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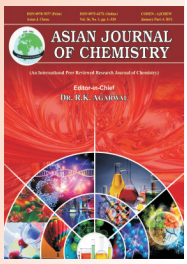

Synthesis and Deprotection of Cyclic Oxalate

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As a new protective group for diols, cyclic oxalates [*trans*-1,2-cyclo-hexane diol 1,2-oxalate (**1**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-oxalate (**2**) and 1,2-propanediol 1,2-oxalate (**3**)] were synthesized by using oxalyl chloride, ethyloxalyl chloride, diethyl oxalate and oxalic acid. Cyclic oxalates were readily cleaved to the corresponding diols by various bases such as sodium methoxide, potassium carbonate, 1 % sodium hydroxide, triethylamine and lithium aluminium hydride, but were stable in acid.

Keywords: Cyclic oxalate, Polyhydroxy compound, Protection, deprotection, Protective group.

INTRODUCTION

In many preparations of delicate organic compounds, some specific parts of their molecules cannot survive the required reagents or chemical environments. Then, these parts or groups, must be protected. The protective group must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. The protective group should form a crystalline derivative that can be easily separated from side products associated with its formation or cleavage. The protective group should have a minimum of additional functionality to avoid further sites of reaction[1-17].

Selective cleavage of protective groups in polyhydroxy compounds are very useful in organic synthesis, especially in the field of carbohydrate and nucleoside chemistry[18-29].

In this paper, we report the preparation of cyclic oxalate by protection of 1,2-diol and 1,3-diol and the cleavage of cyclic oxalate by treatment of acid and base.

EXPERIMENTAL

Melting points were determined using an electrothermal capillary melting point apparatus and uncorrected. Thin layer chromatography (TLC) was performed on glass plates coated with silicon oxide (silica gel $60F_{254}$) and compounds were visualized using a UV lamp. ^1H and ^{13}C NMR spectra were obtained with Bruker AC2000 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use. Except where explicitly stated, all the starting materials were purchased from Aldrich, Fluka, Fisher, Lancaster, or TCI chemical companies and used as received[30,31].

General synthesis of cyclic oxalate with oxalyl chloride: A mixture of *trans*-1,2-cyclohexanediol (1×10^{-2} mol, 1.16 g) and oxalyl chloride (1×10^{-2} mol, 1.18 mL) in pyridine (2×10^{-2} mol, 1.54 mL) and CH_2Cl_2 (20 mL) solution was stirred for 3 h. After 3 h, the reaction mixture was added CH_2Cl_2 (50 mL), water (30 mL) and 0.01 N HCl (20 mL). The combined organic layers were dried over separated, anhydrous Na_2SO_4 filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with ethyl acetate and hexane, to provide *trans*-1,2-cyclohexanediol 1,2-oxalate (67 %) and 1-*O*-carboxycarbonyl *trans*-1,2-cyclohexanediol (25 %).

***trans*-1,2-Cyclohexanediol 1,2-oxalate (1):** R_f : 0.45 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 2:1:4, v/v/v); m.p. : 110-111 °C ; IR (KBr, ν_{max}, cm^{-1}) : 2960s (C-H), 1760s (C=O); ^1H NMR ($CDCl_3$) : δ 1.0-2.4 (m, 8H, CH_2), 4.6-4.73 (m, 2H, CH).

1,2:5,6-Di-*O*-isopropylidene-D-mannitol 3,4-oxalate (2): R_f : 0.70 (TLC eluent; chloroform:methanol = 8:2, v/v); m.p. : 143-144 °C ; IR (KBr, ν_{max}, cm^{-1}): 2980, 1790, 1760; ^1H NMR ($CDCl_3$) : δ 1.4 (d, 12H, CH_3), 4.0-4.5 (m, 8H, mannitol CH).

1,2-Propanediol 1,2-oxalate (3): R_f : 0.38 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 2:1:3, v/v/v) ; m.p. : 119-120 °C; IR (KBr, ν_{max}, cm^{-1}): 2990s (C-H), 1762s, 1745s (C=O), 1185s (C-O); ^1H NMR ($CDCl_3$) : δ 1.2 (d, 3H, CH_3), 4.35 (d, 2H, CH_2), 5.32 (m, 1H, CH).

1-*O*-Carboxycarbonyl *trans*-1,2-cyclohexanediol (4): R_f: 0.20 (TLC eluent; methanol:methylene chloride = 3:7, v/v); IR (KBr, ν_{max}, cm^{-1}): 3400s (O-H), 2920s (C-H), 1770s (C=O); ^1H NMR ($CDCl_3$): δ 1.0-1.8 (m, 8H, CH_2), 3.5-4.0 (m, 1H, OH), 4.6-5.0 (m, 2H, CH).

3-*O*-Carboxycarbonyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (5): R_f : 0.09 (TLC eluent; chloroform:methanol = 8:2, v/v); m.p.: 120-122 °C; IR (KBr, ν_{max}, cm^{-1}): 3400, 1760, 1740; ^1H NMR (Acetone-d_6) : δ 1.35 (d, 12H, CH_3), 2.5-3.0 (m, 2H, OH), 3.5-4.0 (m, 8H, mannitol CH).

***trans*-1,2-Cyclohexanediol 1,2-*bis*-ethyloxalate (6):** R_f: 0.60 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 2:1:3, v/v) ; IR (KBr, ν_{max}, cm^{-1}): 2970s (C-H), 1769s, 1745s (C=O), 1190s (C-O); ^1H NMR ($CDCl_3$) : δ 1.4 (t, 6H, CH_2), 1.4-2.5 (m, 8H, CH_2), 4.25 (q, 4H, OCH_2), 4.8-5.15 (m, 2H, CH).

1,2:5,6-Di-*O*-isopropylidene-D-mannitol 3,4-*bis*-ethyl oxalate (7): R_f: 0.74 (TLC eluent; benzene:acetone = 6:4, v/v); IR (KBr, ν_{max}, cm^{-1}): 2980, 1760, 1740; ^1H NMR ($CDCl_3$) : δ 1.2 (m, 18H, CH_3), 3.8-4.4 (m, 10H, mannitol CH, OCH_2), 5.2-5.5 (dd, 2H, C_3, $_4H$).

1,2-Propanediol 1,2-*bis*-ethyloxalate (8): R_f : 0.51 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 2:1:3, v/v); IR (KBr, ν_{max}, cm^{-1}): 2995s (C-H), 1775s, 1753s (C=O), 1200s (C-O) ; ^1H NMR ($CDCl_3$) : δ 1.4 (dt, 9H, CH_3), 4.35-4.4 (m, 6H, OCH_2), 5.35 (m, 1H, CH).

Methyl-α-D-glucopyranoside 2,3,4,6-tetraethyl oxalate (9): R_f : 0.50 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 2:2:3, v/v) ; IR (KBr, ν_{max}, cm^{-1}): 2935s (C-H), 1775s, 1748s (C=O), 1183s (C-O); ^1H NMR ($CDCl_3$) : δ 1.30 (t, 12H, CH_3), 3.29 (s, 3H, CH_3), 4.23 (m, 11H, OCH_2, C_5H, C_6H) 4.7-5.83 (m, 4H, C_1H, C_2H, C_3H, C_4H).

1-(2'-Deoxy-β-D-ribofuranosyl)-5-methyluracil 3',5'-*bis*-ethyl oxalate (10): R_f : 0.43 (TLC eluent; ethyl acetate: methylene chloride = 5:3, v/v) ; IR (KBr, ν_{max}, cm^{-1}): 3190, 3050, 2993, 1750, 1700, 1190 ; ^1H NMR (Acetone-d_6) : δ 1.33 (t, 6H, CH_3), 1.83 (s, 3H, CH_3), 2.60 (m, 2H, C_2H), 4.1-4.7 (m, 5H, C_3H, C_5H, OCH_2), 5.55 (m, 1H, C_4H), 6.41 (t, 1H, C_1H), 7.67 (s, 1H, C_6H).

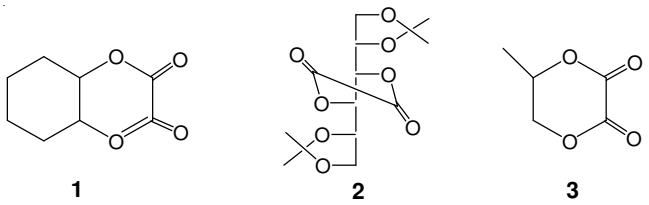
1,2,3-Propanetriol 1,2-*bis*-ethyl oxalate (11): R_f: 0.55 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 4:1:3, v/v); IR (KBr, ν_{max}, cm^{-1}): 3410, 2990, 1760, 1748, 1190; ^1H NMR ($CDCl_3$) : δ 1.4 (t, 6H, CH_3), 4.43 (m, 10H, OCH_2, glycerol CH, OH).

1,2,3-Propanetriol 1,3-diformate (12): R_f: 0.64 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 4:1:3, v/v); IR (KBr, ν_{max}, cm^{-1}): 3420, 2960, 1775, 1175; ^1H NMR ($CDCl_3$) : δ 3.2 (s, 1H, OH), 3.75 (d, 1H, CH), 4.2 (d, 4H, CH_2), 8.1 (s, 2H, CHO).

1,2-Propanetriol 1,3-diformate (13): R_f : 0.46 (TLC eluent; ethyl acetate:chloroform:*n*-hexane = 5:1:2, v/v); IR (KBr, ν_{max}, cm^{-1}): 2985, 1720, 1190; ^1H NMR ($CDCl_3$) : δ 1.25 (dt, 9H, CH_3), 3.5-4.5 (d, 7H, $C_{1,1',1'',2'}H$), 5.3 (m, 2H, $C_{2,2''}H$), 8.1 (s, 2H, CHO).

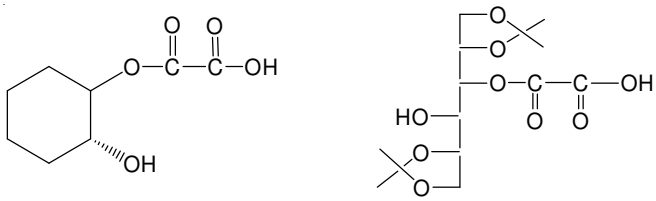
RESULTS AND DISCUSSION

As a new protective group for diols, cyclic oxalates [*trans*-1,2-cyclo-hexane diol 1,2-oxalate (**1**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-oxalate (**2**) and 1,2-propanediol 1,2-oxalate (**3**)] were synthesized by using oxalyl chloride, ethyloxalyl chloride, diethyl oxalate and oxalic acid.



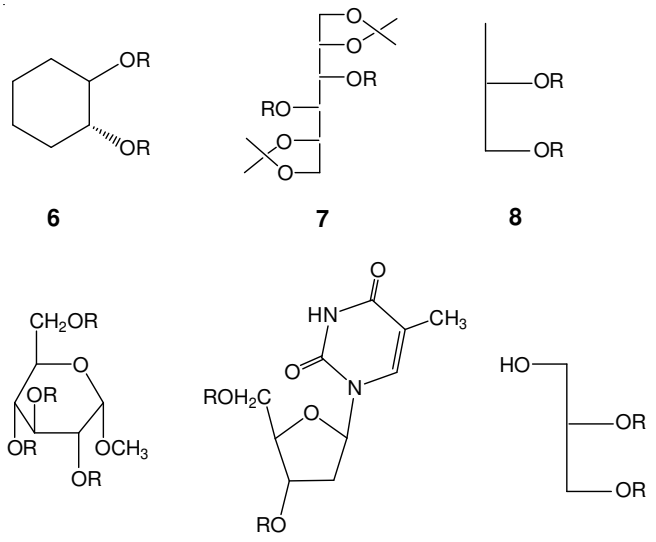
1 **2** **3**

In the reaction of diols with oxalyl chloride, the product was a mixture of the cyclic oxalates *viz.*, *trans*-1,2-cyclohexanediol 1,2-oxalate (**1**) and 1,2:5,6-di-*O*-isopropylidene-D-mannitol and mono oxalates *viz.*, 1-*O*-carboxy-carbonyl *trans*-1,2-cyclohexanediol (**4**) and 3-*O*-carboxycarbonyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**5**) and then the ratio of cyclic oxalate and mono oxalate was 7:3.



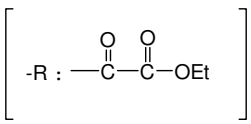
4 **5**

Whereas ethyl oxalyl chloride with triethylamine instead of pyridine, cyclic oxalates [*trans*-1,2-cyclohexanediol 1,2-oxalate (**1**), 1,2:5,6-di-*O*-isopropyl-idene-D-mannitol 3,4-oxalate (**2**) and 1,2-propanediol 1,2-oxalate (**3**)] as well as acyclic oxalates [*trans*-1,2-cyclohexanediol 1,2-*bis*-ethyloxalate (**6**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-*bis*-ethyloxalate (**7**), 1,2-propanediol 1,2-*bis*-ethyloxalate (**8**), methyl-α-D-glucopyranoside 2,3,4,6-tetraethyloxalate (**9**), 1-(2'-deoxy-β-D-ribofuranosyl)-5-methyluracil 3',5'-*bis*-ethyloxalate (**10**) and 1,2,3-propanetriol 1,2-*bis*-ethyl oxalate (**11**)] were obtained.

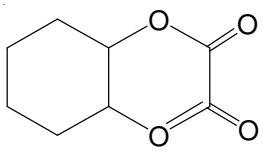


6 **7** **8**

9 **10** **11**



Using diethyl oxalate, the amounts of cyclic oxalates [*trans*-1,2- cyclohexanediol 1,2-oxalate (**1**) and 1,2-propanediol 1,2-oxalate (**3**)] were increased but there were some difficulties in separation of its desired products.



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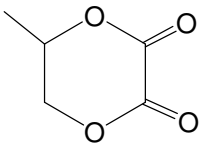

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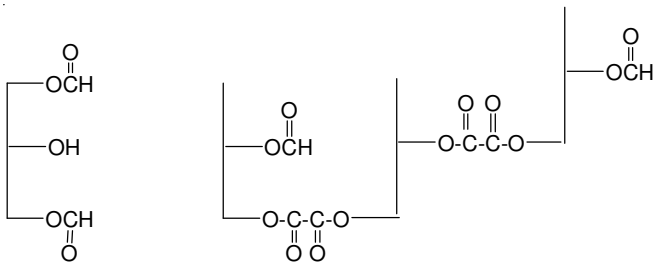
Oxalic acid, however did not afford cyclic oxalates but gave formates which probably were formed by decarboxylation of hydroxyoxalyl group.



12

13

Cyclic oxalates were readily cleaved to the corresponding diols by various bases such as sodium methoxide, potassium carbonate, 1 % sodium hydroxide, triethylamine and lithium aluminium hydride, but were stable in acid.

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