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Mn(III) Acetate Induced Addition of α-Amidomalonic Ester Derivatives to Conjugated Olefins

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Abstract Oxidation of diethyl α-amidomalonate derivatives **1** by Mn(III) acetate in the presence of conjugated olefins **2** leads to addition-oxidation products **3-5** in good to excellent yield In neat furan and thiophene the 2-substitution products **5** are obtained. Side oxidation to α-acetoxymalonic derivatives is the main competitive reaction

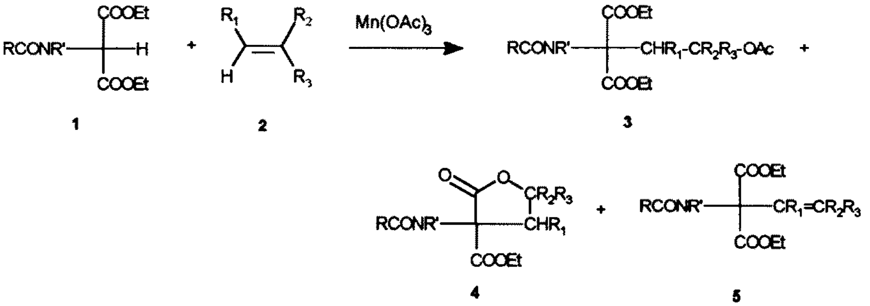
The addition of carbon-centred radicals to unsaturated substrates is an important process in free-radical chemistry, and in recent years such reactions which incorporate this propagation step have acquired remarkable importance in organic synthesis as a valuable method for new C-C bond formation[1] In this context, reductive and oxidative radical initiators have been extensively investigated in both chain and stoichiometric reactions, and the synthetic limits have in part been ascertained Often, when metal oxidants are employed to generate radicals, the competitive oxidation of the initial carbon radicals severely interferes, and, in order to minimise this side reaction, synthetic applications have been restricted to sources of highly electrophilic carbon radicals which posses one or more electron-withdrawing substituents on the radical centre (i e carbonyl, cyano, nitro, or sulphonyl groups)[2], owing to their high redox potential Radicals bearing donor and acceptor groups show a lower electrophilicity, lower redox potentials, and a higher thermodynamic stabilization[3], leading to an increase of the oxidation rate by metal salts and a decrease of the addition rate to the unsaturated substrate This qualitative information makes difficult to asses the potential of the oxidative C-C bond forming processes in reactions of carbonyl compounds α-substituted by electron-releasing groups with alkenes and stimulate us to study the reactivity of ambiphilic radicals towards alkenes and metal oxidants

Herein, we report on the successful trapping of substituted α-amidomalonyl radicals by conjugated olefins **2** in the Mn(III) acetate oxidation of α-amidomalonic ester derivatives **1** to give the addition-acetoxylation/lactonisation or addition-substitution products **3**, **4** and **5** (Eq 1) A previous preliminary report of a similar reaction which $Ce(SO_4)_2$ in heterogeneous medium has revealed severe limits[4]

Conjugated olefins were selected based on their high reactivity towards electrophilic diethyl malonyl radicals ($k = 10^4 - 10^6$ l mol^{-1}s^{-1} at 70 °C)[7,8], assuming a similar electrophilic behaviour for diethyl α-amidomalonyl radicals

The experimental conditions were chosen in order to minimise the oxidation of radical intermediates by Mn(III) Thus, portion wise addition of $Mn(OAc)_3$ 2 H_2O to a rapidly stirred solution of **1** and **2** in acetic acid over 4 h at 80 °C under N_2, and further stirring for 4 h (method A), or heating at 65°C mixtures of **1** and $Mn(OAc)_3$ 2 H_2O in neat **2** in a magnetically stirred closed vessel for 12 h (method B, useful with less reactive furan and thiophene) afforded, after filtration through silica gel and column chromatography, the addition products **3-5** in good to excellent yield[9] (Table 1)

The procedure here reported represents a new valuable approach to the synthesis of α-amino-acids from **1** as an alternative to ionic reactions (i e electrophilic alkylation (Sorensen method)[5] or nucleophilic addition to dehydro derivative **7**[6])

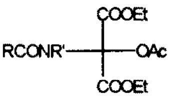


Eq. 1

	R	R'
1a,	Me	H
1b,	H	H
1c,	Ph	Me
1d,	----C_6H_4-CO----------	
1e,	CH=CH-Ph	H
1f,	CH_2-CH=CH-Ph	H

	R_1	R_2	R_3
2a,	H	Ph	H
2b,	H	Me	C(Me)=CH_2
2c,	---CH=CH-CH_2---		H
2d,	---CH=CH-O-------		H
2e,	---CH=CH-S-------		H
2f,	H	Ph	Ph

The products of substitution **5** are obtained selectively with heteroaromatic substrates furan and thiophene using method B, and in lower amounts with substrates yielding tertiary radical adducts (i e **2b**) On the contrary, acetoxy derivatives (**3**) and lactones (**4**) are preferentially obtained with terminal alkenes via the addition of the external acetate nucleophile or the addition of the internal oxygen nucleophile of the pendant ester group The presence of sodium acetate affects the product distribution in favour of the acetate **3** α-Oxidation products of **1** (acetoxy derivative **6** or dehydro derivative **7**) are commonly observed No trace of the previously reported[4] dimer of **1d** is conversely detected in all experiments with **1d** This substrate was less efficiently oxidised to **6** than **1a-c** suggesting that the presence of two electron-withdrawing carbonyl groups on the nitrogen increases the electrophilic character of the resulting radical



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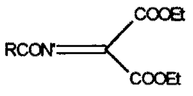

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6a, R = Me, R' = H

6b, R = H, R' = H

6c, R = Ph, R' = Me

6d, R, R' = -CH_2CH_2CO-

6e, R = -CH=CH-Ph, R' = H

6f, R = CH_2-CH=CH-Ph, R' = H

7a, R = Me, R' = H

Table 1. Products Distribution in the Oxidation of α-Aminomalonic ester derivatives 1 in the presence of Conjugated Olefins 2 by Mn(III) Acetate.

Entry	1	2	Method	Conv (%)	---- Products (Yield %)------			
					3	4	5	6(7)
1	1a	2a	A	90	41	39	-	9
2	1a	2a	A	100^a	88	4	-	4
3	1a	2a	A	90^b	68	4	-	13
4	1a	2b	A	88	40	5	28	13
5	1a	2c	A	73	20	--	10	16
6	1a	2d	B	84	--	--	70	8
7	1a	2e	B	74	--	--	60	11
8	1a	2f	A	100^a	--	90	--	4
9	1b	2d	B	86	--	--	74	8
10	1c	2d	B	85	--	--	64	12
11	1d	2a	A	92^a	87	3	--	--
12	1d	2d	B	93	--	--	82	-3
13	1d	2e	B	95	--	--	85	-5
14	1e	--	A	90	--	--	--	81
15	1f	--	A	92	85	--	--	4

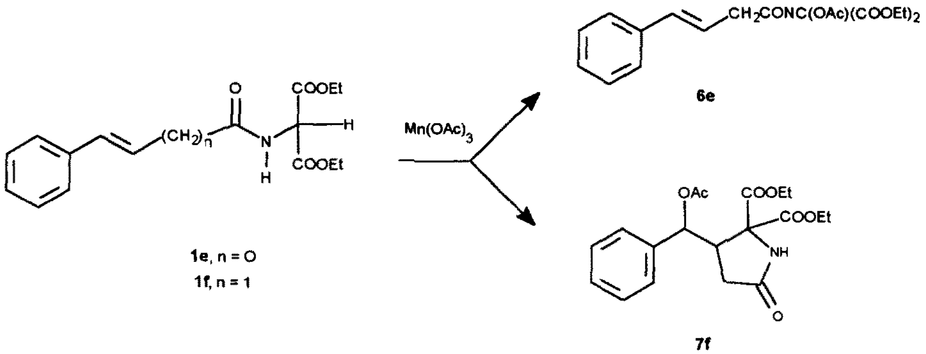
[a] In the presence of NaOAc (0 4 M) [b] In the presence of CF_3COOH (0 1 M)

The oxidation product **6** is depressed in the presence of sodium acetate and increased in presence of trifluoroacetic acid (Table 1, run 1-3), in accord, respectively, with the lower and higher redox potential of Mn(III) acetate in the presence of two additives than in their absence[7] These additives are not useful when the procedure of method B is employed

By monitoring the ratio (**3**/**6**) against the olefin concentration in low conversion experiments of oxidation of diethyl phthalimidomalonate by Mn(III) acetate in the absence of additives and at variable olefin concentration, the following ratios of radical addition to oxidation rates were deduced 5 0, 2 1, 0 16, 0 015 for **2a**, **2b**, **2d**, and **2e**, respectively The higher reactivity of monosubstituted alkenes (i e. styrene derivatives **2a** and **2f**) explains the successful use of Method A with these substrates and the limited synthetic potential with 1,2-disubstituted olefins[4]

With thiophene and furan only substitution products at position 2 are obtained and a similar selectivity for position 5 is observed with 2-substituted thiophenes and furans Competitive studies of addition of diethyl phthalimidomalonate to these last substrates by using method B indicate that both electron-withdrawing and electron-releasing groups on the heteroaromatic substrate favour the process The trend observed is similar to the one recently reported by us in the addition of diethyl benzylmalonyl radicals to substituted olefins[7] However, in neat furan and thiophene the oxidation of **1a-d** by Mn(III) acetate is somewhat faster than the oxidation of diethyl methylmalonate, suggesting a crucial role of the pendant amide group in the formation of metal complexes by β-dicarbonyl derivatives

Intramolecular addition to conjugated double bonds was also observed with formation of five-membered rings, i e with substrate **1f** On the contrary, four-membered rings cannot be formed from **1e** and a quantitative yield of the corresponding acetoxycinnamoyl derivative **4e** is obtained These results are in accord with the higher 1,5- vs 1,4-intramolecular addition rate of carbon radicals to olefins



Work is in progress to provide mechanistic and synthetic information on the effect of substituents NRR', OR', SR', etc , in alpha position to the carbonyl group, on the oxidative addition of malonic ester derivatives to olefins induced by Mn(III) acetate and to apply the method here described to other more structurally complex substrates

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9 The products were isolated and gives satisfactory IR, NMR and mass spectral data and anlysis Compound **5** from **1d** and **2e** shows a m p 81-82 (lit[4] 79 -81)

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