SYNTHESIS OF SOME α,β-UNSATURATED KETONES FROM 3-ACETYL-6-HYDROXY-4-METHYLCOUMARIN

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Abstract

By cyclization reaction of 2,5-dihydroxyacetophenone with ethyl acetoacetate to get 3-acetyl-6-hydroxy-4-methylcoumarin). The product was then transformed by condensation with aromatic aldehydes to form a series of new α,β-unsaturated ketones (6 compounds) and (4-arylvinyl-6-hydroxycoumarin-3-yl) arylvinyl ketones (4 compounds) and (6-hydroxy-4-methylcoumarin-3-yl) (2,3-dihydrobenzofur-2-yl) ketone. Structure of the obtained products was determined by IR, ^{1}H-NMR, and MS spectroscopic data.

1. INTRODUCTION

Coumarin and its derivatives have been found to exhibit antibiotic, antibacterial, antifungal, anticoagulating and plant regulating activities [1 - 5]. Many coumarin compounds, after some suitable structural modification can be used as drugs [6 - 9]. The α,β-unsaturated ketones and their derivatives are also medicinally important. Many α,β-unsaturated ketones derivatives have been reported to possess antimalarial, antibacterial, antifungal and anticancer properties [10 - 12].

In this paper, some new α,β-unsaturated ketones, 4-arylvinyl-6-hydroxycoumarin-3-yl) arylvinyl ketones and (6-hydroxy-4-methylcoumarin-3-yl) (2,3-dihydrobenzofur-2-yl) ketone synthesized from 3-acetyl-6-hydroxy-4-methylcoumarin are reported.

2. EXPERIMENTAL SECTION

Melting points of the synthesized compounds were measured by Stuart SMP3. IR spectra were recorded by Impact 410-Nicolet on KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded by Advance Spectrometer (Bruker, Germany) at 500 MHz, using DMSO-d_6 as solvent and TMS as an internal standard. LC-MS were recorded by LC-MS-ORBITRAP-XL and 5989B Hewlett – Packard Mass spectrometer.

Preparation of 3-acetyl-6-hydroxy-4-methylcoumarin **1**: 2,5-dihydroxyacetophenone (0.1 mole) was dissolved in ethyl acetoacetate (19.8 ml). Then 15.2 g sodium acetate was added to the reaction refluxed for 30 hr. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized by ethanol to give **1:** Yield 50%, mp: 225 - 227^{o}C; IR (cm^{-1}): 3209 (O-H), 1698 (C=O lactone), 1672 (C=O, ketone); ^{1}H-NMR: 2.46 (s, 3H, $COCH_3$), 2.31 (s, 3H, CH_3), 7.12 (dd, 1H, J = 8.5 and 2.5, 7-H), 7.14 (d, 1H, J = 2.5, 5-H), 7.29 (d, 1H, J = 8.5, 8-H), 9.82 (s,1H, OH). MS: m/z 218. Anal. Calcd for $C_{12}H_{10}O_4$.

General procedure for the preparation of **3a-f**, **5a-e** and **6a:** Compound **2a-f, 4a-e** and salycylaldehyde (0.01 mole) were dissolved in chloroform (30 ml). Then 3-acetyl-6-hydroxy-4-methylcoumarin **1** (0.01 mole) was added into solution. Then a few drops of piperidine were added into solution. The reaction was refluxed for 10-20 hr. Products were usually separated during boiling. Then they were filtered, dried and recrystallized by DMF to give **3a-f**, **5a-e** and **6a.**

3a: Yield 41%; mp 247-249^{o}C; IR(KBr, cm^{-1}): 3186 (O-H), 1702(C=O, lactone), 1666 (C=O, ketone), 994 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.04 (d, 1H, -COCH=, J = 16.5), 7.62 (d, 1H, ^{1}ArCH=), 2.28 (s, 3H, CH_3, coumar), 2.33 (s, 3H, CH_3, ^{1}Ar-CH_3), 9.83 (s,1H, OH), 7.12 (d, 1H, J = 2.5, H_{cou}), 7.15 (dd, 1H, J = 9.0 and 2.5, H_{cou}), 7.32 (d, 1H, J = 9.0, H_{cou}), 7.25 (d, 2H, J = 8.0, ^{1}Ar-H), 7.64 (d, 2H, J = 8.0, ^{1}Ar-H).

3b: Yield 46%; mp 216-218^{o}C; IR (KBr, cm^{-1}): 3483 (O-H), 1673 (C=O, lactone), 1655 (C=O, ketone), 975 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 6.79 (d, 1H, J = 16.0, -COCH=), 7.48 (d, 1H, J = 16.0, ^{1}ArCH=), 2.99 (s, 6H, $N(CH_3)_2$), 2.26 (s, 3H, CH_3, coumar), 9.78 (s, 1H, OH), 7.10 - 7.13 (m, 2H, $2H_{cou}$), 7.30 (d, 1H, J = 9.0, H_{cou}), 6.71 (d, 2H, J = 9.0, ^{1}Ar-H), 7.56 (d, 2H, J = 9.0, ^{1}Ar-H).

3c: Yield 46%; mp 240-218°C; IR (KBr, cm^{-1}): 3440 (O-H), 1708 (C=O, lactone), 1665 (C=O, ketone), 976 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.20 (d, 1H, J = 16.5, ^{1}ArCH=), 6.85 (d, 1H, J = 16.5, -COCH=), 2.43 (s, 3H, CH_3, coumar), 3.84 (s, 3H, OCH_3), 9.81 (s, 1H, OH_{cou},), 9.45(s, 1H, OH, 4-HO-^{1}Ar), 7.12(dd, 1H, J = 8.5 and 2.5, H_{cou}), 7.32(d, 1H, J = 9.0, H_{cou}), 7.05 (dd, 1H, J = 8.0 and 2.0, ^{1}Ar-H), 7.31 (s, 1H, ^{1}Ar-H), 7.28 (1H, d, J = 8.0, 1H, H_{cou}), 6.81 (d, 1H, J = 8.0, ^{1}Ar-H).

3d: Yield 49%; mp 255 - 257°C; IR (KBr, cm^{-1}): 3445 (O-H), 1674 (C=O, lactone), 1650 (C=O, ketone), 977 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.59(d, 1H, J = 16.5, ^{1}Ar-CH=), 6.99 (d, 1H, J = 16.5, -COCH=), 2.28 (s, 3H, CH_3, coumar), 3.79 (s, 3H, OCH_3), 7.11 (d, 1H, J = 3.0, H_{cou}), 7.17(dd, 1H, J = 9.0 and 3.0, H_{cou}), 7.32 (d, 1H, J = 9.0, H_{cou}), 6.99 (d, 2H, J = 9.0, ^{1}Ar-H), 6.99 (d, 2H, J = 9.0, ^{1}Ar-H), 9.81 (s, 1H, OH).

3e: Yield 38%; mp 291-293°C; IR (KBr, cm^{-1}): 3300 (O-H), 1689 (C=O, lactone), 978 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.79 (d, 1H, J = 16.5, ^{1}ArCH=), 6.90 (d, 1H, J = 16.5, -COCH=), 2.30 (s, 3H, CH_3, coumar), 3.82 (s, 3H, N-CH_3), 7.12 (d, 1H, J = 2.5, H_{cou}), 7.14 (q, 1H, J = 7.5 and 2.5, H_{cou}), 7.22 (t, 1H, J = 8.0 and 7.0, H_{Indol}), 7.28 - 7.33 (m, 2H, H_{cou}, H_{Indol}), 7.54 (d, 1H, J = 8.0, H_{Indol}), 7.96 (d, 1H, J = 7.5, H_{Indol}), 7.98 (s, 1H, H_{Indol}), 9.79(s, 1H, OH).

3g: Yield 40%; mp 249 - 251°C; IR (KBr, cm^{-1}): 3511 (O-H), 1689 (C=O, lactone), 1655 (C=O, ketone), 988 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.82 (d, 1H, J = 16.5, ^{1}ArCH=), 6.93 (d, 1H, J = 16.5, -COCH=), 2.30 (s, 3H, CH_3, coumar), 5.45 (s, 2H, CH_2), 7.11 - 7.32 (m, 10H, H_{cou}, H_{Indol}, C_6H_5), 7.57 (d, 1H, J = 8.0, H_{Indol}), 7.97 (d, 1H, H_{Indol}), 8.14(s, 1H, H_{Indol}), 9.80 (s, 1H).

5a: Yield 42%, mp 201-203°C; IR (KBr, cm^{-1}): 3220 (O-H), 1722 (C=O, lactone), 1669 (C=O, ketone), 973 ($\gamma_{CH=trans}$). ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.68 and 6.96 (d, 2H, J = 16.0, -COCH=CH-), 7.32 and 7.06 (d, 2H, J = 16.0, -CH=CH-), 9.81 (s, 1H, OH), 7.14 (dd, 1H, J = 9.0 and 3.0, H_{cou}), 7.27 (d, 1H, J= 2.5, H_{cou}), 7.31 - 7.72 (m, 11H, $H_{cou,}$ ^{2}Ar-H). LC-MS $(M+H)^+$ = 395, $(M + Na)^+$ = 417 Calcd for $C_{26}H_{18}O_4$ (M = 394).

5b: Yield 37%, mp 267-269°C; IR (KBr, cm^{-1}): 3430 (O-H), 1712 (C=O, lactone), 1649 (C=O, ketone), 978 ($\gamma_{CH=trans}$). ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.67 and 6.94 (d, 2H, J = 16.5, -COCH=CH-), 7.44 and 7.08 (d, 2H, J = 16.0, -CH=CH-), 7.15 (dd, 1H, J = 8.5 and 3.0, H_{cou}), 7.25 (d, 1H, J = 3.0, H_{cou}), 7.36 (d, 1H, J = 9.0, H_{cou}), 7.43 (d, 2H, J = 9.0, ^{1}Ar-H), 7.46 (d, 2H, J = 8.5, ^{2}Ar-H), 7.61 (d, 2H, J = 8.5, ^{2}Ar-H), 7.75 (d, 2H, J = 8.5, ^{2}Ar-H), 9.79 (s, 1H, OH).

5c: Yield 57%, mp 285-287°C; IR (KBr, cm^{-1}): 3344 (O-H), 1674 (C=O, lactone, ketone), 976 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.65 and 6.62 (d, 2H, J = 16, -COCH=CH-), 7.35 and 7.10 (d, 2H, J = 16, -CH=CH-), 7.15 (dd, 1H, J = 9.0 and 3.0, H_{cou}), 7.25 (d, 1H, J = 3.0, H_{cou}), 7.36 (d, 1H, J = 9.0, H_{cou}), 7.54 (d, 2H, J = 8.5, ^{2}Ar-H), 7.57 (d, 2H, J = 9.0, ^{2}Ar-H), 7.60 (d, 2H, J = 9.0, ^{2}Ar-H), 7.67 (d, 2H, J = 8.5, ^{2}Ar-H), 9.79 (s, 1H).

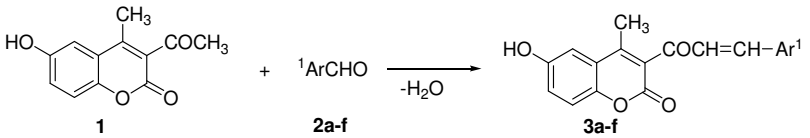
5d: Yield 45%, mp 248-250°C; ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.82 and 7.06 (d, 2H,J = 16.5, -COCH=CH-), 7.60 and 7.25 (d, 2H, J = 16.5, -CH=CH-), 7.17 (dd, 1H, J = 8.0 and 2.0, H_{cou}), 7.24 (d, 1H, J = 2.0, H_{cou}), 7.40 (d, 1H, J = 8.0, H_{cou}), 7.87 (d, 2H, J = 9.0, ^{2}Ar-H), 8.00 (d, 2H, J = 9.0, ^{2}Ar-H), 8.21 (d, 2H, J = 8.0, ^{2}Ar-H), 8.23 (d, 2H, J = 8.5, ^{2}Ar-H), 9.86 (s, 1H, OH).

5e: Yield 45%, mp 265-267°C; IR (KBr, cm^{-1}): 3272 (O-H), 1710 (C=O, lactone), 1656 (C=O ketone), 987 ($\gamma_{CH=trans}$); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 7.54 and 7.17 (d, 2H, J = 16.5, -COCH=CH-), 7.21 and 7.14 (d, 2H, J = 16.5, -CH=CH-), 6.08 (s, 2H, CH_2), 6.04 (s, 2H, CH_2), 7.39 - 6.86 (m, 9H, H_{cou}, ^{2}Ar-H), 9.76 (s, 1H, OH). LC-MS $(M+H)^+$ = 483, $(M + Na)^+$ = 505, Calcd for $C_{28}H_{18}O_8$ (M = 482).

6a: Yield 36%, mp 238-240°C; IR(KBr, cm^{-1}): 1703 (C=O, lactone), 1681 (ketone); ^{1}H-NMR (DMSO-d_6, δ, ppm, J: Hz): 3.10 (d, 1H, Ha, J = 18.5), 3.46 (dd, 1H, Hb, J = 18.5 and 5.5), 5.47(d, 1H, Hc, J = 5.5), 6.80 (d,1H, J = 8.0, Ar-H), 6.90 (q, 1H, J = 7.5 and 1.0, Ar-H), 7.01 (d, 1H, J = 2.5, H_{cou}), 7.05 (dd, 1H, J = 8.0 and 2.5, H_{cou}), 7.14 (m, 1H, Ar-H), 7.20 (d, 1H, J = 8.5, Ar-H), 7.22 (d, 1H, J = 8.0, H_{cou}), 9.80 (s, 1H, OH).

3. RESULTS AND DISCUSSION

Some *α,β*-unsaturated ketones **(3a-f)** were obtained by a reaction between 3-acetyl-6-hydroxy-4-methylcoumarin **1** and aromatic aldehydes **2a-f** in chloroform and a few drops of piperidine (scheme 1):

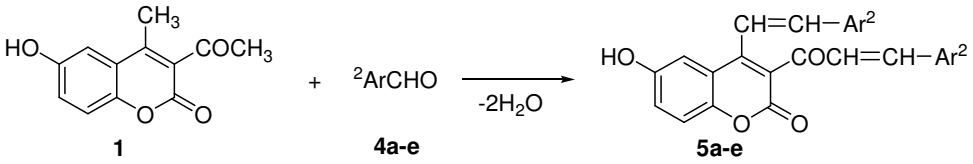


1 **2a-f** **3a-f**

^{1}Ar: 4-$H_3CC_6H_4$ (**3a**); 4-$N(CH_3)_2C_6H_4$ (**3b**)
4-HO-3 -$CH_3OC_6H_3$ (**3c**); 4-$CH_3OC_6H_4$ (**3d**)
N-Methylindol-3-yl (**3e**); N-bezylindol-3-yl (**3f**)

The IR spectra of compound **3a-f** show the characteristic band in the region of 1650 - 1666 cm^{-1}, 1673 - 1702 cm^{-1}, indicating that the presence of carbonyl ketone group and carbonyl lactone. The signals of υ_{OH} at 3186-3483 cm^{-1} and $\gamma_{CH=trans}$ at 975 - 994 cm^{-1}. In ^{1}H-NMR spectra of these compounds **3a-f**, the protons of *α,β*-unsaturated ketones compounds have given two doublets in the range 6.48-7.04 ppm for H_α and 6.79-7.82 ppm for H_β with coupling constant in the range of 16-16.5 Hz. This show that *α,β*-unsaturated ketones have *trans* configuration.

It is particularly interesting when condensation of 6-hydroxy-3-acetyl-4-methylcoumarin **1** with some aromatic aldehydes as *p*-chrlobenzaldehyde, *p*-brominebenzaldehyde, *p*-nitrobenzaldehyde **4a-e**… in the same reaction conditions as described above, some new *α,β*- unsaturated ketones were received in which the condensation occurs group C3-acetyl and C4-methyl of coumarin cycle (**5a-e,** Scheme 2):

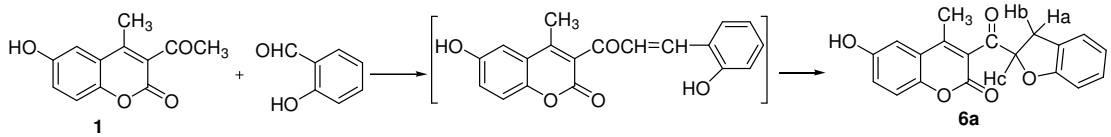


^{2}Ar: C_6H_5 (**5a**); 4-ClC_6H_4 (**5b**)
4-BrC_6H_4 (**5c**); 4-$O_2NC_6H_4$ (**5d**)
3,4-$O_2CH_2C_6H_3$ (**5e**)

Probably, acetyl group at position 3 (aspirate electron group) caused effects to the active 4-methyl group. Moreover, the quantum chemical calculations (by Hyperchem 7.0 software) showed that the charge density on carbon atoms of two methyl groups are also approximately one another (-0.266 on the carbon atom of the 3-acetyl group and -0.213 on carbon atom 4-methyl group). Therefore, the condensation occurred at these methyl groups can be entirely trusted. However, only in a few cases reaction of this type occur because the majority of *α,β*-unsaturated ketones formed and separated from the boiling reaction mixture.

The ^{1}H-NMR spectra of compounds **5a-e** show two pairs of doublet-doublet with roof effect at 6.62 - 7.82 ppm with coupling constant in the range of 16-16.5 Hz. This shows that two vinyl groups have *trans* configuration. LC - mass spectrum of **5a** and **5e** displayed the molecular ion peak $(M+H)^+$ at 395 and 483, in agreement with the molecular formula $C_{26}H_{18}O_4$ and $C_{28}H_{18}O_8$, respectively.

It is particularly exciting that when performing the condensation reaction of **1** with salicylaldehyde in the same reaction conditions above *α,β*-unsaturated ketone was not received. By spectral methods (6-hydroxy-4-methylcoumarin-3-yl) (2,3-dihydrobenzofur-2-yl) ketone **6a** was proposed as product of this reaction. Perhaps, in the first step product of reaction was *α,β*-unsaturated ketone and then it reformed internal ring molecules to give product **6a**:



The ^{1}H-NMR spectrum of **6a** showed two doublet at δ 5.47 ppm for Hc with J = 5.5 and at δ 3.10 ppm for Ha with J = 18.5, doublet doublet at δ 3.46 ppm for Hb with J = 5.5 Hz and 18.5 Hz.

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