Manganese (III)-Promoted Addition of Monomethyl Malonate on Dihydropyran in the Presence of Molecular Oxygen

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Abstract: The effect of oxygen on the course of the Mn^{III}-induced addition of monomethyl malonate on dihydropyran is described.

Introduction :

Intra- and intermolecular additions, on unsaturated substrates, of electrophilic radicals formed by Mn^{III}-promoted oxidation of acetic acid or β-dicarbonyl compounds have been extensively used for the synthesis of γ-lactones and polycyclic compounds (1).

Although most of the results recently published are related to the intramolecular process, the addition of acetic acid derivatives is still promising. This is the case for monoalkyl malonates as their addition on a double bond leads to α-carboalkoxy-γ-lactones which are precursors of α-methylene-γ-lactones (2) (Fig. 1). These lactones are valuable synthons and are found, as substructures, in many natural products (3).

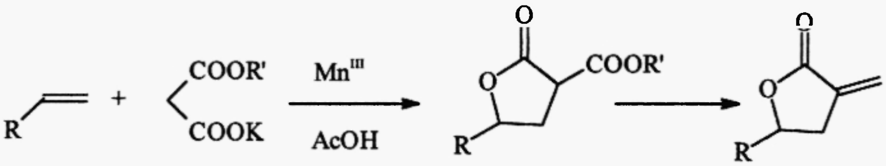
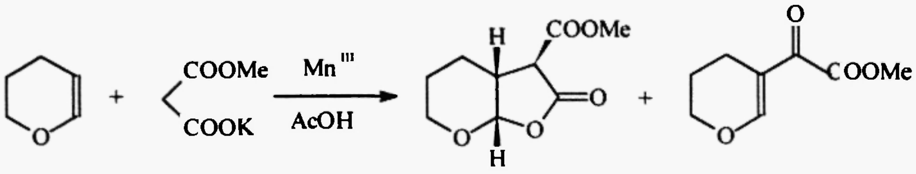


Figure 1 : Mn^{III}-mediated synthesis of α-methylene-γ-lactones

During the course of a study of this reaction with monomethyl malonate applied to 3,4-dihydro-2*H*-pyran we have observed that, if the γ-lactone 1 is indeed obtained, it is always accompanied by another product 2 which is formed in variable amounts depending on the reaction conditions (Fig. 2).



1 2

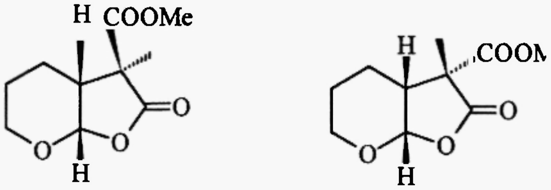
Figure 2 : Reaction of dihydropyran with monomethyl malonate in the presence of Mn^{III}

Results and discussion :

In order to get a better control of the product distribution, we have run several experiments under different conditions and we have observed that the reaction course is very sensitive to oxygen. Indeed, when the reaction was performed at 65°C in degassed acetic acid under an argon or a nitrogen atmosphere (4), the yield of the lactone 1 was 70% as estimated by gas chromatography while the yield of 2 was only 4%. In the same conditions, but under an air atmosphere, 1 and 2 were obtained in 50 and 23% yield respectively. The same reaction run in acetic acid previously saturated with oxygen and under an oxygen atmosphere leads to 1 (12%) and 2 (63%) : clearly 2 is formed by a competitive oxidation process at the expense of 1.

It should be noted that such a behavior has not been observed in our previous studies on carbocyclic unsaturated substrates. The structure determination of the γ-lactone 1 does not present any difficulty since this compound has been previously described (5). The structure of compound 2 has been established by using heteronuclear multiple bond correlation techniques in 2-D NMR spectroscopy (6).

The formation of 2 deserves some comments and has to be compared with recent results which described that either a β-keto ester radical (7) or the radical resulting from the previous addition on a double bond (8-11) can be trapped by molecular oxygen. In the last case, 1,2-dioxolane derivatives are formed. Further experiments were carried out in order to check these two possible pathways. With monomethyl methylmalonate under a nitrogen atmosphere, only the α-methyl-α-carbomethoxy-γ-lactone is formed (15%) as a mixture of diastereomers 3+4 (75/25) (12) (Fig. 3). Under an oxygen atmosphere, the same results are observed except that the ratio of diastereomers is slightly different (65/35).



3 4

Figure 3 : Reaction of monomethyl methylmalonate with dihydropyran

With dimethyl malonate, dihydropyran is recovered unchanged, although the brown color of Mn^{III} has faded to pale yellow, indicating its reduction to Mn^{II}. When lactone 1 is reacted in the same conditions under an air atmosphere, the dihydropyranyl ketoester is formed. Thus the formation of 2 could be accounted for as indicated in Figure 4.

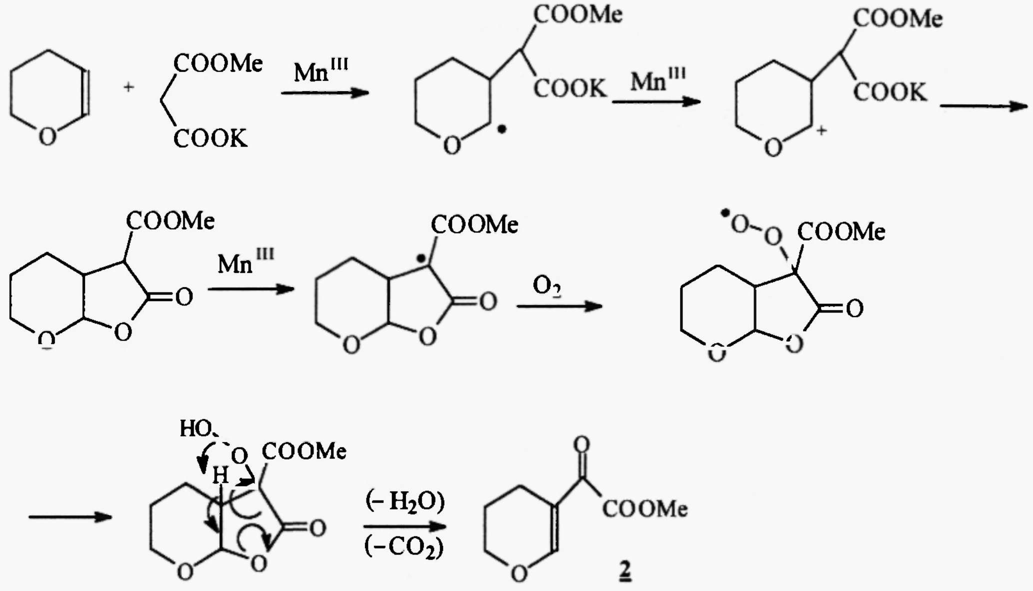


Figure 4 : Proposed mechanism for the formation of the dihydropyranyl ketoester 2

In the first step, the electrophilic malonyl radical adds to the double bond of dihydropyran. The carbon-centered radical α- to the pyranyl oxygen is readily oxidizable and the lactone formation occurs. Further reaction with Mn^{III} gives a new malonyl-like radical, which is trapped by molecular oxygen yielding the corresponding hydroperoxide. Finally, a rearrangement via dehydration and decarboxylation gives the dihydropyranyl ketoester 2. This last step could also be initiated by an alkoxyl radical formed by the homolytic cleavage of the hydroperoxy bond. In that case, a radical mechanism can explain the formation of 2. When monomethyl methyl malonate is used, such a malonyl-like radical cannot be formed and only the corresponding lactones (3+4) are isolated. The α-carbomethoxy-α-hydroperoxy- γ-lactone was never isolated. However, the corresponding alcohols have been prepared and characterized, under these conditions, starting from a series of α-carbomethoxy-γ-lactones (13).

Conclusion :

It should be noted that this is the first example where a β-diester is involved in such a reaction. Neither an epoxide nor an external nucleophile is involved in this process. Furthermore, as shown by the results observed with monomethyl methylmalonate, molecular oxygen adds on the carbon of the malonyl moiety contrariwise to what has been previously reported when *β*-keto esters (8), *β*-diketones (9), *β*-keto amides (10) and *β*-keto sulfoxides (11) are reacted with an olefin in the presence of Mn^{III} and molecular oxygen.

References and notes:

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(4) Typical experimental conditions : the reactions were performed using 4.4 mmol of $Mn(OAc)_3\ 2H_2O$, 5 mmol of potassium monomethyl malonate and 2 mmol of dihydropyran at 65°C in acetic acid (20 ml) until discoloration. All the products gave satisfactory elemental analyses.

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(12) Compound 3 (COOMe *cis* with the vicinal H) : ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 1.23-1.34 (m, 1H); 1.37 (s, 3H); 1.58-1.67 (m, 2H); 1.76-1.87 (m, 1H); 2.66 (ddd, J=10.2, 6.4, 3.9 Hz, 1H); 3.62-3.78 (m, 2H); 3.71 (s, 3H); 5.74 (d, J=3.9 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm: 172.6, 170.8, 99.8, 61.9, 57.5, 53.3, 40.9, 22.5, 20.8, 14.8. Compound 4 (Me *cis* with the vicinal H) : ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 1.39-1.57 (m, 2H); 1.50 (s, 3H); 1.67-1.76 (m, 2H); 2.29 (td, J=7.8, 7.8, 4.2 Hz, 1H); 3.61-3.79 (m, 2H); 3.72 (s, 3H); 5.64 (d, J=4.2 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm: 173.2, 169.9, 98.7, 62.7, 55.2, 52.9, 43.7, 21.7, 21.3, 20.4.

(13) Unpublished results.

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