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Catalytic Synthesis of Aldehydes and Ketones under Mild Conditions Using TEMPO/Oxone

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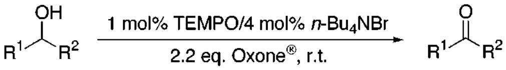
ABSTRACT



A novel, metal-free oxidation system for the catalytic synthesis of aldehydes and ketones—TEMPO/Oxone—has been developed. An optimized reaction protocol proved especially successful for the synthesis of ketones. Additionally, the influence of quarternary ammonium salts on the catalysis was studied. The mild conditions of this novel procedure were shown to tolerate even sensitive silyl protective groups which can otherwise be cleaved in the presence of Oxone.

The development of selective oxidation processes constitutes an active area of both academic and industrial research.[1] The growing number of attractive systems for alcohol oxidations includes examples such as TPAP-[2] and copper-catalyses[3] to give aldehydes or ketones,[4] and reactions with chromium[5] or tungsten[6] catalysts for the synthesis of carboxylic acids. In the area of *metal-free* catalytic alcohol oxidations TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) has emerged as the catalyst of choice, and often very low catalyst loadings are sufficient to achieve complete conversion within minutes.[7] During our program on selective oxidation reactions,[8] we recently developed a recoverable, metal-free TEMPO-based catalyst on silica-support.[9] In this system, aqueous bleach was used as terminal oxidant which is the most common one for the catalytic synthesis of aldehydes.

Within this context, we desired to replace bleach by a milder stoichiometric oxidant[10] which would allow oxidations in purely organic solvents using substrates otherwise prone to hydrolysis under the standard biphasic conditions. We therefore screened a number of different terminal oxidants under homogeneous and heterogeneous conditions and found Oxone[11] to be suitable for the prerequesites mentioned above. Its combination with TEMPO provides an efficient catalyst

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[7] For overviews and leading early contributions, see: (a) de Nooy, A. E. J.; Besemer, A. C.; Bekkum, H. V. *Synthesis* **1996**, 1153−1174. (b) Bobbit, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509−533. (c) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (d) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332−1334.

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[10] In addition, the use of aqueous bleach often leads to chlorinated byproducts which lower the yield and can make product isolation problematic.

[11] Oxone or Caroat is commercially available from DuPont or Degussa-Hüls, respectively, and has the approximate empirical formula 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

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system for the mild oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones.

Because preliminary experiments had shown that optimal catalytic performances in the oxidations of primary and secondary alcohols required different solvents, we began to investigate the influence of the solvent on the catalysis with the goal to optimize the reaction conditions for both kinds of substrates. The most significant results are summarized in Table 1.

Table 1. Solvent Dependence in the TEMPO-Catalyzed Oxidation with Oxone[a]

entry	alcohol	solvent	yield (%)[b]
1	**1**	CH_2Cl_2	90
2	**1**	toluene	83
3	**1**	THF	–
4	**1**	M*t*BE	73
5	**3**	CH_2Cl_2	34
6	**3**	toluene	91
7	**3**	THF	17
8	**3**	M*t*BE	61
9	**5**	CH_2Cl_2	67[c]
10	**5**	toluene	35[c]
11	**6**	CH_2Cl_2	9[c]
12	**6**	toluene	56[c]

[a] Reactions were carried out as a 0.2 M solution of alcohol in the corresponding solvent using catalytic amounts of *n*-Bu_4NBr. [b] Yield referring to isolated amount of product after column chromatography. [c] Yield determined by GC.

Interestingly, in some solvents such as toluene, secondary alcohols reacted even more efficiently than their primary counterparts, resulting in higher yields of the corresponding carbonyl compound.[12] This observation was quite unexpected since it is known that TEMPO usually oxidizes primary alcohols preferentially.[13,14]

In THF, benzyl alcohol (**1**) did not react at all, and acetophenone (**4**) was formed from 1-phenylethanol (**3**) in low yield (entries 3, 7). Experiments with methyl *tert*-butyl ether (M*t*BE) showed that ethereal solvents are suitable for TEMPO/Oxone oxidations though only moderate product yields were obtained (entries 4, 8). Finally, it was found that primary alcohols were best oxidized in dichloromethane while the oxidation of secondary alcohols proceeds with higher ketone yield in toluene. Aliphatic substrates such as 1-nonanol (**5**) and 2-nonanol (**6**) showed the same trend but performed somewhat less efficiently, giving the products in up to 67% and 56% yield, respectively.

Rychnovsky and Vaidjanathan have demonstrated that a combination of TEMPO and *m*-CPBA is very effective for the oxidation of secondary alcohols, and they have also studied the dependence of the catalysis on the presence of various halide ions.[15] They revealed that in their system tetrabutylammonium bromide[16] was the best additive for the oxidation of 2-octanol to 2-octanone and proposed that this effect was due to the formation of hypobromous acid and subsequent oxidation of TEMPO to an *N*-oxoammonium bromide.[17]

We therefore tested several quarternary ammonium salts as additives in the TEMPO/Oxone oxidation and also found a strong influence of the halide on the efficiency of the catalysis (Table 2).[18] Interestingly, the effectiveness of the additive was highly substrate dependent. For example, iodide and bromide had a pronounced beneficial effect on the product yield in the oxidation of **3** (entries 9, 10), while employing chloride led to low yields (entries 8, 11). Contrary, the catalytic oxidation of **1** was most efficient when chloride was present. Furthermore, only tetrabutylammonium chloride was useful as halide source (entry 2), whereas addition of benzyltributylammonium chloride led to a significant reduced yield (entry 5). This was also true in oxidations of **3**, which showed a similar behavior. At present, the reason for this dependence of the catalytic efficiency on the kind of ammonium ion remains unclear, and it seems that benzyl-

Table 2. Influence of the Use of Quarternary Ammonium Salts on the TEMPO-Catalyzed Oxidation with Oxone

entry	alcohol	solvent	additive[a]	yield (%)[b]
1	**1**	CH_2Cl_2	Bu_4NF	–
2	**1**	CH_2Cl_2	Bu_4NCl	92 (6)[c]
3	**1**	CH_2Cl_2	Bu_4NBr	90 (9)[c]
4	**1**	CH_2Cl_2	Bu_4NI	18
5	**1**	CH_2Cl_2	$BnBu_3NCl$	23
6	**1**	CH_2Cl_2	Bu_4NSCN	–
7	**3**	toluene	Bu_4NF	–
8	**3**	toluene	Bu_4NCl	28 (<5)[c]
9	**3**	toluene	Bu_4NBr	91 (18)[c]
10	**3**	toluene	Bu_4NI	91
11	**3**	toluene	$BnMe_3NCl$	13
12	**3**	toluene	Bu_4NSCN	–

[a] In each run 2 mol % of additive were used. [b] Yield referring to isolated amount of product after column chromatography. [c] Yields in parentheses refer to control experiments without TEMPO.

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(12) This result is not due to overoxidation of the aldehydes to their corresponding carboxylic acids.

(13) See reference 7a. For a recent report on the oxidation of primary alcohols to the corresponding carboxylic acids using TEMPO, see: Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.

(14) For selected examples on oxidations of secondary alcohols to ketones, see: (a) Cella, J. A.; Kelley; J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860–1862. (b) Cella, J. A.; McGrath, J. P.; Kelley, J. A.; ElSoukkary, O.; Hilpert, L. *J. Org. Chem.* **1977**, *42*, 2077–2080. (c) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462–466. (d) Banwell, M. G. Bridges, V. S.; Dupuche, J. R.; Richards, S. L., Walter, J. M. *J. Org. Chem.* **1994**, *59*, 6338–6343. (e) Drauz, K.; Kottenhahn, M.; Stingel, K. US Patent 5631385. (f) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Pincatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977. (g) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 1591–1592 and references therein.

(15) Rychnovsky, S. D.; Vaidjanathan, R. *J. Org. Chem.* **1999**, *64*, 310–312.

(16) Chloride ion proved also successful probably due to the formation of the corresponding hypochlorous acid.

(17) The presence of acids inhibited the catalysis.

(18) Control experiments revealed that in the absence of TEMPO aldehydes and ketones were also formed though in low yield. Without ammonium salt no oxidation was observed.

tributylammonium chloride is generally not applicable in the TEMPO/Oxone oxidation.

As expected, fluoride and thiocyanate gave no detectable oxidation product.

With these optimized conditions[19] in hand, we tested the scope of this process and a number of primary and secondary alcohols were oxidized with TEMPO/Oxone and tetrabutylammonium bromide as additive. Table 3 summarizes the results.

Table 3. TEMPO-Catalyzed Oxidation of Various Primary and Secondary Alcohols Using Oxone as Terminal Oxidant

entry	alcohol	solvent	yield (%)[b]
1	**1**	CH_2Cl_2	90
2	**3**	toluene	91
3	**5**	CH_2Cl_2	67[a]
4	**6**	toluene	56[a]
5	1,2,3,4-tetrahydro-1-naphthol	toluene	96
6	1-phenylpropanol	toluene	93
7	1-cyclohexylethanol	toluene	71
8	4-methoxybenzyl alcohol	CH_2Cl_2	37

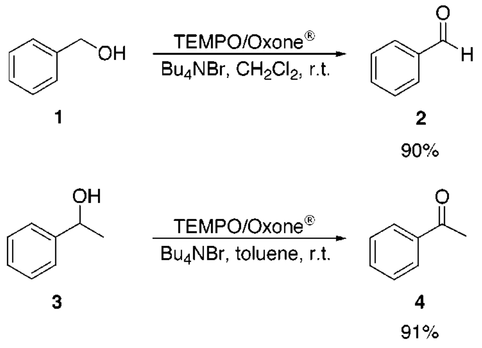
[a] The yield was determined by GC. [b] Yield referring to isolated amount of product after column chromatography.

Benzylic secondary alcohols gave high yields of the corresponding ketones. In addition, 1-cyclohexylethanol was also oxidized in good yield (entry 7), while other aliphatic alcohols regardless of the position of the hydroxyl functionality were oxidized with lower yield: for example, nonanal was obtained from 1-nonanol (**5**) in 67% yield and oxidation of 2-nonanol (**6**) provided the ketone in 56%. In contrast to the high yielding synthesis of benzaldehyde (**2**) from benzyl alcohol (**1**) (entry 1), oxidation of the more electron-rich 4-methoxybenzyl alcohol afforded 4-methoxybenzaldehyde in only 37% yield.

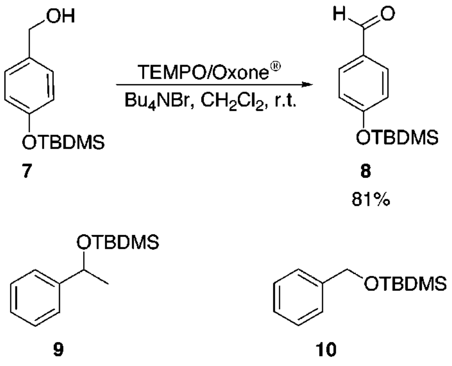
Recently, Sabitha and co-workers reported an Oxone-mediated deprotection of phenolic and benzylic TBDMS-ethers under mild conditions.[20] They also found that silyl-protected hydroxy groups in the benzylic position could be cleaved in the presence of phenolic TBDMS-ethers.

To establish whether TBDMS-ethers were stable under the novel oxidation procedure, we subjected benzyl alcohol **7** bearing a phenolic TBDMS-ether moiety, and the TBDMS-protected benzyl alcohols **9** and **10** to the TEMPO/Oxone oxidation conditions (Scheme 2). In all three cases the ether linkage remained intact, and only **7** was oxidized to the corresponding aldehyde **8** in 81% yield.

Scheme 1



Scheme 2



In summary, we have demonstrated that the combination of TEMPO and Oxone is an efficient system for the oxidation of alcohols to aldehydes and ketones. The performance of the catalyst is largely influenced by the presence of quarternary ammonium salts, and the addition of tetrabutylammonium bromide proved useful for the oxidation of most substrates. Furthermore, the reaction conditions of the TEMPO/Oxone system are much milder than those with previously reported stoichiometric oxidants which results in an improved functional group tolerance avoiding overoxidation to the corresponding carboxylic acids.

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(19) **Representative procedure:** To a solution of the alcohol (1 mmol) and Bu_4NBr (4 mol %, 0.04 mmol) in 5 mL of the indicated solvent is added TEMPO (1 mol %, 0.01 mmol, 0.1 M solution of the indicated solvent) and Oxone (2.2 equiv, 2.2 mmol). The mixture is then stirred for 12 h at room temperature, and the reaction is monitored by TLC. After the rection is complete, the solvent is removed under reduced pressure, and the remaining solid is purified by column chromatography (silica gel, hexanes/ethyl acetate: 10/1).

(20) Sabitha, G.; Syamala, M.; Jadav, J. S. *Org. Lett.* **1999**, *1*, 1701–1703.