Oxidation of ω-(Benzoyloxy)alkanols with an Oxoaminium Salt

Masao Yamaguchi, Toshikazu Takata, and Takeshi Endo*

Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan

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Oxoaminium chloride (**2**), the oxidized derivative of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, **1**), was found to display a novel selectivity in the oxidation of ester group containing alcohols. The oxidations of (2 to 6)-(benzoyloxy)alkanols and related alcohols were carried out at room temperature with 1.0 equiv of the oxoaminium chloride in dichloromethane (method A) or with 0.1 equiv of TEMPO, 1.5 equiv of cupric chloride, and 1.5 equiv of cupric hydroxide (method B). Whereas the oxoaminium chloride did not significantly oxidize 2-(benzoyloxy)ethanol and 3-(benzoyloxy)propanol, it did oxidize 4-(benzoyloxy)butanol, 5-(benzoyloxy)pentanol, and 6-(benzoyloxy)hexanol to the corresponding (benzoyloxy)alkanals. The origin of this selectivity was investigated, and NMR and other studies suggest that the selectivity might be attributed to the inductive effect of the ester group.

Introduction

Since 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, **1**) derivatives were synthesized in 1962 as super stable radical species,[1] various nitroxyl radicals have been prepared and utilized mainly for ESR study.[2] Only recently have the chemical behaviors of these compounds, especially redox reactions, attracted the attention of many chemists, and their interesting features have been gradually clarified by several papers.[3] We have reported that the TEMPO (**1**) constructs the reversible redox system as shown in Scheme I and have shown a variety of reactions utilizing this system as well as these compounds **1–3**.[4] In these studies, oxoaminium salt **2**, which can be obtained by one-electron oxidation of **1**, serves as a selective oxidant for the conversion of aliphatic alcohols to the corresponding aldehydes and ketones.[5] More recently some authors including us have reported the ability of nitroxyl radicals as the catalyst in some alcohol oxidations.[6] Although both oxidants and oxidation systems containing oxoaminium salts have been extensively studied so far, there are few papers concerning the effect of the structure of substrate alcohols on the selectivity of the oxidation. In this paper we describe a new and useful aspect of the oxoaminium salt **2** as a selective (the other selectivity than ones described in literatures[5]) oxidant for alcohols containing an ester group.

Results and Discussion

The oxidations of both 2-cyanoethanol and 2,2,2-trichloroethanol with **2** were carried out under various conditions but failed to give any of the desired aldehyde. We have already reported that the oxidation of poly(vinyl alcohol), as well as its model compound 2,4-pentanediol, occurs partially but not completely.[7] Semmelhack et al.[6b] and Montanari et al.[6e] have reported, however, that various alcohols including nitro- and methoxybenzyl alcohols were oxidized with high efficiency. We, therefore, decided to study various aspects of the oxidation of polar group substituted alcohols such as ω-(benzoyloxy)alkanols.

Scheme I

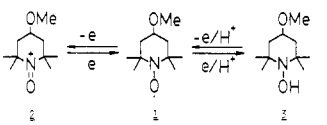

Table I. Oxidation of Alcohols Having an Ester Group[a]

	method A[b]		method B[c]	
	yield of CHO, %	recovery, %	yield of CHO, %	recovery, %
$PhCOO(CH_2)_2OH$	0	78	0	93
$PhCOO(CH_2)_3OH$	trace	37	trace	69
$PhCOO(CH_2)_4OH$	58	0	55	45
$PhCOO(CH_2)_5OH$	42	0	84	20
$PhCOO(CH_2)_6OH$	58	0	35	67

[a] The yield of aldehyde is not optimized. Yield of aldehyde and recovery of starting alcohol were estimated by GC using an internal standard. [b] Oxidation was carried out by use of 1.0 equiv of **2** in dichloromethane at room temperature for 1 h. [c] Oxidation was carried out using **1** as a mediator (0.1 equiv), cupric chloride as an oxidant (1.5 equiv), and cupric hydroxide (1.5 equiv) as an acid scavenger in acetonitrile at room temperature for 20 h.

ω-(Benzoyloxy)alkanols were prepared by the reaction of corresponding diols with benzoyl chloride. Oxidation of them with **2** was examined, and the results are summarized in Table I. 2-(Benzoyloxy)ethanol and 3-(benzoyloxy)propanol gave little or no oxidation with **2** using method A (using 1 equiv of **2** at room temperature for 1 h) or method B (using 1.5 equiv of cupric chloride as an oxidant and 0.1 equiv of **1** as a catalyst in acetonitrile for 20 h[6d]), whereas 4-(benzoyloxy)butanol, 5-(benzoyloxy)-pentanol, and 6-(benzoyloxy)hexanol were oxidized to yield the corresponding aldehydes in moderate yields under the same conditions. In the case of method A, a good material balance would be maintained when the amount of benzoic acid formed presumably by the hydrolysis of the esters is taken into account. Hydrochloric acid generated during the oxidation may catalyze the hydrolysis of the ester. Since such hydrolysis was avoided by the action of the acid-trapping agent, cupric hydroxide, the product by the method B was only the corresponding aldehyde.

The oxidation of 2-hexanol in the presence of hexyl acetate with **2** was conducted as the control experiment and gave 2-hexanone quantitatively. This fact might suggest that intermolecular interaction between alcohol

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Table II. $\nu_{C=O}$ (cm^{-1}) in Various Solvents[a]

	Et_2O	CCl_4	PhH	CH_2Cl_2
$PhCOOCH_3$	1731	1728	1724	1720
$PhCOO(CH_2)_2OH$	1728	1724	1724	1720
$PhCOO(CH_2)_3OH$	1724	1724	1720	1716[b]
$PhCOO(CH_2)_4OH$	1724	1720	1720	1713
$PhCOO(CH_2)_5OH$	1724	1720	1720	1713
$PhCOO(CH_2)_6OH$	1724	1720	1720	1712

[a] 0.1 mol/L solution. [b] $\nu_{C=O}$ of $PhCOO(CH_2)_3OD$ is 1716 cm^{-1}.

Table III. Oxidation of Alcohols Having an EWG[a]

	yield of CHO, %, n =				
	2	3	4	5	6
$PhCO(CH_2)_nOH$	0[b]	0[b,d]	trace[b,d]	42[b]	–
$PhCOO(CH_2)_nOH$	0[c]	trace[c]	58[c]	42[c]	58[c]
$PhO(CH_2)_nOH$	trace[e]	47[e]	–	–	–

[a] Oxidation was carried out by method A. [b] Estimated by NMR using intensity ratio of CHO vs Ph. [c] Estimated by GC using internal standard. [d] Dehydration reaction proceeded. [e] Isolated as the hydrazone of 2,4-dinitrophenylhydrazine.

and ester groups can be ruled out as an explanation for why 2-(benzoyloxy)ethanol and 3-(benzoyloxy)propanol failed to give the desired aldehyde. Considering this result and the fact that most primary and (more hindered) secondary alcohols were oxidized quantitatively under the same conditions, there must exist some intramolecular interaction between the ester and hydroxyl groups which differs in strength with the number of methylene units.

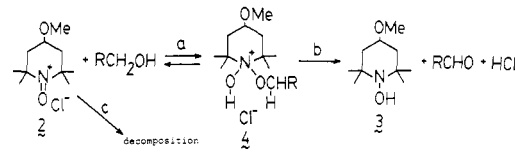
Two possible mechanisms which might explain the selectivity could be speculated. One is the intramolecular hydrogen bonding between carbonyl and hydroxyl groups and the other is the inductive effect of the benzoyloxy group. The former was conceivable from the fact that poly(vinyl alcohol) was not completely oxidized with **2**,[7] though a less nucleophilic benzyl alcohol having an electron-withdrawing group (EWG) was known to be oxidized more slowly in the Swern oxidation condition.[8]

First, we inspected the former possibility by means of IR spectroscopy. It is well known that the wavenumber of the vibrational absorption of carbonyl group is affected by solvent even if it is nonpolar one.[9] Thus if hydrogen bonding is formed intramolecularly and the concentration of the material is sufficiently dilute, $\nu_{C=O}$ of the ester group is expected to be constant. Results of $\nu_{C=O}$ data listed in Table II show no significant deviation with solvent between the alcohols containing two and three methylene units and the others. Furthermore, when a deuterium exchanged alcohol (n = 3) was examined, $\nu_{C=O}$ was identical (1716 cm^{-1}) with that of normal alcohol under the same conditions. These data suggest that intramolecular hydrogen bonding does not occur.

On the other hand, the benzoyloxy group seems too remote to exert a field effect on the hydroxyl group through the methylene units, since it is known that such an effect decreases in strength by a factor of 2.7 for each methylene unit.[10] However, it is worth examining whether this rather small effect is operative or not. We conveniently examined the oxidation of some alcohols having EWGs which differ in inductive effect from the benzoyloxy group, i.e., the ketone and the ether group.

Table III summarizes the results of the oxidation of ω-benzoylalkanols (n = 2–5) and ω-phenoxyalkanols (n = 2 and 3) along with those of the benzoyloxy derivatives. The polar effect seems to be operative even if it might be a rather small one. In the cases of alcohols with benzoyl groups, the polar effect of the benzoyl group influenced the hydroxyl group through four methylene units, though the oxidation of 4-oxo-4-phenylbutanol and 5-oxo-5-phenylpentanol was contaminated by a side reaction (dehydration to give dihydrofuran and dihydropyran derivatives, respectively). On the other hand, in the cases of the alcohols with phenoxy groups, the polar effect appears to have an influence through two methylene units under the same conditions. These results suggest that this selectivity is depended on both the electron-withdrawing power of the EWG and the number of methylene units between EWG and hydroxyl group.

Scheme II



Furthermore, as shown in Table IV, the chemical shift of the methylene protons adjacent to the hydroxyl group (δ_{CH_2OH}) 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 extends 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. This is independent of the nature of the EWG. Therefore, it is not surprising that 2,2,2-trichloroethanol (δ_{CH_2OH} = 4.18) and 2-cyanoethanol (δ_{CH_2OH} = 3.88) did not react with **2** at all as noted above. All things considered, it seems to be rational to attribute the selectivity to the polar effect of the substituent.

Then, this conclusion might give rise to one question why nitrobenzyl alcohol, which has a strong EWG, can be oxidized by **2**.[6] The postulated mechanism as shown in Scheme II[6] can answer this question as well as the origin of the selectivity. In Scheme II, path a (addition to N=O double bond) is regarded as an equilibrium and path b (proton abstraction) as the rate-determining step. In the case of most (nucleophilic) alcohols, the equilibrium a lies to the right, and then the rate of path b is fast enough to give the aldehydes. On the other hand, in the case of less nucleophilic alcohols (having EWG), the equilibrium a should move to the left, and therefore the rate of path b (k_b[4]) cannot predominate over the decomposition rate of **2** (path c, k_c[2]) which is competitive with the oxidation. As the result, such alcohols cannot be oxidized. In the case of nitrobenzyl alcohol, of course, the equilibrium a inclines to the left, but the protons of benzyl position are considerably more acidic than those of aliphatic carbons, which should enhance the rate of path b (or enhances k_b of the total rate k_b[4]). Thus, the enhanced rate of path b is greater than that of path c, resulting in the progression of the oxidation of nitrobenzyl alcohol to nitrobenzaldehyde.

In conclusion, we have established an example of new selective (i.e., only certain alcohols having an EWG are oxidized by **2**) oxidation of alcohols. It is based on neither the steric hindrance nor the difference of reactivity between primary and secondary alcohols but on the relatively small difference between the polar effect of a remote substituent. Whether a specific alcohol reacts with **2** can be predicted by means of ^1H NMR chemical shift of the CH_2OH group. On the basis of this concept, for example, 2-(hydroxyethyl)-4-(hydroxybutyl)phthalate can be selectively converted to 2-(hydroxyethyl)-4-(oxobutyl)phthalate

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Table IV. ^{1}H NMR Spectral Data of the Starting Alcohols

	Ph, ppm	$COOCH_2$, ppm	J, Hz	$(CH_2)_n$, ppm	J, Hz	CH_2OH, ppm	OH, ppm	oxidn[a]
$PhCOO(CH_2)_2OH$	8.1–7.0 (m)	4.27 (m)	–	–	–	3.85[b] (m)	b	–
$PhCOO(CH_2)_3OH$	8.2–7.0 (m)	4.35 (t)	6.2	2.92 (tt)	6.2	3.68 (t)	4.35 (s)	+–
$PhCOO(CH_2)_4OH$	8.1–7.1 (m)	4.27 (t)	6.0	1.76 (m)	5.8	3.62 (t)	3.93 (s)	+
$PhCOO(CH_2)_5OH$	8.1–7.0 (m)	4.18 (t)	5.9	1.47 (m)	5.5	3.52 (t)	3.97 (s)	+
$PhCOO(CH_2)_6OH$	8.1–7.2 (m)	4.17 (t)	6.0	1.47 (m)	–	3.55[b] (m)	b	+
	Ph	$COCH_2$	J	$(CH_2)_n$	J	CH_2OH	OH	oxidn[a]
$PhCO(CH_2)_2OH$	8.1–7.2 (m)	3.18[b] (t)	5.5	–	5.5	4.00 (t)	b	–
$PhCO(CH_2)_3OH$	8.1–7.1 (m)	3.12 (t)	7.0	2.00 (tt)	7.0	3.73 (t)	2.43 (s)	–
$PhCO(CH_2)_4OH$	8.1–7.1 (m)	2.95[b] (m)	–	1.70 (m)	6 0	3.67 (t)	b	+–
$PhCO(CH_2)_5OH$	8.2–6.8 (m)	2.86 (t)	5.8	1.45 (m)	–	3.50[b] (m)	b	+
	Ph	$PhOCH_2$	J	(CH_2)	J	CH_2OH	OH	oxidn[a]
$PhO(CH_2)_2OH$	7.3–6.6 (m)	3.89 (m)	–	–	–	3.89 (m)	3.25 (m)	–
$PhO(CH_2)_3OH$	7.4–6.6 (m)	3.99 (t)	6.0	1.93 (tt)	6.0	3.71 (t)	2.41 (s)	+

[a] +, active; –, inactive to the oxidation with **2**. [b] Signals overwrapped each other.

Table V. ^{1}H NMR Spectral Data of Obtained Aldehydes

	Ph, ppm	$COOCH_2$, ppm	J, Hz	$(CH_2)_n$, ppm	J, Hz	CH_2CHO, ppm	J, Hz	CHO, ppm
$PhCOO(CH_2)_3CHO$	8.2–7.1 (m)	4.28 (t)	7.5	2.03 (m)	8.0	2.55 (dt)	2.0	9.74 (t)
$PhCOO(CH_2)_4CHO$	8.2–7.2 (m)	4.28 (m)[a]	–	1.77 (m)	5.5	2.48 (t)[a]	–	9.76 (s)[a]
$PhCOO(CH_2)_5CHO$	8.2–7.1 (m)	4.23 (t)	6.2	1.56 (m)	6.4	2.40 (t)[a]	2.8	9.63 (t)
	Ph	$COCH_2$	J	$(CH_2)_4$	J	CH_2CHO	J	CHO
$PhCO(CH_2)_4CHO$	8.1–7.0 (m)	2.91 (t)	6.5	1.69 (m)	6.0	2.43 (dt)	1.8	9.66 (t)
	Ph	$PhOCH_2$	J		J	CH_2CHO	J	CHO
$PhO(CH_2)_2CHO$	7.4–6.6 (m)	4.16 (t)	6.0	–	6.0	2.71 (dt)	1.5	9.67 (t)

[a] Signal was somewhat broad and microstructure was lost.

in high yield, as shown previously.[11] And, moreover, this selectivity may be widely applicable to the series of aliphatic alcohols having an EWG such as a ω-cyano or a ω-nitro group, and to monoprotected triols such as 2-(benzoyloxy)-1,5-pentanediol.

Experimental Section

General. IR spectra were recorded on a JASCO FT/IR-3 fourier transform infrared spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX60 NMR spectrometer. Gas chromatograms were recorded on a Shimadzu GC-4C (SE-30 3 m or PEG-20M 3 m columns, FID detector) with a Shimadzu CR-1A integrator and a Shimadzu GC-8A (SE-30 1 m column, FID detector) with a Shimadzu CR-4A integrator.

Materials. 4-Methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**1**) was prepared by the previously reported method.[5] 1-Oxo-4-methoxy-2,2,6,6-tetramethylpiperidinium chloride (**2**) was prepared by chlorine oxidation of **1** in carbon tetrachloride.[5] Solvents were purified by distillation in the presence of common drying agents. Benzoyl chloride, triethylamine, ethylene glycol, and tetramethylene glycol for substrate synthesis were purified by distillation. Other commercially available reagents were used without further purification. All ω-(benzoyloxy)alkanols were prepared by the reaction of benzoyl chloride and the corresponding diol in the presence of triethylamine in tetrahydrofuran and were purified by distillation or column chromatography.[12] All keto alcohols were prepared by the reduction of corresponding keto-acid according to the literature.[13] Phenoxyethanol is commercially available. Phenoxypropanol was prepared by the reaction of aqueous sodium phenoxide with 3-bromopropanol in dichloromethane in the presence of triethylbenzylammonium chloride as a phase-transfer catalyst. All the substrates were purified by distillation or by column chromatography. The structure of the substrates was confirmed by ^{1}H NMR (Table IV) and IR spectroscopy.

Method A: Typical Procedure. To a solution of 6-(benzoyloxy)hexanol (216 mg, 0.97 mmol) and an internal standard (1,2,4,5-tetrachlorobenzene) in dichloromethane (10 mL) was added freshly prepared **2** (225 mg, 1.0 mmol) at room temperature. Reaction progress was monitored by GC, and the yield of the ester–aldehyde was estimated by GC using the internal standard. After completion of reaction (60 min), dichloromethane was removed by evaporation, and the residue was column chromatographed. The product, 6-(benzoyloxy)hexanal, was isolated in 47% yield. The structure of the product was confirmed by ^{1}H NMR (Table V) and IR spectroscopy.

Method B: Typical Procedure. A solution of 6-(benzoyloxy)hexanol (225 mg, 1.0 mmol), cupric chloride (406 mg, 3.0 mmol), cupric hydroxide (194 mg, 2.0 mmol), and **1** (19.2 mg, 0.10 mmol) in acetonitrile (10 mL) was stirred at room temperature. The reaction progress was monitored by the following procedure. A small amount of the reaction mixture (0.10 mL) was withdrawn and was added to 1.0 mL of chloroform containing the internal standard (0.0115 mol/L) as above. The mixture was washed with 1.0 mL of aqueous potassium carbonate and was analyzed by GC.

Registry No. **1**, 95407-69-5; **2**, 95407-70-8; $PhCOO(CH_2)_2OH$, 94-33-7; $PhCOO(CH_2)_3OH$, 6946-99-2; $PhCOO(CH_2)_4OH$, 32651-37-9; $PhCOO(CH_2)_5OH$, 55162-82-8; $PhCOO(CH_2)_6OH$, 60405-63-2; $PhCO(CH_2)_2OH$, 5650-41-9; $PhCO(CH_2)_3OH$, 39755-03-8; $PhCO(CH_2)_4OH$, 1011-62-7; $PhCO(CH_2)_5OH$, 17851-49-9; $PhO(CH_2)_2OH$, 93-56-1; $PhO(CH_2)_3OH$, 4850-49-1; $PhCOO(CH_2)_3CHO$, 22927-31-7; $PhCOO(CH_2)_4CHO$, 55162-83-9; $PhCOO(CH_2)_5CHO$, 122934-55-8; $PhCO(CH_2)_4CHO$, 87258-30-8; $PhO(CH_2)_2CHO$, 22409-86-5.

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