5-*Endo-Trig* Cyclisation and 1,3-Anionic Cycloaddition in Arylimine Derivatives of α-Amino Acid Esters

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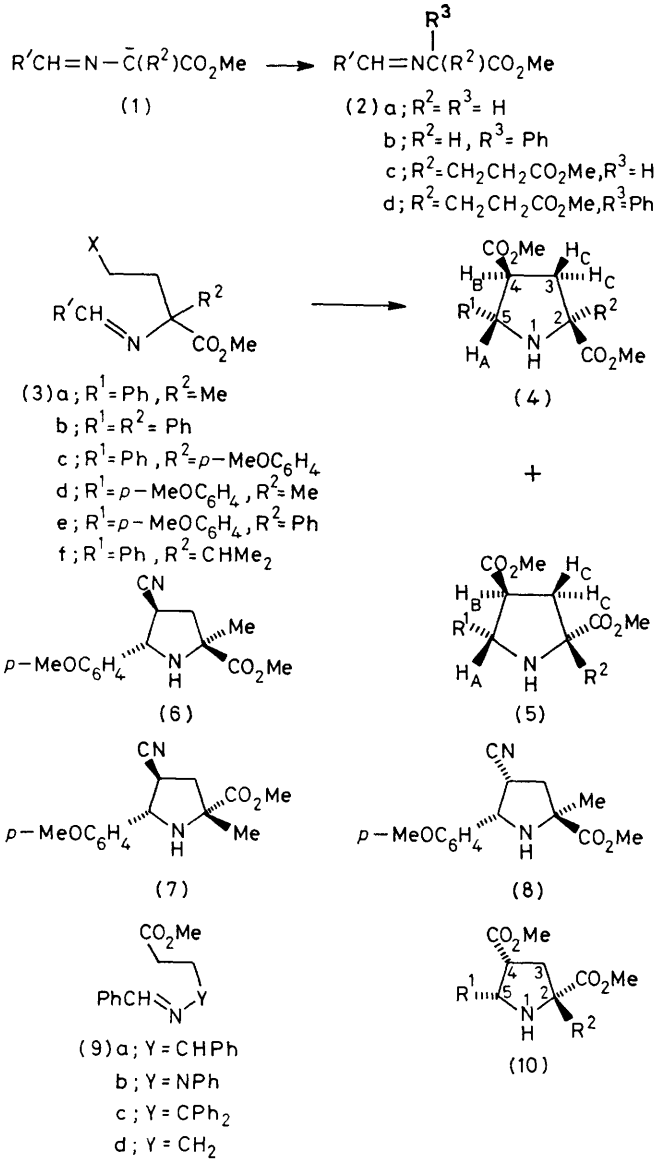
Summary Michael adducts of imines of α-amino acid esters are converted into a mixture of two stereoisomeric pyrrolidines by benzyltrimethylammonium methoxide (BTAM) apparently by a 5-*endo-trig* cyclisation

THE potentially ambident imine anions (**1**) undergo regiospecific Michael addition reactions and alkylation reactions to give (**2**).[1,2] We briefly reported that the imine (**3a**, X = CO_2Et) gives the corresponding pyrrolidine [C(4)

ethyl ester] as a mixture of stereoisomers (**4a**) and (**5a**) on treatment with a stoicheiometric amount of potassium t-butoxide in benzene at room temperature.[3] The cyclisation [(**3**) → (**4**) + (**5**)] is formally an example of a geometrically disfavoured 5-*endo-trig* process.[4,5] We now report that formation of pyrrolidines from imines of α-amino acid esters and activated olefins may be accomplished in either a single step or a two step Michael addition–cyclisation sequence. However, the stereochemistry of the pyrrolidines varies with the base and the composition of the solvent.



The Michael adducts (**3a**—**f**; X = CN or CO_2Me) were prepared in high yield from the corresponding α-amino acid ester imines and methyl acrylate or acrylonitrile in benzene containing 0·1 equiv. of BTAM (40% solution in methanol). Cyclisation of (**3**; X = CO_2Me) to [(**4**) + (**5**)] is best accomplished by 1 equiv. of BTAM or potassium t-butoxide in benzene at room temperature [(**3f**; X = CO_2Me) requires more forcing conditions]. The pyrrolidines are obtained as a mixture of two stereoisomers, (**4**) and (**5**) in the ratio *ca.* 3 : 1, separable by chromatography. Assignment of stereochemistry to the stereoisomeric pyrrolidines is based on both ^1H n.m.r.[6] and an *X*-ray crystal structure of (**4c**). The nitriles (**3**; X = CN) also cyclise to a mixture of stereoisomeric pyrrolidines in which the *trans* arrangement of the C(4)–C(5) substituents is favoured. Thus (**3d**; X = CN) gave 3 : 1 : 1·2 mixture of pyrrolidines (**6**—**8**; 60%). The *cis*-4,5-stereochemistry of (**8**) was assigned on n.m.r. data and by comparison with the products from thermal cycloaddition reactions.[7] The *trans*-4,5-stereochemistry in (**4**—**7**) is expected on steric grounds but might also arise by equilibration of possible *cis*-4,5-isomers of (**4**—**7**). Our present evidence indicates that rate of cyclisation of (**3a**—**f**) ≫ rate of epimerisation of *cis*-4,5-isomers (*e.g.*, see below). However, more evidence on this point is being sought especially with respect to nitriles such as (**8**).

Sodium methoxide (0·1—1 mol) does not effect the cyclisation of (**3a**—**e**; X = CO_2Me) under the same conditions (benzene, room temperature, 24 h). Furthermore, the Michael adducts (**9a**—**d**)† do not cyclise in the presence of BTAM.[8] The failure of (**9c**) to cyclise militates against a simple acceleration of rate of cyclisation by *gem*-disubstitution[9] as does the slow rate of conversion of (**3f**, X = CO_2Me) to [(**4f**) + (**5f**)]. Formation of [(**4**) + (**5**)] might occur *via* a retro-Michael reaction regenerating the 4π-anion (**1**) followed by a slow (compared to Michael addition) 4π + 2π anionic cycloaddition.[10] However, crossed products were not observed when the cyclisation of (**3e**; X = CN or CO_2Me) was conducted in the presence of a 40 mole excess of other Michael acceptors. The absence of crossed products supports a direct 5-*endo-trig* cyclisation of (**3**) to [(**4**) + (**5**)]. Kauffmann[11] has also reported two easy 5-*endo-trig* cyclisations.

Imines derived from glycine (**2a**) and phenylglycine (**2b**) react with methyl acrylate in the presence of 0·1 equiv. of sodium methoxide (methanol free) in benzene to give a mixture of a Michael adduct (**2c**) or (**2d**) and a single pyrrolidine (**10**). Representative examples are given in the Table.

TABLE. Competing Michael addition and cycloaddition of imines with methyl acrylate

	Ratio of Michael adduct [(**2c**) or (**2d**)] : (**10**)[a]
(**2b**; R^1 = Ph)	8 : 92; 24 : 76[b]
(**2b**; R^1 = p-$MeOC_6H_4$)	28 : 72
(**2b**; R^1 = p-ClC_6H_4)	13 : 87
(**2b**; R^1 = 2-furyl)	0 : 100
(**2a**; R^1 = Ph)	56 : 44
(**2b**; R^1 = Me_5C_6)	100 : 0

[a] All ratios estimated by n.m.r. [b] Repeat experiments showing the reaction is sensitive to adventitious traces of moisture or methanol.

The Michael adducts (**2c**) and (**2d**) are not precursors of (**10**) under these conditions and addition of small quantities of methanol to the reaction mixture favours Michael adduct formation. The C(4)–ester group of (**10**) is epimerised on

† Compound (**9d**) was prepared from benzaldehyde and methyl γ-aminobutyrate.

treatment with 1 equiv of BTAM in benzene for 3 days at room temperature, *e g* , (**10**, $R^1 = R^2 = Ph$) gives (**5b**) the minor product from cyclisation of the Michael adduct (**3b**; $X = CO_2Me$). The stereo- and regio-specificity observed (Table) in the formation of (**10**) suggests these pyrrolidines are formed *via* a 1,3-anionic cycloaddition [10]

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