Research Article

Triphenylphosphine Mediated Synthesis of Functionalized Benzo-Fused Coumarins from Some OH Acids and Dialkyl Acetylene Dicarboxylate

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Benzo-fused coumarins are prepared from 4-quinolinol by treatment with PPh_3 and dialkyl acetylenedicarboxylate. Angular coumarins are prepared from 3-isoquinolinol and 7-hydroxyl coumarine with PPh_3 and dialkyl acetylenedicarboxylate.

1. Introduction

Coumarins comprise a very large class of compounds found throughout the plant kingdom [1]. The bioactivity of coumarin and more complex related derivatives appears to be based on the coumarin nucleus [2, 3]. Coumarin compounds can display anticancer, anticoagulant, antimicrobial, anti-inflammatory, and antioxidant activities [4–8].

In addition, as an important class of organic heterocyclic dyes, coumarin derivatives exhibit unique photochemical and photophysical properties, which render them useful in a variety of applications such as optical brighteners, laser dyes, nonlinear optical chromophores, solar energy collectors, fluorescent labels and probes in biology and medicine, and two-photon absorption (TPA) materials [9–12].

Coumarins have been synthesized by several methods [13–18]. In the interest of synthesizing new coumarin ring systems for possible evaluation as biologically active compounds, we have described a synthesis of carboxymethyl coumarins from 3-hydroxyl pyridine [19], carboxylic systems [19–22], we wish to report here the synthesis of some benzo-fused coumarins. The preparations of coumarins are depicted in Schemes 1, 2, and 3.

2. Experimental

2.1. General. Compounds **1**, **2** and Ph_3P were obtained from Fluka and were used without further purification. M. p. Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^1H - and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in CDCl_3 at 300 and 75 MHz, respectively; δ in ppm. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z . Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

2.2. General Procedure for the Preparation of Compound 3. To a stirred solution of 0.52 g of Ph_3P (2 mmol) and 0.28 g **1** (2 mmol) in toluene (10 mL) was added dropwise a mixture of **2** (2 mmol) in toluene (2 mL) at room temperature over 5 min. The reaction mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography (SiO_2 ; hexane/AcOEt) to afford the pure adducts.

Methyl 2-Oxo-2H-pyrano[3,2-c]quinoline-4-carboxylate (4a). Yellow powder, 0.46 g (90%); mp 119–121°C; IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1744 (C=O), 1625 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 4.08 (s, 3H, Me), 7.09 (s, 1H, CH), 7.70

SCHEME 1: Typical procedure for compound 4.

SCHEME 2: Procedure for synthesis of compound 6.

(t, 1H, $J = 6.5$ Hz, CH) 7.88 (t, 1H, $J = 7.0$, CH), 8.15 (d, 1H, $J = 8.4$ Hz, CH), 8.45 (d, 1H, $J = 7.9$ Hz, CH), 9.71 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): δ 53.6 (Me), 107.9 (CH), 117.7 (CH), 119.6 (CH), 127.6 (CH), 129.3 (C), 132.4 (CH), 141.7 (CH), 147.7 (C), 147.8 (C), 148.9 (C), 157.4 (C), 158.6 (C=O), 163.5 (C=O). MS (EI) m/z : 255 (M^+ , 98%), 227 (57), 196 (84), 140 (43). Anal. calcd for $\text{C}_{14}\text{H}_9\text{NO}_4$: C, 65.88; H, 3.55; N, 5.49; Found: C, 65.87; H, 3.57; N, 5.47.

Ethyl 2-Oxo-2H-pyrano[3,2-*c*]quinoline-4-carboxylate (4b). Yellow powder, 0.41 g (77%); mp 128–130°C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1740 (C=O), 1634 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 1.47 (t, 3H, $J = 7.1$ Hz, Me), 4.54 (q, 2H, $J = 7.1$ Hz, OCH_2), 7.09 (s, 1H, CH), 7.81 (t, 1H, $J = 7.3$ Hz, CH), 7.96 (t, 1H, $J = 6.9$, CH), 8.14 (d, 1H, $J = 8.4$ Hz, CH), 8.43 (d, 1H, $J = 8.3$ Hz, CH), 9.64 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): δ 14.3 (Me), 63.5 (OCH_2), 107.9 (CH), 117.7 (CH), 120.1 (CH), 127.6 (CH), 129.3 (C), 132.4 (CH), 141.7 (CH), 147.7 (C), 147.8 (C), 148.9 (C), 157.4 (C), 158.6 (C=O), 163.5 (C=O). MS (EI) m/z : 255 (M^+ , 98%), 196 (72), 196 (69), 154 (100). Anal. calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_4$: C, 66.91; H, 4.12; N, 5.20; Found: C, 66.94; H, 4.11; N, 5.19.

Tert-butyl 2-Oxo-2H-pyrano[3,2-*c*]quinoline-4-carboxylate (4c). Yellow powder, 0.43 g (72%); mp 130–132°C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1723 (C=O), 1628 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 1.70 (s, 9H, 3Me), 7.02 (s, 1H, CH), 7.80 (t, 1H, $J = 6.9$ Hz, CH), 7.95 (t, 1H, $J = 6.9$, CH), 8.13 (d, 1H, $J = 8.4$ Hz, CH), 8.42 (d, 1H, $J = 8.3$ Hz, CH), 9.60 (s, 1H,

CH). ^{13}C NMR (75 MHz, CDCl_3): δ 28.1 (3Me), 85.3 (C), 107.9 (CH), 118.5 (CH), 119.5 (CH), 128.6 (CH), 130.3 (C), 132.8 (CH), 141.7 (CH), 147.7 (C), 148.8 (C), 149.8 (C), 157.4 (C), 159.3 (C=O), 163.4 (C=O). MS (EI) m/z : 255 (M^+ , 98%), 269 (86), 196 (48), 57 (100). Anal. calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_4$: C, 68.68; H, 5.09; N, 4.71; Found: 68.70; H, 5.08; N, 4.69.

Methyl 3-Oxo-3H-pyrano[2,3-*c*]isoquinoline-1-carboxylate (6a). Yellow powder, 0.69 g (76%); mp 105–107°C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1733 (C=O), 1651 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 4.04 (s, 3H, Me), 6.88 (s, 1H, CH), 7.55 (t, 1H, $J = 7.7$ Hz, CH), 7.67 (t, 1H, $J = 8.2$ Hz, CH), 7.70 (d, 1H, $J = 8.1$ Hz, CH), 7.89 (d, 1H, $J = 8.1$ Hz, CH), 9.24 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): δ 53.8 (Me), 110.3 (C), 122.4 (CH), 123.0 (CH), 124.7 (CH), 126.3 (CH), 127.1 (CH), 128.5 (C), 132.9 (C), 140.2 (CH), 143.6 (C), 158.1 (C), 164.0 (C=O), 166.4 (C=O). MS (EI) m/z : 255 (M^+ , 10%), 288 (100), 204 (43), 189 (72), 61 (100). Anal. calcd for $\text{C}_{14}\text{H}_9\text{NO}_4$: C, 65.88; H, 3.55; N, 5.49; Found: C, 65.84; H, 3.56; N, 5.47.

Ethyl 3-Oxo-3H-pyrano[2,3-*c*]isoquinoline-1-carboxylate (6b). Yellow powder, 0.38 g (71%); mp 110–112°C. IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 1739 (C=O), 1636 (C=N); ^1H NMR (300 MHz, CDCl_3): δ 1.43 (t, 3H, $J = 7.1$ Hz, Me), 4.35 (q, 2H, $J = 7.1$ Hz, OCH_2), 6.92 (s, 1H, CH), 7.47 (t, 1H, $J = 7.3$ Hz, CH), 7.50 (t, 1H, $J = 8.0$ Hz, CH), 7.66 (d, 1H, $J = 8.2$ Hz, CH), 7.70 (d, 1H, $J = 8.5$ Hz, CH). ^{13}C NMR (75 MHz, CDCl_3): δ 14.0 (Me), 61.9 (OCH_2), 110.9 (C), 122.6 (CH), 123.5 (CH), 125.1 (CH), 126.1 (CH), 127.7 (CH), 128.7 (C), 133.1 (C), 140.1 (CH),

SCHEME 3: Procedure for synthesis of compounds **8**, **9**.

143.6 (C), 157.9 (C), 164.6 (C=O), 166.0 (C=O). MS (EI) m/z : 296 (M^+ , 10%), 277 (100), 201 (43), 183 (52), 77 (68). Anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20; Found: C, 66.94; H, 4.10; N, 5.21.

Methyl 2,8-Dioxo-2H,8H-pyrano[3,2-*g*]chromene-4-carboxylate. Yellow powder, 0.50 g (90%); mp 135–137°C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1739 (C=O); ^1H NMR (300 MHz, CDCl_3): δ 4.12 (s, 3H, Me), 6.43 (d, 1H, J = 9.6 Hz, CH), 6.50 (s, 1H, CH), 7.28 (d, 1H, J = 8.7 Hz, CH), 7.66 (d, 1H, J = 8.7 Hz, CH), 7.72 (d, 1H, J = 9.6 Hz, CH). ^{13}C NMR (CDCl_3) δ/ppm 53.8, (OMe), 105.4 (C), 113.8 (CH), 114.9 (C), 115.2 (CH), 115.8 (CH), 131.3 (CH), 142.9 (CH), 143.3 (C), 156.1 (C), 157.9 (C), 158.3 (C=O), 165.4 (C=O), 167.6 (C=O); MS (EI) m/z : 272 (M^+ , 30%), 258 (100), 231 (46), 146 (100). Anal. calcd for $C_{14}H_8O_6$: C, 61.77; H, 2.96; Found: C 55.96, H 3.09, N 4.88.

Ethyl 2,8-Dioxo-2H,8H-pyrano[3,2-*g*]chromene-4-carboxylate. Yellow powder, 0.38 g (67%); mp 139–141°C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1728 (C=O); ^1H NMR (300 MHz, CDCl_3): δ 1.43 (t, 3H, J = 7.1 Hz, Me), 4.35 (q, 2H, J = 7.1 Hz, OCH_2), 6.72 (d, 1H, J = 9.6 Hz, CH), 6.95 (s, 1H, CH), 7.33 (s, 1H, CH), 7.60 (d, 1H, J = 9.6 Hz, CH), 8.55 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): δ 14.0 (Me), 59.4 (OCH_2), 105.0 (C), 111.5 (CH), 111.8 (C), 113.4 (CH), 115.0 (CH), 131.7 (CH), 142.2 (CH), 143.7 (C), 155.8 (C), 157.4 (C), 161.3 (C=O), 165.9 (C=O), 167.5 (C=O); MS (EI) m/z : 314 (M^+ , 41%), 258 (53), 231 (65), 170 (24). Anal. calcd for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52; Found: C, 62.97; H, 3.48.

Tert-butyl 2,8-Dioxo-2H,8H-pyrano[3,2-*f*]chromene-10-carboxylate. Yellow powder, 0.55 g (87%); mp 150–152°C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 1747 (C=O); ^1H NMR (300 MHz, CDCl_3): δ 1.65 (s, 9H, 3Me), 6.47 (d, 1H, J = 9.6 Hz, CH), 6.96 (s, 1H, CH), 7.30 (s, 1H, CH), 7.78 (d, 1H, J = 9.6 Hz, CH), 8.62 (s, 1H, CH). ^{13}C NMR (75 MHz, CDCl_3): δ 29.3 (3Me), 84.8 (C), 105.2 (C), 113.7 (CH), 116.6 (C), 119.1 (CH), 127.3 (CH), 132.3 (CH), 142.2 (CH), 142.9 (C), 155.9 (C), 156.1 (C), 159.4 (C=O), 162.5 (C=O), 167.6 (C=O). MS (EI) m/z : 314 (M^+ , 41%), 277 (25), 258 (64), 231 (33), 57 (100). Anal. calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49; Found: C, 64.95; H, 4.48.

3. Result and Discussion

Treatment of 4-hydroxyquinoline **1** with dialkyl acetylene dicarboxylate **2** and PPh_3 in toluene under reflux afforded dimethyl 2-(4-hydroxy-2-methyl-3-quinolinyl)-2-butenedioate (**3**) [22]. When compound **3** was heated at 200–205°C it transformed to methyl 2-oxo-2H-pyrano[3,2-*c*]quinoline-4-carboxylate **4** in good yield. The analytical and spectral data of the product agree with the structure **4** suggested. The products were separated by column chromatography and identified as **4** based on their elemental analyses and their IR, ^1H , and ^{13}C NMR spectral data. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. Its ^1H NMR spectrum showed 3H singlet at δ = 4.08 for only one methoxy group and a singlet (1H) at δ = 7.09 for methine proton. The ^{13}C NMR spectrum one carbon appeared for the coumarin carbonyl (δ = 158.6 ppm) and one carbon for the carbonyl ester moiety (δ = 163.5 ppm). The ^1H and ^{13}C NMR spectra of **4b** and **4c** are similar to those of **4a** except for the alkoxy moieties, which exhibited characteristic resonances with appropriate chemical shifts.

Treatment of 3-isoquinolinol **5** with dialkyl acetylene dicarboxylate **2** and PPh_3 in refluxing toluene for 24 h and separation of the reaction mixture by column chromatography gave methyl 3-oxo-3H-pyrano[2,3-*c*]isoquinoline-1-carboxylate **6** in 76% yield (Scheme 3), obviously via a reaction sequence similar to that depicted in Scheme 1. The reaction with di-*tert*-butyl acetylene dicarboxylate was not detected because of the bulky group (Scheme 2).

Next, we studied the reaction of 7-hydroxy coumarine **7** with dialkyl acetylene dicarboxylate and PPh_3 in refluxing toluene, which resulted in the formation of the methyl 2,8-dioxo-2H,8H-pyrano[3,2-*g*]chromene-4-carboxylate **8** (Scheme 3). The linear product **9** was detected and isolated from the reaction with di-*tert*-butyl acetylene dicarboxylate because of the bulky group.

Mechanistically [13, 19] it is conceivable that the reaction involves the initial formation of a zwitterionic intermediate between Ph_3P and the acetylenic compound and subsequent protonation of reactive 1:1 adduct followed by electrophilic attack of vinyltriphenylphosphonium cation on the aromatic

SCHEME 4

ring at the ortho position relative to the strong activation group. The product is presumably produced by intramolecular lactonization of the unsaturated diester **10** (Scheme 4).

4. Conclusion

From the above results, we conclude that treatment of oxygen atom of the pyran ring belongs to the starting phenol, while the periselectivity in the construction of this new ring depends on the higher reactivity of the free o-positions of the phenol during the aromatic electrophilic substitution sequence. These functionalised coumarins may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The advantages of present method are the fact that it performed under neutral condition and substances are utilized in their basic form without any modification. The simplicity of the present procedure makes it an interesting alternative to other approaches.

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