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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 Compounds[2]

MASAYUKI SATO,* NAOKI YONEDA, and CHIKARA KANEKO*

*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*

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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]

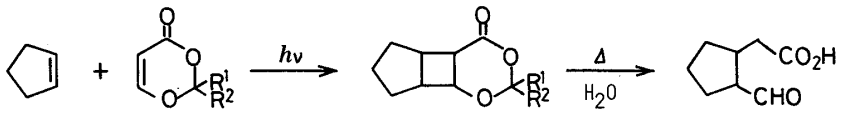



Chart 1

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.

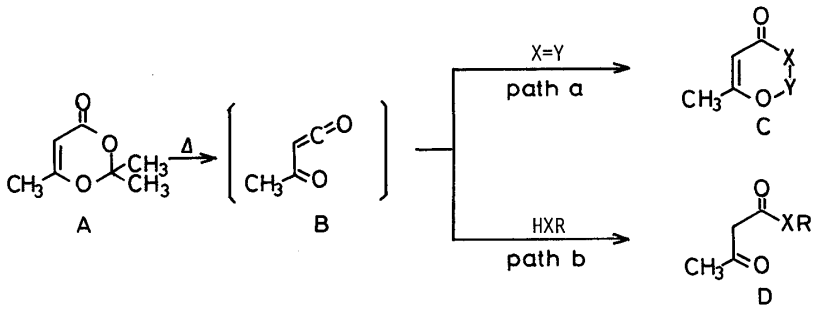



Chart 2

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 reported[3] 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.

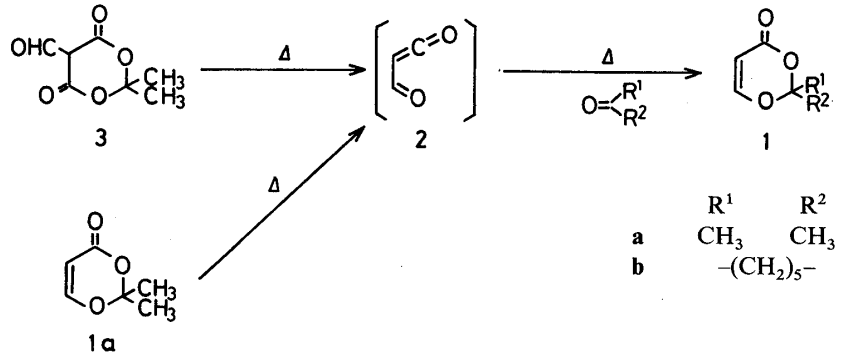



Chart 3

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.

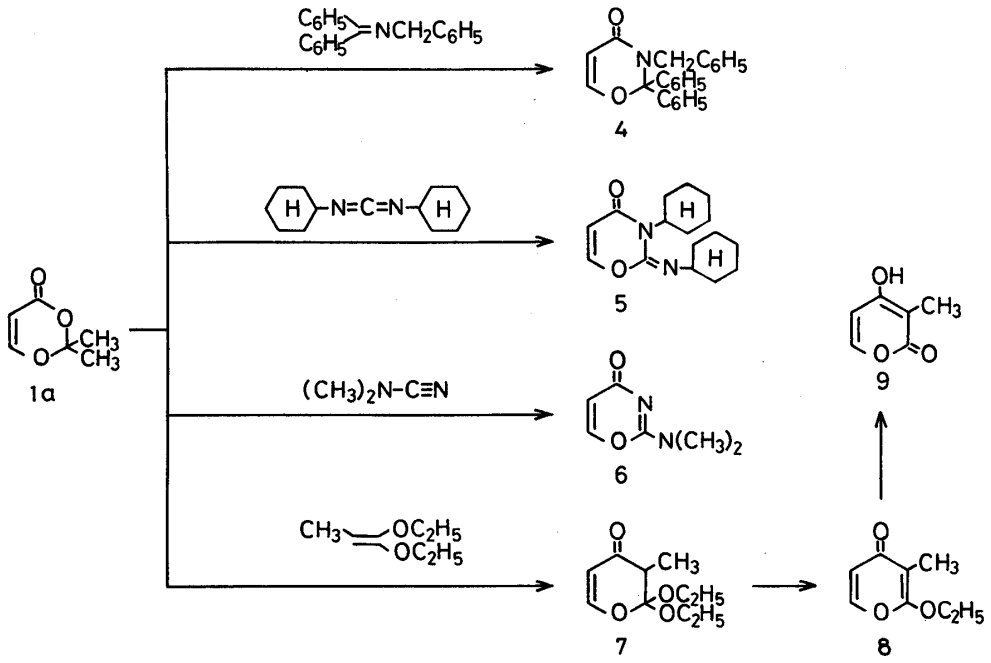



Chart 4

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↔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 intemediacy of E explains well the regioselectivity in the above cycloaddition reactions (Chart 5).

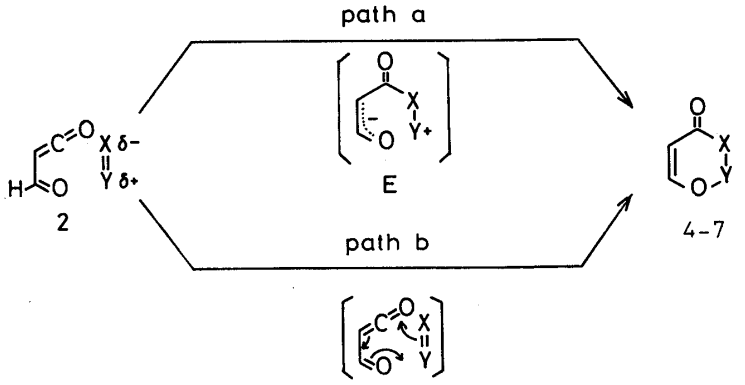
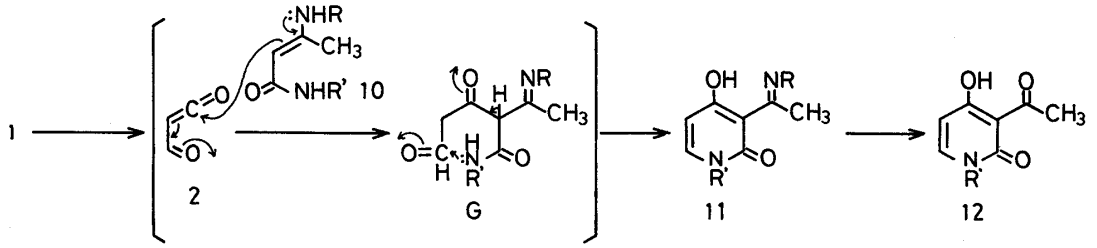



Chart 5

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**.



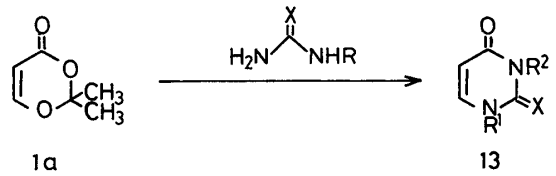

| | R | R′ |
|---|---|---|
| **a** | H | H |
| **b** | $CH_2C_6H_5$ | H |
| **c** | $CH_2C_6H_5$ | $CH_2C_6H_5$ |
| **d** | $CH_2C_6H_5$ | $CH_2CO_2CH_2C_6H_5$ |

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**.




1a 13

| | X | $R^1$ | $R^2$ |
|---|---|---|---|
| **a** | O | H | H |
| **b** | O | H | $CH_3$ |
| **c** | O | $CH_3$ | H |
| **d** | S | H | H |

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 veriety 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 ($^1$H-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-one[3] (**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-2*H*-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 ($CHCl_3$): 1655 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 4.57 (2H, s, $CH_2$), 5.48 (1H, d, $J$=7 Hz, $C_5$-H), 6.60—7.47 (16H, m, $C_6$-H and benzene ring protons). MS *m/z*: 313 ($M^+ - CO$). *Anal.* Calcd for $C_{23}H_{19}NO_2$: 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-2*H*-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 ($CHCl_3$): 1670 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 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, $C_5$-H), 7.10 (1H, d, $J$=6 Hz, $C_6$-H). MS $m/z$: 276 ($M^+$). *Anal.* Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.41; H, 9.03; N, 10.04.

**2-Dimethylamino-4*H*-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 ($CHCl_3$): 1650 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 3.10 (6H, s, 2×Me), 5.97 (1H, d, $J$=6 Hz, $C_5$-H), 7.40 (1H, d, $J$=6 Hz, $C_6$-H). MS $m/z$: 140 ($M^+$). *Anal.* Calcd for $C_6H_8N_2O_2$: 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 ($CHCl_3$): 1675 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.33—1.83 (9H, m, 3×Me), 3.13 (1H, q, $J$=6 Hz, C<u>H</u>–$CH_3$), 3.63—4.33 (4H, m, 2×O<u>C</u>$H_2CH_3$), 5.62 (1H, d, $J$=6 Hz, $C_5$-H), 7.42 (1H, d, $J$=6 Hz, $C_6$-H). *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.21; H, 7.53. High-resolution MS $m/z$: $M^+$ Calcd for $C_{10}H_{16}O_4$: 200.1049. Found: 200.1054.

**2-Ethoxy-3-methyl-4-pyrone (8)**——A solution of 43% $BF_3 \cdot Et_2O$ (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 $CHCl_3$. The organic layer was dried over $MgSO_4$ 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 ($CHCl_3$): 1645 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.42 (3H, t, $J$=7 Hz, $CH_2$C<u>H</u>$_3$), 1.95 (3H, s, $CH_3$), 4.13 (2H, q, $J$=7 Hz, OC<u>H</u>$_2$), 6.22 (1H, d, $J$=6 Hz, $C_5$-H), 7.41 (1H, d, $J$=6 Hz, $C_6$-H). UV $\lambda_{max}^{MeOH}$ nm: 260. MS $m/z$: 154 ($M^+$). *Anal.* Calcd for $C_8H_{10}O_3$: 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) $cm^{-1}$. $^1$H-NMR ($CD_3OD$) $\delta$: 1.92 (3H, s, Me), 6.22 (1H, d, $J$=6 Hz, $C_5$-H), 7.45 (1H, d, $J$=6 Hz, $C_6$-H). UV $\lambda_{max}^{MeOH}$ nm: 282. MS $m/z$: 126 ($M^+$). *Anal.* Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.29; H, 3.72. High-resolution MS $m/z$: $M^+$ Calcd for $C_6H_6O_3$: 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 residue[25] 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) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.67 (3H, s, Me), 5.98 (1H, d, $J$=7 Hz, $C_5$-H), 7.67 (1H, d, $J$=7 Hz, $C_6$-H), 11.33—11.90 (1H, br s, NH), 15.73 (1H, s, OH). UV $\lambda_{max}^{MeOH}$ nm: 320. MS $m/z$: 153 ($M^+$). *Anal.* Calcd for $C_7H_7NO_3$: 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 $CHCl_3$, washed with water and dried over $MgSO_4$. 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 ($CHCl_3$): 1655 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.77 (3H, s, Me), 5.94 (1H, d, $J$=7 Hz, $C_5$-H), 7.39 (1H, d, $J$=7 Hz, $C_6$-H), 15.82 (1H, s, OH). UV $\lambda_{max}^{MeOH}$ nm: 327. MS $m/z$: 243 ($M^+$). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.09; H, 5.24; N, 5.51.

**Benzyl *N*-Acetoacetylglycinate**——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 $CHCl_3$ (50 ml). Stirring was continued at room temperature for 2 h. The mixture was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The oily residue was chromatographed on a silica gel column using ether as an eluent to give benzyl *N*-acetoacetylglycinate as needles, mp 31—33 °C (recrystallized from ether–hexane). Yield, 2.39 g (48%). IR ($CHCl_3$): 3350 (NH), 1740, 1715, 1670 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.30 (3H, s, Me), 3.50 (2H, s, $COCH_2CO$), 4.10 (2H, d, $J$=6 Hz, NHC<u>H</u>$_2$), 5.20 (2H, s, $OCH_2$), 7.35 (6H, br s, Ph and NH). MS $m/z$: 249 ($M^+$). *Anal.* Calcd for $C_{13}H_{15}NO_4$: 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*-acetoacetylglycinate (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 ($CHCl_3$): 3450, 1745, 1630 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.86 (3H, s, Me), 4.08 (2H, d, $J$=5.6 Hz, $CH_2$–CO), 4.33 (1H, s, $C_3$-H), 4.45 (2H, s, $PhC\underline{H}_2N$), 5.18 (2H, s, $OCH_2$), 5.27—5.63 (1H, br s, CO–NH), 6.93—7.50 (10H, m, Ph×2), 9.17—9.80 (1H, br s, $PhCH_2N\underline{H}$). MS *m/z*: 338 ($M^+$). *Anal.* Calcd for $C_{20}H_{22}N_2O_3$: 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 $CHCl_3$, washed with water, and dried over $MgSO_4$. 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 ($CHCl_3$): 1750, 1660 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.73 (3H, s, Me), 4.62 (2H, s, $NCH_2$), 5.23 (2H, s, $OCH_2$), 6.02 (1H, d, $J$=7 Hz, $C_5$-H), 7.32 (1H, d, $J$=7 Hz, $C_6$-H), 7.38 (5H, s, Ph). UV $\lambda_{max}^{MeOH}$ nm: 323. MS *m/z*: 301 ($M^+$). *Anal.* Calcd for $C_{16}H_{15}NO_5$: 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**, 53811*z* (1971)]; K. Tomita and T. Murakami, Japan. Patent 20504 (1979) [*Chem. Abstr.*, **91**, 157755*b* (1979)]; I. Iwataki, S. Makisawa, S. Hashimoto, and A. Nakata, Japan. Patent 46086 (1977) [*Chem. Abstr.*, **87**, 168049*t* (1977)].
19) Recently, we have succeeded in the synthesis of a penam (the basic skeleton of penicillin-type $\beta$-lactams) from 1,3-thiazolidine-2-acetic acid through $\beta$-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 $\beta$-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 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.6 (3H, s, Me), 5.3 (1H, d, $J$=7 Hz, $C_5$-H), 7.3 (1H, t, $J$=7 Hz, $C_6$-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 $C_7H_8N_2O_2$: 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).