Bull. Chem. Soc. Jpn. Vol. 80, No. 4, 780–782 (2007)

Synthesis and Acid- or Base-Catalyzed Cyclization of Various 4-Pentyne-1,3-dione Derivatives

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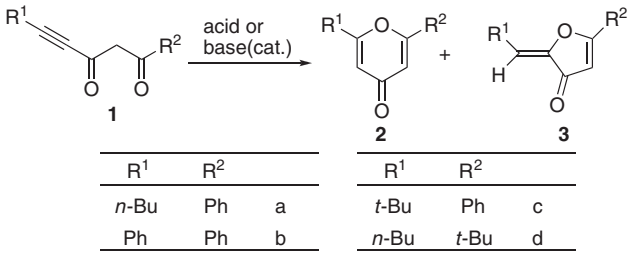
4-Pentyne-1,3-dione derivatives having various substituents were conveniently synthesized from ynals and silyl enol ethers in two steps. The cyclization behaviors of the obtained 4-pentyne-1,3-diones were studied. γ-Pyrones and 3(2*H*)-furanones were obtained by cyclization in the presence of an acid or base as a catalyst. The selectivity of the cyclization was moderately influenced by the substituents at the acetylenic moiety.

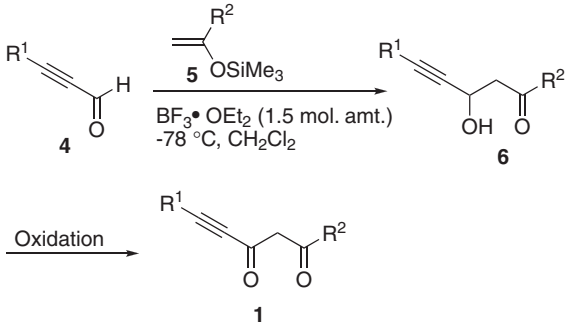
C–C triple bond activated by an electron-withdrawing group is the one of important reactive functional groups for organic synthesis and widely used as a key intermediate.[1] Previously, we have reported syntheses of cyclic compounds containing one oxygen atom, such as furans, by the cyclization of conjugated enynones.[2] Marei and El-Ghanam synthesized[3b] phenylpent-4-yne-1,3-dione derivatives having aryl groups conveniently by the reaction of ethyl phenylpropynoate with methyl ketone having a aryl group in the presence of sodium methoxide and have reported the syntheses of various heterocycles containing γ-pyrones and 3(2*H*)-furanones by using the diones as a key intermediate.[3] However, 4-pentyne-1,3-dione derivatives only having a phenyl group as a substituent on acetylenic moiety, i.e., 1-aryl-4-phenylpent-4-yne-1,3-diones, were synthesized and used in the studies. Synthesis of 4-pentyne-1,3-dione derivatives having an aliphatic group on the acetylenic moiety under basic conditions, such as Marei's procedure, may be difficult because of the high anionic reactivity of acetylenic moiety. The target molecules were not obtained due to complex side-reactions, although we attempted the syntheses of the diones under basic conditions using various methods involving Marei's procedure. Moreover, little has been published about the cyclization conditions and regio selectivity of the cyclization of the diones to afford γ-pyrones and 3(2*H*)-furanones.[3] Herein, we wish to describe a new synthetic method for 4-pentyne-1,3-dione derivatives **1** having various substituents and its cyclization reaction behavior (Scheme 1).

4-Pentyne-1,3-dione derivatives were synthesized from ynals[2c] **4** and silyl enol ethers[4] **5** in two steps (Scheme 2). An acidic Mukaiyama aldol reaction of **4** with **5** was carried out by the procedure[2c] reported by us in the presence of boron trifluoride–diethyl etherate to obtain the corresponding alcohols **6** in excellent yields (80–96%). The oxidation of **6** was



R^1	R^2		R^1	R^2	
n-Bu	Ph	a	*t*-Bu	Ph	c
Ph	Ph	b	*n*-Bu	*t*-Bu	d

Scheme 1. Cyclization reaction of 4-pentyne-1,3-dione derivatives **1**.



Scheme 2. Synthesis of 4-pentyne-1,3-dione derivatives **1**.

Table 1. Oxidation of **6** by Using Activated MnO_2 or Jones Reagent

No.	R^1	R^2	MnO_2[a]		Jones oxidation[b]	
			$Y^{c)}$/%	$R^{d)}$/%	$Y^{c)}$/%	$R^{d)}$/%
1	*n*-Bu	Ph	80	4	70	18
2	Ph	Ph	40	48	22	32
3	*t*-Bu	Ph	61	35	—	—
4	*n*-Bu	*t*-Bu	82	6	—	—

a) The oxidation of **6** (2.1 mmol) was carried out in the presence of activated MnO_2 (3.6 g) in hexane (29 mL). b) To a solution of **6** (14.0 mmol) in acetone (140 mL) was added Jones reagent (14 mmol). c) Isolated yields (column chromatography: SiO_2, EtOAc/Hex). d) Recovered amount of **5** (column chromatography: SiO_2, EtOAc/Hex).

attempted by using **6a** under various conditions (Jones oxidation,[5] Collins oxidation,[6] Swern oxidation,[7] activated manganese dioxide,[8] etc.). Oxidation by activated manganese dioxide or Jones reagent gave relatively favorable results affording **1a** in high yields (70 and 80% yields, respectively). From the results, the oxidation of **6** was carried out by Jones method or manganese dioxide (Table 1). Compounds **1a** and **1d** were obtained in high yield by using manganese dioxide (Nos. 1 and 4). Although various conditions were attempted in the oxidations of **6b** and **6c**, the starting materials were not completely consumed (Nos. 2 and 3).

The cyclization of **6a** was performed by using various catalysts (0.2 mol amt) (Table 2). When the cyclization was carried out without a catalyst in dichloromethane under reflux for 2 days, the amount of γ-pyrone **2a** was small, and almost of the starting material was recovered (No. 1). When sulfuric acid was used as a catalyst in the reaction, **2a** was obtained in 77% yield (No. 2). When *n*-BuLi was used as a basic catalyst, **2a**

Published on the web April 13, 2007; doi:10.1246/bcsj.80.780

Table 2. Cyclization of **1a**[a] under Various Conditions

No.	Catalysts	Solvent	Time/h	Y[b] of **2**/%	R[c]/%
1	H_2SO_4	CH_2Cl_2	47	8	81
2	H_2SO_4	CH_2Cl_2	18	77	20
3	H_2SO_4	CH_2Cl_2	24	62	0
4[d]	*n*-BuLi	THF	49	66	0
5[e]	NaH	THF	20	48	0
6[f]	n-Bu_3P	CH_2Cl_2	2	25	0
7	DMAP	CH_2Cl_2	4	67	0
8	Et_3N	CH_2Cl_2	71	94	0
9	Et_3N	THF	5	99	0

a) The cyclization of **1** (0.943 mmol) was carried out in the presence of an catalyst (0.189 mol) in a solvent (3 mL) under reflux. b) Isolated yields (column chromatography: SiO_2, EtOAc/Hex). c) Recovered amount of **1a** (column chromatography: SiO_2, EtOAc/Hex). d) The cyclization was carried out at 40 °C. e) Oligomeric products were obtained in 36% yield. f) Oligomeric products were obtained in 61% yield.

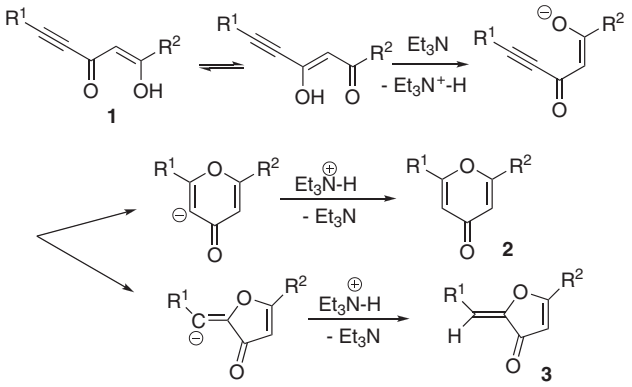
Table 3. Cyclization of **1**[a]

No.	R^1	R^2	Time[b]/h	Y[c] of **2**/%	Y[c] of **3**/%
1	*n*-Bu	Ph	5	99	0
2	Ph	Ph	2	49	34
3	*t*-Bu	Ph	6	93	0
4	*n*-Bu	*t*-Bu	4	93	0

a) The cyclization of **1** (0.943 mmol) was carried out in the presence of Et_3N (0.175 mmol) in THF (3 mL) under reflux. b) The time for complete consumption of **1**. c) Isolated yields (column chromatography: SiO_2, EtOAc/Hex).

was obtained in 66% yield (No. 4). When sodium hydride (No. 5) or tributylphosphine (No. 6) was used, a moderate amount of oligomeric products formed as by-products. When *N*,*N*-dimethylaminopyridine (DMAP) was used as a basic catalyst, the consumption of **1a** was very fast, and **2a** was obtained in good yield (No. 7). Although the reaction needed a long time (71 h) in the case of triethylamine, **2a** was obtained in an almost quantitatively yield (No. 8). Furthermore, when the reaction was carried out by using THF as a solvent under reflux to shorten the reaction time, **2a** was obtained quantitatively in less than 7 h (No. 9).

From the results, the cyclization of **1** having various substituents was performed by using triethylamine in THF (Table 3). The influence of substituents R^1 and R^2 was examined by using **1a**–**1d** (Nos. 1–4). In the cases of R^1 = alkyl groups, the corresponding γ-pyrones **2a** and **2c** were obtained in almost quantitative yields regardless of the size of alkyl groups (Nos. 1 and 3). In the case of **1b** with R^1 = phenyl, γ-pyrones **2b** and 3(2*H*)-furanones **3b**[9] were obtained in 49 and 34% yields, respectively. The selectivity may be affected by a difference in the stabilizing ability between the carbonyl group and R^1 for the resulting carbanion. In the case of **1b**, **3b** might be obtained due to the stabilizing ability of phenyl group toward the anion afforded by the addition of an enolate anion to C–C double bond (Scheme 3). Moreover, **2d** was obtained in almost quantitative yield when R^2 was *t*-butyl (**1d**) instead of a phenyl group (No. 4). From these results, it was found that the selectivity in the cyclization reactions was influenced by



Scheme 3. Plausible mechanism for cyclization reaction of **1**.

R^1 rather than by R^2.

In summary, 4-pentyne-1,3-dione derivatives **1** having various substituents were conveniently synthesized from ynals and silyl enol ethers in two steps. The cyclization behavior of the obtained 4-pentyne-1,3-diones were studied. γ-Pyrones **2** and 3(2*H*)-furanones **3** were obtained by cyclization in the presence of acid or base as a catalyst. The selectivity in the cyclization reaction was moderately influenced by the substituents at the acetylenic moiety. Further work on the reactive characters of 4-pentyne-1,3-dione derivatives **1** is currently being performed.

Experimental

Materials and Instruments. Tetrahydrofuran (THF) was dried over sodium diphenylketyl and distilled under nitrogen. Dichloromethane and triethylamine were dried over calcium hydride and then purified by distillation. Other commercially available chemicals were used without purification. Alcohols **6** were synthesized by the procedure described in the previous report.[2c] Infrared (IR) spectra were obtained on a JASCO FT/IR 8000 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JNM-AL400 spectrometer, in $CDCl_3$ (using tetramethylsilane as an internal standard). MS spectra were measured on a JMS-AX500 mass spectrometer.

Synthesis of 1. Typical Procedure for Oxidation of Alcohols 6 by Using Electrolytic Manganese Dioxide (EMD): To a suspension of EMD (Tosoh, type H–H, 3.60 g) in hexane (28.8 mL) was added alcohol **6** (2.10 mmol), and then the mixture was stirred for 3 h at room temperature under air. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 100/1–20/1) to give corresponding dione **1**. Typical analytical data for **1**. **1a**; R_f = 0.53; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 3065, 2961, 2872, 2834, 2226, 1738, 1599, 1466, 1275, 1203, 1067, 1020, 930, 771, 693. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 0.94 (t, J = 7.2 Hz, 3H, CH_3-CH_2–), 1.50 (m, 2H, –CH_2–), 1.58 (m, 2H, –CH_2–), 2.43 (t, J = 6.8 Hz, 2H, –CH_2C≡C–), 6.34 (s, 1H, –CH=C(OH)–), 7.40–7.60 (m, 3H, –Ph), 7.89 (m, 2H, Ph), 15.77 (bs, 1H, =C(OH)–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 13.6, 14.2, 19.0, 22.0, 29.9, 78.7, 97.2, 100.7, 127.1, 128.6, 128.7, 132.6, 134.4, 171.1, 184.6. MS (EI, m/z) 228 (M^+). **1b**; R_f = 0.46; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 3063, 2963, 2921, 2851, 2209, 1599, 1487, 1262, 1100, 1022, 801, 772, 689. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 6.45 (s, 1H, –CH=C(OH)–), 7.40–7.60 (m, 8H, –Ph), 7.89 (m, 2H,

Ph), 15.74 (bs, 1H, =C(O*H*)–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 86.5, 94.3, 101.7, 120.9, 127.8, 129.2, 129.4, 130.9, 133.2, 133.5, 135.0, 170.9, 186.0. MS (EI, m/z) (M^+) 248. **1c**; $R_f = 0.45$; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 3065, 2973, 2930, 2903, 2869, 2216, 1738, 1568, 1252, 1186, 814, 772, 692. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.25 (s, 9H, *t*-Bu–), 6.28 (s, 1H, –C*H*=C(OH)–), 7.40–7.60 (m, 3H, –Ph), 7.89 (m, 2H, Ph), 15.73 (bs, 1H, =C(O*H*)–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 28.3, 30.4, 101.3, 104.9, 127.7, 129.2, 133.2, 135.0, 172.1, 185.3. MS (EI, m/z) 228 (M^+). **1d**; $R_f = 0.54$; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 2963, 2872, 1591, 1464, 1282, 1221, 1121, 928, 801. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 0.86 (t, $J = 7.32$ Hz, 3H, C*H*$_3$–), 1.10 (s, 9H, *t*-Bu–), 1.37 (m, 2H, –C*H*$_2$–), 1.51 (m, 2H, –C*H*$_2$–), 2.33 (t, $J = 7.32$ Hz, 2H, –C*H*$_2$C≡C–), 5.73 (s, 1H, –C*H*=C(OH)–), 15.34 (bs, 1H, =C(O*H*)–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 13.7, 19.2, 22.1, 27.3, 30.1, 39.8, 96.8, 100.4, 170.5, 203.0. MS (EI, m/z) 208 (M^+).

Typical Procedure for Oxidation of 6 by Using Jones Reagent: To a solution of **6** (14.0 mmol) in acetone (140 mL) was added Jones reagent (CrO_3; 2.50 mol L^{-1}, 5.60 mL, 14.0 mmol) at 0 °C, and then, the mixture was stirred for 1 h at room temperature under air. The mixture was diluted with water (100 mL) and extracted three times with 30 mL of ethyl acetate. The combined organic solution was washed twice with 20 mL of saturated aqueous sodium chloride and then dried over magnesium sulfate. After evaporation, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 100/1–20/1) to give corresponding dione **1**.

Cyclization of 1. A Typical Cyclization Procedure: To a solution of **1b** (0.181 g, 0.730 mmol) in THF (3 mL) was added triethylamine (16.0 mg, 0.158 mmol). The solution was refluxed for 2 h under nitrogen. After the solvent was evaporated, the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate = 100/1–20/1) to obtain **2b** (0.893 g, 0.360 mmol) ($R_f = 0.29$ on TLC, SiO_2, hexane/ethyl acetate = 4/1) and **3b** (0.0616 g, 0.248 mmol) ($R_f = 0.31$ on TLC, SiO_2, hexane/ethyl acetate = 4/1) in 49.3 and 34.0% yields, respectively. **2b**; IR (cm^{-1}, neat) 3061, 2961, 1695, 1641, 1614, 1448, 1386, 1124, 1060, 931, 761, 692. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 6.82 (s, 2H, >C=C*H*CO–), 7.41 (m, 6H, Ph–), 7.74 (m, 4H, Ph-). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 111.1, 125.6, 128.9, 131.1, 131.2, 162.9, 179.8. MS (EI, m/z) 248 (M^+), 220. **3b**; IR (cm^{-1}, neat) 3063, 2961, 2932, 1697, 1653, 1620, 1449, 1402, 1175, 1060, 961, 766, 698. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 6.30 (s, 1H, –OC(Ph)=C*H*CO–), 6.83 (s, 1H, PhC*H*=C<), 7.74–7.62 (m, 6H, Ph–), 7.91 (m, 4H, Ph). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 102.4, 112.6, 126.6, 127.5, 128.7, 128.8, 129.7, 131.2, 131.8, 132.4, 146.3, 176.7, 187.0. MS (EI, m/z) 248 (M^+), 118. **2a**; $R_f = 0.21$; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 3059, 2959, 2932, 2870, 1659, 1613, 1450, 1399, 1377, 1262, 1157, 885, 769, 693. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 0.90 (t, $J = 7.19$ Hz, 3H, C*H*$_3$–), 1.37 (m, 2H, –C*H*$_2$–), 1.65 (m, 2H, –C*H*$_2$–), 2.55 (t, $J = 7.59$ Hz, 2H, –C*H*$_2$C=C–), 6.11 (d, $J = 1.60$ Hz, 1H, >C=C*H*CO–), 6.63 (d, $J = 1.60$ Hz, 1H, >C=C*H*CO–), 7.42 (m, 3H, Ph–), 7.68 (m, 2H, Ph–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 13.8, 22.1, 29.0, 33.4, 110.7, 113.4, 125.5, 128.8, 131.0, 131.2, 163.2, 168.7, 180.0. MS (EI, m/z) 228 (M^+). **2c**; $R_f = 0.07$; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 3067, 2965, 1651, 1612, 1588, 1455, 1389, 1101, 947, 922, 891, 891, 770, 687. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.29 (s, 9H, *t*-Bu), 6.20 (t, $J = 2.08$ Hz, 1H, >C=C*H*CO–), 6.62 (d, $J = 2.08$ Hz, 1H, >C=C*H*CO–), 7.42 (m, 3H, Ph–), 7.68 (m, 2H, Ph–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 28.2, 36.5, 110.8, 110.9, 126.1, 129.5, 131.7, 132.0, 163.8, 176.0, 181.4. MS (EI, m/z) 228 (M^+). **2d**; $R_f = 0.04$; hexane/ethyl acetate = 4/1. IR (cm^{-1}, neat) 2963, 2872, 1660, 1622, 1464, 1399, 1111, 924, 866. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 0.88 (t, $J = 7.33$ Hz, 3H, C*H*$_3$–), 1.19 (s, 9H, *t*-Bu–), 1.32 (m, 2H, –C*H*$_2$–), 1.57 (m, 2H, –C*H*$_2$–), 2.46 (t, $J = 7.57$ Hz, 2H, –C*H*$_2$C=C–), 5.99 (d, $J = 2.19$ Hz, 1H, >C=C*H*CO–), 6.08 (d, $J = 2.19$ Hz, 1H, >C=C*H*CO–). ^{13}C NMR (100 MHz, δ, $CDCl_3$) 13.6, 21.9, 27.7, 28.7, 33.2, 35.9, 110.1, 112.9, 169.5, 176.0, 181.5. MS (EI, m/z) 208 (M^+).

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9 In the ^{1}H and ^{13}C NMR spectra of **3b**, peaks attributed to the geometric isomer were not observed. The geometry is considered to be *Z*-form because a chemical shift of benzylidene proton in **3b** agreed with the analytical data in Marei's report.[3e]