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Bargellini condensation of coumarins. Expeditious synthesis of *o*-carboxyvinylphenoxyisobutyric acids

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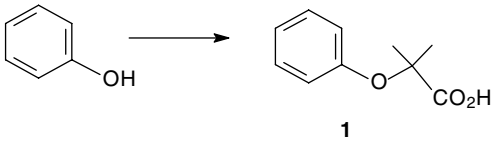
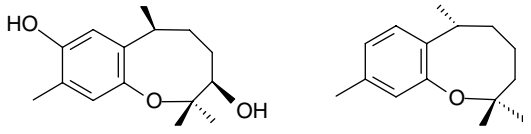
Abstract—Condensation of coumarins with chloroform and acetone in the presence of a base furnished *o*-carboxyvinylphenoxyisobutyric acids in good yields. The diacid **7a** was transformed in a few high yielding steps to the marine sesquiterpene helianane underscoring the importance of this new protocol.

Bargellini reported[1] the interesting condensation of phenol with chloroform and acetone in the presence of sodium hydroxide to yield α-phenoxyisobutyric acid **1** (Scheme 1). This pointed to a general conversion of alcohols to α-alkoxyisobutyric acid systems which could be de-alkoxylated to a methacrylic acid. Later investigators have improved upon this observation with better yields obtained from condensation with acetonechloroform (chloretone) and application to a variety of alcohols and carbonyl substrates.[2] Further transformations of the phenoxyisobutyric acids to provide an alternative to the Birch reduction have also been described.[3] However, the potential of this useful transformation in synthesis has not been thoroughly investigated. The isolation of heliannuol A **2**[4], an important allelochemical from cultivar sun flowers and helianane **3** from a marine sponge,[5] both of which contain an α-phenoxyisobutyl component are good choices as substrates for the exploration of this methodology for their synthesis. Various researchers have exploited this reaction to incorporate a *gem*-dimethyl functionality into a ring system.[6] We have also applied[7] this methodology in our synthesis of heliannuol A wherein the styrenol(s) **4** were subjected to a Bargellini condensation with chloroform and acetone in the presence of sodium hydroxide to furnish the phenoxyisobutyric acid(s) **5** (Scheme 2) which were elaborated to the natural product. Styrenol **4a** itself was obtained from decarboxylative alkaline hydrolysis of coumarin **6a**. It occurred to us that direct condensation of coumarin with chloroform and acetone in the



1

Scheme 1. Reagents and conditions: (i) $CHCl_3$, powdered NaOH, acetone, reflux 6 h; (ii) HCl.



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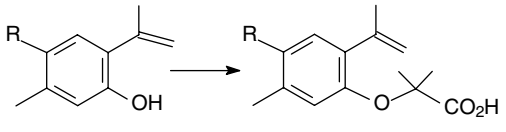
3



4 **5**

a R = H
b R = OMe

Scheme 2. Reagents and conditions: (i) $CHCl_3$, powdered NaOH, acetone, reflux 6 h; (ii) HCl.

Keywords: Coumarins; Bargellini condensation; α-Carboxyvinylphenoxyisobutyric acids; Helianane.
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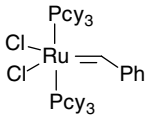
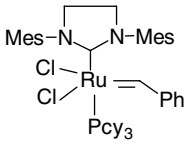
presence of a base would provide a novel one-step route to an α-phenoxyisobutyric acid with the additional advantage of an acrylic acid functionality on the adjacent carbon atom of the phenyl ring for further useful transformations. We describe in this letter, the realization of this process and demonstrate the utility of this strategy by application to the synthesis of the natural product helianane **3**.

Interaction of 4,7-dimethylcoumarin **6a** with chloroform and acetone in the presence of sodium hydroxide followed by acidic work up afforded diacid **7a** in 75% yield as a crystalline solid. The corresponding dimethyl ester **10**, prepared from reaction with diazomethane, was fully characterized by its analytical and spectral data. The methodology was extended to a variety of coumarins **6a**–**d** and in all cases the desired diacids **7a**–**d** were obtained in yields ranging from 70–75%. The benzocoumarins **8a**–**b** also responded identically to the reaction conditions affording the expected diacids **9a**–**b** in 65–70% yields. Thus, the direct Bargellini condensation with coumarins provides a useful single-step procedure for the preparation of highly functionalized phenoxy acids (Scheme 3).

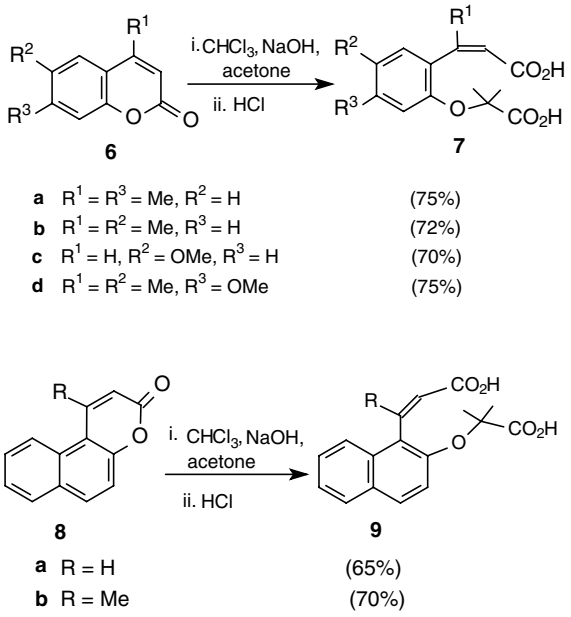


Catalyst **A**

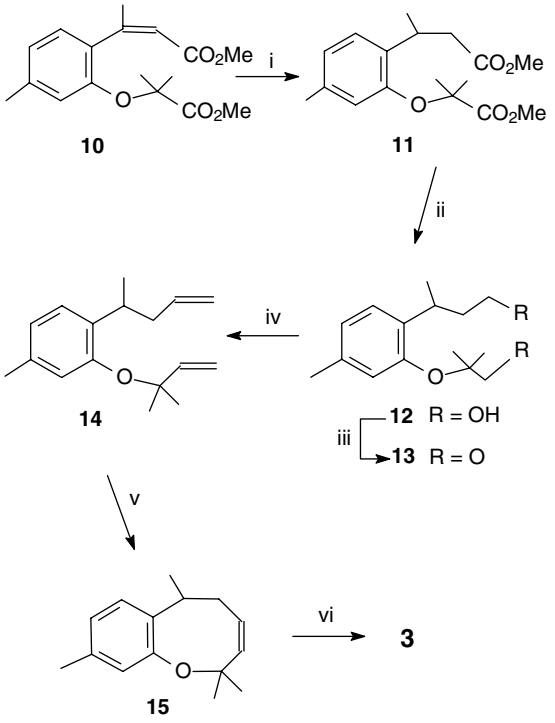


Catalyst **B**

The utility of this novel preparative procedure was demonstrated through the application of one of the product diacids to prepare helianane **3**. Catalytic hydrogenation of diester **10** furnished the saturated diester **11**[8] in quantitative yield which was reduced to diol **12**[8] with lithium aluminium hydride in excellent yield (98%). This diol underwent smooth oxidation under Swern conditions to dialdehyde **13**[8] (93%) which on a double Wittig reaction afforded diene **14**[8] in 70% yield. This diene had previously been taken to helianane **3** by Snieckus et al.[6b] We also carried out the ring-closing metathesis reaction. However, employing Grubbs' first generation catalyst **A** for this cyclization failed to generate any cyclized alkene and furnished only a complex product profile. Employing the later version of the catalyst, catalyst **B**, led to a smooth ring-closing reaction to afford the cyclized alkene **15**[8] in 85% yield. Catalytic hydrogenation of this alkene furnished helianane **3**, which was spectroscopically identical with a sample we had previously synthesized[9] and also with the natural product itself (Scheme 4).[5]



Scheme 3.



Scheme 4. Reagents and conditions: (i) 10% Pd–C, H_2, MeOH, 5 h, 99%; (ii) LAH, Et_2O, reflux, 4 h, 98%; (iii) $(COCl)_2$, DMSO, Et_3N, −78 °C to rt, 5 h, 93%; (iv) methyltriphenylphosphonium iodide, *n*-BuLi, THF, 0 °C, 5 h, 70%; (v) catalyst **B**, CH_2Cl_2, rt, 6 h, 85%; (vi) 10% Pd–C, H_2, MeOH, 5 h, 92%.

In summary, we have described a novel one-step conversion of coumarins to usefully functionalized diacids employing the Bargellini condensation and have demonstrated its synthetic utility. Investigations employing other lactone types (including dihydrocoumarins, higher homologues, etc.) and a variety of carbonyl compounds are expected to further expand the utility of this protocol and these are being actively pursued.

Acknowledgements

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References and notes

1. Bargellini, G. *Gazz. Chim. Ital.* **1906**, *36*, 329–339.
2. Weizmann, C.; Sulzbacher, M.; Bergmann, E. *J. Am. Chem. Soc.* **1948**, *70*, 1153–1158.
3. Corey, E. J.; Barcza, S.; Klotmann, G. *J. Am. Chem. Soc.* **1969**, *91*, 4782–4786.
4. Macias, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G.; Fronzek, F. R. *Tetrahedron Lett.* **1993**, *34*, 1999–2002.
5. Harrison, B.; Crews, P. *J. Org. Chem.* **1997**, *62*, 2646–2648.
6. (a) Grimm, E. L.; Levac, S.; Trimble, L. A. *Tetrahedron Lett.* **1994**, *35*, 6847–6850; (b) Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808–2809.
7. Tuhina, K.; Bhowmik, D. R.; Venkateswaran, R. V. *Chem. Commun.* **2002**, 634–635.
8. All new compounds reported here gave analytical and spectral data consistent with the assigned structures. *Selected spectral data*: For **7a**: IR (KBr) 1695 (br), 1715, 2974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 6H), 2.17 (s, 3H), 2.29 (s, 3H), 5.99 (s, 1H), 6.53 (s, 1H), 6.80 (d, $J = 7.8$, 1H), 6.97 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 24.8, 25.0, 27.1, 79.0, 116.5, 117.6, 122.3, 127.9, 128.4, 138.7, 150.3, 155.1, 169.8, 177.3; HRMS (ES +ve) calcd for $C_{15}H_{19}O_5$ $[M+H]^+$ 279.1237, found 279.1236. For **10**: IR ($CHCl_3$) 1715, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 6H), 2.16 (s, 3H), 2.28 (s, 3H), 3.55 (s, 3H), 3.75 (s, 3H), 5.91 (s, 1H), 6.53 (s, 1H), 6.78 (d, $J = 7.8$ Hz, 1H), 6.92 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 25.1, 25.9, 25.9, 50.6, 52.2, 79.2, 117.9, 118.1, 122.4, 128.3, 130.1, 138.1, 151.2, 154.4, 165.8, 174.9; HRMS (ES +ve) calcd for $C_{17}H_{23}O_5$ $[M+H]^+$ 307.1546, found 307.1540. For **11**: IR ($CHCl_3$) 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, $J = 6.9$ Hz, 3H), 1.63 (s, 6H), 2.24 (s, 3H), 2.45 (dd, $J = 9.1$, 15.0 Hz, 1H), 2.70 (dd, $J = 5.5$, 15.0 Hz, 1H), 3.51–3.88 (m, 1H), 3.64 (s, 3H), 3.76 (s, 3H), 6.40 (s, 1H), 6.73 (d, $J = 7.8$ Hz, 1H), 7.04 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 21.0, 25.1, 25.1, 29.8, 41.1, 51.2, 52.2, 78.5, 116.5, 122.1, 126.7, 132.9, 136.3, 152.5, 173.1, 175.0; HRMS (ES +ve) calcd for $C_{17}H_{25}O_5$ $[M+H]^+$ 309.1703, found 309.1719. For **12**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (d, $J = 6.5$ Hz, 3H), 1.17 (s, 3H), 1.29 (s, 3H), 1.37–1.46 (m, 1H), 1.64–1.71 (m, 1H), 2.21 (s, 3H), 3.17–3.25 (m, 1H), 3.38–3.64 (m, 4H), 6.77 (s, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 21.6, 22.4, 24.3, 27.2, 42.5, 60.6, 71.1, 81.5, 122.8, 124.7, 126.8, 136.3, 137.4, 153.1; HRMS (ES +ve) calcd for $C_{15}H_{25}O_3$ $[M+H]^+$ 253.1804, found 253.1797. For **13**: IR (Neat) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, $J = 6.9$ Hz, 3H), 1.46 (s, 6H), 2.22 (s, 3H), 2.55–2.75 (m, 2H), 3.69–3.76 (m, 1H), 6.39 (s, 1H), 6.77 (d, $J = 7.7$ Hz, 1H), 7.07 (d, $J = 7.7$ Hz, 1H), 9.69 (t, $J = 1.9$ Hz, 1H), 9.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 21.8, 22.2, 22.4, 28.1, 51.3, 83.3, 117.1, 123.4, 127.7, 132.9, 137.4, 152.8, 202.6, 204.0. For **14**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, $J = 6.9$ Hz, 3H), 1.48 (s, 6H), 2.10–2.43 (m, 2H), 2.25 (s, 3H), 3.20–3.27 (m, 1H), 4.93 (d, $J = 11.3$ Hz, 1H), 5.00 (d, $J = 18.8$ Hz, 1H), 5.14 (d, $J = 10.9$ Hz, 1H), 5.22 (d, $J = 17.6$ Hz, 1H), 5.69–5.89 (m, 1H), 6.16 (dd, $J = 10.9$, 17.6 Hz, 1H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.86 (s, 1H), 7.04 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.6, 27.8, 27.8, 32.4, 42.0, 79.6, 113.2, 115.7, 120.0, 122.5, 126.9, 135.8, 135.8, 138.3, 145.5, 153.9. For **15**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, $J = 6.9$ Hz, 3H), 1.40 (s, 3H), 1.62 (s, 3H), 2.29 (s, 3H), 2.85–3.43 (m, 3H), 5.27 (d, $J = 10.8$ Hz, 1H), 5.61–5.74 (m, 1H), 6.75 (s, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 25.5, 28.9, 29.7, 29.8, 34.5, 81.6, 125.7, 127.9, 130.8, 131.2, 135.1, 136.0, 137.4; 152.9; HRMS (ES +ve) calcd for $C_{15}H_{21}O$ $[M+H]^+$ 217.1593, found 217.1587.
9. Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 9653–9655.