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Acyl furans from cyclohexane-1,3-diones – A synthesis of hibiscone C

Yang Qu
Iowa State University

George A. Kraus
Iowa State University and Ames Laboratory, gakraus@iastate.edu

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Abstract

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Acyl furan, Cyclohexane-1, 3-dione, Hibiscone C, Dithiane, Synthesis

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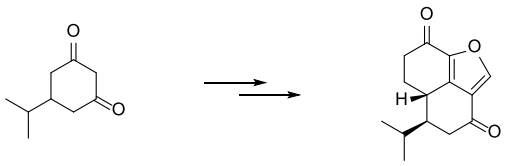

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Acyl furans from cyclohexane-1,3-diones – A synthesis of hibiscone C

Yang Qu, George A. Kraus*

Department of Chemistry, Iowa State University, Ames, IA, 50010

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ABSTRACT

A direct route to acyl furans was developed using dithiane anion addition followed by deprotection/aromatization. This led to an efficient synthesis of hibiscone C.

A number of natural products contain the acyl furan subunit, including viridin (**1**), halenaquinone (**2**), hibiscone C (**3**) and hibiscone D (**4**), shown in Figure 1. There have been total syntheses[1] of **1** and a number of innovative approaches[2] to the ring structure of **1**. Halenaquinone is a novel RAD51 inhibitor that specifically inhibits the RAD51-dsDNA binding.[3] Several researchers have reported total syntheses[4] of **2** and approaches[5] to **2**. Hibiscone C competitively inhibits phosphatidylinositol-3-kinase activity in intact cells.[6] Since the classic synthesis by Smith in 1982, it has been synthesized by Kraus, by Goess and by Lu.[7] Hibiscone D inhibits superoxide anion generation by human neutrophils.[8]

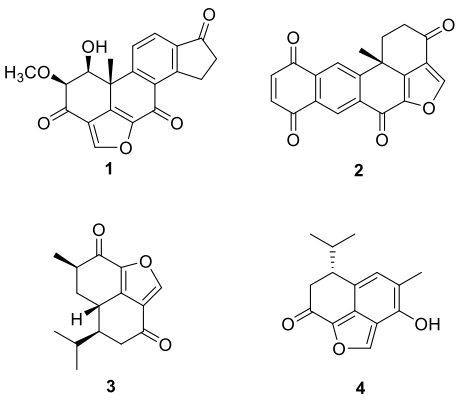
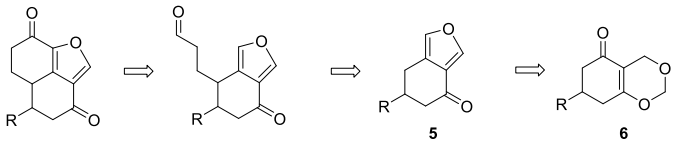


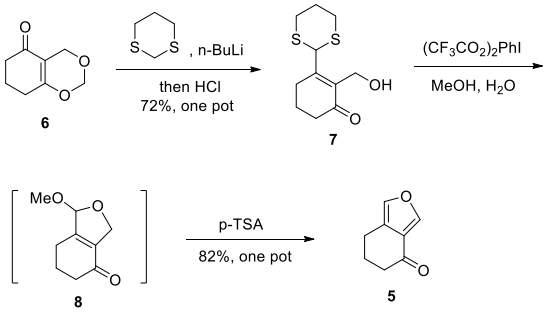
Figure 1. Structures of acyl furans

Our approach began with enone **6**, as shown in the retrosynthetic analysis in Scheme 1. Enones such as 6 are readily constructed from cyclohexane-1,3-diones. Initially, we used enone 6 (R = H)[9] to identify optimal conditions. Interestingly, 5 (R = H) has not previously been reported.



Scheme 1. Retrosynthetic analysis

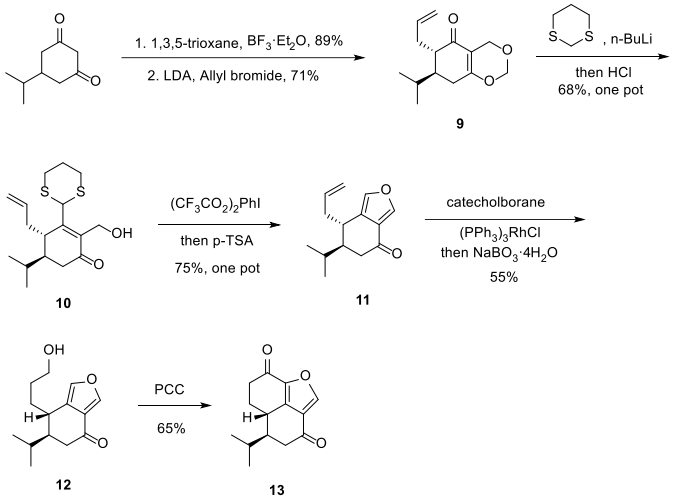
As shown in Scheme 2, the synthesis of furan **5** from **6** required a one-carbon nucleophile. The dithiane anion reacted efficiently with **6** to provide the alkoxide which was quenched with 2M aqueous HCl to afford **7** in 68% yield. The dithiane alcohol **7** was oxidized with bis(trifluoroacetoxy)iodibenzene in wet methanol to provide an acetal **8** which could be convertedinto **5** using PTSA in 75% yield over two steps.



Scheme 2. Synthesis of core structure **5**

* Corresponding author. Tel.: +0-000-000-0000; fax: +0-000-000-0000; e-mail: gakraus@iastate.edu

With a good route to furan **5**, we focused on the pathway to hibiscone C shown in Scheme 3. Commercially available 5-isopropyl-1,3-cyclohexanedione was converted into an acetal which was alkylated with allyl bromide to give **9** in 71% yield. The coupling constant of 4.8 Hz confirmed that the two groups were trans. Reaction with dithianyl lithium followed by quenching with HCl afforded enone **10** in 68% yield. Dithiane removal and aromatization furnished **11** in 75% yield. Conversion of the alkene to the primary alcohol using common hydroboration-oxidation conditions gave low yields. Fortunately, reaction with catechol borane mediated by Wilkenson's catalyst[10] gave a 55% yield of compound **12**. Oxidation of alcohol **12** with excess PCC generated an aldehyde which cyclized to a furanyl alcohol which was oxidized in situ to afford diacylfuran **13**. Since 12 was an intermediate in the synthesis of hibiscone C by Lu[7], this represents a formal total synthesis of **3**.



Scheme 3. Synthesis of compound **13**

The successful synthesis of hibiscone C showcases a direct route to 2,4-diacyl furans. The route is scalable and the individual reactions are operationally convenient.

Acknowledgments

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11. Experimental procedure for the synthesis of **3-(1,3-dithian-2-yl)-2-(hydroxymethyl)cyclohex-2-en-1-one (7):** 1,3-dithiane (574 mg, 4.77 mmol) was dissolved in 15 mL freshly distilled THF in a round bottom flask and cooled to -78 °C. n-BuLi solution (2.5M, 4.4 mmol) was added dropwise and the mixture was stirred at -78 °C for 1.5 hours. **6** (566 mg, 3.67 mmol) in 10 mL THF was added dropwise to the flask at -78 °C, warm up to room temperature and let it stir for additional 6 hours. Quench the reaction with 2M aqueous HCl (5 mL) and stir for overnight. Extract with Ethyl Acetate and dried over sodium sulfate. Concentration and flash column chromatography gave compound **7** in 72% yield; ^{1}H NMR (400 MHz, Chloroform-d) δ = 5.31 (s, 1H), 4.47 (d, J=5.9, 2H), 3.09 – 2.97 (m, 2H), 2.88 (ddd, J=14.6, 4.3, 3.0, 2H), 2.63 (t, J=6.0, 3H), 2.42 (dd, J=7.5, 6.0, 2H), 2.15 (ddt, J=14.2, 4.3, 2.0, 1H), 2.03 – 1.93 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-d) δ = 156.2, 56.4, 50.6, 37.5, 31.0, 28.0, 25.0, 22.1; HRMS (ESI-QTOF) calcd for $C_{11}H_{16}O_2S_2$ $[M+H]^+$ 245.0664, found 245.0663.
12. Experimental procedure for the synthesis of **6,7-dihydroisobenzofuran-4(5H)-one (5):** **7** (319 mg, 1.31 mmol) was dissolved in methanol and water mixture solvent (4.5 mL methanol, 0.5 mL water). To the mixture was added bis(trifluoroacetoxy)iodobenzene (1.127 g, 2.62 mmol) portionwise at 0 °C, warm up to room temperature and let it stir for 1 hour. P-TSA (500mg, 2.62 mmol) was added and the mixture was stirred at 60 °C for 6 hours. The reaction was cooled to room temperature before water was added, extract with Ethyl Acetate and dried over sodium sulfate. Concentration and flash column chromatography gave compound **5** in 82% yield; ^{1}H NMR (400 MHz, Chloroform-d) δ = 7.95 (d, J=1.4, 1H), 7.25 (q, J=1.4, 1H), 2.66 (td, J=6.2, 1.4, 3H), 2.52 – 2.42 (m, 2H), 2.08 – 1.96 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-d) δ = 195.2, 144.2, 138.1, 124.6, 124.0, 39.7, 24.0, 19.6; HRMS (ESI-QTOF) calcd for $C_8H_8O_2$ $[M+H]^+$ 137.0597, found 137.0601.
13. **4-allyl-3-(1,3-dithian-2-yl)-2-(hydroxymethyl)-5-isopropylcyclohex-2-en-1-one (10):** compound **10** was synthesized in 68% yield using the procedure for compound **7**; ^{1}H NMR (400 MHz, Chloroform-d) δ = 5.80 (dddd, J=17.0, 10.2, 8.5, 5.3, 1H), 5.18 – 5.08 (m, 2H), 4.89 (s, 1H), 4.65 (d, J=2.8, 2H), 3.04 – 2.93 (m, 2H), 2.90 – 2.82 (m, 2H), 2.81 – 2.56 (m, 3H), 2.49 – 2.42 (m, 1H), 2.30 – 2.21 (m, 1H), 2.15 (dtt, J=13.7, 4.5, 2.2, 1H), 1.96 – 1.85 (m, 1H), 1.73 – 1.65 (m, 1H), 1.62 – 1.53 (m, 1H); ^{13}C NMR (100 MHz, Chloroform-d) δ = 200.2, 156.1, 137.6, 136.0, 117.4, 57.1, 51.7, 42.2, 41.8, 36.6, 35.9, 32.4, 32.0, 29.2, 25.1, 21.3, 20.8; HRMS (ESI-QTOF) calcd for $C_{17}H_{26}O_2S_2$ $[M+H]^+$ 327.1447, found 327.1445.
14. **7-allyl-6-isopropyl-6,7-dihydroisobenzofuran-4(5H)-one (11):** compound **11** was synthesized in 75% yield using the procedure for compound **5**; ^{1}H NMR (400 MHz, Chloroform-d) δ = 7.95 (d, J=1.4, 1H), 7.30 (t, J=1.4, 1H), 5.79 (dddd, J=17.4, 9.7, 7.5, 6.4, 1H), 5.10 (dq, J=4.9, 1.7, 1H), 5.07 (d, J=2.0, 1H), 2.91 (d, J=5.9, 1H), 2.63 – 2.47 (m, 2H), 2.43 – 2.36 (m, 2H), 1.86 – 1.77 (m,

2H); ^{13}C NMR (100 MHz, Chloroform-d) δ = 194.9, 143.5, 139.0, 135.3, 127.3, 123.5, 117.1, 45.3, 38.6, 37.1, 33.0, 27.7, 21.1, 17.9; HRMS (ESI-QTOF) calcd for $C_{14}H_{18}O_2$ $[M+H]^+$ 219.1380, found 219.1378.

15. **5-isopropyl-5,5a,6,7-tetrahydro-3H-naphtho[1,8-bc]furan-3,8(4H)-dione (13): 12** (115 mg, 0.49 mmol) was dissolved in 2 mL DCM, to the solution PCC (431 mg, 1.96 mmol) was added and the mixture was stirred for 3 hours at room temperature. Short column was performed before drying over sodium sulfate. Concentration and Flash column chromatography gave compound **13** in 65% yield; 1H NMR (400 MHz, CDCl3) δ = 8.09 (s, 1H), 2.96 (td, J = 11.4, 4.8 Hz, 1H), 2.72 – 2.65 (m, 2H), 2.60 (dd, J = 16.8, 2.8 Hz, 1H), 2.45 (dq, J = 12.5, 4.1 Hz, 1H), 2.34 (dd, J = 16.8, 13.3 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.90 (ddd, J = 13.7, 5.5, 2.7 Hz, 1H), 1.75 (ddd, J = 24.4, 12.5, 5.6 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-d) δ = 193.4, 185.0, 147.4, 145.8, 145.6, 48.0, 39.9, 38.7, 34.2, 29.7, 26.7, 20.9, 15.5; HRMS (ESI-QTOF) calcd for $C_{14}H_{16}O_3$ $[M+H]^+$ 233.1172, found 233.1173.