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A Very Mild and Chemoselective Oxidation of Alcohols to Carbonyl Compounds

Lidia De Luca, Giampaolo Giacomelli,* and Andrea Porcheddu

Dipartimento di Chimica, Università degli Studi di Sassari, via Vienna 2,
I-07100 Sassari, Italy

ggp@ssmain. uniss.it

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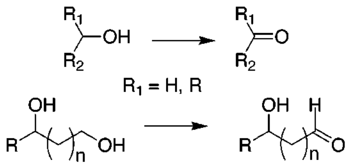
ABSTRACT



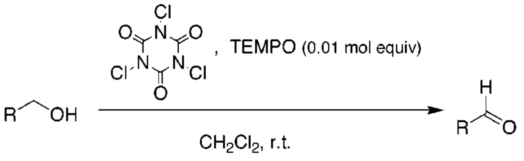
Efficient oxidation of primary alcohols and β-amino alcohols to the corresponding aldehydes and α-amino aldehydes can be carried out at room temperature and in methylene chloride, using trichloroisocyanuric acid in the presence of catalytic TEMPO: aliphatic, benzylic, and allylic alcohols, and β-amino alcohols are rapidly oxidized without no overoxidation to carboxylic acids. Secondary carbinols are slowly oxidized so that the reaction is highly chemoselective.

In view of their importance as intermediates in organic synthesis, many methods for oxidation of primary alcohols to aldehydes have been documented in the literature.[1] In particular, oxidation of β-amino alcohols to the corresponding α-amino aldehydes is synthetically useful as the carbonyl group present in the amino carbonyl compounds readily undergoes successive transformations.[2] Moreover, there is a continuous demand to develop synthetic methods for discriminating efficiently various functional groups. In this context, chemoselective methods allowing for oxidation of primary alcohols without competition of secondary alcohols remain challenging. Relatively few methods allow this type of selectivity,[3] and often the restrictions that accompany some of them make new, mild, and selective procedures highly desirable.

Until now, Swern oxidation has been shown to be a favorable method for the oxidation of alcohols:[4] however, this procedure suffers from the use of activated dimethyl sulfoxide as a reagent and very low temperatures and, mainly, from the presence of dimethyl sulfide as a byproduct. Moreover, the oxidation is not chemoselective.

On this basis and following our interest in the use of [1,3,5] triazine derivatives in organic synthesis,[5] herein we report a very mild, efficient procedure for the general oxidation of carbinols into the corresponding carbonyl compounds that is easy to use and chemoselective for the quantitative conversion of primary alcohols into aldehydes (Scheme 1).

Scheme 1



The procedure is based on the addition of 1 molar equiv of 1,3,5-trichloro-2,4,6-triazinetrione (trichloroisocyanuric acid), a very cheap reagent, to a CH_2Cl_2 solution of the alcohol followed by catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[6] This system operates rapidly,

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(1) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 5th ed.; Wiley-Interscience: New York, 2001; pp 1514−1517.

(2) Jurczak, J.; Golebiowski, A, *Chem. Rev.* **1989**, *89*, 149.

(3) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L. *J. Org. Chem.* **1996**, *61*, 7452 and references therein.

(4) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

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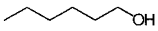
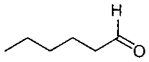
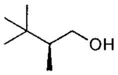
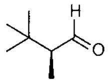
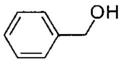
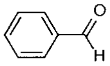
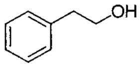
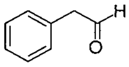
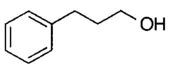
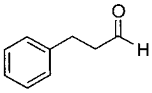
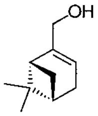
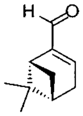
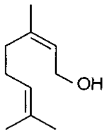
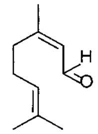
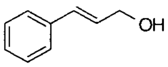
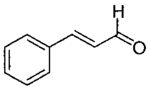
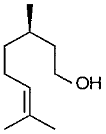
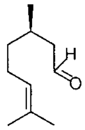
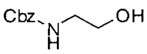
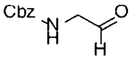
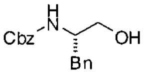
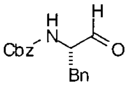
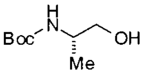
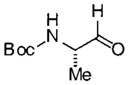
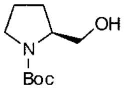
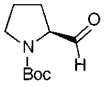
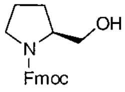
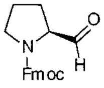
at room temperature, without addition of water or base, with the oxidation of the primary alcoholic group being practically quantitative within 20 min (Table 1). No noticeable overoxidation to carboxylic acids was detected even using a 2-fold excess of trichloroisocyanuric acid.

Table 1. Conversion of Alcohols into the Corresponding Carbonyl Compounds

entry	alcohol	product	conversion[a] (%)
1			96
2			98
3			98
4			97
5			99
6			99
7			99
8			90[b]
9			90
10			83
11			70
12			81
13			70
14			88

[a] After 15 min. [b] (3-Chloropropenyl)benzene (7%) was recovered too.

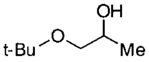
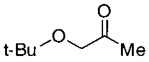
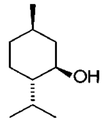
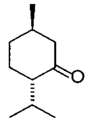
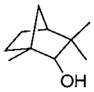
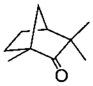
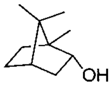
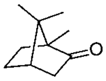
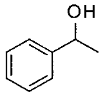
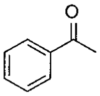
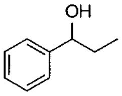
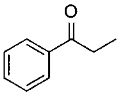
Aliphatic, benzylic, and allylic alcohols are oxidized at the same rate. With cinnamyl alcohol, the reaction is very rapid (5 min) and furnishes a high yield of the cinnamaldehyde along with the corresponding chloride (<10%). In this case, a reverse addition procedure has to be followed: the trichloroisocyanuric acid is added portionwise to a CH_2Cl_2 solution of the alcohol containing TEMPO (0.01 molar equiv). Indeed, employing the normal procedure causes an exothermic reaction with prevalent formation of (3-chloropropenyl)benzene.

Under the usual conditions, even *N*-protected *β*-amino alcohols are oxidized to *N*-protected α-amino aldehydes, with slightly reduced rates: however, the oxidation is complete within 20 min. Moreover, the method is compatible with the common *N*-protecting groups and no deprotection was noted.

Upon comparison to previously studied reactions of this type,[7] the data collected show that significant racemization of the chiral center on the α-carbon atom does not occur. In fact, a sample of (*S*)-2,3,3-trimethyl-1-butanol, $[\alpha]^{25}_{D}$ +39.1 (*c* 2, EtOH), gave (*S*)-2,3,3-trimethylbutanal, $[\alpha]^{25}_{D}$ +79.4 (*c* 4, heptane).[8,9] Analogously, (*S*)-*N*-benzyloxycarbonyl-2-amino-3-phenylpropan-1-ol, $[\alpha]^{20}_{D}$ −40.2 (*c* 0.5, MeOH), gave (*S*)-*N*-benzyloxycarbonyl-2-amino-3-phenylpropionaldehyde, with $[\alpha]^{20}_{D}$ −51.3 (*c* 1, MeOH).[10]

The system we report on allows oxidation of secondary carbinols too, under the same reaction conditions (Table 2). The reaction gives quantitatively the corresponding ketones, but the rate is very low and the process requires more than 6 h for completion.[11] The reaction rate seems to be particularly reduced with sterically constrained alcohols.

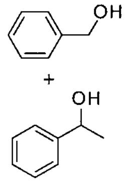
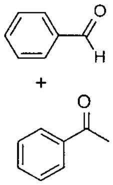
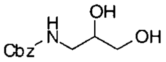
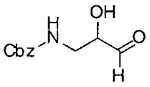
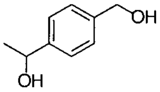
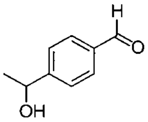
Table 2. Conversion of Secondary Alcohols into Ketones

entry	alcohol	product	conversion[a] (%)
1			95
2			93
3			75
4			78
5			98
6			97

[a] After 6 h.

This observation suggested a possible use of this reaction as a chemoselective method for oxidizing primary alcohols in the presence of secondary ones. Indeed, the present system is highly chemoselective. The reaction of a 1:1 mixture of a primary alcohol with a secondary one occurs after 15 min in a quantitative conversion of the primary alcohol into an aldehyde, with the reduction in the amount of ketone formed (Table 3). Even better results are obtained when primary and secondary carbinol groups are in competition on the same skeleton. In the reaction carried out with 3-(*N*-benzyloxycarbonyl)aminopropane-1,2-diol,[12] the only product recovered after 15 min is 3-(*N*-benzyloxycarbonyl)amino-2-hydroxypropionaldehyde, without contamination of either the dicarbonyl compound or the isomeric keto alcohol. The oxidation of 1-(4-hydroxymethylphenyl)ethanol gives similar results, with 4-(1-hydroxyethyl)benzaldehyde being the only product recovered.

Table 3. Selective Oxidations of Diols

entry	alcohol	product	conversion[a] (%)
1			96 4
2			95
3			98

[a] After 15 min.

The procedure for the oxidation of 3-(*N*-benzyloxycarbonyl)aminopropane-1,2-diol is representative for all cases. Trichloroisocyanuric acid (2.32 g, 10.0 mmol) was added to a solution of the alcohol (2.14 g, 9.5 mmol) in CH_2Cl_2 (20 mL), and the solution was stirred and maintained at 0 °C, followed by addition of TEMPO (0.015 g, 0.1 mmol). After the addition, the mixture was warmed to room temperature and stirred for 15 min and then filtered on Celite, and the organic phase was washed with 15 mL of a saturated solution of Na_2CO_3, followed by 1 N HCl and brine. The organic layer was dried (Na_2SO_4), and the solvent was evaporated to yield 3-(*N*-benzyloxycarbonyl)amino-2-hydroxypropionaldehyde that was isolated without further purification (95%): ^{1}H NMR δ 10.1 (s, 1H), 7.99 (s, 1H), 7.44−7.38 (m, 5H), 5.22 (m, 1H), 5.17 (bs, 2H), 3.67 (m, 2H), 3.40 (bs, 1H); ^{13}C NMR δ 192.4, 157.4, 134.4, 129.7, 128.0, 66.9, 58.8, 29.7. Anal. Calcd for $C_{11}H_{13}NO_4$ (223.08): C, 59.19; H, 5.87; N, 6.27. Found C, 59.19, H, 5.89, N, 6.24.

In conclusion, the procedure reported here is simple and allows for rapid oxidation of primary alcohols to aldehydes under very mild conditions with a high degree of chemoselectivity. The method seems to be as convenient for oxidizing both primary and secondary carbinols as other methods reported in the literature and can be used as a valid alternative to the classical Swern oxidation, therefore avoiding very low temperature and the use of toxic reagents.

Acknowledgment. The work was financially supported by the University of Sassari (Fondi ex-60%).

OL016501M

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(5) (a) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962. (c) Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275. (d) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519.

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(8) Marcacci, F.; Giacomelli, G.; Menicagli, R. *Gazz. Chim. Ital.* **1980**, *110*, 195.

(9) On the basis of this datum, it is possible to conclude that this oxidation method proceeds with better stereochemistry than the DCC-DMSO system.[6]

(10) (a) Sharma, R. P.; Gore, M. G.; Akhtar, M. *J. Chem. Soc., Chem. Commun.* **1979**, 875. (b) Soucek, M.; Urban, J *Collect. Czech. Chem. Commun.* **1995**, *60*, 693.

(11) Hiegel and Nalbandy (Hiegel, G. A.; Nalbandy, M. *Synth. Commun.* **1992**, *22*, 1595) reported that in combination with pyridine secondary alcohols are rapidly oxidized to ketones by trichloroisocyanuric acid.

(12) Finn, P. J.; Gibson, N. J.; Fallon, R.; Hamilton, A.; Brown, T. *Nucleic Acids Res.* **1996**, *24*, 3357.