Selective oxidation of secondary over primary hydroxyl group

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Selective oxidation of oligoethylene glycol ether methyl 12(13)-hydroxy-13(12)-[11-hydroxy-3,6,9-trioxa-undecyl-1-oxy]-octadec-9-enoate 3 has been studied using pyridinium chloro chromate (PCC). The reaction has resulted in the formation of methyl 12(13)-oxo-13(12)-[11-hydroxy-3,6,9-trioxa-undecyl-1-oxy]-octadec-9-enoate 5 as an unexpected product wherein only the secondary hydroxyl group has been oxidized while the primary hydroxyl group has remained intact.

**Keywords**: Selective oxidation, pyridinium chloro chromate (PCC), vernolic acid, *Vernonia anthelmintica*

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Despite the availability of many reagents for oxidation of alcohols (primary, secondary, allylic etc.), there still exists a need for new methods, especially for complex or highly sensitive substances where selectivity and effectiveness coupled with mildness of conditions are pre-requisites for success. Pyridinium chloro chromate (PCC), C₅H₅NH⁺CrO₃Cl⁻ is a mild, selective and stable reagent for the oxidation of wide variety of alcohols to corresponding carbonyl compounds with high efficiency¹. It allows the efficient oxidation of a wide variety of alcohols to carbonyl compounds in methylene chloride with only a modest excess of oxidant whereas, aqueous chloro chromate is not a very effective oxidizing species¹. However, the mildly acidic character²,⁵ of PCC precludes its use with acid sensitive substrates or products. Pyridinium chlorochromate oxidizes primary and secondary alcohols in yields equal to or greater than those obtained by Collins oxidation and has advantage that large excess is not necessary. The oxidations are usually conducted in methylene chloride at room temperature (1-2 hr).

Synthetic applications of PCC are well known⁵⁻⁸. Both catalysed and un-catalysed oxidation reaction of alcohols⁸ have been studied in dry chloroform. The chief advantage of the catalysed reaction is that the reaction proceeds smoothly with no side reactions. Also the removal of catalyst from the reaction mixture is easy.

**Results and Discussion**

*V. anthelmintica* seed oil on reaction with diol in the presence of BF₃-etherate as catalyst followed by saponification and esterification yielded the oligoethylene glycol ether 3 and diol 4¹⁰ along with non oxygenated part of oil ([Scheme I](#)). The oligoethyleneglycol ether 3 contains two oxidizable

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\text{Vernonia anthelmintica seed oil} \\
R_1 = \text{CH}_3(\text{CH}_2)_4 \\
R_2 = \text{CH}_2\text{CH} = \text{CH}(\text{CH}_2)_7\text{CO}_2\text{CH}_3 \\
\text{OH} \\
(R_2)R_1\text{-CH-C-R}_2(R_1) \\
\text{OCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH} \quad + \quad \text{OHCH}_2(\text{CH}_2\text{OCH}_2)_n\text{CH}_2\text{OH} \\
\text{(i) BF}_3\text{-etherate} \\
\text{(ii) Alcoholic NaOH} \\
\text{(iii) CH}_3\text{OH} / \text{H}^+ \\
n = 0, 1, 2, 3
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[Scheme I](#)
hydroxyl groups, one primary and one secondary. On oxidation of 3 with pyridinium chlorochromate (PCC), it was expected that the oxidation of both the hydroxyl groups would lead to the formation of an aldehyde and a ketone. But in the IR spectra of product 5, hydroxyl stretching was observed at 3450 and stretchings for the carbonyl groups were observed at 1740 for ester carbonyl and 1720 cm\(^{-1}\) for the keto-carbonyl. This gave an indication that only one hydroxyl group has been oxidized to the corresponding oxo group and one of the hydroxyl group is still intact.

The \(^1\)H NMR spectra of 5 gave a multiplet at \(\delta 5.4\) integrating for 2-olefinic protons. While a broad singlet at 3.6 integrating for 20 protons was assigned to the ethereal protons and the ester-methyl protons. A doublet at \(\delta 3.29 (J = 5.2Hz)\) integrating for 2 protons was assigned to the methylene group sandwiched between the keto carbonyl and the olefin functionality. The other signals for \(\alpha\)-methylene, chain-methylene and the terminal methyl groups were observed at their usual positions.

The aldehyde carbonyl carbon was not observed in \(^1\)C NMR spectra of 5. Similarly, the aldehyde proton was also absent in the \(^1\)H NMR spectra. This indicated that the primary hydroxyl group was not oxidized under present conditions while the secondary hydroxyl group was oxidized to give the respective carbonyl group. This result is supported by a previous report of Kasmai\(^{11}\) where a complex of 18-Crown-6 with pyridinium chlorochromate and \(n\)-butyl ammonium chlorochromate has been shown to act as a selective oxidizing agent. It is reported in the present study that the oxidation of secondary alcohols takes place at a much faster pace giving higher yields as compared to the primary alcohols. It is observed that the presence of polyether linkage in 3 might have resulted in the formation of a crown-ether pyridinium chlorochromate type complex. The complex caused oxidation of the secondary hydroxyl group in preference to the primary hydroxyl group, and resulted in the formation of the unexpected product 5.

The mass spectra of the product (Figure 1) further supported the above results where the parent ion (m/z 502) was absent due to the presence of hydroxyl and labile ether linkages. The largest ion observed in the mass spectrum was at m/z 470, which could be obtained by the loss of a molecule of methanol from the parent ion.

Thus, in the present study, a new molecule has been synthesised by selective oxidation and a new method has been reported for the preferential oxidation of secondary hydroxyl groups over to primary hydroxyl groups.

Materials and Methods
Thin layer chromatography (TLC) was carried out on silica gel G coated (0.25 mm thick) plates with petroleum ether : diethyl ether : acetic acid (80:20:1) or (60:40:1) as the mobile phase. Spots were visualised with iodine. Infrared (IR) spectra were recorded on a Shimadzu Dr-8001 (Kyoto, Japan) FTIR instrument. The \(^1\)H and \(^13\)C nuclear magnetic resonance (NMR) spectra were recorded on a Brucker-AC-200 Fourier transform NMR spectrometer (Switzerland) in CDCl\(_3\) with TMS as an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP 2000A gas chromatograph mass spectrometer. Oligoethylene glycol 3 was synthesised according to the previously reported method\(^{10}\) (Scheme I).

Synthesis of pyridinium chlorochromate. To 184 mL of 6 M HCl (100 g, 1.1 mole) was added CrO\(_3\) (100g, 1 mole) rapidly with stirring. After 5 minutes the homogeneous solution was cooled to 0°C and pyridine (79.1g, 1 mole) was carefully added over 10

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\text{Figure 1 --- Mass spectral fragments (m/z) of product 5; (figures in parenthesis are intensities relative to base peak (m/z=56))}
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min. Re-cooling to 0°C gave a yellow-orange solid which was collected on a sintered glass funnel and dried for 1 hr in vacuo to give pyridinium chlorochromate in 84% yield (180.8 g).  

Experimental procedure. Pyridinium chlorochromate (9.5 g, 4.5 mmoles) was taken in a 250 mL conical flask and dichloromethane (50 mL) was added to it. The above mixture was stirred on a magnetic stirrer for 5-7 minutes to get a more or less homogeneous solution. To this oligoethylene glycol ether 3 (10 g, 2.0 mmoles) dissolved in CH₂Cl₂ (20 mL) was added in about 10 minutes. The mixture was stirred on a magnetic stirrer. The reaction (Scheme II) was monitored by TLC and 2,4-DNP test and was completed in 1.5 hr. The product formed was isolated with the help of column chromatography using silica gel as a stationary phase and eluting the column with petroleum ether, petroleum ether - chloroform, chloroform and chloroform methanol mixture to get oxidised product 5 in quantitative yield.

Methyl 12(13)-oxo-13(12)-[11-hydroxy-3,6,9-trioxa-undecyl-1-oxyl-octadec-9-enoate 5: IR (neat): 3450 (OH –stretching), 1740 (C=O of ester), 1720 cm⁻¹ (C=O of keto); ¹H NMR (CDCl₃): δ 5.4 (m, 2H, CH=CH), 3.6 (br s, 20H, CH-O, 7 × O-CH₂, CH₂-OH and OCH₃), 3.29 (d, J = 5.2, 2H, -CO–CH₂–CH=CH–), 2.0 to 2.4 (m, 6H, CH₂-CO, CH₂-CO₂ and CH₂-CH=CH–), 1.59 (m, 2H, CH₂=CH₂-CO₂), 1.3 (br. s, 16H, CH₂-chain); 0.9 (dt, 3H, CH₃-terminal); ¹³C NMR (CDCl₃): δ 211.3 and 209.8 (C-12/C-13, keto carbonyl), 173.11 (C-1,ester carbonyl), 131 and132 (C-9), 123 and 125.3 (C-10), 37.35(C-11), along with other normal chemical shifts for other carbons. MS (m/z): 502 (M⁺, absent), 470 (M⁺ - CH₃OH, 0.15), 431 (0.0) / 305(0.3), 277 (30.0)/99 (1.5), 225 (0.3) / 403 (25.0), 305 (0.3), 56(base peak).

References