Stereochemistry of Base-catalysed Addition of Methyl Mercaptoacetate to Acetylenic Ketones and Esters. Effects of Activating Groups and Solvents

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Piperidine-catalysed addition of methyl mercaptoacetate to benzoyl- and *p*-chlorobenzoyl-phenylacetylenes in ethanol gave the corresponding (*Z*)-1-aryl-3-(methoxycarbonylmethylthio)-3-phenyl-2-propen-1-one. However, *p*-anisoylphenylacetylene gave a mixture of (*Z*)- and (*E*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-ones in the ratio of 4: 1. This ratio was completely inverted when the latter addition was carried out in dry benzene. Rationalisation of these results is presented which depends on the effect of activating groups and solvents on the stereochemistry of addition. Piperidine-catalysed addition of methyl mercaptoacetate to methyl phenylpropiolate in ethanol gave methyl (*Z*)-3-(methoxycarbonylmethylthio)cinnamate. Hydrazine hydrate converted some of the above mono-adducts into some pyrazole derivatives.

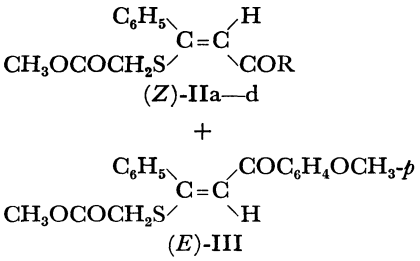
As the continuation of our work[1,2] on the stereochemistry of the base-catalysed addition of thiols to non-terminal acetylenes, we now report the results obtained from such addition of methyl mercaptoacetate to aroylphenylacetylenes, which has not been investigated previously. Furthermore, the addition to methyl phenylpropiolate was also investigated. The work was undertaken primarily to obtain more precise information on the effect of activating groups and solvents on the stereochemistry of the addition.

Thus, when methyl mercaptoacetate was added to benzoyl- and *p*-chlorobenzoyl-phenylacetylenes Ia and Ib in the presence of a catalytic amount of piperidine in ethanol at room temperature, the solid products obtained were proved to be (*Z*)-3-(methoxycarbonylmethylthio)-1,3-diphenyl-2-propen-1-one IIa and (*Z*)-3-(methoxycarbonylmethylthio)-1-(*p*-chlorophenyl)-3-phenyl-2-propen-1-one IIb, respectively. However, *p*-anisoylphenylacetylene Ic reacted with methyl mercaptoacetate under the same experimental conditions, giving two mono-adducts, that is, (*Z*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-one IIc and its (*E*)-isomer III in the ratio of about 4: 1.

C_6H_5–C≡C–COR + $HSCH_2CO_2CH_3$ ⟶

Ia—d

a: R = C_6H_5
b: R = C_6H_4Cl-*p*
c: R = $C_6H_4OCH_3$-*p*
d: R = OCH_3



(*Z*)-IIa—d

+

(*E*)-III

The structures of the mono-adducts IIa—c and III were determined from the following evidence: i) analytical data, ii) the infrared spectra, which show,

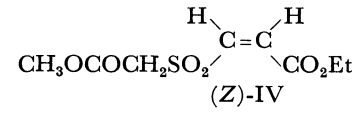
TABLE 1. SPECTRAL DATA FOR COMPOUNDS II AND III

Compound	Infrared spectra $\nu_{C=O}$ / cm^{-1}	Electronic spectra λ_{max} / nm	ε_{max}	NMR spectra (in $CDCl_3$) δ	Assignment
IIa	1780 (sh)	327	18475		
	1760	256	9105		
	1640				
IIb	1760 (sh)	330	18150	7.07—8.0	(10H, m, Ar–H and –C=CH)
	1740	272	9790	3.27	(2H, s, SCH_2)
	1640			3.6	(3H, s, CO_2CH_3)
IIc	1760	332	24500	6.8—8.14	(10H, m, Ar–H and –C=CH)
	1740	≈280—285	12100	3.23	(2H, s, SCH_2)
	1640			3.6	(3H, s, CO_2CH_3)
				3.9	(3H, s, OCH_3)
IId[a]	1760 (sh)	276	10625		
	1730	210	10915		
III	1740 (sh)	323	19825	6.8—8.0	(10H, m, Ar–H and –C=CH)
	1725			3.63	(2H, s, SCH_2)
	1660			3.83	(3H, s, CO_2CH_3)
				3.9	(3H, s, OCH_3)

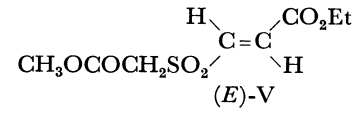
a) Lit,[5] $\nu_{C=O}$ at 1730 cm^{-1} and λ_{max} (ε) 275(10500), 211(10580).

inter alia, the bands at 1640—1660 cm^{-1} and 1725—1780 cm^{-1}. The low frequency band may be correlated with $\nu_{C=O}$ of α,β-unsaturated ketones[3] and the higher frequency one with $\nu_{C=O}$ of saturated esters,[3] iii) the electronic spectral data exhibit absorption maxima at 323—332 nm characteristic of chalcones[4] and iv) the NMR spectra of the mono-adducts IIb, IIc, and III agree quite well with the structures assigned to them (*cf.* Table 1).

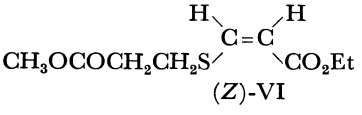
Tentative assignment of configuration to the mono-adducts IIc and III, obtained from methyl mercaptoacetate and *p*-anisoylphenylacetylene, as (*Z*) and (*E*), respectively, was based on the following: it has been reported by Bohlmann and Bresinsky[5] that in (*Z*)- and (*E*)-sulfones IV and V, respectively, the signal for SCH_2 protons in the former appears at higher field than that for the corresponding protons of the latter. Also, Halphen and Owen[6] have found that the signals for SCH_2 and $C\underline{H}_2CO_2CH_3$ in ethyl *cis*-3-[2-(methoxycarbonyl)ethylthio]acrylate VI appear at higher field when compared with those of the corresponding *trans* isomer. Since in the present investigation the signal for the SCH_2 protons in the major isomer appears at relatively higher field than that for the minor isomer, the former may be similarly assigned the (*Z*)-configuration and the latter the (*E*)-configuration. It is worth noting that the signal for the ester methyl protons of the (*Z*)-isomer appears at higher field than that of the corresponding protons of the (*E*)-isomer whereas the signals for the methoxyl groups of both isomers appear at the same position (with same strength) (*cf.* Table 1).



(*Z*)-IV



(*E*)-V

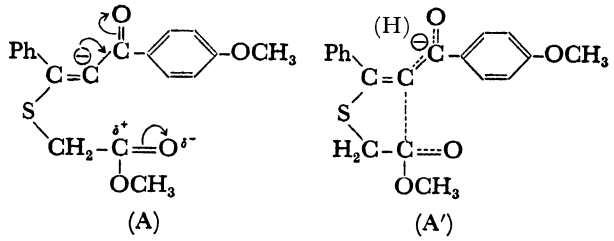


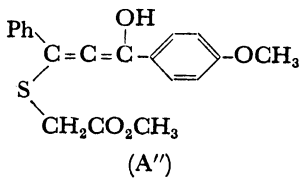
(*Z*)-VI

However, this tentative assignment was further confirmed from the following evidence: a) the electronic spectral data of the two isomers IIc and III. Thus, it is evident from Table 1 that the absorption maxima of IIc are shifted slightly to longer wave lengths with increasing strength, compared with those of III. This indicates that III has the (*E*)-configuration whereas IIc must have the (*Z*)-configuration which is consistent with the cis-trans relationship[7] on the one hand and with the configurations of *cis*- and *trans*- chalcones[4] on the other, and b) the infrared spectra of the two isomers which show $\nu_{C=O}$ of α,β-unsaturated ketone system at 1640 and 1660 cm^{-1} (Table 1). The higher value must be of the (*E*)-isomer III and the lower of the (*Z*)-isomer IIc. This is consistent with those of transoid and cisoid enones,[8] respectively.

Similarly, the mono-adducts IIa and IIb were assigned the (*Z*)-configuration on the basis of the results that their electronic spectra are similar to that of (*Z*)-IIc and also from the value of $\nu_{C=O}$ of the α,β-unsaturated ketone system (*cf.* Table 1). Moreover, the signals for SCH_2 and CO_2CH_3 protons in IIb are the same as those of (*Z*)-IIc in position and strength.

Formation of only the (*Z*)-isomers IIa and IIb in the case of addition of methyl mercaptoacetate to acetylenic ketones Ia and Ib, respectively, and (*Z*)-IIc as a major product in the case of Ic is in accord with the rule of *trans* nucleophilic addition.[9] However, formation of some (*E*)-isomer III from the addition of methyl mercaptoacetate to *p*-anisoylphenylacetylene Ic merits explanation, since it has been reported[2] that the piperidine-catalysed addition of arenethiols to Ic under the same experimental conditions, gives only the (*Z*)-mono-adducts, namely (*Z*)-3-arylthio-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-ones, *via* a concerted mechanism. It seems, therefore, that the mercaptoalkanoate moiety had played a role that facilitates formation of the (*E*)-isomer III and that a different mechanism, most probably a stepwise one might be operating in such addition. According to this mechanism, the mercaptoalkanoate anion adds first to Ic to give the anion (A) in which an interaction between the positively polarized carbon atom of the ester carbonyl group and the negatively charged α-acetylenic carbon atom is possible (*cf.* transition state A′). As a result of this interaction, proton abstraction from the protic solvent is no longer localized on the α-acetylenic carbon atom but can occur at the ketonic carbonyl oxygen atom as well, since the basicity of the latter is enhanced owing to the activating effect of the *p*-methoxyl group. Thus, addition of the proton can occur either to the α-acetylenic carbon atom or to the oxygen atom of the ketonic group. It is evident that in the former case addition of the proton will lead to formation of only the (*Z*)-isomer IIc, whereas in the latter case an enolate A″ is formed. Tautomerisation of A″ to the carbonyl compound can then lead to a mixture of the (*Z*)-IIc and its (*E*)-isomer III.



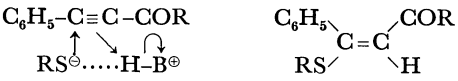


Formation of only the (*Z*)-isomers IIa and IIb on treating Ia and Ib, respectively, with methyl mercaptoacetate under the same experimental conditions can be explained on the basis that in the transition state, the proton will add preferentially to the α-acetylenic carbon atom, since in these cases the basicity of the oxygen atom of the ketonic group is not enhanced as a result of the absence of activating *p*-substituent groups.

It is worth noting that the degree of *trans* stereoselectivity for nucleophilic additions of arenethiols to terminal acetylenes of the type H–C≡C–Y in methanol has been reported,[10] depending on the nature of the activating group Y and decreasing in the case that Y is a carbonyl-containing group, *i.e.* CO_2CH_3 or $COCH_3$. An enolate intermediate has also been proposed in these cases.[10]

Since (*Z*)-IIc is configurationally stable under the same experimental conditions (see Experimental), formation of its (*E*)-isomer III could not arise from it by post-isomerisation.

If concerted addition of a proton from a protic solvent is indeed a major factor in *trans* addition, a change of solvent might produce a change in product stereochemistry. An aprotic solvent would be incapable of making such an involvement and, if in such a solvent a thiol and a basic catalyst were to behave as thiolate-protobase ion pair, protonation might, perforce, take place on the same side as thiolate coordination, so that a *trans* product might be formed by *cis* addition. This postulate has been tested previously by Halphen and Owen[6] who studied the addition of mercaptoalkanoic acid to ethyl propiolate in different solvents and concluded that the base-catalysed addition of thiols to terminal acetylenes, *i.e.* propiolates, in dilute solution of aprotic solvents will, in general, favour the formation of *trans* enesulfides (by *cis* addition). The results obtained from the present investigation may be taken as an added proof for the validity of this mechanism in the case of addition of thiolates to non-terminal acetylenes in an aprotic solvent. Thus, when methyl

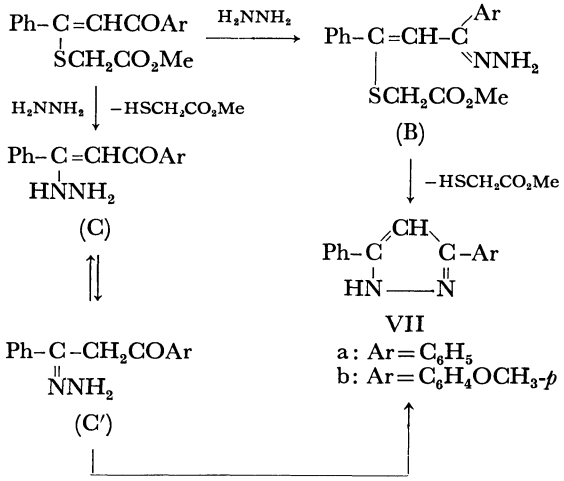


mercaptoacetate was allowed to add at room temperature to *p*-anisoylphenylacetylene Ic in dry benzene and in the presence of piperidine as a catalyst, two mono-adducts were separated (see Experimental), the major product (45%) being identical (mp, mixed mp, and IR spectroscopy) with (*E*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-one III and the minor product (10%) being identical with (*Z*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-one IIc. It is worth noting that the ratio of the (*Z*)-isomer IIc to its (*E*)-isomer III when the addition was carried out in ethanol at room temperature was found to be 4: 1.

It may, therefore, be concluded that the presence of the activating groups, namely COAr, in conjugation with the triple bond of non-terminal acetylenes can affect the stereochemistry of the base-catalysed addition of methyl mercaptoacetate in such a manner as to permit some *cis* addition, and that the change of solvent from a protic to an aprotic solvent can produce a dramatic change in product stereochemistry, *i.e.* gives predominantly *trans* or (*E*)-mono-adducts resulting from *cis* addition. Furthermore, a total stereoselectivity was observed during the addition of the same nucleophile to the non-terminal acetylenic ester, namely methyl phenylpropiolate.

Thus, piperidine-catalysed addition of methyl mercaptoacetate to methyl phenylpropiolate Id in ethanol gave methyl 3-(methoxycarbonylmethylthio)cinnamate IId which was analytically pure and showed the infrared-spectral bands for $\nu_{C=O}$ at 1760 (sh), 1730, and 1720 cm^{-1}, which may be correlated with $\nu_{C=O}$ of saturated esters[3] and α,β-unsaturated esters.[3] It is worth noting that Bohlmann and Bresinsky[5] have studied the addition of methyl mercaptoacetate to ethyl phenylpropiolate in dimethyl sulfoxide containing potassium *t*-butoxide as a catalyst and obtained a mono-adduct whose spectral data (see Table 1) are in good agreement with those of the product obtained from the present investigation, namely IId. They[5] did not assign any configuration to the mono-adduct. However, the compound in our hands may be tentatively assigned the (*Z*)-configuration on the basis of the results that similar addition of thiolates to ethyl phenylpropiolate proceeded exclusively by *trans* addition.[11]

The mono-adducts IIa and IIc reacted with hydrazine hydrate to give 3,5-diphenylpyrazole VIIa and 1*H*- or 2*H*-3-(*p*-methoxyphenyl)-5-phenylpyrazole VIIb, respectively. The reaction may be represented as involving an *in situ* formation of the hydrazone (B) whose NH_2 group then attacked the β-carbon atom to give the cyclised product with elimination of methyl mercaptoacetate or alternatively the hydrazine may attack the β-carbon atom first with expulsion of methyl mercaptoacetate to give (C), not isolated, which is tautomeric with (C'). Condensation of the NH_2 group with the carbonyl group can then lead to the pyrazole derivative.



Experimental

All melting points are not corrected. Infrared and electronic spectra were measured on a Unicam SP 1200 spectrophotometer (KBr discs) and Beckmann DK 2 spectrophotometer (in ethanol), respectively. NMR spectra (in $CDCl_3$) were determined on a Varian T 60 instrument using TMS as an internal reference.

(Z)-IIa—c and (E)-III 1-Aryl-3-(methoxycarbonylmethylthio)-3-phenyl-2-propen-1-ones. To a solution of the ketone Ia, b, or c (0.005 mol) in ethanol (10 ml) was added a solution of methyl mercaptoacetate (0.005 mol) in ethanol (10 ml) followed by one drop of piperidine. The reaction mixture was then allowed to stand at room temperature for *ca.* 20 h. The precipitated solids were filtered off and recrystallized from an

Table 2. (*Z*)-1-Aryl-3-(methoxycarbonylmethylthio)-3-phenyl-2-propen-1-ones IIa—c and (*E*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-one III

Compound	Melting point °C	Yield %	Formula	Found (%)			Calcd (%)		
				C	H	S	C	H	S
IIa	108—109[a]	65	$C_{18}H_{16}SO_3$	69.6	5.3	10.3	69.2	5.1	10.25
IIb	94—95[b]	60	$C_{18}H_{15}ClSO_3$	62.7	4.6	9.1	62.3	4.3	9.2
IIc	88—89[c]	47	$C_{19}H_{18}SO_4$	66.5	5.4	9.4	66.7	5.3	9.35
III	112—113[d]	12	$C_{19}H_{18}SO_4$	66.6	5.3	9.8	66.7	5.3	9.35

a) From light petroleum (bp 80—100 °C). b) From light petroleum (bp 60—80 °C). c) From light petroleum (bp 60—80 °C), mixed mp with III 60—65 °C. d) From benzene–light petroleum (bp 60—80 °C).

appropriate solvent to give the *(Z)-title compounds*. Evaporation of the mother-liquor at room temperature after separation of the (*Z*)-IIc gave a solid residue which was fractionally recrystallized from light petroleum (bp 60—80 °C) to which had been added few drops of benzene to give (*E*)-III. The combined mother-liquors after isolation of (*E*)-III were evaporated at room temperature to give a small amount of (*Z*)-IIc. The results are given in Table 2.

When dry benzene was used as a solvent in the case of addition of methyl mercaptoacetate to *p*-anisoylphenylacetylene Ic, the precipitated solid was fractionally crystallized from benzene–light petroleum (bp 60—80 °C) to give the (*E*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-one III in 45% yield, mp and mixed mp with the sample obtained from the addition in ethanol 112—113 °C. The mother-liquors gave a precipitated solid which was recrystallized from light petroleum (bp 60—80 °C) to give the (*Z*)-3-(methoxycarbonylmethylthio)-1-(*p*-methoxyphenyl)-3-phenyl-2-propen-1-one IIc in 10% yield, mp 88—89 °C, not depressed upon admixture with the (*Z*)-IIc obtained from the reaction using ethanol as a solvent.

Attempted Isomerisation of (Z)-3-(Methoxycarbonylmethylthio)-1-(p-methoxyphenyl)-3-phenyl-2-propen-1-one, IIc. Piperidine (0.1 ml) was added to a solution of the *title compound* (0.001 mol) in ethanol or benzene (5 ml) and the solution kept at room temperature for 20 h. The solid obtained after allowing the solvent to evaporate at room temperature was crystallized from light petroleum (bp 60—80 °C) to give unchanged starting material (mp, mixed mp, and IR spectroscopy) in *ca.* 95% recovery.

Methyl (Z)-3-(Methoxycarbonylmethylthio)cinnamate, IId. To a solution of methyl phenylpropiolate Id (0.01 mol) in ethanol (20 ml) was added methyl mercaptoacetate (0.01 mol) followed by one drop of piperidine and the solution was allowed to stand at room temperature until crystallization occurred. Recrystallization of the filtered solid product from benzene–light petroleum (bp 60—80 °C) gave the title compound as colourless crystals in 55% yield, mp 97—98 °C. Found: C, 58.5; H, 5.3; S, 12.4%. Calcd for $C_{13}H_{14}SO_4$: C, 58.6; H, 5.3; S, 12.0%. Evaporation of the mother-liquors left an oil which contained unchanged starting materials since infrared spectroscopy shows, *inter alia*, $\nu_{C\equiv C}$ at 2200 cm^{-1}.

3,5-Diphenylpyrazole, VIIa, and 1H- or 2H-3-(p-Methoxyphenyl)-5-phenylpyrazole, VIIb. To a solution of the monoadducts IIa or IIc (0.003 mol) in ethanol (20 ml) was added excess hydrazine hydrate and the reaction mixture was refluxed for 2.5 h. After 24 h the solid product was collected by filtration and recrystallized from ethanol. 3,5-Diphenylpyrazole VIIa was obtained as colorless crystals in 86% yield, mp 199—200 °C, undepressed upon admixture with an authentic specimen.[12] 1*H*- or 2*H*-3-(*p*-methoxyphenyl)-5-phenylpyrazole VIIb was obtained in 82% yield, mp 155—156 °C, undepressed upon admixture with an authentic specimen.[12]

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