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Towards a Rationalisation of Regioselectivity Patterns in Reactions of 2-(Halogenomethyl)-2-alkenoic Esters with Carbon Nucleophiles

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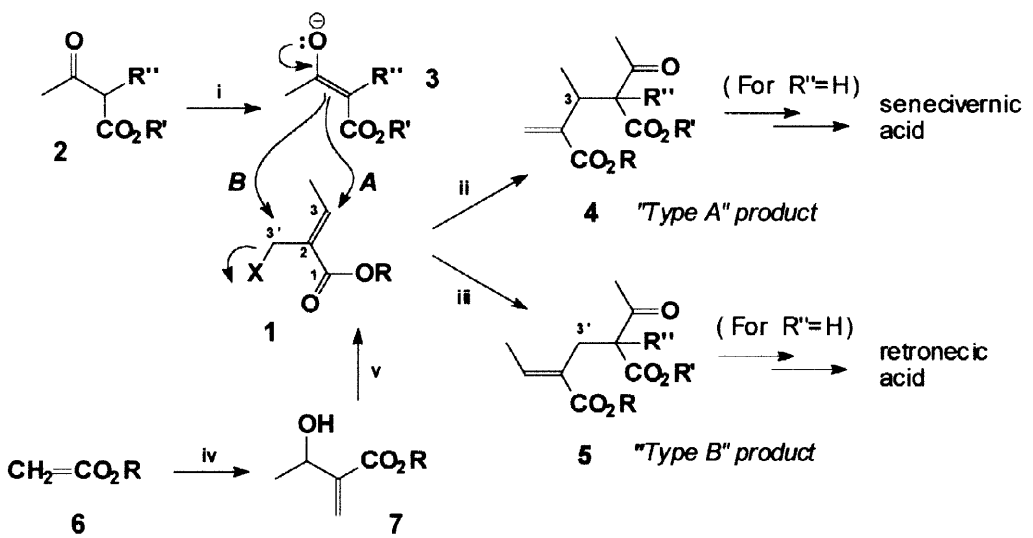
Abstract: A ^{1}H NMR study of reactions of methyl 2-(bromomethyl)-2-butenoate with the sodium enolate of methyl 2-methyl-3-oxobutanoate has permitted rationalisation of the observed, solvent-dependent regioselectivity in terms of addition-elimination sequences. © 1998 Elsevier Science Ltd. All rights reserved.

Regiocontrol in reactions of carbon nucleophiles with 2-(halogenomethyl)-2-alkenoic esters [1,2] has been exploited previously in the synthesis of necic acids.[3] It was found that the regioselectivity of these reactions was particularly sensitive to change in the base – solvent system. Thus, with NaH – THF, *effective* allylic (S_N2') displacement of the halide ion favoured formation of the rearranged "*Type A*" products **4** (Scheme 1), whereas with NaOEt – EtOH, direct (S_N2) displacement appeared to predominate with preferential formation of the "*Type B*" products **5**. It was postulated [1] that, in the more polar solvent, EtOH, a *unimolecular* (S_N1) mechanism was favoured with preferential attack at the less hindered, primary *allylic* carbon (C-3′) of the carbocation intermediate,



Reagents : i, NaH, THF or NaOEt, EtOH ; ii, THF (R ' = Et ; R " = H ; X = Br) ; iii, EtOH (R ' = Et ; R " = H ; X = Br); iv, CH_3CHO, DABCO ; v, HBr - H_2SO_4 or HCl - H_2SO_4 or HI - H_3PO_4.

Scheme 1

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while in the less polar THF, *bimolecular* (S_N2') displacement favoured nucleophilic attack at the more accessible, vinylic centre (C-3) in the substrate **1** with concomitant migration of the double bond. Eagen and Cromwell [4] have adduced an S_N2' type mechanism to account for the formation and subsequent rearrangement of amino analogues. There is, however, some controversy concerning S_N2' mechanisms,[5] and kinetic studies have been undertaken in order to confirm our earlier, tentative explanations [1] for the observed regiocontrol.

Reactions between the unsaturated bromo ester **9** and methyl 2-methyl-3-oxobutanoate enolate **8** (Scheme 2) were monitored by ^{1}H NMR spectroscopy,[6] which required the use of deuteriated solvents. Consequently, reactions were conducted using the base – solvent systems, NaH – THF-d_8 and NaOMe – CD_3OD, the latter to model the NaOEt – EtOH system used previously ; furthermore, the *methyl* esters **8** and **9** were used to minimise complications due to transesterification. Surprisingly, in none of the cases examined were simple first- or second-order kinetics observed. Moreover, the ^{1}H NMR data indicated that preferential formation of the "*Type A*" products **11**, rather than the expected "*Type B*" products **13**, was typical of the initial phase of reactions conducted in CD_3OD. However, when the NMR tube was returned to the NMR probe on the following day, a dramatic change in the product distribution was apparent, with the "*Type B*" product **13** having become the predominant isomer! In fact, the final product ratios (*Type A*: *Type B* ; 17 : 83) were comparable to those observed previously.[1] It thus appears that, in CD_3OD, initial, rapid formation of the "*Type A*" product **11** is followed by slow isomerisation to the ultimately dominant,"*Type B*" product **13** – a sequence of events graphically illustrated by the kinetic data in Figure 1. Such isomerisation can be rationalised by the establishment of an equilibrium between the "*Type A*" and "*Type B*" products, in which the enolate species **8** acts as both nucleophile and resonance-stabilised leaving group. Predominance of the "*Type B*" product **13** under equilibrium conditions may be attributed to the fact that the double bond is non-terminal in **13**, whereas in the isomeric "*Type A*" system **11** the double-bond is terminal.[7] This mechanistic hypothesis is supported by the observation that isolation and subsequent treatment of the "*Type A*" product **11** with the enolate **8** in CD_3OD resulted in the formation of the "*Type B*" product **13**.

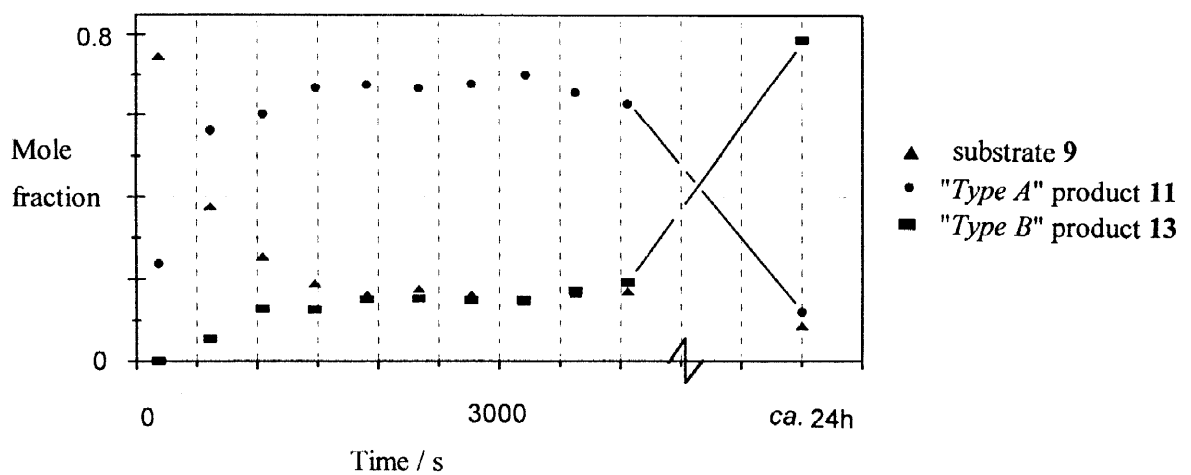
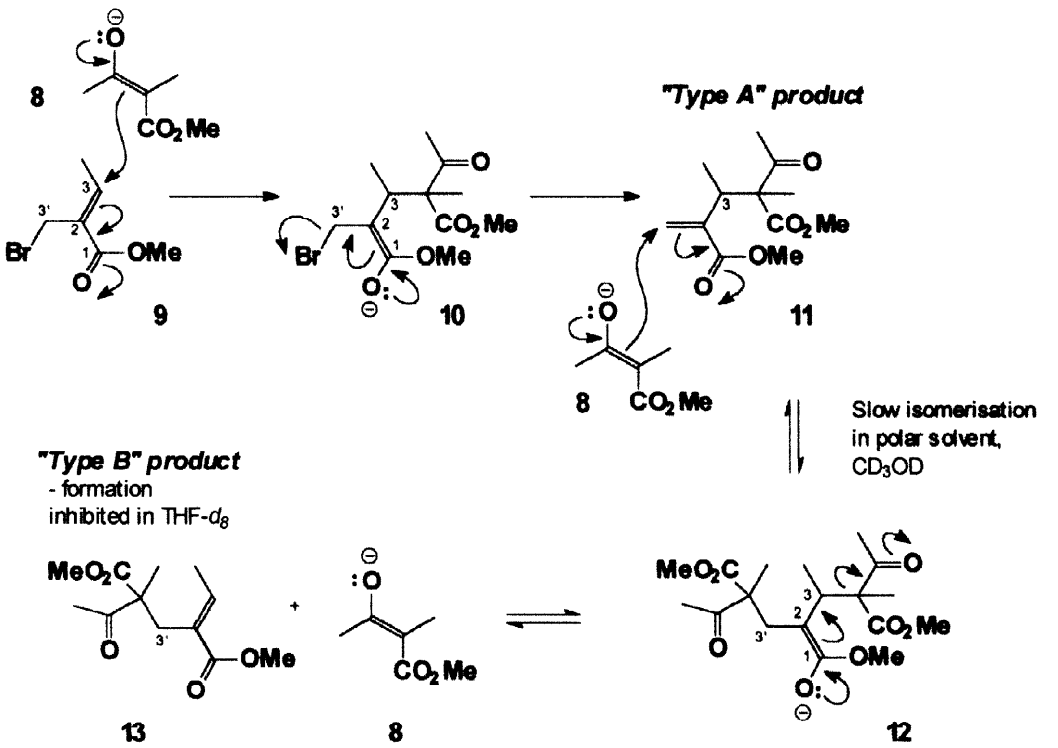


Figure 1. Kinetic data for the reaction of the bromo ester **9** (0.023*M*) and the enolate **8** (0.037*M*) in CD_3OD.

When the reactions were conducted using the base – solvent system, NaH – THF-d_8, preferential formation of the "*Type A*" product was again clearly evident. In THF-d_8, however, the initially established product ratios did not appear to change with time. It thus seems that, in the less polar solvent, THF-d_8, and in the absence of a good leaving group, the second addition-elimination sequence (Scheme 2) is inhibited and the "*Type A*" product **11**

predominates. The reactions (as judged by $t_{½}$ values for the formation of the "*Type A*" product **11**) are faster in CD_3OD than in THF-d_8, and it is apparent that, irrespective of whether the solvent is THF-d_8 or CD_3OD, they do not follow the simple unimolecular or bimolecular mechanisms [8] postulated previously.[1] We conclude that the observed regioselectivity switch does not reflect a fundamental change in mechanism but, rather, inhibition of the second addition-elimination sequence in the less polar solvent, THF-d_8.



Scheme 2. Proposed mechanistic sequence

EXPERIMENTAL

Methyl (*Z*)-2-bromomethyl-2-butenoate **9** was prepared by treating the corresponding Baylis-Hillman product **7** (R = Me) with HBr–H_2SO_4.[1] Methyl 2-methyl-3-oxobutanoate was obtained by the standard methylation of methyl acetoacetate, and all reagents were distilled prior to use.

Kinetic procedure.

Reactions were monitored at 303 K on a Bruker AMX400 NMR spectrometer. In each case, the NMR tube, fitted with a septum and containing the enolate solution under dry N_2, was inserted into the NMR probe to permit temperature equilibration and instrument shimming. The NMR tube was then removed, the required quantity of substrate injected through the septum into the NMR tube, which was shaken ($t = t_o$) and returned to the NMR probe. Spectra were run (16 - 32 scans) at 3 - 5 min intervals using an automatic routine. Reactant concentrations were varied and kinetic data were obtained for 12 reactions (9 in CD_3OD and 3 in THF-d_8).

Generation of the enolate solutions.

Reactions in THF-d_8. – Sodium hydride (60% dispersion in oil) was accurately weighed into a dry reaction flask and THF-d_8 (Aldrich; 99.5% D; *ca.* 1.0 mL) was added, using a 1000 μL syringe, to obtain the required NaH concentration. Methyl 2-methyl-3-oxobutanoate (1 eq.) was then added and the mixture stirred under dry N_2 for 1 h to generate the enolate **8**. The resulting enolate solution was divided into two equal aliquots, each being injected through a septum, into separate NMR tubes which had been previously flushed with dry N_2.

Reactions in CD_3OD. – The procedure described above for reactions in THF-d_8 was followed, using NaOMe (accurately weighed) and CD_3OD (Merck, Uvasol®; 99.5% D; *ca.* 1.5 mL) to achieve the required concentration. After generation of the enolate **8**, the solution was divided into three equal aliquots (*ca.* 0.5 mL).

***Isolation of the "Type A" product* 11.**

The "*Type A*" product **11** was isolated from a reaction of the sodium enolate **8** [generated *in situ* by treating methyl 2-methyl-3-oxobutanoate (1 g) with NaH (1.2 eq.)] and the bromo ester **9** (1.48 g, 1.2 eq.) in dry THF (20 mL). The crude product **11** was then treated with the sodium enolate **8** in CD_3OD and, after 4 d, substantial transformation to the "*Type B*" product **13** was confirmed by ^{1}H NMR spectroscopy.

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4. Eagen, M.C.; Cromwell, N.H. *J. Org. Chem.*, **1974**, 39, 3863-3866.
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6. At preparative concentrations (*ca.* 0.3*M*) the reactions are too fast to be monitored by ^{1}H NMR spectroscopy, but the relative insensitivity of the technique precludes excessive dilution. It was found, however, that at concentrations of *ca.* 0.02*M* the reactions could be conveniently followed.
7. See March, J. *Advanced Organic Chemistry : Reactions, Mechanisms and Structure*, 4th Edn., Wiley, New York, **1992**, p. 999.
8. Unimolecular (S_N1, S_N1') or bimolecular (S_N2, S_N2') mechanisms would, of course, exhibit first- or second-order kinetic behaviour, respectively. However, given the observed complexity of the kinetic data, their implication as minor, competing pathways is not precluded.