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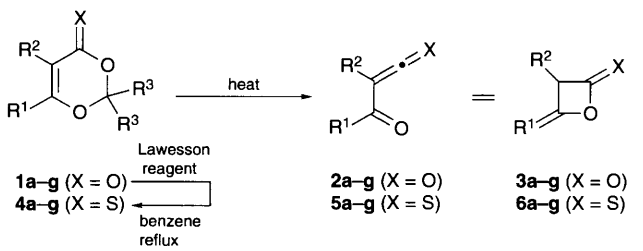
Thermal cycloreversion of 4*H*-1,3-dioxine-4-thiones gives acyl thioketenes as reactive intermediates, trapping of which by nucleophiles provides a general synthesis for β-keto thioic *O*-acid derivatives.

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-dioxin-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 P_2S_5 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.



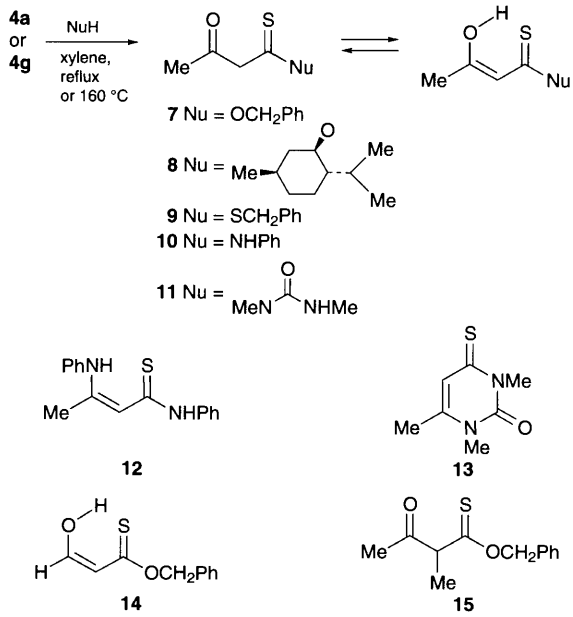
a R^1 = Me, R^2 = H, R^3 = Me
b R^1 = Ph, R^2 = H, R^3 = Me
c R^1 = R^2 = R^3 = Me
d R^1–R^2 = -$(CH_2)_4$-, R^3 = Me
e R^1 = R^2 = H, R^3–R^3 = -$(CH_2)_5$-
f R^1 = Me, R^2 = H, R^3–R^3 = -$(CH_2)_5$-
g R^1 = R^2 = Me, R^3–R^3 = -$(CH_2)_5$-

Scheme 1

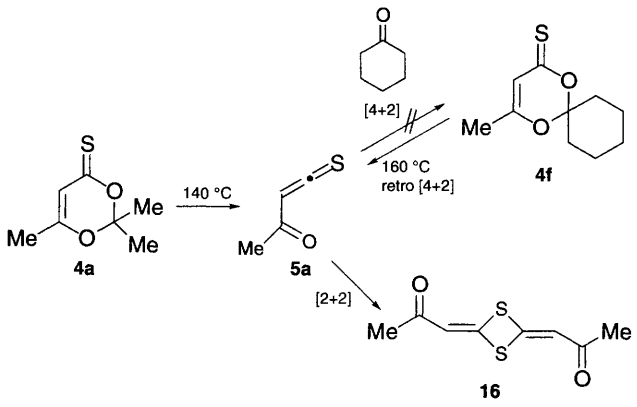
Table 1 4*H*-1,3-Dioxine-4-thione derivatives

Derivative **4**	Substituent R^1	R^2	R^3	Yield (%)	mp/°C
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

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 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** occured 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 ^{1}H 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 dithiethane 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 subsituents 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**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.73 (6 H, s), 1.95 (3 H, s) and 6.13 (1 H, s); IR ($CHCl_3$) υ_{max}/cm^{-1} 1610. For **4b**: ^{1}H 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 ($CHCl_3$) υ_{max}/cm^{-1} 1604 and 1580. For **4c**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.72 (6 H, s), 2.01 (3 H, s) and 2.06 (3 H, s); IR ($CHCl_3$) υ_{max}/cm^{-1} 1607. For **4d**: ^{1}H NMR (60 MHz, $CDCl_3$) 1.68 (6 H, s) and 2.0–2.7 (8 H, m); IR ($CHCl_3$) υ_{max}/cm^{-1} 1620. For **4e**: ^{1}H 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 ($CHCl_3$) υ_{max}/cm^{-1} 1602. For **4f**: ^{1}H 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 ($CHCl_3$) υ_{max}/cm^{-1} 1613. **4g**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.1–2.4 (10 H, m), 2.03 (3H, s) and 2.07 (3 H, s); IR ($CHCl_3$) υ_{max}/cm^{-1} 1623. For **16**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.27 (6 H, s) and 6.55 (2 H, s); IR ($CHCl_3$) υ_{max}/cm^{-1} 1665 and 1523.

References

1 (*a*) T. T. Tidwell, *Ketenes*, John Wiley & Sons, New York, 1995; (*b*) C. Wentrup, W. Heilmayer and G. Kollenz, *Synthesis*, 1994, 1219; (*c*) C. Kaneko, M. Sato, J. Sakaki and Y. Abe, *J. Heterocycl. Chem.*, 1990, **27**, 25.

2 See for example (*a*) R. J. Clemens and J. S. Witzeman, *J. Am. Chem. Soc.*, 1989, **111**, 2186; (*b*) M. Sato, M. Murakami, S. Sunami, C. Kaneko, T. Furuya and H. Kurihara, *J. Am. Chem. Soc.*, 1995, **117**, 4279; (*c*) M. Sato, H. Ogasawara, K. Oi and T. Kato, *Chem. Pharm. Bull.*, 1983, **31**, 1896; (*d*) R. K. Boeckman, Jr. and J. R. Pruit, *J. Am. Chem. Soc.*, 1989, **111**, 8286. (*e*) R. S. Coleman and E. B. Grant, *Tetrahedron Lett.*, 1990, **31**, 3677.

3 (*a*) D. M. Birney and P. E. Wagenseller, *J. Am. Chem. Soc.*, 1994, **116**, 6262; (*b*) P. E. Wagenseller, D. M. Birney and D. Roy, *J. Org. Chem.*, 1995, **60**, 2853; (*c*) S. W. E. Eisenberg, M. J. Kurth and W. H. Fink, *J. Org. Chem.*, 1995, **60**, 3736; (*d*) S. L. Gong, M. A. McAllister and T. T. Tidwell, *J. Am. Chem. Soc.*, 1991, **113**, 6021; A. D. Allen, M. A. McAllister and T. T. Tidwell, *Tetrahedron Lett.*, 1993, **34**, 1095; (*e*) M. W. Wong and C. Wentrup, *J. Org. Chem.*, 1994, **59**, 5279; (*f*) R. Lopez, D. Suarez, M. F. Ruiz-Lopez, J. Gonzalez, J. A. Sordo and T. L. Sordo, *J. Chem. Soc., Chem. Commun.*, 1995, 1677.

4 Y. Oikawa, K. Sugano and O. Yonemitsu, *J. Org. Chem.*, 1978, **43**, 2087.

5 R. J. Clemens, *Chem. Rev.*, 1986, **86**, 241; T. Kato, *J. Heterocycl. Chem.*, 1982, **6**, 105.

6 E. Schaumann, *Tetrahedron*, 1988, **44**, 1827.

7 (*a*) J. Boss, in *The Chemistry of Acid Derivatives, part 2, Supplement B*, ed. S. Patai, John Wiley & Sons, Ltd., Chichester, 1979; pp 1021-1062; (*b*) A. J. Bridges and G. H. Whithan, *J. Chem. Soc. Perkin Trans 1*, 1975, 1603; (*c*) M. A. Palominos, R. Rodriguez and J. C. Vega, *Chem. Lett.*, 1986, 1251; (*d*) W. Walter and T. Fleck, *Liebigs Ann. Chem.*, 1976, 670.

8 R. A. Cherkazov, G. A. Kutyrev and A-N. Pudovik, *Tetrahedron*, 1985, **41**, 2567; M. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061.

9 A. N. Mirskova, G. G. Levkovskaya, I. D. Kalikhman, T. I. Vakul'skaya, V. A. Pestunovich and M. G. Voronkov, *Izv. Akad. Nauk SSR, Ser. Khim.*, 1976, 2040; (*Chem. Abstr.*, 1977, **86**, 106 439r).

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