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The Selective Functionalization of Saturated Hydrocarbons. Part 38.† Bis(Trimethylsilyl) Peroxide: an Efficient Oxidant for the Functionalization of Hydrocarbons Involving the Fe^{II}-Fe^{IV} Manifold.††

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Abstract: The selective functionalization of alkane was achieved in a good yield. by a simple $Fe^{II}Cl_2$ salt and bis(trimethylsilyl) peroxide in pyridine. Unlike the Fe^{II}-H_2O_2 system, no extra ligand was needed. The presence of a carbon radical from the Fe^{II}-Fe^{IV} manifold was proposed to explain the results.

INTRODUCTION

In prior studies on what we call Gif Chemistry, we have been able to demonstrate that saturated hydrocarbons can be selectively functionalized at room temperature and near neutral pH. The major oxidation products are always ketones.[1] The existence of two manifolds has been established: Fe^{II}-Fe^{IV} and Fe^{III}-Fe^{V}. For example, the reactions of Fe^{II} and Fe^{III} with hydrogen peroxide in pyridine show the same kinetic isotope effect and a similar selectivity for the secondary positions of saturated hydrocarbons. However, the reagent from Fe^{II} affords eventually radical chemistry, whilst that from Fe^{III} only gives carbon radicals in a few well-defined, exceptional cases.[1,2] Carbon radicals, when present, couple with solvent pyridine and also with chloride ligated[3] to Fe^{III}. Other radical traps can also be used in the Fe^{II}-Fe^{IV} manifold.[4] Hydroxyl radicals are not involved in Gif Chemistry.[5]

It has been shown in the precedent publication,[7] that $Me_3SiOOSiMe_3$[8] was able to replace H_2O_2 in the oxidation of saturated hydrocarbons. The presence of a suitable carboxylic acid to obtain ketonization was also necessary. So, it was logical that we investigated the Fe^{II} chemistry using the bis(trimethylsilyl) peroxide.

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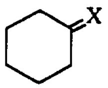
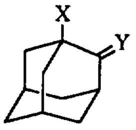
† Part 37: Barton, D. H. R. and Chabot, B. M. Submitted with this paper.

†† This paper is dedicated with appreciation and admiration to Prof. Nelson J. Leonard on the occasion of his eightieth birthday.

RESULTS AND DISCUSSION



1 $X=H_2$
2 $X=Cl,H$
3 $X=O$
4 $X=OH,H$
5 X=-2-pyridine,H
6 X=-4-pyridine,H



7 $X=H, Y=H_2$
8 $X=H, Y=O$
9 $X=H, Y=Cl,H$

10 X=-2-pyridine, $Y=H_2$
11 X=-4-pyridine, $Y=H_2$
12 $X=Cl, Y=H_2$

In **Table 1**, the reaction of cyclohexane carried out with $Fe^{II}Cl_2$ in presence of 3 equivalents of picolinic acid (PA) gave, as major product, cyclohexyl chloride 2 with a good efficiency (entries 1 and 2). The oxidation products 3 and 4 were obtained in identical amounts when the reaction was carried out under argon or air. Surprisingly, the absence of carboxylate ligands did not stop chloride formation (entry 3) as was seen in the Fe^{II}-H_2O_2 system.[2] The formation of alkyl chloride 2 decreased somewhat, but the formation of pyridine coupled products 5 and 6 increased instead. The competition between chloride or pyridine coupled product formation is evident in entry 4. When the concentration of chloride anions was increased by addition of LiCl, the formation of alkyl chloride 2 increased. Finally, the addition of both, LiCl and PA, did not produce a good effect (entry 5 and 6). It must be noted that a precipitate was formed at the end of the reaction. This can explain the low efficiency. Because the picolinic acid did not have a major effect on the reaction, it was not added in further studies.

Table 1: Activation of cyclohexane 1 with $Fe^{II}Cl_2$- $Me_3SiOOSiMe_3$

Entry	Conditions	Products (mmol)					Eff.
		R-Cl 2	R=O 3	R-OH 4	R-*2*-Pyr 5	R-*4*-Pyr 6	(%)
1	Argon, PA 1.5 mmol	0.74	0.20	n.d.	0.07	0.03	62
2	Air, PA 1.5 mmol	0.77	0.25	0.05	0.03	n.d.	70
3	Argon	0.58	n.d.	n.d.	0.54	0.26	69
4	Argon, LiCl 10 mmol	0.71	n.d.	n.d.	0.36	0.20	64
5	Air, LiCl 10 mmol, PA 1.5 mmol *	0.32	0.26	0.03	0.04	0.01	33
6	Argon, LiCl 10 mmol, PA 1.5 mmol	0.36	0.09	0.01	0.04	traces	30

These reactions were carried out with 20 mmol of cyclohexane 1, 0.5 mmol of $Fe^{II}Cl_2$ and 2 mmol of $Me_3SiOOSiMe_3$ in 15 ml of pyridine at RT, overnight. * In the end of the reaction a precipitate was formed. n.d. refers to not detected, RT to room temperature, Eff. to efficiency and was calculated assuming that 1 mmol of $Me_3SiOOSiMe_3$ was used to formed 1 mmol of products when it is considered as Fe^{II} chemistry.

The influence of water was studied as in the Fe^{III} experiments. Whether carried out under dry or standard conditions, the reaction gave the same result, showing that the trimethylsilylhydroperoxide was not involved in this reaction.

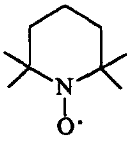
To study the selectivity, adamantane was oxidized with Fe^{II} in presence of LiCl. In **Table 2**, the selectivities observed with H_2O_2 and $Me_3SiOOSiMe_3$, involving the ratio C_2/C_3 (ratio defined as the total secondary products divided by the total tertiary products), are similar but different from the radical value.[2a] In both experiments, the major product was the 2-adamantyl chloride. These results confirm the high selectivity of the Fe^{II}-Fe^{IV} manifold for secondary attack on saturated hydrocarbons. Also, we observed that the activation by $Me_3SiOOSiMe_3$ was more efficient and more tertiary chloride was observed than in the case of H_2O_2. The Kinetic Isotope Effect values[9] were also identical using Fe^{II}-PA-H_2O_2[2a] or Fe^{II}-$Me_3SiOOSiMe_3$, k_H/k_D=2.1.

Table 2: Activation of adamantane 7.

Entry	Oxidant	Products (mmol)						C_2/C_3	Mb
		R-H 7	R=O 8	R*s*-Cl 9	R*t*-Cl 10	R*t*-*2*-Pyr 11	R*t*-*4*-Py 12		(%)
1	$Me_3SiOOSiMe_3$	9.36	0.02	0.40	0.20	0.06	0.05	1.37	101
2	H_2O_2	9.54	n.d.	0.22	0.01	0.10	0.04	1.52	99

These reactions were carried out with 10 mmol of adamantane 7, 3 mmol of $Fe^{II}(ClO_4)_2$, 10 mmol of LiCl and 3 mmol of oxidant in 30 ml of pyridine at 0°C to RT, under argon overnight. 9 mmol of PA were added in the case of H_2O_2. MB refers to mass balance.

The results already found are in agreement with an insertion of an Fe^{IV}=O species into the C-H bond of the hydrocarbon. Also, the formation of chloride, instead of the oxidation products as in the Fe^{III} system, confirms the presence of carbon radicals in this reaction. To further establish this hypothesis, different radical traps were added to the system such as Tempo 13,[4c] diphenyl diselenide 15[4b] and 2-methyl-1,4-naphthoquinone 17.[4a] In all these experiments, no oxidation products were formed. Trapping products were the major derivatives detected in good yields (based on the trap added). Cyclohexyl Tempo 14 was produced in 41 % yield and, if a reducing agent such as H_2S was introduced in the system to keep the iron catalyst in the Fe^{II} state, the yield could reach 95%. Cyclohexyl phenyl selenide 16 (25%) and 2-methyl-3-cyclohexyl-1,4-naphthoquinone 18 (54%) were also found under these conditions. It was clear that carbon radicals were involved in this system.



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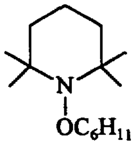

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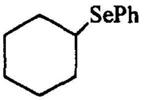

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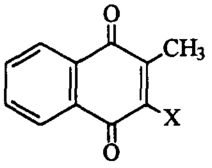


17 X= H
18 X=C_6H_{11}

The formation of chloride was followed kinetically as is presented in **Figure 1**. First, we can see that this reaction is faster than the Fe^{III}- $Me_3SiOOSiMe_3$ reaction, but slower than in the Fe^{II}-H_2O_2 system. The half-life is 30 minutes at room temperature. Another difference with the H_2O_2 system is that the efficiency is almost doubled. Starting with 3 mmol of Fe^{II}, more than 3 mmol of cyclohexyl chloride were formed. Pyridine coupled products 5 and 6 were also formed at the same rate (0.84 and 0.44 mmol for the *-2* and *-4* positions) accompanied by a small amount of 2,2-; 2,4- and 3,3-dipyridyl (0.30, 0.13 and 0.12 mmol). For convenience, we omitted these compounds in **Figure 1**. At 60 minutes, no Fe^{II} was detected by titration,[6] but peroxide was still present in the solution. We believe that all the Fe^{II} was oxidized to Fe^{III} , but in absence of picolinic acid, it was not expected that oxidation products would be formed. Also, the amount of chloride was almost constant.

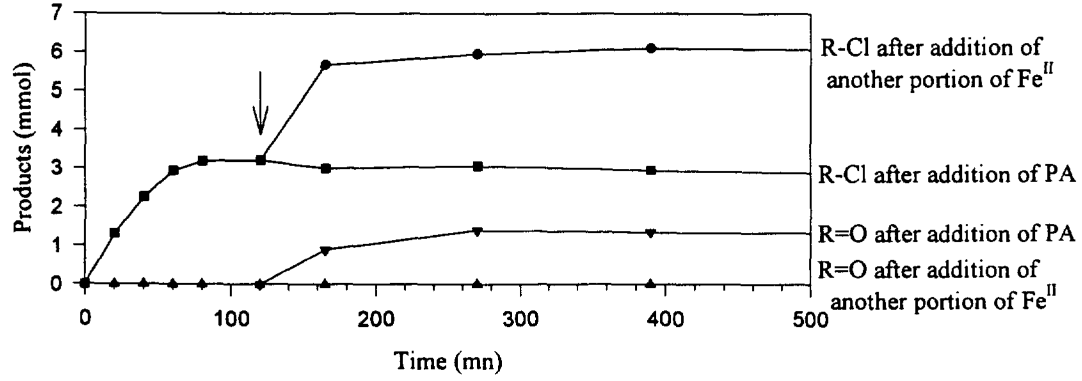


Figure 1: Kinetic of the Fe^{II}-$Me_3SiOOSiMe_3$ reaction.
Conditions: 20 mmol of cyclohexane 1, 3 mmol of $Fe^{II}Cl_2$ and 20 mmol of LiCl in 30 ml of pyridine under argon at RT. 3×6 mmol of $Me_3SiOOSiMe_3$ was added every 20 mn.

Addition of another portion of Fe^{II} after 120 minutes (as shown by the arrow on **Figure 1**) to half of the solution produced another 3 mmol of alkyl chloride 2 without any traces of ketonization. To the original solution, picolinic acid was added. The amount of alkyl chloride 2 stayed constant, but now that all the ketonization conditions were present (Fe^{III}-Fe^{V} manifold), the formation of ketone 3 appeared slowly. Here also, alcohol 4 was formed (0.16 mmol), but for the clarity of the figure it was omitted. We can definitely define two different mechanisms as in the H_2O_2 system. The two mechanisms are the Fe^{II}-Fe^{IV} manifold (involving a carbon radical and which does not need a special ligand to produce chloride and pyridine coupled products) and the Fe^{III}-Fe^{V} manifold (which does not involve any radical, but needs the presence of a carboxylate ligand to produce ketones).

Then, the effect of oxygen on the product distribution was studied using various conditions. The reaction was carried out under air, argon and oxygen. The results are presented in **Table 3**. Under air (entry 1), the major product was the cyclohexyl chloride 2, followed by the pyridine coupled products 5 and 6. Ketone 3 was also formed in a lesser amount by the reaction of oxygen with the alkyl radical. Under argon (entry 2), chloride 2 was still the major product with the pyridine coupled products 5 and 6 increased. The fact that the chloride formation did not increase while radicals were present to produce 5 and 6 indicates that the chloride ligands on Fe^{III} were not sufficient to produce more alkyl chloride.

Table 3: Effect of oxygen on the activation of cyclohexane 1 with Fe^{II}- $Me_3SiOOSiMe_3$

Entry	Conditions	Products (mmol)					Fe^{II}	Eff.
		R-Cl 2	R=O 3	R-OH 4	R-*2*-Pyr 5	R-*4*-Pyr 6	(%)	(%)
1	Air	0.83	0.23	0.04	0.37	0.10	---	39
2	Argon	0.78	0.10	0.01	0.62	0.22	---	43
3	Oxygen	n.d.	0.30	0.02	0.02	traces	3	9

These reactions were carried out with 40 mmol of cyclohexane 1, 1 mmol of $Fe^{II}Cl_2$, and 4 mmol of $Me_3SiOOSiMe_3$ in 30 ml of pyridine at RT overnight.

By reducing the amount of oxygen in the mixture, we decreased the formation of ketone 3. When the reaction was carried out under oxygen (entry 3), the oxygen trapped all the carbon radicals and oxidized Fe^{II} to Fe^{III} quickly. This explains the exclusive formation of oxidation products and the very low efficiency of the reaction. It was observed also, that the color of the solution of these different reactions was different. The solution, which was yellow before the addition of the peroxide, slowly became brown with different intensities which increased in this order: O_2 > air > Argon.

Even with all the similarities of the Fe^{II}-$Me_3SiOOSiMe_3$ and the Fe^{II}-H_2O_2 systems, the differences have to be explained. First, the efficiency of the reaction based on the iron is at least two times greater than with H_2O_2. In the beginning, we thought that the chloride 2 formation was faster than the oxidation of Fe^{II} to

Fe^{III}, but the kinetic data showed that the chloride 2 formation was complete after 60 minutes. Also, when 1 mmol of Fe^{II} was mixed with 3 mmol of Me$_3$SiOOSiMe$_3$, the titration showed no more Fe^{II} was present in the solution after 3 minutes and no oxygen formation was detected. These results, added to the kinetic data, showed that after 2 minutes, Fe^{II} was oxidized by Me$_3$SiOOSiMe$_3$ into a species, different from Fe^{III}, which was nevertheless able to activate the hydrocarbon. The fact that the system does not need chelating ligands such as picolinic acid makes the formation of a μ-peroxo-dimer improbable.

In order to find out how long this species was stable in solution, a series of experiments was carried out. After different periods of time, cyclohexane was added to Fe^{II} with Me$_3$SiOOSiMe$_3$ in pyridine at room temperature (**Figure 2**). Impressively, the species is stable at room temperature for at least more than 60 minutes. The half life of this species is around 15 minutes at room temperature.

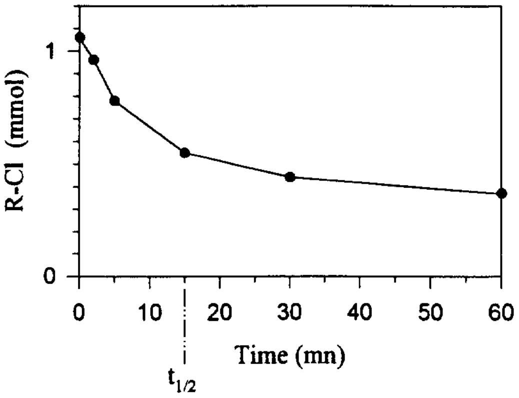
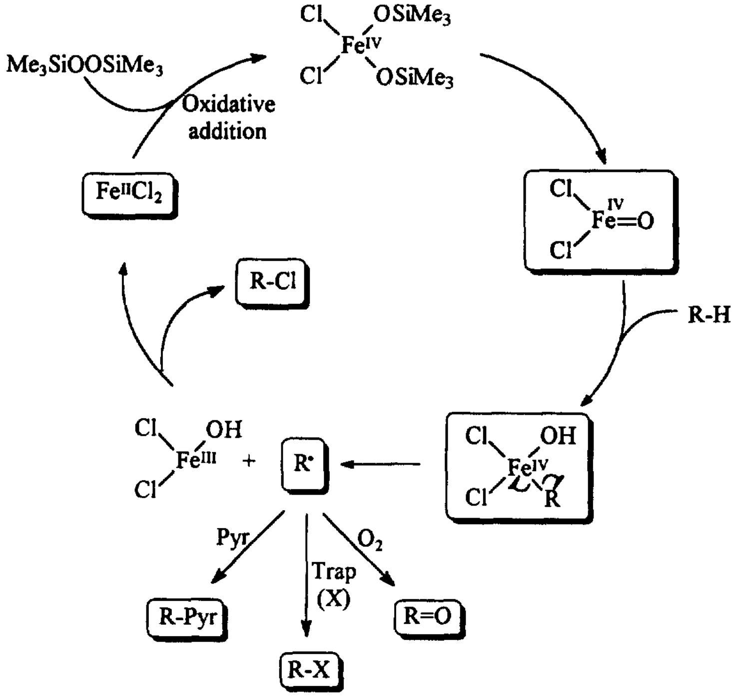


Figure 2: Study of the stability of the Fe species responsible for the activation of the hydrocarbon. Conditions: 1 mmol of Fe^{II}Cl$_2$, 5 mmol of LiCl and 3 mmol of Me$_3$SiOOSiMe$_3$ in 15 ml of pyridine. 20 mmol of cyclohexane 1 was added after different periods of time.

We propose, for the activation of the Fe^{II}-Me$_3$SiOOSiMe$_3$ system, the mechanism shown in **Scheme 1**. The oxidative addition of bis(trimethylsilyl) peroxide onto the Fe^{II}Cl$_2$ gives an Fe^{IV} species. Its insertion into the C-H bond of the hydrocarbon gives the σ Fe^{IV}-C bond which, by homolytic fragmentation, leads to the alkyl radical and Fe^{III}-Cl. The reaction between these two species gives alkyl chloride and Fe^{II}.[3]



Scheme 1: Proposed mechanism for hydrocarbon activation with the Fe^{II}-$Me_3SiOOSiMe_3$ system.

CONCLUSION

A system composed of an $Fe^{II}Cl_2$ salt and bis(trimethylsilyl) peroxide in a mixture of hydrocarbon and pyridine afforded in 1h, alkyl chloride or alkyl trapping in good yield. The addition of a reducing agent to keep Fe^{II} in solution, gave impressive results. This system, which involves an Fe^{IV}=O produces a carbon radical. Unlike the H_2O_2 system, no carboxylate ligand is needed to perform the reaction, giving a very simple system. Also, the efficiency with respect to the iron catalyst is higher.

Finally, we show that bis(trimethylsilyl) peroxide can be a versatile oxidant for hydrocarbon activation in Gif systems. The advantage in using this oxidant is the possibility of carrying out the experiments in very dry conditions at room temperature or even at relatively higher temperature without any risk of decomposition (no exothermic reaction between Fe^{II} or Fe^{III} and $Me_3SiOOSiMe_3$ as with H_2O_2).

EXPERIMENTAL

Unless otherwise stated, all chemicals were purchased from commercial sources and, after verification, used without further purification. ^1H and ^{13}C spectra were performed in deuterochloroform with tetrachloroethane as an internal standard on a Varian XL-200 spectrometer. Chemical shifts are reported relative to TMS ($\delta = 0.00$ ppm). UV-visible spectra were recorded on a Beckmann Du-7 spectrophotometer. Melting pts, were measured using a Thomas-Hoover apparatus. Gas chromatographic analyses were performed on a Hewlett-Packard 5890 series II gas chromatograph using a DB-Wax or a DB-1 capillary column (15 meters long, film thickness 0.25 μm, J&W scientific). GC-MS analysis were carried out on a Hewlett-Packard 5890 series II gas chromatograph coupled to a Hewlett-Packard 5791 mass selective detector using a DB-5 column (30 meters long, film thickness 0.25 μm).

The pyridine was dried under reflux over sodium when it is stated in the text.

Authentic samples (when not commercially available)

Bis(trimethylsilyl) peroxide was prepared according to a published procedure[10] and can be kept under argon at -18°C for months. Despite its stability, all precautions should be taken during its preparation and especially during the distillation. One explosion occurred in our laboratory during the distillation.

The authentic samples of the *2- and 4-cyclohexylpyridines* **5** and **6**, *sec-and tert-adamantylpyridines* **11** and **12**, the cyclohexyl Tempo **14** were prepared as in Part 37.[7] *Cyclohexyl phenyl selenide* **16**[11] was synthesized according to a known procedure. The NMR data was in agreement with those already reported.

2-Methyl-3-cyclohexyl-1,4-naphthoquinone **18**: Cyclohexyl Barton PTOC[12] ester (5 mmol) was added to a solution of 2-methyl-1,4-naphthoquinone (8 mmol) in CH_2Cl_2 at 0°C under argon. The solution was irradiated at room temperature until the total consumption of the Barton PTOC ester. The solvent was removed by evaporation and the residue was purified by column chromatography (silicagel, CH_2Cl_2) affording 51% of a yellow solid. Mp: 78°C.

^1H NMR ($CDCl_3$), δ (ppm): 8.0 (m, 2H), 7.65 (m, 2H), 2.8-3.0 (m, 1H), 2.2 (s, 3H), 1.2-2.1 (m, 10H); ^{13}C NMR ($CDCl_3$), δ (ppm): 150.5, 143.0, 133.3, 133.0, 132.8, 131.8, 126.2, 126.0, 40.7, 29.9, 27.0, 25.9, 12.6.

The general work-up procedure, the titration of peroxide remaining in solution and the measurement of the amount of oxygen evolved were already described in Part 37.[7]

General procedure for the reactions with Fe^{II}-$Me_3SiOOSiMe_3$

The $Fe^{II}Cl_2$ anhydrous (0.5 mmol) and cyclohexane (20 mmol) were dissolved in 15 ml of pyridine. The reaction was initiated by the addition of 2 mmol of $Me_3SiOOSiMe_3$ under argon at room temperature. The reaction mixture was stirred at room temperature overnight. The general work-up procedure (see above) was followed to quantify the products by gas chromatography.

General procedure for the titration of Fe^{II} [6]

An aliquot of the reaction mixture (2 ml) was added to H_2SO_4 solution (30 ml at 25%) at room temperature under an argon stream. After 5 minutes, the mixture was diluted to 250 ml with distilled water. 5 ml of this solution was added to a mixture of $NH_4H_2PO_4$ (10 ml at 10%) and 15 ml of distilled water to make a total volume to 30ml. The pH of the solution was adjusted to 2.0-2.1 with a H_2SO_4 solution (25%). The solution was transferred to a separatory funnel and 4,7-diphenyl-1,10-phenanthroline solution in absolute ethanol (30 ml at 0.36mM) was added. After shaking for a few seconds and allowing the solution to stand for several minutes, the solution was extracted with 10 ml of $CHCl_3$. The organic phase was transferred in a 25 ml volumetric flask and the solution was made to volume with absolute ethanol. The absorbance was measured in a 1 cm cell at 540 nm. The quantity of Fe^{II} was calculated as 1 μg of Fe^{II} corresponding to 0.0156 absorbance.

ACKNOWLEDGMENTS

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