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Synthesis of 3,5,6-trisubstituted α-pyrones from Baylis–Hillman adducts

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Abstract—3,5,6-Trisubstituted α-pyrones were synthesized starting from the Baylis–Hillman adducts. The synthesis was carried out via the sequential introduction of ketone at the primary position of Baylis–Hillman adduct, lactonization, and the following oxidation with PCC.

Recently, considerable efforts have been devoted to the synthesis of α-pyrones and related compounds by numerous approaches involving transition metal-catalyzed reactions.[1–3] α-Pyrones have been used as synthetic intermediates[4] and are found in a wide variety of biologically active natural products.[1–3,5]

Recently, a variety of chemical transformations using the Baylis–Hillman adducts have been investigated thoroughly.[6,7] Especially the usefulness of the Baylis–Hillman adducts for the synthesis of many heterocyclic compounds is noteworthy.[6,7] Basavaiah and Satyanarayana have reported the synthesis of functionalized [4.4.3] and [4.4.4]propellano-bislactones starting from the Baylis–Hillman acetate and indanone derivatives.[8] Based on the Basavaiah's brilliant paper[8] and our recent studies on the chemical transformations of the Baylis–Hillman adducts,[7] we found an effective route to α-pyrone derivatives from the acetate of the Baylis–Hillman adducts as shown in Scheme 1.

The reaction of Baylis–Hillman acetate **1a** and deoxybenzoin (**2a**) in the presence of *t*-BuOK in THF afforded the corresponding methyl ester of **3a** together with some hydrolyzed compound **3a** in a variable ratio. We converted the ester derivative into the acid compound **3a** by NaOH hydrolysis of the crude reaction mixture after simple aqueous extractive workup. With this compound **3a** in our hands, we examined the lactonization reaction, which occurred easily by treatment of **3a** with TFAA (trifluoroacetic anhydride) in CH_2Cl_2 at room temperature to give 3-benzylidene-5,6-diphenyl-3,4-dihydropyran-2-one (**4a**) in 83% yield.[8,9]

At the earliest stage of this project, we expected that we could prepare 3-benzyl-5,6-diphenyl-α-pyrone (**5a**), the double bond-isomerized compound. However, **4a** was not converted to **5a** under various acidic or basic conditions. In addition, compound **4a** has limited stability and decomposed slowly even at room temperature to many intractable mixtures. Thus, we examined the oxidation of **4a** with a variety of conditions. Among the conditions, PCC oxidation[10] was found to be the best one and to our delight we could obtain 3-benzoyl-5,6-diphenyl-α-pyrone (**6a**)[11] in 59% yield from **4a**.[10,11] Such an allylic oxidation accompanying the isomerization of double bond has been reported[10a,f] and the structure of **6a** was confirmed by comparison with the reported spectroscopic data.[9,11]

Encouraged by the successful results, we examined the reactions of Baylis–Hillman acetates **1a–d** and various ketone derivatives **2a–f** and the results are summarized in Table 1. As ketone compounds we examined deoxybenzoin (**2a**), desoxyanisoin (**2b**), propiophenone (**2c**), acetophenone (**2d**), cyclohexanone (**2e**), and α-tetralone (**2f**) as the representative examples. As shown in Table 1, the 3-arylidene-3,4-dihydropyran-2-one derivatives **4a–h** were obtained in moderate to good yields (50–83%). The following oxidations of **4a–h** with PCC afforded the desired α-pyrones **6a–h** in moderate yields (51–64%).

Keywords: α-Pyrones; Baylis–Hillman adducts; Lactonization; TFAA; PCC oxidation.
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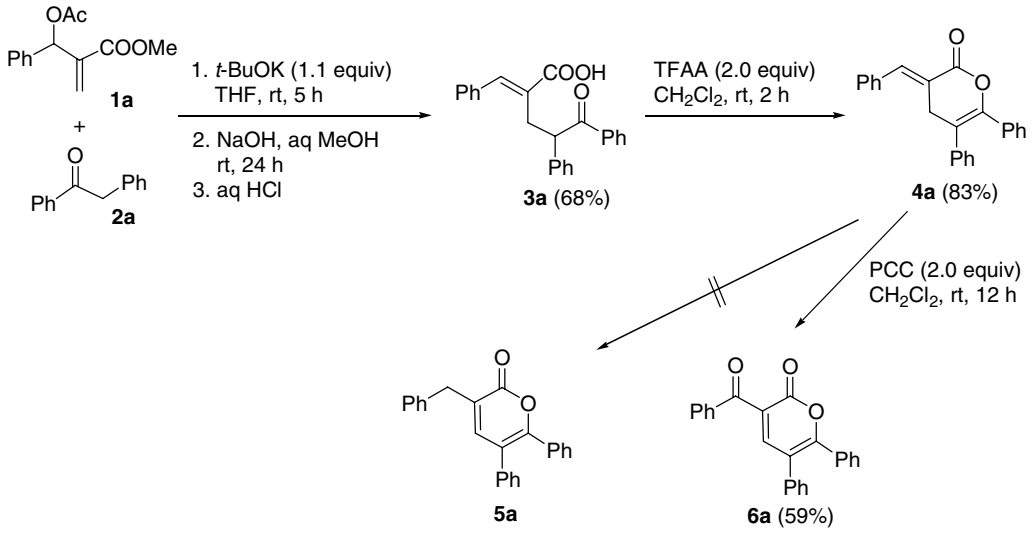
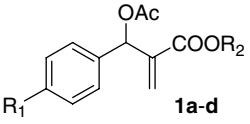


Scheme 1.

Table 1. Synthesis of benzylidene lactones **4** and 3-arol-α-pyrones **6**



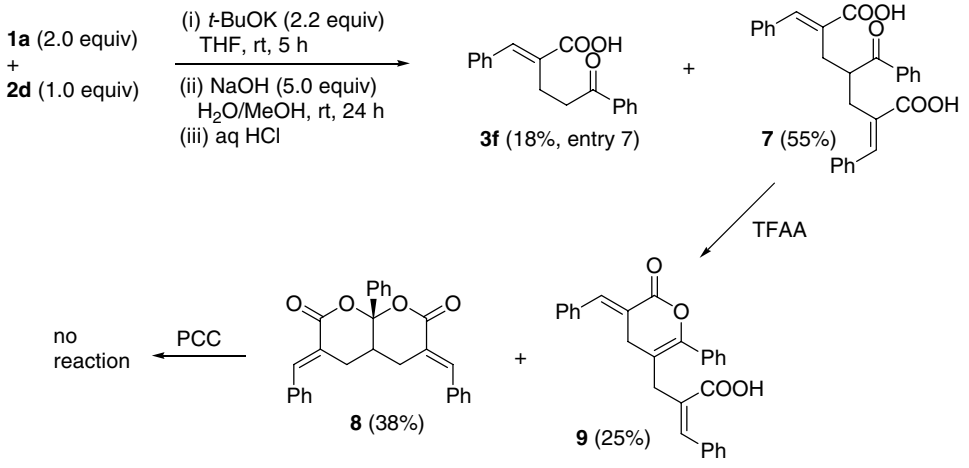
1a: R_1 = H, R_2 = Me
1b: R_1 = Me, R_2 = Me
1c: R_1 = Cl, R_2 = Me
1d: R_1 = H, R_2 = Et

2a: deoxybenzoin
2b: desoxyanisoin
2c: propiophenone

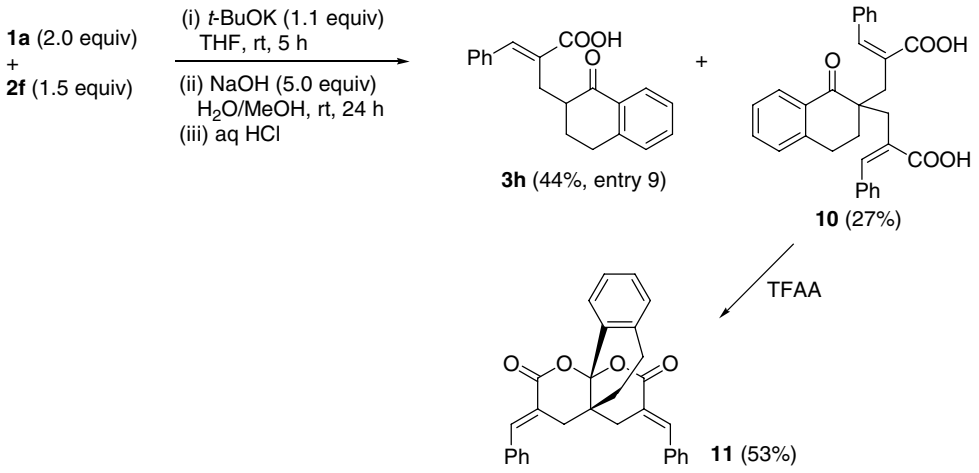
2d: acetophenone
2e: cyclohexanone
2f: α-tetralone

Entry	Substrates	Acid **3**[a] (%)	Lactone **4**[b] (%)	α-Phyrone **6**[c] (%)
1	**1a** + **2a**	**3a** (68)	**4a** (83)	**6a** (59)
2	**1b** + **2a**	**3b** (70)	**4b** (80)	**6a** (55)
3	**1c** + **2a**	**3c** (—)[d]	**4c** (50)	**6c** (60)
4	**1d** + **2a**	**3a** (—)[d]	**4a** (61)	—[e]
5	**1a** + **2b**	**3d** (—)[d]	**4d** (50)	**6d** (64)
6	**1a** + **2c**	**3e** (—)[d]	**4e** (70)	**6e** (58)
7	**1a** + **2d**	**3f** (18)	**4f** (51)	**6f** (51)
8	**1a** + **2e**	**3g** (43)	**4g** (52)	–[e]
9	**1a** + **2f**	**3h** (44)	**4h** (72)	**6h** (52)

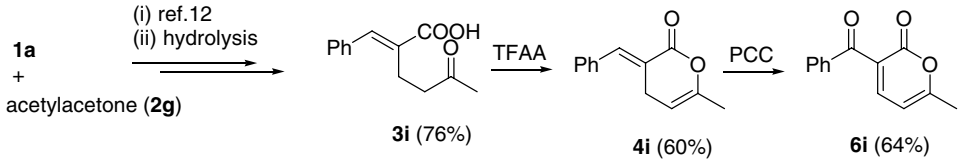
[a] Conditions: (i) *t*-BuOK (1.1 equiv), dry THF, rt, 5 h; (ii) NaOH (3.0 equiv), H_2O/MeOH, rt, 24 h; and (iii) aq HCl.
[b] Conditions: TFAA (2.0 equiv), CH_2Cl_2, rt, 2 h.
[c] Conditions: PCC (2.0 equiv), CH_2Cl_2, rt, 12 h.
[d] Yield was not determined.
[e] Oxidation was not tried.



Scheme 2.



Scheme 3.



Scheme 4.

When we used acetophenone (**2d**), we could not obtain the mono-adduct **3f** in good yield. Instead bis-adduct **7** was isolated as the major product (Scheme 2). As already shown in entry 7 in Table 1, compound **3f** showed similar reactivity in the following reactions. Bis-adduct **7** could be converted into bicyclic compound **8** (38%) according to the similar mechanism reported[8] together with mono-cyclic compound **9** (25%).

Similar results were observed in the reaction of **1a** and α-tetralone (**2f**) as in Scheme 3. We obtained mono-adduct **3h** (44%) and bis-adduct **10** (27%)[8] together. As in entry 9, mono-adduct **3h** was converted into **4h** and **6h** similarly. Bis-adduct **10** gave the tricyclic compound **11** in 53% yield as in Basavaiah's paper.[8]

As shown in Scheme 4, we used acetylacetone (**2g**) in order to introduce the simplest substituent, acetonyl group, at the primary position of Baylis–Hillman adduct as in our previous letter.[12] By using compound **3i**, we prepared **4i** and **6i** similarly in moderate yields.

In summary, we developed a facile and efficient procedure for the synthesis of 3-arylidene-5,6-disubstituted-3,4-dihydropyran-2-ones and 3,5,6-trisubstituted α-pyrones starting from the Baylis–Hillman adducts.

Acknowledgments

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9. Spectroscopic data of some selected compounds are as follows:

   Compound **4a**: 83%; white solid, mp 149–150 °C; IR (film) 1728, 1612, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.87 (d, $J = 2.4$ Hz, 2H), 7.11–7.27 (m, 10H), 7.37–7.45 (m, 5H), 8.03 (t, $J = 2.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.96, 113.35, 122.57, 127.38, 127.80, 128.49, 128.61, 128.71, 128.92, 129.04, 129.61, 130.42, 133.14, 134.68, 138.44, 142.13, 145.35, 164.17; LCMS *m*/*z* 338 (M^+). Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 85.02; H, 5.53.

   Compound **4b**: 80%; white solid, mp 164–165 °C; IR (film) 1726, 1603, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.86 (d, $J = 2.7$ Hz, 2H), 7.11–7.27 (m, 12H), 7.36 (d, $J = 8.1$ Hz, 2H), 8.01 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.46, 33.11, 113.35, 121.45, 127.34, 127.78, 128.44, 128.60, 128.94, 129.04, 129.46, 130.59, 131.95, 133.20, 138.55, 140.13, 142.24, 145.29, 164.32. Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.38; H, 5.86.

   Compound **4i**: 60%; colorless oil; IR (film) 1719, 1577, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.89 (s, 3H), 3.32–3.36 (m, 2H), 4.89–4.93 (m, 1H), 7.34–7.45 (m, 5H), 7.92 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.75, 25.41, 97.60, 122.41, 128.46, 129.32, 130.24, 134.70, 141.81, 147.49, 164.43. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.79; H, 6.13.

   Compound **6a**:[11] 59%; yellow solid, mp 169–170 °C; IR (film) 1728, 1651, 1523, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.63 (m, 13H), 7.91 (d, $J = 8.4$ Hz, 2H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 118.10, 123.45, 128.25, 128.28, 128.44, 129.09, 129.14, 129.41, 129.53, 130.81, 131.33, 133.49, 135.35, 136.45, 150.71, 158.97, 161.41, 191.71. Anal. Calcd for $C_{24}H_{16}O_3$: C, 81.80; H, 4.58. Found: C, 81.58; H, 4.77.

   Compound **6b**: 55%; yellow solid, mp 185–186 °C; IR (film) 1732, 1657, 1531, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 7.20–7.46 (m, 12H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.77, 118.09, 123.84, 128.23, 128.28, 129.09, 129.16, 129.20, 129.43, 129.77, 130.76, 131.40, 133.86, 135.43, 144.58, 150.38, 159.08, 161.16, 191.30. Anal. Calcd for $C_{25}H_{18}O_3$: C, 81.95; H, 4.95. Found: C, 81.92; H, 5.11.

   Compound **6i**: 64%; yellow solid, mp 77–78 °C; IR (film) 1729, 1659, 1558, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 6.18 (d, $J = 6.9$ Hz, 1H), 7.42–7.48 (m, 2H), 7.54–7.60 (m, 1H), 7.71 (d, $J = 6.9$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.36, 103.67, 122.55, 128.32, 129.31, 133.26, 136.50, 147.31, 159.77, 167.42, 191.92; LCMS *m*/*z* 214 (M^+). Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.81; H, 4.98.

   Compound **8**: 38%; pale yellow solid, mp 84–85 °C; IR (film) 1724, 1612, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.79–2.82 (m, 4H), 2.88–2.96 (m, 1H), 7.25–7.54 (m, 15H), 8.10 (t, $J = 2.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.39, 33.94, 105.33, 121.18, 125.41, 128.73, 128.94, 129.83, 129.90, 130.46, 134.22, 137.94, 144.83, 164.19; LCMS *m*/*z* 422 (M^+). Anal. Calcd for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.45; H, 5.31.
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