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*Research Note*

# Solvent-free synthesis of 3-benzylpyrano[3,2-c]pyran/chromene-2,5-diones via tandem reaction of 4-hydroxy-6-methyl-pyran-2-one and 4-hydroxycoumarin with Baylis-Hillman adduct acetates

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**KEYWORDS**
Baylis-Hilman adduct acetate;
4-hydroxycoumarin;
Annulated 2-pyrone;
Solvent-free conditions.

**Abstract.** 4-hydroxycoumarin **2a** and 4-hydroxy-6-methyl-pyran-2-one **2b** were applied in a one-pot reaction with Baylis-Hillman adduct acetates **1** to form novel 3-benzyl-pyrano [3, 2-c] pyran-2, 5-diones **3** in high yields (70-85%). The synthesized framework is available in many biologically active moieties. The reaction was carried out under different conditions to achieve optimum conditions. The results indicated that $Et_3N$, as a base under solvent-free conditions, was optimum. The reaction procedure and purification method are mild and straightforward.



## 1. Introduction

Generally, 2-pyrone derivatives are an important class of organic compound forming building blocks of many natural and biologically active compounds [1-2]. In particular, annulated pyrones exhibit outstanding natural and biological activities. For instance, Norneolambertellin **(1)**, isolated from a mycroparasite Lambertella sp.1346, functions as an antifungal [3], fordianin A **(2)** and fordianin B **(3)** have cytotoxicity against A549 (human lung cancer) and human cervical carcinoma, coumestrol **(4)** acts as an anti-breast cancer [4-6] and Arisugacin A (5) possesses significance in the treatment of dementia such as Alzheimer's disease [7] (Figure 1).

Because of the importance of fused pyrones, several methods have been described for the synthesis of these frameworks. The synthesis of derivatives of 2H,5H-2,5-dioxo-3-pyrano[3,2c] benzopyranoic acids by the reaction of 3-formyl-4-hydroxycoumarin has been reported in low yields [8]. Mild conversion of 4-hydroxycoumarin to pyranobenzopyran was performed via a modified Pechman reaction [9]. In 2006, Sheibani et al. reported a one-pot synthesis of 2H,5H-pyrano[3,2-c]chromene-2,5-dione derivatives by the reaction of chlorocarbonyl ketenes with 4-hydroxycoumarin [10]. Leutbecher applied enzymatic biotransformation of 4-hydroxy-6-methyl-2H-pyran-2-one into coumestans and related heterocycles in 51 to 99% yields [11].

However, synthesis of the annulated pyrone skeleton is restricted by the lack of enough available methods to construct the desired ring bearing functional groups, and many of them are prepared in multistep procedures. As a result, extension of simple, efficient, green and, specifically, one-pot, methodologies for the

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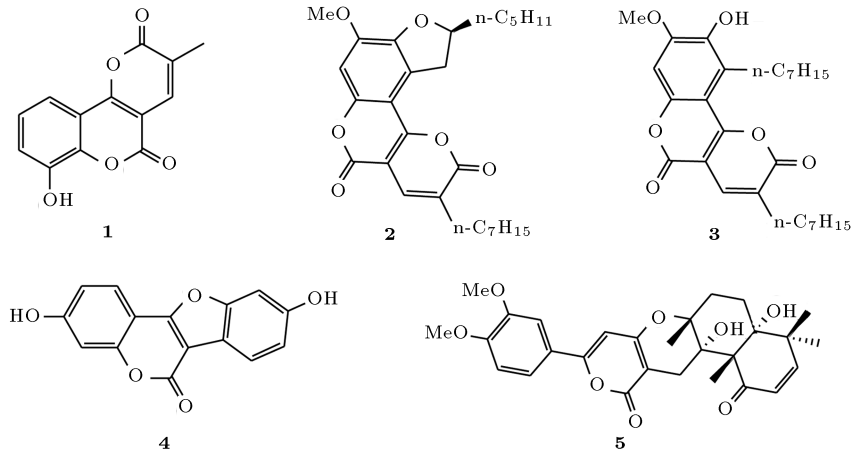
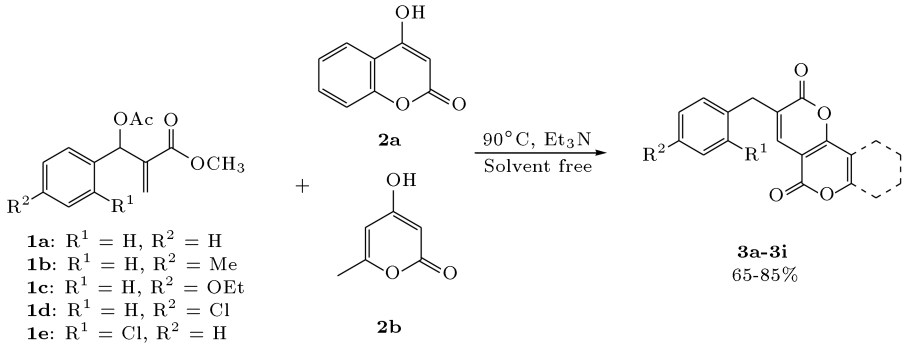



**Figure 1.** Biologically important molecules containing annulated pyrone skeleton.




**Scheme 1.** Synthesis of different 2-pyrone based dilactones under solvent free conditions.

synthesis of annulated 2-pyrone derivatives remains crucial.

The Baylis-Hillman reaction recently received considerable attention as a straightforward reaction to form C-C bonds [12-18]. Furthermore, adduct acetates of Baylis-Hillman have been utilized as a versatile synthon to form varieties of biologically active frameworks such as coumarines [19], quinolones [20],quinolines [21],benzazepines [22], benzisoxazolines [23], ozocines [24] and poly substituted phenols and benzenes [25-29].

Moreover, 4-hydroxycoumarin and 4-hydroxy-6-methyl-pyran-2-one were found to be effective 1,3-dinucleophiles, reacting with a variety of electrophiles, and were used mainly for the synthesis of heterocyclic compounds [30-31]. Earlier, we reported the novel and efficient synthesis of a broad spectrum of polycyclicbenzoxazocines via the unique tandem 1,3-dinucleophilic addition of different bifunctional nucleophiles to quinolinium and isoquinolinium salts [32-36]. Thus, we concluded that 4-hydroxy-2-quinolinones, 4-hydroxycoumarin and 4-hydroxy-6-methyl-pyran-2-one could also react with Baylis-Hillman adduct acetates to give pyranopyran systems.

According to the above-mentioned priorities, we decided to develop an efficient and one-pot synthetic method for the preparation of annulated pyrone frameworks. In this regard, we investigated the reaction of Baylis–Hillman adduct acetates **(1)**, which were synthesized according to the method in the literature [37], with 4-hydroxycoumarin **(2a)** or 4-hydroxy-6-methyl-2h-pyran-2-one **(2b)**, under different conditions, to prepare 2-pyrone based dilactones **(3)**.

Finally, we wish to report a convenient and efficient synthesis of 3-benzyl-pyrano[3,2-c]pyran/chromene -2,5-diones in the presence of triethylamine under solvent-free conditions (Scheme 1).

## 2. Experimental

### *2.1. Materials and method*

All materials used are commercially available and were purchased from Merck and used without any additional purification. $SiO_2$ TLC plates $60F_{254}$ were purchased from Merck. Melting points were determined (in sealed capillaries) on a BÜCHI Melting Point B-540 apparatus. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker (Avance DRX-500) spectrometer, using $CDCl_3$ as the solvent at ambient temperature. Chemical shifts, $\delta$, are reported in ppm relative to tetramethylsilane as the internal standard. Elemental analysis was performed by a Perkin Elmer 2004 (II)

CHN analyzer. The FT-IR spectra were recorded from KBr pallets in the range of 4000-400 $cm^{-1}$ on a Perkin Elmer Spectrum 2000 infrared spectrometer.

### 2.2. General procedure for alcohol oxidation to carbonyl compound

A magnetically stirred mixture of Baylis-Hillman acetates **1** (1 mmol), **2a** or **2b** (1.2 mmol), and $Et_3N$ (1.5 mmol) was heated at 90°C, and the reaction monitored by TLC. After completion, the reaction mixture was cooled down to room temperature. Then, the pure product was obtained with recrystallization of the reaction mixture with methonal. No further purification is needed.

*3-benzylpyrano[3,2-c]chromene-2,5-dione (**3a**)*

White powder; M.p. 183-185 °C, IR (KBr): $\nu_{max}$. 2924, 1744, 1717, 1076,1012$cm^{-1}$, $^1$H NMR (500 MHz, $CDCl_3$): 3.90 (s, 2H),7.27-7.30 (m, 3H), 7.34-7.38 (m, 2H), 7.40-7.43 (m, 2H),7.68 (dd, J= 8.9, 1.5 Hz, 2H), 8.08 (d, J= 7.89 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 36.8,103.7, 113.1, 117.3, 123.3, 125.2, 127.2, 129.0, 129.3, 129.4, 134.0, 136.4,136.7, 153.2, 159.1, 159.5, 160.0. Anal. calcd for $C_{19}H_{12}O_4$ : C, 74.99; H, 3.97%. found: C, 74.89; H, 3.96%.

*3-benzyl-7-methylpyrano[4,3-b]pyran-2,5-dione (**3b**)*

Pale yellow powder; M.p. 162-164°C, IR (KBr): $\nu_{max}$ 3102, 2917, 1744, 1728, 1032, 1027 $cm^{-1}$, $^1$H NMR (500 MHz, $CDCl_3$): 2.25 (s, 3H), 3.73 (s, 2H), 6.09 (s, 1H), 7.16-7.19 (m, 3H), 7.24-7.27 ( m, 2H), 7.44 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 20.6, 36.6, 101.7, 127.1, 127.7, 128.9, 129.0, 129.2, 136.1, 136.9, 159.8, 160.4, 164.4, 164.9. Anal. calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. found: C, 71.52; H, 4.49%.

*3-(4-methylbenzyl)pyrano[3,2-c]chromene-2,5-dione (**3c**)*

White powder; M.p. 163-165°C, IR (KBr): $\nu_{max}$ 3044, 2917, 1740, 1719, 1040, 1025 $cm^{-1}$, $^1$H NMR (500 MHz, $CDCl_3$): 2.37 (s, 3H), 3.84 (s, 2H), 7.14-7.22 (m, 4H), 7.39-7.43 (m, 2H), 7.62-7.68 (m, 2H), 8.08 (d, J= 8.0 Hz, 1H));$^{13}$C NMR (125 MHz, $CDCl_3$): 21.5, 36.7, 104.0, 113.6, 117.6, 123.6, 125.4, 129.4, 129.9, 130.0, 132.0, 133.9, 134.2, 136.3, 136.9, 153.6, 159.0, 159.4. Anal. calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. found: C, 75.38; H, 4.46%.

*7-methyl-3-(4-methylbenzyl)pyrano[4,3-b]pyran-2,5-dione (**3d**)*

White powder; M.p. 155-157°C, IR (KBr): $\nu_{max}$ 3202, 2925, 1752, 1733, 1044, 1033 cm−1, $^1$H NMR (500 MHz, $CDCl_3$): 2.40 (s, 6H), 3.80(s, 2H), 6.20 (s, 1H), 7.13-7.22 (m, 4H), 7.52 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): 20.5, 36.2, 101.7, 128.0, 129.1, 129.3, 129.4, 129.6, 133.8, 135.9, 136.7, 159.8, 160.4, 164.3, 164.9. Anal. calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. found: C, 72.27; H, 4.95%.

*3-(4-ethoxybenzyl)pyrano[3,2-c]chromene-2,5-dione (**3e**)*

White powder; M.p. 176-178°C, IR (KBr): $\nu_{max}$ 3074, 2986, 1740, 1722, 1112, 1037 $cm^{-1}$, $^1$H NMR (500 MHz, $CDCl_3$): 1.30 (t, J= 6.9 Hz, 3H), 3.67 (s, 2H), 3.89 (q, J= 6.9 Hz, 2H), 6.71 (d, J= 8.4 Hz, 2H), 7.04 (d, J= 8.4 Hz, 2H), 7.25-7.30 (m, 3H), 7.53 (t, J= 7.9 Hz, 1H), 7.92 (d, J=7.8 Hz, 1H);$^{13}$C NMR (125 MHz, $CDCl_3$): 15.2, 36.3, 63.6, 113.5, 115.1, 117.6, 123.6, 125.4, 129.2, 130.1, 130.5, 133.3. 134.2, 136.2, 153.2, 158.4, 159.5, 160.0, 160.1. Anal. calcd for $C_{21}H_{16}O_5$: C, 72.41; H, 4.63. found: C, 72.38; H, 4.57%.

*3-(4-chlorobenzyl)pyrano[3,2-c]chromene-2,5-dione (**3f**)*

Yellow powder; M.p. 173-175°C, IR (KBr): $\nu_{max}$ 3086, 2920, 1734, 1719, 1040, 1016 $cm^{-1}$,$^1$H NMR (500 MHz, $CDCl_3$): 3.82 (s, 2H), 6.88 ( dd, J= 6.9, 2.8 Hz, 2H), 7.20 (d, J= 8.6 Hz, 2H), 7.39-7.43 (m, 2H), 7.64-7.68 (m, 2H), 8.07 (d, J= 7.9 Hz, 1H);$^{13}$C NMR (125 MHz, $CDCl_3$): 35.9, 103.7, 113.1, 114.3, 117.3, 123.3, 125.2, 128.6, 129.9, 130.3, 134.0, 136.1, 153.1, 158.7, 159.1, 159.5, 159.9. Anal. calcd for $C_{19}H_{11}ClO_4$: C, 67.37; H, 3.27. found: C, 67.42; H, 3.22%.

*3-(4-chlorobenzyl)-7-methylpyrano[4,3-b]pyran-2,5-dione (**3g**)*

Pale yellow powder; M.p. 159-161°C, IR (KBr): $\nu_{max}$3082, 2925, 1752, 1728, 1085, 1043 $cm^{-1}$,$^1$H NMR (500 MHz, $CDCl_3$): 2.26 (s, 3H), 3.73 (s, 2H), 6.09 (s, 1H), 7.17-7.19 (m, 2H), 7.24-7.26 (m, 2H), 7.44 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): 20.6, 39.6, 101.7, 127.1, 127.7, 128.8, 128.9, 129.2, 136.0, 136.9, 159.8, 160.4, 164.3, 164.9. Anal. calcd for $C_{16}H_{11}ClO_4$: C, 63.48; H, 3.66. found: C, 63.42; H, 3.69%.

*3-(2-chlorobenzyl)pyrano[3,2-c]chromene-2,5-dione (**3h**)*

Pale yellow powder; M.p. 138-140°C, IR (KBr): $\nu_{max}$ 3058, 2926, 1749, 1722, 1041, 1013 $cm^{-1}$, $^1$H NMR (500 MHz, $CDCl_3$): 3.93 (s, 2H), 7.18-7.21 (m, 2H), 7.29-7.35 (m, 4H), 7.47 (s, 1H), 7.57-7.59 (m, 1H), 8.00 (d, J= 7.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): 34.4, 103.7, 113.1, 117.3, 123.3, 125.2, 127.3, 127.4, 129.0, 130.0, 131.9, 134.1, 134.2, 134.5, 136.5, 153.2, 159.0, 159.4, 160.0. Anal. calcd for $C_{19}H_{11}ClO_4$: C, 67.37;

H, 3.27. found: C, 67.42; H, 3.31%.

*3-(2-chlorobenzyl)-7-methylpyrano[4,3-b]pyran-2,5-dione (**3i**)*

White powder; M.p. 157-159°C, IR (KBr): $\nu_{max}$ 3080, 2926, 1725, 1717, 1057, 1032 $cm^{-1}$, $^1H$ NMR (500 MHz, $CDCl_3$):$^1H$ NMR (500 MHz, $CDCl_3$): 2.43 (s, 3H), 4.32 (s, 2H), 6.21 (s, 1H), 7.28-7.36 (m, 3H), 7.36-7.48 (m, 2H).; $^{13}C$ NMR (125 MHz, $CDCl_3$): 21.6, 38.7, 101.7, 127.3, 128.8, 128.9, 129.0, 130.9, 131.8, 136.0, 136.1, 159.7, 160.3, 164.3, 165.0, 167.8. Anal. calcd for $C_{16}H_{11}ClO_4$: C, 63.48; H, 3.66. found: C, 63.52; H, 3.65%.

## 3. Results and discussion

Initially, we examined the reaction of Baylis-Hillman adduct **1a** and 4-hydroxycoumarin **2a** with a variety of bases, such as $K_2CO_3$, $Et_3N$, NaOH and LDA, in different solvents and temperatures. According to Table 1, when water, as a green solvent, was used in the presence of $K_2CO_3$, the reaction did not produce **3a**, even under reflux conditions (Table 1, entries 1, 2). Using $K_2CO_3$ under solvent-free conditions yielded **3a** in 33% (Table 1, entry 3).

Using acetone under different conditions resulted in no further optimization of yields (entries 4-5). To investigate the effects of other bases, we used NaOH and LDA as stronger bases. When NaOH and LDA were applied, several products were formed, but not the desired product, **3a**. We did not make any effort to separate the products (Table 1, entries 6, 7). Fortunately, when the reaction was carried out under solvent-free conditions with $Et_3N$, the desired $\alpha$-pyrone **3a** was formed at 85% yield (entry 8). With the optimal reaction conditions in hand, we continued the transformation of different Baylis-Hillman adduct acetates into pyrano[4,3-b]pyran-2,5-dione derivatives and the results are summarized in Table 2.

As a result, the desired fused pyrones were obtained in good to excellent yields. The presence of electron-withdrawing or electron-donating groups has obviously influenced the time of the reaction. The substrates with electron-withdrawing groups proceeded with longer reaction times (Table 2, entries 7-9). However, the other substrates afforded the corresponding products at shorter reaction times. In most cases, the reaction times for 4-hydroxycoumarin **2a** are shorter than 4-hydroxy-6-methyl-pyran-2-one **2b**, but there is no significant difference amongst yields.

The proposed mechanism for the formation of **3a** is depicted in Scheme 2. Initially, this reaction starts with the base mediated deprotonation of **2a** to form intermediate **6**. Subsequently, $SN_2^{/}$ type reaction between **6** and Baylis-Hillman adduct acetate **1a** forms **7**. Then, **7** undergoes cyclization, by losing MeOH, to enhance the reaction to form dilactone intermediate **8**. Finally, base-catalyzed tautomerization gives the more stable and highly conjugated product, **3a**. (Scheme 2).

Structures of compounds **3a-i** were characterized by $^1H$ and $^{13}C$-NMR and elemental analysis, and the data was consistent with the calculated values. The IR spectrum of compound **3a** showed two strong absorption peaks at 1744 and 1717 $cm^{-1}$, which are attributed to asymmetric stretching of two carbonyl groups. The $^1H$-NMR spectrum of **3a** exhibited a singlet ascribed to $CH_2$ ($\delta = 3.90$ ppm) groups, and the resonance of aromatic hydrogens appears in the region 7.75-8.08$\delta_{ppm}$. The $^{13}C$-NMR spectrum of **3a** showed 17 signals in agreement with the proposed structure. In this spectrum, the carbonyl group signals appeared at $\delta = 159.5$ and 160.0 ppm.

**Table 1.** Synthesis of **3a** from Baylis-Hillman adduct **1a** and **2a** under various conditions[a].

| Entry | Solvent | Base | Δ(°C) | Yield[b] |
|---|---|---|---|---|
| 1 | $H_2O$ | $K_2CO_3$ | rt | - |
| 2 | $H_2O$ | $K_2CO_3$ | reflux | - |
| 3 | - | $K_2CO_3$ | 90 | 33[c] |
| 4 | acetone | $K_2CO_3$ | rt | - |
| 5 | acetone | $Et_3N$ | rt | - |
| 6 | $CH_3CN$ | NaOH | reflux | - |
| 7 | $CH_3CN$ | LDA | reflux | - |
| 8 | - | $Et_3N$ | 90 | 85[c] |

[a]: Reaction conditions: 1 mmol **1a**; 1.2 mmol **2a**; 1.5 mmol base; 5ml solvent;

[b]: Isolated product;

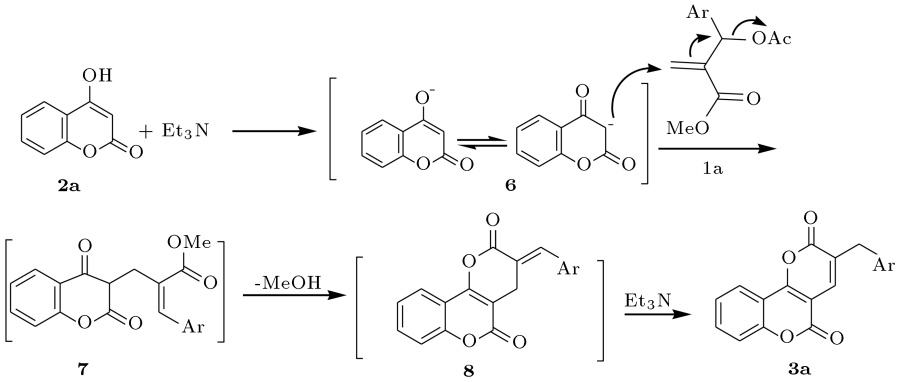
[c]: Solvent-free conditions.

**Table 2.** Synthesis of **3** from Baylis-Hillman adduct acetate **1** under solvent-free condition[a].

| Entry | 1 | 2 | 3 | Time (h) | Yield[b] |
|---|---|---|---|---|---|
| 1 | 1a | 2a | 3a | 4 | 85 |
| 2 | 1a | 2b | 3b | 6 | 76 |
| 3 | 1b | 2a | 3c | 2 | 73 |
| 4 | 1b | 2b | 3d | 8 | 77 |
| 5 | 1c | 2a | 3e | 2.5 | 80 |
| 6 | 1d | 2a | 3f | 8 | 82 |
| 7 | 1d | 2b | 3g | 10 | 79 |
| 8 | 1e | 2a | 3h | 12 | 82 |
| 9 | 1e | 2b | 3i | 16 | 70 |

[a]: Reaction conditions: 1 mmol **1a**; 1.2 mmol **2a**; 1.5 mmol base;

[b]: Isolated product.




**Scheme 2.** Mechanism for the formation of **3a**.

## 4. Conclusion

In conclusion, we have developed a one-pot, efficient, and 'green' methodology for the synthesis of various annulated pyrones from the reaction of Baylis-Hillman acetates with 4-hydroxycoumarin or 4-hydroxy-6-methylpyran-2-one under solvent-free conditions. The major benefits of the current work are solvent-free conditions, simple experimental procedure, high yields, short reaction times, easy workup and the similarity of synthesized derivatives to the biologically active moieties.

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