

Thermal cycloreversion of 4*H*-1,3-dioxine-4-thiones to acyl thioketenes: a general synthesis of β -keto thioic *O*-acid derivatives

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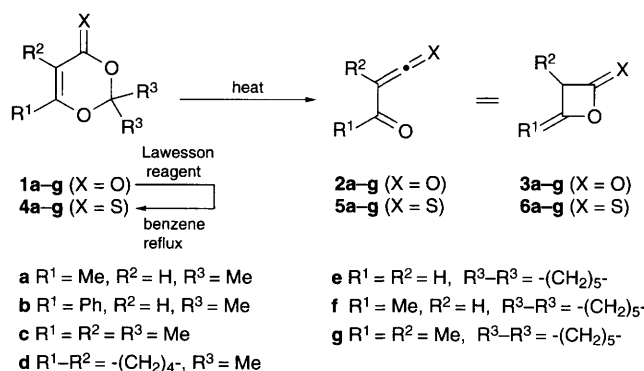
Thermal cycloreversion of 4*H*-1,3-dioxine-4-thiones gives acyl thioketenes as reactive intermediates, trapping of which by nucleophiles provides a general synthesis for β -keto thioic *O*-acid derivatives.

Acyl ketenes **2** are currently of major interest in synthetic and mechanistic studies.^{1–3} The most important methods for the production of these reactive molecules are the thermolysis of 4*H*-1,3-dioxine-4-ones **1** or 2,3-dihydrofuran-2,3-diones and the photolysis of α -diazo- β -diketones.^{1b} Among these methods, the thermal cycloreversion of **1** to **2** is the most attractive from the synthetic viewpoint because a variety of substituents can be readily introduced into the 5- and 6-positions of the precursor and the cycloreversion can be conducted at a practical temperature (100–160 °C).² Thus, **1** acted as the chemical equivalent of the mixed diketene **3**^{1c,4} which is not readily accessible and thus broadened its chemistry.⁵ On the other hand, the chemistry of the acyl thioketenes **5** has not been studied extensively due to the general unavailability of these reactive molecules.^{1a,6} Here we report the first synthesis of 4*H*-1,3-dioxine-4-thiones **4** and their successful use as chemical equivalent of the thionated mixed diketene **6** through **5** providing a general preparation β -oxo thioic *O*-acid derivatives whose syntheses are usually troublesome.^{7,†}

Heating a mixture of **1** and Lawesson's Reagent (2–3 equiv.)⁸ in refluxing benzene for 4–6 h followed by silica gel column chromatography afforded **4**,[‡] (Table 1). The low yield of

5,6-unsubstituted derivative **4e** seemed to be due to the significant decomposition of **1e** and **4e** during the thionation. Attempted thionation of **1a** and **1e** with P₂S₅ in pyridine at 60–80 °C resulted in decomposition of **1a** and **1e**, respectively. Mass spectroscopy of **4** showed, besides the molecular ion peak, very pronounced peaks of compound **5** and a ketone. By analogy with the mass spectral fragmentation of **1** to **2**,^{2c} this implies the possible retro [4+2] cycloreversion of **4** by heating.

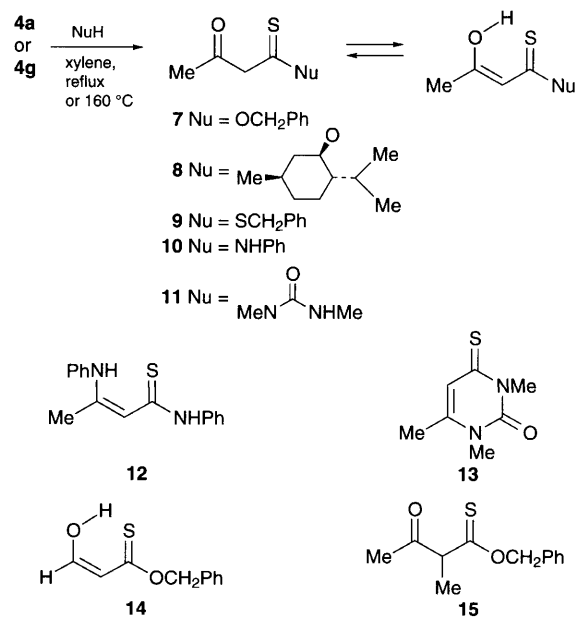
In order to recognize the cycloreversion of **4** to **5**, the thermal reaction of **4** in the presence of nucleophiles was examined. The reaction of **4a** with benzyl alcohol and benzyl thiol in boiling xylene for 1.5 h gave **7** (50%) and **9** (50%), respectively. The reaction with aniline (2 equiv.) gave **10**, which reacted *in situ* with another mole of aniline to give enaminothioamide **12** in 61% yield. Hydrolysis of **12** with 10% HCl quantitatively gave **10**.^{7d} The reaction with 1,3-dimethylurea also gave the thioacylated product **11**, which cyclized *in situ* to the thiouracil derivative **13** (83%, mp 176–177 °C). The consumption rate of **4a** in these reactions was independent of the nucleophiles and all the reactions ran to completion within 1.5 h as shown by TLC. This observation strongly supports the initial cycloreversion of **4a** to acetyl thioketene **5a**, which is spontaneously trapped by nucleophiles to give thioacylated products. In an alternative mechanism involving nucleophilic attack of the thiocarbonyl group of **4a**, the rate should be different depending on nucleophilicity of attacking reagents.^{2a} Other 1,3-dioxine-4-thiones also gave thioacylated products on reaction with alcohols with heating. For example, the treatment of the spiro derivative **4f** with benzyl alcohol and L-menthol at 160 °C in xylene (sealed tube) gave **7** (82%) and **8** (88%), respectively.



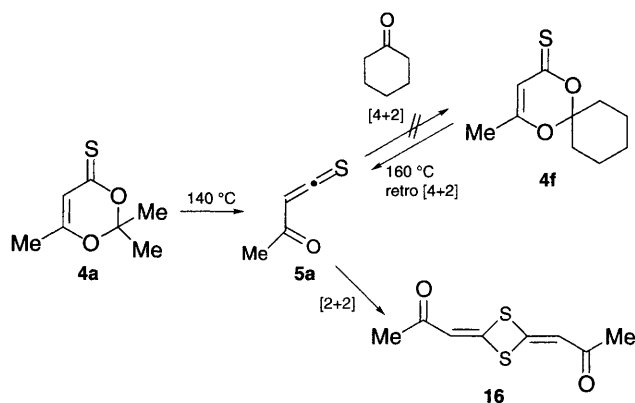
Scheme 1

Table 1 4*H*-1,3-Dioxine-4-thione derivatives

Derivative 4	Substituent			Yield (%)	mp/°C
	R ¹	R ²	R ³		
a	Me	H	2 × Me	50	45–46
b	Ph	H	2 × Me	63	46–47
c	Me	Me	2 × Me	52	59–60
d	–(CH ₂) ₄ –		2 × Me	50	oil
e	H	H	–(CH ₂) ₅ –	9	oil
f	Me	H	–(CH ₂) ₅ –	46	oil
g	Me	Me	–(CH ₂) ₅ –	69	49–50



Scheme 2



Scheme 3

Treatment of **4e** with benzyl alcohol gave **14** in 29% yield. This low yield is due mostly to the polymerization of **14** during purification by distillation. The reaction of **4c** occurred at 170 °C (xylene, sealed tube) to give **15** (90%). All of the β -keto thioic esters except for **15** existed as enol forms to a great extent as shown by ^1H NMR spectroscopy.

Acylketenes are known to undergo hetero-Diels–Alder reactions with a variety of dienophiles including ketones.¹ However, treatment of **4a** with cyclohexanone at 140 °C did not give **4f** but gave the dithietane derivative **16** (mp 214–215 °C),⁹ in 22% yield, instead. Product **1b** was also obtained by heating **4f** at 160 °C. The formation of **16** also supports the intermediate **5** in the thermal reaction of **4**, because dithietanes of this type are known to be formed by [2+2]-dimerization of acyl thioketenes and thioketenes (Scheme 3).⁶

It should be noted that the required cycloreversion temperature of **4** (140 °C for **4a** and **4e**, 160 °C for **4f**, and 170 °C for **4c**) is higher than that for the corresponding compound **1** by 10–20 °C and affected by substituents at the 2-, 5- and 6-positions by analogy to **1**. These substituent effects including that of the thiocarbonyl group are important in discussing the detailed reaction mechanism of the cycloreversion of **1** which has been suggested to be slightly different from the usual retro-Diels–Alder process based on *ab initio* calculations of the transition structure.^{3a,b}

Footnotes

†All new compounds gave satisfactory analytical and/or spectral data.

‡Selected data for **4a**: ^1H NMR (60 MHz, CDCl_3) δ 1.73 (6 H, s), 1.95 (3 H, s) and 6.13 (1 H, s); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1610. For **4b**: ^1H NMR (60

MHz, CDCl_3) δ 1.82 (6 H, s), 6.77 (1 H, s) and 7.3–8.0 (5 H, m); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1604 and 1580. For **4c**: ^1H NMR (60 MHz, CDCl_3) δ 1.72 (6 H, s), 2.01 (3 H, s) and 2.06 (3 H, s); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1607. For **4d**: ^1H NMR (60 MHz, CDCl_3) 1.68 (6 H, s) and 2.0–2.7 (8 H, m); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1620. For **4e**: ^1H NMR (60 MHz, CDCl_3) δ 1.1–2.3 (10 H, m) 6.15 (1 H, d, J 6.0 Hz) and 7.00 (1 H, d, J 6.0 Hz); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1602. For **4f**: ^1H NMR (60 MHz, CDCl_3) δ 0.9–2.2 (10 H, m), 1.96 (3 H, s) and 6.12 (1 H, s); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1613. **4g**: ^1H NMR (60 MHz, CDCl_3) δ 1.1–2.4 (10 H, m), 2.03 (3H, s) and 2.07 (3 H, s); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1623. For **16**: ^1H NMR (60 MHz, CDCl_3) δ 2.27 (6 H, s) and 6.55 (2 H, s); IR (CHCl_3) $\nu_{\text{max}}/\text{cm}^{-1}$ 1665 and 1523.

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