

Iron-Catalyzed Oxidation of Cycloalkanes and Alkylarenes with Hydrogen Peroxide

Chiara Pavan, Julien Legros, Carsten Bolm*

Institut für Organische Chemie der RWTH Aachen, Landoltweg 1, 52056 Aachen, Germany
 Fax: (+49)-241-809-2391; e-mail: carsten.bolm@oc.rwth-aachen.de

Received: October 12, 2004; Accepted: January 24, 2005

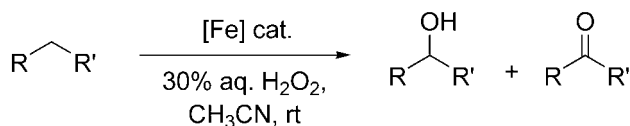
Abstract: An iron-catalyzed process for the oxidation of saturated hydrocarbons (cycloalkanes and alkylarenes) to alcohols and ketones with aqueous H₂O₂ in acetonitrile at room temperature is reported. Addition of a carboxylic acid increases the selectivity towards the ketone formation. Best results were ob-

tained with ethylbenzene as substrate and acetic acid as additive, affording acetophenone as the main product.

Keywords: C–H activation; homogeneous catalysis; hydrogen peroxide; iron; oxidation

Introduction

The synthesis of functionalized compounds, such as alcohols and ketones, *via* CH oxidation generally requires drastic conditions and non-benign oxidants and metals.^[1] Oxidation processes involving green oxidants and non-toxic metals are urgently needed. In this line, iron catalysts in combination with hydrogen peroxide^[2] are highly desirable systems to be tested and developed. In fact, many studies have been devoted towards this goal and investigations on the use of iron complexes for the oxidation of saturated hydrocarbons^[3] have been exemplified by Fenton chemistry^[4] and Gif systems,^[5] to name only two. Most reports in this area, however, focus on elucidating mechanistic and kinetic details rather than on using the catalysts for synthetic purposes. Here, we report a very simple iron-catalyzed oxidation of hydrocarbons giving alcohols and ketones under mild reaction conditions using H₂O₂ as terminal oxidant (Scheme 1).



Scheme 1.

Results and Discussion

For the first experiments, ethylbenzene was chosen as the model substrate. Its oxidation to 1-phenylethanol and acetophenone was performed at room temperature

with 30% aqueous H₂O₂ and catalytic amounts (10 mol %) of various iron complexes easily available in bulk at reasonable, or even low, prices. As suggested by previous reports,^[6] acetonitrile was used as solvent. The results of this initial metal salt screening are summarized in Table 1.

Iron(II) acetate, iron(II) acetylacetonate, iron(III) chloride, iron(II) oxalate and iron(II) bromide gave poor conversions of the starting material ($\leq 20\%$) and led to the rapid decomposition of hydrogen peroxide. In contrast, by using iron(II) chloride, iron(III) nitrate, iron(II) tetrafluoroborate and iron(II) perchlorate, more than 60% of ethylbenzene was converted into oxidized products and no significant decomposition of hydrogen peroxide was observed. Moreover, the latter iron salts showed a pronounced selectivity for the oxidation of the benzylic position ($\geq 50\%$), with acetophenone being the major product.

An important drawback of the protocol described above was the pronounced exothermicity of the reaction, which could become a severe safety issue in large-scale reactions. We presumed that the use of additives could improve the behavior and increase the efficiency of the catalytic system. In the field of iron-catalyzed oxidations, carboxylic acids have been shown to be particularly effective.^[2d,7] In the system described here, simple carboxylic acids (20 mol %), typically acetic and benzoic acid, were added to the reaction medium prior to the addition of the oxidant. The reaction became very well-behaved and the undesirable exothermicity was no longer observed. Moreover, without any decrease in conversion ($> 50\%$) the only detected benzylic oxidation product was acetophenone.^[8,9]

Acetic acid, benzoic acid and 4-nitrobenzoic acid proved to be the most effective additives for increasing

Table 1. Oxidation of ethylbenzene to acetophenone and phenylethanol.

Catalyst	Conversion ^[a] [%]	Selectivity ^[a, b] [%]	Ketone:Alcohol	TON
FeBr ₂	20	15	88:12	0.3
FeCl ₂	60	15	90:10	0.9
FeCl ₃	–	–	–	–
Fe(OAc) ₂	–	–	–	–
Fe(acac) ₂	–	–	–	–
FeC ₂ O ₄	–	–	–	–
Fe(NO ₃) ₃	63	50	83:17	3.2
Fe(BF ₄) ₂	60	59	89:11	3.5
Fe(ClO ₄) ₂	65	64	90:10	4.2

^[a] Based on substrate. Determined by GC/MS and GC analysis using nitrobenzene as internal standard.

^[b] Selectivity towards benzylic oxidation: (mmol acetophenone + mmol phenylethanol)/mmol substrate converted.

Table 2. Iron-catalyzed oxidation of saturated hydrocarbons.

Substrate	Major product	Yield ^[a] [%]	Conversion [%]	Selectivity [%]	TON
Ethylbenzene (1)	Acetophenone (6)	50	67	75	5.0
(4-Nitro)ethylbenzene (2)	(4-Nitro)acetophenone (7)	48 ^[b]	65	74	4.8
Diphenylmethane (3)	Benzophenone (8)	35 ^[b]	48	73	3.5
Cyclooctane (4)	Cyclooctanone (9)	44 ^[b]	55	80	4.4
Cyclohexane (5)	Cyclohexanol (10)	20 ^[c]	–	–	2.0
	Cyclohexanone (11)	20 ^[c]	–	–	2.0

^[a] Based on substrate.

^[b] Determined by GC analysis using internal standard.

^[c] Determined by ¹H NMR analysis.

the selectivity towards ketone formation [$>60\%$ with Fe(ClO₄)₂]. 4-Methoxybenzoic acid, on the other hand, showed a detrimental effect [only 43% with Fe(ClO₄)₂]. Since the results do not correlate with the strength of the acid (acetic acid $<$ 4-methoxybenzoic acid $<$ benzoic acid $<$ 4-nitrobenzoic acid) the additive effect does not seem to be a simple consequence of an acidity change of the reaction medium. Other acids such as CF₃CO₂H^[10] and 2-picolinic acid (which is known to be very efficient in the Gif systems^[5]) gave unsatisfactory results. Solvents other than acetonitrile were also examined. When the reaction was performed in ethyl acetate, dichloromethane or methanol, decomposition of the oxidant occurred and no oxidation of the substrate was observed. Decreasing the catalyst loading (5 mol %) had also a clear negative effect on the conversion ($<40\%$), while the selectivity remained unchanged.

After having established the best conditions for the oxidation of ethylbenzene, we focused our attention on the substrate scope. The conversion of a series of hydrocarbons was assessed applying a combination of Fe(ClO₄)₂ (10 mol %) and AcOH (20 mol %) for the CH activation. The results are presented in Table 2. (4-Nitro)ethylbenzene (**2**) afforded the corresponding ketone **6** with a conversion and selectivity comparable to the ones observed for ethylbenzene. Diphenylmethane (**3**) gave benzophenone (**8**) with a good selectivity (73%), although the conversion was only moderate

(48%). More challenging oxidations of fully saturated cycloalkanes were also attempted. To our delight we found that cyclooctane (**4**) was smoothly oxidized, giving a ratio of ketone/alcohols of 8.8 with cyclooctanone (**9**) as the major product (44% yield). Other compounds were detected by GC/MS analysis and their masses indicated the formation of diketones. Finally, the less reactive cyclohexane (**5**) was converted giving an equimolar mixture of cyclohexanol (**10**) and cyclohexanone (**11**) in 40% yield. This result is remarkable and can be compared well with the best ones reported so far in the literature for systems involving Fe species as catalyst and aqueous hydrogen peroxide as terminal oxidant.^[11]

Conclusion

In summary, we report an iron-catalyzed oxidation of saturated hydrocarbons, using aqueous hydrogen peroxide as terminal oxidant. The process exhibits great advantages: the reaction proceeds under truly catalytic conditions, the catalyst does not require any ligand, and water is the only by-product formed. These features, combined with the mild reaction conditions (aerobic atmosphere and room temperature), make the system a promising tool for large-scale applications and provide a simple method to access alcohols and ketones starting from unfunctionalized substrates.

Experimental Section

Materials

All the chemicals are commercially available and have been used as provided, without further purification. Acetonitrile with HPLC grade purity has been used.

General Procedure for the Oxidation of Cycloalkanes or Alkylarenes

To a stirred solution of the substrate **1–5** (1 mmol), Fe(ClO₄)₂ · 6 H₂O (36.6 mg, 0.1 mmol), acetic acid (12.0 mg, 0.2 mmol) and nitrobenzene (as internal standard, 0.2 mmol, 24.6 mg) in MeCN (5 mL) was added 30% aqueous H₂O₂ (5 mmol, 567 mg) over 4 h (1 mmol/h). After 5 h, the reaction was quenched with MnO₂, filtered on Na₂SO₄ and analyzed. Compounds **6–11** were isolated by column chromatography (pentane/diethyl ether, 3:1).

Analyses

NMR and GC analyses were performed on a Varian Inova 400 (400 MHz) and a Hewlett-Packard HP 5890 Series II gas chromatograph, respectively. Authentic samples of **6–11** were used to assign the peaks in chromatograms.

Alkylarenes (1–3): GC analyses were conducted using a FS-Phenyl-Sil capillary pre-column (3 m × 0.250 mm) and a Cyclo-dex β-I/P capillary column (25 m × 0.250 mm), with N₂ as the carrier gas.

Cycloalkanes (4, 5): GC analyses were conducted using a HP Ultra 2 capillary column (25 m × 0.2 mm), with N₂ as the carrier gas.

The yield of compound **5** was determined by ¹H NMR (CD₃CN) using benzene as internal standard.

Acknowledgements

We are grateful to the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (SPP 1118) for financial support. C. P. thanks the Graduiertenkolleg (GRK 440) for a predoctoral stipend, and J. L. acknowledges the Alexander von Humboldt Foundation for a postdoctoral fellowship.

References and Notes

- [1] a) R. A. Sheldon, J. K. Kochi, *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, **1981**; b) M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, American Chemical Society, Washington DC, **1990**; c) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, 97, 2879; d) R. Sheldon, I. W. C. E. Arends, in: *Transition Metals for Organic Synthesis*, Vol. 2, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd edn., **2004**, p. 201; e) G. B. Shul'pin, in: *Transition Metals for Organic Synthesis*, Vol. 2, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, 2nd edn., **2004**, p. 215; f) X. Baucherel, L. Gonsalvi, I. W. C. E. Arends, S. Ellwood, R. A. Sheldon, *Adv. Synth. Cat.* **2004**, 346, 286; g) Y. Ishii, S. Sakagushi, in: *Modern Oxidation Methods*, (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, **2004**, p. 119.
- [2] For overviews on the use of hydrogen peroxide in oxidation reactions, see: a) *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*, (Ed.: G. Strukul), Kluwer Academic, Dordrecht, **1992**; b) C. W. Jones, *Applications of Hydrogen Peroxides and Derivatives*, Royal Society of Chemistry, Cambridge, **1999**; c) R. Noyori, M. Aoki, K. Sato, *Chem. Commun.* **2003**, 1977; d) B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, 103, 2458.
- [3] Reviews on iron-catalyzed oxidations: a) M. Fontecave, S. Menage, C. Duboc-Toia, *Coord. Chem. Rev.* **1998**, 178–180, 1555; b) M. Costas, K. Chen, L. Que Jr., *Coord. Chem. Rev.* **2000**, 200–202, 517; c) M. Costas, M. P. Mehn, M. P. Jensen, L. Que Jr., *Chem. Rev.* **2004**, 104, 939; d) see also: G. B. Shul'pin, G. V. Nizova, Y. N. Kozlov, L. G. Cuervo, G. Süß-Fink, *Adv. Synth. Cat.* **2004**, 346, 317 and references cited therein.
- [4] a) D. T. Sawyer, A. Sobkowiak, T. Matsushita, *Acc. Chem. Res.* **1996**, 29, 409; b) D. T. Sawyer, *Coord. Chem. Rev.* **1997**, 165, 297; c) C. Walling, *Acc. Chem. Res.* **1998**, 31, 155; d) P. A. MacFaul, D. D. M. Wayner, K. U. Ingold, *Acc. Chem. Res.* **1998**, 31, 159; e) S. Goldstein, D. Meyerstein, *Acc. Chem. Res.* **1999**, 32, 547.
- [5] a) D. H. R. Barton, D. Doller, *Acc. Chem. Res.* **1992**, 25, 504; b) D. H. R. Barton, *Tetrahedron* **1998**, 54, 5805; c) P. Stavropoulos, R. Çelenligil-Çetin, A. E. Tapper, *Acc. Chem. Res.* **2001**, 34, 745.
- [6] For the use of acetonitrile in oxidation reactions see, for example: a) J. T. Groves, M. Van Der Puy, *J. Am. Chem. Soc.* **1976**, 98, 5290; b) R. H. Fish, M. S. Konings, K. J. Oberhausen, R. H. Fong, W. M. Yu, G. Christou, J. B. Vincent, D. K. Coggin, R. M. Buchanan, *Inorg. Chem.* **1991**, 30, 3002; b) D. H. R. Barton, F. Launay, *Tetrahedron* **1998**, 54, 12699.
- [7] a) M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, 123, 7194; b) J. Legros, C. Bolm, *Angew. Chem. Int. Ed.* **2004**, 43, 4225.
- [8] Noteworthy is the fact that this system is also capable of oxidizing alcohols to ketones. For example, 1-phenylethanol was converted into acetophenone with an excellent selectivity (>90%). For a recent report on FeBr₂-mediated oxidations of alcohols, see: E. Martin, A. Garrone, *Tetrahedron Lett.* **2003**, 44, 549.
- [9] In some cases, small amounts of oxidation products of the aromatic ring have also been detected by GC analysis.
- [10] Non-catalyzed oxidations of alkanes with H₂O₂ in pure CF₃CO₂H are known to afford alkyl trifluoroacetates as major products: a) N. C. Deno, L. A. Messer, *J. Chem. Soc. Chem. Commun.* **1976**, 1051; b) N. C. Deno, E. J. Jedziniak, L. A. Messer, M. D. Meyer, S. G. Stroud, E. S. Tomeszko, *Tetrahedron* **1977**, 33, 2503.
- [11] U. Schuchardt, D. Cardoso, R. Sercheli, R. Pereira, R. S. da Cruz, M. C. Guerreiro, D. Mandelli, E. V. Spinacé, E. L. Pires, *Appl. Catal. A: General* **2001**, 211, 1.