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# PREPARATION AND REACTION OF CYCLIC OXALATE OF DIOLS

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**ABSTRACT :** Cyclic oxalates were efficiently prepared by the reaction of diols with ethyl oxalyl chloride in the presence of triethylamine. They were stable under acidic conditions but cleaved to diols under basic conditions.

Although there are a great number of protective groups available for alcohols, cyclic protective groups such as cyclic acetals, cyclic ketals, cyclic orthoesters, and cyclic esters are more convenient for protection of polyhydroxy compounds in terms of efficiencies and selectivities compared to the usual acyclic protective groups for alcohols. Most of these

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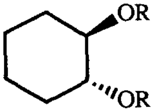
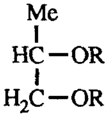
cyclic protective groups are unstable under acidic conditions and stable in basic medium whereas there are only a few acid-stable and base-labile cyclic protective groups are available such as 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene) derivatives[1] and cyclic carbonates.[2] We thought that the cyclic oxalate might be a useful acid-stable and base-labile protective group. Surprisingly, however, the cyclic oxalate has never been used for the protection of diols and the practical method for its preparation from diols is not available. Although there have been two reports for the preparation of cyclic oxalates from diols; one method by the reaction of diols with oxalic acid[3] and another by the reaction of dioxastannolans with oxalyl chloride,[4] these methods can not be applicable to other diols, especially to acid-labile complex polyfunctional compounds and the reactivity of the oxalate has not been examined.

The present communication describes an efficient method for the synthesis of cyclic oxalates from diols and usefulness of the cyclic oxalate as an acid-stable and base-labile protective group. We examined various possible oxalating agents for diols such as ethyl oxalyl chloride(**1**), oxalyl chloride, diethyl oxalate, oxalic acid, and 1,1'-oxalyl diimidazole. We have found that ethyl oxalyl chloride was the most satisfactory oxalating agent for diols. Diols used in this work were *trans* -1,2-cyclohexandiol(**2**), 1,2-propandiol(**3**), and 1,2;5,6-di-*O*-isopropylidene-D-mannitol(**4**) which represent a cyclic diol, an acyclic diol, and an acyclic diol containing an acid-labile protective group, respectively. A representative example is the reaction of diol **4** with **1**. To a solution of compound **4** (0.50g, 1.9mmol) and triethylamine (0.38g, 3.8mmol) in methylene chloride(10ml), ethyl oxalyl chloride (0.52g, 3.8mmol) was added dropwise with stirring at 0°C under nitrogen. After stirring at 0°C for 2 hrs, the reaction mixture was diluted with methylene chloride (30ml) and the organic phase was washed with water. The product in organic layer was purified by column



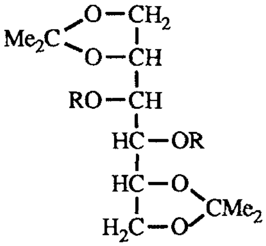
**2** R = H

**8** $R = \overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}OEt$



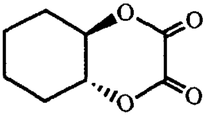
**3** R = H

**9** $R = \overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}OEt$



**4** R = H

**10** $R = \overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}OEt$



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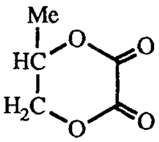

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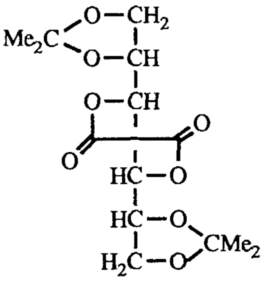


**7**

chromatography of silica gel to afford 1,2;5,6-di-*O*-isopropylidene-D-mannitol 3,4-oxalate (**7**)[5](0.35g, 61%) and 1,2;5,6-di-*O*-isopropylidene-D-mannitol 3,4-bis(ethyloxalate)(**10**)[6](0.15g, 17%).

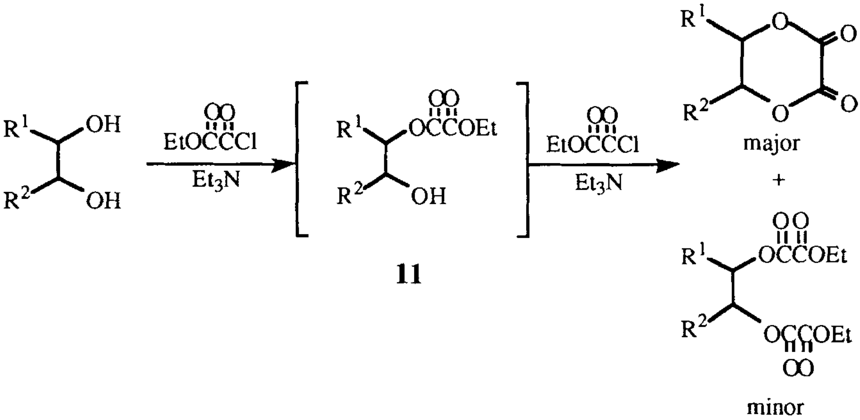
Table 1. Reactions of Diols with Ethyl Oxalyl Chloride

| Diol | Base | Product[a] | |
|---|---|---|---|
| | | Cyclic Oxalate | Bis(ethyloxalate) |
| **2** | $Et_3N$ | **5** (65%) | **8** (14%) |
| **2** | $C_5H_5N$ | | **8** (88%) |
| **3** | $Et_3N$ | **6** (66%) | **9** (7%) |
| **3** | $C_5H_5N$ | | **9** (67%)[b] |
| **4** | $Et_3N$ | **7** (61%) | **10** (17%) |
| **4** | $C_5H_5N$ | | **10** (70%)[b] |

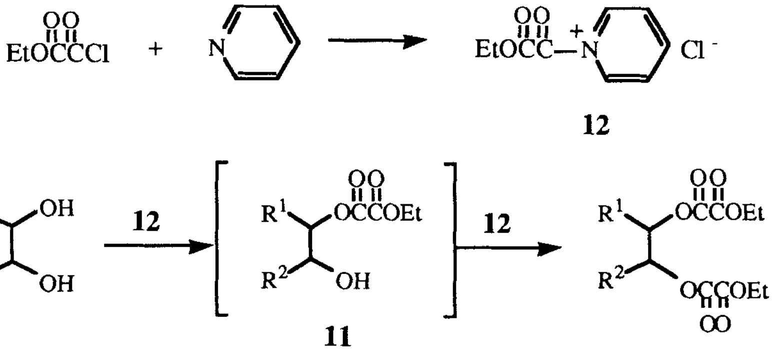
[a] Yields in parentheses are isolated ones.

[b] A small amount of acyclic mono(ethyloxalate) was also detected.

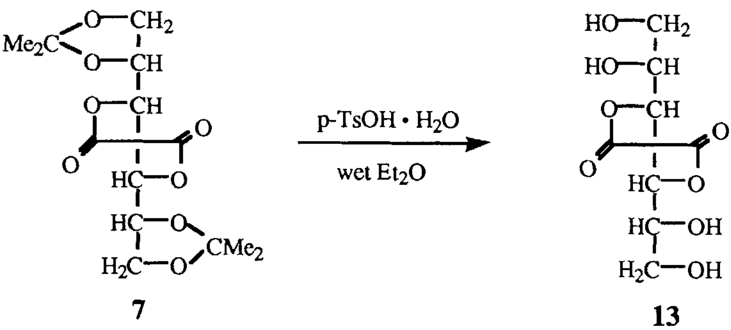
The product ratio of this reaction was very sensitive to the base employed. Thus, triethylamine provided cyclic oxalates as the major products whereas pyridine afforded only acyclic bis(ethyloxalate). The results are summarized in Table 1. Mono(ethyloxalate) **11** is a probable intermediate for the formation of both the cyclic oxalate and the acyclic bis(ethyloxalate) as shown in Scheme 1 and 2. In fact, it was observed that a small amount of acyclic mono(ethyloxalate) was produced in the reaction of diols **2** and **3** employing pyridine as a base. In the presene of triethylamine, the intramolecular cyclization of intertmediate **11** is faster than the further oxalation of a remaining hydroxy group of **11**, whereas the formation of bis(ethyloxalate) is faster process in the presence of pyridine probably because ethyl oxalyl pyridinium salt **12** is very reactive species. It



Scheme 1



Scheme 2



Scheme 3

is known that the acylpyridinium ion reacts more rapidly with the alcohol than the acid chloride.[7]

Deprotection of cyclic oxalates was readily accomplished. Cyclic oxalates **5**, **6**, and **7** were converted to the corresponding diols in almost quantitative yields at room temperature by various reagents ; (i) sodium methoxide in methanol, (ii) potassium carbonate in methanol, (iii) triethylamine in methylene chloride-water, or (iv) 1% aqueous sodium hydroxide in methylene chloride. On the other hand, cyclic oxalates were stable under acidic conditions. Thus, compounds **5** and **6** were not affected by *p*-TsOH • $H_2O$ in wet ether while two isopropylidene groups of compound **7** were cleaved to give rise to compound **13**[8] as shown in scheme 3.

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5. Compound **7** ; TLC ($SiO_2$, ether) $R_f = 0.70$; mp 143-144°C; IR (KBr) 2980, 1790, 1760 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$1.36 (s, 6H), 1.97(s, 6H),

4.0-4.5(m, 8H).

6. Compound **10** ; TLC ($SiO_2$, ether) $R_f$ = 0.74; IR (KBr) 2980, 1760, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$); δ1.2 (m, 18H, $CH_3$), 3.8-4.4 (m, 10H) 5.2-5.5 (dd, 2H).

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8. Compound **13** ; TLC ($SiO_2$, 8:2 chloroform/methanol) $R_f$ = 0.23; mp 180-181°C; IR (KBr) 3400, 1780 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ3.4-3.7 (m, 6H), 3.7-4.2(m, 2H).

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