Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 49 (2008) 2457–2460

Tetrahedron Letters

CuCl catalyzed selective oxidation of primary alcohols to carboxylic acids with *tert*-butyl hydroperoxide at room temperature

Sreedevi Mannam, G. Sekar *

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India

Received 25 June 2007; revised 23 January 2008; accepted 7 February 2008
Available online 10 February 2008

Abstract

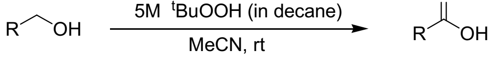
Direct oxidation of primary alcohols to the corresponding carboxylic acids is performed highly efficiently at room temperature with anhydrous *tert*-butyl hydroperoxide in the presence of a catalytic amount of easily available CuCl under ligand free conditions in acetonitrile. Benzylic alcohols are more reactive than aliphatic alcohols, and these benzylic alcohols are selectively oxidized to the corresponding acids in the presence of aliphatic alcohols such as 1-octanol and 1-decanol.

Keywords: CuCl; Alcohol oxidation; Selective oxidation; Carboxylic acid; Benzylic alcohols

Oxidation is one of the most fundamental reactions in synthetic organic chemistry and a variety of reagents have been developed as oxidants, which is a testimony to the importance of this reaction.[1] However, relatively few general methods exist for the direct oxidation of alcohols to carboxylic acids. Traditionally, this oxidation involves a two-step process involving oxidation of the alcohol to an aldehyde followed by further oxidation to the carboxylic acid. Several reaction conditions have been developed for the direct oxidation of alcohols to acids such as Jones,[2] CrO_3/H_5IO_6,[3] $RuCl_3/H_5IO_6$,[4] RuO_4,[5] $RuCl_3/K_2S_2O_8$,[6] Ru–Co bimetallic catalyzed oxidation,[7] $Cu(MnO_4)_2$ oxidation,[8] TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy)-catalyzed oxidation with sodium hypochlorite,[9] Na_2WO_4/H_2O_2[10] and Cu(II)–salen complex/H_2O_2.[11] However, all of these methods have some limitations such as strongly acidic conditions, a requirement for stoichiometric or super stoichiometric amounts of costly or hazardous oxidizing reagents and/or elevated temperatures. Therefore, mild, catalytic, economic and efficient alternative methods are still desirable.

Very recently, we developed an efficient method for the selective oxidation of alcohols to the corresponding aldehydes and ketones using a DABCO–Cu complex as a catalyst.[12] As a part of our ongoing research towards copper catalyzed oxidation chemistry, herein, we report a CuCl catalyzed direct oxidation of benzylic and allylic primary alcohols to the corresponding carboxylic acids using anhydrous *tert*-butyl hydroperoxide at room temperature under ligand free conditions (Scheme1). This procedure is very simple, mild, clean and works efficiently without any additives.

In preliminary studies, we used the DABCO–CuCl complex/O_2/TEMPO for the oxidation of *p*-methoxybenzyl alcohol in nitromethane. The reaction provided only the corresponding aldehyde with no trace of carboxylic acid (Table 1, entry 1). When we replaced molecular oxygen with 70% ^{t}BuOOH (in water), the reaction produced a 51% isolated yield of aldehyde and a 23% yield of acid



Scheme 1. CuCl catalyzed oxidation of alcohols to acids.

---

* Corresponding author. Tel.: +91 44 2257 4229; fax: +91 44 2257 4202.
E-mail address: gsekar@iitm.ac.in (G. Sekar).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.031

Table 1
Optimizing the conditions for direct oxidation of *p*-methoxybenzyl alcohol to *p*-methoxybenzoic acid

Entry	Catalyst	Additive	Oxidant	Solvent	Time (h)	Isolated yield (%)	
						Aldehyde	Acid
1	DABCO–CuCl	TEMPO	O_2	CH_3NO_2	5	95	0
2	DABCO–CuCl	TEMPO	70% ^{t}BuOOH	CH_3NO_2	12	51	23
3	DABCO–CuCl	TEMPO	70% ^{t}BuOOH	CH_3CN	6	35	59
4	DABCO–CuCl	TEMPO	KIO_4	CH_3CN	24	0	0
5	DABCO–CuCl	TEMPO	30% H_2O_2	CH_3CN	24	51	20
6	DABCO–CuCl	TEMPO	5 M ^{t}BuOOH (in decane)	CH_3CN	1	Trace	92
7	DABCO–CuCl	—	5 M ^{t}BuOOH (in decane)	CH_3CN	1	Trace	91
8	CuCl	TEMPO	5 M ^{t}BuOOH (in decane)	CH_3CN	1	Trace	92
9	***CuCl***	—	***5 M ^{t}BuOOH (in decane)***	***CH_3CN***	***1***	—	***93***
10	—	—	5 M ^{t}BuOOH (in decane)	CH_3CN	24	20	0
11	CuCl	—	5 M ^{t}BuOOH (in decane)	THF	24	42	32
12	CuCl	—	5 M ^{t}BuOOH (in decane)	DCM	24	20	24
13	CuCl	—	5 M ^{t}BuOOH (in decane)	EtOAc	6	5	89
14	CuCl	—	5 M ^{t}BuOOH (in decane)	Benzene	24	37	45
15	CuBr	—	5 M ^{t}BuOOH (in decane)	CH_3CN	6	2	90
16	CuI	—	5 M ^{t}BuOOH (in decane)	CH_3CN	12	33	48
17	$CuNO_2 \cdot 3H_2O$	—	5 M ^{t}BuOOH (in decane)	CH_3CN	12	27	71
18	$CuCl_2 \cdot 2H_2O$	—	5 M ^{t}BuOOH (in decane)	CH_3CN	8	14	80
19	$Cu(OAc)_2 \cdot H_2O$	—	5 M ^{t}BuOOH (in decane)	CH_3CN	14	47	25
20	$Cu(OTf)_2$	—	5 M ^{t}BuOOH (in decane)	CH_3CN	12	45	49

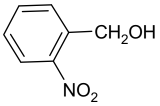
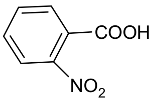
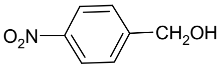
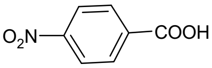
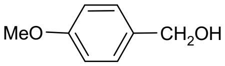
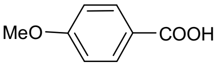
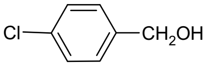
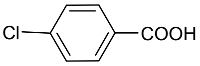
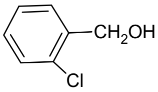
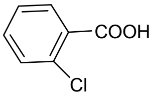
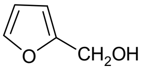
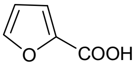
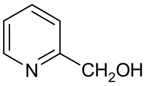
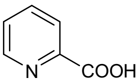
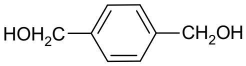
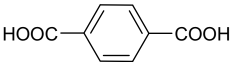
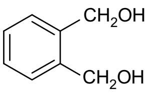
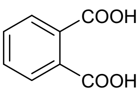
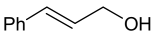
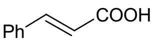
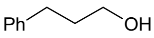
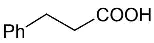
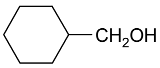
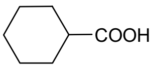
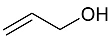
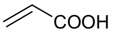
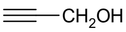
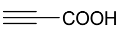
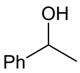
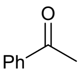
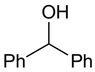
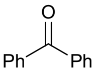
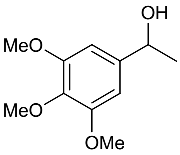
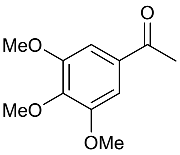
but the reaction took 12 h (entry 2). Changing the solvent from nitromethane to acetonitrile led to the acid as the major product (entry 3). Replacement of aq 70% ^{t}BuOOH by H_2O_2 reduced the yield of acid and the reaction took one day to complete (entry 5).

Surprisingly, when 70% ^{t}BuOOH was replaced with anhydrous ^{t}BuOOH (5 M in decane) all the starting material was consumed in 1 h at room temperature and the reaction afforded a 92% yield of acid and a trace amount of aldehyde (entry 8). To our surprise, the real catalyst in this reaction is ligand free CuCl. CuCl without DABCO or TEMPO or without both gave similar results (entries 6–9). However, without CuCl, the reaction produced only 20% of aldehyde after 24 h and not even a trace amount of acid was present in the reaction mixture (entry 10). Next, the reaction was screened with several other solvents and acetonitrile proved to be the best. Other solvents led to longer reaction times and gave a mixture of aldehyde and acid with poor conversion. Similarly, CuCl was the Cu salt of choice in view of the selectivity, yield and reaction rate.

To determine the scope of this new catalytic system, a wide range of alcohols were oxidized under the optimized conditions (5 mol % ligand free CuCl, 5 equiv of anhydrous *tert*-butyl hydroperoxide in acetonitrile at room temperature) and the results are summarized in Table 2. All the benzylic, allylic and propargylic primary alcohols were oxidized directly to the corresponding acids at room temperature in a very short time (1–6 h) with almost quantitative conversion and excellent isolated yields. Heteroatom-containing primary alcohols such as furan-2-ylmethanol gave a 90% yield of furan-2-carboxylic acid at room temperature (entry 7). However, pyridin-2-ylmethanol needed refluxing conditions and 7 equiv of ^{t}BuOOH for the direct oxidation (entry 8). Benzylic diols yielded the corresponding dicarboxylic acids at room temperature with good yields when 14 equiv of ^{t}BuOOH was used (entries 9 and 10). Benzylic secondary alcohols were quantitatively oxidized to the corresponding ketones at room temperature (entries 16–19). Aliphatic primary alcohols such as *n*-octanol and *n*-decanol were not oxidized even at elevated temperature. To our surprise, 3-phenylpropan-1-ol and cyclohexylmethanol were oxidized to the corresponding acids at room temperature in 91% and 87% isolated yields, respectively (entries 11 and 12). Similarly, cyclohexanol (aliphatic secondary alcohol) was converted to the corresponding ketone in 76% yield. Importantly, we were able to selectively oxidize benzylic, allylic primary and secondary alcohols in the presence of aliphatic primary alcohols such as *n*-octanol and *n*-decanol.[13] When the substrate is a diol, having both primary and secondary benzylic alcohol groups, under the optimized conditions both alcoholic groups oxidized to give the corresponding keto acid as the major product (entry 20).

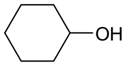
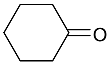
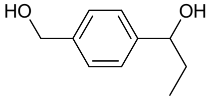
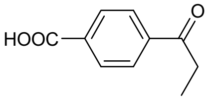
In view of the mechanism of this direct oxidation, we assume that the primary alcohol is oxidized to the aldehyde and the resulting aldehyde is further oxidized to the acid. We assume that initially copper(I) will be oxidized to copper(II) by ^{t}BuOOH and hydroperoxide homolysis is catalyzed by the copper salt. However, detailed mechanistic studies of this reaction and increasing the catalytic activity

Table 2
CuCl catalyzed alcohol oxidation with *tert*-butyl hydroperoxide in acetonitrile at room temperature[a]

Entry	Alcohol	Product	Time (h)	Isolated yield (%)
1	Ph–CH_2OH	Ph–COOH	6	92
2			2	88[b]
3			5	89[c]
4			1	93
5			4	90[c]
6			5	91
7			5	90
8			6	82[d]
9			6	83[e]
10			6	85[e]
11			5	86[f]
12			3	91
13			6	87
14			4	75
15			5	93
16			3	93
17			2	96
18			2.5	91

(*continued on next page*)

Table 2 (*continued*)

Entry	Alcohol	Product	Time (h)	Isolated yield (%)
19			4	76
20			1.5	82

[a] All reactions were carried out with 5 mol % of CuCl and 5 equiv of ^{t}BuOOH (5 M in decane) in MeCN at rt unless otherwise mentioned. All the products gave satisfactory spectral data.[14]

[b] 5% Aldehyde isolated.

[c] 2% Aldehyde isolated.

[d] Refluxing conditions and 7 equiv of ^{t}BuOOH (5 M in decane) were required.

[e] 14 equiv of ^{t}BuOOH (5 M in decane) was used. The reaction provided a 10% yield of the mono acid as well.

[f] The reaction produced a 5% yield of benzoic acid.

towards the oxidation of aliphatic alcohols such as *n*-octanol and *n*-decanol are under study.

In conclusion, we have developed a new procedure for the direct oxidation of primary alcohols to acids using a catalytic amount of CuCl and anhydrous ^{t}BuOOH (5 M in decane) in acetonitrile under very mild conditions. Secondary benzylic alcohols were also oxidized to the corresponding ketones efficiently using CuCl at room temperature. Benzylic alcohols are more reactive than aliphatic alcohols and these benzylic alcohols can be oxidized to the corresponding acids in the presence of aliphatic alcohols such as *n*-octanol and *n*-decanol. This procedure is very simple and works efficiently without any additives.

Acknowledgements

We thank DST, New Delhi (SERC Fast Track Research Project No.: SR/FTP/CS-19/2004) for the financial support. S.M. thanks CSIR for a Junior Research Fellowship.

References and notes

1. March, J. *Advanced Organic Chemistry; Reaction, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, 1992.
2. (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39; (b) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548; (c) Millar, J. G.; Oehlschlager, A. C.; Wong, J. W. *J. Org. Chem.* **1983**, *48*, 4404.
3. Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.
4. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
5. Berkowitz, L. M.; Rylander, P. N. *J. Am. Chem. Soc.* **1958**, *80*, 6682.
6. Varma, R. S.; Hogan, M. E. *Tetrahedron Lett.* **1992**, *33*, 7719.
7. (a) Murahashi, S. I.; Naota, T.; Hirai, N. *J. Org. Chem.* **1993**, *58*, 7318; (b) Hongbing, J.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2002**, *43*, 7179.
8. Noureldin, N. A.; Donald, G. L. *J. Org. Chem.* **1982**, *47*, 2790.
9. (a) Nooy, A. E. J. de.; Besemer, A. C.; Bekkum, H. V. *Synthesis* **1996**, 1153; (b) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559; (c) Tashino, Y.; Togo, H. *Synlett* **2004**, 2010; (d) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332; (e) Rychnovsky, S. D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, *64*, 310; (f) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564; (g) Zhao, M.; Li, J.; Song, Z.; Tschaen, D. M.; Mano, E. *Org. Synth.* **2005**, *81*, 195.
10. (a) Sato, K.; Aoki, M.; Tagaki, J.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 12386; (b) Sato, K.; Tagaki, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* **1998**, *39*, 7549.
11. Salen–Cu(II) complex (synthesized by three steps) was used as catalyst with H_2O_2 at 80 °C. Velusamy, S.; Punniyamurthy, T. *Eur J. Org. Chem.* **2003**, 3913.
12. Sekar, G.; Sreedevi, M.; Alamsetti, S. K. *Adv. Synth. Catal.* **2007**, *349*, 2253.
13. When a mixture of *p*-methoxybenzyl alcohol and *n*-octanol (1 mmol each) was reacted with 5 mol % CuCl and 5 mmol of 5 M ^{t}BuOOH in CH_3CN for 1 h, *p*-methoxybenzyl alcohol was fully consumed and produced a 92% isolated yield of the corresponding carboxylic acid and *n*-octanol was left intact. Similarly, allylic and propargylic alcohols were selectively oxidized over aliphatic alcohols.
14. *Typical experimental procedure*: To a solution of CuCl (4.95 mg, 0.05 mmol) in 2 mL of CH_3CN and *p*-methoxybenzyl alcohol (138.16 mg, 1 mmol) was slowly added ^{t}BuOOH (1.23 mL, 5 mmol, 5 M solution in decane). The resulting mixture was stirred at room temperature until the disappearance of starting material (observed by TLC). After completion of the reaction, the solvent was evaporated and to the resulting crude reaction mixture water (5 mL) was added. The pH of the reaction mixture was adjusted to 8.0–8.5 with saturated $NaHCO_3$ and was then extracted with ethyl acetate. The aqueous layer was acidified to pH 2.0 using 2 N HCl and extracted with ethyl acetate. The organic layer was concentrated and purified using silica gel column chromatography to give *p*-methoxybenzoic acid (141.6 mg, 93% yield).