



0040-4039(94)00907-4

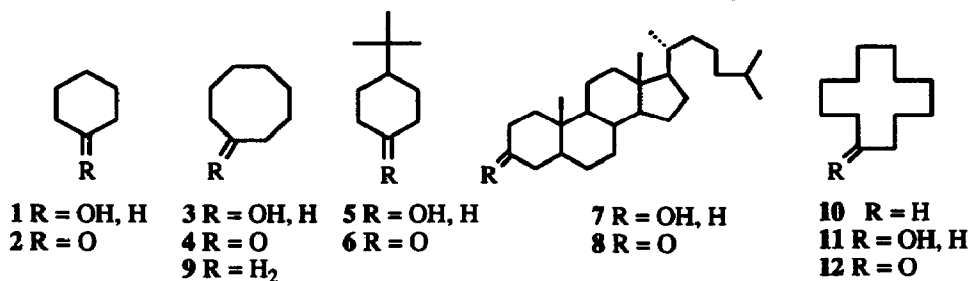
Studies on the Oxidation of Alcohols Employing *t*-Butyl Hydroperoxide (TBHP) and Fe(III) Catalysts.

Derek H. R. Barton,* Stéphane D. Bévière, Béatrice M. Chabot, Warinthorn Chavasiri, and Dennis K. Taylor.

Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA.

Abstract: New methodology for the oxidation of alcohols to ketones in good yield utilizing catalytic amounts of Fe^{III} salts and TBHP as the oxidant is highlighted. Competition between alcohol and hydrocarbon oxidation has been clearly demonstrated. The "normal" Gif-type solvent system (pyridine / acetic acid) can be replaced by the alcohol itself.

Systems composed of an Fe(III) salt suspended in a mixture of pyridine / acetic acid in the presence of an extra ligand (generally picolinic acid) and utilizing TBHP as an oxidant have recently been added to the arsenal of Gif-type oxidative reactions.^{1,2} These systems oxidise saturated hydrocarbons to produce ketones as the major component. The amount of oxidised products and the ratio of ketone / alcohol was found to be superior than in earlier Gif-type oxidative reactions.¹ Although the regio- and chemoselectivity was typical of earlier Gif-type oxidations,¹ the adamantane selectivity ($C^2/C^3 \approx 0.7$)^{1,3} and kinetic isotope effect (8.0 ± 0.3)^{4,5} of this system was found to be distinctly different from systems employing H₂O₂ as the oxidant ($C^2/C^3 \approx 1.1$, KIE = 2.2 ± 0.1).³⁻⁵



During the course of investigating the reaction pathway for the functionalization of saturated hydrocarbons by the Fe(III) / TBHP systems, we observed that besides the normal oxidation of saturated hydrocarbons, alcohols could also be transformed into the corresponding ketones in good yield. This is in contrast to the Fe(II) / Zn⁰ / O₂ (Gif^{IV}), Fe(III) / H₂O₂ (GoAgg^{II}) and Fe(III) / picolinic acid / H₂O₂ (GoAgg^{III}) Gif-type oxidative systems. This paper deals with the synthetic utility of the Fe(III) / TBHP system for oxidation of alcohols to ketones.

Control experiments revealed that in the absence of an Fe^{III} catalyst or an oxidant, only 1-3% of ketone was detected. The rate of the oxidation reaction was found to be dependent on the Fe^{III} catalyst. For instance, the use of FeCl₃·6H₂O, Fe(NO₃)₃·9H₂O, Fe(acac)₃, FeBr₃ and Fe(ClO₄)₃ as catalysts revealed large differences in the half-lives for the conversion of cyclooctanol into cyclooctanone. These half-life values were found to vary from 0.5 to 2, 4, 4 and 5 days, respectively. Acceleration of the reaction could be achieved upon the addition of picolinic acid to the system. Thus, the addition of 3 equivalents of picolinic acid to the system containing Fe(NO₃)₃·9H₂O as a catalyst decreased the half-life sharply from 2 days to 8 min giving the same overall yield of ketone. Some selected examples of the oxidation of alcohols under these conditions are shown in Table 1.

Table 1. The oxidation of selected alcohols by the Fe(III) / TBHP system.^a

Entry	Alcohol (mmol)	Product (%) ^b	
		2	1
1	1 (2.0)	2 (91.7)	1 (5.6) ^c
2	3 (2.0)	4 (78.8)	3 (21.8) ^c
3 ^d	5 (2.0)	6 (85.1) ^c	—
4 ^d	7 (2.0)	8 (78.5) ^c	—

^a Employing Fe(NO₃)₃·9H₂O (0.5 mmol), picolinic acid (1.5 mmol) and TBHP. (5 mmol), See typical experiment; ^b Based on substrate; ^c Recovered substrate; ^d Using TBHP (10 mmol); ^e Isolated yield.

The results of competition studies between cyclooctane **9** and cyclohexanol **1** toward the Fe(III) / TBHP oxidation reaction are shown in Table 2. It was clearly observed that the activation of the process remained constant. Increasing the alcohol **1** / hydrocarbon **9** ratio in the oxidation system resulted in a corresponding decrease in the amount of oxidized products from cyclooctane **9** (Entries 1 and 2).

Table 2. Competitive oxidation of cyclooctane **9** / cyclohexanol **1** and cyclododecane **10** / cyclohexanol **1** under Fe(III) / TBHP conditions.^a

Entry	Substrate (mmol)	Products (mmol)				Σ products (mmol)
		4	3	1 ^b	2	
1	9 (10) + 1 (10)	1.00	0.12	6.34	4.24	5.36
2	9 (38) + 1 (10)	2.55	0.38	6.93	2.84	5.77
3	1 (10)	—	—	4.26	5.02	5.02
4	9 (10)	3.84	0.43	—	—	4.27
		12	11	1^b	2	
5	10 (5.0)	1.30	0.05	—	—	1.35
6	10 (5.0) + 1 (2.0)	0.99	0.14	0.78	1.26	2.39
7	10 (5.0) + 1 (5.0)	0.77	0.10	2.41	2.62	3.49
8	10 (5.0) + 1 (10)	0.62	0.12	5.58	3.78	4.52

^a Employing Fe(NO₃)₃·9H₂O (0.5 mmol), picolinic acid (1.5 mmol) and TBHP. (5 mmol), reaction time = 10hr, See typical experiment ; ^b Recovered substrate.

Although it is conceivable that the hydrocarbon activation and alcohol oxidation processes result from two different iron species in solution, it is also possible that the oxidation of the saturated hydrocarbon and that of the alcohol depend upon the same high-valent Fe species. At a first consideration it is surprising that the oxidation of saturated hydrocarbons can compete with that of secondary alcohols. However, if the competition is expressed per hydrogen actually involved then the facts are different. Per hydrogen Entries 1 and 2 (Table 2) show a relative reactivity of 70 and 60 respectively in favour of the cyclohexanol whilst for the two separately (Entries 3 and 4) the ratio is about 70.

The results of competition studies between cyclododecane 10 and cyclohexanol 1 oxidation are also depicted in Table 2. Increasing the amount of alcohol 1 present in solution once again increases the amount of ketone 2 observed at the expense of alkane oxidation with approximately the same relative reactivity per hydrogen.

Recently, it was demonstrated that oxidation of saturated hydrocarbons with soluble Fe^{III} chelates can be achieved by replacing the traditional solvent system (pyridine / acetic acid) by the hydrocarbon itself.² The same was also found to be true for the oxidation of alcohol 1 to ketone 2 as displayed in Table 3. Oxidation of alcohol 1 using Fe(acac)₃ as the catalyst (Entries 1-3) was found to proceed with high efficiencies (Entries 1 and 3) when the temperature was elevated to 70°C.

Table 3: Oxidation of Cyclohexanol Employing Iron(III) Catalysts.^a

Entry	Catalyst ^b	TBHP ^c (mmol)	Temp. (°C)	Time (hr)	Cyclohexanol (mmol)	Cyclohexanone (mmol)	Effic. ^d (%)
1	Fe(acac) ₃	10	70	24	42.07	9.35	98
2	Fe(acac) ₃	50	25	72	28.11	20.28	55
3	Fe(acac) ₃	50	70	72	15.17	34.82	89
4	Fe(PA) ₃	10	70	15	40.61	8.07	81
5	Fe(PA) ₃ ^e	10	25	15	40.83	9.22	92
6	Fe(PA) ₃	50	25	72	10.83	38.12	77
7	Fe(fod) ₃	10	25	24	48.36	1.39	45
8	Fe(fod) ₃ ^e	10	25	24	39.11	9.39	99
9	Fe(fod) ₃	50	25	72	23.25	25.62	67
10	Fe(fod) ₃	10	70	24	39.3	9.42	94

^a All experiments employed 1 (50 mmol) in air; ^b Fe(acac)₃ = Iron(III)tris(acetylacetonate), Fe(PA)₃ = Iron(III)tris(picolinate), Fe(fod)₃ = Iron(III)tris(2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionate), Amount of Fe(III) catalyst employed in each case (0.2 mmol), except entry 2 (1.0 mmol) and entries 4,5 and 7 (0.5 mmol); ^c For reactions employing 50 mmol, the TBHP was added in five portions (1.1 mL) every 3 hours; ^d Calculated efficiency based on oxidant consumed assuming that one mole of oxidant gives one mole of ketone; ^e Reaction carried out in the presence of pyridine (2 mL).

In contrast, Fe(PA)₃ (Entries 4-6) yielded superior oxidative conversions and efficiencies over shorter reaction times. Addition of pyridine (2 mL) (Entry 5) further accelerated the reaction allowing the oxidation to proceed smoothly at room temperature. Elevated temperatures or the addition of pyridine also accelerated the oxidation of 1 when the catalyst Fe(fod)₃ was employed (Entries 7-10), however the overall oxidative conversion was lower.

Less oxidation and substantially lower efficiencies were noted when *tert*-butanol was added to the reaction mixture, while the addition of extra catalyst and TBHP after several days led to small amounts of over-oxidation with the formation of adipic acid.⁶

The oxidation of alcohols to the corresponding carbonyl compounds is well known to be achieved by employing high-valent metal complexes.⁷ The mechanistic pathway of the alcohol oxidation under Fe(III) / TBHP conditions was therefore conceived to take place via a high-valent iron species (formally $V\text{Fe}=\text{O}$). This high-valent $V\text{Fe}$ oxenoid species subsequently reacts with the alcohol before collapsing to the final carbonyl compounds with concomitant reduction of the iron, regenerating Fe^{III}.

Typical procedure for the oxidation of alcohols by the Fe(III) / TBHP system. To a solution of pyridine (30 ml) and acetic acid (3 ml) containing Fe(NO₃)₃·9H₂O (202 mg, 0.5 mmol), picolinic acid (78 mg, 0.6 mmol) and cyclooctanol 3 (256 mg, 2 mmol) was added *tert*-butyl hydroperoxide (1.1 ml, 10 mmol). The reaction was stirred at room temperature for 1-2 h and subjected to the usual work-up.^{1,8} The amount of the desired product was quantified by GLC or purification by recrystallization. For oxidations employing no pyridine / acetic acid the reactions were simply stirred in air according to the conditions outlined in table 3.

Acknowledgements. We are indebted to the National Science Foundation, British Petroleum and Quest International for financial support of this work. We thank Dr. Dario Doller and Dr. David R. Hill for their help in earlier stages of this work.

References and notes.

1. Barton, D. H. R.; Chavasiri, W. *Tetrahedron*, **1994**, *50*, 19-30; Barton, D. H. R.; Chavasiri, W. *Tetrahedron*, **1994**, *50*, 47-60; Barton, D. H. R.; Bévière, S. D.; Chavasiri, W. *Tetrahedron*, **1994**, *50*, 31-46; Also see, Kojima, T.; Leising, R. A.; Yan, S.; Que, L. Jr. *J. Am. Chem. Soc.*, **1993**, *115*, 11328-11335; Sheu, C.; Richert, S. A.; Cofré, P.; Ross, B. Jr.; Sobkowiak, A.; Sawyer, D. T.; Kanofsky, R. R. *J. Am. Chem. Soc.*, **1990**, *112*, 1936-1942; Tung, H. C.; Kang, C.; Sawyer, D. T. *J. Am. Chem. Soc.*, **1992**, *114*, 3445-3455; Kang, C.; Redman, C.; Cepak, V.; Sawyer, D. T. *Bioorganic and Med. Chem.*, **1993**, *1*, 125-140.
2. Barton, D. H. R.; Bévière, S.; Hill, D. R. *Tetrahedron*, in press.
3. Barton, D. H. R.; Bévière, S. D.; Chavasiri, W.; Doller, D.; Hu, B. *Tetrahedron Lett.*, **1992**, *33*, 5473-5376.
4. Barton, D. H. R.; Csuhai, E.; Doller, D.; Ozbalik, N.; Balavoine, G. *Proc. Natl. Acad. Sci. U.S.A.*, **1990**, *87*, 3401-3404.
5. Barton, D. H. R.; Boivin, J.; Ozbalik, N.; Schwartzenruber, K. M. *Tetrahedron Lett.*, **1985**, *26*, 447; Barton, D. H. R.; Doller, D.; Geletii, Y. V. *Tetrahedron Lett.*, **1991**, *32*, 3811.
6. As discussed earlier the oxidation of saturated hydrocarbons can compete with that of secondary alcohols which is consistent with the formation of over-oxidized products.
7. Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidation of Organic Compounds*, Academic Press, New York, 1981, Chapter 12.
8. Barton, D. H. R.; Csuhai, E.; Ozbalik, N.; *Tetrahedron*, **1990**, *46*, 3743-3752.

(Received in USA 14 March 1994; revised 29 April 1994; accepted 6 May 1994)