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New Entry to 9-Acetyl/Formyl-Substituted 2*H*,8*H*-Pyrano[2,3-*f*]Chromen-2-ones through Baylis–Hillman Reaction

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Abstract: A new facile route to 9-acetyl/formyl-substituted 2*H*,8*H*-pyrano[2,3-*f*]chromen-2-ones is described. The Baylis–Hillman reaction involving the condensation of methyl vinyl ketone/acrolein with 7-hydroxy-2-oxo-2*H*-chromen-8-carbaldehydes in the presence of diazabicyclo[2.2.2]octane (DABCO) under N_2 atmosphere at room temperature furnished the desired compounds in good yields.

Keywords: Acrolein; DABCO; Methyl vinyl ketone

INTRODUCTION

Naturally occurring 2*H*-chromen-2-ones have several biomedical applications such as platelet aggregation, enzyme inhibition, cytotoxic activity, and antiviral, antibacterial, antifungal activities.[1–10] Dicoumarol,[11] which has anticoagulant activity, antibiotics novobiocin and chlorobiocin,[12,13] and Calonides A and B,[14] which inhibit HIV-1 replication in vitro, represent some of the bioactive substituted 2*H*-chromen-2-ones.

In view of this diverse bioactivity, we have planned the synthesis of new 2*H*-chromen-2-ones with a pyran ring fused at the 7,8-position employing the Baylis–Hillman protocol.

The Baylis–Hillman reaction[15–17] is an efficient carbon–carbon bond-forming reaction and provides convenient access to several benzannulated

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heterocyclic molecules. Various 2*H*-1-chromenes were prepared[18–20] by Key and coworkers using Baylis–Hillman adducts, obtained from the reaction of salicylaldehyde with activated alkenes.

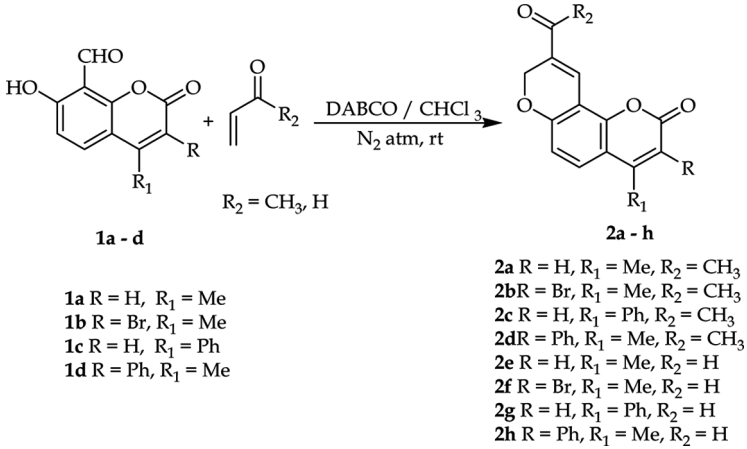
In our present study, we have chosen 7-hydroxy-2-oxo-2*H*-chromen-8-carboxaldehydes (**1a–d**) as starting compounds to access the desired new 2*H*,8*H*-pyrano[2,3-*f*]chromen-2-one derivatives.

RESULTS AND DISCUSSION

7-Hydroxy-2-oxo-2*H*-chromen-8-carbaldehydes (**1a–d**), on reaction with methyl vinyl ketone in the presence of a catalytic amount of 1, 4-diazabicyclo [2.2.2] octane (DABCO) in chloroform under N_2 atmosphere at room temperature for 48 h, followed by column chromatography purification, yielded a crystalline compound characterized as 9-acetyl-4-methyl-2*H*,8*H*-pyrano[2,3-*f*] chromen-2-one (**2a**). IR spectrum of **2a** showed carbonyl absorptions at 1677 cm^{-1} and 1721 cm^{-1}. In the ^{1}HNMR ($CDCl_3$) spectrum, the 8-OCH_2 protons of the new pyran ring appeared at δ 5.06 ($J = 1.5$ Hz), and an H-10 signal appeared as a singlet at δ 7.82. A signal corresponding to methyl protons of 9-$COCH_3$ appeared at δ 2.45. Formation of a new fused pyran ring at the 7,8-position of the chromenone is evident from these signals. In the ^{13}CNMR ($CDCl_3$) spectrum of **2a**, the signal due to the acetyl carbonyl carbon resonated at δ 195.9, and that of 8-OCH_2appeared at δ 64.8. The signals of olefinic carbons C_9 and C_{10} appeared at δ 130.3 and 127.7, respectively. The other carbon signal assignments are δ 160.2 (C-2), 158.2 (C-6a), 152.2 (C-10b), 151 (C-4), 126.6 (C-5), 114.1 (C-4a), 112.8 (C-3), 112.2 (C-6), 109.2 (C-10a), 25.3 (carbonyl CH_3), and 18.8 (C-4, CH_3). EI mass spectrum is characterized by the presence of M + 1 peak at m/z 280. Similar reaction conditions were used for the preparation of other 9-acetyl-2*H*,8*H*-pyrano[2,3-*f*] chromen-2-ones (**2b–d**) (Scheme 1). Reaction of 2*H*-chromen-2-ones **1a–d** with acrolein in the presence of DABCO under a nitrogen atmosphere afforded 9-formyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-2-ones (**2e–h**) (Scheme 1).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was checked by thin-layer chromatography (TLC) on silica-gel-coated plates. IR spectra were recorded in KBr pellets, ^{1}HNMR spectra were recorded on a Varian 200-MHz instrument with TMS as internal standard, and chemical shifts are expressed in δ ppm. Mass spectra were measured on MS 30 and MS 9 (AEI) at 70 eV.



Scheme 1. Synthesis of 2*H*,8*H*-pyrano[2,3-*f*]chromen-2-one derivatives.

General Procedure for the Synthesis of 9-Acetyl-2*H*,8*H*-pyrano [2,3-*f*]chromen-2-ones (2a–d)

To a solution of 7-hydroxy-2-oxo-2*H*-chromen-8-carbaldehyde derivatives (**1a–d**, 0.001 mmol) in chloroform (5 mL), methyl vinyl ketone (0.002 mmol) and DABCO (0.001 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 48 h. The solvent was evaporated and the solid residue was chromatographed over silica gel (60–120 mesh), eluting with petroleum ether and ethyl acetate (9:1), to provide the corresponding 9-acetyl-2*H*,8*H*-pyrano[2,3-*f*]chromen-2-ones **2a–d**. They were recrystallized from chloroform.

Data

9-Acetyl-4-methyl-2*H*,8*H*-pyrano [2,3-*f*]chromen-2-one (2a)

Greenish white crystals; yield 80%; mp 220 °C; ^{1}HNMR ($CDCl_3$) δ 2.4 (s, 3H, CH_3), 2.46 (s, 3H, $COCH_3$), 5.06 (s, 2H, 8-CH_2), 6.78 (d, 1H, H-6, $J = 8.73$ Hz), 7.6 (d, 1H, H-5, $J = 8.73$ Hz), 7.82 (s, H-10). Anal. calcd for $C_{15}H_{12}O_4$: C, 70.21; H, 4.32; O, 24.72. Found C, 69.96; H, 4.08, and O, 24.53.

9-Acetyl-3-bromo-4-methyl-2*H*,8*H*-pyrano [2,3-*f*]chromen-2-one (2b)

Pale yellow crystals; yield 72%; mp 252°C; IR (KBr) 1662 and 1727 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.4 (s, 3H, CH_3), 2.6 (s, 3H, $COCH_3$), 5.2 (s, 2H,

8-CH_2), 6.8 (d, 1H, H-6, $J = 8.7$ Hz), 7.6 (d, 1H, H-5, $J = 8.7$ Hz), 7.8 (s, H-10); EI-MS m/z (%) 337 (M + 2). Anal. calcd. for $C_{15}H_{11}BrO_4$: C, 53.68; H, 3.26; O, 19.2. Found C, 53.32; H, 3.12; O, 19.02.

9-Acetyl-4-phenyl-2*H*,8*H*-pyrano [2,3-*f*]chromen-2-one (2c)

Brown color crystals; yield 75%; mp 192 °C; IR (KBr) 1656 and 1714 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.5 (s, 3H, $COCH_3$), 5.3 (s, 2H, 8-CH_2), 6.2 (s, 1H, H-3), 6.7 (d, 1H, H-6, $J = 8.76$ Hz), 7.4–7.6 (m, 5H, Ar-H), 7.8 (d, 1H, H-5, $J = 8.76$ Hz), 7.82 (s, H-10); EI-MS m/z (%) 342 (M + 1). Anal. calcd. for $C_{20}H_{14}O_4$: C, 75.20; H, 4.29; O, 20.2. Found C, 75.01; H, 4.16; O, 19.86.

9-Acetyl-4-methyl-3-phenyl-2*H*,8*H*-pyrano [2,3-*f*]chromen-2-one (2d)

Brown color crystals; yield 69%; mp 231 °C; IR (KBr) 1666 and 1713 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.3 (s, 3H, CH_3), 2.48 (s, 3H, $COCH_3$), 5.21 (s, 2H, 8-CH_2), 6.6 (d, 1H, H-6, $J = 8.72$ Hz), 7.2–7.6 (m, 5H, Ar-H), 7.82 (d, 1H, H-5, $J = 8.72$ Hz), 7.86 (s, 1H, H-10); EI-MS m/z (%) 291 (M + 1). Anal. calcd. for $C_{21}H_{16}O_4$: C, 75.86; H, 4.78; O, 19.20. Found C, 75.61; H, 4.66; O, 19.06.

General Procedure for the Preparation of 2e–h

To a solution of 7-hydroxy-2-oxo-2*H*-chromen-8-carbaldehyde (**1a-d**, 0.001 mmol) in chloroform (5 mL), acrolein (0.002 mmol), and DABCO (0.001 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 36 h. The chloroform was stripped off and the solid residue was chromatographed over silica gel (60–120 mesh) by eluting with petroleum ether and ethyl acetate (9:1) to provide compounds **2e–h**, which were crystallized from chloroform.

Data

4-Methyl-2-oxo-2*H*,8*H*-pyrano [2,3-*f*]chromen-9-carbaldehyde (2e)

Greenish white colored crystals, yield 83%, mp 232–234 °C; IR (KBr) 1676 and 1724 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.4 (s, 3H, CH_3), 5.1 (s, 2H, 8-CH_2), 6.1 (s, 1H, H-3), 6.8 (d, 1H, H-6, $J = 8.76$ Hz), 7.5 (d, 1H, H-5, $J = 8.76$ Hz), 7.8 (s, 1H, H-10), 9.6 (s, 1H, CHO); ^{13}CNMR ($CDCl_3$) 189.5, 160.4, 152.8, 152.5, 149.2, 129.8, 126.6, 126.4, 124.2, 113.2,

112.6, 108, 64, 18.7; EI-MS m/z (%) 243 (M + 1). Anal. calcd. for $C_{14}H_{10}O_4$: C, 69.38; H, 4.12; O, 26.40. Found C, 69.13; H, 3.95; O, 26.13.

3-Bromo-4-methyl-2-oxo-2*H*,8*H*-pyrano [2,3-*f*]chromen-9-carbaldehyde (2f)

Pale yellow crystals; yield 74%; mp 211 °C; IR (KBr) 1669 and 1716 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.4 (s, 3H, CH_3), 5.2 (s, 2H, 8-CH_2), 6.8 (d, 1H, H-6, $J = 8.8$ Hz), 7.6 (d, 1H, H-5, $J = 8.8$ Hz), 7.8 (s, 1H, H-10), 9.6 (s, 1H, CHO); EI-MS m/z (%) 321 (M^+). Anal. calcd. for $C_{14}H_9BrO_4$: C, 52.28; H, 2.76; O, 19.32. Found C, 52.03; H, 2.55; O, 19.13.

4-Phenyl-2-oxo-2*H*,8*H*-pyrano [2,3-*f*]chromen-9-carbaldehyde (2 g)

White crystals; yield 76%; mp 198 °C; IR (KBr) 1662 and 1731 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 5.1 (s, 1H, 8-CH_2), 6.2 (d, 1H, H-6, $J = 8.72$ Hz), 7.42–7.6 (m, 5H, Ar-H), 7.9 (d, 1H, H-5, $J = 8.72$ Hz), 7.98 (s, 1H, H-10), 9.7 (s, 1H, CHO); EI-MS m/z (%) 305 (M + 1). Anal. calcd. for $C_{19}H_{12}O_4$: C, 74.93; H, 3.96; O, 20.0. Found C, 75.71; H, 3.74; O, 19.86.

4-Methyl-3-phenyl-2-oxo-2*H*,8*H*-pyrano [2,3-*f*]chromen-9-carbaldehyde (2 h)

Brown crystals; yield 68%; mp 216 °C; IR (KBr) 1689 and 1731 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.4 (s, 3H, CH_3), 5.2 (s, 2H, 8-CH_2), 6.2 (d, 1H, H-6, $J = 8.76$ Hz), 7.42–7.6 (m, 5H, Ar-H), 7.92 (d, 1H, H-5, $J = 8.76$ Hz), 7.98 (s, 1H, H-10), 9.7 (s, 1H, CHO); EI-MS m/z (%) 318 (M + 1). Anal. calcd. for $C_{20}H_{14}O_4$: C, 75.39; H, 4.40; O, 20.60. Found C, 75.16; H, 4.18; O, 20.36.

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