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

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

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Acyl furans from cyclohexane-1,3-diones – A synthesis of hibiscone C
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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 syntheses1 of 1 and a number of innovative approaches2 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 syntheses4 of 2 and approaches5 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

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.

Figure 2. Synthesis of core structure 5

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)iodobenzene in wet methanol to provide an acetal 8 which could be converted into 5 using p-TSA in 75% yield over two steps.

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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 dithiinyl lithium followed by quenching with HCl afforded enone 10 in 68% yield. Dithiane removal and aromatization furnished 11 in 75% yield. Conversion of the alkenone to the primary alcohol which was oxidized to an aldehyde which was 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, 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-diacylfurans. The route is scalable and the individual reactions are operationally convenient.

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References and Notes


6. Experimental procedure for the synthesis of 6,7-dihydrodibenzofuran-4(5H)-one (5): (a) 319 mg (1.31 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 mL) 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; 1H NMR (400 MHz, Chloroform-d) δ = 5.31 (s, 1H), 4.47 (d, J=5.9, 2H), 3.99 – 3.27 (m, 2H, 2.88 (d, 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 (dtt, J=14.2, 4.3, 2.0, 1H), 2.03 – 1.93 (m, 2H, 13C NMR (100 MHz, Chloroform-d) δ = 156.2, 156.4, 50.6, 35.7, 31.0, 28.0, 25.0, 22.1; HRMS (ESI-QTOF) cale for C15 H26 O3 Si [M+H] + 245.0664, found 245.0663.

7. Experimental procedure for the synthesis of 6,7-dihydrodibenzofuran-4(5H)-one (11): 6 was synthesized in 68% yield using the procedure for compound 7; 1H NMR (400 MHz, Chloroform-d) δ = 7.95 (d, J=1.4, 1H), 7.25 (q, J=1.4, 1H), 2.56 (dd, J=6.2, 1.4, 3H), 2.52 – 2.42 (m, 2H), 2.08 – 1.96 (m, 2H); 13C NMR (100 MHz, Chloroform-d) δ = 179.2, 143.2, 138.1, 124.6, 124.0, 39.7, 24.0, 19.6; HRMS (ESI-QTOF) cale for C16 H28 O4 Si [M+H] + 237.0597, found 237.0601.

8. This compound was synthesized in 75% yield using the procedure for compound 5; 1H NMR (400 MHz, Chloroform-d) δ = 7.95 (d, J=1.4, 1H), 7.30 (t, J=1.4, 1H), 5.79 (d, J=17.4, 9.7, 5.6, 6.4, 5H), 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); 13C 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 C14H18O2 [M+H]+ 219.1380, found 219.1378.

15. 5-isopropyl-5a,6,7-tetrahydro-3H-naphtho[1,8-be]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), 2.45 (dq, 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); 13C 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 C14H16O3 [M+H]+ 233.1172, found 233.1173.