A NOVEL AND FACILE SYNTHESIS OF 5-SUBSTITUTED 1,3-DIOXOLANE-2,4-DIONES USING TRICHLOROMETHYL CHLOROFORMATE

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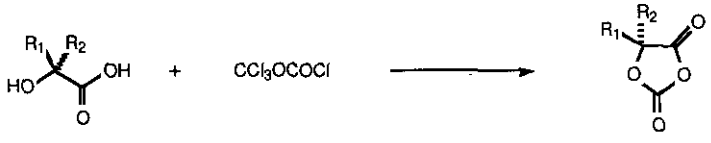
Abstract——5-Substituted 1,3-dioxolane-2,4-diones including the chiral derivatives were synthesized by the reaction of α-hydroxy carboxylic acids with trichloromethyl chloroformate.

(R)-5-Phenyl-1,3-dioxolane-2,4-dione (D-mandelic acid O-carboxyanhydride) (**1a**) is an important mandelylation reagent for the preparation of cephalosporin antibiotics with enhanced activity.[1-5]

The synthesis of 5-substituted 1,3-dioxolane-2,4-diones (**1**) reported by Davies[6] involved the direct reaction of α-hydroxy carboxylic acids with large excess of phosgene for a long reaction time at room temperature. The yields of **1** by this procedure are poor due to the predominant formation of impurity of the corresponding α-chlorinated acid chloride. It has been reported that use of the copper(II) salt of α-hydroxy carboxylic acid drastically reduces the amount of this impurity.[7]

Trichloromethyl chloroformate (TCF)[8] was used for the synthesis of N-carboxy α-amino acid anhydride in place of phosgene.[9] This method involves the decomposition of TCF to phosgene in a warm solution,[9] or with activated charcoal,[10] and the reaction of the resulting phosgene with the amino acids.

We now report a novel facile synthesis of **1** including chiral derivatives (**1a,b,e**) by the reaction of the corresponding α-hydroxy carboxylic acids with TCF.



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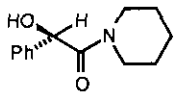
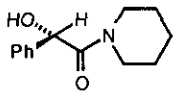
Typical procedure for the preparation of **1** is as follows. A solution of TCF in THF was mixed with a solution of an equimolar amount of (R)-mandelic acid in THF at room temperature and the mixture was refluxed for 6 h. Then the mixture was concentrated and the residual oil solidified on addition of n-hexane. The solid was crystallized from ether to give **1a**: mp 74-75°C; $[\alpha]_D^{20}$ -17.3° (c=1.965, $CHCl_3$). (S)-5-Phenyl-1,3-

dioxolane-2,4-dione (L-mandelic acid O-carboxyanhydride) (**1b**) was also obtained from (S)-mandelic acid in 75 % yield: mp 74-75°C; $[\alpha]_D^{20}$+17.4° (c=2.012, $CHCl_3$). The compound **1b** showed the same ir and ^{1}H-nmr spectra as those of (R)-compound. (S)-5-Methyl-1,3-dioxolane-2,4-dione (**1e**) obtained from (S)-lactic acid showed mp 58-60°C; $[\alpha]_D^{20}$ -19.1° (c=0.99, $CHCl_3$).

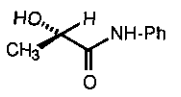
The optical purities of the dioxolanediones **1a**,**1b**, and **1e** were determined on the basis of their ^{1}H-nmr analysis, using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium (III) as a chiral shift reagent, of the amides (**(-)-2**, **(+)-2**, and **(-)-3**), which obtained from the reaction of **1a** or **1b** with piperidine and **1e** with aniline.



(-)-2



(+)-2



(-)-3

The amides **(-)-2**, **(+)-2**, and **(-)-3** are optically pure in a sense of nmr spectroscopic accuracy, and the reaction of these chiral α-hydroxy carboxylic acids with TCF under the reaction conditions described above is found to proceed without racemization.

Similarly, compounds (**1c**,**d**,**f**,**g**) were prepared. The reaction conditions and results are summarized in Table 1.

Table 1. 5-Substituted 1,3-dioxolane-2,4-diones

compound	R_1	R_2	yield (%)	mp (°C)	reaction time (h)	recryst. solvent	absolute configuration
1a	H	C_6H_5	72	74-75	6	ether	R
1b	C_6H_5	H	75	74-75	6	ether	S
1c	C_6H_5	H	68	56-57[a]	6	ether	racemic
1d[e]	C_6H_5	C_6H_5	78	69-70[b]	1	n-hexane	-
1e[f]	CH_3	H	46	58-60	2	ether	S
1f[f]	CH_3	H	49	27-28[c]	2	ether	racemic
1g[e]	CH_3	CH_3	52	40-41[d]	1	n-hexane	-

a) literature 6; mp 55-57°C, literature 7; mp 54-55°C. b) literature 7; mp 68-69°C. c) literature 6; mp 27-28°C. d) literature 11; mp 38°C. Satisfactory analytical results have been obtained for all compounds. e) This reaction proceeded in the presence of pyridine (2 equiv.) at room temperature. f) The TCF remained in the reaction mixture was decomposed by the addition of activated charcoal.

EXPERIMENTAL

Melting points were determined by the capillary method and uncorrected. Infrared (Ir) spectra were determined with a Hitachi 215 spectrophotometer and ^{1}H-nmr spectra with a JEOL JMS SP100 spectrometer or a JEOL JMS FX200 spectrometer using tetramethylsilane as an internal reference. Column chromatography was performed on silica gel (K-100-S, from Katayama Chemicals). Optical rotations were measured with a Union Giken PM-201 polarimeter.

(R)-5-Phenyl-1,3-dioxolane-2,4-dione (1a). A solution of an equimolar amount of TCF (0.79 ml, 6.57 mmol) in THF (5 ml) was added dropwise to a stirred solution of (R)-mandelic acid (1.0 g, 6.57 mmol) in THF (15 ml) at room temperature. After being refluxed for 6 h, the reaction mixture was concentrated to a viscous oil under reduced pressure. n-Hexane was added to the oil and the mixture was allowed to stand at 5°C overnight. The resulting solid was triturated and washed with n-hexane several times and crystallized from ether to give 839 mg (72 %) of the dioxolanedione **1a**. Ir(KBr) 1900, 1820 (C=O) cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ 5.99 (1H, s, CH), 7.38-7.58 (5H, m, ArH). Ms m/z 178 (M^+), 152 [(M^++2)-CO].

(S)-5-Phenyl-1,3-dioxolane-2,4-dione (1b). The dioxolanedione **1b** was obtained from (S)-mandelic acid and TCF in a similar manner to that described for compound **1a**. The compound **1b** showed the same ir and ^{1}H-nmr spectra with those of **1a**.

(S)-5-Methyl-1,3-dioxolane-2,4-dione (1e). A solution of an equimolar amount of TCF (1.34 ml, 11.1 mmol) in THF (5 ml) was added dropwise to a stirred solution of (S)-lactic acid (1.0 g, 11.1 mmol) in THF (20 ml) at room temperature. After being refluxed for 2 h, the reaction mixture was treated with activated charcoal and filtered. The filtrate was concentrated under reduced pressure to give a viscous oil which solidified by cooling at -78 °C. The solid was crystallized from ether to give the dioxolanedione **1e** (598 mg, 46 %). Ir(KBr) 1890, 1820 (C=O) cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ 1.72 (3H, d, J=7 Hz, CH_3), 5.25 (1H, q, J=7 Hz, CH). Ms m/z 116 (M^+).

Reaction of 1a with Piperidine. A solution of **1a** (208 mg, 1.17 mmol) in CH_2Cl_2 (10 ml) was added to a stirred solution of piperidine (0.12 ml, 1.21 mmol) in CH_2Cl_2 (5 ml) at 0°C. After being stirred for 10 min, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel to give the amide **(-)-2** (214 mg, 84 %); mp 68-69°C. $[\alpha]_D^{20}$ -75.2° (c=1.37, $CHCl_3$). Ir(KBr) 3350 (OH), 1640 (C=O) cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ 0.60-1.70 (6H, m, CH_2), 3.00-3.92 (4H, m, CH_2), 4.85 (1H, d, J=6 Hz, OH), 5.19 (1H, d, J=6 Hz, CH), 7.35 (5H, s, ArH). Ms m/z 219 (M^+). Anal. Calcd for $C_{13}H_{17}NO_2$: C,71.21; H,7.81; N,6.39. Found: C,70.99; H,7.90; N,6.36.

Reaction of 1b with Piperidine. The amide **(+)-2** was obtained from **1b** (230 mg, 1.29 mmol) and piperidine (0.12 ml, 1.21 mmol) in a similar manner to that described for compound **(-)-2**. Yield, 192 mg (75 %); mp 67-68°C. $[\alpha]_D^{20}$ +73.9° (c=1.03, $CHCl_3$). The amide **(+)-2** showed the same ir and ^{1}H-nmr spectra with those of **(-)-2**. Ms m/z 219 (M^+). Anal. Calcd for $C_{13}H_{17}NO_2$: C,71.21; H,7.81; N,6.39. Found: C,71.09; H,7.91; N,6.28.

Reaction of 1e with Aniline. The amide **(-)-3** was obtained from **1e** (150 mg, 1.29 mmol) and aniline (0.12 ml, 1.32 mmol) in a similar manner to that described for compound **(-)-2**. Yield, 203 mg (95 %). $[\alpha]_D^{20}$ -9.7° (c=1.75, $CHCl_3$). Ir(KBr) 3350 (OH), 1660 (C=O) cm^{-1}. ^{1}H-Nmr($CDCl_3$) δ 1.48 (3H, d, *J*=7 Hz, CH_3), 3.50-3.80 (1H, br, OH), 4.32 (1H, q, *J*=7 Hz, CH), 7.09-7.55 (5H, m, ArH), 8.50-8.70 (1H, br, NH). Ms m/z Calcd for $C_9H_{11}NO_2$ 165.0790, Found 165.0797.

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