Iron-surfactant nanocomposite catalyzed benzylic oxidation in water

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Benzylic oxidation the presence of iron-surfactant nanocomposite catalyst under aqueous conditions is described. The significant reaction rate acceleration by the presence of anionic surfactants was demonstrated. Several benzylic substrates were efficiently transformed to ketones under mild conditions.

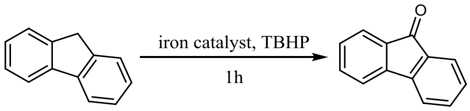
Oxidation of methyl or methylene group to carbonyl compounds is one of the most important synthetic transformation in organic chemistry.[1] Activated methylene group by neighboring carbonyl moiety can be easily oxidized with selenium dioxide to obtain keto-aldehydes and diketones.[2] Benzylic CH_2 group also have high reactivity toward oxidizing agents, and aryl ketones are synthesized with high efficiency. However, to achieve this transformation toxic heavy metal based oxidants such as CrO_3,[3] Jones reagent,[4] PCC is necessary.[5] Development and utilization of environmentally benign catalytic oxidation processes have high relevance in current organic synthesis. Iron based catalyst system for the oxidation of alkanes was introduced by Barton in the early 80's.[6] Since its discovery, several developments and extensions of the Gif chemistry have been achieved in the last decades.[7] Besides the advantageous application of non-toxic iron catalysts for the oxidation of methylene group, the utilization of aqueous *tert*-butyl hydroperoxide (TBHP) as oxidant in pyridine[8] or in water[9] makes the process even more environmentally friendly.

Catalytic transformations under micellar conditions in water can be performed efficiently with the aid of surfactant molecules.[10] The formed micelles in aqueous solutions ensures better solubility of non polar organic molecules, and microcompartmentalize reactants which results improved reaction rates due to increased local concentrations inside the micelles.

Besides the significant influence of surfactant molecules on solubility of organic compounds in water, alkyl sulfates and iron salts are able to build up organized composites with controlled thickness of inorganic layers containing bridged iron ions[11]. The close proximity of iron ions bridged by oxide in non-heme type metalloenzyme models is responsible for oxygen activation and oxidation of alkanes.[12] Based on the well defined structure of self assembled iron oxide/surfactant composites we aimed to utilize iron-oxide/sodium dodecylsulfate composite material to mimic the enhanced oxidation ability of diiron complexes.

Herein, we describe an efficient protocol for the iron catalyzed benzylic oxidation of organic compounds with iron-surfactant nanocomposites using ^{t}BuOOH as oxidant. In our study, we examined several reaction parameters and the effect of surfactants on the reaction rate. TBHP solution is frequently used as applicable oxidant for the iron catalyzed oxidation of benzylic CH_2 group.[8, 9, 13, 14] Therefore we chose aqueous solution of TBHP as oxidant for the preliminary studies. The aqueous reactions were carried out in 5w/w% solution of sodium-dodecylsulfate (SDS) to build up ironoxide/surfactant composite and ensure better solubility of the nonpolar substrate. As a model reaction, oxidation of fluorene was achieved at 50°C in the presence of 5 eq. TBHP and 2 mol % $FeCl_3$.[15]

Table 1. Optimization of reaction conditions[a]



Entry	Detergent	Catalyst loading	Conv. [%][b]
1	-	2% $FeCl_3$	23
2	SMS	2% $FeCl_3$	23
3	SOS	2% $FeCl_3$	44
4	SDS	2% $FeCl_3$	96
5	SDS	0,5% $FeCl_3$	59
6	SDS	1% $FeCl_3$	77
7	SDS	1,5% $FeCl_3$	87
8	SDS	2% $Fe_2(acac)_3$	4
9	SDS	2% FeF_3	7
10	SDS	2% $Fe(NO_3)_3$	82
11	SDS	1% $Fe_2(SO_4)_3$	70

12	SDS	2% $FeCl_3$[c]	5
13	SDS	2% $FeCl_3$[d]	22

[a] Fluorene (1mmol), TBHP (70 % aq, 5 mmol); iron salt (0.02 mmol, 0-2%), detergent (0.02 mmol) water (1mL), 50°C. [b] % composition of the product determined by GC. [c] reaction was conducted at 30°C. [d] reaction was conducted at 40°C.

When the reaction was driven in the absence of SDS we observed only 42% conversion even after 24 hours reaction time, while oxidation of fluorene took place completely in 2 hours when 5wt% aqueous SDS solution was the reaction media.[16] When the sufficient amount of SDS necessary for the oxidation was studied, we found that even 0.1 mol% SDS caused significant rate acceleration compared to the detergent free version, and the presence of 1 mol% of SDS is enough to maximize the reaction rate and the conversion in fluorene oxidation.[16]

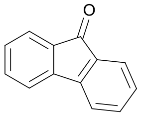
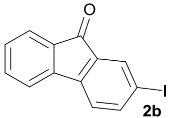
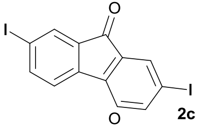
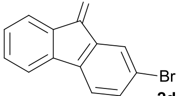
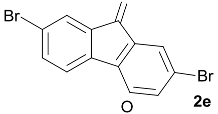
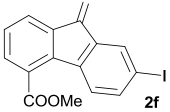
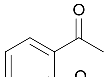
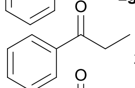
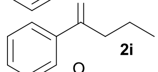
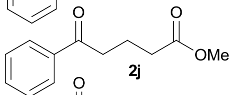
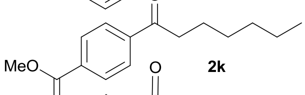
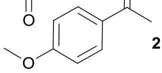
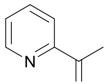
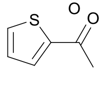
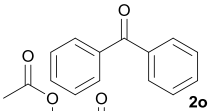
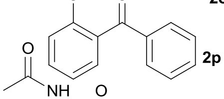
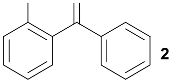
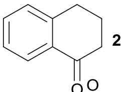
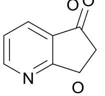
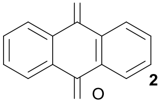
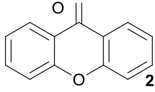
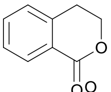
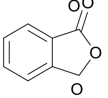
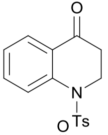
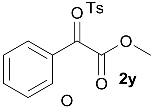
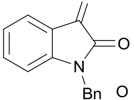
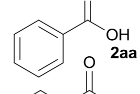
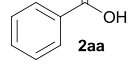
After demonstration of the importance of SDS in the transformation we aimed to study the effect of chain length and the type of detergent on the reaction. Comparison of sodium dodecyl, octyl and methyl sulfate revealed the importance of the long nonpolar chain motif within the surfactant. We have found significant rate acceleration when surfactant with longer alkyl chain was utilized in the oxidation of fluorene. However, methyl sulphate (SMS, 23%) gave similar result to surfactant free conditions (23%). The presence of sodium octylsulfate (SOS, 44%) increased the reaction rate, and dodecylsulfate (SDS, 96%) gave even higher conversions (Table 1., Entries 1-4).[16]

Attempt to lower the iron catalyst loading below 2 mol% caused lower conversions (Table 1, Entries 5-7.) The choice and amount of iron catalyst were also important for the successful oxidation. $Fe_2(acac)_3$, FeF_3 and $Fe(NO_3)_3$ was not efficient, but $FeCl_3$ and $Fe_2(SO_4)_3$ proved to be excellent catalysts for the oxidation of fluorene (Entries 8-11). Performing the oxidation of fluorene at lower temperature (30°C and 40°C) gave significantly lower conversions, demonstrating the importance of the temperature effect (Entries 12-13).

Having an optimal condition in our hand for the iron catalyzed oxidation of benzylic CH_2 group we intended to extend the scope of the reaction to other substrates and examine the generality of rate acceleration effect of sodium dodecyl sulphate. To achieve this we compared the conversions of reactions performed in the presence and in the absence of detergent after an appropriate reaction time. The benzylic oxidation of fluorene took place smoothly under the developed conditions in 2 hours and fluorenone **(2a)** was isolated in good yield (99%). Substituents on the fluorene frame strongly determine the rate of oxidation. When 2-iodo-9H- fluorene was subjected to oxidation longer reaction time (5h) was required to reach full conversion. The appropriate 2-iodo-9H-fluoren-9-one **(2b)** was isolated with 79% yield (Entry 2.). However, 2,7-diiodo-9H-fluorene did not react and formation of 2,7-diiodo-9H-fluoren-9-one **(2c)** was not observe at all (Entry 3.). Replacing the iodine with bromine the oxidations in the presence of 2 mol% $Fe_2(SO_4)_3$ took place in case of both 2-bromo and 2,7 dibromo fluorene, and both fluorenone **(2d-e)** derivatives were obtained in high yield after the workup procedure (86% and 95% respectively, Table 2., Entries 4-5). When methyl 7-iodo-9H-fluorene-4-carboxylate was oxidized under the developed conditions we isolated the appropriate carbonyl compound **(2f)** with 85% isolated yield. However, oxidative transformation of free acid derivative instead of ester did not afford the 2,7 substituted fluorenone compound. Oxidation of ethylbenzene with $Fe_2(SO_4)_3$/TBHP system afforded acetophenone **(2g)** straightforwardly (75% yield, Entry 7). Substrates with longer alkyl chain such as propyl and butylbenzene gave propiophenone **(2h)** and butyrophenone **(2i)** with 42% and 43% yield respectively. Substituents on alkylbenzene derivative on the alkyl chain did not affect the reactivity of the substrate and ketone **2j** was isolated with 42% yield. Substrates with either electron withdrawing or electron donating groups in the aromatic core were oxidized with the same efficiency, and ketones **5k** and **2l** were isolated with 40% yield. However, the presence of electron donating methoxy group para position to the ethyl group caused significant change in reactivity. In the presence of 5 mol% $FeCl_3$ the reaction stopped after 90 minutes at 50°C, but addition of further 5 equivalent of TBHP was necessary to reach full conversion in 150 minutes. When the aromatic group was replaced with heteroaromatic pyridine core, the oxidation become sluggish, and the 1-(pyridin-2-yl)-ethanone **(2m)** was detected with GCMS and only 1% conversion was observed (Entry 13). The oxidation of this heteroaromatic substrate was also unsuccessful at 80°C. Other ethyl substituted heterocyle such as 2-ethylthiophene was easily and selectively oxidized in the presence of 2 mol% $FeCl_3$ (Entry 14). The utilization of $FeCl_3$ instead of sulphate was advantageous, because overoxidation of the substrate was observed when iron-sulfate was used as catalyst, and several sideproduct was detected by GCMS analysis.

Oxidation of diphenylmethane took place excellently under our conditions providing benzophenone **(2o)** with high yield (90%, Entry 15). Benzylic CH_2 group in 2-benzylphenylacetate and N-(2-benzylphenyl)-acetymide was oxidized under the developed conditions and ketones **2p** and **2q** were isolated with 28% and 62% yields. Compounds containing condensed ring systems with saturated chain were also subjected to oxidation. 1,2,3,4-tetrahydronaphthalene was easily transformed to 3,4-dihydronaphthalen-1(2H)-one **(2r)** with 26% yield, together some 2,3-dihydronaphthalene-1,4-dione sideproduct, which is the result of double oxidation of two benzylic methylene group of the substrate in the presence 5 mol% $Fe_2(SO_4)_3$. When 6,7-dihydro-5H-cyclopenta-[b]pyridine was attempted to oxidized with TBHP in the presence of 5 mol% $Fe_2(SO_4)_3$ at 80°C 64% conversion was observed, but several isomers (mono and double oxidized products) were identified. Double oxidation occurred when 9,10-dihydroanthracene was oxidized in the presence of 2 mol% $FeCl_3$ and TBHP. The desired anthracene-9,10-dione **(2t)** was isolated in high yield (88%, Entry 20). Benzylic methylene group of 9H-xanthene was also easily oxidized and 9H-xanthen-9-one **(2u)** was obtained in excellent yield (97%, Entry 21). Methylene group next to aromatic carbon in a saturated heterocyclic ring can also be oxidized. We oxidized 9H-xanthene, isochroman and 1,3-dihydroisobenzofuran in the presence of 5 mol% $FeCl_3$. Interestingly the oxidation of these latter two substrates took place very rapidly at 50°C (10 minutes, full conversion, only one product) the appropriate products were isolated with 28% and 33% yield respectively (Entries 21-22.). When longer reaction times were applied complex reaction mixture was obtained. Similarly to the previously examined N-heterocyclic compounds oxidation of tosyl protected tetrahydroquinoline took place slowly and the dihydroquinolinone **(2x)** was obtained in 30% yield (Entry 24.). Methyl 2-phenylacetate was easily oxidized to the appropriate β-keto ester **(2y)** in the iron catalyzed transformation with good yield (80% yield, Entry 25.). When benzylcyanide was subjected to the catalytic transformation the oxidation took place completely on the benzylic position, but the ketocyanide was hydrolyzed immediately to benzoic acid **(2aa)** under the aqueous conditions (Entry 27.). When N-benzylindole was subjected to oxidation in iron catalysed process we obtained the appropriate N-benzylisatine **(2z)** (Entry 26.).

Table 2. Subtrate scope[a]

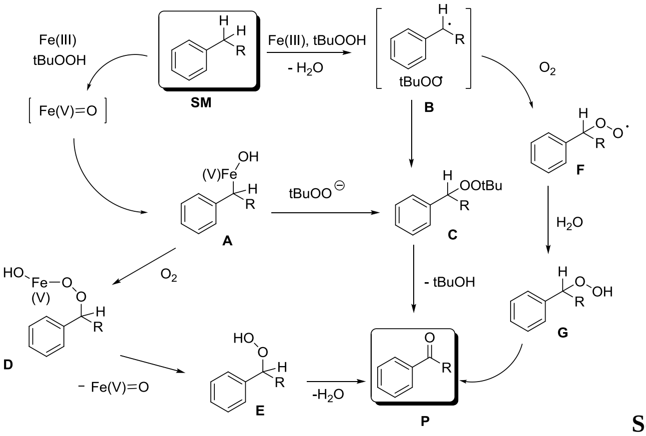
Entry	Product	Catalyst	Conv., [%]	t, [h]	Yield
1	 **2a**	2% $FeCl_3$	20/100	3	23
2	 **2b**	2% $Fe_2(SO_4)_3$	0/52	5	79
3	 **2c**	2% $Fe_2(SO_4)_3$	nd	24	0
4	 **2d**	2% $Fe_2(SO_4)_3$	16/90	24	86
5	 **2e**	2% $Fe_2(SO_4)_3$	5/9	24	95
6	 **2f**	2% $Fe_2(SO_4)_3$	7/100	24	85
7	 **2g**	2.5 % $Fe_2(SO_4)_3$	28/72	24	75[c] 98[d]
8	 **2h**	2.5 % $Fe_2(SO_4)_3$	27/49	24	42
9	 **2i**	2.5 % $Fe_2(SO_4)_3$	26/47	24	43
10	 **2j**	2.5 % $Fe_2(SO_4)_3$	nd.	24	42
11	 **2k**	2.5 % $Fe_2(SO_4)_3$	nd.	24	40
12	 **2l**	5% $FeCl_3$	24/73	2.5	40
13	 **2m**	5% $FeCl_3$	nd	24	0[e]
14	 **2n**	5% $FeCl_3$	50/63	3	33
15	 **2o**	2% $Fe_2(SO_4)_3$	33/93	24	90
16	 **2p**	2% $Fe_2(SO_4)_3$	47/58	24	28
17	 **2q**	2% $Fe_2(SO_4)_3$	39/87	24	62
18	 **2r**	5% $Fe_2(SO_4)_3$	29/67	24	26
19	 **2s**	5% $Fe_2(SO_4)_3$	0/3	24	64[f]
20	 **2t**	2% $FeCl_3$	40/100	24	88
21	 **2u**	2% $FeCl_3$	36/100	24	97
22	 **2v**	5% $FeCl_3$	27/92	10 min	28
23	 **2w**	5% $FeCl_3$	35/10	10 min	33
24	 **2x**	5% $Fe_2(SO_4)_3$	3/22	24	30
25	 **2y**	2.5% $Fe_2(SO_4)_3$	2/49	24	80
26	 **2z**	5% $Fe_2(SO_4)_3$	nd.	24	21
27	 **2aa**	5% $Fe_2(SO_4)_3$	18/100	24	46[g]
28	 **2aa**	5% Fe2(SO4)3	0/93	24	41[h]

[a] aIron(III) ion, SDS, water , 1 eq. substrate and 5 eq TBHP (70% aq.) was stirred at 50°C for the indicated time. [b] isolated yield. [c] Ethylbenzene was used as substrate. [d] 1-phenyl-1-ethanol was used as substrate. [e] Reaction was performed at 80°C. [f] GCMS conversion. Product distribution: 2%, 7% and 40% monooxidized isomers, 3% and 8% dioxidized isomers, 3% tricarbonyl product. [g] Benzylcyanide was used as substrate. [h] Benzylalcohol was used as substrate The reaction was conducted in anoxic conditions.

Besides the C-H bond oxidations we successfully oxidized alcohols to ketones or carboxylic acids. From benyzl alcohol we prepared benzoic acid **(2aa)** (41% yield Entry 28), and acetophenone **(2g)** was isolated with 98% yield when 1-phenyl-1-ethanol was oxidized with TBHP in the presence of 5 mol% $Fe_2(SO_4)_3$.

Besides the preparation of oxidized compound we compared the reactivity of each substrate in the presence and absence of SDS to generalize the rate accelerating effect of the detergent additives. On the basis of the conversions (Table 2., Column 4.) we can conclude that the presence of SDS significantly accelerate the reaction rate independently from the electronic structure of benzylic substrates.

As a proposed mechanism for the oxidation of benzylic CH_2 group we suppose that Fe(V)=O species forms from Fe(III) and TBHP, then this reactive species inserts into the activated C-H bond to form compound A. The benzylic iron species can react with oxygen gas in an insertion reaction affording iron peroxo compound D, or with ^{t}BuOO$^-$ anion in nucleophilic substitution during the formation of ^{t}Bu-benzyl peroxide (C). Intermediate D give benzyl peroxide species during the loose of Fe(V)=O. Each peroxides (C and E) can be decomposed to the desired ketone product (P). Taking account other possible opening step, formation of benzylic radical B is also supposed. This benzylic radical can react with ^{t}BuOO$^\cdot$ radical or with oxygen gas resulting the formation of the appropriate peroxo species C and F. Decomposition of these compound with the loose of H_2O or ^{t}BuOH gave the oxidation product (P).



Scheme 1. Proposed mechanistic pathways for benzylic oxidation

Summarizing our results, we developed new and efficient conditions for the iron catalyzed benzylic oxidation of organic compound under mild and economic aqueous conditions. The transformation utilizes easily accessible iron sources, such as $FeCl_3$ or $Fe_2(SO_4)_3$. We established the importance and rate accelerating effect of in situ formed iron-surfactant nanocomposite from sodium dodecyl sulphate and iron salts. We also demonstrated the applicability and limitations of the developed conditions through the functionalization of different molecular architecture in order to obtain important compounds bearing carbonyl functional group.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data, and copies of the 1H NMR and 13C NMR spectra]. See DOI: 10.1039/b000000x/

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