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OXIDATIVE DEPROTONATION OF CARBONYL COMPOUNDS BY Fe(III) SALTS

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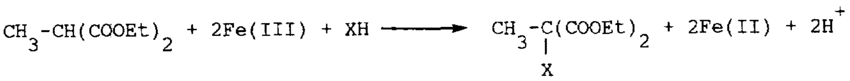
Abstact. Iron (III) salts (perchlorate and nitrate nonahydrate) in acetonitrile or acetic anhydride at 0-50°C oxidize the α-position of malonic esters efficiently via the corresponding radicals. In the presence of olefins and aromatics, inter- and intramolecular free radical chain or oxidative additions are observed.

Since its discovery some 20 years ago, the oxidative deprotonation of carbonyl compounds by Mn(III) acetate in acetic acid has received large mechanistic and synthetic attention[1]. The electrophilic α-carbonylalkyl radicals (or its Mn(II) complex), formed in the initiation step, generally propagate the homolytic reaction by inter- or intramolecular addition to olefins[2] or aromatics[3], followed by hydrogen atom transfer in a free radical chain reaction or termination by oxidation of radical intermediates in a stoichiometric redox process. However, it is known that other high valent metal salts (Ce(IV))[4], Pb(IV)[5], Co(III)[6], Cu(II)[7], Ag(II)[8]) are able to give similar reactions with lower efficiency. Because recent investigations[2,3] on Mn(III) acetate indicate that the initiation and the oxidative termination of these radical reactions occur via electron-transfer from Mn(III) complexed enolates and ligand-transfer oxidation of intermediate radicals, respectively, the ligand on the metal and the solvent used can be expected to play a key role in the efficiency of the overall process.

Now we report evidences that α-carbonylalkyl radicals are generated in the interaction of dialkyl malonates with iron(III) salts of weakly nucleophilic anions (perchlorate and nitrate) in acetonitrile or acetic anhydride as solvents. Iron(III) salts have been sporadically used for the α-oxidation of carbonyl compounds.[9]
Reactions of diethyl methylmalonate **1** with 2 eq. mol of $Fe(ClO_4)_3 \cdot 9H_2O$ in acetic anhydride at 5°C give the corresponding α-acetoxy derivative **2** in 60% yield. $Fe(NO_3)_3 \cdot 9H_2O$ under similar conditions affords **2** and the α-nitrato derivative **3** in 40 and 44% yield, respectively).[10]



$$CH_3\text{-}CH(COOEt)_2 + 2Fe(III) + XH \longrightarrow CH_3\text{-}\underset{X}{\underset{|}{C}}(COOEt)_2 + 2Fe(II) + 2H^+$$

1

2 X = OAc

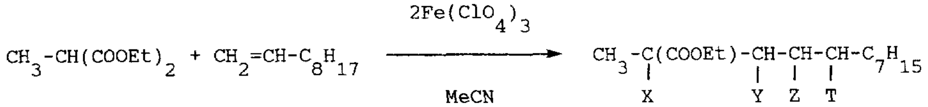
3 X = ONO_2

4 X = OH

5 X = $C(COOEt)_2CH_3$

6 X = $CH_2CH(COOEt)_2$

The oxidation of **1** by ferric nitrate in acetonitrile at 33°C for 12 h under heterogeneous conditions results in a mixture of α-hydroxy **4** and α-nitrato derivatives **3** in 42 and 45% yield, respectively, whereas the perchlorate affords traces of **4** and mainly the symmetric and unsymmetric dimers of **1** (**5** and **6** in 33 and 26% yield, respectively). α-Oxidation products conversely were formed in low yield when 2 eq. of $Fe(ClO_4)_3 \cdot 9H_2O$ in acetonitrile were allowed to react with 1 eq. of **1** in the presence of 4 eq. of 1-decene; products of oxidative addition (the olefins **7** and **8** and diastereoisomeric lactones **9**) were formed in 7, 27, 24 and 32 % yield, respectively.



$$CH_3\text{-}CH(COOEt)_2 + CH_2{=}CH\text{-}C_8H_{17} \xrightarrow[MeCN]{2Fe(ClO_4)_3} CH_3\text{-}\underset{X}{\underset{|}{C}}(COOEt)\text{-}\underset{Y}{\underset{|}{CH}}\text{-}\underset{Z}{\underset{|}{CH}}\text{-}\underset{T}{\underset{|}{CH}}\text{-}C_7H_{15}$$

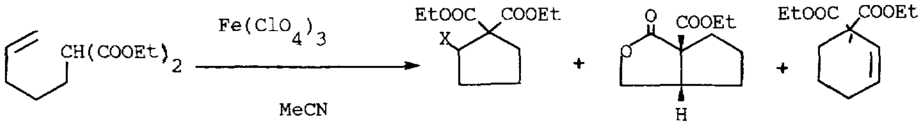
1

7 X = COOEt; Y,Z = bond; T = H

8 X = COOEt; Y = H; Z,T = bond

9 X,Z = -COO-; Y,T = H

The intramolecular version of this reaction with diethyl α-(4-pentenyl)malonate **11** (1 M) in acetonitrile at 20°C by slow addition of a 0.3 M solution of $Fe(ClO_4)_3 \cdot 9H_2O$ at 0°C results in a 40% yield of the free radical chain five-membered cyclization product **12a** and traces of oxidative cyclization products **12b-d** and **13** at 50% conversion of **11**.



11 **12** **13** **14**

12a X = CH_3

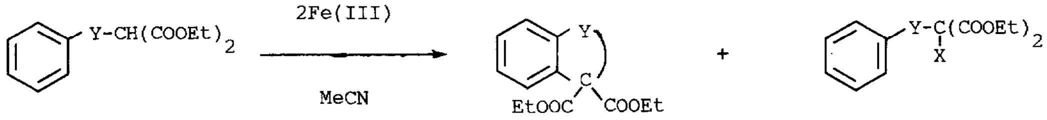
12b X = methylene

12c X = CH_2OH

12d X = $CH_2NHCOCH_3$

Reverse addition of 0.1 M solutions of **11** in acetonitrile to 0.2 M solutions of ferric perchlorate in the same solvent at 20°C results mainly in oxidative cyclization products **12b**, **12c**, **12d** and **13** (4, 10, 6 and 44% yield, respectively) along with **12a** (7%) and the six-membered cyclization product **14** (7%).

Under these conditions oxidative substitution in the aromatic series can also be obtained. Compounds **15** and **16** were converted in 12 h at 30°C to cyclic derivatives **18** and **19** in 90 and 60% yield using two and three equivalents, respectively, of ferric perchlorate. The hydroxy-ester **21** was a side product in the latter reaction. No oxidation was conversely observed when water (20 eq.) was present in the medium or when $Fe_2(SO_4)_3 \cdot 9H_2O$ or $FeO(OAc)_2$ were used instead of $Fe(ClO_4)_3 \cdot 9H_2O$. However, **19** is obtained in 95% yield when **18** is oxidized by 2 eq. of ferric perchlorate in acetic anhydride alone or in mixture with acetonitrile at 20°C. Under these conditions compound **17** is oxidized to the cyclic derivative **20** (18%) and the α-acetoxylation product **23** (75%). On the other hand, compounds **21** and **22** were obtained by oxidation of **16** with $Fe(NO_3)_3 \cdot 9\,H_2O$ in acetonitrile in 42 and 45% yields, respectively.



15 Y = OCH_2CH_2
16 Y = $CH_2CH_2CH_2$
17 Y = CH_2CH_2

18 Y = OCH_2CH_2
19 Y = $CH_2CH_2CH_2$
20 Y = CH_2CH_2

21 Y = $CH_2CH_2CH_2$; X = OH
22 Y = $CH_2CH_2CH_2$; X = ONO_2
23 Y = CH_2CH_2; X = OAc

All these results taken together are strongly indicative of the involvement of malonyl radicals in these oxidations and parallel the behaviour of Mn(III) acetate towards the same substrates. The 1:10 preference for the five- over six-membered ring closure observed with **11** is in accord with the behaviour of diethyl α-4-pentenylmalonyl radicals as generated by Mn(III) acetate or by iodine transfer cyclization from the corresponding α-iodo-derivative[11], whereas the oxidation of **11** by dibenzoyl peroxide[12] was less conclusive on account of poor material balance.

The formation of α-oxigenation products follows the increase of redox potential of Fe(III) complexes in the media examined.[13] The hexaquo complex is inefficient in preventing the dimerization or disproportionation of radical intermediates and their inter and intramolecular addition to double bond of olefins and aromatics ($K_L < 10^3\ M^{-1}\ s^{-1}$), whereas with acetonitrile or acetic acid complexes[13], only particularly fast intramolecular processes can be observed (cf. reactions of **16** and **17**). With the nitrato complex only α-oxigenation products are obtained.

The results suggest a close analogy in the oxidation of carbonyl derivatives between high valent metal salts which present appropriate ligands able to give sufficiently fast ligand exchange with carbonyl derivatives and a redox potential high enough to oxidize by inner-sphere electron-transfer, the enolate ligand to the corresponding radicals ($E^\circ > 1 - 1.2$ V because $E^\circ[\dot{C}H(COOEt)_2] = 0.9 - 1.1$ V[14]) or having a M-OR bond weak enough to homolyze thermally. A relatively low rate constant of ligand transfer oxidation of the α-carbonylalkyl radicals formed appears to be fundamental for valuable synthetic applications.

An analysis of the factors affecting the generation and trapping of carbon free radicals by high valent metal salt is currently under study in our laboratory.

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