A New Synthesis of Indolizines *via* Thermal Cyclisation of 2-Pyridyl Derivatives

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Thermal cyclisation of methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**3a**) and analogues affords convenient access to indolizine derivatives.

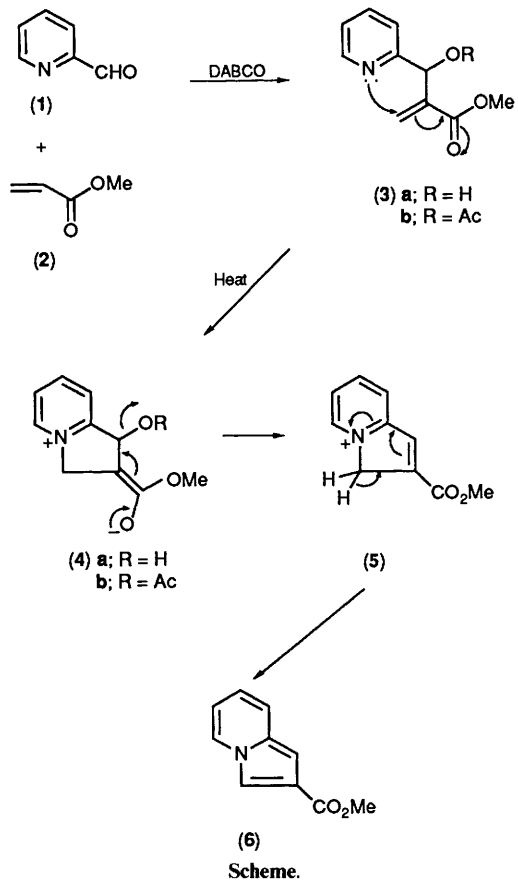
Synthetic indolizines have been found to exhibit a variety of pharmacological effects and their use in azo dyes is well established.[1] Not surprisingly, new methods for preparing these compounds continue to be developed, recent examples being the reactions reported by Acheson and Ansell,[2] Nugent and Murphy,[3] Erbach and Maier,[4] and Goti *et al.*[5] Here we describe the serendipitous discovery of an additional route to indolizine derivatives.

In an earlier study of rate enhancement effects in the DABCO† catalysed coupling of aldehydes and acrylate esters,[6] attempted distillation of a liquid adduct, methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate(**3a**) afforded a colourless solid. Spectroscopic (IR; ^1H and ^{13}C NMR) analysis of this crystalline material clearly indicated the absence of certain structural features characteristic of the methyl ester (**3a**). Consideration of a possible nucleophilic addition–elimination sequence [involving intermediates (**4a**) and (**5**); Scheme] led to identification of the transformation product as methyl indolizine-2-carboxylate (**6**).[7]

Unfortunately, thermal cyclisation (at *ca.* 140 °C) of the hydroxy ester (**3a**) is accompanied by significant charring and the yield of chromatographed product obtained from this precursor has not exceeded *ca.* 22%. Replacement of the hydroxy function in compound (**3a**) by a better leaving group (e.g. OAc) was expected to facilitate the elimination step [(**4**) ⟶ (**5**)] and various acetylation procedures were, consequently, explored [*e.g.* AcCl–THF, reflux; Ac_2O–Et_3N–DMAP, 60 °C; i, BuLi–THF; ii, AcCl, 0 °C]. Of the methods examined, treatment of the hydroxy ester (**3a**) with neat acetic anhydride, at 100 °C, proved to be the most effective, affording the acetylated derivative (**3b**) in 78% yield. When heated at 120 °C, this compound (**3b**), in fact, cyclised smoothly to the indolizine (**6**) in 68% yield.

Preliminary studies have indicated applicability of the reaction to ethyl acrylate and acrylonitrile derived analogues of compound (**3a**) and attention is now being given to optimising

† DABCO is 1,4-diazabicyclo[2.2.2]octane.



Scheme.

yields and exploring the generality of this interesting transformation.

Experimental

The hydroxy ester (**3a**) was prepared as described previously.[6] Acetylation was effected by heating the hydroxy ester (**3a**) (1 g) in Ac_2O (5 ml) at 100 °C for 0.5 h. The cooled mixture was poured into aq. $NaHCO_3$–ice and stirred for 0.5 h. Basification, extraction (Et_2O), washing of the organic solution (aq. $NaHCO_3$ and then aq. NaCl), and evaporation of the solvent afforded the crude acetate (**3b**) [shown by TLC to contain a small amount of the indolizine (**6**)]. Purification by flash chromatography on silica [elution with hexane–EtOAc (4:6)] gave the acetate (**3b**) as a colourless oil, δ_H (60 MHz; solvent $CDCl_3$) 2.16 (3 H, s, Ac), 3.74 (3 H, s, CO_2Me), 6.02 and 6.56 (2 H, 2 × br s, $C{=}CH_2$), 6.85 (1 H, s, CHOAc), and 7.15–8.77 (4 H, ArH); ν_{max} (thin film) 1 750 and 1 730 cm^{-1}.

The acetate (**3b**) was heated at 120 °C for 1 h and the resulting mixture was chromatographed [flash chromatography on silica; elution with hexane–EtOAc (7:3)] to give methyl indolizine-2-carboxylate (**6**), m.p. 99–100 °C (from hexane) (lit.,[7] 97–99 °C) (Found: C, 68.4; H, 5.1; N, 8.1. Calc. for $C_{10}H_9NO_2$: C, 68.6; H, 5.2; N, 8.0%); δ_H(60 MHz; solvent $CDCl_3$) 3.91 (3 H, s, CO_2Me) and 6.52–8.02 (6 H, m, ArH); ν_{max}(KBr) 1 715 cm^{-1}.

Acknowledgements

The authors thank AECI Ltd. for a post-graduate fellowship (M. L. B.) and the Foundation for Research Development and Rhodes University for generous financial support.

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Paper 0/01392G
Received 30*th March* 1990
Accepted 8*th June* 1990