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An Efficient Method for Generation of α-Oxoketenes: Cycloreversion of Enolized Meldrum's Acid Derivatives

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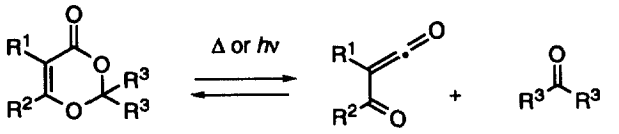
Abstract: A series of 6-methoxy- or siloxy-4*H*-1,3-dioxin-4-ones was synthesized from Meldrum's acids. These dioxinones underwent 4+2 cycloreversion to methoxy- or siloxycarbonylketenes and ketones quantitatively at 20-50 °C. The ketenes were characterized by IR spectroscopy as well as by trapping with *t*-butanol. The ready cycloreversion of these enolized Meldrum's acid derivatives strongly indicates that the anomalously high susceptibility of Meldrum's acids to nucleophilic reagents is due to the participation of carboxyketenes generated through the cycloreversion of tautomeric 6-hydroxydioxinones. © 1997 Elsevier Science Ltd.

Conjugated ketenes such as α-oxoketene (acylketene: **2**),[1] vinylketnes,[2] and bisketenes[3] are currently of major interest in synthetic and theoretical studies. Among the several methods for generating **2**, cycloreversion of 4*H*-1,3-dioxin-4-ones **1** is the most attractive from the synthetic viewpoint because the reaction can be conducted under completely neutral conditions either thermally (110-160 °C)[4,5] or photochemically.[6] The thermal cycloreversion of **1** has been also a subject of theoretical study,[7] and recent analysis of the molecular orbitals by *ab initio* calculations has revealed the unique mechanism described as a pseudopericyclic reaction.[7b]

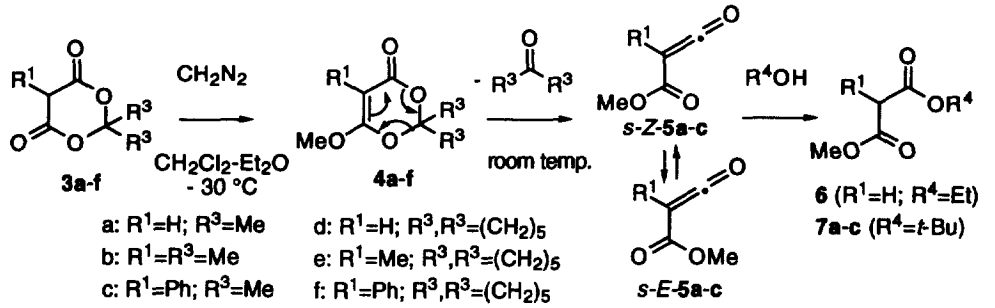


1 **2**

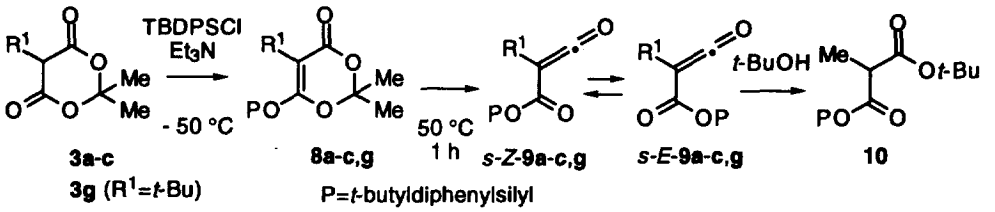
In order to develop an efficient method for generating ketenes with conjugated functionality as well as to examine the generality of the cycloreversion of dioxinones, we studied the synthesis of 6-oxygenated dioxinones and their behaviors under heating.

Methylation of Meldrum's acid **3a** with diazomethane in ethanol at 0 °C has been reported to produce ethyl methyl malonate **6**.[8] When the methylation was conducted at - 30 °C, the desired 6-methoxydioxinone **4a** was obtained as the sole product. A series of methoxydioxinones **4a-f** was readily prepared by this method, all in excellent yields.[9,10] Compounds **4a-f** are not stable at room temperature especially in solution, due to ready cycloreversion to methoxycarbonylketenes **5a-f** and ketones. However, they are stable at below -20 °C allowing ^{1}H and ^{13}C NMR measurements at low temperatures. The ketene formation was first confirmed chemically; reaction of **4a-c** with *t*-butanol (2.0 mol equiv.) in dichloromethane at room temperature for 1 h afforded *t*-butyl ester **7** in quantitative yields. IR spectroscopic study provided direct evidence for the ketene formation.

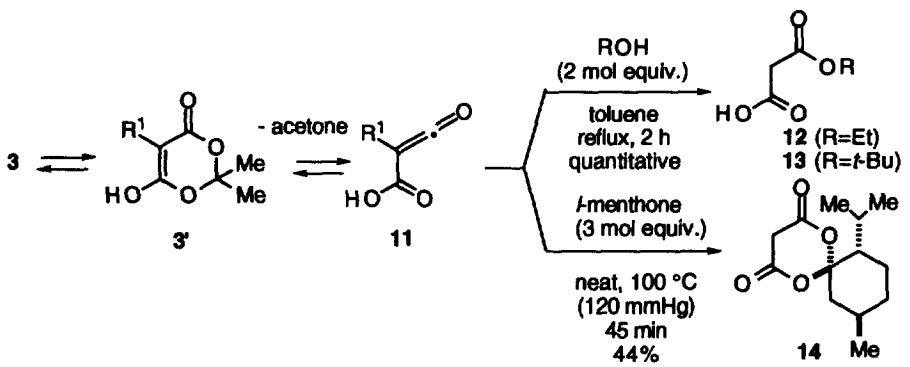
In the IR spectrum of **4** in dry chloroform at 23 °C, the absorption for the enone carbon-carbon double bond (1610-1640 cm^{-1}) gradually decreased, accompanied by the appearance of strong absortions at 2130-2149 cm^{-1} characteristic of ketenes.[11] Ketenes **5a** (2149 cm^{-1}) and **5b** (2140 cm^{-1}) are assigned to *s-Z* form whereas **5c** (2130 cm^{-1}) is assigned to *s-E* form according to the literature.[12] From the decay of the carbon-carbon double bond absorption, the half-life period of 2,2-dimethyl derivative **4a** at 23 °C in chloroform was estimated to be about 5 min and that of 5-phenyl derivative **4c** was about 20 min. The spiro derivatives **4d-f** are more stable than the corresponding dimethyl derivatives **4a-c**; the half-life period of **4f** at 23 °C was about 3 h. The cycloreversion of **4** was also confirmed by ^1H NMR spectroscopy at 23 °C as clearly shown by the decay of the signal for **4** and the appearance of the signals for **5** and acetone or cyclohexanone. Repeated NMR measurements at 23 °C indicated that **5a** and **5b** dimerize and/or oligomerize with an increase of their concentrations resulting in the formation of complex mixtures, whereas the phenyl derivative **5c** is very stable. Thus, **5c** produced by heating **4c** at 60 °C without a solvent was isolated by distillation.[11] The result clearly shows the participation of intermediate **5a** for the formation of **6** from **3a** in the previous work.[8]



Silylation of **3a-c** and **3g** (R^1=*t*-Bu) with *t*-butylchlorodiphenylsilane and triethylamine proceeded at - 50 °C to afford siloxydioxinones **8a-c** and **8g** as crystalline materials in excellent yields.[13,14] These are thermally more stable than the corresponding methoxydioxinones as shown by their IR and ^1H NMR spectra at 23 °C that did not change to any extent over several hours. On heating to 50 °C without a solvent, **8a-c** cycloreverted to ketenes **9a-c**, which polymerized rapidly under the heating as indicated by ^1H NMR analyses of the products. However, these ketenes were efficiently trapped by nucleophiles as exemplified by the reaction of **8b** with *t*-butanol (1.1 mol equiv.) in toluene at 50 °C to produce ester **10** in 98% yield. On heating to 50 °C without a solvent, **8g** afforded ketene **9g** assigned to *s-E* form (IR: 2125 cm^{-1})[15] quantitatively because it does not polymerize owing to steric protection by the *t*-butyl group on the ketene carbon.



As clearly demonstrated by the above work, 6-oxygenated dioxinones undergo the fragmentation to ketenes at much lower temperature compared to 6-alkyl or aryl substituted ones that undergo the cycloreversion at above 110 °C.[4,5] This remarkable substituent effect provides a strong suggestion concerning the mechanism for the reaction of Meldrum's acids with nucleophilic reagents.[16-20] Meldrum's acid and the 5-monoalkyl or acyl derivatives are highly susceptible to nucleophilic reagents, as exemplified by the reaction of **3a** with alcohol at 80-110 °C to produce the malonic acid derivatives **12** (R=alkyl).[17] Heretofore, the ring opening has been explained by the initial attack of the nucleophile at the C-4 of **3**,[16,17c,18] while we and others have proposed the intermediary of carboxyketene **11** in the reaction of acylated Meldrum's acids with alcohol,[19] ketones,[20] and imines.[21] The present study strongly indicates that the high susceptibility of Meldrum's acids to nucleophiles is due to the participation of **11**.[22] It is quite reasonable to assume that strongly acidic **3** (*pK* 4.83 for **3a**)[23] tautomerizes to 6-hydroxydioxinone **3'** to some extent through the conjugate base. Owing to the electron-donating hydroxyl group, **3'** undergoes the thermal cycloreversion to **11**, which is trapped by the nucleophiles to afford malonic acid derivatives. Consistent with this mechanism, reaction of **3a** with ethanol and the much less nucleophilic *t*-butanol proceeded under the same conditions (refluxing in toluene for 2 h) at comparable rates, affording the esters **12** and **13** in quantitative yields, respectively. The reaction of **3a** with *l*-menthone (3.0 mol equiv.) under reduced pressure, eliminating acetone, afforded chiral Meldrum's acid **14** (45% yield based on **3a**) which is a useful intermediate in asymmetric synthesis.[24] This transformation is best rationalized in terms of the 4+2 cycloaddition of **11** with the ketone.



In conclusion, we succeeded for the first time in the preparation of enolized derivatives of Meldrum's acids. These compounds underwent cycloreversion to α-oxoketenes under mild heatings strongly indicating the participation of carboxyketene intermediates in the reaction of Meldrum's acids with nucleophilic reagents. Synthetic applications of this efficient method for generating α-oxoketenes are in progress.

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9. General procedure for preparation of **4**: To a solution of **3** (3.0 mmol) in dichloromethane (10 ml) was added an ethereal solution of diazomethane (*ca.* 5 mmol) at -30 °C. The solution was stirred for 10 min and then evaporated *in vacuo* at -30 °C. Washing the crystalline residue with a mixture of ether and pentane afforded **4**.
10. **4a**: 82% yield; mp<20 °C; IR ($CHCl_3$) 1710, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, -40 °C) δ 1.70 (6H, s), 3.81 (3H, s), 4.60 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$, -40 °C) δ 24.6, 56.2, 68.6, 106.4, 163.4, 169.2. **4b**: 87% yield; mp<20 °C; IR ($CHCl_3$) 1714, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 0 °C) δ 1.67 (6H, s), 1.68 (3H, s), 3.78 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, -40 °C) δ 6.4, 24.3, 54.6, 76.2, 105.2, 163.3, 164.4. **4c**: 99% yield; mp<20 °C; IR ($CHCl_3$) 1710, 1610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, -40 °C) δ 1.83 (6H, s), 3.84 (3H, s), 7.34-7.39 (5H, m). **4d**: 83% yield; mp<20 °C; IR ($CHCl_3$) 1708, 1640 cm^{-1}. **4e**: 87% yield; mp 44-45 °C; IR ($CHCl_3$) 1709, 1620 cm^{-1}. **4f**: 90% yield; mp 55-56 °C; IR ($CHCl_3$) 1709, 1620 cm^{-1}.
11. **5a**: IR ($CHCl_3$) 2149 cm^{-1}. **5b**: IR ($CHCl_3$) 2140 cm^{-1}. **5c**: bp 65 °C (0.1 mmHg); IR ($CHCl_3$) 2130, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (3H, s), 7.23-7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 52.6, 125.7, 126.9, 127.4, 129.0, 166.5, 192.4.
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13. General procedure for preparation of **8**: A solution of **3** (3.0 mmol), *t*-butylchlorodiphenylsilane (3.3 mmol), and triethylamine (3.3 mmol) in dichloromethane (10 ml) was stirred at -50 °C for 2 h. The solution was evaporated *in vacuo* at below -20 °C. Ether was added to the residue and the solution was passed through a short column of silica gel cooled to -20 °C. Evaporation of the solvent at -20 °C followed by washing the crystalline residue with pentane furnished **8**.
14. **8a**: 70 % yield; IR ($CHCl_3$) 1712, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.30 (6H, s), 4.59 (1H, s), 7.4-7.8 (10H, m). **8b**: 95% yield; IR ($CHCl_3$) 1711, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (9H, s), 1.23 (6H, s), 1.86 (3H, s), 7.4-7.5 (3H, m), 7.6-7.7 (2H, m). **8c**: 82% yield; IR ($CHCl_3$) 1712, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.22 (6H, s), 7.2-7.7 (15H, m). **8g**: 98% yield; IR ($CHCl_3$) 1704, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (6H, s), 1.09 (9H, s), 1.41 (9H, s), 7.3-7.5 (3H, m), 7.6-7.7 (2H, m).
15. **9g**: 95% yield; IR ($CHCl_3$) 2125, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (6H, s), 1.09 (9H, s), 1.41 (9H, s), 7.3–7.5 (3H, m), 7.6–7.7 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.7, 26.6, 30.7, 32.2, 93.1, 102.9, 128.0, 130.5, 132.1, 135.3, 160.5, 163.6.
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