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MECHANISM OF DECARBALKOXYLATION OF ARYLMETHYLENE-PROPANEDIOIC ACID DIMETHYL ESTERS

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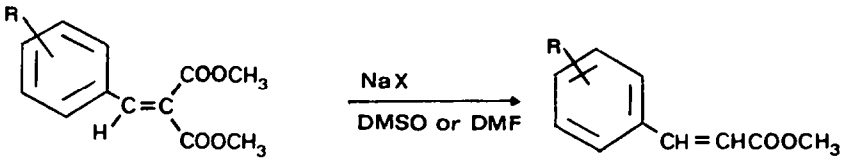
Abstract - The decarbalkoxylation in DMSO-NaX-H_2O, of some arylmethylene propanedioic acid dimethyl esters is studied. Both the relative rates of the para ($R = NO_2$, H, CH_3, OCH_3) and the ortho [$R = H$, OCH_3, $OCH(CH_3)_2$] substituted aryl derivatives, together with the stereochemical outcome, support a preliminary nucleophilic attack by water followed by decarbalkoxylative elimination.

Many studies on synthetic applications of the decarbalkoxylation reaction using various salts in different dipolar aprotic solvents have appeared in the literature[1]. In spite of the extensive use of this reaction in synthetic organic chemistry, few examples[2,3] are reported studying the stereochemistry of the final products.

Krapcho[2] recently published a study on the stereochemical consequences of the decarbalkoxylation of some cyclic geminal diesters. Diethyl 2-methyl-1,1-cyclohexane dicarboxylate gave a product ratio of 60:40 cis to trans esters upon decarbalkoxylation in LiCl-H_2O-DMSO, while the analogous 3- and 4-methyl-1,1-cyclohexane dicarboxylate gave a 50:50 distribution of cis to trans esters. The moderate stereoselection shown in the 2-methyl derivative was accounted for by the approach of a water molecule from the less hindered equatorial direction. In the other cases the substituents are quite distant from the reaction site to be able to influence the direction of approach of the water molecule which can now occur as easily from either the equatorial or the axial direction.

In this paper we examined the stereochemical outcome of the decarbalkoxylation of some aryl-methylene propanedioic acid dimethyl esters (Scheme 1) for which preliminary results have already been published[4].

SCHEME 1



1 2

1,2 : a, R = H
b, R = o-CH_3
c, R = o-OCH_3
d, R = o-$OCH(CH_3)_2$
e, R = p-CH_3
f, R = p-OCH_3
g, R = p-NO_2

RESULTS AND DISCUSSION

The substrates were reacted in different solvents (DMF and DMSO at reflux temperature; DMSO-H_2O at 165 °C) using sodium chloride or bromide as decarbalkoxylating reagent. We found that by carrying out the reaction of compounds 1 in anhydrous DMSO-NaX at 190 °C for 2h, the trans cinnamic esters 2 were always obtained in yields ranging from 60-70% as major products (more than 95%) irrespective of the halide used or of the substituent on the aromatic ring. Sometimes, probably as a consequence of adventitious acidity in the reaction mixture, when using NaBr, extensive decomposition of the solvent occurred[5], leading to isolation from a strongly acidic mixture of the corresponding cinnamic acid instead of the ester.

Interestingly when the reaction was carried out in aqueous DMSO, the results were quite different and appeared to be dependent on the halide and on the substituent present on the aromatic ring (Table 1). In the case of 1a the use

of chloride ion gave practically 100% of trans cinnamic ester, while bromide gave a notable increase in the amount of cis derivative and a decrease in the reaction rate (higher amount of starting material).

Table 1 - Decarbalkoxylation[a] of dimethylesters 1 in DMSO/H_2O

$$R\text{-}C_6H_4\text{-}CH{=}C(COOCH_3)_2 \xrightarrow[DMSO/H_2O]{NaX} R\text{-}C_6H_4\text{-}CH{=}CH\text{-}COOCH_3 + CO_2 + CH_3OH$$

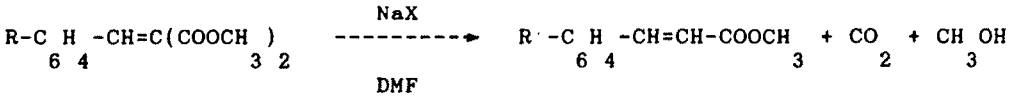
R	X	Starting material%	Starting aldehyde%	Cis:trans%	Yield%[b]
H	-	85	11	25:75	3
H	Cl	--	15	1:99	53
H	Br	5	13	16:82	55
o-CH_3	Cl	--	14	29:71	53
o-CH_3	Br	24	13	15:85	30
o-OCH_3	Cl	--	15	20.80	50
o-OCH_3	Br	10	17	22:78	61
p-CH_3	Cl	--	16	2:98	54
p-CH_3	Br	4	15	15:85	52
p-OCH_3	Cl	2	20	4:96	58
p-OCH_3	Br	15	16	10:90	60
o-$OCH(CH_3)_2$	Cl	21	19	24:76	53
o-$OCH(CH_3)_2$	Br	55	11	25:75	30
p-NO_2	Cl	--	10	2:98	42
p-NO_2	Br	4	12	15:85	40

[a] All the reactions were carried out for 6h at 165 °C; [b] GLC yields of the cinnamic derivatives.

In the same way introduction of an ortho substituent on the aromatic ring led to an increased proportion of the cis derivative and significantly slowed

down the reaction rate. The same results were obtained when the reaction was carried out for 23h in DMF at reflux temperature (Table 2).

Table 2 - Decarbalkoxylation[a] of dimethyl esters 1 in DMF



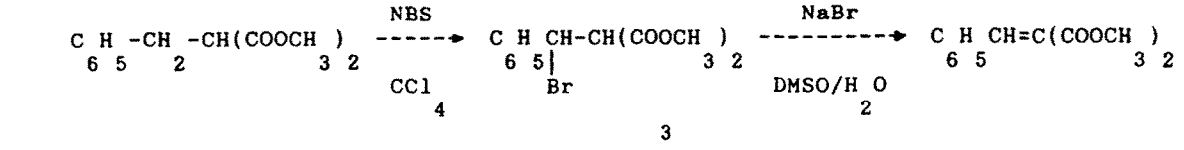
R	X	Starting material%	Starting aldehyde%	Cis:trans %	Yield%[b]
H	Cl	5	3	8:92	75
H	Br	-	-	31:69	90
o-CH_3	Cl	2	6	25:75	45
o-CH_3	Br	31	-	28:72	50
o-OCH_3	Cl	45	3	30:70	30
o-OCH_3	Br	52	-	40:60	38
p-OCH_3	Cl	13	4	9:91	72
p-OCH_3	Br	--	-	22:78	90

[a] Commercial DMF was used at reflux temperature for 23h; [b] GLC yields of the cinnamic derivatives.

In this case, as a consequence of the introduction of an ortho substituent[6] the slowing down of the reaction rate was more dramatic and the increase in the amount of the cis cinnamate more consistant.

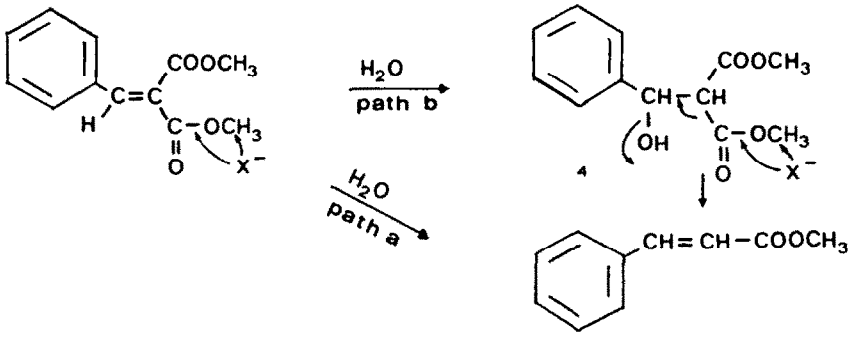
There are various possibilities for the mechanism of this reaction. First of all decarbalkoxylation at reflux temperature, as a consequence of neutral water hydrolysis[7], should be negligible in wet DMSO and quite notable in dry DMSO[8] (4% and 33% of decarbalkoxylation were respectively recorded in the absence of halide ions). Secondly in the reaction mixture there are two nucleophilic species: the halide ions and the water. Addition of the halide ion, leading to compound 3 can be excluded because when 3, which was prepared by reaction of NBS on benzyl-malonic acid dimethyl ester, was reacted at

160 °C with NaBr in aqueous DMSO, only 1a was recovered from a strongly acidic mixture [9].



Therefore if the double bond undergoes nucleophilic attack before the decarbalkoxylation it will be from a water molecule to afford intermediate 4 (Scheme 2). The decarbalkoxylation can occurr either through alkylic ($B_{AL}2$) or acylic ($B_{AC}2$) nucleophilic attack of the halide ion at one of the activated ester groups, through two probable reaction pathways (Scheme 2): a) attack at one of the two vinylic carbomethoxy groups [10]; b) Michael addition of water molecule to afford the intermediate 4 that can either undergo a retro-Knoevenagel reaction or a decarbalkoxylative elimination [11].

SCHEME 2



We believe that the mechanism is dependent on the reaction medium, and precisely, that path "b" should be the more important in DMSO-H_2O, whereas path "a" should be mainly operative in dry DMSO. The evidences supporting path "b" are :

1) The rate of the decarbalkoxylation of the <u>para</u> substituted derivatives 1a, e,f,g follows the order $NO_2 > H > CH_3 > OCH_3$ (Table 3).

2) The introduction of a substituent in the <u>ortho</u> position of the aromatic ring causes a decrease in the rate proportional to the bulk of the substituent and increases the amount of <u>cis</u> cinnamate.

3) The use of bromide ions, instead of chloride, slows down the reaction rate and increases the amount of cis cinnamate.

The relative rates, together with the presence of a strong ortho effect are in accordance with a preliminary rate-determining nucleophilic addition on the double bond [15]

Table 3 - Relative rates[a] of 1a,e,f,g derivatives in DMSO-H_2O-LiCl

R	% remaining ester	K_{rel}[b]
OCH_3	78.4	0.38
CH_3	59.9	0.83
H	53.9	1.00
NO_2	14.0	3.18

[a] The reactions were carried out in sealed ampoules in a DMF bath at reflux temperature for 40 minutes. The relative rates have been calculated from [7,14] $K_R/K_H = \log (xR/x_o R)/\log (xH/x_o H)$ where x = % unreacted diester (by GLC using benzyl cinnamate as internal standard) and $x_o = 100$ for the diesters;

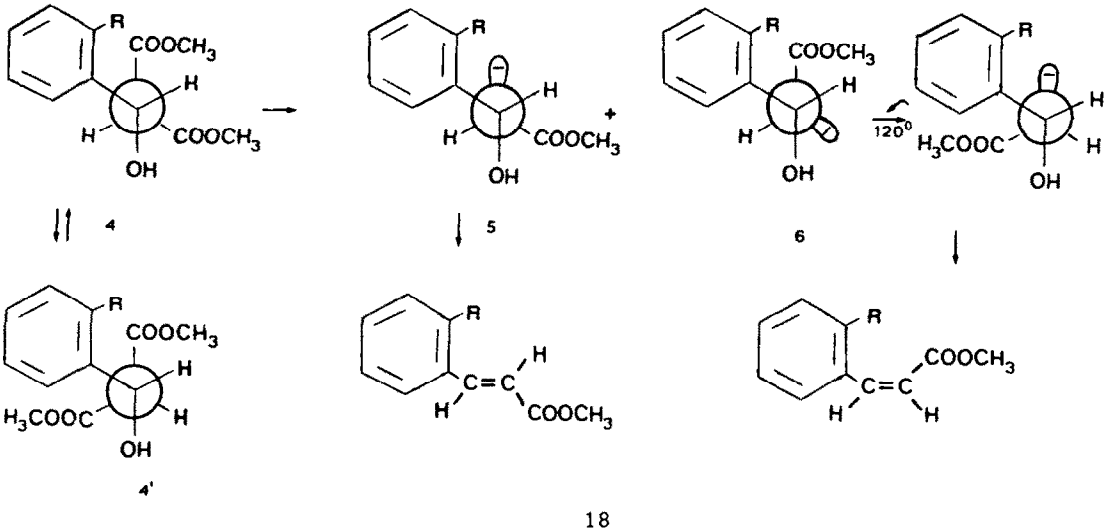
[b] average values for two runs.

Arguments against mechanism "a" are:

1) If decarbalkoxylation of the unsaturated malonic esters occurred according to path "a" also in aqueous DMSO, we should measure a sequence of relative rates similar to the one reported in Table 3, as a consequence of the fact that, the electronic effects of the para susbtituents can be transmitted [16], although to a less extent, up to the carbomethoxy groups. On the other hand steric interference between the carbomethoxy group and the ortho substituent would favour decarbalkoxylation [17], and therefore on increasing the bulk of the substituent the rate should increase and not decrease as experimentally observed.

2) Deconjugation of the double bond by water before the decarbalkoxylation

step is furthemore supported by the stereochemical outcome of the reaction on varying the bulks of the ortho substituent and of the halide. The regular increase in the amount of the cis cinnamate could not be rationalized if the reaction occurred on the vinylic carbomethoxy group. In the latter case we should detect an increase in the trans cinnamate on increasing the bulk of the ortho substituent because the Z-carbomethoxy group would become more reactive for steric reasons[17]. On the other hand, if the reaction is occurring via route "b" with the intermediacy of 4 we can easily explain the stereochemical results. Considering 4 in its most stable conformation, two carbanionic species[18], 5 and 6, could be obtained by attack to either of the carbomethoxy groups.



Starting from the reasonable assumption[18] that an anti elimination is the most energetically favoured, we believe that as the bulk of the halide or the ortho substituent increase, the ester group "gauche" to the aromatic ring becomes more protected from being attacked, so that an increasing amount of decarbalkoxylation on the other ester group will take place, yielding increasing quantities of the anion 6.

This anion can reach the suitable conformation for an anti elimination, that

will lead to the cis cinnamate, by a 120°C counterclockwise (or a 240° clockwise) rotation. The fact that the stereochemical outcome may be the result of the composition of the mixture of the two conformers (4 and 4') which carry a carbomethoxy group anti to the hydroxyl group can be excluded because, as the bulk of the ortho substituent increases, conformation 4', which can lead to the cis cinnamate through an anti elimination, will be further disfavoured with respect to the conformation 4.

The results of the decarbalkoxylation in dry DMSO support a mechanism through path "a" on the basis of the following evidences:

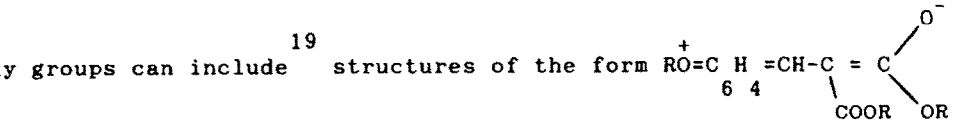
1) The relative rates of the decarbalkoxylation of 1a,e,f,g (Table 4), show the same tendency as in table 3, although the differences among the rates are less evident. What is particularly interesting is that 1d (R=o-$OCH(CH_3)_2$) reacts slightly faster than 1c, (R=o-OCH_3) and both react slower than 1a.

Table 4 - Relative rates[a] of 1a, c - g in dry DMSO-LiCl

R	% remaining ester	Relative rates[b]
H	11.90	1.00
o-OCH_3	19.90	0.76
o-$OCH(CH_3)_2$	15.35	0.88
p-CH_3	12.00	0.99
p-OCH_3	14.40	0.91
p-NO_2	7.90	1.50

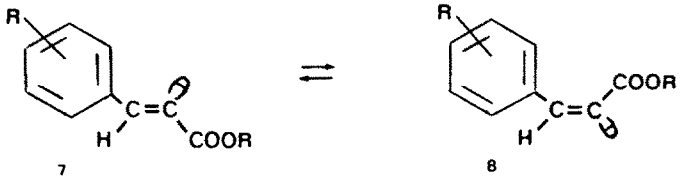
[a] The reactions have been carried out at 190°C in sealed ampoules in a DMSO bath at reflux temperature for 4 minutes; [b] calculated as in Table 3. Average values for two runs.

From the above, we should expect that for path "a" an ortho substituent increases the reaction rate[17] with respect to an unsubstituted ring. We can overcome this apparent contradiction if we remember that derivatives such as

1 with alkoxy groups can include[19] structures of the form  which are responsible for the reduced reactivity of the vinylic ester groups. With regard to the effect of an ortho substituent, the comparison is to be made between the two alkoxy substituted derivatives, that have the same conjugative electron releasing effect, but different steric requirements. As expected the ortho isopropoxy substituted derivative (1d) reacts faster than the analogous ortho methoxy (1c).

2) All derivatives in series 1, gave the corresponding trans cinnamate as the sole product, regardless of the substituent or the halide used.

If a vinylic carbanion is formed under these condition, the barrier of interconversion[20] between the two bent conformations 7 and 8 will be too low (around 5 Kcal/mole) and it will only be possible to isolate the equilibrium mixture of the cis and trans isomers.



7 8

3) The decarbalkoxylation in dry DMSO at 160 °C is much slower than the analogous reaction in wet DMSO at the same temperature for the same time (2h) (70% of starting material in the former and 30% in the latter case were obtained by g.l.c.). This fact is in accordance with Corey's conclusion[17] that direct decarboxylation of α,β -unsaturated malonic acid is in general quite slow.

An attempt was made to capture the likely intermediate vinylic anion $C_6H_5CH{=}\underline{C}\text{-}COOCH_3$, by carrying out the reaction for 24 hours in dry DMF and sodium bromide in the presence of benzyl bromide. The only products we were able to isolate, was a mixture of unreacted starting material and trans benzyl cinnamate (10:90), together with traces of phenyl-methylene propanedioic acid dibenzyl ester 9, that indicates that in this solvent the first step of the reaction is demethylation with consequent capture of the benzyl bromide by the carboxylate ion. In no case were we able to substantiate the

presence[21] of $C_6H_5CH{=}C(CH_2C_6H_5)COOCH_3$

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian FT 80-A spectrometer, GLC analyses were performed on a Carlo Erba HRGC 5300 using SE-30 as a stationary phase and nitrogen as carrier gase. Elemental analyses were performed on a Carlo Erba model 1106 Elemental Analyzer. Melting points were determined on a Kofler microscope and are uncorrected. DMSO was distilled from CaH under reduced pressure and stored over molecular sieves. DMF was distilled under vacuum from BaO. All salts were used as receved (Carlo Erba). Compounds 1a-g, 9 were prepared by Knoevenagel condensation[22] and 1a,b,e,f,g, were known products[23] Trans methyl and trans benzyl cinnamates were purchased from Aldrich Chemie. All the other trans cinnamates were known products[24] except 2d that was synthesized by esterification with absolute methanol of the corresponding acid[25]. The cis cinnamates were first detected in the NMR spectrum of the reaction mixture and then quantitatively evaluated by GLC.

2-Isopropoxy phenyl-methylene-propanedioic acid dimethyl ester (1d) b.p. 167-168°C (1,5 mm); n_D^{25} 1,5400; NMR ($CDCl_3$):δ1,25 (d, 6H); 3,75 (d, 6H, $COOCH_3$), 4,49 (m, 1H); 7,15 (m, 4H, Ar-H); 8,10 (s, 1H, CH=C). Yield 95%. Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73 ; H, 6.52. Found : C, 64.65 ; H, 6.48.

2-methoxy phenyl methylene-propanedioic acid dimethyl ester (1c) m.p. 50-52°C (from ethanol-water); NMR ($CDCl_3$) : δ 3.65 (s, 3H, OCH_3); 3.80 (s, 6H, $COOCH_3$); 7.10 (m, 4H, Ar-H); 8.05 (s, 1H,CH=C). Yield 97%. Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.51; H, 5.55

3-(2-isopropoxy phenyl)-propenoic acid methyl ester (2d) b.p. 150°C-152°C (4.5 mm). n_D^{20} 1.5545; NMR ($CDCl_3$):δ 1.30 (d, 6H); 3.40 (s, 3H, $COOCH_3$), 4.55 (m, 1H); 6.45 (d, 1H, CH=C); 7.20 (m, 4H, Ar-H); 8.00 (d, 1H, CH=C). Yield 95%. Anal. calcd. for $C_{13}H_{16}O_3$; C, 70.89; H, 7.32. Found: C, 71.00, H, 7.41.

Phenyl methylene propanedioic acid dibenzyl ester (9) m.p. 65°C (from ethanol); NMR ($CDCl_3$): δ 5.20 (s, 4H); 7.25 (d, 15H); 7.75 (s, 1H). Yield 95%. Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.65, H, 5.60.

Decarbalkoxylation of phenyl-methylenepropanedioic acid dimethyl ester (1a). Typical procedure in DMSO-H_2O. The diester 1a (g 2, 0.009 mol) with sodium chloride (g 0.59, 0.011 mol) is refluxed for 6 h in Me_2SO (25 ml) and water (1.8 ml, 0.1 mol). The mixture is then poured into 100 ml of brine and extracted with diethyl ether. The ether layer is washed with water, then dried over Na_2SO_4 and concentrated to give 1.1 g of a brown oil (75.8%). GLC analysis of the oil revealed 99% of trans methyl cinnamate.

Typical procedure in dry DMSO. A solution of 1a (g 2, 0.009 mol) in dry Me_2SO (25 ml) is added with sodium cloride (g 0.59, 0.011 mol) previously kept in a oven at 100°C for two hours, and then refluxed for 2 hours and worked up as above.

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5) The decomposition of DMSO begins 15-20 minutes after refluxing is reached. At that time the decarbalkoxylations should be already finished (Table 4), therefore we believe that DMSO decomposition should have no influence on the course of the reaction.

6) Alkoxy groups led to variable amounts of ether bond cleavage.

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8) Water arises from DMSO decomposition.

9) Hydrobromic acid coming from a 1,2-elimination triggers DMSO decomposition lowering dramatically the boiling point of the mixture (190°C ⟶ 100°C).

10) The resulting vinyl anion, of course, can not have a real existence as an intermediate in aqueous medium : most likely the C-C cleavage and the protonation from water are occurring at the same time.

11) This intermediate is expected to be instable and lose a molecule of water under our reaction conditions (165 °C) as previously reported [12, 13]. On the other hand, as the reaction is carried out in DMSO/H_2O it can reasonably be suggested that the equilibrium $1 \underset{-H_2O}{\overset{H_2O}{\rightleftharpoons}} 4$ is driven to the right. The intermediacy of 4 is furthermore substantiated from the isolation of variable amounts of the starting aldehydes (Table 1).

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