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The application of the Baker–Venkataraman rearrangement to the synthesis of benz[*b*]indeno[2,1-*e*]pyran-10,11-dione

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Abstract—A tetracyclic benzocyclopentabenzopyran-4-one was synthesized via a domino reaction involving an initial aroyl transfer as in the Baker–Venkataraman rearrangement. The derived 1,3 diketone underwent the intramolecular acylation followed by cyclization to give the product. © 2002 Elsevier Science Ltd. All rights reserved.

Benz[*b*]indeno[2,1-*e*]pyran-10,11-dione **1a** and analogues have been prepared and studied for enhancing the biosynthesis of erythropoietin (Epo), a hematopoietic growth factor which stimulates differentiation and supports the survival of cells of the erythroid lineage, by Williams's group.[1] Their synthetic route to **1b** involved sulfoxide chemistry and a symmetrical dialdehyde followed by further manipulation which led to benz[*b*]indeno[2,1-*e*]pyran-10,11-dione **1a** (Fig. 1).[1] Similarly, a multi-step synthesis of coniochaetone A **2**, an antifungal cyclopentabenzopyran-4-one from a coprophilous fungus *Coniochaeta sarcardoi*,[2] involving sulfoxide chemistry was reported by Mori.[3]

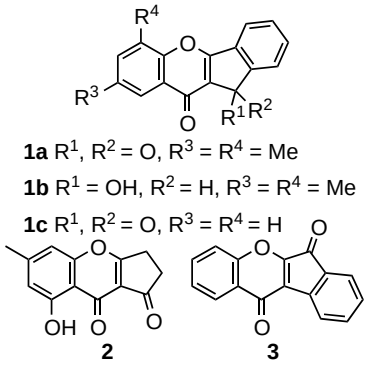

Figure 1.

We have recently reported a successful synthesis of wrightiadione **3**,[4] a rare and unusual oxygen heterocycle isolated from the bark of *Wrightia tomentosa*,[5] a medicinal plant of Thailand. The methanol extract of the dried leaves and stems of this plant showed weak activity against human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT). With this finding and the reported interesting biological activity of benz[*b*]indeno[2,1-*e*]pyran-10,11-dione, we undertook a study of the synthesis of these compounds.

Herein, we present our strategy leading to a short synthesis of **1c** and 2-benzyl benzofuran-3-one **11**. Compound **1c** has been previously synthesized by two routes, however the use of symmetrical intermediates in both of these reports[1,6] creates difficulties when the indenone moiety is to be substituted.

We envisaged that benz[*b*]indeno[2,1-*e*]pyran-10,11-dione **1c** could be obtained via two synthetic routes as shown in the retrosynthetic analysis in Scheme 1. It was expected that ring closure of the chalcone intermediate[7] **5** could lead to the flavanone **6** which could undergo further intramolecular acylation and oxidation to give the product. Alternatively, the flavone **7** could be obtained by application of the Baker–Venkataraman rearrangement (BK–VK).[8,9] Further cyclization either through flavanone **6** or directly could then lead to the required compound.

Having the above ideas in mind, we studied the first route. We attempted to prepare chalcone **6** using a

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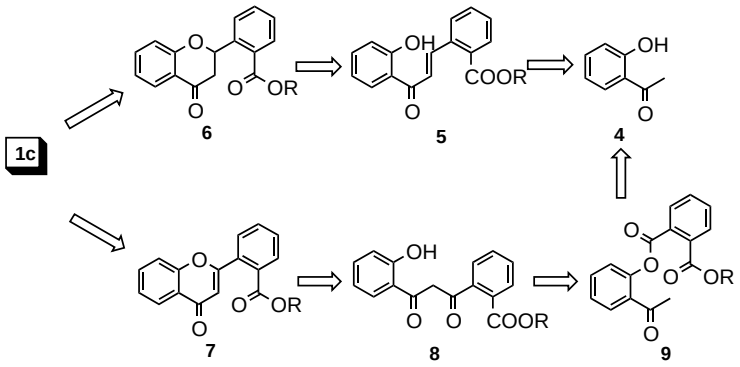

Scheme 1.

general procedure by treatment of 2-hydroxy acetophenone **4** and phthaldehydic acid **10** with KOH in MeOH under reflux for 8 h. Acidification (2N HCl) of the mixture yielded not the expected chalcone **5** but the 2-benzyl benzofuran-3-one **11** in 76% yield after recrystallization from ethanol (Scheme 2). The structure of **11** was confirmed using IR and ^{1}H NMR.[10] The IR spectrum of **11** exhibited a band at 1634 cm^{-1} (C=O of carboxylic group) and a band at 1764 cm^{-1} (C=O of furanone system). The ^{1}H NMR spectrum of **11** showed a triplet at δ_H 6.14 for the methine C-2 proton. The formation of the 2-benzyl benzofuran-3-one **11** can be explained through the preferred 5-*exo* trig cyclization of chalcone **5** (R = H) induced by the electron withdrawing group at the C-2′ position rather than the 6-*endo* trig cyclization.

To investigate the second route, acylation of **4** with *mono* methyl phthalate **12** using Steglich esterification[11] gave *o*-benzoylacetophenone **9** in 68% yield (Scheme 2).

The BK–VK rearrangement of **9** was carried out with potassium hydroxide in pyridine, under reflux for 30 min. The mixture was then poured into 2N hydrochloric acid solution which led to the precipitation of a yellow solid.

After recrystallization from ethanol, yellow crystals were obtained in 72% yield. The structure of the product obtained under these conditions was elucidated by IR, NMR and MS and it was gratifying to find that the product was ***not*** the expected flavanone **7** (R = Me) but the ultimate target compound **1c**.[12] The IR spectrum of **1c** showed a band at 1620 cm^{-1} (C=O of chromone system) and a band at 1710 cm^{-1} (C=O of indenone system) which corresponded with two peaks due to the ketone carbonyls in the ^{13}C NMR at δ 179.2 and 187.6. The mechanism of formation of **1c** could be rationalized as involving formation of the 1,3-diketone intermediate **8** through the BK–VK rearrangement. Intramolecular cyclization of diketone **8** could lead to the 1,3-indanedione **13**. Formation of hemiketal **14** followed by dehydration could then give the product as shown in Scheme 3.

In conclusion, we have developed an operationally simple, highly efficient domino reaction for the synthesis of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones. The method should be amenable to other complex analogues.

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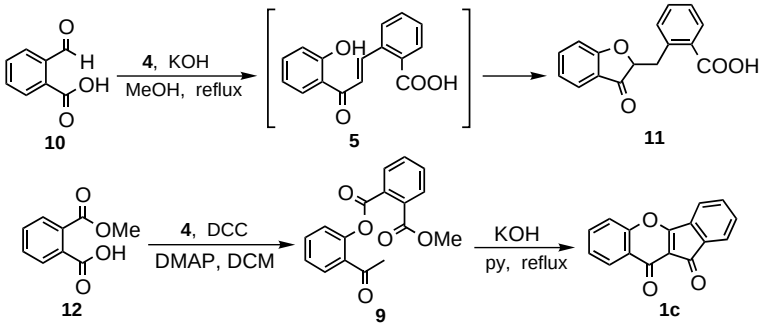
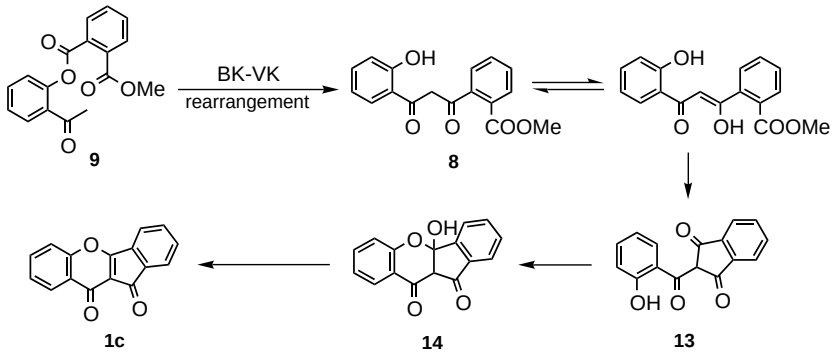


Scheme 2.



Scheme 3.

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10. 2-Benzyl benzofuran-3-one (**11**) mp (EtOH): 148–150°C; FTIR (KBr): ν_{max} 3042 (OH), 1764 (C=O), 1634 (C=O), 1470, 1443, 1376 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.44 (dd, 1H, $J=6.4$, 17.4 Hz, *H* β), 3.75 (dd, 1H, $J=6.2$, 18.0 Hz, *H* β), 6.14 (t, 1H, $J=6.2$, 6.6 Hz, *H* 2), 6.88 (t, 1H, $J=7.4$, 8.0 Hz, *H* 5), 7.00 (d, 1H, $J=8.6$ Hz, *H* 7), 7.59 (m, 5H, Ar*H*), 7.90 (d, 1H, $J=7.6$ Hz, *H* 6′), 12.00 (s, 1H, O*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.7, 170.0, 162.5, 149.3, 137.2, 134.4, 129.8, 129.6, 125.8, 122.6, 119.3, 119.0, 118.7, 76.5, 43.1; MS (EI) m/z 268 (M^+, 23), 250 (19), 223 (18), 147 (100), 132 (38), 121 (60). HRMS calcd for $C_{16}H_{12}O_4$: 269.0814. Found: 269.0816.
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12. Isowrightiadione (**1c**) mp (EtOH): >260°C; FTIR (KBr): ν_{max} 1710 (C=O), 1620, 1591, 1464, 1385, 1260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45 (ddd, 1H, $J=1.3$, 6.8, 7.8 Hz, *H* 8), 7.53–7.74 (m, 6H, Ar*H*), 8.29 (dd, 1H, $J=1.2$, 7.6 Hz, *H* 9); ^{13}C NMR (50 MHz, $CDCl_3$) δ 187.6, 179.2, 171.6, 155.8, 134.8, 134.1, 133.9, 133.7, 133.0, 127.1, 126.7, 126.5, 123.7, 121.3, 118.6, 111.4; MS (EI) m/z 248 (M^+, 88), 220 (100), 192 (7), 164 (20), 163 (49). HRMS calcd for $C_{16}H_8O_3$: 248.0473. Found: 248.0474. Anal calcd for $C_{16}H_8O_3$: C, 77.42; H, 3.25. Found: C, 77.43; H, 3.24%.