Synthesis of 3-phenyl-4-styryl and 3-phenyl-4-hydroxy coumarins

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الخلاصة

تم في هذا البحث تحضير معوضات 3–فنيل– 4–ستايريل و 3–فنيل– 4–هيدروكسي كومارين. اعطى تفاعل معوضات البنزالديهايد مع 2–هيدروكسي اسيتوفينون مركبات الجالكون المقابلة. تم مفاعلة هيدروكسي جالكون مع حامض فنيل الخليك في البيريدين وبوجود اوكسي كلوريد الفسفور ليعطي مركبات الاسترات الوسطية والتي تم تحولقها الى 3–فنيل–4–اسيتايريل كومارين من خلال تفاعلها مع هيدروكسيد البوتاسيوم.

تم تحويل ساليسالات المثيل الى استرات من خلال تفاعلها مع فنيل حامض الخليك واوكسي كلوريد الفسفور في البيريدين ثم تحولقها باستخدام هيدروكسيد البوتاسيوم في البيريدين لتعطي 3–فنيل–4– هيدروكسي كومارين.

شخصت المركبات المحضرة بالطرق الفيزياوية والطيفية.

ABSTRACT

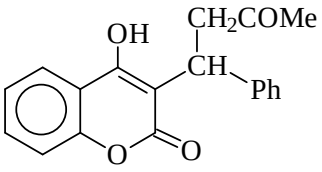
In this paper the synthesis of substituted 3-phenyl-4-styryl and 3-phenyl-4-hydroxy coumarins is reported. The substituted benzaldehydes were treated with 2-hydroxy acetophenone to give the corresponding chalcone, the hydroxy chalcone then reacted with phenyl acetic acid in pyridine and phosphorus oxychloride to give the intermediates esters, which then cyclized to 3-phenyl-4-styryl coumarins by their reaction with potassium hydroxide. Substituted methyl salicylate were converted to the esters by their reaction with phenyl acetic acid and phosphorous oxychloride in pyridine, followed by cyclization with potassium hydroxide in pyridine to give 3-phenyl-4-hydroxy coumarins. The structures of the synthesized compounds were established by physical and spectral methods.

INTRODUCTION

Six membered oxygen heterocyclic compounds which occur widely in vegetable some of these compounds were used as drugs, or they possess various biological activity[(1)]. Coumarins are one of these important heterocycles which show physiological action upon human[(2)].

The biological activity of coumarines varies according to the substituents on the benzyopyran ring[(3)], they used as antibacterial[(4)],

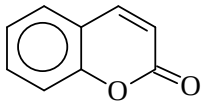
anticoagulant[5] and analgesic agent[5]. 7-Hydroxy-4-methyl coumarin could be used as cardioactive drug by inhibition of calcium influx[7] and has antiasthmatic activity[8], while 4-hydroxy coumarin behaves as a blood anticoagulant[9,10] like warfarin (I).



(I)

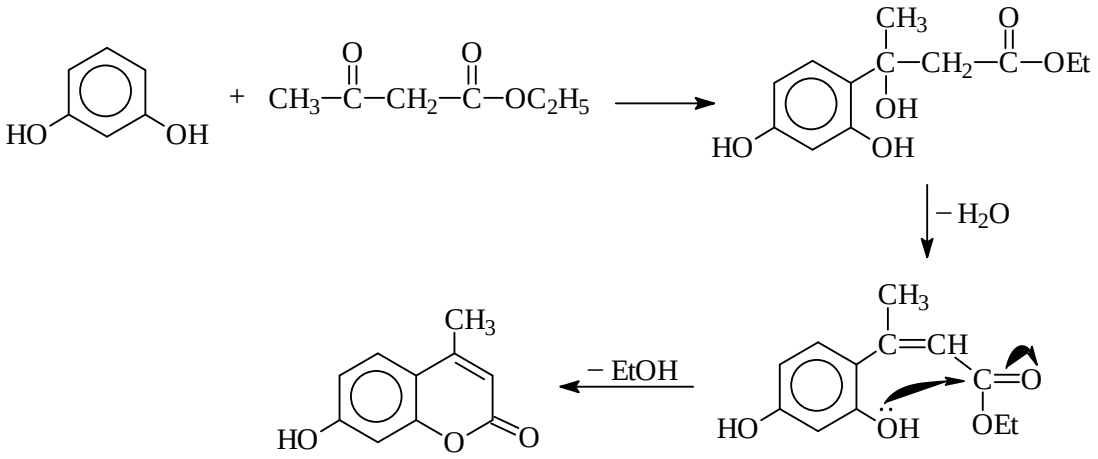
Coumarins are an important group of organic compounds that are used as additives to food and cosmetics, or a optical brightening agent[9].

Coumarin (II) was synthesized from salicylaldehyde by its reaction with acetic anhydride in presence of anhydrous sodium acetate (Perkin reaction)[11].

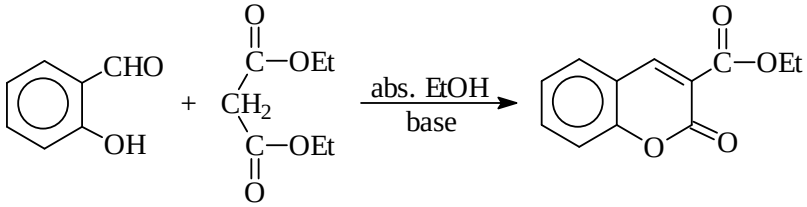


(II)

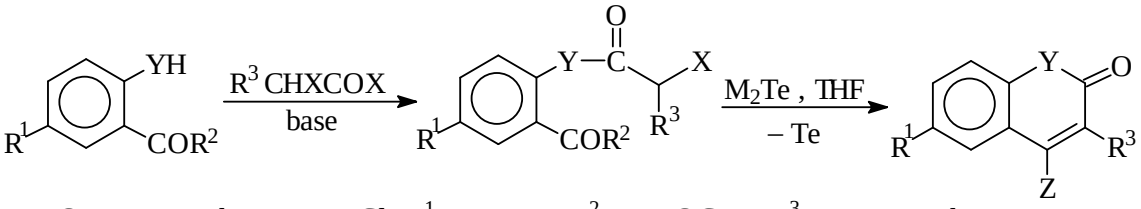
Unsubstituted coumarin was also synthesized by Pechmann reaction using phenol and malic acid[12] or from the reaction of resorcinol with ethyl acetoacetate in presence of concentrated sulfuric acid which follow the following mechanism[13].



Therefore coumarins can be synthesized by different methods as Claisen rearrangement, and Knoevenagel condensation, the following equation represents Knoevenagel condensation[14].



4-Hydroxy coumarin and 4-hydroxy quinolin-2-(1H)-ones can be prepared from α-halocarboxylic acid esters of salicyladehyde, methyl salicylate and methyl N-methyl or N-phenyl anthranilates with sodium or lithium telluride[15].



Y = O, NMe, NPh; X = Br, Cl, R^1 = H, Me; R^2 = H, OCH_3; R^3 = H, Me, Ph

Condensation of salicylaldehyde or its derivatives with various derivatives of ethyl acetate in presence of piperidine leads to the synthesis of coumarins by solvent free reaction under microwave irradiation[16].

EXPERIMENTAL

All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs. UV spectra were recorded on Shimadzu Double-Beam Spectrophotometer UV-210 A using ethanol as a solvent.

2-Hydroxy chalcone (1-3):

2-Hydroxy acetophenone (1.5 g, 0.01 mole) was dissolved in a mixture of 10% NaOH and ethanol (5 ml, 15 ml), substituted benzaldehyde (0.01 mole) was added with shaking, the mixture then stirred for 3 hours and left to stand overnight. The precipitate was filtered, washed with cold water and recrystallized from ethanol-water, Tables (1,2).

The esters (4-6):

The chalcone (1-3) (0.01 mole) and phenyl acetic acid (0.01 mole, 1.36 g) were dissolved in pyridine (30 ml) and $POCl_3$ (3 ml) was added dropwise to the solution with stirring. The mixture was kept for 1 hr and diluted with dilute HCl, the solid formed filtered, washed with water and dried to give the esters, Tables (1,2).

The coumarins (7-9):

The esters (4,5 or 6) (0.01 mole) was added to a solution of KOH in pyridine (1.5 g, 15 ml) and the mixture was kept for (2) hours, dilute HCl was then added. The resulting solid was filtered, washed with water and recrystallized from ethanol, Tables (1,2).

The salicylate (10-12):

Substituted methyl salicylate (0.05 mole) was dissolved in pyridine (20 ml), phenyl acetic acid (0.05 mole) was added to the solution followed by $POCl_3$ (3 ml) with stirring. The mixture was kept for (1 h)

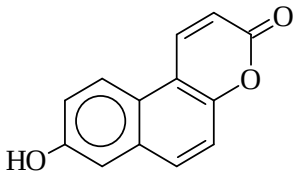
then acidified with dilute HCl with cooling. The solid was filtered, washed with water and crystallized from ethanol, Tables (1,2).

4-Hydroxy coumarins (13-15):

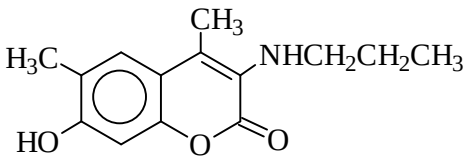
a mixture of ester (10-12) and KOH (1.5 g) in pyridine (15 ml) was kept for (2 h) at room temperature. The resulting white solid was filtered and washed with water and crystallized from ethanol, Table (1,2).

RESULTS AND DISCUSSION

Some of substituted coumarins (benzo-2-pyran) possess various biological activities, compound (III) show anticarcinogenic property[17,18], and compound (IV) acts as antifungal or pesticides agent[19].



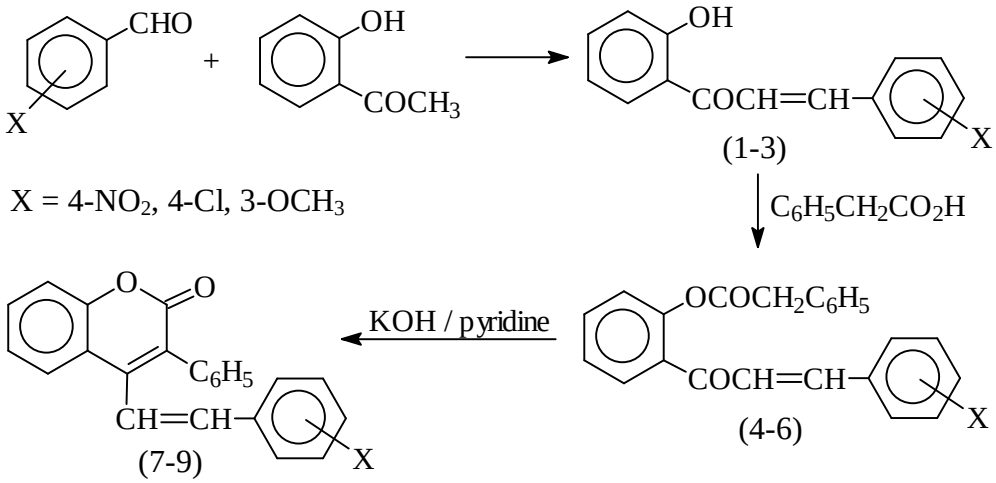
(III)



(IV)

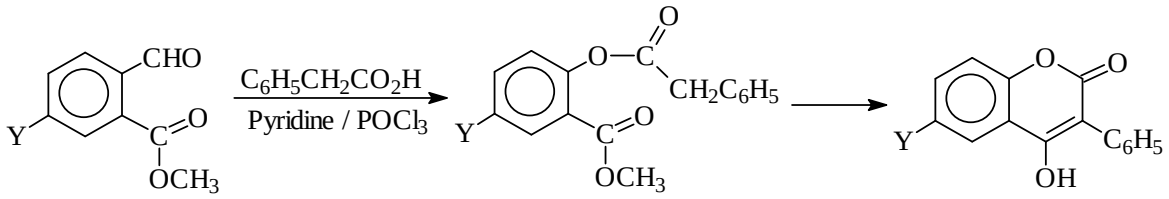
In the present work the synthesis of some substituted coumarins is reported. 2-Hydroxy acetophenone was treated with substituted benzaldehydes to give the corresponding chalcone (1-3). The chalcone (1) show absorption ν_{max} cm^{-1} at 3400 (O-H), 3030 (Ar-H) and 1690 (C=O), and U.V. spectra λ_{max} at 274 nm due to n-π^* transition.

The chalcone then treated with phenyl acetic acid in pyridine to give the esters (4-6). Compound (4) shows absorption at 3010 (Ar-H), 1685 (C=O), 1625 (C=C) and 1135 (C-O-C), the spectra show the disappearance of peak related to (O-H) of the chalcones. Esters (4-6) were cyclized in pyridine / potassium hydroxide to the (7-9) (Scheme 1), compound (7) show absorption at ν_{max} cm^{-1} 3015 (Ar-H), 1708 (C=O).



Scheme (1)

3-Phenyl-4-hydroxy coumarins (13-15), were synthesized from substituted methyl salicylate which was treated with phenyl acetic acid in pyridine and phosphorous oxychloride to give the esters (10-12), compound (10) show absorption at ν cm^{-1} at 3032 (Ar-H) and 1710 (C=O), the resultant compounds were cyclized to the final products (13-15) by their reaction with potassium hydroxide in pyridine, compound (13) show absorption ν cm^{-1} at 3300 (OH), 3020 (Ar-H), 1690 (C=O) and 1632 (C=C) (Scheme 2). Physical and spectral data listed in Tables (1,2).



Y = H, Me, OCH_3

(10-12) (13-15)

Scheme (2)

Table (1): Physical data for compounds (1-15)

Comp. No.	Molecular formula	m.p. °C	Yield %	Color
1	$C_{15}H_{11}NO_4$	109-112	73	Yellow
2	$C_{15}H_{11}O_2Cl$	81-83	81	Yellow
3	$C_{16}H_{14}O_3$	95-97	75	Pale yellow
4	$C_{23}H_{17}NO_5$	102-104	63	White
5	$C_{23}H_{17}ClO_3$	133-135	70	White
6	$C_{24}H_{20}O_4$	118-120	77	Pale yellow
7	$C_{23}H_{15}NO_4$	164-166	65	Yellow
8	$C_{23}H_{15}ClO_2$	173-175	80	White
9	$C_{24}H_{18}O_3$	185-187	85	White
10	$C_{16}H_{14}O_4$	58-60	75	White
11	$C_{17}H_{16}O_4$	66-68	66	White
12	$C_{17}H_{16}O_5$	70-73	68	White
13	$C_{15}H_{10}O_3$	224-226	40	White
14	$C_{16}H_{12}O_3$	180-182	48	White
15	$C_{16}H_{12}O_4$	165-167	54	Pale yellow

Table (2): Spectral data of compounds (1-15)

Comp. No.	IR ν cm^{-1} (KBr)					UV EtOH λ_{max}
	O-H	C-O-C	C=O	Ar-H	C=C aliphatic	
1	3400	-	1690	3030	1620	274
2	3320	-	1680	3028	1622	268
3	3350	-	1675	3034	1630	270
4	-	1135	1685	3010	1625	287
5	-	1083	1670	3022	1628	283
6	-	1120	1695	3028	1624	294
7	-	-	1708	3015	1620	270
8	-	-	1710	3014	1624	263
9	-	-	1713	3026	1627	275
10	-	1096	1710	3032	-	231
11	-	1170	1725	3013	-	235
12	-	1158	1718	3026	-	230
13	3300	-	1690	3020	1632	290
14	3280	-	1704	3030	1640	292
15	3350	-	1716	3036	1616	308

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