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Synthesis of 1,3-Dioxin-4-ones and Their Use in Synthesis. XI.¹⁾ 2,2-Dimethyl-1,3-dioxin-4-one as a Synthetic Equivalent of Formylketene: Synthesis of Heterocyclic Compounds²⁾

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Cycloaddition of formylketene generated *in situ* by thermolysis of 2,2-dimethyl-1,3-dioxin-4-one with *N*-benzhydrylidenebenzylamine yields 3-benzyl-2,2-diphenyl-1,3-oxazin-4-one. Analogous reactions with a carbodiimide, cyanamide, and keteneacetal afford the corresponding 4+2 cycloadducts. Reaction of formylketene with 3-amino-2-butenamides affords 4-hydroxy-2-pyridones having a C-2 unit at the 3-position.

Keywords—1,3-dioxin-4-one; formylketene; cycloaddition; 1,3-oxazin-4-one; 4-pyrone; 3-acetyl-4-hydroxy-2-pyridone; thermolysis; uracil derivative

We recently established a general and efficient synthetic method for 5,6-unsubstituted 1,3-dioxin-4-ones^{3,4)} and demonstrated their usefulness as a viable alternative for formyl acetic ester in the so-called de Mayo reaction. The method provides a novel means for the introduction of carboxaldehyde and acetic acid appendages at the vicinal position of alkanes starting from the corresponding alkenes, as shown in Chart 1.⁵⁾

Chart 1

Meanwhile, Jäger and Wenzelburger,⁶⁾ Sato *et al.*⁷⁻¹³⁾ and Hyatt *et al.*¹⁴⁾ have demonstrated that 2,2,6-trimethyl-1,3-dioxin-4-one (the so-called diketene-acetone adduct: A) upon heating affords acetylketene B, which reacts either with polarized unsaturated functions (1,2-dipoles: $X=Y \leftrightarrow X^--Y^+$) in a 4+2 manner to give a variety of six-membered heterocycles C (path a) or with appropriate nucleophiles (HXR) to give acetoacetic acid derivatives D (path b) as shown in Chart 2.

Chart 2

It was therefore expected that these 5,6-unsubstituted 1,3-dioxin-4-ones **1** would also afford formylketene **2** upon heating, and **2** might react further with a variety of reagents just like acetylketene **B**. Hence, we have investigated the reaction of 2,2-dimethyl-1,3-dioxin-4-one (**1a**) as a representative of these dioxinones **1** with a variety of unsaturated compounds ($X=Y$) and demonstrated that it yields formylketene (**2**) merely upon refluxing in toluene, and **2** thus formed reacts *in situ* with these reagents in the expected manner. These and related reactions of **2** generated from **1a** are reported in this paper.

Previously, we reported³⁾ a general synthetic method for 5,6-unsubstituted dioxinones **1** by adding finely powdered formyl Meldrum's acid **3**¹⁵⁾ to a refluxing toluene solution containing an excess of a ketone or aldehyde.

Chart 3

Though the formation of **1** from **3** surely involved **2** as an intermediate formed by electrocyclic ring cleavage of **3**, it was not clear whether or not the dioxinone **1** thus formed would also revert to **2** under these conditions. Hence, we first examined the reaction of **1a** with a ketone in refluxing toluene. When cyclohexanone was used, 4-oxo-1,5-dioxaspiro[5.5]undec-2-ene (**1b**) was obtained in 70% yield. The yield of **1b** is comparable to that (67%) obtained previously by using **3** as a masked formylketene.³⁾ This experiment clearly shows that **2** is also formed from **1a** under reflux in toluene.

Chart 4

When **1a** was heated with *N*-benzhydrylidenebenzylamine, 3-benzyl-2,2-diphenyl-1,3-oxazin-4-one **4** was obtained in 85% yield. The same 4+2 cycloaddition reaction also proceeded smoothly with a carbodiimide to give 3-cyclohexyl-2-cyclohexylimino-3,4-dihydro-1,3-oxazin-4-one (**5**) again in high yield. *N,N*-Dimethylcyanamide also reacted with **1a** to give 2-dimethylamino-1,3-oxazin-4-one **6**. Though **1** could not react with simple alkenes such as allyl benzyl ether (in this case, only a tarry material, probably formed by self-polymerization of formylketene, was obtained), a ketene acetal reacted with **1a** to afford a 2,3-dihydro-4*H*-pyran-4-one **7**. It should be noted that the dihydropyran-4-one **7** obtained from **1a** and methylketene diethylacetal gave 2-ethoxy-3-methyl-4*H*-pyran-4-one **8** by Lewis acid-catalyzed elimination of ethanol. Mild acid hydrolysis of **8** then afforded 4-hydroxy-3-methyl-2*H*-pyran-2-one **9**.

These results indicate clearly that suitable dienophiles ($X=Y$) in these cycloaddition reactions are those having a highly dipolar character ($X=Y \leftrightarrow X^- - Y^+$), such as ketones, aldehydes, imines, and ketene acetals.¹⁶⁾ Hence, it seems reasonable to consider that these cycloaddition reactions proceed in a stepwise manner *via* a zwitterion **E** as shown in path a. Though a concerted mechanism (path b) is not rigorously excluded at present, an intermediacy of **E** explains well the regioselectivity in the above cycloaddition reactions (Chart 5).

Chart 5

Preference for path a over path b was also suggested when **1a** was reacted with 3-amino-2-butenamide and its derivatives **10a—d** under heating in an appropriate aprotic solvent. Thus, reaction of **1a** with **10a** (which is barely soluble in toluene) in refluxing dioxane afforded 4-hydroxy-3-(1-iminoethyl)-2-pyridone **11a** which, though isolable, was hydrolyzed without further purification by dilute hydrochloric acid to give 3-acetyl-4-hydroxy-2-pyridone **12a** in 35% overall yield. Similar conversion using the substituted butenamides **10b—d** also proceeded in refluxing toluene with more satisfactory overall yields to give **12a**, **12c**, and **12d**.

Chart 6

According to the stepwise mechanism, the formation of **11** can be rationalized in terms of the intermediacy of **G**, formed by nucleophilic attack of the C-2 carbon of **10** on the ketene carbonyl carbon, followed by cyclization of **G** to give the final product **11** (Chart 6).

Formylketene generated from **1a** was thus used successfully for the synthesis of a variety of six-membered heterocycles, 1,3-oxazin-4-ones **4–6**, pyranones **7–9**, and 2-acetyl-4-hydroxy-2-pyridones **12**. Though some related heterocyclic compounds have already been prepared from acetylketene (generated from **A**) or from diketene, all of them necessarily carry a methyl substituent at the 6-position. Hence, the use of **1a** as a masked formylketene now provides a new preparative route to these classes of heterocyclic compounds unsubstituted at the 6-position.¹⁷⁾ This method should be especially suitable for the preparation of new analogues of 1,3-oxazin-4-ones, whose potential biological properties are currently of much interest.¹⁸⁾

Finally, we will comment on the use of **1a** in the synthesis of uracil and its derivatives. Thus, refluxing of **1a** in a mixture of toluene and dimethylformamide in the presence of urea or thiourea afforded uracil **13a** or thiouracil **13d** in a yield of 43 or 57%, respectively. Though the use of mono-methylurea in the above reaction afforded methyluracils in good yield (71%), both isomers (**13b** and **13c**) were obtained in comparable amounts. The lack of regioselectivity in this reaction probably reflects the high electrophilicity of the ketene carbonyl carbon in **2**.

Chart 7

In the present study, it became clear that **1a** generates formylketene **2** under quite mild conditions (heating at about 100–120 °C) in an aprotic solvent, just like formyl Meldrum's acid.³⁾ We are currently attempting to prepare formylacetic esters (especially *tert*-butyl formylacetate, a so-far unknown compound having a versatile utility in organic synthesis)¹⁹⁾ by trapping **2** (generated *in situ* from either **1a** or **3**) with a variety of alcohols.²¹⁾ The result of these studies will be reported separately.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were taken on a JEOL JNM-PMX 60 or a JEOL FX-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a Hitachi M-52G or a JEOL JMS-01SG-2 spectrometer. Ultraviolet (UV) spectra were recorded on a Hitachi 320 spectrometer.

4-Oxo-1,3-dioxaspiro[5.5]undec-2-ene (1b)—A solution of 2,2-dimethyl-1,3-dioxin-4-one³⁾ (**1a**, 128 mg, 1 mmol) and cyclohexanone (490 mg, 5 mmol) in dry toluene (2 ml) was refluxed for 20 min. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from pentane to give 118 mg (70%) of prisms, mp 40–42 °C (lit.³⁾ mp 40–42 °C). The IR spectrum was identical with that of an authentic sample.

3-Benzyl-3,4-dihydro-2,2-diphenyl-2H-1,3-oxazin-4-one (4)—A solution of **1a** (128 mg, 1 mmol) and *N*-benzhydrylidenebenzylamine (271 mg, 1 mmol)²²⁾ in dry toluene (2 ml) was refluxed for 10 min. The solvent was evaporated off *in vacuo* and the residue was recrystallized from acetone to give **4** as prisms, mp 163–165 °C. Yield, 288 mg (85%). IR (CHCl₃): 1655 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 4.57 (2H, s, CH₂), 5.48 (1H, d, *J* = 7 Hz, C₅-H), 6.60–7.47 (16H, m, C₆-H and benzene ring protons). MS *m/z*: 313 (M⁺ – CO). *Anal.* Calcd for C₂₃H₁₉NO₂: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.18; H, 5.57; N, 3.75.

3-Cyclohexyl-2-cyclohexylimino-3,4-dihydro-2H-1,3-oxazin-4-one (5)—A solution of **1a** (128 mg, 1 mmol) and dicyclohexylcarbodiimide (206 mg, 1 mmol) in dry toluene (2.5 ml) was refluxed for 10 min. The solvent was evaporated off *in vacuo*, and the residue was recrystallized from pentane to give **5** as needles, mp 80.5–81.5 °C. Yield,

242 mg (88%). IR (CHCl₃): 1670 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.83–3.00 (20H, m, cyclohexyl), 3.33–3.89 (1H, br s, C=NCH), 4.37–5.00 (1H, m, CONCH), 5.60 (1H, d, *J* = 6 Hz, C₅-H), 7.10 (1H, d, *J* = 6 Hz, C₆-H). MS *m/z*: 276 (M⁺). Anal. Calcd for C₁₆H₂₄N₂O₂: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.41; H, 9.03; N, 10.04.

2-Dimethylamino-4H-1,3-oxazin-4-one (6)—A solution of **1a** (128 mg, 1 mmol) and dimethylcyanamide (70 mg, 1 mmol) in toluene (2.5 ml) was refluxed for 15 min. The solvent was evaporated off *in vacuo* and the residue was recrystallized from a mixture of acetone and hexane to give **6** as needles, mp 174–175 °C. Yield, 129 mg (92%). IR (CHCl₃): 1650 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 3.10 (6H, s, 2 × Me), 5.97 (1H, d, *J* = 6 Hz, C₅-H), 7.40 (1H, d, *J* = 6 Hz, C₆-H). MS *m/z*: 140 (M⁺). Anal. Calcd for C₆H₈N₂O₂: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.33; H, 5.46; N, 19.88.

2,2-Diethoxy-2,3-dihydro-3-methyl-4-pyrone (7)—A solution of **1a** (128 mg, 1 mmol) and methylketene diethyl acetal (149 mg, 1.15 mmol)²³ in toluene (2 ml) was refluxed for 7 min. The solvent was evaporated off *in vacuo* and the residue was recrystallized from pentane to give **7** as prisms, mp 49–51 °C. Yield, 196 mg (98%). IR (CHCl₃): 1675 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.33–1.83 (9H, m, 3 × Me), 3.13 (1H, q, *J* = 6 Hz, CH–CH₃), 3.63–4.33 (4H, m, 2 × OCH₂CH₃), 5.62 (1H, d, *J* = 6 Hz, C₅-H), 7.42 (1H, d, *J* = 6 Hz, C₆-H). Anal. Calcd for C₁₀H₁₆O₄: C, 59.98; H, 8.05. Found: C, 59.21; H, 7.53. High-resolution MS *m/z*: M⁺ Calcd for C₁₀H₁₆O₄: 200.1049. Found: 200.1054.

2-Ethoxy-3-methyl-4-pyrone (8)—A solution of 43% BF₃·Et₂O (75 mg, 0.5 mmol) was added to a stirred solution of **7** (100 mg, 0.5 mmol) in benzene (5 ml). The mixture was stirred for 30 min at room temperature, then made alkaline with saturated sodium bicarbonate solution and extracted with CHCl₃. The organic layer was dried over MgSO₄ and concentrated to dryness *in vacuo*. The residue was chromatographed on a silica gel column (4 g) with a mixture of hexane and AcOEt (1 : 2, v/v) as an eluent to give **8**, which was recrystallized from hexane–ether to give **8** as prisms, mp 97–99 °C. Yield, 52 mg (68%). IR (CHCl₃): 1645 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.42 (3H, t, *J* = 7 Hz, CH₂CH₃), 1.95 (3H, s, CH₃), 4.13 (2H, q, *J* = 7 Hz, OCH₂), 6.22 (1H, d, *J* = 6 Hz, C₅-H), 7.41 (1H, d, *J* = 6 Hz, C₆-H). UV λ_{max}^{MeOH} nm: 260. MS *m/z*: 154 (M⁺). Anal. Calcd for C₈H₁₀O₃: C, 62.32; H, 6.54. Found: C, 62.02; H, 6.42.

4-Hydroxy-3-methyl-2-pyrone (9)—A solution of **8** (20 mg, 0.13 mmol) in 10% HCl (1.5 ml) was heated at 95–100 °C for 1 h. The solution was concentrated *in vacuo*. The crystalline residue was washed with water and dried. Recrystallization from acetone–hexane gave **9** as needles, mp 199–202 °C. Yield, 10 mg (63%). IR (KBr): 3140–2300 (OH), 1660 (C=O) cm⁻¹. ¹H-NMR (CD₃OD) δ: 1.92 (3H, s, Me), 6.22 (1H, d, *J* = 6 Hz, C₅-H), 7.45 (1H, d, *J* = 6 Hz, C₆-H). UV λ_{max}^{MeOH} nm: 282. MS *m/z*: 126 (M⁺). Anal. Calcd for C₆H₆O₃: C, 57.14; H, 4.80. Found: C, 57.29; H, 3.72. High-resolution MS *m/z*: M⁺ Calcd for C₆H₆O₃: 126.0316. Found: 126.0310.

3-Acetyl-4-hydroxy-2-pyridone (12a)—a) A mixture of 3-amino-2-butenamide **10a** (300 mg, 3 mmol),²⁴ **1a** (768 mg, 6 mmol), and dry dioxane (5 ml) was refluxed for 4.5 h. The solvent was evaporated off *in vacuo* and the oily residue²⁵ was heated in 2.5% hydrochloric acid (4 ml) for 30 min on a water bath (80–90 °C). The mixture was concentrated *in vacuo*. The crystalline residue was filtered off, washed with water, and dried. Recrystallization from MeOH gave **12a** as needles, mp 212–214 °C. Yield, 160 mg (35%). IR (Nujol): 1660 (C=O) cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ: 2.67 (3H, s, Me), 5.98 (1H, d, *J* = 7 Hz, C₅-H), 7.67 (1H, d, *J* = 7 Hz, C₆-H), 11.33–11.90 (1H, br s, NH), 15.73 (1H, s, OH). UV λ_{max}^{MeOH} nm: 320. MS *m/z*: 153 (M⁺). Anal. Calcd for C₇H₇NO₃: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.97; H, 4.50; N, 9.09.

b) A solution of **1a** (192 mg, 1.5 mmol) in toluene (4 ml) was added dropwise to a refluxing solution of 3-benzylamino-2-butenamide **10b** (190 mg, 1 mmol)²⁶ in toluene (2 ml) over 15 min. The mixture was refluxed for 1 h, then the solvent was evaporated off *in vacuo*. The oily residue was heated with a mixture of conc. hydrochloric acid (1 ml) and MeOH (3 ml) for 30 min under reflux. The mixture was concentrated *in vacuo* and the residue was purified in the same way as described under method a) to give 88 mg (58%) of **12a**.

3-Acetyl-1-benzyl-4-hydroxy-2-pyridone (12c)—A solution of **1a** (192 mg, 1.5 mmol) was added dropwise to a refluxing solution of *N*-benzyl-3-benzylamino-2-butenamide **10c** (280 mg, 1 mmol)²⁷ over 25 min. The mixture was refluxed for an additional 1 h, and then the solvent was evaporated off *in vacuo*. The oily residue was heated with a mixture of conc. hydrochloric acid (1 ml) and MeOH (5 ml) for 30 min under reflux. The mixture was concentrated *in vacuo*. The oily residue was dissolved in CHCl₃, washed with water and dried over MgSO₄. Evaporation of the solvent left a crystalline residue, which was chromatographed on a silica gel column. Elution with a mixture of hexane and EtOAc (5 : 1, v/v) gave **12c** as needles of mp 111–112 °C (recrystallized from MeOH). Yield, 147 mg (65%). IR (CHCl₃): 1655 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.77 (3H, s, Me), 5.94 (1H, d, *J* = 7 Hz, C₅-H), 7.39 (1H, d, *J* = 7 Hz, C₆-H), 15.82 (1H, s, OH). UV λ_{max}^{MeOH} nm: 327. MS *m/z*: 243 (M⁺). Anal. Calcd for C₁₄H₁₃NO₃: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.09; H, 5.24; N, 5.51.

Benzyl *N*-Acetoacetylglucinate—Triethylamine (2.02 g, 20 mmol) was added to a stirred mixture of diketene (1.68 g, 20 mmol), benzyl glycinate *p*-toluenesulfonic acid salt (6.75 g, 20 mmol), and CHCl₃ (50 ml). Stirring was continued at room temperature for 2 h. The mixture was washed with water, dried over MgSO₄, and concentrated *in vacuo*. The oily residue was chromatographed on a silica gel column using ether as an eluent to give benzyl *N*-acetoacetylglucinate as needles, mp 31–33 °C (recrystallized from ether–hexane). Yield, 2.39 g (48%). IR (CHCl₃): 3350 (NH), 1740, 1715, 1670 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.30 (3H, s, Me), 3.50 (2H, s, COCH₂CO), 4.10 (2H, d, *J* = 6 Hz, NHCH₂), 5.20 (2H, s, OCH₂), 7.35 (6H, br s, Ph and NH). MS *m/z*: 249 (M⁺). Anal. Calcd for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.38; H, 6.05; N, 5.74.

3-Benzylamino-*N*-(benzyloxycarbonylmethyl)-2-butenamide (10d)—A solution of benzylamine (112 mg, 1.05 mmol) and benzyl *N*-acetoacetyl glycinate (249 mg, 1 mmol) in benzene (2 ml) was refluxed for 30 min. The solvent was evaporated off *in vacuo*. The residue was recrystallized from ether–hexane to give **10d** as prisms, mp 87–88 °C. Yield, 270 mg (80%). IR (CHCl₃): 3450, 1745, 1630 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.86 (3H, s, Me), 4.08 (2H, d, *J* = 5.6 Hz, CH₂–CO), 4.33 (1H, s, C₃–H), 4.45 (2H, s, PhCH₂N), 5.18 (2H, s, OCH₂), 5.27–5.63 (1H, br s, CO–NH), 6.93–7.50 (10H, m, Ph × 2), 9.17–9.80 (1H, br s, PhCH₂NH). MS *m/z*: 338 (M⁺). Anal. Calcd for C₂₀H₂₂N₂O₃: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.81; H, 6.55; N, 7.99.

3-Acetyl-1-(benzyloxycarbonylmethyl)-4-hydroxy-2-pyridone (12d)—A solution of **1a** (179 mg, 1.4 mmol) in dry toluene (10 ml) was added dropwise to a refluxing solution of **10d** (388 mg, 1 mmol) in dry toluene (10 ml) over 30 min. The solvent was evaporated off *in vacuo* and the oily residue was heated with a mixture of 10% hydrochloric acid (1 ml) and tetrahydrofuran (10 ml) under reflux for 2 h. The reaction mixture was dissolved in CHCl₃, washed with water, and dried over MgSO₄. Evaporation of solvent left a crystalline residue, which was purified by silica gel column chromatography using a mixture of hexane and EtOAc (1 : 1, v/v) as an eluent to give **12d** as leaves of mp 120–121 °C (recrystallized from MeOH). Yield, 150 mg (50% from the amide **10d**). IR (CHCl₃): 1750, 1660 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.73 (3H, s, Me), 4.62 (2H, s, NCH₂), 5.23 (2H, s, OCH₂), 6.02 (1H, d, *J* = 7 Hz, C₅–H), 7.32 (1H, d, *J* = 7 Hz, C₆–H), 7.38 (5H, s, Ph). UV λ_{max}^{MeOH} nm: 323. MS *m/z*: 301 (M⁺). Anal. Calcd for C₁₆H₁₅NO₅: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.66; H, 4.97; N, 4.43.

Uracil (13a)—A solution of **1a** (179 mg) in dry toluene (2 ml) was added dropwise over 5 min to a refluxing mixture of urea (60 mg, 1 mmol), *N,N*-dimethylformamide (DMF, 2 ml), and dry toluene (10 ml). The mixture was refluxed for an additional 10 min and evaporated to dryness *in vacuo*. The residue was washed with 3 ml of MeOH and the insoluble solid was recrystallized from water to give **13a** as prisms of mp > 300 °C. Yield, 48 mg (43%). The IR spectrum (KBr) was identical with that of an authentic specimen.

3-Methyluracil (13b) and 1-Methyluracil (13c)—Methylurea (74 mg, 1 mmol) was reacted with **1a** (179 mg, 1.4 mmol) in the same manner as described for **13a**. The solvents were evaporated off *in vacuo* and the oily residue was chromatographed on a silica gel column. Elution with AcOEt gave **13c** as needles of mp 176–178 °C (recrystallized from hexane–AcOEt). Yield, 49 mg (39%). Further elution with AcOEt gave **13b** as needles of mp 234–235 °C (recrystallized from AcOEt–MeOH). Yield, 40 mg (32%). The IR spectra of **13b** and **13c** were identical with those of corresponding authentic specimens.

2-Thiouracil (13d)—Thiourea (76 mg, 1 mmol) was reacted with **1a** (179 mg, 1.4 mmol) in the same manner as described for **13a**. The solvents were evaporated off *in vacuo* and the crystalline residue was recrystallized from water to give **13d** as needles of mp > 300 °C. Yield, 73 mg (57%). The IR spectrum (KBr) was identical with that of an authentic specimen.

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References and Notes

- 1) The following papers are included in this series. Part 1, reference 7; Part 2, reference 8; Part 3, reference 4; Part 4, reference 9; Part 5, reference 10; Part 6, reference 11; Part 7, reference 12; Part 8, reference 13; Part 9, reference 5; Part 10, reference 3.
- 2) This paper also forms Part XXV of "Cycloadditions in Syntheses." For Part XXIV: T. Naito and C. Kaneko, *Chem. Pharm. Bull.*, **33**, 5328 (1985).
- 3) M. Sato, K. Sekiguchi, H. Ogasawara, and C. Kaneko, *Synthesis*, **1985**, 224.
- 4) M. Sato, H. Ogasawara, K. Oi, and T. Kato, *Chem. Pharm. Bull.*, **31**, 1896 (1983).
- 5) M. Sato, H. Ogasawara, K. Sekiguchi, and C. Kaneko, *Heterocycles*, **22**, 2563 (1984).
- 6) G. Jäger and J. Wenzelburger, *Justus Liebigs Ann. Chem.*, **1976**, 1689, and references cited therein.
- 7) M. Sato, N. Kanuma, and T. Kato, *Chem. Pharm. Bull.*, **30**, 1315 (1982).
- 8) M. Sato, N. Kanuma, and T. Kato, *Chem. Pharm. Bull.*, **30**, 4359 (1982).
- 9) M. Sato, H. Ogasawara, E. Yoshizumi, and T. Kato, *Chem. Pharm. Bull.*, **31**, 1902 (1983); *idem*, *Heterocycles*, **17**, 297 (1982).
- 10) M. Sato, H. Ogasawara, K. Kato, M. Sakai, and T. Kato, *Chem. Pharm. Bull.*, **31**, 4300 (1983).
- 11) M. Sato, N. Kanuma, and T. Kato, *Chem. Pharm. Bull.*, **32**, 106 (1984).
- 12) M. Sato, H. Ogasawara, and T. Kato, *Chem. Pharm. Bull.*, **32**, 2602 (1984).
- 13) M. Sato, H. Ogasawara, S. Komatsu, and T. Kato, *Chem. Pharm. Bull.*, **32**, 3848 (1984).
- 14) J. A. Hyatt, P. L. Feldman, and R. J. Clemens, *J. Org. Chem.*, **49**, 5105 (1984).
- 15) G. A. Bihlmayer, G. Derflinger, J. Derkosch, and O. E. Polansky, *Monatsh. Chem.*, **98**, 564 (1967).
- 16) A similar observation was noted in the cycloaddition of acylketene to dienophiles. See refs. 6–14.
- 17) Use of formyl Meldrum's acid as a masked formylketene in these and other reactions seems to be promising, and is currently under investigation.

- 18) T. Haneishi, T. Okazaki, T. Hata, C. Tamura, M. Nomura, A. Naito, I. Seki, and M. Arai, *J. Antibiot., Ser. A*, **24**, 797 (1971); S. Ozaki, Japan. Patent 31663 (1970) [*Chem. Abstr.*, **74**, 53811z (1971)]; K. Tomita and T. Murakami, Japan. Patent 20504 (1979) [*Chem. Abstr.*, **91**, 157755b (1979)]; I. Iwataki, S. Makisawa, S. Hashimoto, and A. Nakata, Japan. Patent 46086 (1977) [*Chem. Abstr.*, **87**, 168049t (1977)].
- 19) Recently, we have succeeded in the synthesis of a penam (the basic skeleton of penicillin-type β -lactams) from 1,3-thiazolidine-2-acetic acid through β -lactam formation.²⁰⁾ If *tert*-butyl formylacetate is available, synthesis of 1,3-thiazolidine-2-acetic acids having an alkoxycarbonyl group at the 2-position should be possible.
- 20) T. Chiba, J. Sakaki, T. Takahashi, and C. Kaneko, *Chem. Lett.*, **1985**, 659. See also, T. Chiba, T. Takahashi, J. Sakaki, and C. Kaneko, *Chem. Pharm. Bull.*, **33**, 3045 (1985).
- 21) It should be noted that Yonemitsu *et al.* reported a general synthetic method for β -ketoesters which consisted of reacting acyl Meldrum's acid with alcohols under comparable conditions. See, Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).
- 22) G. Charles, *Bull. Soc. Chim. Fr.*, **1963**, 1576.
- 23) P. M. Walters and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1482 (1940).
- 24) T. Kato, H. Yamanaka, and T. Shibata, *Tetrahedron*, **23**, 2965 (1967).
- 25) After being triturated in a small amount of ether and stored in a refrigerator, this oily residue crystallized. Recrystallization from AcOEt gave the iminoethylpyridone (**11a**) as needles, mp 232 °C (dec.). IR (KBr): 3300—2400, 1700, 1620 cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ : 2.6 (3H, s, Me), 5.3 (1H, d, $J=7$ Hz, $\text{C}_5\text{-H}$), 7.3 (1H, t, $J=7$ Hz, $\text{C}_6\text{-H}$), 9.5 (1H, br s, NH), 10.1 (1H, br s, NH), 12.8 (1H, br s, OH). High-resolution MS m/z : M^+ Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$: 152.0579. Found: 152.0574.
- 26) T. Kato, T. Chiba, M. Sasaki, and M. Kamo, *Yakugaku Zasshi*, **101**, 40 (1981).
- 27) C. Ringel and R. Mayer, *J. Prakt. Chem.*, **26**, 333 (1964).