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Synthesis of 1,3-Dioxin-4-ones and Their Use in Synthesis. XIII.[1] Synthesis of 5-Halo-1,3-dioxin-4-ones and Their Conversion to 5-Alkyl Derivatives

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A novel method for the introduction of an alkyl group at the 5-position of 1,3-dioxin-4-ones is described. Reaction of 5,6-unsubstituted 1,3-dioxin-4-ones with *N*-halosuccinimide in acetic acid followed by treatment with a base gave 5-bromo- and 5-iodo-1,3-dioxin-4-ones, which were converted to the corresponding 5-alkylated dioxinones either by palladium-catalyzed cross-coupling or by photochemical allylation reactions. Successful conversion of 5-ethyl-2,2-dimethyl-1,3-dioxin-4-one either to a 5-ethyl-1,3-oxazin-4-one derivative or an α-ethylformylacetate upon heating in xylene demonstrated that these 5-substituted 1,3-dioxin-4-ones can serve as chemical equivalents for substituted formylketenes.

Keywords——5-halo-1,3-dioxin-4-one; 5-alkyl 1,3-dioxin-4-one; cross-coupling; formylketene derivative; 4+2 cycloaddition; photoallylation; thermolysis; acylation

Recently we have established a general and efficient synthetic method for 5,6-unsubstituted 1,3-dioxin-4-ones (**1**)[2] and demonstrated the usefulness of these compounds as a viable alternative for formyl acetic ester (**2**) in the so-called de Mayo reaction.[3]

In addition to their usefulness in photochemical reactions, **1**, when heated at 100—120 °C, generated formylketene (**3**), which reacted *in situ* either with polarized unsaturated functions (1,2-dipoles: $X=Y \leftrightarrow X^- - Y^+$) in a [4+2] manner to give six-membered heterocycles or with nucleophiles (RXH) to give formylacetylated products.[4]

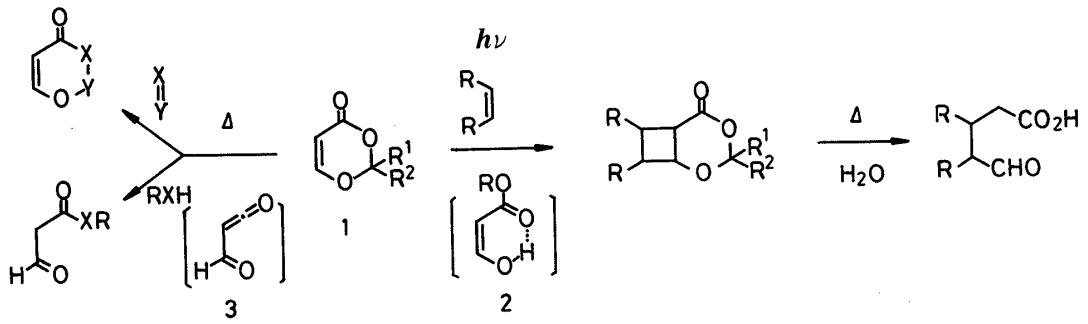
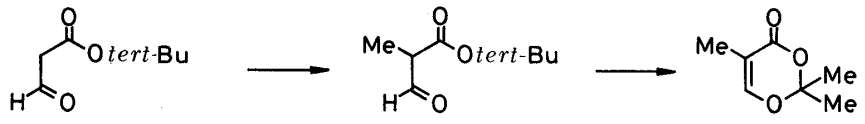


Chart 1

In order to explore further the utilization of 1,3-dioxin-4-ones in organic synthesis, a study was undertaken to investigate methods for synthesizing 5-substituted 1,3-dioxin-4-ones; only the 5-phenyl derivative has previously been synthesized, at our laboratory.[2b] In our previous work it was shown that the reaction of β-ketoacids or their *tert*-butyl esters with acetone under acidic conditions afforded 6- and 5,6-substituted 1,3-dioxin-4-ones. The use of *tert*-butyl 2-phenylformylacetate instead of β-ketoacid derivatives in this method afforded the 5-phenyl derivative. Hence, we first attempted the synthesis of 2,2,5-trimethyl-1,3-dioxin-4-one (**6**) by an application of the above method. Since *tert*-butyl formylacetate (**4**) is now

readily available,[1] this ester (**4**) was treated with iodomethane in the presence of a base to give the 2-methyl ester (**5**), though in a low yield.[5] Cyclo-condensation of **5** with acetone under the above conditions then afforded the desired product (**6**). However, the yield of **6** was again low (*ca.* 17%).

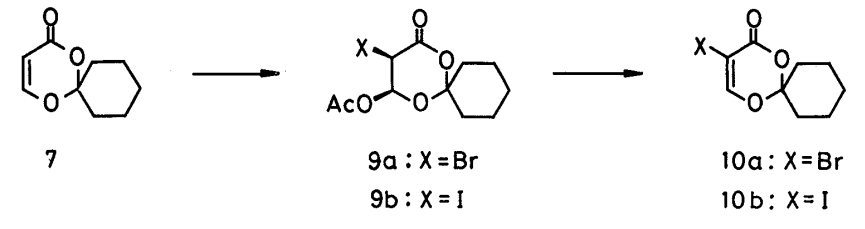


4 5 6

Chart 2

The above result has led us to develop an entirely new method for the synthesis of 5-substituted 1,3-dioxin-4-ones from the now readily available 5,6-unsubstituted derivatives.[2a] The method consists of halogenation of the latter compounds at the 5-position to give 5-halogenated 1,3-dioxin-4-ones, followed by replacement of the halogen atom with an alkyl group by an appropriate method.

5-Halogeno-1,3-dioxin-4-one derivatives were readily prepared from the 5,6-unsubstituted derivatives by the following two-step reaction. Thus, treatment of 4-oxo-4*H*-1,3-dioxin-2-spirocyclohexane (**7**) with *N*-bromosuccinimide (NBS) in acetic acid gave 6-acetoxy-5-bromo-1,3-dioxan-4-one (**9a**) in 69% yield. We tentatively assigned the *cis*-configuration at the 5- and 6-positions in **9a**, because two protons appeared as two sets of doublets at δ 4.27 (J = 6 Hz) and 6.38 (J = 6 Hz) in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. By treatment with triethylamine in dichloromethane, **9a** was transformed to the 5-bromo-1,3-dioxin-4-one (**10a**) in 80% yield. The iodo derivative (**10b**) was similarly prepared from **7** by treatment with *N*-iodosuccinimide (NIS) followed by treatment of the crude iodinated product (**9b**) with triethylamine. 2,2-Dimethyl-1,3-dioxin-4-one (**8**) was also converted to the corresponding 5-bromo- and 5-iodo derivatives (**11a** and **11b**) without isolation of the addition products (Chart 3).



7 9a : X = Br 9b : X = I 10a : X = Br 10b : X = I

8 11a : X = Br 11b : X = I

Chart 3

Since synthesis of 5-halogenated 1,3-dioxin-4-ones was thus accomplished, replacement of these halogen atoms with an alkyl group was then investigated. Recently, Saito *et al.* reported that when 5-iodouracil derivatives were irradiated ($\geq$ 300 nm) in a transparent solvent in the presence of allyltrimethylsilane, 5-allyluracils were formed.[6] Thus, **10b** was irradiated ($\geq$ 300 nm) in acetonitrile containing an excess of allyltrimethylsilane, and the 5-allyl derivative (**12**) was obtained in 52% yield.

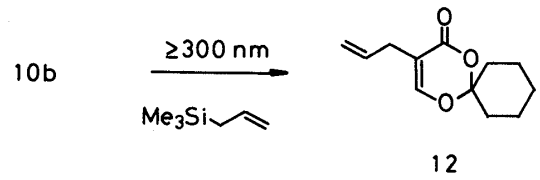


Chart 4

In order to develop a more general and efficient method for the synthesis of 5-alkylated 1,3-dioxin-4-ones, we then examined the palladium-catalyzed cross-coupling reactions of these 5-halogenated dioxinones with a variety of 1-alkenes and 1-alkynes. Palladium-catalyzed cross-coupling of aryl- or vinylhalides with monosubstituted acetylenes[7] and ethylenes[8] is well known, and the reaction has been extended successfully to the corresponding heteroaromatic compounds.[9]

When the bromo compound (**10a**) was allowed to react with phenylacetylene at 70 °C for 12 h in the presence of bis(triphenylphosphine)palladium dichloride,[7b] the 5-phenylethynyl derivative (**13**) was obtained in 38% yield, with recovery (34%) of the starting **10a**. However, if the same reaction was applied to the corresponding iodo derivative (**10b**), the reaction proceeded even at room temperature and the same product (**13**) was obtained in high yield (72%). The difference in reactivity between the 5-bromo (**10a**) and 5-iodo (**10b**) derivatives was also seen when trimethylsilylacetylene was used as an alkylation reagent. Thus, while the cross-coupling of the acetylene with **10a** did not take place at room temperature, the same reaction with **10b** proceeded smoothly to give a trimethylsilylethynyl compound (**14**) in 92% yield. Such a high reactivity of iodides as compared with bromides in palladium-catalyzed cross-coupling reactions has been well documented.[7-9]

The 5-iodo-2,2-dimethyl compound (**11b**) was similarly treated with trimethylsilylacetylene, 1-hexyne, and propargyl alcohol to give the corresponding alkynyl derivatives (**15**, **16**, and **17**), all in satisfactory yields (Chart 5).

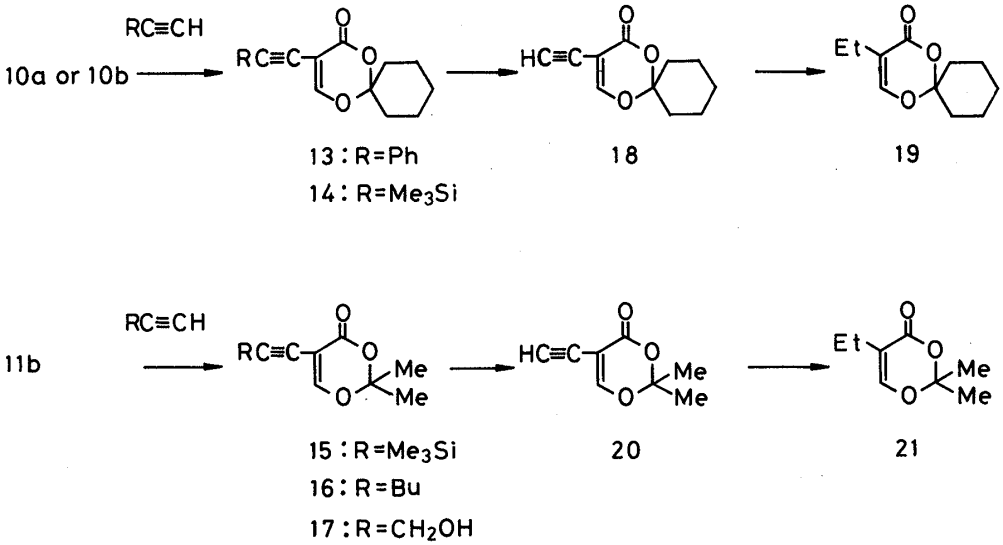


Chart 5

Compound **14** was desilylated to give **18** in 89% yield when treated with potassium fluoride in *N*,*N*-dimethylformamide (DMF).[10] Though the same desilylation also proceeded with tetrabutylammonium fluoride[11] the yield of **18** was rather poor (43%). By catalytic hydrogenation with palladium–carbon, **18** was reduced selectively at the ethynyl moiety to give the 5-ethyl derivative (**19**). The 5-ethyl-2,2-dimethyl derivative (**21**) was also synthesized from **15** *via* the ethynyl compound (**20**) in the same manner.

The 5-iodo derivatives (**10b** and **11b**) were also found to undergo cross-coupling with monosubstituted ethylenes. Among several methods reported so far, we chose Jeffery's method,[8d] which utilizes a phase transfer catalyst. The method, which requires only mild heating, seems to be suitable for our compounds, which are expected to be unstable above 100 °C (*vide infra*).

When **10b** was allowed to react with 2 molar equivalents of ethyl acrylate at about 60 °C in DMF containing sodium bicarbonate in the presence of palladium acetate and tetrabutylammonium chloride, the coupling product (**22**) was obtained in 67% yield. Under the same conditions, the dimethyl derivative (**11b**) also reacted with ethyl acrylate and methyl vinyl ketone to give the corresponding coupling products (**23** and **24**) in satisfactory yields. Catalytic reduction of **23** over palladium–carbon gave the propionate (**27**). In contrast to the satisfactory results in the reactions with electron-poor olefins, the reactions with electron-rich olefins afforded poor results. Thus, reaction of **11b** with *N*-allylphthalimide was sluggish and the desired product (**25**) was obtained in only 16% yield. The reaction with acrolein diethyl acetal was also sluggish, giving the coupling product (**26**) in 24% yield. The structure of **26**, determined unequivocally (see Experimental), was rather unexpected, because acrolein diethyl acetal, like other alkenes, is known to react in these reactions exclusively at the terminal carbon atom.[12]

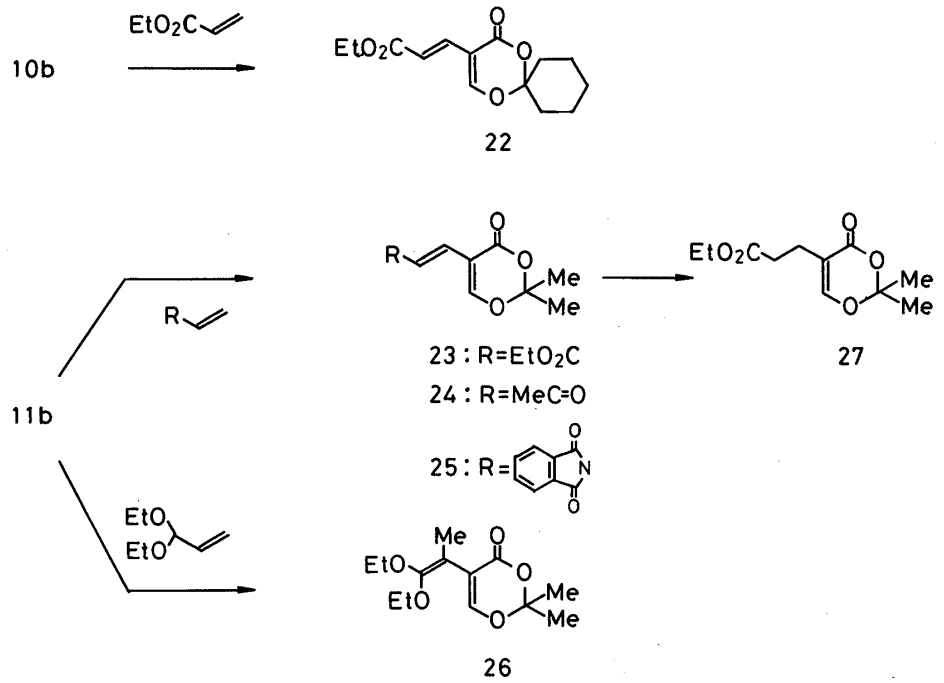


Chart 6

Thus, we have developed a novel synthetic method for 1,3-dioxin-4-ones having a variety of carbon substituents at the 5-position. As a representative of these 5-substituted 1,3-dioxin-4-ones, 5-ethyl-2,2-dimethyl-1,3-dioxin-4-one (**21**) was submitted to thermal reaction. Thus, **21** was heated in boiling xylene containing dimethylcyanamide. As expected, 5-ethyl-2-dimethylamino-1,3-oxazin-4-one (**29**) was obtained in a good yield. This fact, as well as the formation of the formyl ester (**30**) when **21** was heated in xylene containing *tert*-butyl alcohol, clearly shows that **21** generates the corresponding formylketene (**28**) under these conditions.

In conclusion, we have elaborated a novel method for the synthesis of 5-halogenated 1,3-dioxin-4-ones from the 5,6-unsubstituted compounds. Palladium-catalyzed cross-coupling and photochemical allylation reactions of these halo compounds provide methods for the introduction of a variety of carbon substituents at the 5-position of 1,3-dioxin-4-ones. In

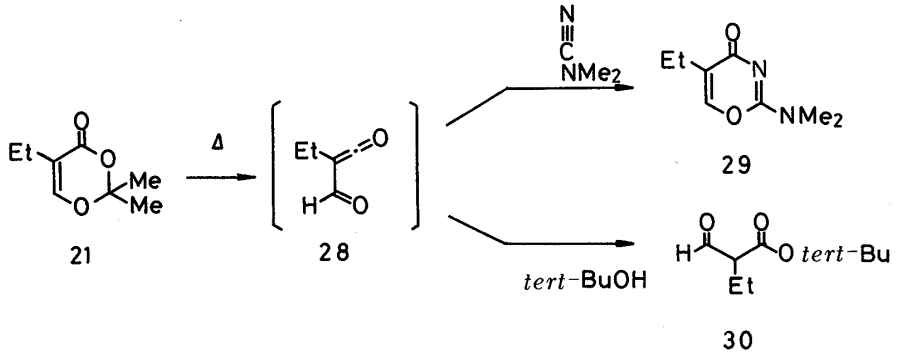


Chart 7

addition, as demonstrated in the conversion of the 5-ethyl-1,3-dioxin-4-one (**21**) to ethylformylketene (**28**), it is considered that these 5-substituted 1,3-dioxin-4-ones may serve as equivalents of substituted formylketenes, which are potential synthons for various 5-substituted six-membered heteroaromatics and substituted formyl acetic esters.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. Infrared spectra (IR) were taken on a JASCO A-102 spectrometer. ^{1}H-NMR 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.

***tert*-Butyl 2-Formylpropionate (5)**——*tert*-Butyl formylacetate (2.88 g, 20 mmol)[1] was added dropwise over 5 min to a stirred mixture of potassium *tert*-butoxide (2.24 g, 20 mmol) and dry DMF (40 ml) under ice–salt cooling. Iodomethane (3.10 g, 22 mmol) was then added to the stirred mixture in one portion, and the whole was stirred under ice–salt cooling for 2 h. The mixture was diluted with water (100 ml), acidified with dil. HCl, and extracted with ether. The organic layer was extracted with cold 2.5% NaOH (10 ml × 3). The aqueous layer was acidified with dil. HCl and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g) with hexane–ethyl acetate (20 : 1, v/v) to give **5** (485 mg, 15%) as an oil. IR ($CHCl_3$): 1715, 1690 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.23 (3H × 2/5, d, J=7 Hz, MeCHCO$_2$), 1.52 (9H, s, *tert*-Bu), 1.63 (3H × 3/5, s, =CMe–), 3.22 (1H × 2/5, dq, J=2, 7 Hz, MeCHCO$_2$), 6.92 (1H × 3/5, d, J=12 Hz, HOCH=), 9.68 (1H × 2/5, d, J=2 Hz, HC=O), 11.35 (1H × 3/5, d, J=12 Hz, HOCH=) (keto form : enol form = *ca.* 2 : 3).

Semicarbazone: mp 126—128 °C (ether–hexane). *Anal.* Calcd for $C_9H_{17}N_3O_3$: C, 50.22; H, 7.96; N, 19.52. Found: C, 50.22; H, 8.16; N, 19.51.

2,2,5-Trimethyl-1,3-dioxin-4-one (6)——Concentrated sulfuric acid (196 mg, 2 mmol) was added dropwise to a mixture of **5** (316 mg, 2 mmol), acetone (232 mg, 4 mmol), and acetic anhydride (612 mg, 6 mmol) with stirring below −5 °C. The mixture was stirred under ice-cooling for 1 h. The reaction mixture was poured into 10% sodium bicarbonate solution, stirred for 30 min, and then extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (9 g) with hexane–ethyl acetate (5 : 1, v/v) to give **6** (50 mg, 18%) as an oil. IR ($CHCl_3$): 1720, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, s, 2 × Me), 1.76 (3H, s, Me), 6.87 (1H, s, =CH–). High-resolution MS *m/z*: M$^+$ Calcd for $C_7H_{10}O_3$: 142.0628. Found: 142.0627.

6-Acetoxy-5-bromo-4-oxo-1,3-dioxane-2-spirocyclohexane (9a)——A mixture of **7** (504 mg, 3 mmol),[2a] NBS (641 mg, 3.6 mmol) and acetic acid (10 ml) was stirred at room temperature for 6 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from hexane–ether to give **9a** (634 mg, 69%) as needles of mp 90—91 °C. IR ($CHCl_3$): 1760 (sh), 1750, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18—2.15 (10H, m), 2.18 (3H, s), 4.27 (1H, d, J=6 Hz, C_5-H), 6.38 (1H, d, J=6 Hz, C_6-H). High-resolution MS *m/z*: M$^+$ Calcd for $C_{11}H_{15}BrO_5$: 306.0101 (^{79}Br), 308.0082 (^{81}Br). Found: 306.0059 (^{79}Br), 308.0060 (^{81}Br).

5-Bromo-4-oxo-4*H*-1,3-dioxine-2-spirocyclohexane (10a)——A mixture of **9a** (430 mg, 1.4 mmol), triethylamine (156 mg, 1.56 mmol), and CH_2Cl_2 (5 ml) was stirred at room temperature for 15 min. The mixture was diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. The solvent was evaporated off, and the residue was recrystallized from hexane–ether to give **10a** (278 mg, 80%) as prisms of mp 74—74.5 °C. *Anal.* Calcd for $C_{19}H_{11}BrO_3$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.72; H, 4.40; Br, 32.43. IR ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07—2.30 (10H, m), 7.40 (1H, s). MS *m/z*: 248 (^{81}Br) (M$^+$), 246 (^{79}Br) (M$^+$).

5-Iodo-4-oxo-4*H*-1,3-dioxine-2-spirocyclohexane (10b)——A mixture of **7** (1.68 g, 10 mmol),[2a] NIS (2.7 g, 12 mmol), and acetic acid (30 ml) was stirred at room temperature for 7.5 h. The reaction mixture was diluted with

CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. A solution of triethylamine (1.37 g, 13.5 mmol) in CH_2Cl_2 (30 ml) was added to the residue, and the whole was stirred at room temperature for 20 min. The reaction mixture was washed with water and dried over $MgSO_4$. The solvent was evaporated off, and the residue was recrystallized from hexane–ether to give **10b** (1.97 g, 67%) as needles of mp 97—98 °C. *Anal.* Calcd for $C_9H_{11}IO_3$: C, 36.76; H, 3.77. Found: C, 36.56; H, 3.63. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.30 (10H, m), 7.37 (1H, s). MS *m/z*: 294 (M^+).

5-Bromo-2,2-dimethyl-1,3-dioxin-4-one (11a)——A mixture of **8** (128 mg, 1 mmol),[2a] NBS (215 mg, 1.2 mmol), and acetic acid (4 ml) was stirred at room temperature for 3 h. The reaction mixture was worked up in the same way as described for **9a** to give an oily residue. A solution of triethylamine (87 mg, 0.86 mmol) in CH_2Cl_2 (5 ml) was added to the residue, and the whole was stirred at room temperature for 15 min. The mixture was diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave an oily residue, which was chromatographed on silica gel (7 g) with hexane–ethyl acetate (15 : 1, v/v) to afford **11a** (74 mg, 36%) as an oil. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.73 (6H, s), 7.33 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_7H_{12}BrO_2$: 207.0019 (^{79}Br), 208.9907 (^{81}Br). Found: 206.9981 (^{79}Br), 208.9907 (^{81}Br).

5-Iodo-2,2-dimethyl-1,3-dioxin-4-one (11b)——A mixture of **8** (1.31 g, 10.2 mmol),[2a] NIS (2.76 g, 1.23 mmol), and acetic acid (25 ml) was stirred at room temperature for 5 h. The reaction mixture was worked up in the same way as described for **9a**. A solution of triethylamine (1.13 g, 11 mmol) in CH_2Cl_2 (30 ml) was added to the residue, and the whole was stirred at room temperature for 20 min. The mixture was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave an oily residue, which was chromatographed on silica gel (30 g) with hexane–ethyl acetate (15 : 1, v/v) to afford **11b** (1.89 g, 75%) as a pale yellowish oil. IR ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.72 (6H, s), 7.34 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_6H_7IO_3$: 253.9438. Found: 253.9448.

5-Allyl-4-oxo-4*H*-1,3-dioxine-2-spirocyclohexane (12)——A solution of **10b** (118 mg, 0.4 mmol) in acetonitrile (50 ml) containing allyltrimethylsilane (686 mg, 6 mmol) was irradiated through a Pyrex filter with a Riko 100W high-pressure mercury lamp for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel (10 g). Elution with hexane–ethyl acetate (15 : 1, v/v) gave 43 mg (52%) of **12** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.30 (10H, m, cyclohexyl), 2.97 (2H, ddd, J=1.4, 2.8, 6 Hz, $CH_2=CHC\underline{H}_2$–), 4.89—5.40 (2H, m, $C\underline{H}_2=CHCH_2$–), 5.81 (1H, ddt, J=6, 9, 16 Hz, $CH_2=C\underline{H}$–CH_2–), 6.86 (1H, t, J=1.4 Hz, C_6-H). High-resolution MS *m/z*: M^+ Calcd for $C_{12}H_{16}O_3$: 208.1100. Found: 208.1103. IR ($CHCl_3$): 1720 cm^{-1}.

General Procedure for Cross-Coupling of 10 and 11 with Acetylenes——A mixture of **10** or **11** (0.5 mmol), an acetylene derivative (2.5 mmol), $Pd(Ph_3P)_2Cl_2$ (18 mg, 0.025 mmol), CuI (8 mg, 0.04 mmol), triethylamine (101 mg, 1 mmol), and DMF (4 ml) was stirred in a glass cylinder with a stopcock at a room temperature or an elevated temperature. The reaction mixture was diluted with ether, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave a crude product.

4-Oxo-5-phenylethynyl-4*H*-1,3-dioxine-2-spirocyclohexane (13)——a) Following the general procedure, **10a** was treated with phenylacetylene at 70 °C for 12 h. The crude product was chromatographed on silica gel (20 g) with hexane–ethyl acetate (20 : 1, v/v) to give **13** (51 mg, 38%) as leaves of mp 101—102 °C (recrystallized from hexane–ether) and **10a** (42 mg, 34%). *Anal.* Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.95; H, 5.80. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.33 (10H, m), 7.20—7.70 (6H, m). MS *m/z*: 268 (M^+).

b) Following the general procedure, **10b** was reacted with phenylacetylene at room temperature for 30 min. Work-up in the same way as in method a) gave **13** (97 mg, 72%).

5-Trimethylsilylethynyl-4-oxo-4*H*-1,3-dioxine-2-spirocyclohexane (14)——Following the general procedure, **10b** (1.058 g, 3.6 mmol) was reacted with trimethylsilylacetylene at room temperature for 40 min. The crude product was chromatographed on silica gel (58 g) with hexane–ethyl acetate (20 : 1, v/v) to give **14** (873 mg, 92%) as needles of mp 73—74 °C (recrystallized from pentane). *Anal.* Calcd for $C_{14}H_{20}O_3Si$: C, 63.60; H, 7.62. Found: C, 63.30; H, 7.89. IR ($CHCl_3$): 2160, 1740 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 0.22 (9H, s), 1.30—2.30 (10H, m), 7.37 (1H, s). MS *m/z*: 264 (M^+).

2,2-Dimethyl-5-trimethylsilylethynyl-1,3-dioxin-4-one (15)——Following the general procedure, **11b** was reacted with trimethylsilylacetylene at room temperature for 35 min. The crude product was chromatographed on silica gel (6 g) with hexane–ethyl acetate (25 : 1, v/v) to give **15** (99 mg, 88%) as a yellowish oil. IR ($CHCl_3$): 2160, 1740 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 0.21 (9H, s), 1.75 (6H, s), 7.33 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{16}O_3Si$: 224.0867. Found: 224.0864.

5-(1-Hexynyl)-2,2-dimethyl-1,3-dioxin-4-one (16)——Following the general procedure, **11b** was reacted with 1-hexyne at room temperature for 90 min. The crude product was chromatographed on silica gel (12 g) with hexane–ethyl acetate (20 : 1, v/v) to give **16** (76 mg, 73%) as a yellowish oil. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 0.73—1.67 (7H, m), 1.72 (6H, s), 2.00—2.83 (2H, m), 7.27 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_{12}H_{16}O_3$: 208.1100. Found: 208.1122.

5-(3-Hydroxy-1-propynyl)-2,2-dimethyl-1,3-dioxin-4-one (17)——Following the general procedure, **11b** was reacted with propargyl alcohol at 50 °C for 50 min. The crude product was chromatographed on silica gel (10 g) with hexane–ethyl acetate (2 : 1, v/v) to give **17** (43 mg, 47%) as a yellowish oil. IR ($CHCl_3$): 3450, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (6H, s), 3.08 (1H, br s), 4.45 (2H, br s), 7.40 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_9H_{10}O_4$: 182.0580. Found: 182.0590.

5-Ethynyl-4-oxo-1,3-dioxine-2-spirocyclohexane (18)——a) A 1 M solution of Bu_4NF in tetrahydrofuran (THF, 0.4 ml) was added in one portion to a solution of **14** (106 mg, 0.4 mmol) in THF (3 ml) with stirring at below −10 °C. After 1 min, the reaction mixture was diluted with ether, washed with water, and dried over $MgSO_4$. The solvent was evaporated off, and the residue was chromatographed on silica gel (4.5 g) with hexane–ethyl acetate (7 : 1, v/v) to give **18** (33 mg, 43%) as needles of mp 87—87.5 °C (recrystallized from hexane). *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.80; H, 6.04. IR ($CHCl_3$): 3300 (HC≡C), 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12—2.28 (10H, m), 3.10 (1H, s, HC≡), 7.53 (1H, s). MS *m/z*: 192 (M^+).

b) A solution of $KF \cdot 2H_2O$ (38 mg, 0.4 mmol) in DMF (1.5 ml) and water (0.5 ml) was added to a solution of **14** (106 mg, 0.4 mmol) with stirring under ice-cooling. After 1 min, the reaction mixture was diluted with ether, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was recrystallized from hexane to give **18** (68 mg, 89%).

5-Ethyl-4-oxo-4*H*-1,3-dioxine-2-spirocyclohexane (19)——Compound **18** (192 mg, 1 mmol) was hydrogenated over 10% Pd–C (20 mg) in ethyl acetate (7 ml) at room temperature. The catalyst was filtered off. The filtrate was concentrated and chromatographed on silica gel (10 g) with hexane–ethyl acetate (20 : 1, v/v) to give **19** (169 mg, 86%) as needles of mp 34—35 °C (recrystallized from pentane). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.17; H, 8.17. IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.07 (3H, t, J=7 Hz), 1.33—2.43 (10H, m), 2.16 (2H, dq, J=1, 7 Hz), 6.79 (1H, t, J=1 Hz). MS *m/z*: 196 (M^+).

5-Ethynyl-2,2-dimethyl-1,3-dioxin-4-one (20)——Compound **15** (90 mg, 0.4 mmol) was desilylated according to procedure b) given for **18**. Purification by chromatography (silica gel, 4 g) with hexane–ethyl acetate (7 : 1, v/v) gave **20** (46 mg, 76%) as prisms of mp 54—55 °C. IR ($CHCl_3$): 3300 (HC≡), 1740 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.72 (6H, s), 2.98 (1H, s, HC≡), 7.37 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_8H_8O_3$: 152.0472. Found: 152.0452.

5-Ethyl-2,2-dimethyl-1,3-dioxin-4-one (21)——Compound **20** (208 mg, 1.37 mmol) was hydrogenated over 10% Pd–C (20 mg) in ethyl acetate (7 ml) at room temperature. Purification by chromatography (silica gel, 6 g) with hexane–ethyl acetate (5 : 1, v/v) gave **21** (179 mg, 84%) as an oil. IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.10 (3H, t, J=7 Hz), 1.63 (6H, s), 2.18 (2H, q, J=7 Hz), 6.78 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_8H_{12}O_3$: 156.0785. Found: 156.0783.

General Procedure for Cross-Coupling of 10b or 11b with Alkenes——A mixture of **10b** or **11b** (0.5 mmol), an alkene (1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), Bu_4NCl (139 mg, 0.5 mmol), $NaHCO_3$ (105 mg, 1.25 mmol), and DMF (7 ml) was stirred at 60—70 °C.[8d]

The reaction mixture was diluted with ether, washed with water, and dried over $MgSO_4$. After evaporation of the solvent, the product was purified by chromatography using a mixture of hexane and ethyl acetate (10 : 1—3 : 1, v/v) as an eluent.

Ethyl (*E*)-3-(4-Oxo-4*H*-1,3-dioxine-2-spirocyclohexan-5-yl)acrylate (**22**): Yield 67%. Leaves of mp 66—67 °C (recrystallized from hexane). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 62.96; H, 6.69. IR ($CHCl_3$): 1735, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 1.13—2.27 (10H, m), 4.22 (2H, q, J=7 Hz), 6.76 (1H, d, J=15 Hz), 7.20 (1H, d, J=15 Hz), 7.40 (1H, s). MS *m/z*: 168 ($M^+ - C_6H_{10}O$).

Ethyl (*E*)-3-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-5-yl)acrylate (**23**): Yield 67%. Prisms of mp 64—65 °C (recrystallized from hexane). *Anal.* Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.48; H, 6.36. IR ($CHCl_3$): 1735, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 6.60 (1H, d, J=16 Hz), 7.07 (1H, d, J=16 Hz), 7.32 (1H, s). MS *m/z*: 226 (M^+).

(*E*)-2,2-Dimethyl-5-(3-oxo-1-butenyl)-1,3-dioxin-4-one (**24**): Yield 32%. Needles of mp 87—89 °C (recrystallized from hexane–ether). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.46; H, 5.92. IR ($CHCl_3$): 1740, 1680, 1670 (sh), 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (6H, s), 2.30 (3H, s), 7.07 (2H, s, HC=CH), 7.52 (1H, s). MS *m/z*: 196 (M^+).

(*E*)-2,2-Dimethyl-5-(2-phthalimidovinyl)-1,3-dioxin-4-one (**25**): Yield 16%. Leaves of mp 148—149 °C (recrystallized from hexane–CH_2Cl_2). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.36; H, 5.13; N, 4.41. IR ($CHCl_3$) 1740, 1680, 1670 (sh), 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68 (6H, s), 4.35 (2H, d, J=5 Hz), 6.08 (1H, d, J=16 Hz), 6.50 (1H, dt, J=5, 6 Hz), 7.17 (1H, s). MS *m/z*: 255 ($M^+ - C_3H_6O$).

2,2-Dimethyl-5-(2,2-diethoxy-1-methylvinyl)-1,3-dioxin-4-one (**26**): Yield 24%. Yellowish oil. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, t, J=7 Hz), 1.70 (6H, s), 2.50 (3H, s), 4.12 (4H, q, J=7 Hz), 7.00 (1H, s). MS *m/z*: 256 (M^+). *Anal.* Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.72; H, 7.95.

Ethyl 3-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-5-yl)propionate (27)——Compound **23** (24 mg, 0.106 mmol) was hydrogenated over 10% Pd–C (6 mg) in ethyl acetate at room temperature. Purification by chromatography (silica gel, 2.5 g) with hexane–ethyl acetate (5 : 1, v/v) gave **27** as an oil. IR ($CHCl_3$): 1720, 1715 (sh) cm^{-1}. ^{1}H-NMR (CCl_4) δ: 1.23 (3H, t, J=7 Hz), 1.63 (6H, s), 2.43 (4H, s), 4.06 (2H, q, J=7 Hz), 6.93 (1H, s). High-resolution MS *m/z*: M^+ Calcd for $C_{11}H_{16}O_5$: 228.0998. Found: 228.0999.

5-Ethyl-2-dimethylamino-4*H*-1,3-oxazin-4-one (29)——A solution of **21** (68 mg, 0.44 mmol) and dimethylcyanamide (61 mg, 0.87 mmol) in dry xylene (1 ml) was refluxed for 30 min. The reaction mixture was separated by column chromatography (silica gel, 4 g) with ethyl acetate to give **29** (53 mg, 72%) as needles of mp 104—104.5 °C (recrystallized from ether). *Anal.* Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.91; H, 7.21; N,

16.41. IR ($CHCl_3$): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7 Hz), 2.38 (2H, dq, J=1, 7 Hz), 3.12 (6H, s), 7.19 (1H, t, J=1 Hz). MS m/z: 168 (M^+).

***tert*-Butyl 2-Formylbutyrate (30)**——A solution of **21** (63 mg, 0.4 mmol) and *tert*-butanol (60 mg, 0.8 mmol) in dry xylene (1 ml) was refluxed for 1 h. The reaction mixture was subjected to column chromatography (silica gel, 3.5 g) with hexane–ethyl acetate (10 : 1, v/v) to give **30** (35 mg, 51%) as an oil. IR ($CHCl_3$): 1735 (sh), 1720 (sh), 1715, 1660 cm^{-1}. ^{1}H-NMR (CCl_4) δ: 0.97 (3H × 1/3, t, J=7 Hz, $C\underline{H}_3CH_2CH$), 1.00 (3H × 2/3, t, J=7 Hz, $C\underline{H}_3CH_2C{=}C$), 1.48 (9H × 1/3, s, *tert*-Bu), 1.53 (9H × 2/3, s, *tert*-Bu), 1.97 (2H × 1/3, quintet, J=7 Hz, $CH_3CH_2C\underline{H}$), 2.08 (2H × 2/3, q, J=7 Hz, $CH_3C\underline{H}_2C{=}$), 2.97 (1H × 1/3, dt, J=2, 7 Hz, $CH_3CH_2C\underline{H}$), 6.97 (1H × 2/3, d, J=13 Hz, $HOC\underline{H}{=}$), 9.58 (1H × 1/3, d, J=2 Hz, $HC{=}O$), 11.87 (1H × 2/3, d, J=13 Hz, $\underline{H}OCH{=}$) (keto form : enol form = 1 : 3). High-resolution MS m/z: M^+ Calcd for $C_9H_{16}O_3$: 172.1098. Found: 172.1052. Semicarbazone: needles of mp 126—127 °C (recrystallized from hexane–CH_2Cl_2).

References and Notes

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