JOC Note

Trichloroisocyanuric/TEMPO Oxidation of Alcohols under Mild Conditions: A Close Investigation

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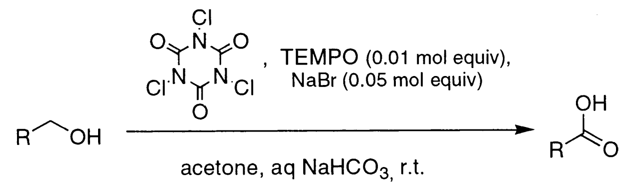
Abstract: Efficient oxidation of primary alcohols to the corresponding carboxylic acids can be carried out at room temperature and in acetone/water, using trichloroisocyanuric acid (TCCA) in the presence of catalytic TEMPO. The mild conditions of this procedure and the total absence of any transition metal make this reaction suitable for safe laboratory use. A possible mechanism is presented and discussed.

The development of oxidation processes constitutes an active area of both academic and industrial research[1] and is a topic of current interest. However, direct conversion of primary alcohols to the corresponding carboxylic acids is still a challenge, and the most commonly used methods include transition-metal-assisted oxidations.[1] Only a few examples of reactions with chromium,[2] ruthenium,[3] or tungsten[4] catalysts for the synthesis of carboxylic acids have been reported up to now.

In the area of metal-free alcohol oxidations,[5] Swern oxidation[6] has emerged, along with the use of TEMPO-based ones,[7] as an important reaction to be used under mild conditions too.[8] During our program on the use of 1,3,5-triazine derivatives in organic synthesis,[9] we have reported a very mild and chemoselective oxidation of alcohols to carbonyl compounds that uses trichloroisocyanuric acid in the presence of catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[10] In particular, this last system operates rapidly, at room temperature, and in an organic solvent such as dichloromethane. However, the resulting aldehyde has to be oxidized in a second step.

SCHEME 1



Oxidation of primary alcohols to carboxylic acids through TEMPO-catalyzed procedures was recently reported.[11, 12] Bleach and sodium chlorite solution have to be used as oxidants at 35 °C in MeCN in an economical and practical methodology. The reaction is efficient but the procedure employed is quite complicated, as caution has to be taken in the mixing of bleach and $NaClO_2$.

Within this context, we report here a safe and efficient one-pot oxidation of primary carbinols to their carboxylic acids, using the same trichloroisocyanuric acid/TEMPO couple, simply using acetone as solvent. In this case, the reaction proceeds more slowly than the oxidation carried out in CH_2Cl_2[11] and the entire process requires from 20 min to several hours to completion in relation to the structure of the alcohol. Nevertheless the yields are quantitative, and the acids can be recovered without any additional purification (Scheme 1).

The procedure is based on the addition of 2 molar equiv[13] of 1,3,5-trichloro-2,4,6-triazinetrione (trichloroisocyanuric acid), a very cheap and nontoxic reagent, to an acetone solution of the alcohol followed by catalytic amounts (0.1 equiv) of TEMPO and of NaBr[14] and then 1 equiv of aq $NaHCO_3$. This system operates at room temperature, the oxidation of the primary alcoholic group being practically quantitative (Table 1).

The reaction is reasonably fast (generally less than 6 h) and only in a few cases requires up to 24 h for completion (e.g., run 13). Moreover, this method can be successfully applied on a large scale. On examination of Table 1, some observations can be made.

The reaction rate is related to the structure of the primary alcohol employed, apparently to its steric hindrance. Under the usual conditions, even N-protected β-amino alcohols are oxidized to N-protected α-amino acids, with slightly reduced rates (entries 9−14); how-

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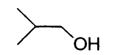
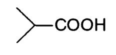
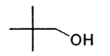
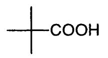
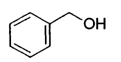
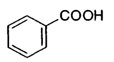
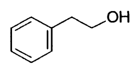
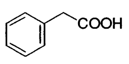
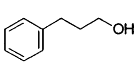
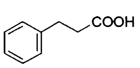
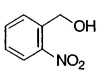
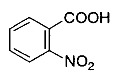
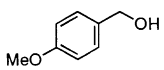
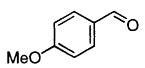
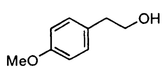
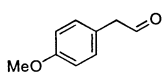
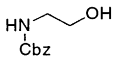
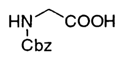
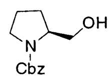
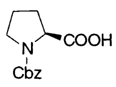
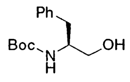
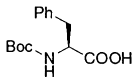
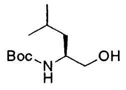
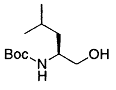
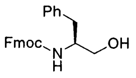
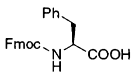
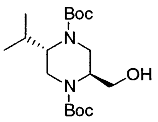
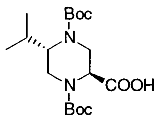
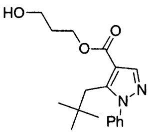
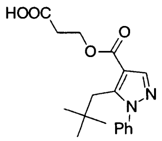
(13) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowsky, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.

(14) Using 1 equiv of TCCA the reaction is very slow and requires longer reaction time for completion.

10.1021/jo034276b CCC: $25.00

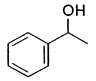
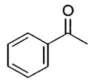
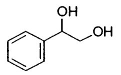
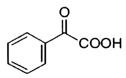
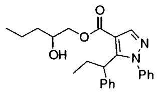
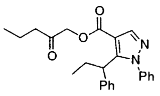
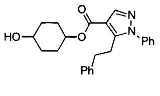
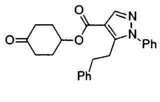
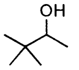
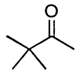
TABLE 1. Oxidation of Primary Alcohols into Carboxylic Acids

entry	alcohol	acid	reaction time	conv. (%)
1			3 h	100
2			12 h	75
3			1 h	100
4			1 h	100
5			6 h	100
6			6 h	90
7			6 h	98
8			6 h	95
9			24 h	85
10			24 h	100
11			6 h	98
12			6 h	92
13			18 h	90
14			24 h	100
15			1 h	100

ever, the oxidation is complete within 24 h, the method is compatible with the common N-protecting groups, and no deprotection was noted.

According to this kind of reaction,[15] the data collected show that significant racemization of the chiral center on the α-carbon atom does not occur. For example, a sample of (*S*,*S*)-5-isopropyl-1,4-di(*tert*-butoxycarbonyl)-2-hydroxymethylpiperazine, $[\alpha]^{25}_{D}$ +99.8 (*c* 2, $CHCl_3$) (entry 14) gave (*S*,*S*)-5-isopropyl-1,4-di(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid, $[\alpha]^{25}_{D}$ +69.2 (*c* 1, $CHCl_3$).[17]

TABLE 2. Oxidation of Secondary Alcohols into Ketones

entry	alcohol	acid	reaction time	conv. (%)
1			1 h	100
2			5 h	75
3			1 h	94
4			1 h	93
5			1 h	98

The system we report allows oxidation of secondary carbinols too, under the same reaction conditions (Table 2). The reaction gives fast and quantitatively the corresponding ketones, the rate being reduced in the case of the presence of other primary hydroxyl groups. It is to note that this procedure allows us to obtain 3,3-dimethylbutan-2-one from the corresponding alcohol without rearrangement of the skeleton to 2,3-dimethylbut-2-ene due to Wagner−Meerwein reactions.[18] Contrary to what was reported in a similar procedure, this procedure is not chemoselective.

This methodology is mild and efficient and is compatible with several functional groups other than the alcohol. Substrates with methoxy-substituted aromatic rings are subjected to the TEMPO/TCCA oxidation, but surprisingly the reaction affords only the corresponding aldehydes (Table 1, entries 7 and 8). Unexpectedly, this procedure failed in the oxidations of unsaturated alcohols as well. Contrary to what was observed carrying out the oxidation in the absence of water,[11] the treatment of unsaturated alcohols with 2 equiv of trichloroisocyanuric acid and catalytic TEMPO, under the present conditions, proceeded to the corresponding carboxylic acid and to the contemporary addition to the double bond. The oxidation of *trans*-cinnamic alcohol furnished in fact (2*RS*,3*SR*)-2,3-dichloropropionic acid.[19,20] The amount of chlorination

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[15] The presence of sodium or lithium halide is essential for the oxidation process, with no reaction taking place without it. NaBr is preferred owing to its higher solubility in acetone.

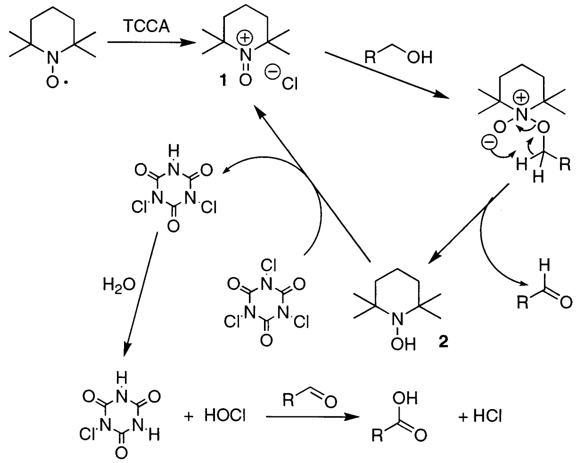
[16] Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

[17] Falorni, M.; Giacomelli, G.; Satta, M.; Cossu, S. *Synthesis* **1994**, 391.

[18] For a review see Kaupp, G. *Top. Curr. Chem.* **1988**, *146*, 57.

[19] Cabaleiro, M. C.; Johnson, M. D.; Swedlund, B. E.; Williams, J. G. *J. Chem. Soc. B* **1968**, 1022.

SCHEME 2



reaction is diminished operating with equimolar amounts of TCCA, but in this case the rate of the reaction is very reduced. To determine if this behavior was general for the double bond, we carried out the reaction with (*E*)-1,1-diethoxy-3-phenyl-2-propene under the same conditions. After complete conversion of the alkene, (2*RS*,3*SR*)-1,1-diethoxy-2,3-dichloro-3-phenylpropane was obtained quantitatively. [21]

To clarify some mechanistic aspects of the oxidation, we have conducted some additional runs. The course of the oxidation does not change using catalytic alkaline salts (NaBr, NaI, LiF) other than NaCl or using Bu_4NBr. The use of only 1 equiv of TCCA causes a very slow reaction: in the case of oxidation of benzyl alcohol, the reaction requires 15 h at 25 °C for completion. The reaction is very slow even when NCS (2 equiv) is used instead of TCCA. The oxidation to carboxylic acid does not occur in the absence of water in the reaction mixture, and the reaction stops with the formation of the aldehyde. The reaction can be conducted both in acetone and MeCN, under the reported experimental conditions, with the same identical results, while only carbonyl compounds are formed using dry dichloromethane.[11] Increasing the amount of water increased the formation of chlorinated products; under these conditions, benzyl alcohol is oxidized slowly to a mixture of chloro-substituted benzoic acids.

It is noteworthy that the oxidation of the intermediate aldehyde does not require TEMPO as catalyst. In fact, the aldehyde is rapidly oxidized to the corresponding carboxylic acid by treatment with 1 equiv of TCCA in acetone/water, without addition of the catalyst.

On these bases, and according to that reported for similar cases, we can formulate the mechanism shown in Scheme 2. A catalytic amount of TCCA should react with TEMPO to form the *N*-oxoammonium ion **1**,[8d] which oxidizes the alcohol to the corresponding carbonyl compound giving the hydroxylamine **2**. Then this intermediate is in turn oxidized to the oxoammonium derivative **1** from TCCA. At last, the slow hydrolysis of TCCA[22] or its derivatives should form hypochlorous acid able to oxidize the aldehyde to the carboxylic acid.[23] The reaction between hypochlorous and hydrocloric acid, formed upon oxidative process, should form chlorine that is able to chlorinate unsaturated carbonyl compounds[19] in the last step of the reaction.

In conclusion, this oxoammonium oxidation of alcohols can afford the corresponding carboxylic acids in excellent yields and high optical purity. This method is characterized by mild reaction conditions, transition metal absence, nontoxic byproducts, and easy reaction workup, making it ideal for both laboratory and large scale.

Experimental Section

All solvents and reagents were used as obtained from commercial sources. L-Prolinol was a commercial product, while other *N*-amino alcohols were prepared according standard methods from their N-protected amino acids.[24,25] Standard ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz from $CDCl_3$ solutions. All runs were conducted at least in duplicate.

General Procedure. The procedure for the oxidation of (2*S*)-*N*-(benzyloxycarbonyl)prolinol (run 9) is representative for all cases. An aqueous 15% solution of $NaHCO_3$ (15 mL) was added to a solution of the alcohol (1.11 g, 5.0 mmol), $[\alpha]^{25}_D$ −42.4 (c = 2, $CHCl_3$),[26] in acetone (50 mL) stirred and maintained at 0 °C, followed by solid NaBr (0.1 g, 1 mmol) and TEMPO (0.015 g, 0.1 mmol). Trichloroisocyanuric acid (2.32 g, 10.0 mmol) was then slowly added within 20 min at 0 °C. After the addition, the mixture was warmed to room temperature and stirred for the required time until completion, and then 2-propanol (3 mL) was added. The mixture was filtered on Celite, concentrated under vacuum, and treated with 15 mL of a saturated solution of Na_2CO_3. The aqueous phase was washed with portions of AcOEt, treated with 1 N HCl, and extracted twice with AcOEt. The organic layers were dried (Na_2SO_4), and the solvent was evaporated to yield (2*S*)-*N*-(benzyloxycarbonyl)proline that was isolated without other purifications (1.18 g, 100%): $[\alpha]^{25}_D$ −40.4 (c = 1, EtOH);[27] mp 78 °C; ^1H NMR δ 10.9 (s, 1H), 7.30 (s, 5H), 5.13 (s, 2H), 4.40 (m, 1H), 3.52 (m, 2H), 2.22 (m, 2H), 1.95 (m, 2H).[28]

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Supporting Information Available: Physical and spectroscopic data for all compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] From the stereochemistry of the recovered compounds it can be deduced that the chlorination of the double bond might arise from addition of chlorine, formed by oxidation of chloride ions, present in the solution, owing to the long reaction times.

[21] Using NaBr as catalyst, traces of incorporation of bromine (<8%) are revealed from ^1H NMR analysis. In the absence of catalytic TEMPO, no reaction occurs.

[22] The hydrolysis of TCCA seems to be catalyzed by the presence of even catalytic amounts of halide ions; in the absence of traces of sodium halides, no oxidation to carboxylic acids takes place.

[23] It is noteworthy that bleach is not able to oxidize both 4-methoxybenzaldehyde and 4-methoxyphenyl acetaldeyde to the corresponding carboxylic acid, thus confirming the hypothesis that hypochlorous acid is formed in this step. In addition, TCCA is inactive in the absence of water.

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