680 (C=O), 1610 (C=C), 1550 (C=C).

3-Oxo-3H-naphto[2,1-b]pyran-2-carboxylic acid ethyl ester (5b):

m.p.= 117 °C [lit (16c) =118 °C]; ^{1}H-NMR ($CDCl_3$, δ ppm): 1.40 (t, 3H, J=7.10 Hz, CH_3), 3.90 (q, 2H, J=7.10 Hz, CH_2), 7.20-8.20 (m, 6H, Ar), 9.30 (s, 1H, H-4); IR (KBr, cm^{-1}): 1750 (C=O), 1700 (C=O), 1610 (C=C), 1560 (C=C).

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