Alkylation of the Sodium Enolate of Ethyl Acetoacetate in Dimethoxyethane. Leaving Groups Effect on Rate and Orientation

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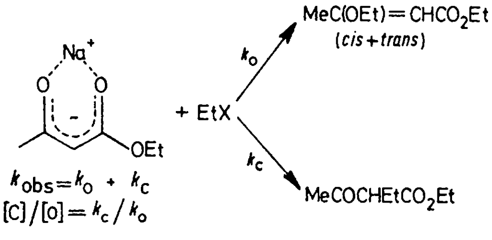
Summary There is no evident relationship between rate and the ratio of C- to O-alkylation products in the reaction of the sodium enolate of ethyl acetoacetate with EtI, EtBr, TsOEt, FSO_3Et, and CF_3SO_3Et in dimethoxyethane.

THE effect of the leaving group of the electrophile in alkylation reactions of ambident nucleophiles, such as enolate anions, is well known.[1] Several explanations have been proposed; some involve 'hardness' or 'softness' of the leaving group (HSAB theory),[2] and others exothermicity of the reaction[3] or electrophilicity of the alkylating agent.[4]



We have studied the kinetics and sites of alkylation of ethyl acetoacetate sodium enolate by a series of ethylating electrophiles, EtX, of very different reactivities, *e.g.* ethyl fluorosulphonate ('magic ethyl') and ethyl trifluoromethanesulphonate ('ethyl triflate') which are known to be very reactive.[5,6]

TABLE

	I^-	Br^-	TsO^-	$EtSO^-$	FSO^-	CF_3SO^-
C/O	>100	60	6·6	$4{\cdot}8_4$	$3{\cdot}5_3$	$3{\cdot}7_3$
$10^5 \times k_{obs}$[a]	500	8	1·3	40	$6{\cdot}1 \times 10^5$	$17{\cdot}8 \times 10^5$
$10^5 \times k_C$[a]	500	7·9	1·1	33	$4{\cdot}8 \times 10^5$	14×10^5
$10^5 \times k_O$	<5	0·1	0·2	7	$1{\cdot}3 \times 10^5$	$3{\cdot}8 \times 10^5$

[a] $l\ mol^{-1}\ min^{-1}$; $T = 0\ °C$; [enolate] $= 5 \times 10^{-2}$M.

The results‡ (Table) show no evident relationship between rate and orientation of the reaction: for ratio of C- to O-attack, k_C/k_O, the sequence is: $I^- > Br^- >> TsO^- > EtSO_4^- > CF_3SO_3^- = ca.\ FSO_3^-$, but for the overall rate

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‡ In the case of fluorosulphonate and triflate overall rate constants, k_{obs}, were measured by g.l.c. analysis of alkylation product in the presence of an internal standard. With the other electrophiles, alkalimetric titration of the remaining enolate was used. The C/O ratios were determined by g.l.c. analysis. In each case, good second-order plots were obtained at least up to 50% of the reaction.

constants, the sequence is: $CF_3SO_3^- =$ *ca.* $FSO_3^- >> I^- > EtSO_4^- > Br^- > TsO^-$.

The orientation of the attack mainly depends on the 'hardness' or 'softness'[2] of the leaving group atom linked to carbon. 'Soft' leaving groups (X = Br,I) lead to almost exclusive C-alkylation, whereas carbon–oxygen cleavage in the case of 'hard' leaving groups ($X = OSO_2R$) leads to substantial O-alkylation.

In the homogeneous series of hard sulphate and sulphonates, electrophilic reactivity (*cf.* FSO_3^-, $CF_3SO_3^-$ compared to TsO^-, $EtSO_4^-$) has little effect on the orientation of the reaction: for instance, while CF_3SO_3Et strikingly reacts 4×10^4 times faster than SO_4Et_2 and 10^6 times faster than TsOEt, the percentage of O-ethylation changes only slightly from 21% (C/O = 3·7) to 17% (C/O = 4·8) and 13% (C/O = 6·6).

Thus, despite a great difference in rates, alkyl triflates and tosylates seem to react by very similar mechanisms, both in alkylation and in solvolysis reactions.[6]

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