Efficient and Highly Selective Oxidation of Primary Alcohols to Aldehydes by *N*-Chlorosuccinimide Mediated by Oxoammonium Salts

Jacques Einhorn,* Cathy Einhorn, Fabien Ratajczak, and Jean-Louis Pierre

Laboratoire de Chimie Biomimétique, LEDSS/UMR CNRS 5616, Université J. Fourier,
38041 Grenoble, France

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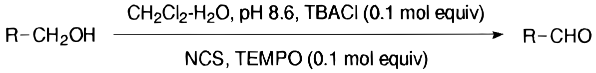
2,2,6,6-Tetramethyl-1-piperidinyloxy catalyzes efficient oxidation of primary alcohols to aldehydes by *N*-chlorosuccinimide, in a biphasic dichloromethane−aqueous pH 8.6 buffer system in the presence of tetrabutylammonium chloride. Aliphatic, benzylic, and allylic alcohols are readily oxidized with no overoxidation to carboxylic acids. Secondary alcohols are oxidized to ketones with a much lower efficiency. Very high chemoselectivities are observed when primary alcohols are oxidized in the presence of secondary ones. Primary−secondary diols are selectively transformed into hydroxy aldehydes, with, in some cases, no detectable formation of the isomeric keto alcohols.

As synthetic chemists are concerned with increasingly sophisticated targets, it is a permanent demand to develop more and more selective synthetic methods able to discriminate efficiently various functional groups. Therefore, selective methods allowing for oxidation of primary alcohols to aldehydes without overoxidation to carboxylic acids and without competitive oxidation of secondary alcohols remain challenging. Relatively few methods allow this type of selectivity.[1] During the past few years, *N*-oxoammonium salts have become synthetic reagents of growing importance, mainly for the oxidation of alcohols to carbonyl compounds. They can be used stoichiometrically, either in an isolated form[2] or generated "in situ" via nitroxide dismutation.[3] Several catalytic procedures have also been developed, the active species being regenerated by stoichiometric amounts of various cooxidants, including *m*-chloroperbenzoic acid,[3c,4] high-valence metal salts,[5] sodium bromite,[6] sodium or calcium hypochlorite,[7] and electrooxidation.[8] Interestingly, a proper choice of the nitroxide catalyst, of the cooxidant, and of the reaction conditions is able to tune very finely the selectivity of these oxidizing systems. For example, several chemoselective systems of preparative value for the oxidation of primary alcohols have recently been developed.[2a,5c,6,7b,c,8a,b] In this paper we describe a new *N*-oxoammonium salt based oxidation method where catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) are used in combination with *N*-chlorosuccinimide (NCS) as the stoichiometric oxidant. This system operates efficiently at room temperature under biphasic conditions (CH_2Cl_2−water) in the presence of tetrabutylammonium chloride (TBACl) as a phase transfer agent, the aqueous phase being buffered at pH 8.6 ($NaHCO_3$−K_2CO_3) (Scheme 1).

Scheme 1



$$\mathrm{R{-}CH_2OH} \xrightarrow[\text{NCS, TEMPO (0.1 mol equiv)}]{\mathrm{CH_2Cl_2\text{-}H_2O}\text{, pH 8.6, TBACl (0.1 mol equiv)}} \mathrm{R{-}CHO}$$

Under these conditions, primary alcohols are quantitatively oxidized to aldehydes (Table 1), without any noticeable overoxidation to carboxylic acids even with an excess of NCS (entry 2). Moreover, the TEMPO inhibits a possible autoxidation of the aldehyde by molecular oxygen, making unnecessary the use of an inert atmosphere during the reaction.[9] No residual oxidation is observed in the absence of TEMPO (entry 1′),[10] whereas the absence of phase transfer catalyst leads to a much slower reaction (entry 3′). Under standard reaction conditions aliphatic and benzylic primary alcohols are oxidized within 0.5−6 h using 1−1.6 equiv of NCS. The experiments, usually performed on a 1 mmol scale, can be scaled up to 0.1 mol without diffictuies (entry 3). In the case of benzylic alcohols, electron-donating groups slow down the reaction (entry 4) whereas electron-

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(1) (a) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605−1608. (b) Nakano, T.; Terada, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1986**, 774−776. (c) Singh, J.; Kolsi, P. S.; Jawanda, G. S.; Chhabra, B. R. *Chem. Ind.* **1986**, *21*, 751−752. For examples of reversed selectivity, see: (d) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647−4650. (e) Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 539−542. (f) Kaneda, K.; Kawanishi, Y.; Jitsukawa, K.; Teranishi, S. *Tetrahedron Lett.* **1983**, *24*, 5009−5010. (g) Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 105−108. (h) Rozen, S.; Bareket, Y.; Kol, M. *Tetrahedron* **1993**, *49*, 8169−8178.

(2) (a) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332−1334. (b) Miyazawa, T.; Endo, T. *J. Org. Chem.* **1985**, *50*, 3930−3931. (c) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509−533 and references cited therein.

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(5) (a) Miyazawa, T.; Endo, T. *J. Mol. Catal.* **1985**, *31*, 217−220. (b) Miyazawa, T.; Endo, T. *J. Mol. Catal.* **1985**, *32*, 357−360. (c) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374−3376.

(6) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462−466.

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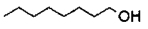
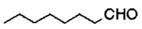
(8) (a) Semmelhack, M. F.; Chou, C. S.; Cortes, D. A. *J. Am. Chem.* Soc. **1983**, *105*, 4492− 4494. (b) Inokuchi, T.; Matsumoto, S.; Torii, S. *J. Org. Chem.* **1991**, *56*, 2416−2421. (c) For a review, see: Yamaguchi, M.; Miyazawa, T.; Takata, Y.; Endo, T. *Pure Appl. Chem.* **1990**, *62*, 217−222.

(9) See ref 7c for similar observations.

(10) Some residual oxidation can be observed when crude commercial NCS is used. It is completely absent when the NCS is recrystallized from toluene before use.

S0022-3263(96)00979-6 CCC: $12.00

Table 1. Oxidation of Primary and Secondary Alcohols[a]

Entry	Substrate	NCS mol equiv	Time h	Product	Yield %[b]
1		1.3	3.5		100
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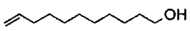
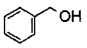
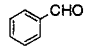
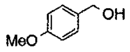
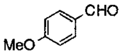
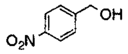
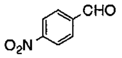
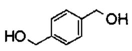
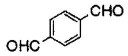
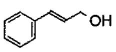
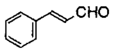
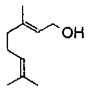
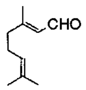
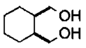
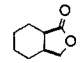
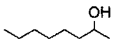
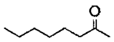
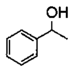
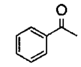
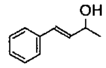
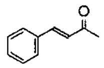
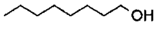
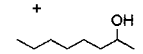
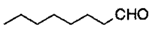
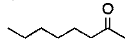
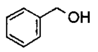
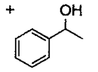
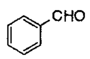
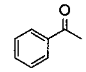
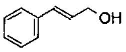
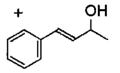
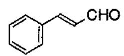
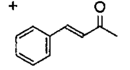
2		2	24		92
3		1.25	2		99^{d}
3'	"	1	5	"	13^{e}
4		1.1	0.5		34
4'	"	1.3	7	"	100
5		1.1	0.5		100
6		2.6	6		95
7		1.6	2		83
8		1.8	3		100
9		3	2		94
10		1.2	6		26
11		1.2	3.5		68
12		2.2	24		55

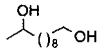
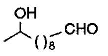
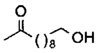
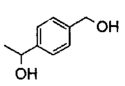
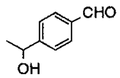
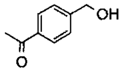
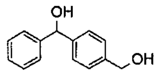
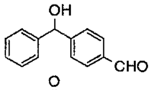
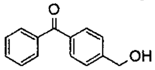
[a] In CH_2Cl_2-H_2O (pH 8.6) at room temperature with 10 mol % TEMPO and 10 mol % TBACl, on a 1 mmol scale. [b] Yields were determined by calibrated quantitative GLC analysis using an internal standard. [c] Without TEMPO. [d] Performed on a 0.1 mol scale. [e] Without TBACl.

Table 2. Oxidation of Primary Alcohols in the Presence of Secondary Ones[a]

Entry	Substrates	NCS mol equiv	Time h	Products	Yield %[b]
1	 + 	1.3	3.5	 + 	100 $< 0.1^{c}$
2	 + 	1.25	4	 + 	100 $< 0.1^{c}$
3	 + 	1.75	4	 + 	85 4

[a] The reactions were carried out, on a 1 mmol scale, on a 1:1 mixture of primary and secondary alcohols . [b] The yields were determined by calibrated quantitative GLC analysis using an internal standard. [c] Estimated by adding 0.1 mol % of ketone to the crude reaction product.

Table 3. Selective Oxidation of Primary−Secondary Diols[a]

Entry	Substrates	NCS mol equiv	Time h	Products	Yield %[b]
1		1.5	2.15	 	82^{c} < 0.1
2		1.1	2.15	 	65^{d} < 0.1
3		1.1	3	 	77^{e} 0.5

[a] The reactions were performed on a 1 mmol scale, under standard conditions. [b] Yields based on weight of pure product after chromatography. [c] 5 % Ketoaldehyde were also isolated. [d] 12 % Ketoaldehyde and 11 % starting diol were also isolated. [e] 11 % Ketoaldehyde and 5 % starting diol were also isolated.

withdrawing groups accelerate it (entry 5). Allylic alcohols are oxidized to the corresponding aldehydes with excellent yields (entries 7 and 8).[11] Primary diols are converted into dialdehydes (entry 6) or lactones (entry 9) according to the structure.

On the contrary, aliphatic, benzylic, and even allylic secondary alcohols are oxidized into ketones with much lower efficiency under the same reaction conditions (entries 10−12). This observation suggested a possible chemoselective oxidation of primary alcohols in the presence of secondary ones. Indeed, the present oxidation system proved to be exceptionally chemoselective: the reaction of a 1:1 mixture of 1-octanol and 2-octanol, using 1.3 equiv of NCS resulted, after 3.5 h, in the complete conversion of the primary alcohol into aldehyde whereas virtually no ketone (<0.1%) could be detected by GC (Table 2, entry 1). The competitive oxidation of benzylic alcohol and 1-phenylethanol exhibits a similar degree of selectivity: after complete transformation of the primary alcohol into aldehyde, the amount of ketone formed remains under the GC detection level.[12] In both cases, the relative oxidation rates for primary and secondary alcohols can be estimated to be at least 1 order of magnitude higher than those of previously described methods.[6,7c,8b] An even more difficult problem of selectivity is that of primary versus secondary allylic alcohols (entry 3).[13] A 85:4 ratio of aldehyde to ketone is obtained in this case.

We next turned to the synthetically more useful case of intramolecular competition between primary and secondary alcohols (Table 3). Oxidation of 1,10-undecanediol gave an 82% isolated yield of 10-hydroxyundecanal, the amount of isomeric keto alcohol remaining less than 0.1%. Intramolecular selectivity between primary and secondary benzilic positions proved to be equally

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[11] This result is in sharp contrast with those obtained when other sources of positive halogen such as NaOCl or $Ca(OCl)_2$ are used as cooxidants, where low yields of aldehydes are obtained. For example, see ref 7a.

[12] The detection level has been estimated by adding known amounts of the corresponding ketone to the crude reaction product. As little as 0.1 mol % can be detected unambiguously by GC on a OV17 capillary column.

[13] Kulkarni, M. G.; Mathew, S. T. *Tetrahedron Lett.* **1990**, *31*, 4497−4500.

successful (entry 2). Even in the case of doubly activated secondary alcohols the methods ensures oxidation of primary alcohols with a very high chemoselectivity (entry 3).

In conclusion, the procedure reported here allows a convenient and high-yielding method for the oxidation of primary alcohols to aldehydes with no overoxidation to carboxylic acids. Furthermore, this process exhibits an unprecedented degree of chemoselectivity for the oxidation of primary hydroxy groups in the presence of secondary ones. These features should make it of significant synthetic value.

Experimental Section

Materials. TEMPO was purchased from Lancaster and used as received. NCS, purchased from Aldrich, was recrystallized from toluene before use. All alcohols and symmetrical diols used for the oxidations were commercial samples except *trans*-4-phenyl-3-buten-2-ol obtained by reduction of the commercial ketone by $NaBH_4/CeCl_3$.[14] Primary secondary diols used for the competition experiments, already known, were prepared by simplified procedures: 1,10-undecanediol[1g] prepared with an 81% yield by oxymercuration−demercuration of 10-undecen-1-ol, α-methyl-1,4-benzenedimethanol[1g] in quantitative yield by lithium aluminum hydride reduction of commercial ethyl 4-acetylbenzoate, α-phenyl-1,4-benzenedimethanol[15] in quantitative yields by borane·THF reduction of 4-benzoylbenzoic acid.

General Procedure for the Oxidations. A solution of alcohol or diol (1 mmol), TEMPO (0.1 mmol, 15.6 mg), TBACl (0.1 mmol, 27.7 mg), and an appropriate amount of an internal standard in 10 mL of dichloromethane and 10 mL of an aqueous solution of $NaHCO_3$ (0.5 M) and K_2CO_3 (0.05 M) were vigorously stirred at room temperature. The indicated amount (see table) of solid NCS was then added. Stirring was maintained and the reaction monitored by TLC and /or GC. After the indicated time the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The dichloromethane extracts were washed with brine (2 × 10 mL), dried, and evaporated. The residue was distilled or chromatographed.

Intermolecular Competition Experiments. The standard procedure was applied to an equimolecular mixture of primary and secondary alcohols with the indicated amount of NCS. After workup the residue was analyzed by GC.

Intramolecular Competition Experiments. The standard procedure was applied to a primary−secondary diol with the indicated amount of NCS. The residue was analyzed by GC, and the main products were isolated by column chromatography on silica gel. Keto alcohols being virtually absent in the crude products, they have been prepared independently in each case by appropriate procedures.[1d,16] Very small amounts of these keto alcohols in the corresponding crude oxidation products were estimated by GC analysis after calibration with authentic samples.

Oxidation Products. Simple aldehydes and ketones obtained by oxidation were characterized by usual spectral data (IR, ^1H and ^{13}C NMR) and compared with the literature values. The oxidation products of primary−secondary diols were already described: 10-hydroxyundecanal,[8b] 10-oxoundecan-1-ol,[1g] 10-oxoundecanal,[7b] 4-(1-hydroxyethyl)benzaldehyde,[1g] 4-(hydroxymethyl)acetophenone,[1g] 4-acetylbenzaldehyde,[1g] 4-(α-phenylhydroxymethyl)benzaldehyde,[17] 4-(hydroxymethyl)benzophenone,[15] 4-benzoyl benzaldehyde.[15]

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