A CARBON-CARBON BOND FORMATION BY THE REACTION OF 4-CHLORO-6-METHYL-3-PHENYLETHYNYL-2*H*-PYRAN-2-ONE WITH ACTIVE METHYLENE DERIVATIVES

Yutaka Azuma,* Atsuko Sato, and Mieko Morone

Tohoku College of Pharmacy, 4-4-1 Komatsushima, Aoba-ku, Sendai 981, Japan

Abstract- The reaction of 4-chloro-6-methyl-3-phenylethynyl-2*H*-pyran-2-one (**2**) with compounds containing active methylene group, such as diethyl malonate, acetylacetone, ethyl cyanoacetate, and malononitrile, in the presence of NaH gives 4-substituted 6-methyl-3-phenylethynyl-2*H*-pyran-2-one (**3**) and / or 6-methyl-3-phenylacetyl-2*H*-pyran-2-one (**5**).

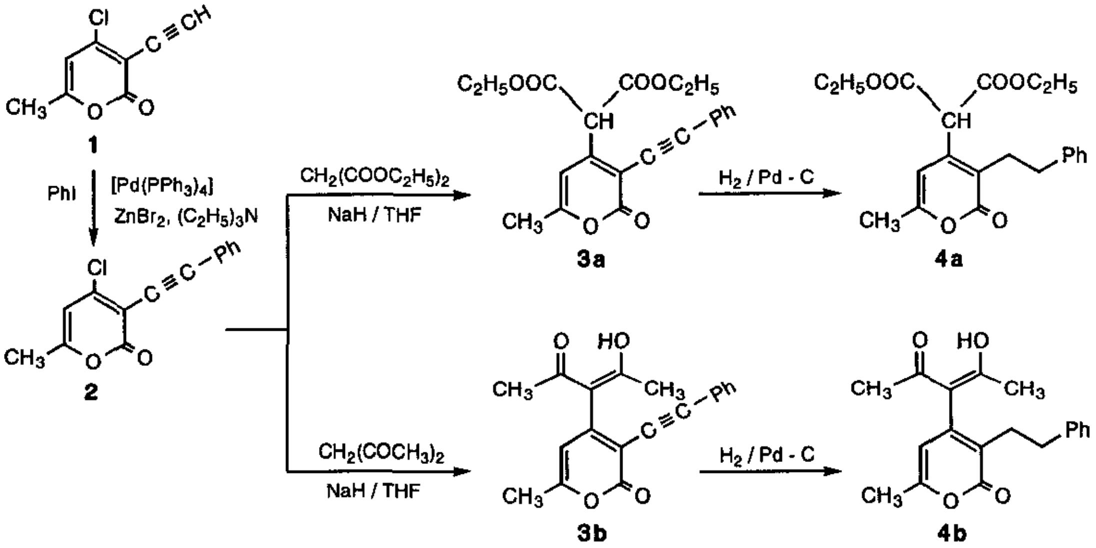
It has been reported that 4-chloro-3-ethynyl-6-methyl-2*H*-pyran-2-one (**1**) is a useful building block in the synthesis of heterocycles containing pyrone ring system, such as pyranopyrazole,[1] pyranobenzodiazepine,[2] and pyranoquinoline.[3] These reports were described for the reaction of **1** with hydrazines and amines. However, the reaction of **1** with carbanions has not been examined yet. In this paper, we describe the carbon-carbon bond formation by the reaction of **1** and 4-chloro-6-methyl-3-phenylethynyl-2*H*-pyran-2-one (**2**), obtained from the reaction between **1** and iodobenzene in the presence of palladium catalyst, with compounds containing active methylene group.

The reaction of **1** with 1.2 molar eq. amount of diethyl malonate in the presence of 1.1 molar eq. amount of NaH in an atmosphere of nitrogen gave mixtures of diethyl malonate (above 80 % recovery) and tar. However, the use of **2** instead of **1** in this reaction resulted in 81 % yield to afford 4-diethoxycarbonylmethyl-3-phenylethynylpyrone (**3a**). The results of these experiments appear that the hydrogen of terminal acetylene of **1** is replaced by sodium ion due to sodium enolate of diethyl malonate. In the same procedure, the reaction of **2** with acetylacetone gave 4-diacetylmethyl-3-phenyl-

---

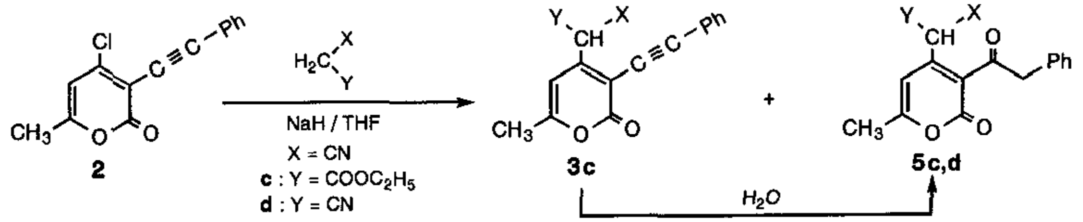
This paper is dedicated to the memory of Professor Yoshio Ban.

ethynylpyrone (**3b**) in 52 % yield. In order to confirm the presence of phenylethynyl group, hydrogen was added to these products (**3a**) and (**3b**) in the presence of 5 % palladium carbon to give 3-phenethylpyrones (**4a**) and (**4b**) in good yields, respectively.



Scheme 1

On the other hand, **2** reacted with ethyl cyanoacetate in the same procedure to give 3-phenylethynylpyrone (**3c**) in 9.5 % yield and 3-phenylacetylpyrone (**5c**) in 51 % yield. Additionally, **3c** was treated with 10 % HCl to give **5c** in 95 % yield. The substituent at 3-position on pyrone ring of **5c** was determined by the mass spectral data shown in Figure 1. Thus, phenylethynyl group of **3c** is hydrolyzed into phenylacetyl or benzoylmethyl group. Product (**5c**) shows the benzyl ion peak at *m/z* 91 due to phenylacetyl group. The characteristic benzoyl ion peak can be seen at *m/z* 105 when the substituent is benzoylmethyl group, but the peak isn't observed in the spectrum. The reaction of **2** with malononitrile gave 3-phenylacetylpyrone (**5d**) in 45 % yield ; the 3-phenethylpyrone (**3d**) wasn't obtained. The structures of all products were determined by the spectral and analytical evidence.



Scheme 2

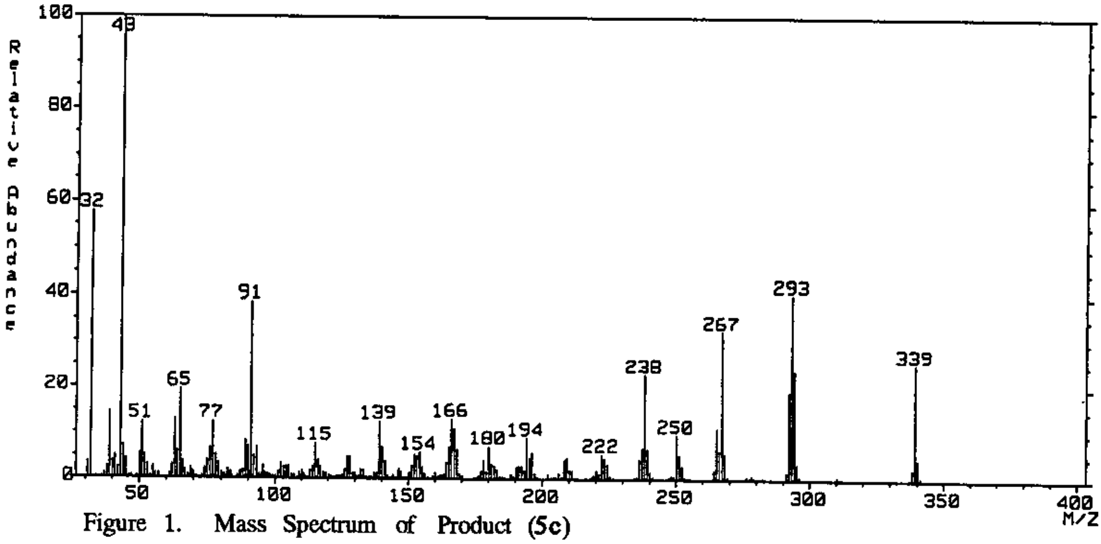
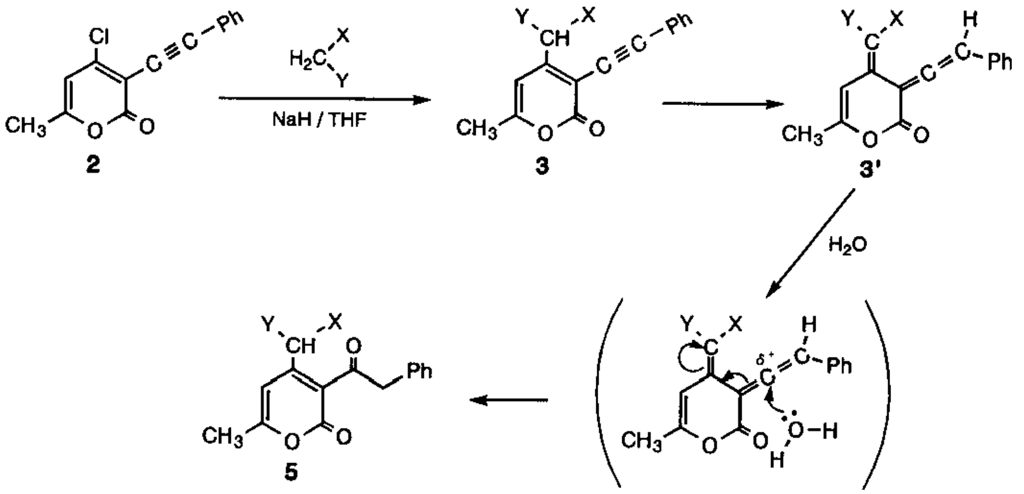


Figure 1. Mass Spectrum of Product (5c)

A probable pathway of the reaction of **2** with compounds containing active methylene group may be postulated as shown in Scheme 3. Thus, **2** reacts with active methylene derivatives in the presence of NaH to give 3-phenylethynylpyrone (**3**). If X and Y of **3** are bulky groups, **3** isn't converted to **3'** owing to the steric hindrance, so that **3** isn't hydrolyzed. However, if X and / or Y are a less hindered group such as cyano group, the hydrolysis of **3** is easily carried out to give 3-phenylacetylpyrone (**5**).



Scheme 3

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were taken with Hitachi Model 260-10 spectrophotometer. Ms spectra were measured on JEOL JMS-DX303/LMA-DA5000 instrument. ^{1}H-Nmr spectra were recorded on JEOL JNM-GSX400 and JNM-PMX60SI spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard.

Preparation of 4-chloro-6-methyl-3-phenylethynyl-2*H*-pyran-2-one (2) : A mixture of **1** (5 g, 29.7 mmol), iodobenzene (6.7 g, 32.8 mmol), [Pd(PPh$_3$)$_4$] (1 g, 0.9 mmol), ZnBr$_2$ (8 g, 35.6 mmol), and Et$_3$N (3.6 g, 35.6 mmol) in THF (300 ml) was heated under reflux for 6 h in an atmosphere of nitrogen. The reaction mixture was diluted with water (200 ml), extracted with CHCl$_3$ (3×50 ml). The combined organic solutions were dried over anhydrous Na$_2$SO$_4$ and reduced *in vacuo*. Chromatography of the residue on silica gel with CHCl$_3$ provided **2** (6 g, 83 %) : mp 138-139 ℃ (Et$_2$O), ir (KBr) : 2210, 1725 cm^{-1}, ^{1}H-nmr (CDCl$_3$) δ 2.28 (s, 3H, 6-CH$_3$), 6.19 (s, 1H, 5-H), 7.25-7.78 (m, 5H, Ar-H), ms (*m/z*) : 244 (M$^+$). *Anal.* Calcd for $C_{14}H_9O_2Cl$: C, 68.73 ; H, 3.71. Found : C, 68.82 ; H, 3.60.

Reaction of 2 with compounds containing active methylene group ; General procedure : All reactions were carried out in an atmosphere of nitrogen. To a suspension of 60 % NaH[4] (0.18 g, 4.5 mmol) in THF[5] (50 ml) was slowly added a solution of compounds containing active methylene group (5.0 mmol) at room temperature with stirring. After 40 min at that temperature, a solution of **2** (1 g, 4.1 mmol) in THF (20 ml) added to the mixture over 40 min at 0 ℃. The reaction mixture was heated under reflux for 4 h. The reaction was quenched by the addition of 10 % HCl (20 ml). To the resulting mixture was added a saturated aqueous NaCl solution (50 ml) and the solution was extracted with CHCl$_3$ (3×50 ml). The combined organic solutions were dried over anhydrous Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with CHCl$_3$.

4-Diethoxycarbonylmethyl-6-methyl-3-phenylethynyl-2*H*-pyran-2-one (3a) : Yield of 81 %, mp 106 ℃ (cyclohexane - CH$_2$Cl$_2$), ir (KBr) : 2220, 1735 cm^{-1}, ^{1}H-nmr (CDCl$_3$) δ 1.30 (t, J = 7 Hz, 6H, $\underline{CH_3}CH_2\times2$), 2.32 (s, 3H, 6-CH$_3$), 4.28 (q, J = 7 Hz, 4H, $CH_3\underline{CH_2}\times2$), 5.20 (s, 1H, $\underline{CH}(COOC_2H_5)_2$), 6.30 (s, 1H, 5-H), 7.25-7.70 (m, 5H, Ar-H), ms (*m/z*) : 368 (M$^+$). *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47 ;

H, 5.47. Found : C, 68.36 ; H, 5.46.

4-Diacetylmethyl-6-methyl-3-phenylethynyl-2*H*-pyran-2-one (3b) : Yield of 52 %, mp 155 ℃ (Et_2O), ir (KBr) : 2220, 1735 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 2.09 (s, 6H, $CH_3CO \times 2$), 2.34 (s, 3H, 6-CH_3), 6.01 (s, 1H, 5-H), 7.23-7.53 (m, 5H, Ar-H), 16.82 (s, 1H, enol-OH), ms (*m/z*) : 308 (M^+). *Anal.* Calcd for $C_{19}H_{16}O_4$: C, 74.01 ; H, 5.23. Found : C, 74.05 ; H, 5.26.

4-Cyanoethoxycarbonylmethyl-6-methyl-3-phenylethynyl-2*H*-pyran-2-one (3c) : Yield of 9.5 %, mp 183 ℃ (decomp., AcOEt), ir (KBr) : 2220, 1715 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.42 (t, *J* = 7 Hz, 3H, $C\underline{H_3}CH_2$), 2.27 (s, 3H, 6-CH_3), 4.53 (q, *J* = 7 Hz, 2H, $CH_3C\underline{H_2}$), 6.11 (s, 1H, 5-H), 7.13-7.60 (m, 6H, Ar-H and $C\underline{H}(CN)(COOC_2H_5)$), ms (*m/z*) : 321 ($M^+$). *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02 ; H, 4.71 ; N, 4.36. Found : C, 70.93 ; H, 4.93 ; N, 4.32.

4-Cyanoethoxycarbonylmethyl-6-methyl-3-phenylacetyl-2*H*-pyran-2-one (5c) : Yield of 51 %, mp 231-232 ℃ (AcOEt), ir (KBr) : 1740 , 1710 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.30 (t, *J* = 7 Hz, 3H, $C\underline{H_3}CH_2$), 2.23 (s, 3H, 6-CH_3), 4.39 (q, *J* = 7 Hz, 2H, $CH_3C\underline{H_2}$), 4.73 (s, 2H, $ArCH_2$), 6.48 (s, 1H, 5-H), 7.23-7.67 (m, 5H, Ar-H), 13.03 (br, 1H, enol-OH), ms (*m/z*) : 339 (M^+). *Anal.* Calcd for $C_{19}H_{17}NO_5$: C, 67.25 ; H, 5.05 ; N, 4.13. Found : C, 67.40 ; H, 4.80 ; N, 3.97.

4-Dicyanomethyl-6-methyl-3-phenylacetyl-2*H*-pyran-2-one (5d) : Yield of 45 %, mp 260 ℃ (decomp., AcOEt), ir (KBr) : 2230 , 1750 cm^{-1}, ^{1}H-nmr ($CDCl_3$-DMSO-*d6*) δ 2.29 (s, 3H, 6-CH_3), 4.63 (s, 2H, $ArCH_2$), 5.20 (br, 1H, $CH(CN)_2$), 6.38 (s, 1H, 5-H), 7.33 (s, 5H, Ar-H), ms (*m/z*) : 292 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86 ; H, 4.14 ; N, 9.58. Found : C, 70.04 ; H, 4.05 ; N, 9.47.

Catalytic hydrogenation of 3a,b ; General procedure : A mixture of **3a,b** (1 g) and 5 % palladium carbon (0.5 g) in MeOH (70 ml) was shaken in an atmosphere of hydrogen at room temperature until **2** molar eq. amount of hydrogen were absorbed. The solution was filtered and reduced *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$.

4-Diethoxycarbonylmethyl-6-methyl-3-phenethyl-2*H*-pyran-2-one (4a) : Yield of 95 %, mp 60-61 ℃ (petroleum ether), ir (KBr) : 1720 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.28 (t, *J* = 7 Hz, 6H, $C\underline{H_3}CH_2 \times 2$), 2.24 (s, 3H, 6-$CH_3$), 2.82 (s, 4H, ArC<u>H2</u>C<u>H2</u>), 4.21 (q, *J* = 7 Hz, 4H, $CH_3C\underline{H_2}\times 2$), 4.58 (s, 1H, C<u>H</u>($COOC_2H_5)_2$), 6.15 (s, 1H, 5-H), 7.25 (s, 5H, Ar-H), ms (*m/z*) : 372 (M^+). *Anal.* Calcd for $C_{21}H_{24}O_6$: C, 67.73 ; H, 6.50. Found : C, 67.73 ; H, 6.68.

4-Diacetylmethyl-6-methyl-3-phenethyl-2*H*-pyran-2-one (4b) : Yield of 90 %, mp 113-114 ℃ (petroleum ether), ir (KBr) : 1720 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.77 (s, 6H, $CH_3CO\times 2$), 2.25 (s, 3H, 6-CH_3), 2.60-3.02 (m, 4H, $ArC\underline{H_2}C\underline{H_2}$), 5.73 (s, 1H, 5-H), 7.18 (s, 5H, Ar-H), 16.62 (s, 1H, enol-OH), ms (*m/z*) : 312 (M^+). *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06 ; H, 6.45. Found : C, 72.95 ; H, 6.52.

Hydrolysis of 3c with 10 % HCl : A mixture of **3c** (0.5 g, 1.6 mmol) and 10 % HCl (1 ml) in EtOH (20 ml) was heated for 20 min at 60 ℃. The solvent was removed and the residue was diluted with $CHCl_3$ (50 ml). The solution was washed with water, dried on anhydrous Na_2SO_4, and reduced *in vacuo*. The residue was recrystallized from AcOEt to give **5c** (0.5 g, 95 %).

REFERENCES AND NOTES

1. A. Cantos, P. De March, M. Moreno-Manas, A. Pla, F. Sanchez-Ferrando, and A. Virgili, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4425 ; *Idem*, *Chem. Lett.*, **1986**, 295.
2. Y. Azuma, A. Sato, and M. Morone, *Heterocycles*, 1993, **35**, 599.
3. Y. Azuma, A. Sato, and M. Morone, *Heterocycles*, 1994, **38**, 1573.
4. 60 % dispersion of NaH in mineral oil was washed several times by decantation with THF.
5. In the reaction of **2** with ethyl cyanoacetate, NaH was suspended into a mixture of THF (30 ml) and DMF (20 ml).

Received, 31st July, 1995