Pergamon

Tetrahedron 54 (1998) 3871–3876

TETRAHEDRON

Indolizine Studies Part 4.[1] Kinetics and Mechanism for the Formation of Indolizines *via* Thermal Cyclisation of 2-Pyridyl Derivatives

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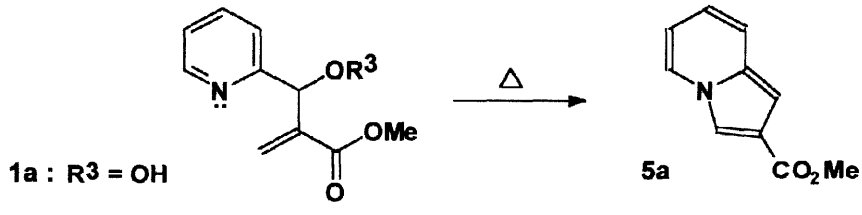
Received 9 December 1997; revised 3 February 1998; accepted 5 February 1998

Abstract: The influence of substituents and temperature on the thermal cyclisation of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoic esters and analogues has been explored using ^{1}H NMR spectroscopy, and mechanistic proposals for the formation of the resulting indolizines are presented.

In addition to exhibiting a spectrum of pharmacological effects, synthetic indolizines have found application as photographic sensitisers, fabric brighteners and dyes.[2,3] Methods for the preparation of these compounds continue to be developed [4] and we have previously reported a convenient and relatively efficient synthesis of 2-cyano- and 2-carbonylindolizines *via* thermal cyclisation of 2-pyridyl precursors.[5] Formation of methyl indolizine-2-carboxylate **5a** (Scheme 1) during an attempted distillation of the Baylis-Hillman product, methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **1a**,[6] first alerted us to the synthetic potential of this reaction,[7] and a kinetic study has been undertaken to elucidate the mechanistic details of this useful transformation.



Scheme 1

On a preparative scale, cyclisation to indolizine derivatives is typically effected by heating the neat, acetylated pyridyl precursors **2** at *ca.* 100°C.[5] In order to follow the reactions by ^{1}H NMR spectroscopy, however, a suitable solvent was required and DMSO-d_6 proved to be ideal, permitting smooth and efficient cyclisation in the temperature range of interest (*ca.* 363-383 K). In all cases examined, good linear correlations [$(R)^2 > 0.99$] were observed for first-order plots of the kinetic data, and further confirmation of the first-order character of the cyclisation reaction was provided by varying the substrate concentration (*cf.* entries 2 and 3; 14 and 15; Table 1). The substrates (**2a-f**)

0040-4020/98/$19.00
PII: S0040-4020(98)00113-6

were chosen to illustrate substituent effects on the reaction rate and so facilitate interpretation of the kinetic data.

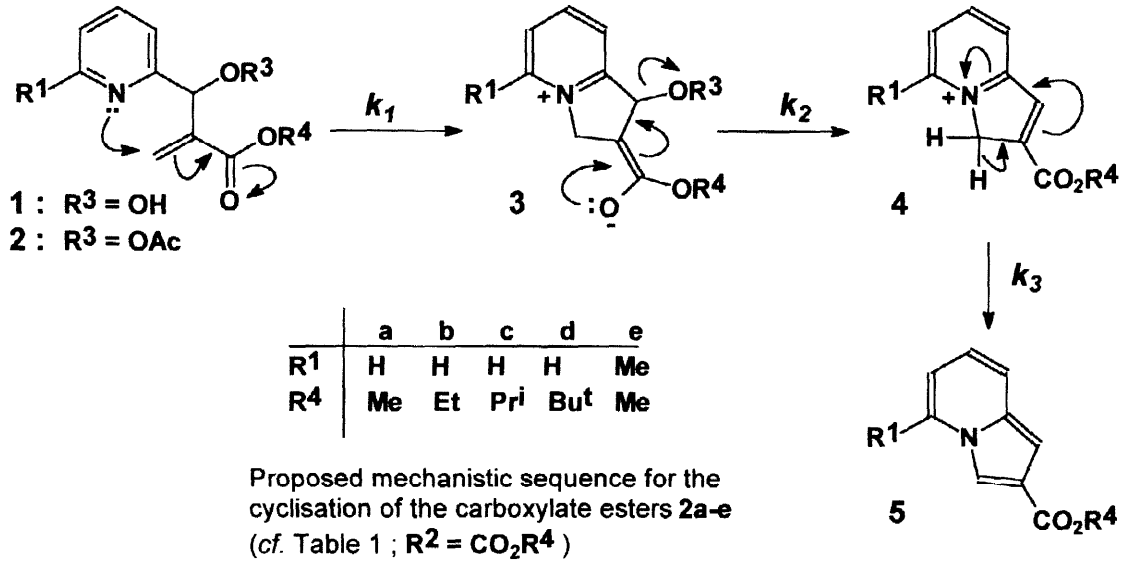
Examination of the results summarised in Table 1 reveals several significant features.

i) The first-order constants for the esters **2a - d** decrease as the *O*-alkyl substituent is changed [k_{obs} for $R^2 = CO_2Me$(**2a**) > CO_2Et(**2b**) > CO_2Pr^i(**2c**) > CO_2Bu^t(**2d**)].

ii) The rate constant is effectively doubled by introduction of the 6′-methyl substituent on the pyridine nucleus (*cf.*entries 2 and 14).

iii) The rate constants for the nitrile **2f** are lower, at corresponding temperatures, than for the methyl-(**2a**), ethyl-(**2b**) and isopropyl ester (**2c**).

These observations are accommodated by the nucleophilic addition - elimination sequence detailed in Scheme 2.† The initial step of the proposed mechanism (**2** → **3**) involves conjugate addition of the pyridyl nitrogen to the α,β-unsaturated moiety. The kinetic significance of this Michael-type addition is apparent not only in the increased reactivity of the 6-methylpyridyl system **2c** (*cf.* entries 2 and 14), reflecting *nucleophilic* enhancement by the 6′-methyl group, but also in the influence of substituents R^2 on the *electrophilicity* of the vinyl system. The observed decrease in first-order rate constants for the series of esters **2a-2d** may be attributed to a progressive reduction



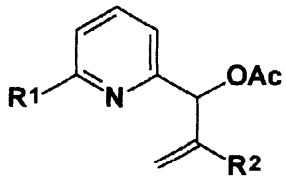
Scheme 2

† Illustrated for the carboxylate esters **2a-e**; in the case of the nitrile **2f**, cyclisation is expected to proceed *via* the resonance stabilised anion **3f** (see Figure 1).

in the electrophilicity of the "Michael acceptor" as a result of the increasing electron-releasing inductive effect of the respective *O*-alkyl groups. The lower reactivity of the nitrile **2f** (relative to the carboxylate esters **2a-c**) follows the trend reported for nucleophilic addition of amines to Michael acceptors, *i.e.*, $CH_2 = CHCO_2Me > CH_2 = CHCN$.[8]

In the absence of unsaturated electron-withdrawing R^2 substituents (*e.g.* R^2 = CN; CO_2R), the conjugate addition step would not be possible and cyclisation would require direct allylic displacement (S_N') of the acetoxy group. Thus, in contrast to the relatively easy cyclisation of the α,β-unsaturated carbonyl and carbonitrile substrates discussed here, Boekelheide and Windgassen [9] found it necessary to heat 3-acetoxy-3-(6-methyl-2-pyridyl)propene to 450°C to obtain 5-methylindolizine in 30% yield!

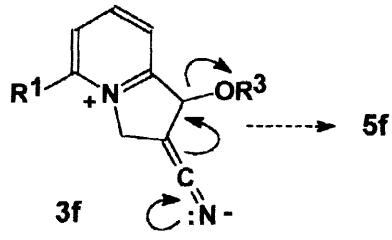
Table 1. Kinetic Data for the Thermal Cyclisation of 2-Pyridyl Derivatives **2a-f** in DMSO-d_6.



Entry	Substrate	R^1	R^2	Substrate Conc.[a] /mol.dm^{-3}	Temperature[b] /K	Completion /%	$k_{obs.}$[c] x 10^5/s^{-1}
1	**2a**	H	CO_2Me	0.07-0.08	363 (367.3)	42 - 43	9.2 ± 0.2
2				0.06-0.16	373 (378.0)	71 - 72	24.3 ± 1.1
3				0.8	373 (378.0)	87 - 91	26.2 ± 2.4
4				0.06-0.07	383 (388.8)	94	56.3 ± 2.8
5	**2b**	H	CO_2Et	0.07	363 (367.3)	55-57	6.2 ± 0.5
6				0.07	373 (378.0)	79-89	15.4 ± 1.3
7				0.06-0.08	383 (388.8)	99	34.0 ± 0.1
8	**2c**	H	CO_2Pr^i	0.06-0.07	363 (367.3)	31-32	4.4 ± 0.1
9				0.07-0.08	373 (378.0)	58 - 60	10.8 ± 0.3
10				0.07	383 (388.8)	89	26.5 ± 1.8
11	**2d**	H	CO_2Bu^t	0.06-0.07	363 (367.3)	12 - 13	1.5 ± 0.2
12				0.006	373 (378.0)	30 - 32	4.4 ± 0.1
13				0.06	383 (388.8)	57 - 58	10.1 ± 0.3
14	**2e**	Me	CO_2Me	0.1	373 (378.0)	96 - 99	52.0 ± 2
15				0.05	373 (378.0)	93	50.0 ± 1
16	**2f**	H	CN	0.08	363 (367.3)	26 - 29	3.7 ± 0.3
17				0.08-0.09	373 (378.0)	54 - 57	9.5 ± 0.1
18				0.09	383 (388.8)	84 - 86	22.9 ± 0.3

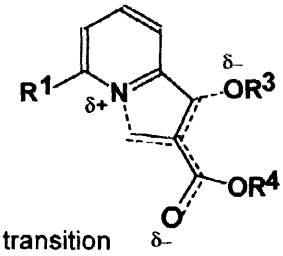
[a] Initial nominal concentration [b] Nominal setting followed, in parentheses, by the corrected temperature.
[c] First order rate constant; mean of duplicate runs.

It is also apparent that the nature of the leaving group (OAc or OH) is kinetically significant, the 3-acetoxy compound **2a** (*cf.* entry 4; Table 1) cyclising two orders of magnitude faster than its 3-hydroxy precursor **1a** at *ca.* 389 K.‡ We conclude that, for the acetates **2a-f**, the initial cyclisation step (**2** → **3**) is rate limiting (*i.e.* $k_{obs} = k_1$) but, in the absence of a good leaving group (*e.g.* when R^3 = OH), the elimination step (**3** → **4**) assumes greater importance. The possibility of an S_N2' mechanism, involving direct transformation (**2** → **4**) *via* the transition state complex **6** (Figure 2) is not precluded, but the evidence for such concerted processes has been questioned.[10] The deprotonation-aromatization step (**4** → **5**) is assumed to be rapid.



(*cf.* Table 2 ; **R2 = CN**)

Figure 1



Putative transition state complex for SN2' process.

Figure 2

From the kinetic data obtained at three different temperatures, for each of the substrates **2a - d, f** it is apparent that increasing the temperature influences the cyclisation rate dramatically, each 10 K increment more than doubling the rate constant k_{obs}. Plots of ln k_{obs} against 1/T for each of these compounds gave good linear correlations [$(R)^2 > 0.99$] and permitted evaluation of the respective enthalpies of activation, the similarity of which ($\Delta H^{\ddagger}$ = 97±6 kJmol^{-1}) is indicative of a common mechanism. The observed rate constants for the series **2a-d, f** correspond to the expected reactivity order and, although the interpretation of the entropy of activation ($\Delta S^{\ddagger}$) can be complicated by solvent effects,[11] the negative values ($\Delta S^{\ddagger}$ = - 413 ± 11 JK^{-1} mol^{-1}) obtained in this study are consistent with a common, rate-limiting cyclisation step (**2** → **3**). The electronic effects of the *O*-alkyl substituents (R^4) are considered to be essentially inductive in nature and, although exhibiting some deviation from linearity [$(R)^2$ = 0.897], a plot of log k_X/k_{Me} (378 K) against the corresponding Taft σ^* values [12] supports this assumption. The sign of the derived reaction constant (ρ^*= +3.75) clearly reflects the influence of the electron-withdrawing R^2 substituent on the reactivity of the vinyl moiety in the rate-limiting step.

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‡ In duplicate runs at this temperature, the 3-hydroxy compound **1a** underwent *ca.* 5% cyclisation during 3-4h, commensurate with a first-order rate constant, k_{obs} = *ca.* 0.4 x 10^{-5} s^{-1}.

EXPERIMENTAL

The acetoxy compounds **2a-f** were obtained from the corresponding hydroxy precursors **1a-f** as described previously,[5] and were purified by flash chromatography prior to use. Cyclisation was monitored, for 2-3h, by ^{1}H NMR analysis of solutions in DMSO-d_6 on a Bruker AMX 400 NMR spectrometer, equipped with a variable temperature unit which has been calibrated using 80% ethylene glycol in DMSO-d_6; temperature stability is judged to be ±0.1 K. In order to obviate complications due to spinning side-bands, the samples were not spun during the kinetic runs. Data acquisition, processing, integration and final plotting were effected using automatic routines.

Integral changes associated with corresponding signals (typically, *both* acetate methyl *and* ester *O*-alkyl signals) for precursors and products were used to follow cyclisation, which was shown, in all cases, to satisfy the first-order rate equation, Rate = k_{obs} [A], where [A] = substrate concentration. The first-order rate constants, (k_{obs}) (Table 1), were obtained by linear regression of plots of ℓn[A] against time and represent, in each case, the mean of duplicate determinations.

ACKNOWLEDGEMENTS

The authors thank the Foundation for Research Development (FRD) and Rhodes University for generous financial support, and Professor M.E. Brown for helpful discussions.

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