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A Convenient and Practical Preparation of 4-Chloromethyl-5-methyl-1,3-dioxol-2-one

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A new synthetic method for 4-chloromethyl-5-methyl-1,3-dioxol-2-one (**1c**), which is useful for preparing prodrugs, has been developed. Ene-chlorination of 4,5-dimethyl-1,3-dioxol-2-one (**2**) with chlorine or sulfuryl chloride afforded 4-chloro-4-methyl-5-methylene-1,3-dioxolan-2-one (**3**) in good yield. Compound **3** underwent allylic rearrangement to afford **1c** quantitatively. The overall yield of **1c** from **2** was approximately 80%.

Keywords——4-chloromethyl-5-methyl-1,3-dioxol-2-one; 4,5-dimethyl-1,3-dioxol-2-one; 4-chloro-4-methyl-5-methylene-1,3-dioxolan-2-one; ene-chlorination; allylic rearrangement; (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group; promoiety; prodrug

The (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group is a very useful promoiety for ester-type prodrugs (Lenampicillin,[1] mecillinam prodrug[2]) and also for an amine-type prodrug (norfloxacin prodrug[3]). We have described[1] the syntheses of 4-halomethyl-5-methyl-1,3-dioxol-2-ones (**1a**: X=Br, **1b**: X=I, **1c**: X=Cl), used to prepare the above prodrugs. In a previous paper,[1] we also reported that allylic bromination of 4,5-dimethyl-1,3-dioxol-2-one (**2**)[4] occurred to give **1a** easily under radical conditions using bromine or *N*-bromosuccinimide. However, in the reaction of **2** with *N*-chlorosuccinimide under ultraviolet (UV) irradiation, **1c** was obtained in a low yield, and the dichloride **4**[5] was formed as a by-product.

In order to obtain **1c** in high yield, chlorinations of **2** under non-radical conditions were examined. Here we report a convenient and practical synthesis of **1c**.

Sulfuryl chloride was added slowly to a refluxing solution of **2** in dichloromethane to afford a monochlorinated compound (**3**) in nearly 85% yield together with dichlorides (**4**),

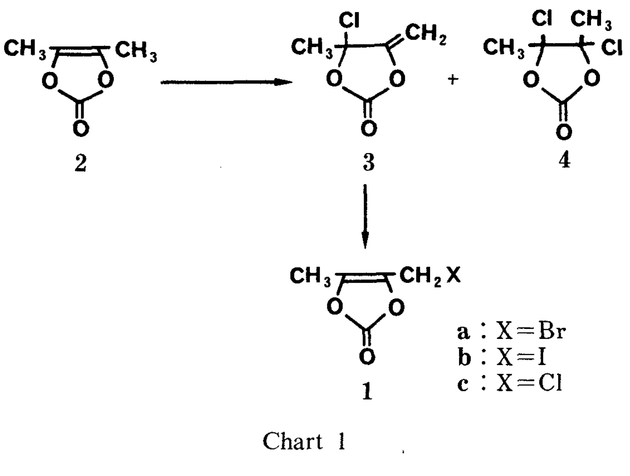

Chart 1

Table I. The Effect of Solvent on Ene-chlorination

Solvent[a]	Temp. (°C)[b]	Cl_2[c] (eq)	Yield (%) from **2**[d]			
			3	**1c**	**4**	
Dichloromethane	43—45	1.17	87.5	1.4	3.2	8.8
1,2-Dichloroethane	82—83	1.21	65.5	11.7	5.7	11.5
1,1-Dichloroethane	59—60	1.31	11.6	55.5	3.9	15.7
1,1,2-Trichloroethane	118—119	1.48	31.2	44.7	5.7	9.2
1,1,1-Trichloroethane	74—75	1.23	74.7	4.9	3.9	15.5
Carbon tetrachloride	73—74	1.20	53.7	13.4	13.3	13.5
Trichloroethylene	81—83	1.26	61.4	18.8	3.2	12.4
Tetrachloroethylene	122—125	1.28	23.2	31.7	24.9	8.9

a) Ene-chlorination was carried out using 0.35 M **2** in 100 ml of solvent. *b*) Refluxing temperature. *c*) Chlorine was passed until **2** disappeared. *d*) The yields were determined by gas chromatography on a 3 mm × 1 m PEG-20M (10%) column at 120—200 °C (5 °C/min), using acenaphthene as an internal standard.

which were probably a mixture of *cis* and *trans* products, in 13% yield and a very small amount of **1c**. Compound **3** was also obtained in the same yield by reacting **2** with chlorine.

The structure of **3** was determined on the basis of spectroscopic data. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3** exhibited one singlet at 2.19 ppm and two doublet peaks ($J = 5$ Hz) at 4.86 ppm and 5.05 ppm which suggested the presence of an exomethylene group. From the infrared (IR) absorption at 1820 cm^{-1} and the parent peak (M^+) of the mass spectrum (MS) at 148, the structure of **3** was assigned as 4-chloro-4-methyl-5-methylene-1,3-dioxolan-2-one, which is a structural isomer of **1c**. It was presumed that the small amount of **1c** was formed by rearrangement of **3**, because the amount of **1c** varied from runs to run, though the combined yield of **3** and **1c** was nearly constant. Actually, **3** underwent allylic rearrangement on heating to afford **1c**, as mentioned later. It was thought that this chlorination took place by an ene-mechanism. There have been several reports on ene-type chlorination using various reagents,[6-9] but few ene-chlorinations with sulfuryl chloride have been reported previously.[10] In this ene-chlorination, a chlorinated hydrocarbon, especially dichloromethane, was suitable as a solvent and chlorine or sulfuryl chloride as a chlorinating reagent, giving a high combined yield of **1c** and **3** as shown in Table I. The use of other solvents such as benzene, cyclohexane and ethyl acetate resulted in an increase of the dichloride (**4**).

When this chlorination was carried out below the refluxing temperature of dichloromethane, the formation of the dichloride (**4**) increased. When dry hydrogen chloride was conducted together with chlorine into the well-refluxing solution, the yield of **4** did not change. From these result, it was considered that the resulting hydrogen chloride in this chlorination accelerated the formation of **4** since the hydrogen chloride was difficult to remove from the reaction system below the refluxing temperature. In order to inhibit the formation of the dichloride (**4**), inorganic bases or metallic salts were added to the reaction solution, but the yield of **3** was little improved. In the reaction of **2** with bromine under the same conditions, ene-bromination took place partially, but addition to the double bond was preferred.

The allylic rearrangement of **3** was accomplished by heating neat at 70—80 °C for 4—6 h to afford **1c** quantitatively. This rearrangement without using a solvent was accelerated 2 to 3 times by bubbling dry hydrogen chloride gas or adding a catalytic amount of copper salt (CuCl, CuO, $CuCl_2$, *etc.*). However, the catalytic effect of hydrogen chloride gas or copper salt was negligible when the reaction was carried out in refluxing dichloromethane. Thus, we investigated the catalytic abilities of other salts, even in dichloromethane, and found that copper powder was effective. After the chlorination of **2** in dichloromethane, copper powder was added to the refluxing solution, and the mixture was refluxed for 1.5 h. Thus **1c** was obtained from **2** in approximately 80% yield by a one-pot reaction, *i.e.*, ene-chlorination followed by allylic rearrangement.

In the preparation of **1a**, the radical bromination of **2** with *N*-bromosuccinimide or bromine accompanied the di-substitution reaction to afford a small amount of 4,5-bis(bromomethyl)-1,3-dioxol-2-one,[4c)] which reacted with the parent drug to give by-products. Consequently, purification of **1a** was needed, but distillation was difficult on a large scale because of the thermoinstability of **1a**. On the other hand, no 4,5-bis(chloromethyl)-1,3-dioxol-2-one was formed in this procedure, and the chloride (**1c**) was more stable than the bromide (**1a**) and easier to distill. Compound **1c** was less reactive than **1a** and **1b**, but in the presence of iodide salt it could be used similarly to **1a** and **1b** for the preparation of the prodrugs. The byproduct **4** hardly reacted with the parent drug, so purification of **1c** was not required. These are important benefits of this convenient and practical procedure.

Experimental

^{1}H-NMR spectra were determined on a Nihon Denshi PS-100 NMR spectrometer and a Hitachi R-24B NMR spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded with a Shimadzu IR-440 instrument. MS were measured with a Hitachi M-80 B mass spectrometer.

4-Chloro-4-methyl-5-methylene-1,3-dioxolan-2-one (3)——Sulfuryl Chloride Method: Sulfuryl chloride (68 g) was added dropwise to a refluxing solution of **2** (55 g) in dichloromethane (200 ml) over 20 min. The mixture was refluxed for 30 min and then evaporated *in vacuo*. The residue was distilled *in vacuo* to give 54 g (75%) of **3** as a colorless liquid. bp 45—48 °C (2 mmHg). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1820 (C=O), 1695 (C=C). ^{1}H-NMR (CDCl$_3$) δ: 2.19 (3H, s, CH$_3$), 4.86 (1H, d, $J=5$ Hz, C=CH), 5.05 (1H, d, $J=5$ Hz, C=CH). MS *m/z*: 148 (M$^+$).

Chlorine Method: Chlorine gas (41 g) was bubbled into a refluxing solution of **2** (55 g) in dichloromethane (150 ml) for 60 min. The reaction mixture was refluxed for 30 min, and then worked up as described above to give 53 g (73.7%) of **3** as a colorless liquid. The physical properties were in agreement with those of the product obtained by the sulfuryl chloride method.

4-Chloromethyl-5-methyl-1,3-dioxol-2-one (1c)——From **3**: Compound **3** (50 g) was stirred at 75—80 °C for 4 h, then distilled *in vacuo* to give 43.5 g (87%) of **1c** as a colorless liquid. bp 91—93 °C (2 mmHg). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1820 (C=O), 1730 (C=C). ^{1}H-NMR (CDCl$_3$) δ: 2.18 (3H, s, CH$_3$), 4.31 (2H, s, CH$_2$Cl). *Anal.* Calcd for $C_5H_5ClO_3$: C, 40.43; H, 3.39. Found: C. 40.46; H, 3.25.

One-Pot Reaction from **2**: Chlorine gas (41 g) was bubbled into a refluxing solution of **2** (55 g) in dichloromethane (150 ml) for 60 min. The reaction mixture was refluxed for 30 min further. Copper powder (0.2 g) was added, and the mixture was refluxed for 2 h. After filtration, the filtrate was evaporated *in vacuo*, and the residue was distilled *in vacuo* to give 55.3 g (77%) of **1c** as a colorless liquid. The physical properties were in agreement with those of the product obtained above.

The distillation was carried out to obtain a sample for determination of the physical properties, but was not necessary for preparations of prodrugs.

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