Tetrahedron Letters, Vol 32, No 40, pp 5611-5614, 1991
Printed in Great Britain

0040-4039/91 $3.00 + 0
Pergamon Press plc

A KINETIC AND MECHANISTIC STUDY OF THE BAYLIS-HILLMAN REACTION

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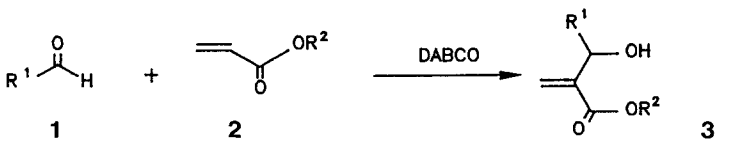
Abstract: Reactions of acrylate esters with pyridinecarboxaldehydes, in the presence of 3-hydroxyquinuclidine or 1,4-diazabicyclo[2 2.2] octane, have been followed by ^{1}H NMR spectroscopy, and a mechanism which accommodates the kinetic data has been presented.

The Baylis-Hillman reaction,[1] which involves 1,4-diazabicyclo[2.2.2]octane (DABCO) catalysed coupling of aldehydes and acrylate esters (Scheme 1), has found use in the synthesis of necic acids such as integerrinecic-,[2] retronecic-[3] and senecivernic acid,[4] and other compounds.[5] These coupling reactions, which tend to be very slow (typically requiring 4-7 days or longer for completion), may be accelerated by using electrophilic heterocyclic aldehydes or by substituting 3-hydroxyquinuclidine for DABCO.[6] Such acceleration has made a ^{1}H NMR kinetic study feasible, and in this communication, we present a mechanistic sequence which accommodates the experimental data.

SCHEME 1



1 2 3

Various reaction systems were selected in order to explore the effects of varying :- the 3°amine catalyst; the substrate substituents, R^1 and R^2, and the component concentrations. The reactions[7] were followed by monitoring the integral ratios of adequately resolved substrate (1) and product (3) ^{1}H NMR heteroaromatic signals. For given concentrations of 3°amine, the reactions exhibit linear second-order plots[8] as illustrated in Figure 1.[9] The experimental data are, in fact, consistent with third-order kinetics overall (Equation 1) or, assuming the concentration of 3°amine to be constant, pseudo second-order kinetics (Equation 2). The third-order rate constants (k_{obs}) are detailed in Table 1

$$\text{Rate} = k_{obs}[1][2][3°\text{amine}] \quad (1)$$

$$\text{Rate} = k_a[1][2] \quad (2)$$

$$\text{where } k_a = k_{obs}[3°\text{amine}]$$

$$\text{Rate} = k_2K_1[1][2][3°\text{amine}] \quad (3)$$

The proposed mechanism,[10] which is detailed in Scheme 2, is consistent with the experimentally determined rate equations and with earlier suggestions reviewed by Drewes and Roos.[1] This mechanism involves an addition-elimination sequence which is initiated by nucleophilic attack of the 3°amine on the acrylate ester substrate **2** to form a transient dipolar enolate species **4**, which subsequently attacks the electrophilic aldehyde **1** to afford the intermediate adduct **5**

The rate of formation of the adduct **5** may be expressed in terms of Equation (3) which, for $k_{obs} = k_2K_1$, is identical to the experimentally determined rate Equation (1) and this step is considered to be rate-determining Proton transfer and elimination of the 3°amine catalyst then affords the coupled product **3** From the rate constants (k_{obs}, Table 1) it is apparent that the reaction rate is sensitive to variation of both the aldehyde substituent (R^1, entries 1 and 10) and the alkyl substituent (R^2, entries 1, 2 and 3). Thus, the reduction in rate constant (k_{obs}) with the increasing electron-releasing inductive effect of the alkyl substituent (R^2 = Me < Et < Pr^i) may be attributed to relative destabilisation of the dipolar enolate **4** and a consequent decrease in the equilibrium constant, K_1 (Equation 3) The rate-enhancement associated with substitution of 3-hydroxyquinuclidine for DABCO (compare entries 8 and 9) may be rationalised in terms of hydrogen-bonding stabilisation[6] of the dipolar intermediate **4** (Figure 2) and a consequent increase in the equilibrium constant, K_1 (Equation 3). This hydrogen-bonding model is supported by the small kinetic isotope effect (k_H/k_D = 1 3) observed with use of deuteriated 3-hydroxyquinuclidine[11] (compare entries 1 and 7, Table The decrease in rate-constant observed on doubling the proportions of non-polar reactants (compare entries 1 and 5 with 4, 6 and 9) is attributed to a decrease in the overall polarity of the concentrated solutions, which were used to ensure convenient reaction times.

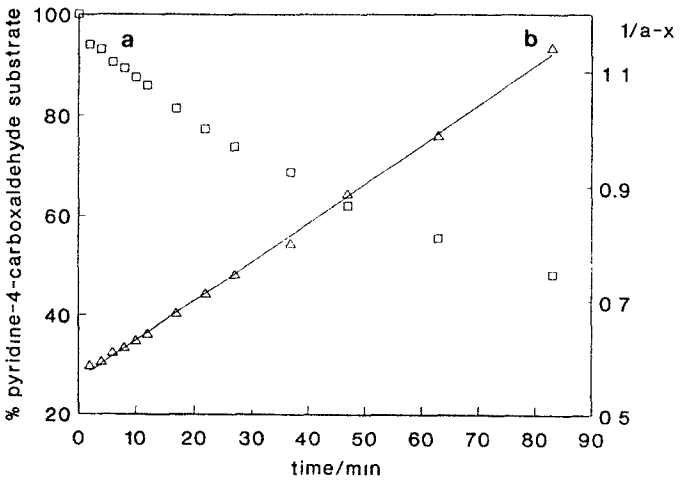


FIGURE 1. Kinetic plots for the 3-hydroxyquinuclidine catalysed coupling of methyl acrylate with pyridine-4-carboxaldehyde (entry 1, Table)
(a) rate of consumption of pyridine-4-carboxaldehyde,
(b) pseudo second-order plot

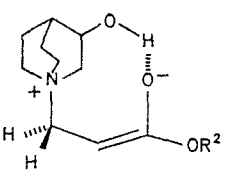
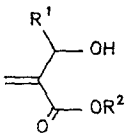


FIGURE 2

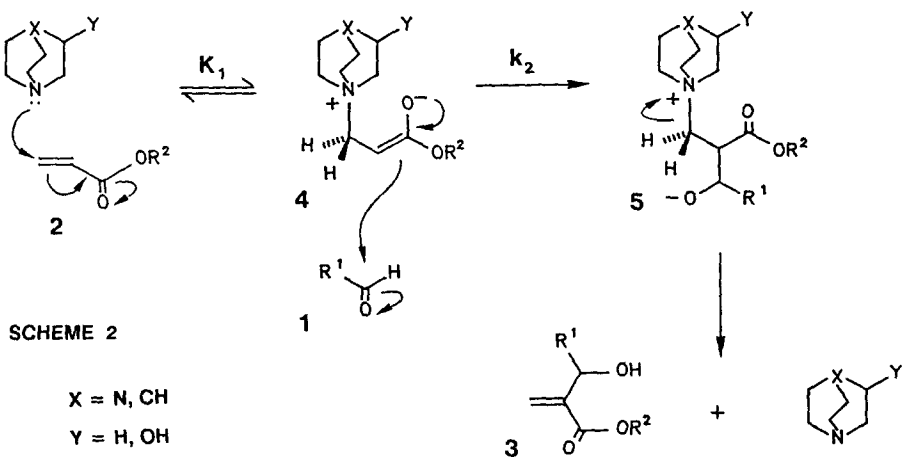
TABLE 1. Kinetic data for the synthesis of the adducts (3) from acrylate esters (2) and pyridine-2- or pyridine-4-carboxaldehydes (1) in $CDCl_3$.



3

Entry	R^1	R^2	Catalyst	Molal conc./mol.kg^{-1} (1):(2):catalyst	k_{obs}[a]/mol^{-2}kg^{2}s^{-1}
1	pyr-4	Me	Hq[b]	1.82 : 1.82 : 0.10	(1.42 ± 0.04) x 10^{-3}
2	pyr-4	Et	Hq	1.82 : 1.82 : 0.10	(9.03 ± 0.01) x 10^{-4}
3	pyr-4	Pr^i	Hq	1.82 : 1.82 : 0.10	(4.60 ± 0.14) x 10^{-4}
4	pyr-4	Me	Hq	3.63 : 1.82 : 0.10	(1.32 ± 0.02) x 10^{-3}
5	pyr-4	Me	Hq	1.82 : 1.82 : 0.19	(1.42 ± 0.06) x 10^{-3}
6	pyr-4	Me	Hq	1.82 : 3.63 : 0.10	(9.77 ± 0.10) x 10^{-4}
7	pyr-4	Me	D-Hq[c]	1.82 : 1.82 : 0.10	(1.09 ± 0.06) x 10^{-3}
8	pyr-4	Me	DABCO[d]	3.63 : 3.63 : 0.18	(1.51 ± 0.02) x 10^{-4}
9	pyr-4	Me	Hq	3.63 : 3.63 : 0.19	(1.11 ± 0.09) x 10^{-3}
10	pyr-2	Me	Hq	1.82 : 1.82 : 0.10	(2.89 ± 0.04) x 10^{-4}

[a]Mean of duplicate determinations. [b]Hq is 3-hydroxyquinuclidine. [c]D-Hq is monodeuteriated 3-hydroxyquinuclidine. [d]DABCO is 1,4-diazabicyclo[2.2.2]octane.



SCHEME 2

ACKNOWLEDGEMENTS

The authors thank AECI Ltd for a Post-graduate Fellowship (M L.B.), Rhodes University and the Foundation for Research Development for generous financial support, and Dr C McClelland (University of Port Elizabeth) for assistance with EPR spectroscopy

REFERENCES AND NOTES

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7 The aldehydes **1** and acrylate esters **2** were distilled prior to use All reactants were thermostatted, prior to mixing, at the probe temperature (37°C) of the Perkin Elmer R12A 60 MHz NMR spectrometer used to follow the reactions In a typical procedure, pyridine-4-carboxaldehyde (0 107 g, 1 0 mmol), 3-hydroxyquinuclidine (0 007 g, 0 06 mmol) and $CDCl_3$ (0 550 g) were weighed into a 1 ml flask and heated to probe temperature After equilibration, methyl acrylate (0 086 g, 1 0 mmol) was added ($t = t_0$) and the reaction mixture transferred to an NMR tube *The measured rate constants (Table 1) represent, in each case, the mean of two determinations which* agreed within acceptable limits

8 Plots of 1/(a-x) versus t (for $a = b$) or ln (a-x)/(b-x) versus t (for $a \neq b$) (where a and b correspond to the initial concentrations of aldehyde **1** and acrylate ester **2** respectively, and x corresponds to the concentration of product **3** at time t) gave essentially straight lines over the initial 50-70% of each reaction, with slopes equal to k_a or $k_a(a-b)$ respectively

9 In some instances, data-point scatter and curvature was more pronounced, but linear regression analysis of points corresponding to at least 50% completion still afforded acceptable correlation coefficients ($\geq$ 0 99)

10 The possibility of an electron transfer process, involving the 3°amine, was explored by conducting a reaction (comparable to entry 1, Table 1) in the probe of a Varian E-Line Century EPR spectrometer operating at 9 5 GHz (magnetic field · 3360 G, field scan · 1000 G) Three scans, using various gain, modulation amplitude and microwave power settings failed to provide any evidence for the presence of radical species

11 Deuteriation of 3-hydroxyquinuclidine was effected by stirring 3-hydroxyquinuclidine (1 g) in CD_3OD (1 ml) for 20 min , evaporating the solvent and repeating the process until no hydroxyl signal was visible in the ^1H NMR spectrum of the deuteriated product.

(Received in UK 23 July 1991)