TEMPO-Mediated Environmentally Benign Oxidation of Primary Alcohols to Carboxylic Acids with Poly[4-(diacetoxyiodo)styrene]

Yousuke Tashino,[a] Hideo Togo*[a,b]

[a] Graduate School of Science and Technology, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522 Japan

[b] Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522 Japan
E-mail: togo@faculty.chiba-u.jp

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Abstract: An operationally simple and environmentally benign oxidation of primary alcohols to the corresponding carboxylic acids with a TEMPO-mediated poly[4-(diacetoxyiodo)styrene] system in acetone and water was carried out.

Key words: oxidation, alcohol, carboxylic acid, aldehyde, TEMPO, poly[4-(diacetoxyiodo)styrene], environmentally benign

Oxidation of hydroxyl groups to carbonyl groups are fundamental and important for functional group transformation in organic synthesis.[1] One most useful approach is the chemoselective oxidation of alcohols with *N*-oxoammonium salts. Especially, oxidation of alcohols to ketones, aldehydes, and carboxylic acids using a catalytic amount of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) and a stoichiometric amount of an oxidant is very attractive, because the reactions can be carried out under mild and neutral reaction conditions, giving high yield of products with high chemoselectivity. Therefore, TEMPO-mediated oxidation of alcohols to aldehydes and ketones together with a stoichiometric amount of a metal-free oxidant has been extensively studied.[2] Here, generally reactive *N*-oxoammonium salt is generated in situ by the oxidation of TEMPO with an oxidant. Hypervalent iodines also work as an oxidant for TEMPO-mediated oxidation of alcohols to aldehydes or ketones. This system is useful since hypervalent iodines are non-metallic, less toxic, and easily handled oxidants. Recently, TEMPO-mediated $PhI(OAc)_2$ oxidation of alcohols to aldehydes and ketones in high yields with high chemoselectivity under mild reaction conditions was reported,[3] especially by Piancatelli,[3a] and 1,5-diols gave the corresponding γ-lactones under the same conditions.[3c] As a part of our study on polymer-supported hypervalent iodines,[4] we have recently reported the TEMPO-mediated oxidation of alcohols to the corresponding aldehydes and ketones with poly[4-(diacetoxyiodo)]styrene (PSDIB).[5] Primary and secondary alcohols were successfully oxidized to the corresponding aldehydes and ketones in good yields in a small amount of an acetone solvent, and the products were obtained by simple filtration of the reaction mixture, and, moreover, the recovered poly(4-iodostyrene) could be regenerated to PSDIB and reused for the same oxidation. On the other hand, oxidation of primary alcohols to carboxylic acids with metal-free, less toxic reagents, instead of Jones oxidation,[6] is also important, therefore, the study of TEMPO-mediated direct oxidation of primary alcohols to the carboxylic acids with metal-free less toxic reagent has been studied.[2c,d,j] However, study on a polymer-supported reagent system for the oxidation of alcohols is rather limited.[2l–q] TEMPO-mediated oxidation of alcohols to the corresponding carboxylic acids with NaOCl or $NaClO_2$ is rather complicated in experimental operation, i.e., such as preparation of aqueous basic phosphate buffer solution, etc.[7] Recently, Widlanski reported the TEMPO-mediated oxidation of 5′-hydroxymethyl groups in 2′,3′-isopropylidene protected purine- and pyrimidine-containing nucleosides to the corresponding nucleoside-5′-carboxylic acids in good yields, with $PhI(OAc)_2$ in a mixture of acetonitrile and water.[8] Kita et al. reported the oxidation of primary alcohols to the corresponding carboxylic acids and esters with PhIO–KBr, PSDIB–KBr in water[9a] and methanol[9b], respectively. As a part of our study on environmentally friendly organic synthesis with polymer-supported hypervalent iodines, we would like to report an operationally simple and environmentally benign oxidation of primary alcohols to the corresponding carboxylic acids, using a TEMPO-mediated PSDIB system at room temperature. Here, the reactive species, *N*-oxoammonium salt, is formed in situ by the oxidation of TEMPO with PSDIB.

As shown in Table 1, TEMPO-mediated oxidative conversion of primary alcohols with PSDIB proceeds smoothly at room temperature, to provide the corresponding carboxylic acids in high yields. The oxidative conversion did not proceed at all without TEMPO (entry 1). The reaction with 0.1 equiv of TEMPO was rather slow (entry 2), and the reaction with 0.5 equiv of TEMPO was the most effective (entry 3). When the present TEMPO-mediated oxidation was carried out in a mixture of acetone and water, or a mixture of acetonitrile and water, the yield of carboxylic acid was decreased. This reason may come from that the granular PSDIB becomes the paste by the addition of water. Therefore, it is important that a small amount of acetone (1 mL) alone is used in the initial oxidation of alcohols to the aldehydes, and then, a small amount of water (1–3 mL) is added to the reaction mixture for the formation of the corresponding carboxylic acids effectively. Here, only a small amount of acetone and subsequent water is required as a solvent, and carboxylic

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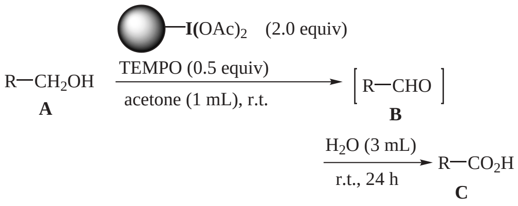
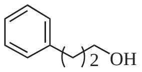
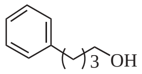
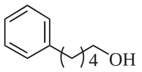
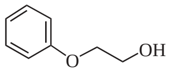
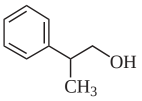
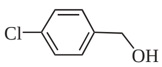
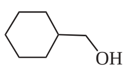
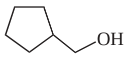
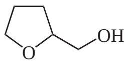
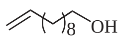
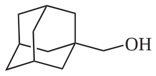
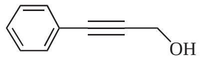
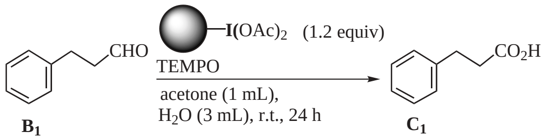
Table 1 Oxidation of Alcohols to Carboxylic Acids with TEMPO-Mediated PSDIB System



Entry	Substrate	Time (**A** to **B**, h)	Yield of **C** (%)
1		4[a]	0[c,d]
2		4[b]	54[c,e]
3		4	95[c]
4		3	92
5		3	83
6		3	82
7		3	77
8		2	74
9		9	78
10		5	73
11	$CH_3(CH_2)_7OH$	5	81
12	$CH_3(CH_2)_{12}OH$	6	82
13		4	85
14		4	84
15		6	58[f]
16		4	71

[a] Without TEMPO.
[b] TEMPO (0.1 equiv).
[c] 1 mL of H_2O was used.
[d] Alcohol was recovered in 88% yield.
[e] Aldehyde was obtained in 31% yield.
[f] Reaction time (**B** to **C**) was 72 h, and 3.0 equiv of PSDIB were used, and aldehyde was obtained in 27% yield.

Table 2 Oxidation of Aldhehyde to Carboxylic Acid with PSDIB



TEMPO	Yields	
	B$_1$	**C**$_1$
–	51	29
0.2 Equiv	5	82
0.5 Equiv	Trace	91

acids can be obtained by filtration of the reaction mixture, followed by extraction from the filtrate with diethyl ether. The used PSDIB is recovered quantitatively as poly(4-iodostyrene) by simple filtration, and PSDIB can be regenerated by the oxidation with peracetic acid, prepared from the reaction of hydrogen peroxide and acetic anhydride, and the regenerated PSDIB can be reused without any loss of activity for the same oxidation of alcohols to carboxylic acids. Aldehydes can be also oxidized to the corresponding carboxylic acids smoothly by the same treatment with TEMPO and PSDIB, and a typical example is shown in Table 2. Here again, addition of TEMPO promotes the oxidation of aldehydes to the corresponding carboxylic acids. Thus, the present method is an operationally simple and environmentally benign oxidation of the primary alcohols to the corresponding carboxylic acids. Further elaboration of the TEMPO-mediated PSDIB oxidation of alcohols is now under way in this laboratory.

Typical Procedures are as follows.

Oxidation of Alcohols to Carboxylic Acids:[10] TEMPO (0.5 mmol) was added to a stirred mixture of 3-phenyl-1-propanol (1 mmol) and PSDIB (2.0 mmol, loading rate ca. 1.7 mmol/g) in acetone (1 mL), and the mixture was stirred for 4 h at r.t. Water (1 mL) was added to the mixture which solution was then stirred for 24 h. After the reaction, the mixture was diluted with Et_2O (5 mL), HCl (1 N, 3 mL) was added, and then the obtained mixture was stirred for 10 min. The mixture was filtered to remove the polymer species and was washed with Et_2O. The filtrate was extracted with Et_2O three times. The combined organic layer was dried over Na_2SO_4 and filtered, and then the solvent was removed to give 3-phenylpropionic acid as a crude state. Pure 3-phenylpropionic acid was obtained by short column chromatography on silica gel (142 mg, 95%, mp 48 °C).

Oxidation of Aldehydes to Carboxylic Acids:[10] Water (3 mL) was added to a stirred mixture of 3-phenylpropionaldehyde (1 mmol), PSDIB (1.2 mmol), and TEMPO (0.5 mmol) in acetone (1 mL), and the mixture was stirred for 24 h at r.t. After the reaction, the mixture was diluted with Et_2O (5 mL), HCl (1 N, 3 mL) was added, and then the obtained mixture was stirred for 10 min. The mixture was filtered to remove the polymer species and was washed with Et_2O. The filtrate was extracted with Et_2O three times. The combined organic layer was dried over Na_2SO_4 and filtered, and then the solvent was removed to give 3-phenylpropionic acid as a crude state. Pure 3-phenylpropionic acid was obtained by short column chromatography on silica gel (136 mg, 91%, mp 48 °C).

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