Chem. Pharm. Bull. 51(7) 888—889 (2003) Vol. 51, No. 7

A Simple and Highly Practical Oxidation of Primary Alcohols to Acids Mediated by 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO)

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Received March 3, 2003; accepted April 24, 2003

Primary alcohols were quantitatively oxidized in one-pot to acids *via* 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) mediated oxidation. The reported method is simple and suitable for large scale synthesis.

Key words 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO); oxidation; alcohol; acid; one-pot

Conversion of alcohols to the corresponding acids is an important transformation in organic and pharmaceutical synthesis and a number of methods have been developed to date. These include the classical and most well known methods using chromium(VI) oxides, represented by Jones reagent,[1,2] Collins reagent,[3,4] and pyridinium chlorochromate (PCC).[5,6] Although these methods are commonly applied on a laboratory scale, and are efficient enough to give materials in gram quantities, the highly toxic chromium salts produced in the reaction, strict control of reaction temperature (*ca.* −20 °C) or preparation of unstable reagent are problematic from the standpoint of large scale synthesis of pharmaceutical products. The Parikh–Doering reaction was found to be useful to solve these problems and has been applied to the large scale synthesis of pharmaceutical intermediate.[7] However, this method involves stench (dimethyl sulfide), and in addition, pyridine-sulphur trioxide complex is rather expensive and should be stored under low humidity conditions. As an alternative reagent, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) is especially attractive since this reagent is inexpensive and readily available in large quantities from Koei Chemical Co. and Degussa AG. A number of oxidative methods mediated by TEMPO have been reported to convert alcohols to the corresponding aldehydes and ketones.[8,9] Recently Ley and Yasuda reported one-pot conversion of primary alcohols to the corresponding carboxylic acids using polymer-supported TEMPO.[10] However there appears to be few practical methods for direct conversion to acids amenable to a large scale synthesis. Conceptually, alcohols are converted to the corresponding aldehydes in the presence of catalytic amounts of TEMPO and sodium hypochlorite (NaClO) as cooxidant, followed by oxidation to acids by sodium chlorite ($NaClO_2$). Both NaClO and $NaClO_2$ are inexpensive and readily available in large quantities. The problematic feature in the process is that NaClO easily reacts with $NaClO_2$. Zhao *et al.* developed a one-pot conversion of primary alcohols to the corresponding acids in the presence of catalytic amount of TEMPO in a mixture of acetonitrile and sodium phosphate buffer ($pH=6.7$).[11] The success of this process was attributed to the dilute conditions and reduced quantities of NaClO (10 mol%) to avoid the side reaction between NaClO and $NaClO_2$. Whilst efficient enough to afford the materials in less than several hundreds grams quantities, the reported methods involved several drawbacks from the viewpoints of multi-kilogram scale manufacturing; (1) productivity is low due to diluted reaction conditions, (2) simultaneous addition of both NaClO and $NaClO_2$, which easily react with each other, over 2 h is difficult to control on a large scale, (3) conversion of alcohols to aldehydes proceeded sluggishly due to the presence of the reduced amount of NaClO in the system. In addition, the mixture of $NaClO_2$ and NaClO appears to be unstable under the reported condition ($pH=6.7$) as described in the paper.[11] In order to develop more practical methods we investigated conditions where $NaClO_2$ selectively reacted with aldehydes to give the corresponding acids without reacting with NaClO. Herein, we report an efficient procedure for one-pot conversion of primary alcohols to the corresponding acids suitable for a large scale synthesis.

We initiated studies by evaluating reaction conditions that allow easy conversion of alcohols to the corresponding aldehydes. As pointed out in the previous paper,[12,13] the reactivity is critically dependent on the pH employed, and the reaction was dramatically accelerated under slight basic conditions ($pH=8$—10) compared with neutral conditions ($pH=6.7$). Sodium carbonate contained in NaClO was smoothly neutralized by hydrogen chloride produced during the reaction due to high reactivity, and sodium phosphate was not needed in the system. Next, we investigated oxidation of aldehydes to the corresponding acids by $NaClO_2$. Whilst the reaction proceeded sluggishly under basic conditions ($pH=8$—10), $NaClO_2$ was unstable and easily led to decomposition under acidic conditions ($pH=<4.0$). Surprisingly though, the reactivity was dramatically increased at a pH of 4.0—6.0, and neither decomposition of $NaClO_2$ nor side reaction between $NaClO_2$ and NaClO was detected to any significant degree. Thus, this finding led us to realize a selective reaction of aldehydes to the corresponding acids by $NaClO_2$ in the presence of NaClO in significant amounts. As can be seen in Table 1, many alcohols were cleanly and quantitatively converted to aldehydes by TEMPO mediated oxidation when NaClO was added dropwise to the mixture over 30 min at pH of 8—10. Next, to the mixture was added $NaClO_2$ dropwise over 30 min at pH of 5.0, giving the materials in quantitative yield.[14] According to theses limited studies, acetonitrile and ethyl acetate are suitable for these conversions. When toluene or methylenechloride was used as solvent, the conversion of aldehydes to acids proceeded slightly sluggishly, leading to aldehydes remained in traceable amounts. The result in entry 2 is noteworthy. In general, oxidation of β-arylalcohols proceeded to give the corresponding aldehydes in low yields since the aldehydes are unstable under basic conditions.[15] On the other hand TEMPO mediated oxidation of phenylethanol gave the product in quantitative yield presumably due to mild and nearly neutral reaction conditions.

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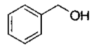
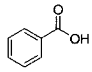
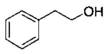
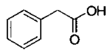
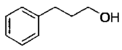
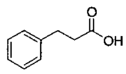
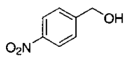
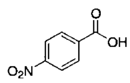
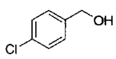
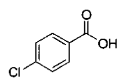
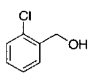
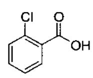
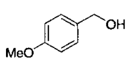
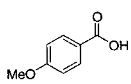
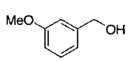
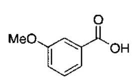
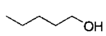
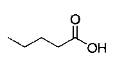
Table 1. TEMPO-Catalyzed Oxidation of Primary Alcohols

Entry	Substrate	Product	Solvent	Yield (%)[a]
1			CH_3CN	98
2			AcOEt	92
3			AcOEt	93
4			AcOEt	100
5			CH_3CN	99
6			CH_3CN	95
7			AcOEt CH_3CN	16 (65)[b] 17 (70)[b]
8			AcOEt	24 (55)[c]
9			AcOEt	84

a) Isolated yield. *b*) Yields in parentheses refer to percent of aldehyde. *c*) Yield in parenthesis refers to percent of 2-chloro-5-methoxybenzoic acid.

Entries 7 and 8 show the limitation of this method. *p*-Methoxybenzyl alcohol was quantitatively oxidized to the corresponding aldehyde, however, the following conversion to the acid proceeded sluggishly (entry 7). The hypochlorite formed in the system may interfere with substrate at pH of 5.0 in the absence of Cl scavenger.[16] For example ring chlorinated material was obtained as a main product in the oxidation of *m*-methoxybenzyl alcohol (entry 8).

In summary, a new method for one-pot conversion of alcohols to acids has been revealed. Alcohols were efficiently oxidized to aldehydes in the presence of a catalytic amount of TEMPO and stoichiometric NaClO, followed by one-pot conversion to acids by $NaClO_2$. The described procedures using only inexpensive reagents are safe and practically and environmentally advantageous over the reported methods especially from the standpoints of large scale manufacturability.

Acknowledgment I especially thank Dr. David Barrett, Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co. Ltd., for his interest and on-going advice in this work.

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14) General procedure for oxidation of alcohol: Ethyl acetate (750 ml) was added to a mixture of phenylethanol (61.1 g, 0.5 mol) and KBr in water (0.5 M, 100 ml), followed by addition of TEMPO (1.6 g, 10 mmol). A solution of 12% NaClO in water (390 g, 625 mmol) was added dropwise to the mixture over 30 min at 5 °C at pH of 8.0—10.0. Stirring continued for 30 min at ambient temperature. Then, pH was adjusted to 5.0 by addition of 35% hydrochloric acid, followed by addition of 25% $NaClO_2$ in water (227 g, 625 mmol) over 30 min maintaining the temperature of 27—33 °C. Stirring continued for 3 h at ambient temperature. The product was extracted with ethyl acetate, washed with brine, followed by concentration to give 62.6 g of phenylacetic acid (92 % yield).
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