

## Application of redox system based on nitroxides to organic synthesis

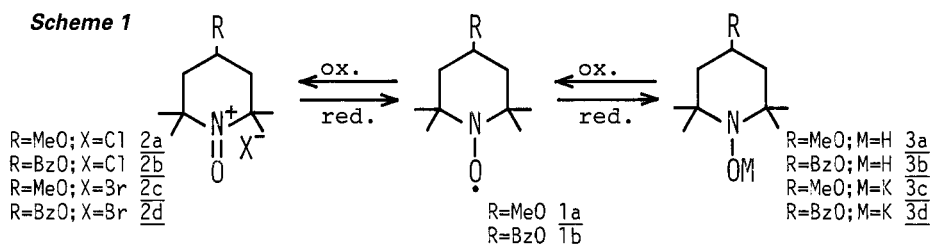
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**Abstract** - 2,2,6,6-Tetramethylpiperidine-1-oxyl known as a stable radical is reduced to the hydroxylamine and is also oxidized to the oxoammonium ion. These redox reactions are chemically reversible. In this review, some applications of nitroxyl radical to organic reactions based on its redox function were described. The hydroxylamine was demonstrated to work as a hydration reagent of nitriles to produce amides. Further, it was found that oxygen is reduced by an anion of hydroxylamine to give superoxide ion. The oxoammonium salt could selectively oxidized hydroxide ion and alcohols to hydrogen peroxide and the corresponding carbonyl compounds, respectively. Furthermore hydroxyl groups of poly(vinyl alcohol)s were partially oxidized to carbonyl groups. The redox systems using oxoammonium salt as a mediator were investigated, and it was found that the polymeric mediator was superior to the corresponding monomeric mediator. A new kind of selectivity was found in the oxidation of ester-containing alcohols. That is, whereas 2a could little or not oxidize 2-benzoyloxyethanol and 3-benzoyloxypropanol, it did 4-benzoyloxybutanol, 5-benzoyloxy-pentanol, and 5-benzoyloxyhexanol to the corresponding benzoyloxyalkanals. The origin of the selectivity might be attributed to the inductive effect of the ester group.

### INTRODUCTION

Since 2,2,6,6-tetramethylpiperidine-1-oxyl and its derivatives were firstly reported as super stable radicals in 1976 (ref.1), many derivatives were prepared and many methods of utilizing the radicals were devised. The progress of the ESR techniques has established the value of these radicals as the spin labeling agent and the radical trapping agent. However, studies on their chemical behavior are less progressed, though it was known that 1 forms reversible redox system as shown in Scheme 1 (ref.2). We have been interested in this reversible redox system from view point of synthetic organic chemistry, and have been applied to various organic reactions.



### Hydration of nitriles (ref. 3)

The preparation of amides from nitriles by use of hydrogen peroxide under basic conditions is well known (ref.4). Furthermore, the mild and selective conversion of nitriles to amides by activation of the cyano group with metal ions has been also reported (ref.5). We have found that nitriles are easily hydrated to amides by compounds 3b which is obtained by reduction of the corresponding stable nitroxyl 1b with ascorbic acid. As shown in Table 1, various nitriles was converted to the corresponding amides. For aromatic amides the yields range from 74 to 100%; from terephthalonitrile the exclusive formation of the monoamide is observed, while aliphatic nitriles seem to be less reactive than aromatic derivatives. In the reaction of acrylonitrile with 3b, acrylamide is formed in 22% yield together with the Michael addition product. In contrast, 2-chloroacrylonitrile affords the corresponding amide in 59% yield. The reaction is completely inhibited by the presence of a radical trapping agent such as 1,1-diphenyl-2-picrylhydrazyl. The following mechanistic rationalization is suggested to account for the formation of amides according to Scheme 2. Initially, the nucleophilic addition of 3b yields the intermediate iminohydroxylamine (4) which, by homolytic cleavage, forms the acylamino radical and the aminyl radical. Both radicals may abstract hydrogen from 3b, thus affording the corresponding amide, the piperidine derivative, and 2 moles of nitroxyl 1b.

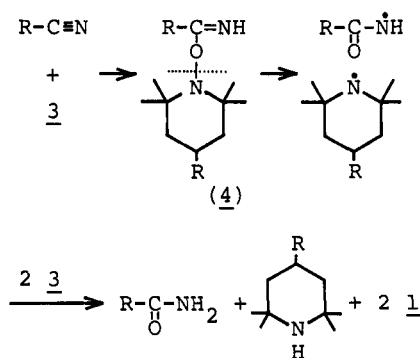
Table 1 Hydration of Nitriles to Amides Using 3

substrate	time(h)	yield(%) <sup>a</sup>
benzointrile	43	99
p-acetylbenzointrile	65	93
p-nitrobenzointrile	2	100
terephthalonitrile	2	93
3-cyanopyridine	65	74
phenylacetointrile	65	33
butyronitrile	65	43
acrylonitrile	65	22 <sup>b</sup>
$\alpha$ -chloroacrylonitrile	1	69

a) Yields after recrystallization.

b) The Michael addition product is formed as a by-product in 19% yield.

Scheme 2



### Reduction of molecular oxygen (ref. 6)

Molecular oxygen is reduced to superoxide ion by the action of hydroxylamine (3b). Using 3d instead of 3b, potassium superoxide was isolated in the purity of 33%. Obtained  $KO_2$  was characterized by ESR spectroscopy (ref.7), the reaction with nitrotetrazolium blue (to give diformazan)(ref.8), and the reaction with methyl octate (to give octanoic acid)(ref.9). These data corresponded completely to those of the authentic  $KO_2$ . These results represent a new method for the preparation of the chemically and biologically important superoxide anion.

### Oxidation of hydroxide ion by 2c (ref. 10)

1-Oxo-2,2,6,6-tetramethylpiperidinium bromide (2c), the oxidized form of 1, could oxidize hydroxide ion to hydrogen peroxide. The amount of the produced hydrogen peroxide was only dependent on the pH and not the buffer composition. Especially in the range of pH 9-11, the yield of hydrogen peroxide was high and 1a was quantitatively recovered. In nonaqueous solvent, solubilized (by benzyltrimethylammonium or by crown-ether) hydroxide ion was oxidized in 31-33%. This method might be important in the chemical field using hydroxyl radical, because this method would contain hydroxyl radical in the reaction course.

### Selective oxidation of alcohols by 2a and 2c (ref. 11)

Various alcohols were converted to the corresponding carbonyl compounds by oxoammonium salt (2a and 2c) as shown in Table 2. In the oxidation of aliphatic alcohols by 2c, prolonged reaction times were required but the oxidation by 2a proceeded smoothly (within 5 min) in quantitative yield. In the oxidation of cinnamyl alcohol with 2c, the brominated alcohols were produced as a main product, while the starting alcohol still remained. When 2a was used instead of 2c, allylic alcohols were oxidized rapidly in quantitative yield to  $\alpha,\beta$ -unsaturated aldehydes. These differences in the reactivity between 2a and 2c may be attributable to the nucleophilicity of the counter anion of this cationic oxidizing agent. The oxidation rates of primary and secondary alcohols with 2c were estimated. The relative rates of oxidation are shown in Table 3. Most primary alcohols are oxidized more rapidly than methanol, while secondary alcohols are oxidized faster than primary alcohols by 2c. On the other hand, oxidations with 2a were too fast to measure the oxidation rate by the usual method. Thus, equimolar hexanol and 3-hexanol were oxidized in one pot by the small amount of 2a. In this case, hexanal was obtained in a 1.7 times excess over 3-hexanone, suggesting that primary alcohols are oxidized faster than secondary alcohols by 2a. When the oxidation was carried out by use of 2c in the similar manner, 3-hexanone was obtained in a 3.6 times

Table 2 Oxidation of Alcohols with 2a

substrate	product	oxidant (equiv)	time	yield <sup>b</sup> (%)
hexanol	hexanal	<u>2c</u> (1)	5h	79
		<u>2a</u> (1)	5min	100
2-hexanol	2-hexanone	<u>2c</u> (1)	1.7h	97
3-hexanol	3-hexanone	<u>2c</u> (1)	1.7h	88
		<u>2a</u> (1)	5min	92
MeCH=CHCH <sub>2</sub> OH	MeCH=CHCHO	<u>2c</u> (1)	1min	9
		<u>2a</u> (1)	1min	92
PhCH=CHCH <sub>2</sub> OH	PhCH=CHCHO	<u>2c</u> (1)	1min	22 <sup>c</sup>
		<u>2a</u> (1)	1min	100
Ph <sub>2</sub> CHOH	Ph <sub>2</sub> C=O	<u>2c</u> (1)	1h	97
benzoin	benzyl	<u>2c</u> (1)	17h	13 <sup>d</sup>
		<u>2a</u> (1)	17h	45 <sup>d</sup>

a) In  $CH_2Cl_2$  at 25°C. b) GLC c) PhCHBrCHBrCH<sub>2</sub>OH was obtained in 39% yield. d) Isolated.

Table 3 Relative Rate of Oxidation<sup>a</sup>

alcohol	rel. rate
methanol	1
ethanol	21
propanol	22
hexanol	32
benzyl alcohol	462
2-propanol	62
3-pentanol	52
3-hexanol	37

a) In  $CH_2Cl_2$  at 30°C. [alcohol]/[2c]=10

excess over hexanal. These results show that the relative rate of the oxidation of primary and secondary alcohols is very dependent on the counter anion of the oxoammonium salt (2).

### Oxidation of diols with 2a (ref. 12)

Some diols were converted by two equivalent of 2a to lactones but not di-aldehydes. The oxidation was successful for 1,4-butanediol and 1,5-pentanediol (to give  $\gamma$ -butyrolactone and  $\delta$ -valerolactone, respectively), while the oxidation of 1,3-propanediol and 1,6-hexanediol to give three and seven membered lactones was unsatisfactory. 1,4-Pentanediol containing primary and secondary hydroxyl groups was oxidized to give  $\gamma$ -valerolactone in 33% yield and no other carbonyl products such as hydroxy ketone or hydroxy aldehyde were detected. This result might support the selective oxidation of primary alcohol by 2a as mentioned above.

### Oxidative cleavage of benzylic ethers (ref. 13)

Benzylic alkyl ethers were oxidatively cleaved by two equivalent of 2a or 2c to benzaldehyde and the corresponding alkyl halides in excellent yield. As shown in Table 4, benzyl methyl ether was oxidized quantitatively to benzaldehyde with two equivalent of 2c at room temperature in dichloromethane. However, the yield of benzaldehyde was low in the case of using 2a, because 2a is less stable than 2c. Dibenzyl ether was also oxidized to benzaldehyde (98%) and benzylbromide (76%). When three equivalent of water was added in the reaction mixture of dibenzyl ether and three equivalent of 2c, the yield of benzaldehyde reached to 200%, suggesting that benzylic cation may form as an intermediate of the reaction. That is, the reaction was initiated by the single electron transfer from ether to 2, followed by deprotonation and second single electron transfer. Resulting oxonium ion was attacked by the counter ion or the water to yield benzaldehyde and benzylic halide or alcohol. In the latter case, generated benzylic alcohol was oxidized by 2 to give another equivalent of benzaldehyde.

Table 4 Oxidative Cleavage of Benzylic Alkyl Ether<sup>a</sup>

substrate	oxidant	water equiv	time (hr)	products PhCHO	Y.(%) RX
CH <sub>3</sub> OCH <sub>2</sub> Ph	<u>2a</u>	0	17	22	-
	<u>2c</u>	0	17	66	-
C <sub>5</sub> H <sub>11</sub> OCH <sub>2</sub> Ph	<u>2c</u>	0	17	60	0
	<u>2c</u>	3	5	100	0
(PhCH <sub>2</sub> ) <sub>2</sub> O	<u>2a</u>	0	17	36	-
	<u>2c</u>	0	3	98	76
	<u>2c</u>	3	6	140	0

a) Two equiv of 2, in dichloromethane at 30°C

### Oxidation of benzyl alcohol by Fe(III) mediated by 1 or polymer-supported 1 (ref. 14, 15)

Since hydroxylamine (3) generated during the oxidation reaction with 2 can be re-oxidized to 2 by several oxidant, it is possible to use 1 as an oxidation catalyst. Some authors utilize 1 as an oxidation catalyst in the oxidation of alcohols (ref.16) and amines (ref.17). We have also been interested in such oxidations using 1 as a catalyst for organic compounds as a means of making good use of inexpensive and readily available oxidizing agents such as potassium ferricyanide, cupric salt, and chlorine. In this section, Fe(III) is chosen as an apparent oxidant, and the other oxidants (Cu(II) and Cl<sub>2</sub>) appear in the subsequent sections. While benzyl alcohol was not oxidized in an alkaline two-phase solution of potassium ferricyanide (1.5eq) in water/acetonitrile (4:3), addition of small amounts of 1a to this solution induced smooth oxidation to give benzaldehyde, as shown in Fig. 1. Using tetrabutylammonium bromide instead of 1a resulted in poor yield of benzaldehyde, suggesting that ferricyanide anion transported into the organic phase does not oxidize benzyl alcohol. Hence, it is reasonable to assume that the oxoammonium salt is acting as an interfacial electron-transfer catalyst.

Such features were available in the polymer-supported nitroxyl radicals. Polymers having nitroxyl radical moieties were prepared in the following manner. At first, 4-(p-vinylbenzyloxy)-2,2,6,6-tetramethylpiperidine 5 as a monomer was prepared from p-chloromethylstyrene and 4-hydroxy-2,2,6,6-tetramethylpiperidine. Then, the monomer was homopolymerized (P1) or copolymerized with several comonomer such as styrene (P2 & P3; 60% & 40% 4 respectively), vinylpyrrolidone (P4; 25% 4), and acrylamide (P5; 25% 4). Resulting polymers were then oxidized with hydrogen peroxide in the presence of sodium tungstate to yield polymer-supported nitroxyl radical. Using these copolymers, the oxidation of benzyl alcohol was carried out under the same conditions (1N KOH aq./acetonitrile =4/3, ferricyanide 1.5 eq., nitroxyl moiety=4 mol%).

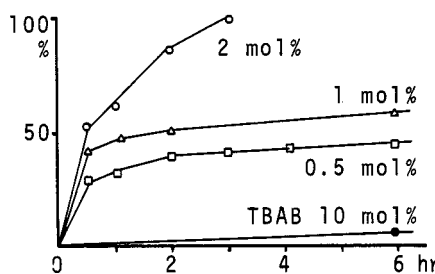


Fig.1 Two-phase Oxidation of Benzyl Alcohol with Fe(III) Mediated by 1a

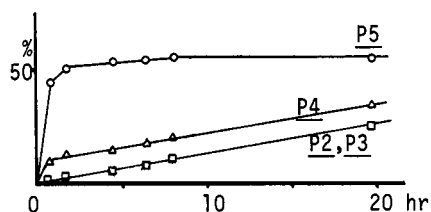


Fig.2 Tri-phase Oxidation of Benzyl Alcohol with Fe(III) Mediated by Polymer-supported Nitroxyl Radical

As shown in Fig. 2, the hydrophilic polymers (P4, P5) were more effective than hydrophobic polymers (P1-P3) in this system, because the oxidant, ferricyanide, was hydrophilic.

### Oxidation of alcohols with Cu(II) mediated by 1 or polymer-supported 1 (ref. 18, 19)

Cupric salts can be used as an apparent oxidant in the oxidation of some alcohols mediated by 1. In this case, the oxidation system was nearly homogenous in acetonitrile, and acid trapping agent was required. As shown in Table 5, benzyl alcohol and hexanol were oxidized by various cupric salts. While cupric bromide and cupric chloride were not so effective for the oxidation and cupric acetate required a long time to complete the oxidation, cupric perchlorate and cupric nitrate were excellent as oxidants. The efficiency of the cupric salt decreases with the increase of the basicity of the counter ion, in the order perchlorate>nitrate>bromide>chloride>acetate, though an explanation for this behavior is not evident at the present time.

Table 5 Oxidation of Alcohols with Cu(II) Mediated by 1b<sup>a</sup>

substrate	oxidant <sup>b</sup> (equiv)	1b (equiv)	time (hr)	yield (%)	turn over (turns)
benzyl alcohol	Cl (4)	0.1	17	100	10
	Br (4)	0.1	2	69	7
	AcO (4)	0.1	40	93	9
	ClO <sub>4</sub> (4)	0.1	2	100	10
	NO <sub>3</sub> (4)	0.1	17	100	10 <sup>c</sup>
hexanol	NO <sub>3</sub> (3)	0.01	8	94	94
	Cl (1.5)	0.1	40	47	5
	ClO <sub>4</sub> (1.5)	0.1	40	94	9
	NO <sub>3</sub> (1.5)	0.1	40	86	9

a) In acetonitrile at 25°C. An equivalent of Cu(OH)<sub>2</sub> was used as an acid trapping agent.

b) Cupric salt.

c) In the absence of Cu(OH)<sub>2</sub>.

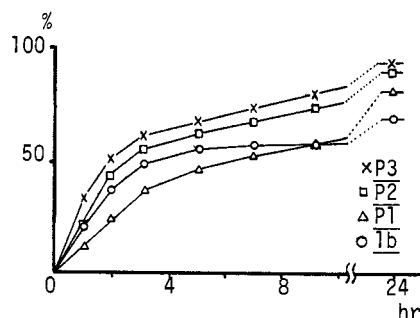


Fig. 3 Oxidation of Benzyl Alcohol by Use of Polymer 1

Of course, polymer-supported nitroxyl radical mentioned in the preceding section can catalyze the oxidation of alcohols with cupric salt. As shown in Fig. 3, the rate of the oxidation using monomeric nitroxyl radical (1b) is initially faster than that using P1. However, the yield of benzaldehyde in the case of P1 went beyond that of 1b after 9 hr, and after 24 hr the yields reached 83% (P1) and 79% (1b). The polymers P2 and P3 are more effective catalysts than monomeric 1b in both the oxidation rates and the yields of benzaldehyde. The observation of the polymer effect may be ascribed to the dispersion of oxoammonium moiety (2b) on the polymer chain. The monomeric 2b might convert to 1b via electron transfer from 3b generated during the oxidation. Therefore, the efficiency of the mediator would decrease due to the decrease in the apparent concentration of 2b. On the other hand, the intramolecular reaction of 2b and 3b moieties in the polymer might be inhibited by the polymer chain.

### Oxidation of cyclic alcohols with chlorine mediated by 1a (ref. 20)

Although chlorine itself oxidizes cyclic alcohols to the corresponding cyclic ketones, addition of a small amount of 1a to the reaction mixture provides these ketones with higher conversion and higher selectivity. As shown in Table 6, in the case using 10 mol% of 1a to the alcohol, the conversion of cyclohexanol reached 76% with an equivalent of chlorine, and with 1.4 equivalent of chlorine the conversion reached 100%. Moreover, the oxidation selectivity was over 80% even at the last stage where the concentration of cyclohexanol became low and that of cyclohexanone high. In contrast, the control experiment without 1a resulted in a low conversion of cyclohexanol and a low selectivity. In the case where using 1 mol% of 1a, both the conversion and the selectivity were unsatisfactory. Probably, the rate of the chlorine introduction may be too fast, since an easy calculation suggests

Table 6 Chlorine oxidation of cyclohexanol mediated by 1a

rate (eq/hr)	chlorine (equiv)	1a (mol%)	conv. <sup>b</sup> (%)	yield <sup>b</sup> (%)	select. <sup>c</sup> (%)
0.35	1.0	10	76	63	83
0.35	1.4	10	100	85	85
0.35	0.8	1	21	14	67
0.035	0.8	0.5	40	28	71
0.35	1.0	0	21	12	56
0.35	1.6	0	30	16	55

a) Oxidation was carried out in the presence of finely ground sodium carbonate as an acid trapping agent in dichloromethane at r.t.

b) Conversion of cyclohexanol and yield of cyclohexanone were determined by GC using an internal standard.

c) selectivity=yield of ketone/conv of alcohol.

that 0.35 eq/hr roughly equals to 2 min/cycle. Actually, slower introduction of chlorine enhanced the selectivity even with 0.5 mol% of 1a. In addition, the other cycloalkanol were oxidized by this system in a high selectivity (over 80 %) under the same conditions.

### Oxidation of poly(vinyl alcohols) with 2a (ref. 21)

Attempts (ref.22) to obtain poly(ketone)s by oxidation of poly(vinyl alcohol)s (PVA) have been made by use of several oxidants such as Oppenauer's oxidant, N-bromosuccinimide, and so on. But the oxidized polymer had very low amount of carbonyl groups on its main chain, and some side reactions caused degradation of the polymer chain. On the other hand, 2a is an excellent and selective oxidant for aliphatic alcohols and is expected to cause no side reactions such as overoxidation or C-C bond scission. From these interests, we have examined the oxidation of PVA with 2a. As shown in Table 7, two PVAs with different degree of polymerization were oxidized by an equivalent of 2a in water and N-methylpyrrolidone (NMP). The content of the ketone group was estimated by means of both NMR and IR. Inspection of data of Table 9 indicates that about 30 % of hydroxyl groups are converted to ketone groups, largely independent of the degree of polymerization of the original PVA and of the solvent.

Table 7 Oxidation of PVA with 2a (1 eq.)

DP of PVA	solvent	Ketone content (%)	
		NMR <sup>a</sup>	IR <sup>b</sup>
25	water	39	29
1650	water	24	36
1650	NMP <sup>c</sup>	30	34

a) Estimated by using the intensity ratio of CHOH vs. the other CH<sub>2</sub> protons.

b) Determined by absorbance ratio of  $\nu(\text{OH})$  vs.  $\nu(\text{C=O})$  using a calibration curve established with 2,4-pentanediol and 2,4-pentanedione.

c) N-methylpyrrolidone.

Table 8 Oxidation of 2,4-Pentanediol with 2a

<u>2a</u> (equiv)	products (%) <sup>b</sup>	
	hydroxyketone	diketone
1.0	23	25
>2	18	29

a) In dichloromethane at room temperature.

b) Determined by GLC using an internal standard.

This value is higher than those reported in previous work. The reason why the hydroxyl group of PVA was not quantitatively oxidized may be attributed to the low activity of the oxidant 2a in water and NMP or to the steric hindrance by the polymer chain. If the above factors were operative, the oxidation of a model compound (2,4-pentanediol) in dichloromethane would occur efficiently to give 2,4-pentanedione in high yield. Results are listed in Table 8. The product was a mixture of 4-hydroxy-2-pentanone and 2,4-pentanedione, although various monofunctional alcohols can be oxidized quantitatively as described above. In addition, the hydroxyl group of partially (25%) saponificated PVA was not oxidized at all even by using ten-fold amount of 2a, whereas its model compound (4-acetoxy-2-pentanol) was partially oxidized. On the other hand, 2-hexanol was quantitatively oxidized to 2-hexanone in the presence of hexyl acetate, suggesting that some intramolecular interaction such as intramolecular hydrogen bonding or the other effect between alcohol and ketone groups prevented the oxidation. The origin of these behavior is extensively investigated and will be described in the succeeding section.

### New selective oxidation of alcohols containing ester group with 2a (ref. 23, 24)

As mentioned above, the alcohols having functional group (ketone, or ester) seemed to have a low reactivity toward 2a. From these results described above, it was suggested that the ester group present in the same molecule does prevent the oxidation intramolecularly. Then, the oxidation of  $\omega$ -benzoyloxyalkanol ( $n=2-6$ ),  $\omega$ -benzoylalkanol ( $n=2$  to 5), and  $\omega$ -phenoxyalkanol ( $n=2$  and 3) by 2a was planned on the basis of the presumption that the change of the functional group and the chain length between hydroxyl and ester groups would vary the strength of the interaction between them. Results are summarized in Table 9. As expected, the oxidation profile depends on both the functional group and the chain length. There must exist some intramolecular interaction between ester and hydroxyl groups which differs in strength with the number of methylene units. Two possible mechanisms which explains the selectivity was speculated. One is the intramolecular hydrogen bonding between carbonyl (ether) and hydroxyl groups and the other is the inductive effect of the functional group (electron withdrawing group EWG).

Firstly we inspected the former possibility by means of IR. It is well known that the wave number of the vibrational absorption of carbonyl group is affected by solvent even if it is nonpolar one. Thus if intramolecular hydrogen bonding is formed and the concentration of the material is sufficiently dilute,  $\nu(\text{C=O})$  of the ester group is expected to be constant. Results listed in Table 9 show no significant deviation about solvent effect between methylene number  $n=2,3$  and the others. Furthermore, when a deuterium exchanged alcohol ( $n=3$ ) was examined,  $\nu(\text{C=O})$  was identical with that of normal alcohol under the same conditions. These data suggest that the intramolecular hydrogen bonding is not formed.

Table 9 Oxidation of Alcohols Having EWG<sup>a</sup>

substrate	yield (%) <sup>b</sup> of CHO	$\delta\text{CH}_2\text{OH}^c$ (ppm)	$\nu(\text{C}=\text{O})$ (cm <sup>-1</sup> ) <sup>d</sup>			
			Et <sub>2</sub> O	CCl <sub>4</sub>	PhH	CH <sub>2</sub> Cl <sub>2</sub>
PhCOO(CH <sub>2</sub> ) <sub>2</sub> OH	0	3.95	1728	1724	1724	1720
PhCOO(CH <sub>2</sub> ) <sub>3</sub> OH	trace	3.68	1724	1724	1720	1716 <sup>e</sup>
PhCOO(CH <sub>2</sub> ) <sub>4</sub> OH	58	3.62	1724	1720	1720	1713
PhCOO(CH <sub>2</sub> ) <sub>5</sub> OH	42	3.52	1724	1720	1720	1713
PhCOO(CH <sub>2</sub> ) <sub>6</sub> OH	58	3.55	1724	1720	1720	1712

substrate	yield (%) <sup>f</sup>	$\delta\text{CH}_2\text{OH}$	substrate	yield (%) <sup>h</sup>	$\delta\text{CH}_2\text{OH}$
PhCO(CH <sub>2</sub> ) <sub>2</sub> OH	0	4.00	PhO(CH <sub>2</sub> ) <sub>2</sub> OH	trace	3.84
PhCO(CH <sub>2</sub> ) <sub>3</sub> OH	0 <sup>g</sup>	3.73	PhO(CH <sub>2</sub> ) <sub>3</sub> OH	47	3.71
PhCO(CH <sub>2</sub> ) <sub>4</sub> OH	trace <sup>g</sup>	3.67			
PhCO(CH <sub>2</sub> ) <sub>5</sub> OH	42	3.50			

a) In dichloromethane at r.t. Using an equivalent of 2a.

b) Estimated by GC using an internal standard.

c) Proton NMR chemical shift in CDCl<sub>3</sub>.

d) 0.1 mol/l solution.

e)  $\nu(\text{C}=\text{O})$  of PhCOO(CH<sub>2</sub>)<sub>3</sub>OD is also 1716 cm<sup>-1</sup>.

f) Estimated by NMR using intensity ratio of CHO vs. Ph.

g) Dehydration reaction proceeded.

h) Isolated yield as the hydrazone of 2,4-dinitrophenylhydrazine.

On the other hand, although it seems too remote for an EWG to affect the field effect on hydroxyl group through methylene chain (since it is known that such effect decreases in strength by a factor of 2.7 by one methylene unit), as shown in Table 9, the chemical shift of the methylene protons adjacent to hydroxyl group ( $\delta\text{CH}_2\text{OH}$ ) of various alcohols shifted to upper field with an increase in number of the methylene groups between hydroxyl group and EWG, suggesting that the polar effect of the EWG exerts to the remote hydroxyl group to some extent. Noteworthy are the chemical shifts of methylene protons adjacent to the inactive alcohol which appear at a lower field than about 3.7 ppm independent on the nature of EWG. All things considered, it seems to be rational to attribute the selectivity to the polar effect of the substituent.

On the basis of this concept, for example, it is expected that the oxidation of 2-hydroxyethyl 4-hydroxybutyl phthalate (6) by 2a will selectively give 2-hydroxyethyl 4-oxobutyl phthalate (7). Actually, the oxidation of 6 with two equivalent of 2a in dichloromethane at 0°C in the presence of sodium carbonate as an acid scavenger yielded only 7 in high yield (81% in GLC, 46% isolated yield by column chromatography). As expected, no other products such as 2-oxoethyl 4-oxobutyl phthalate or 2-oxoethyl 4-hydroxybutyl phthalate were detected even with the use of excess 2a (ref.23).

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