

Iron(III)-Catalyzed Tandem Sequential Methanol Oxidation/Aldol Coupling

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Abstract: Iron(III)-catalyzed methanol oxidations have been performed using hydrogen peroxide as oxidant. Formaldehyde is formed *in situ* and reacts subsequently with activated ketones to give α -hydroxymethyl carbonyl compounds in good yields. As side

reactions iron-catalyzed α -hydroxylations have been observed.

Keywords: aldol reaction; catalysis; hydrogen peroxide; iron; methanol oxidation

Introduction

Formaldehyde is an important C_1 electrophile in organic synthesis,^[1] and the aldol coupling remains one of the most potent carbon-carbon bond forming reactions.^[2] Aldol products (and especially hydroxymethyl derivatives) have extensively been used for the synthesis of important biologically active compounds,^[3] and in order to avoid the use of formaldehyde or its derivatives, new procedures are continuously being developed.^[4]

Investigating the use of iron complexes in organic synthesis,^[5] our group has recently described an efficient asymmetric sulfide oxidation and an oxidative hydrocarbon functionalization.^[6] Iron catalysts and hydrogen peroxide are attractive for these purposes, since both are environmentally and economically friendly. Thus we focused our attention on the use of iron and hydrogen peroxide in the field of alcohol oxidation. Particularly, the conversion of methanol into formaldehyde and its subsequent reaction in a carbon-carbon bond forming process was regarded as challenge.

Catalytic alcohol oxidation has been widely developed mainly with dioxygen,^[7] or hydrogen peroxide as oxidants.^[8] Since Fenton's work,^[9] however, iron has remained rather underexploited in the field of alcohol oxidation. Apart from Fe(III)/*tert*-butyl hydroperoxide, Fe(III) nitrate, some iron-porphyrin and iron-non-heme systems,^[10] only the combination of FeBr₃ and H₂O₂ has been used for selective oxidation of secondary alcohols.^[11]

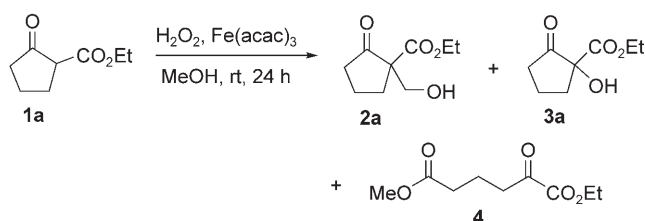
Here, we present our first results concerning the use of the commercially available Fe(acac)₃ as a catalyst for a tandem sequential methanol oxidation/aldol coupling reaction^[12] to afford a range of activated ketones, furnishing α -(hydroxymethyl)ketones in good yields.

Results and Discussion

For the development of an iron-catalyzed tandem sequential process involving a methanol oxidation followed by a C–C bond formation, all reagents and starting materials as well as test reactions and conditions had to be carefully selected. For the second catalytic step the aldol reaction appeared particularly attractive due to its synthetic relevance. Furthermore, to the best of our knowledge, the challenging catalytic oxidation of methanol to formaldehyde^[13] has never been combined with an aldol process, making the investigation on such tandem sequential catalysis scientifically interesting.

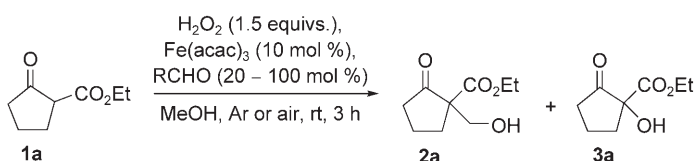
Since some iron(III) salts are water-tolerant Lewis acids, which have already been used in Mukaiyama-type aldol reactions,^[14] and considering the findings by Schwarz, who showed that iron(III) could efficiently coordinate to 1,3-diketo compounds,^[15] we began our studies by mixing 3.5 mol % of Fe(acac)₃, 1.5 equivalents of H₂O₂ and 1 equivalent of ethyl 2-cyclopentanonecarboxylate (**1a**) in methanol as shown in Scheme 1. Two major reactions resulted, and to our delight one of them was the methanol oxidation/aldol coupling tandem reaction affording aldol product **2a** in 23% yield. In addition, α -hydroxylated ketone **3a** and open-chain product **4** were isolated in 25% yield and trace amounts,^[16] respectively. No reaction was observed in the absence of Fe(acac)₃ or when dioxygen (1 atm) was used as oxidant.^[17]

These initial results prompted us to investigate the reaction in more detail and to determine, which factors influenced its outcome. Interestingly, the presence of a sub-stoichiometric amount of an aldehyde favored the aldol product formation. The ratio of products **2a** versus



Scheme 1. Iron-catalyzed conversion of **1a** in the presence of methanol and H_2O_2 .

Table 1. Effect of aldehydes in iron-catalyzed oxidation reactions of β -keto ester **1a**.



Entry	RCHO	mol % of RCHO	Yield [%] ^[a]	
			2a	3a
1 ^[b]	Ph-	100	52	20
2 ^[b]	Ph-	20	53	14
3	Ph-	20	73	25
4	<i>p</i> -Me-C ₆ H ₄ -	20	73	25
5 ^[c]	<i>p</i> -MeO-C ₆ H ₄ -	20	65	28
6	<i>p</i> -Cl-C ₆ H ₄ -	20	73	27
7	<i>o</i> -Br-C ₆ H ₄ -	20	76	22
8	<i>i</i> -Bu-	20	8	18
9	<i>t</i> -Bu-	20	46	31

^[a] After column chromatography.

^[b] Reaction performed in air.

^[c] At the end of the reaction 65% of the aldehyde was recovered.

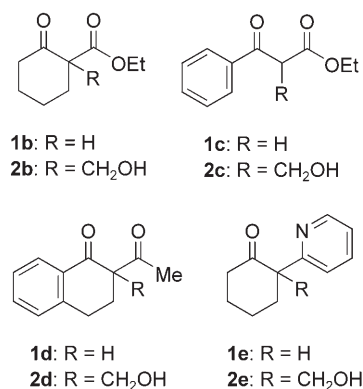
3a was thus used as an indicator for the two oxidation reactions and the results, using different aldehydes, are presented in Table 1.

Thus, by performing the iron catalysis in the presence of 1 equivalent of benzaldehyde (in air) the yield of **2a** was increased to 52% (Table 1, entry 1). Under argon and with only 20 mol % of this aldehyde, **2a** was even obtained in 73% yield (entry 3). No aldol product stemming from benzaldehyde was formed. The reaction was slightly dependent on the substitution pattern of the benzaldehyde, electron-withdrawing groups on the aromatic ring being better for the product formation than electron-donating substituents (Table 1, entries 6 and 7 *versus* 4 and 5, respectively). No clear trend was found for the α -hydroxylation reaction to give **3a**, which seemed to be independent of the type of aromatic aldehyde. The use of aliphatic aldehydes gave unsatisfying results in the formation of **2a** (entries 8 and 9), and again, the α -hydroxylation remained almost unchanged. With $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ as catalyst only **3a** was formed (35%

yield), suggesting that the acac^- ligand plays a decisive role during the course of the reaction. When dioxygen was used as oxidant the starting material was quantitatively recovered.

The formation of formaldehyde during the course of the reaction was assessed and confirmed by the Nash test.^[18] In this case, the catalysis was performed in the absence of β -keto ester **1a**, and the analysis was done after precipitation of the iron salts by pentane.

For a first evaluation of the substrate scope, both processes (oxidation and C–C bond formation) were decoupled and the transformations were studied in a two steps-one pot version. Thus first methanol was oxidized using a catalytic amount of $\text{Fe}(\text{acac})_3$ and hydrogen peroxide as oxidant (with or without benzaldehyde as co-catalyst), and then, in a separate step, various carbonyl compounds were added to the resulting mixture containing the preformed formaldehyde. As test substrates, β -carbonyl esters **1a–1c**, β -diketone **1d**, and 2-(2-pyridinyl)-cyclohexanone (**1e**) were chosen.



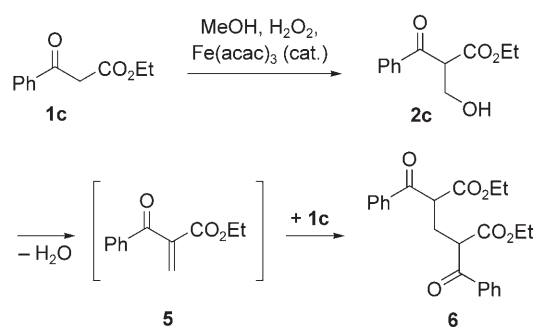
In Table 2 the results of this screening are summarized. In most cases, the yield of **2** was higher when the catalysis was performed in the presence of benzaldehyde (20 mol %; method B). Apparently, α -carboxycycloalkanones **1a** and **1b** were good substrates giving under these modified conditions the corresponding α -hydroxymethylated compounds **2a** and **2b** in 97 and 63%, respectively (Table 2, entries 1 and 2). 2-Pyridinyl-substituted **1e** also reacted well, but the yield of **2e** was only moderate (44% in the absence of benzaldehyde; entry 5). Diketone **1d** proved to be unsuitable as substrate (entry 4), and β -keto ester **1c** gave the corresponding α -hydroxymethylated product **2c** only as a minor product. With the latter starting material diketone diester **6** was predominantly formed (in up to 65% yield).

Presumably, the formation of **6** is related to the presence of the two enolizable α hydrogens in **1c**, which leads to water elimination of **2c** followed by Michael-type addition to the resulting α,β -unsaturated keto ester **5** to give **6** (Scheme 2).^[19]

The excellent yield of **2a** in the conversion of **1a** (Table 2, entry 1) under these stepwise conditions indicates that the conversion of methanol to formaldehyde (with

Table 2. Iron-catalyzed conversions of **1a–e** to give products **2a–e** and **6**.

Entry	Ketone	Product	Yields [%] ^[a]	
			Method A ^[b]	Method B ^[b]
1	1a	2a	78	97
2	1b	2b	39	63
3	1c	2c	28	22
		6	65	61
4	1d	2d	traces	traces
5	1e	2e	44	41

^[a] After column chromatography.^[b] Method A: no aldehyde was added; method B: addition of 20 mol % of PhCHO.**Scheme 2.** Iron-catalyzed conversion of **1c** in the presence of H_2O_2 and methanol.

respect to hydrogen peroxide) is essentially quantitative. The limiting step appears to be the aldol reaction, which is substrate-dependent.

The role of benzaldehyde remained unclear at this stage, and its conversion into perbenzoic acid through iron-catalyzed reaction with hydrogen peroxide was hy-

pothesized. In order to test the intermediacy of such oxidizing agent, various reactions of **1a** in the presence of $\text{Fe}(\text{acac})_3$ and peracids were performed. The results are shown in Table 3.

Apparently, compared to the standard conditions the ratio between **2a** and **3a** decreased, when *m*-CPBA was used as oxidant (Table 3, entries 1 and 2). Thus, less α -hydroxymethylated product **2a** was formed, whereas the amount of hydroxylated ketone **3a** increased (or remained constant). In the presence of a carboxylate (entry 3), more methanol was oxidized, leading to an increased amount of aldol product **2a**.

From all of these data we conclude that **2a** and **3a** are formed in concurrent processes and that the ratio between the two pathways is influenced by the presence of the added benzaldehyde, which acts as catalyst for the oxidation of methanol by hydrogen peroxide. With or without benzaldehyde the activated ketone (here **1a**) is directly oxidized (by hydrogen peroxide or air, if present) to give α -hydroxylated **3a**. In a parallel process methanol is converted into formaldehyde, which undergoes a subsequent aldol reaction with **1a** affording **2a**. In the presence of benzaldehyde the methanol oxidation becomes fast(er) and therefore the amount of aldol product **2a** increases. When the process is performed in two steps (compare data in Table 2) all hydrogen peroxide is first consumed by the oxidation of methanol, and the subsequently added ketone **1a** reacts rapidly with the *in situ* formed formaldehyde in the aldol-type C–C bond formation. Since at that stage no oxidant is present anymore, the amount of α -hydroxylated product **3a** is low. The activating effect of benzaldehyde presumably stems from its conversion into the corresponding (per)carboxylic acid by activated hydrogen peroxide,^[20] which is even known to proceed in the presence of FeCl_3 in acetonitrile.^[21] Alternatively, α -hydroxy hydroperoxides arising from a pre-activation of the aldehyde by the hydrogen peroxide may be involved. Being more soluble they could act as ligands for iron, and consequently, several catalytically active species might exist in solution. Their identification and pH-dependent for-

Table 3. Dependence of the ratio between **2a** and **3a** on the oxidizing system.

Entry	Oxidizing system	Yield [%]	
		2a	3a
1	<i>m</i> -CPBA (1.5 equivs.)	26	40
2	<i>m</i> -CPBA (20 mol %) + H_2O_2 (1.5 equivs.)	18	21
3	<i>p</i> -MeOC ₆ H ₄ COONa (20 mol %) + H_2O_2 (1.5 equivs.)	46	25

Table 4. Solvent effect in the α -hydroxylation of **1a** and **1b**.^[a]

Entry	Ketone	Solvent	Yield [%]	
1	1a	MeOH	23 (2a)	25 (3a)
2	1a	<i>i</i> -PrOH	–	43 (3a)
3	1a	<i>t</i> -BuOH	–	47 (3a)
4	1a	CH ₂ Cl ₂	–	9 (3a)
5	1b	<i>i</i> -PrOH	–	47 (3b)

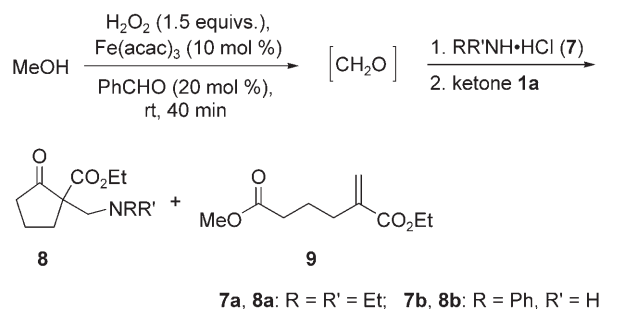
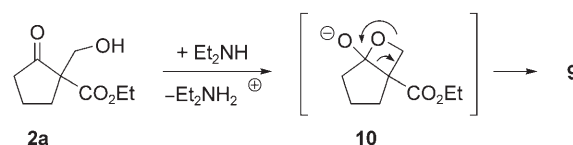
^[a] Reaction conditions: **1a** or **1b** (1 mmol), Fe(acac)₃ (0.1 mmol), H₂O₂ (1.5 mmol) in solvent (2.5 mL) at rt for 24 h.

mation are currently under investigation. From the current data it is difficult to propose clearly defined intermediates, but the results presented in Table 3 suggest that upon addition of an aldehyde a species such as a carboxylate is involved in the catalytic cycle. Under standard conditions, the presence of radicals cannot be excluded, and additional studies shall reveal, which step of the reaction sequence is most prone to involve such intermediates.

Another interesting aspect relates to the formation of the α -hydroxylated products **3**. Their metal-catalyzed formation with dioxygen as the oxidant is well known.^[22] To the best of our knowledge, however, the use of diluted aqueous hydrogen peroxide (30%) activated by an iron complex has never been reported.^[23] We therefore briefly examined this reaction as well and studied the influence of the solvent first. The results are shown in Table 4.

In all solvents the formation of the corresponding α -hydroxylated products **3a** and **3b** starting from β -keto esters **1a** or **1b**, respectively, was observed (Table 4). The yields of **3a** ranged from 9–43% with isopropyl alcohol being the best solvent. Only in the catalysis performed in methanol (starting from **1a**) was an aldol product formed.

Since the iron-catalyzed oxidative formaldehyde formation from methanol proceeded so well, we decided to extend this chemistry and to investigate a Mannich-type reaction. Due to their synthetic relevance such metal-catalyzed azo-aldolization processes between imines and silylenol ethers have already been studied in great detail,^[24,25] but, as far as we know, no example of a catalyzed tandem sequential methanol oxidation/Mannich reaction has even been reported. Scheme 3 shows our approach. For having a high concentration of formaldehyde, the reaction was performed in a sequential mode (compare with the two steps-one pot version described above). Thus, methanol was first oxidized with hydrogen peroxide under iron catalysis, and subsequently the amine (in the form of its HCl salt) followed by the ketone (here **1a**) were added to the formaldehyde-containing reaction mixture. With diethylamine (Et₂NH·HCl; **7a**) as amine, a new product was formed within a few minutes, but unfortunately it was not the expected Man-

**Scheme 3.** Iron-catalyzed Mannich-type reaction starting from methanol.**Scheme 4.** Mechanism for the deacylation of **2a** upon treatment with base.

nich-type product **8a**. Instead, the open-chain acrylic ester **9** was quantitatively obtained.

The formation of **9** was attributed to a deacylation of aldol product **2a**,^[26] which proceeded intramolecularly via **10** with the amine acting as base. This hypothesis was confirmed in a control experiment starting from **2a**, which afforded **9** upon treatment with diethylamine (Scheme 4).

All other attempts with diethylamine **7a** were unsuccessful, but, finally, Mannich product **8b** was obtained using the aniline hydrochloride **7b** and isolated in 22% yield (not optimized).

Conclusion

For the first time, a tandem sequential methanol oxidation/aldol coupling reaction catalyzed by a simple iron (III) complex is described. The reaction utilizes 30% aqueous hydrogen peroxide as oxidant and avoids the use of formaldehyde or surrogates in the preparation the industrially interesting β -keto α -hydroxymethylated carbonyl compounds. In the presence of a substoichiometric amount of an aldehyde the reaction rate is increased. Under optimized conditions the products are formed (at room temperature) in moderate to excellent yield. Furthermore, an iron-catalyzed α -hydroxylation of keto esters has also been disclosed. Although at the present stage the yields in this reaction are only moderate, the transformation itself is interesting, and these results served already as starting point for further investigations, which are currently ongoing in our laboratories.

Experimental Section

Materials

Ketones **1a–d** as well as the aldehydes were purchased from commercial suppliers and used without further purification. 2-(2-Pyridinyl)cyclohexanone (**1e**) was prepared according to ref.^[27] The solvents were distilled prior to use by standard procedures. All reactions were conducted under argon unless otherwise specified. Products **2a**,^[28] **3a**,^[22a] **2b**,^[3e] **2c**,^[29] **6**,^[19] **7b**,^[30] **9**,^[26] were in accordance to published data, **2e** was fully characterized.

Representative Procedure for the Tandem Sequential Methanol Oxidation/Aldol Coupling

In a Schlenk tube equipped with a magnetic stirring bar under argon, a solution of Fe(acac)₃ (35.3 mg, 0.1 mmol) and benzaldehyde (20 μ L, 0.2 mmol) in methanol (2.5 mL) was treated hydrogen peroxide (170 μ L, 1.5 mmol) at room temperature. The tube was capped, and the solution was stirred for 40 min (small exothermic effect). Then, ketone **1e** (175 mg, 1.0 mmol) was added, and the resulting solution was stirred for 3 h. The mixture was then hydrolyzed with a saturated aqueous solution of NaHCO₃ (10 mL), and the organic phase was extracted with CH₂Cl₂ (3 $\times$ 5 mL). The organic fractions were collected, dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel; petroleum ether/ethyl acetate, 6:4) to afford **2e**; yield: 84 mg (41%); ¹H NMR: δ = 1.42–2.04 (m, 5H), 2.31–2.60 (m, 3H), 3.69 (d, CH₂-O, *J* = 11.6 Hz), 3.81 (d, CH₂-O, *J* = 11.6 Hz), 7.12–7.20 [m, CH(Py)], 7.64 [dt, CH(Py), *J* = 1.7, 7.7 Hz], 8.53 [m, CH(Py)]; ¹³C NMR: δ = 20.31, 26.89, 32.31, 39.89 (4 CH₂), 60.93 (C-2), 67.91 (C-OH), 120.74, 121.09, 135.83, 148.37, 158.90, 213.68 (C=O); MS (EI, 70 eV): *m/z* (%) = 205 [M⁺, 13], 190 (31), 175 [(M – CH₂O)⁺, 100], 160 (27), 146 (63), 131 (37), 118 (41), 105 (49), 77 (17), 51 (10); IR (CHCl₃): ν = 3453, 3058, 2937, 2865, 1708, 1633, 1589, 784, 751, 550 cm^{–1}; anal. calcd. for C₁₂H₁₅NO₂ (205.06): C 70.22, H 7.37, N 6.82; found: C 70.04, H 7.70, N 6.42.

Acknowledgements

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