DABCO-Catalyzed Reaction of 2,6-Disubstituted 6-Hydroxy-2*H*-pyran-3(6*H*)-ones to 1,2,5-Triketones

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Abstract: The DABCO-catalyzed isomerization/redox rearrangement readily converts 2,6-dialkyl-6-hydroxy-2*H*-pyran-3(6*H*)-ones into 1,2,5-triketones.

Key words: furans, ketones, oxidation, isomerization, catalysis

Furans exhibit multifaceted reactivity that can be exploited for the synthesis of diverse natural products.¹ The oxidative rearrangement of α -hydroxyalkylfurans **1**, the Achmatowicz reaction,² has been one of the most heavily utilized reactions (Scheme 1). The resulting pyranones **2** have been further manipulated into various polyfunctional intermediates for the total synthesis of biologically important compounds such as the seco-acids of erythromycin A and B,³ englerin A,⁴ and anthrax tetrasaccharide.⁵



Scheme 1

Although the manipulation of pyranones 2 into 1,2,5triketones 3 is conceptually possible through a suitable series of oxidation and reduction steps, there are no reports of the synthesis of 3 based on 2. The 1,2,5-triketone moiety has appeared in some natural products,^{6,7} and has served as an intermediate for the synthesis of spiroacetals of marine natural products.⁸ Given the general availability of pyranones 2 and the importance of triketones 3, we report the direct synthesis of 3 from 2 by the DABCOcatalyzed isomerization/redox rearrangement reactions (Table 1).

The preferred catalyst for the conversion of 2 into 3 is DABCO (40 mol%), with more basic amines such as Hünig's base, triethylamine, DBU, and DBN giving lower yields due to unidentified side reactions. Acetonitrile was the optimal solvent, although reactions conducted in chloroform and dichloromethane gave comparable yields, but at a slower rate of reaction. Higher catalyst loadings, lower reaction temperature, and longer reaction times gave

Table 1DABCO-Catalyzed Reaction of 2,6-Disubstituted 6-Hy-droxy-2H-pyran-3(6H)-ones 2



Starting material	\mathbb{R}^1	\mathbb{R}^2	Yield (%) of 3	
2a	Me	$c - C_6 H_{11}$	86	
2b	Me	Me	33	
2c	Me	<i>n</i> -Bu	79	
2d	Me	Me(CH ₂) ₉	78	
2e	Me	<i>i</i> -Pr	83	
2f	Me	allyl	55 ^a	
2g	Me	4-MeC ₆ H ₄	81	
2h	Et	Me	55	
2i	Et	Et	62	
2j	(CH ₂) ₃ CH=CH ₂	<i>i</i> -Pr	75	

^a Product was (*E*)-MeCOCH₂CH₂COCOCH=CHMe.

good yields of **3**, although comparable to the optimized procedure. With a lower catalyst load (10 mol% DABCO) and longer reaction times, slightly diminished yields were obtained (e.g., 78% for **2a**). In the case of allylic pyranone **2f**, further isomerization to the unsaturated ketone was observed (Table 1).

The potential to prepare aldehydes by this method was briefly investigated with pyranones **2k** and **2l** (Figure 1). Pyranone **2k** was unreactive under the standard reaction conditions; forcing the reaction by increasing the catalyst loading and longer reaction times gave unidentified compounds with a very low yield of the desired aldehyde, as evidenced by the crude ¹H NMR spectrum. In the case of pyranone **2l**, the conversion of starting material was rapid, but the yields of the desired aldehyde product again were very low.

When the DABCO-catalyzed reaction of **2** was monitored by ¹H NMR spectroscopy, an intermediate was observed, which was identified as the diketone (*E*)-**4** (Scheme 2). In the case of the DABCO-catalyzed rearrangement of **2a** to

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Figure 1 Pyranones 2k and 2l

3a, the formation of substantial amount of (*E*)-**4a** was observed [40% yield of (E)-4a at 70% conversion of 2a]. With smaller R^2 groups (such as 2c), a much lower concentration of the intermediate diketone (E)-4 was observed. Based on this limited information and the previously described amine-catalyzed conversion of chaetoglobosin B [possessing the (E)-4 substructure] to chaetoglobosin G (a 1,2,5-triketone),⁶ the conversion of **2** into **3** is proposed to proceed by the pathway shown in Scheme 2. Tautomerism of 2 to the unobserved openchain tautomer (Z)-4 is followed by the attack by DABCO and subsequent isomerization to (E)-4. DABCO-catalyzed keto-enol tautomerism of (E)-4 gives enol 5, which gives 6 and then triketone 3. The larger R^2 groups would impede tautomerism of (E)-4 to 5 due to steric effects, but would have limited effect on the isomerization of (Z)-4 to (*E*)-4, hence the build-up of (*E*)-4a in our NMR studies.





The one-pot DABCO-catalyzed reaction of 2 to 3 is a practical method for the synthesis of 1,2,5-triketones. Since the disconnection for a given 1,2,5-triketone synthetic target would be different from the disconnection based on alkyne intermediates,⁸ this method compliments existing methodology. The conversion of 2 into 3 by this methodology is inherently 'greener' with greater atom economy⁹ than a series of oxidation and reduction steps. Finally, the conversion of 2 into 3 adds to the long and

ever-growing list of useful synthetic transformations using furan intermediates.

All reactions were carried out under argon. IR spectra were obtained on a Mattson Satellite FT-IR spectrophotometer. The ¹H and ¹³C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a JEOL Eclipse+400 spectrometer; all chemical shifts are reported in ppm relative to TMS ($\delta = 0.00$ ppm) or CHCl₃ ($\delta = 7.26$ ppm) in the ¹H NMR and relative to CDCl₃ ($\delta = 77.16$ ppm) in the ¹³C NMR. HRMS were obtained on a GCT Premier mass spectrometer at the MSU Mass Spectrometry Facility. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Pyranones **2** were prepared according to literature procedures.¹⁰

1-Cyclohexylhexane-1,2,5-trione (3a); Typical Procedure

To a reaction flask charged with 2-cyclohexyl-6-hydroxy-6-methyl-2*H*-pyran-3(6*H*)-one¹⁰ (0.423 g, 2.01 mmol) and MeCN (15 mL) was added a solution of DABCO (0.0899 g, 0.801 mmol) in MeCN (5 mL) under argon while stirring. The flask was kept in an oil bath and the solution was heated to reflux for 2 h. The contents of the reaction flask were transferred to a separatory funnel with EtOAc (75 mL). The organic phase was washed with H₂O (50 mL), aq 0.1 M HCl (25 mL), H₂O (25 mL), and brine (50 mL). The organic phase was dried (Na₂SO₄) and evaporated on the rotary evaporator to give the crude 1,2,5-triketone **3a**. Kugelrohr distillation (75 °C/0.1 mmHg) gave pure **3a**; yield: 0.365 g (86%); yellow oil.

¹H NMR (400 MHz, CDCl₃): δ = 3.11 (m, 1 H), 2.92 (m, 2 H), 2.80 (m, 2 H), 2.19 (s, 3 H), 1.87–1.64 (m, 5 H), 1.40–1.14 (m, 5 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.5, 202.2, 199.1, 43.3, 37.1, 30.7, 29.7, 27.8, 25.9, 25.5.

HRMS: *m*/*z* calcd for C₁₂H₁₈O₃: 210.1256; found: 210.1252.

Heptane-2,3,6-trione (3b)¹¹

Yield: 33%; yellow oil (60 $^{\circ}$ C/0.1 mmHg).

¹H NMR (400 MHz, CDCl₃): δ = 2.92 (m, 2 H), 2.82 (m, 2 H), 2.34 (s, 3 H), 2.19 (s, 3 H).

Decane-2,5,6-trione (3c)

Yield: 79%; yellow solid (60 °C/0.1 mmHg); mp 29-31 °C.

¹H NMR (400 MHz, CDCl₃): δ = 2.93 (m, 2 H), 2.81 (m, 2 H), 2.74 (t, *J* = 7.4 Hz, 2 H), 2.19 (s, 3 H), 1.57 (pent, *J* = 7.5 Hz, 2 H), 1.34 (sext, *J* = 7.4 Hz, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.7, 199.8, 198.6, 37.5, 35.8, 30.1, 29.7, 25.1, 22.4, 13.9.

HRMS: *m*/*z* calcd for C₁₀H₁₆O₃: 184.1099; found: 184.1095.

Hexadecane-2,5,6-trione (3d)

Yield: 78%; yellow solid (140 °C/0.1 mmHg); mp 62-64 °C.

¹H NMR (400 MHz, CDCl₃): δ = 2.94 (m, 2 H), 2.82 (m, 2 H), 2.74 (t, *J* = 7.3 Hz, 2 H), 2.20 (s, 3 H), 1.59 (m, 4 H), 1.27 (m, 12 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.7, 199.8, 198.6, 37.4, 36.2, 32.0, 30.1, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 23.1, 22.8, 14.2.

HRMS: m/z calcd for $C_{16}H_{28}O_2$ (M – H_2O): 250.1933; found: 250.1935.

7-Methyloctane-2,5,6-trione (3e)

Yield: 83%; yellow oil (60 °C/0.1 mmHg).

¹H NMR (400 MHz, CDCl₃): δ = 3.34 (sept, *J* = 6.9 Hz, 1 H), 2.94 (m, 2 H), 2.80 (m, 2 H), 2.19 (s, 3 H), 1.10 (d, *J* = 7.0 Hz, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.6, 202.9, 199.0, 37.1, 33.9, 30.8, 29.7, 17.5.

HRMS: *m/z* calcd for C₉H₁₄O₃: 170.0943; found: 170.0944.

(7*E*)-Non-7-ene-2,5,6-trione (3f)

Yield: 55%; yellow oil (60 °C/0.1 mmHg). Decomposed on standing at r.t.

¹H NMR (400 MHz, CDCl₃): δ = 7.17 (dq, *J* = 16.1, 6.9 Hz, 1 H), 6.64 (dm, *J* = 15.8 Hz, 1 H), 2.99 (t, *J* = 6.0 Hz, 2 H), 2.81 (t, *J* = 6.0 Hz, 2 H), 2.20 (s, 3 H), 1.98 (dd, *J* = 7.0, 1.5 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.7, 200.2, 187.9, 149.9, 124.9, 37.1, 30.9, 29.8, 19.2.

HRMS: *m*/*z* calcd for C₉H₁₂O₃: 168.0786; found: 168.0790.

1-(4-Methylphenyl)hexane-1,2,5-trione (3g)

Yield: 81%; yellow oil (110 °C/0.1 mmHg).

¹H NMR (400 MHz, CDCl₃): δ = 7.90 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 3.08 (m, 2 H), 2.90 (m, 2 H), 2.41 (s, 3 H), 2.23 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.7, 202.0, 192.0, 145.9, 130.6, 129.6, 129.4, 36.9, 32.5, 29.8, 22.0.

HRMS: m/z calcd for $C_{13}H_{12}O_2$ (M – H_2O): 200.0837; found: 200.0835.

Octane-2,3,6-trione (3h)

Yield: 55%; yellow oil (60 °C/0.1 mmHg).

¹H NMR (400 MHz, CDCl₃): δ = 2.92 (m, 2 H), 2.79 (m, 2 H), 2.48 (q, *J* = 7.4 Hz, 2 H), 2.34 (s, 3 H), 1.06 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 209.6, 198.3, 197.3, 36.3, 35.7, 29.7, 23.8, 7.8.

HRMS: *m*/*z* calcd for C₈H₁₂O₃: 156.0786; found: 156.0784.

Nonane-3,4,7-trione (3i)¹²

Yield: 62%; yellow solid (80 °C/0.1 mmHg); mp 35-37 °C.

¹H NMR (400 MHz, CDCl₃): δ = 2.95 (m, 2 H), 2.80 (m, 2 H), 2.79 (q, *J* = 7.4 Hz, 2 H), 2.49 (q, *J* = 7.3 Hz, 2 H), 1.10 (t, *J* = 7.0 Hz, 3 H), 1.07 (t, *J* = 7.3 Hz, 3 H).

2-Methyldodec-11-ene-3,4,7-trione (3j)

Yield: 75%; yellow oil (100 °C/0.1 mmHg).

¹H NMR (400 MHz, CDCl₃): δ = 5.57 (ddt, *J* = 17.2, 10.3, 6.6 Hz, 1 H), 4.94–5.05 (m, 2 H), 3.34 (sept, *J* = 7.0 Hz, 1 H), 2.94 (m, 2 H), 2.77 (m, 2 H), 2.46 (t, *J* = 7.3 Hz, 2 H), 2.05 (br q, *J* = 7.1 Hz, 2 H), 1.68 (pent, *J* = 7.3 Hz, 2 H), 1.10 (d, *J* = 7.0 Hz, 6 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 208.7, 202.9, 199.1, 138.0, 115.4, 41.8, 36.3, 33.9, 33.1, 30.8, 22.9, 17.5.

HRMS: m/z calcd for $C_{13}H_{18}O_2$ (M – H_2O): 206.1307; found: 206.1309.

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