Lactonization of \( \omega \)-Hydroxycarboxylic Acids Using
(4,5-Dichloro-6-oxo-6\( ^{6} \)-pyridazin-1-yl)phosphoric Acid Diethyl Ester

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(4,5-Dichloro-6-oxo-6\( ^{6} \)-pyridazin-1-yl)phosphoric acid diethyl ester (3) is an efficient coupling agent for lactonization of aliphatic and aromatic \( \omega \)-hydroxycarboxylic acids. Lactonization of \( \omega \)-hydroxycarboxylic acids with 3 in the presence of equimolar amounts of a base gave the corresponding mono-olides, diolides, triolides and/or tetraolides.

Key Words: Lactonization, \( \omega \)-Hydroxycarboxylic acid, (6-Oxo-6\( ^{6} \)-pyridazin-1-yl)phosphoric acid diethyl ester, Lactone

Introduction

Lactonization is an important process in the synthesis of the natural product. Accordingly, preparation of lactones from \( \omega \)-hydroxycarboxylic acids is also major concern in synthetic organic chemistry. Although several useful methods have therefore been reported, the research in this field still active even now.

In connection with the research on the synthetic application of 2-substituted pyridazin-3(2\( ^{6} \))-ones, we found that 2-benzenesulfonyl-4,5-dichloropyridazin-3(2\( ^{6} \))-ones serve as a coupling reagent. However, this coupling regent requires two equivalents of carboxylic acids for the esterification and the amidation of carboxylic acids. We therefore developed (4,5-disubstituted-6-oxo-6\( ^{6} \)-pyridazin-1-yl)phosphoric acid diethyl esters as novel and efficient coupling agent. Herein we report a lactonization of \( \omega \)-hydroxycarboxylic acids using (4,5-dichloro-6-oxo-6\( ^{6} \)-pyridazin-1-yl)phosphoric acid diethyl ester (3) as a coupling agent.

Results and Discussion

(4,5-Dichloro-6-oxo-6\( ^{6} \)-pyridazin-1-yl)phosphoric acid diethyl ester (3) was easily prepared in 96% yields via the reaction of 4,5-dichloropyridazin-3(2\( ^{6} \))-ones (1) with diethyl chlorophosphate (2) in the presence of triethylamine in acetonitrile at room temperature.

Initially, direct lactonization of 2-hydroxyphenylacetic acid (4a) using 3 was studied in a variety of representative organic solvents and bases (Table 1). From the preliminary experiments, we selected potassium carbonate/ethyl acetate and N,N-dimethylaminopyridine/tetrahydrofuran system for the lactonization of \( \omega \)-hydroxycarboxylic acids using 3.

Results of the lactonization using various \( \omega \)-hydroxycarboxylic acids listed in Table 2. The corresponding mono-olides, diolides, triolides and/or tetraolides were obtained in moderate to high yields under the reaction conditions mentioned above. Lactonization of 2-hydroxybenzoic acid (4b) using 3 in the presence of DMAP in tetrahydrofuran at room temperature gave the corresponding triolide 7b as the main (Table 2 entry 1). Whereas, treatment of 2-hydroxybenzoic acid (4b) using 3 in the presence of potassium carbonate in...
ethyl acetate or tetrahydrofuran at room temperature gave trisalicylide \( (7b) \) and \( 8b \) as main instead of the corresponding monoolide (Table 2 entries 2 and 3).

Lactonization of 3-(2-hydroxyphenyl)propanoic acid (4c) using 3 at room temperature gave trisalicylide \( (7b) \) and \( 8b \) as main instead of the corresponding monoolide (Table 2 entries 2 and 3). On the other hand, \( trans \)-3-(2-hydroxyphenyl)acrylic acid (4d) was reacted with 3 under three reaction conditions to give coumarin \( 5d \) in 11-36% yields and the corresponding diolide \( 6d \) in 44-59% yields, respectively (Table 2 entries 7-9). The synthesis of \( 5d \) from 4d was also reported. \(^{21}\) Lactonization of 12-hydroxystearic acid (4e) using 3 under \( N,N \)-dimethylaminopyridine/THF and potassium carbonate/EtOAc system gave the corresponding lactone \( 5e \) (2-11%) and diolide \( 6e \) (55%), respectively. However, the reaction of 4e did not occur when potassium carbonate/THF system was used. Lactonization of 10-hydroxystearic acid (4f) using 3 in the presence of potassium carbonate in refluxing ethyl acetate gave the corresponding diolide \( 6f \) in 81% yield (Table 2 entry 14), whereas the reaction of 4e did not occur when potassium carbonate/THF system was used. Although reaction of 4f with 3 under \( N,N \)-dimethylaminopyridine/THF system gave \( 6f \), the reaction did not occur completely. On the other hand, we could not detect the characteristic effect of the amounts of 3, solvents and/or bases on the selectivity of the products under our conditions.

In order to cyclize \( trans \)-3-(2-hydroxyphenyl)acrylic acid (4d), \( trans \)-isomer must change to the corresponding cis-isomer. The lactonization of \( trans \)-3-(2-hydroxyphenyl)- acrylic acid (4d) to \( 5d \) using compound 3 may proceed via the Pathway A, B, and C. Among three pathways, the Pathway B and the Pathway C may be more favorable under the basic condition. On the other hand, the diolide \( 6d \) may be yield by the cyclization between two \( trans \)-phenoxide intermediates.

The structures of all synthesized compounds were esta-
established by ir, nmr, elemental analysis and/or mass spectroscopy. In all the reactions described above, reusable 4,5-dichloropyridazin-3(2H)-one (1) was isolated quantitatively.

Conclusions

In conclusion, compound 3 is an efficient coupling agent for lactonization of aliphatic and aromatic ω-hydroxycarboxylic acids. It is noted that a simple method for the synthesis of various lactones was established by using equimolar amounts of ω-hydroxycarboxylic acids and 3 in the presence of equimolar amounts of a base. Compound 1 can be recovered quantitatively for reuse.

Experimental Section

General. Melting points were determined with a capillary apparatus and uncorrected. NMR spectra were recorded on a 300 MHz spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a Hitachi 270-50 or Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with CHNS-932 (Leco). Mass spectra were obtained on a GC Mate 2, JEOL. The open-bed chromatography was carried out on silica gel (70-230 mesh, Merck) using gravity flow. The column was packed with slurries made from the elution solvent.

Typical procedure for lactonization. A solution of ω-
hydroxy-carboxylic acids (3.0 mmol), compound 3 (1.36 g, 4.5 mmol) and a base (3.3 mmol) in solvent (30 mL) was stirred until ω-hydroxy-carboxylic acids were disappeared at room temperature (or at reflux temperature). After filtering, the solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (3.5 × 15 cm). The column was eluted with ethyl acetate/n-hexane (1:2, v/v). Fractions containing the product were combined and evaporated under reduced pressure to give the corresponding lactone, diolide, triolide and/or tetrolide, respectively.

**Compound 5a**: Liquid. R_f = 0.74 (EtOAc:n-hexane = 1:1, v/v). IR (KBr): 3070, 2950, 1810, 1620, 1460, 1400, 1330, 1300, 1230, 1120, 1060, 900, 760 cm⁻¹. ¹H NMR (CDCl₃): δ 7.28 (d, 2H, J = 7.6 Hz), 7.05-7.14 (m, 2H), 3.70 ppm (s, 2H). ¹³C NMR (CDCl₃): δ 174, 154.7, 132.9, 128.8, 124.7, 124.1, 123.1, 111.0 ppm. Elemental analysis calcd for C₁₉H₁₆O₅: C, 72.96; H, 5.44. Found: C, 73.05; H, 5.49. MS (EI): Exact mass calcd for C₁₉H₁₆O₅: m/z 292.1346. Found: m/z 292 (M⁺).

**Compound 7a**: mp 195-197 °C. R_f = 0.44 (CH₂Cl₂). IR (KBr): 3100, 2950, 1740, 1620, 1500, 1460, 1300, 1260, 1230, 1135, 1090, 1040, 760, 700, 540 cm⁻¹. ¹H NMR (CDCl₃): δ 7.97 (d, 3H, J = 7.6 Hz), 7.66 (t, 3H, J = 7.7 Hz), 7.52 (d, 3H, J = 7.6 Hz), 7.41 ppm (s, 2H). ¹³C NMR (CDCl₃): δ 164.7, 148.6, 133.3, 126.2, 123.9, 123.8 ppm. Elemental analysis calcd for C₁₅H₁₂O₅: C, 70.00; H, 3.36. Found: C, 70.05; H, 3.39. MS (EI): Exact mass calcd for C₁₅H₁₂O₅: m/z 292.0634. Found: m/z 292 (M⁺).
17. For some examples of recent mediating agents, see refs. (9), (10), (12), and (16).