TEMPO-Catalyzed Oxidations of Alcohols Using *m*-CPBA: The Role of Halide Ions

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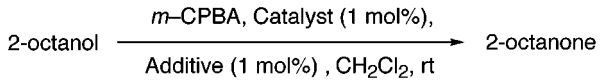
Received September 18, 1998

Nitroxyl radical catalyzed oxidations of alcohols play an increasingly important role in organic synthesis.[1] Desirable characteristics of these oxidations include the use of 1 mol % or less of the catalyst and only 1 equiv of the bulk oxidant and good selectivity for primary alcohols. Many different bulk oxidants have been used in this reaction including *m*-CPBA,[2,3] sodium hypochlorite,[4] *N*-chlorosuccinimide,[5] sodium bromite,[6] [bis(acetoxy)iodo]-benzene,[7] high-valent metal salts,[8] and electrooxidation.[1,9] The TEMPO-bleach oxidation developed by Anelli is the most useful for large-scale oxidations,[4] although it does not work well with unsaturated alcohols. Our interest was drawn to the TEMPO-catalyzed *m*-CPBA oxidations[2,3] when we observed an unprecedented racemization of a chiral nitroxyl radical under similar conditions.[10] The results of our investigation are reported below.

The development of nitroxyl radical catalyzed peracid oxidations arose from Cella's report of an unexpected alcohol oxidation.[2c] Cella found that the reaction was catalyzed by HCl and developed a convenient oxidation procedure using *m*-CPBA and 2,2,6,6-tetramethylpiperidinium hydrochloride (TMP·HCl) as the catalyst precursor.[2a] The HCl was reported to act as a general acid catalyst to facilitate the oxidation of the nitroxyl radical to an *N*-oxo ammonium salt, the ultimate oxidant in the catalytic cycle.[1] Although the reaction was reported to be catalyzed by mineral acids, HCl was the only acid investigated.

Table 1 outlines our initial investigation of the oxidation reaction. A solution of *m*-CPBA (1.2 equiv) and 2-octanol was allowed to react with 1 mol % of the catalyst and additive shown for 2 h at 23 °C, and the conversion to 2-octanone was determined by GC analysis. TEMPO and *m*-CPBA together led to 54% conversion under these conditions (Table 1, entry 1). Tetramethylpiperidine (TMP), a catalyst precursor, gave a 66% conversion with *m*-CPBA (Table 1, entry 2). Surprisingly, the addition of camphorsulfonic acid (CSA) as an additive reduced the conversion to only 6% (Table 1, entry 4).[11] Addition of 5 mol % trifluoroacetic acid also inhibited the reaction. The TMP·HBr salt, on the other hand, led to 100% conversion without any additives (Table 1, entry 3). Clearly the reaction is not catalyzed by acid, but the counterion is implicated.

Table 1. Effect of additives on *m*-CPBA/TEMPO Oxidations of 2-octanol[a]



entry	catalyst	additive	conversion (%)
1[b]	TEMPO	None	54
2	TMP	None	66
3	TMP·HBr	None	100
4[b]	TEMPO	CSA	6
5[b]	TEMPO	Bu_4NPF_6	70
6[b]	TEMPO	Bu_4NOTf	73
7[b]	TEMPO	Bu_4NOTf, CSA	5
8	None	Bu_4NCl	6
9	TEMPO	Bu_4NCl	92
10	None	Bu_4NBr	8
11	None	Bu_4NBr, CSA	5
12	TEMPO	Bu_4NBr	100
13	TEMPO	Bu_4NBr, CSA	100

[a] See the Experimental section for reaction conditions. [b] The control reaction without TEMPO led to <1% conversion.

The effect of redox-inert counterions is outlined in entries 5−7 of Table 1. Without TEMPO, none of the reactions show any significant conversion. TEMPO-catalyzed oxidation in the presence of PF_6^- or OTf^- leads to a slightly higher conversion than in the presence of TEMPO alone (Table 1, entries 5 and 6 vs entry 1). Once again, added CSA strongly inhibits the oxidation, reducing the conversion from 73% to only 5% (Table 1, entry 6 vs 7). Inert counterions have little effect on the oxidation.

Redox-active counterions have a profound effect on the oxidation reaction. Addition of 1 mol % Bu_4NCl increased the conversion from 54% to 92% (Table 1, entry 9). Addition of 1 mol % Bu_4NBr increased the conversion to 100% (Table 1, entry 12). In this case, addition of CSA had no effect (Table 1, entry 13). Both Bu_4NCl and Bu_4NBr gave a small amount of oxidation even without the TEMPO catalyst (Table 1, entries 8 and 10). These slow background oxidations are akin to the phase-transfer oxidations of alcohols using hypochlorite solutions.[12] Both bromide and chloride catalyze the TEMPO-mediated oxidation of alcohols with *m*-CPBA.

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(11) Use of 5 mol % trifluoroacetic acid with *m*-CPBA and TEMPO did not lead to oxidation. However, TFA with *m*-CPBA, TEMPO and Bu_4NBr led to complete oxidation.

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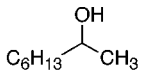
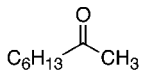
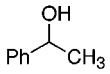
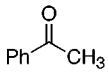
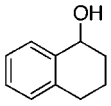
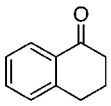
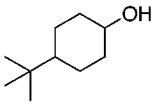
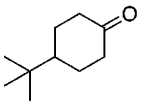
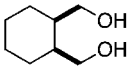
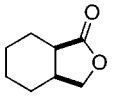
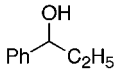
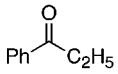
10.1021/jo9819032 CCC: $18.00
Published on Web 12/17/1998

Table 2. Oxidation of Alcohols with *m*-CPBA Catalyzed by TEMPO and Bu_4NBr[a]

Entry	Substrate	Product	Yield (%)[b]
1			92
2			91
3			97
4			94
5[d]			89[c]
6[e]			98

[a] Consult the Experimental Section for reaction conditions. Unless otherwise noted, all reactions were performed on a 10-mmol scale with 1 mol % TEMPO and 1 mol % Bu_4NBr. [b] Yields are based on the weight of pure product. [c] The yield was adjusted to reflect 94% GC purity of the product. [d] Reaction was carried out on a 5-mmol scale; 2.4-mol equiv of *m*-CPBA was used. [e] TMP·HBr (1 mol %) was used instead of TEMPO and Bu_4NBr.

Discussion

General acids inhibit rather than catalyze the oxidation of secondary alcohols with *m*-CPBA and TEMPO.[11] Both bromide and chloride anions catalyze the oxidation, and bromide is more effective than chloride. These conclusions are related to Anelli's observation that the TEMPO-bleach oxidations are catalyzed by bromide ion. Anelli explained that the bromide is oxidized to hypobromous acid by the hypochlorite solution and that the hypobromous acid rapidly oxidizes the nitroxyl radical to the ultimate oxidant, an *N*-oxo ammonium ion. Presumably the Bu_4N**Br** or TMP·H**Br** in the present reactions leads to the formation of hypobromous acid, which oxidizes the nitroxyl radical to *N*-oxo ammonium ion. In Cella's catalyst system, TMP·HCl is the source of both TEMPO and the HCl cocatalyst. The role of the HCl is not as an acid catalyst, but rather it is a source of hypochlorous acid, which oxidizes TEMPO to the *N*-oxo ammonium ion. For efficient oxidations, both a nitroxyl radical and a halide ion should be present.

Two new procedures for the oxidation of alcohols to ketones have been developed. Both are modifications of Cella's procedure. A catalyst composed of 1 mol % TEMPO and 1 mol % Bu_4NBr led to rapid oxidation of alcohols to ketones. Table 2, entries 1−5, show that this catalyst system gave a nearly quantitative yield in the oxidation reaction.[13] An alternative is to use 1 mol % of TMP·HBr as a catalyst. The bromide ion is a more efficient counterion than Cella's TMP·HCl, and unlike the hydrochloride, TMP·HBr is nonhygroscopic.[14] Table 2, entry 6, shows that TMP·HBr and *m*-CPBA together constitute an effective oxidant system for the conversion of alcohols into ketones.

(13) The oxidation was not effective with unsaturated alcohols.

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Conclusions

Nitroxyl radicals catalyze peracid oxidations of alcohols. Bromide and chloride ions are effective as cocatalysts, whereas general acids inhibit the oxidation. Inert counterions have almost no effect on the oxidation. Two new catalysts were found to be effective in this transformation: TEMPO with Bu_4NBr or TMP·HBr. Both of these catalysts lead to rapid and efficient oxidations of secondary alcohols to ketones.

Experimental Section

General Experimental. All reagents were purchased from Aldrich Chemical Co. or Acros and were used as received, unless otherwise stated. TMP·HBr was prepared as described by Collum.[14]

Oxidation of 2-Octanol under Various Conditions. A 20-mL vial was charged with 1.5 mL of a CH_2Cl_2 solution containing 0.5 mmol of 2-octanol, 0.005 mmol of the appropriate catalyst, and 0.005 mmol of the appropriate additive. A solution of 0.6 mmol of *m*-CPBA in 1.0 mL of CH_2Cl_2 was added dropwise, and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of 1 N NaOH. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, passed through a plug of SiO_2, and analyzed by GC.

General Procedure for the Oxidation of Secondary Alcohols Using TEMPO and Bu_4NBr. A 100-mL flask was charged with a solution of 10 mmol of the alcohol, 0.1 mmol of TEMPO, and 0.2 mmol of Bu_4NBr in 25 mL of CH_2Cl_2 and cooled to 0 °C. A solution of *m*-CPBA (12 mmol) in 20 mL of CH_2Cl_2 was added dropwise over a period of 15 min. The reaction mixture turned bright orange upon addition of *m*-CPBA. The reaction was stirred at 0 °C for 10 min and at 23 °C for 30 min, by which time the orange color had faded away. The reaction was quenched by the addition of 1 N NaOH (20 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated, and the residue was chromatographed.

Oxidation of *cis*-Cyclohexane-1,2-dimethanol. A 100-mL flask was charged with a solution of 5 mmol of the diol, 0.1 mmol of TEMPO, and 0.2 mmol of Bu_4NBr in 25 mL of CH_2Cl_2 and cooled to 0 °C. A solution of *m*-CPBA (12 mmol) in 20 mL of CH_2Cl_2 was added dropwise over a period of 15 min. The reaction mixture turned bright orange upon addition of *m*-CPBA. The reaction was stirred at 0 °C for 10 min and at 23 °C for 30 min, by which time the orange color had faded away. The reaction was quenched by the addition of 0.25 M Na_2SO_3 (10 mL) and saturated $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated, and the residue was chromatographed.

Oxidation of Secondary Alcohols Using TMP·HBr. A 100-mL flask was charged with a solution of 10 mmol of the alcohol and 0.1 mmol of TMP·HBr in 25 mL of CH_2Cl_2 and cooled to 0 °C. A solution of *m*-CPBA (12 mmol) in 20 mL of CH_2Cl_2 was added dropwise over a period of 15 min. The reaction mixture turned bright orange upon addition of *m*-CPBA. The reaction was stirred at 0 °C for 10 min and at 23 °C for 30 min, by which time the orange color had faded away. The reaction was quenched by the addition of 0.25 M Na_2SO_3 (10 mL) and saturated $NaHCO_3$ (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The

combined organic layers were washed with saturated $NaHCO_3$ (2×20 mL), brine (2×20 mL), dried (Na_2SO_4), filtered, and concentrated, and the residue was chromatographed.

Oxidation Products. Simple ketones and lactones obtained by oxidation were characterized by the usual techniques (^1H NMR, ^{13}C NMR, GC) and compared with literature data.

Acknowledgment. Support has been provided by the University of California, Irvine. S.D.R. acknowledges Pfizer and Zeneca for support of his research program.

JO9819032