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Base Catalyzed Dimerization of ω -Formyl-2-Hydroxyacetophenones

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Abstract: Refluxing ω -formyl-2-hydroxyacetophenones **1** in ethanol containing triethylamine as a basic catalyst produced the dimerized product identified as 2-(2-hydroxyaryl)-4H,5H-pyrano[2,3-*b*]chromen-5-ones **2**. Meanwhile, heating ω -formyl-2-hydroxyacetophenones **1** in 2 M aqueous sodium hydroxide solution afforded another type of dimeric product identified as 3-[2-(2-hydroxy-5-substituted benzoyl)vinyl]-6-substituted-4H-chromen-4-ones **3**. The proposed mechanisms were discussed. The mode of dimerization of ω -formyl-2-hydroxyacetophenones **1** depends on the type of catalyst used and the reaction conditions. Structures of the synthesized compounds were deduced on the basis of their analytical and spectral data.

Keywords: ω -formyl-2-hydroxyacetophenones, dimerization, chromone, spectral data, α , β -unsaturated ketones.

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INTRODUCTION

A large number of nitrogen heterocyclic rings of a broad spectrum of pharmaceutical activity were synthesized using 1,3-dicarbonyl compounds as precursors [1-6]. Typically, these nitrogen heterocyclic systems are synthesized through condensation of 1,3-dicarbonyl compounds with bifunctional nucleophiles under mild reaction conditions [7-9]. The research on the synthesis and reactions of β -keto-aldehydes is rare [10]. ω -Formyl-2-hydroxyacetophenones **1** represent one of the simplest β -keto-aldehyde and only few publications described its chemical reactivity under basic reaction conditions [10, 11]. In 1966, Kostka [12] reported that heating ω -formyl-2-hydroxyacetophenone (**1a**) with triethylamine (Et_3N) to 60 °C led to an unidentified product with a high melting point. In the present work, we aimed to try to explain and identify this unidentified product, via the elemental microanalysis and different spectroscopic techniques.

EXPERIMENTAL

General

Melting points of the synthesized compounds were measured on a digital Stuart SMP3 apparatus. Fourier Transform Infrared spectra were measured on Perkin-Elmer 293 spectrometer (cm^{-1}), using KBr disks. Mass spectrometry were obtained using GC-2010 Shimadzu Gas chromatograph-mass spectrometer (70 eV). ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO- d_6 as a solvent and TMS (δ) as the internal standard. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer. ω -Formyl-2-hydroxyacetophenones **1** were prepared according to the published method [13].

Dimerization of ω -formyl-2-hydroxyacetophenones **1a-c** using Et_3N

General procedure: ω -Formyl-2-hydroxyacetophenones **1a-c** (5 mmol) in absolute ethanol (10 mL) containing few drops of triethylamine (Et_3N) was heated under reflux for 15 min. The white crystals obtained during heating were filtered and recrystallized to give compounds **2a-c**.

2-(2-Hydroxyphenyl)-4H,5H-pyrano[2,3-b]chromen-6-one (**2a**)

Crystallized from DMF/EtOH as white crystals, mp > 300 °C (lit. mp > 300 °C) [14], yield (41%). FTIR (KBr, cm^{-1}): 3423 (br, OH), 3071 ($\text{CH}_{\text{arom.}}$), 2911 ($\text{CH}_{\text{aliph.}}$), 1632 ($\text{C}=\text{O}_{\gamma\text{-pyrone}}$), 1600 ($\text{C}=\text{C}$). ^1H -NMR (DMSO- d_6 , δ): 3.90 (d, 2H, J = 7.2 Hz, CH₂), 4.79 (t, 1H, J = 7.2 Hz, H-3), 6.95 (t, 1H, J = 8.1 Hz, Ar-H) 7.47–7.63 (m, 2H, Ar-H), 7.61 (t, 1H, Ar-H), 7.78 (t, 1H, Ar-H), 7.97–8.17 (m, 2H, Ar-H), 8.41 (d, 1H, H-6), 11.60 (brs, 1H, OH exchangeable with D_2O). MS (m/z, %): 293 (M+1, 6 %), 292 (M+, 20), 275 (8), 258 (19), 205 (14), 156 (12), 129 (17), 91 (24), 77 (100), 65 (32). Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{O}_4$ (292.29): C, 73.97; H, 4.14. Found: C, 73.72; H, 4.05.

2-(2-Hydroxy-5-methylphenyl)-7-methyl-4H,5H-pyrano[2,3-b]chromen-5-one (2b)

Crystallized from DMF as white crystals, mp > 300 °C, yield (40%), FTIR (KBr, cm⁻¹): 3419 (br, OH), 3052 (CH_{arom.}), 2940, 2884 (CH_{aliph.}), 1637 (C=O_{γ-pyrone}), 1602 (C=C). ¹H-NMR (DMSO-d₆, δ): 2.31 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 3.80 (d, 2H, CH₂), 4.20 (t, 1H, H-3), 7.53-7.85 (m, 5H, Ar-H), 7.95 (s, 1H, H-6), 11.56 (brs, 1H, OH exchangeable with D₂O). MS (m/z, %): 321 (M+1, 30 %), 320 (M+, 100), 292 (85), 276 (27), 260 (34), 134 (70), 108 (25), 92 (65), 77 (19), 65 (55). Anal. Calcd for C₂₀H₁₆O₄ (320.34): C, 74.99; H, 5.03. Found: C, 74.60; H, 5.00.

7-Bromo-2-(5-bromo-2-hydroxyphenyl)-4H,5H-pyrano[2,3-b]chromen-5-one (2c)

Crystallized from DMF as white crystals, mp > 300 °C, yield (39%), FTIR (KBr, cm⁻¹): 3420 (br, OH), 3039 (CH_{arom.}), 2916 (CH_{aliph.}), 1635 (C=O_{γ-pyrone}), 1599 (C=C). ¹H-NMR (DMSO-d₆, δ): 3.86 (d, 2H, CH₂), 4.30 (t, 1H, H-3), 7.51-7.78 (m, 5H, Ar-H), 7.91 (s, 1H, H-6), 11.96 (brs, 1H, OH exchangeable with D₂O). MS (m/z, %): 452 (M+4, 35 %), 450 (M+2, 72 %), 448 (M+, 34 %), 424 (49 %), 422 (100 %), 420 (47 %), 412 (12 %), 410 (25), 408 (11), 201 (14), 199 (14), 185 (35), 183 (34), 173 (50), 171 (49), 158 (11), 156 (11), 77 (31), 65 (19). Anal. Calcd for C₁₈H₁₀Br₂O₄ (450.08): C, 48.03; H, 2.24. Found: C, 47.90; H, 2.20.

Dimerization of ω-formyl-2-hydroxyacetophenones 1b,c using 2 M aqueous NaOH solution

General procedure: ω-Formyl-2-hydroxyacetophenones **1b,c** (5 mmol) in 2 M aqueous sodium hydroxide solution (10 mL) was stirred at 60 °C for 2h. After cooling, the reaction mixture was neutralized with conc. HCl. The solid so formed was filtered and recrystallized to give compounds **3a,b**.

3-[2-(2-Hydroxy-5-methylbenzoyl)vinyl]-6-methyl-4H-chromen-4-one (3a)

Crystallized from AcOH as yellow crystals, mp, 196 °C, yield (42%). FTIR (KBr, cm⁻¹): 3390 (br, OH), 3071 (CH_{aromatic}), 2930, 2892 (CH_{aliph.}), 1645 (C=O_{γ-pyrone}), 1630 (C=O_{ketones}), 1604 (C=C). ¹H-NMR (DMSO-d₆, δ): 2.30 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 6.91 (d, 1H, J = 8.1 Hz, H-3'), 7.32 (d, 1H, J = 8.1 Hz, H-4'), 7.43 (d, 1H, J = 8.4 Hz, H-8), 7.56 (d, 1H, J = 8.4 Hz, H-7), 7.60 (d, 1H, J = 15.3, α-H_{olefinic}), 7.80 (s, 1H, H-6'), 7.92 (s, 1H, H-8), 8.12 (d, 1H, J = 15.3, β-H_{olefinic}), 8.50 (s, 1H, H-2), 12.40 (br, 1H, OH exchangeable with D₂O). ¹³C-NMR (DMSO-d₆, δ): 20.2, 22.6, 116.3, 117.2, 119.5, 122.0, 123.4, 129.1, 130.7, 131.5, 134.8, 135.1, 136.3, 143.3, 148.2, 151.2, 157.5, 176.0, 188.4. MS (m/z, %): 320 (M+, 18), 292 (61), 276 (53), 214 (30), 185 (45), 160 (14), 135 (100), 108 (33), 92 (65), 77 (40), 65 (23). Anal. Calcd for C₂₀H₁₆O₄ (320.34): C, 74.99; H, 5.03. Found: C, 74.70; H, 4.80.

3-[2-(2-Hydroxy-5-bromobenzoyl)vinyl]-6-bromo-4H-chromen-4-one (3b)

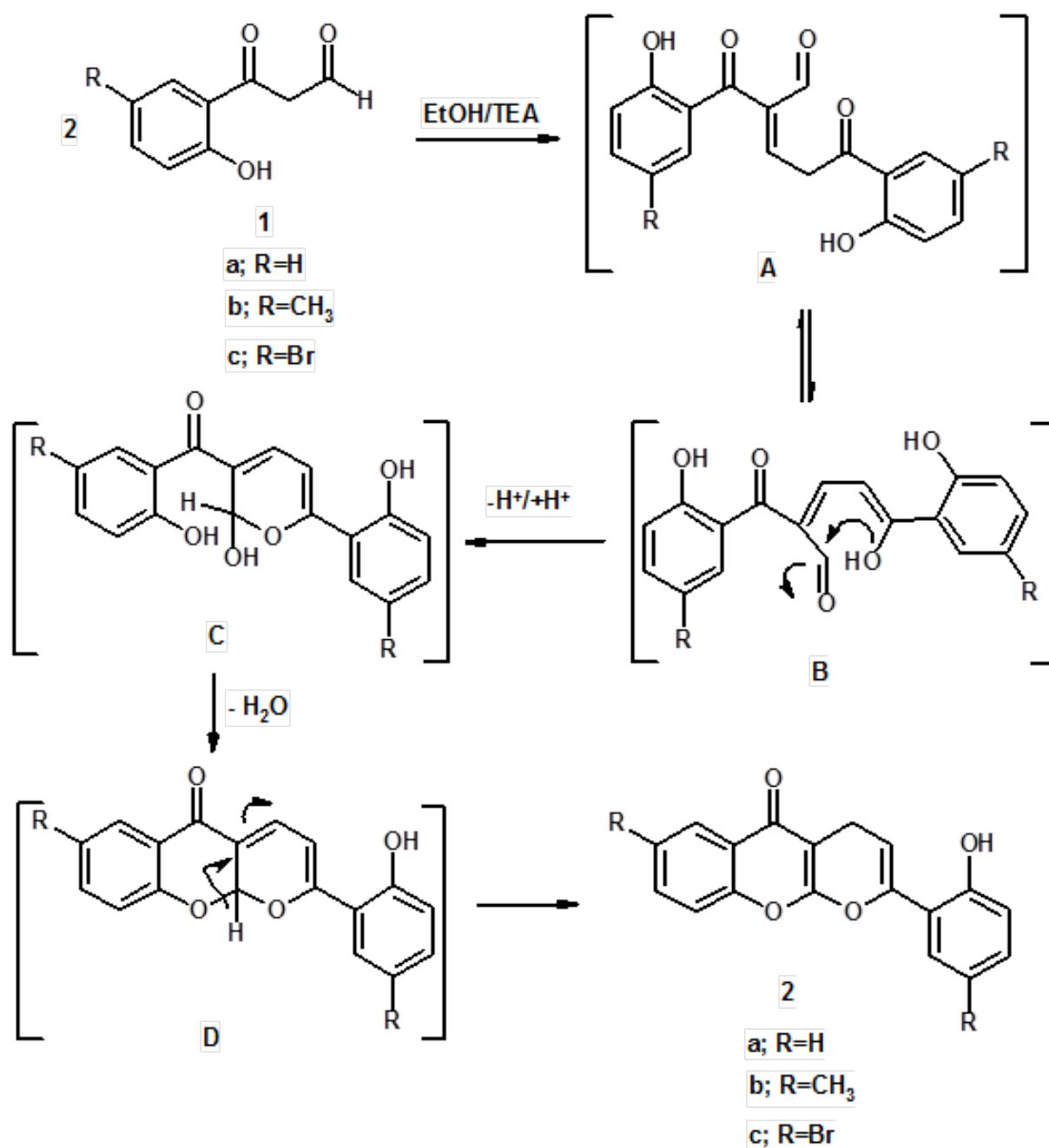
Crystallized from DMF/MeOH as dark yellow crystals, mp, 290-291 °C, yield (45%), FTIR (KBr, cm^{-1}): 3402 (br, OH), 3040 ($\text{CH}_{\text{aromatic}}$), 2932, 2879 ($\text{CH}_{\text{aliph.}}$), 1649 ($\text{C}=\text{O}_{\text{v-pyrone}}$), 1633 ($\text{C}=\text{O}_{\text{ketones}}$), 1601 ($\text{C}=\text{C}$). $^1\text{H-NMR}$ (DMSO-d_6 , δ): 7.02 (d, 1H, $J = 6.7$ Hz, H-3'), 7.40 (d, 1H, $J = 6.7$ Hz, H-4'), 7.62 (d, 1H, $J = 8.1$ Hz, H-8), 7.70 (d, 1H, $J = 8.1$ Hz, H-7), 7.79 (d, 1H, $J = 14.4$, $\alpha\text{-H}_{\text{olefinic}}$), 7.87 (s, 1H, H-6'), 7.99 (s, 1H, H-8), 8.18 (d, 1H, $J = 14.4$, $\beta\text{-H}_{\text{olefinic}}$), 8.56 (s, 1H, H-2), 12.55 (br, 1H, OH exchangeable with D_2O). Anal. Calcd for $\text{C}_{18}\text{H}_{10}\text{Br}_2\text{O}_4$ (450.08): C, 48.03; H, 2.24. Found: C, 47.75; H, 2.12.

RESULTS AND DISCUSSION

The present work aimed to study the chemical reactivity of a variety of substituted ω -formyl-2-hydroxyacetophenone upon refluxing in absolute ethanol containing few drops of triethylamine (Et_3N) as a basic catalyst. Previously Kostka [12] found that, heating ω -formyl-2-hydroxyacetophenone (**1a**) with triethylamine (Et_3N) to 60 °C led to an unidentified product having a high melting point, but he was not able to identify the isolated product. Herein, we repeat this reaction under the same conditions and we succeeded to identify the isolated product using the different spectroscopic techniques.

The basic condition of the previous reaction may involve dimerization process and the reaction may proceed via deprotonation of the active methylene group, by Et_3N , followed by condensation with the formyl group of another molecule leading to intermediate A (self-condensation) which tautomerized to the enolic form (intermediate B) followed by cycloaddition of the hydroxyl group onto the carbonyl function (intermediate C) with concomitant intramolecular dehydration producing intermediate D. The latter intermediate underwent proton transfer to afford the final dimeric product, 2-(2-hydroxyphenyl)-4H,5H-pyrano[2,3-b]chromen-5-one (**2a**) (Scheme 1). The mass spectrum of compound **2a** showed the molecular ion peak at m/z 292 which is consistent with its molecular formula and supports the proposed structure. Its ^1H NMR spectrum revealed distinctive doublet and triplet signals at δ 3.90 and 4.79 attributable to CH_2 and H-3 protons, respectively, while the phenolic OH proton appeared at δ 11.60 as a broad D_2O -exchangeable signal. Also, the ^{13}C NMR spectrum exhibited three characteristic signals at δ 28.9, 94.0 and 175.8 assignable to CH_2 , C-3 and C=O, respectively.

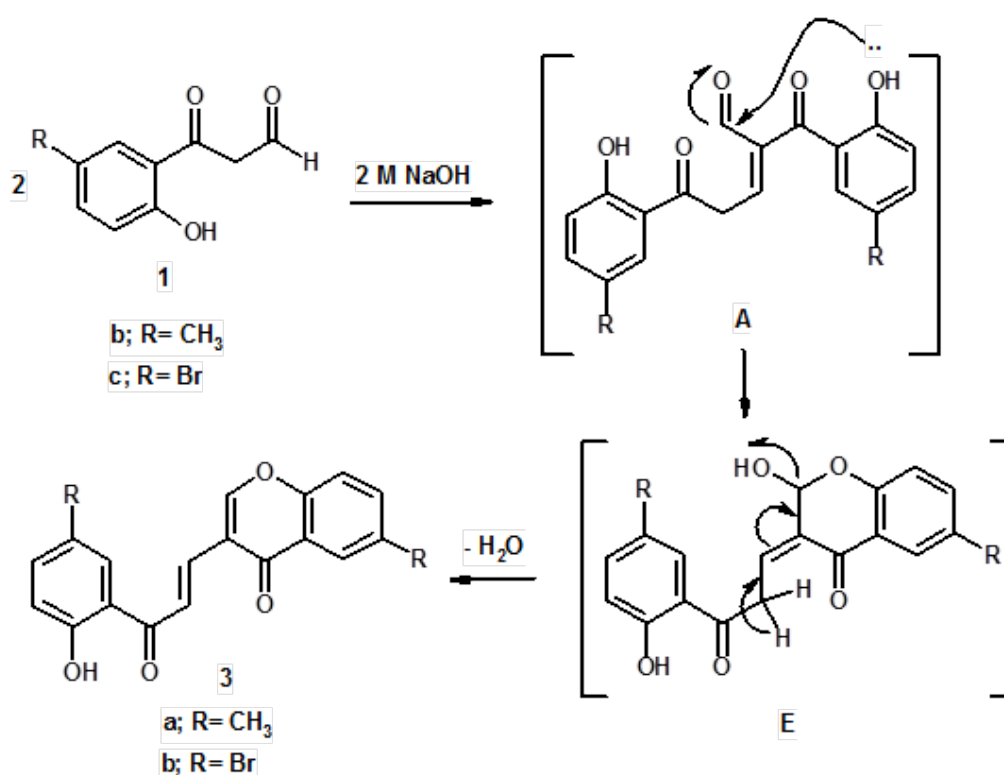
In the same manner, boiling ω -formyl-2-hydroxy-5-methylacetophenone (**1b**) and ω -formyl-5-bromo-2-hydroxyacetophenone (**1c**) in ethanol containing few drops of Et_3N yielded pyrano[2,3-b]chromene derivatives **2b** and **2c**, respectively, via the suggested mechanism depicted in Scheme 1. The ^1H NMR spectra of compounds **2b** and **2c** showed distinctive doublet and triplet signals attributed to CH_2 and H-3 protons, respectively. In addition, their mass spectrum revealed their molecular ion peaks which agree well with the proposed structures.



Scheme 1. The suggested mechanism for the dimerization of ω -formyl-2-hydroxyacetophenones **1a-c**, in the presence of TEA.

On the other hand, treatment of compounds **1b,c** with 2 M aqueous NaOH solution under stirring at 60 °C gave another type of dimeric products; 3-[2-(2-hydroxy-5-methylbenzoyl)vinyl]-6-methyl-4H-chromen-4-one (**3a**) and 3-[2-(5-bromo-2-hydroxybenzoyl)vinyl]-6-bromo-4H-chromen-4-one (**3b**), respectively (Scheme 2). The ¹H NMR spectra of compounds **3a,b** showed characteristic two doublets (at δ 7.60 and 8.12 for compound **3a** and δ 7.79 and 8.18 for compound **3b**) with high coupling constant indicating the presence of two hydrogen atoms in E-configuration around the olefinic bond. In addition, the spectra also revealed characteristic downfield singlet attributed to H-2_{chromone} at δ 8.50 and 8.56 for compounds **3a,b**, respectively.

Formation of chromone derivatives **3a,b** may occur via self-condensation of ω -formyl-2-hydroxyacetophenones **1b,c** leading to intermediate A which underwent cyclization reaction producing intermediate E followed by dehydration to yield the final products (Scheme 2).



Scheme 2. The suggested mechanism for the dimerization of ω -formyl-2-hydroxyacetophenones **1b,c** in the presence of 2 M NaOH.

The proposed mechanisms depicted in Schemes 1 and 2 indicate that, the mode of dimerization of ω -formyl-2-hydroxyacetophenones **1** depend on the type of catalyst used and the reaction conditions.

CONCLUSION

In conclusion, the present work studied the effect of triethylamine and sodium hydroxide on the active substrate ω -formyl-2-hydroxyacetophenones **1**. The dimerization process of ω -formyl-2-hydroxyacetophenones **1** depends on the basic catalyst used and the reaction conditions. Et₃N mediated self-dimerization of ω -formyl-2-hydroxyacetophenones **1** producing 2-(2-aryl)-4H,5H-pyrano[2,3-b]chromen-5-ones **2**, while NaOH mediated self-dimerization of ω -formyl-2-hydroxyacetophenones **1** affording 3-[2-(2-hydroxy-5-substituted benzoyl)vinyl]-6-substituted-4H-chromen-4-ones **3**.

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ω -FORMİL-2-HİDROKSİASETOFENONLARIN BAZ KATALİZLİ DİMERLEŞMESİ

Magdy Ahmed Ibrahim and Salah Sayed Ibrahim

Öz: ω -formil-2-hidroksiasetofenon bileşikleri (**1**) bazik katalizör olarak trietilamin içerecek şekilde etanolde reflüks edildiğinde 2-(2-hidroksiaril)-4H-5H-pirano[2,3-*b*]kromen-5-on bileşiklerini (**2**) vermektedir. Bu arada, ω -formil-2-hidroksiasetofenon bileşiklerini (**1**) 2 M sulu sodyum hidroksit çözeltisinde ısıtmakla 3-[2-(2-hidroksi-5-süstitüe benzoil)vinil]6-süstitüe-4H-kromen-4-on bileşikleri (**3**) ele geçmektedir. Önerilen mekanizmalar tartışılmıştır. ω -formil-2-hidroksiasetofenon (**1**) bileşiklerinin dimerleşme biçimi kullanılan katalizöre ve tepkime koşullarına bağlıdır. Sentezlenmiş bileşiklerin yapıları analitik ve spektral verilere dayanarak sonuca bağlanmıştır.

Anahtar kelimeler: ω -Formil-2-hidroksiasetofenonlar, dimerleşme, kromon, spektral veriler, α , β -doymamış ketonlar.

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