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Regioselective Synthesis of Pyrroloquinolines - Approaches to Martinelline.

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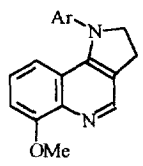
Abstract. Indium trichloride catalysed Diels-Alder reaction of imines derived from anilines with cyclic enamides regioselectively gave the biologically important pyrroloquinoline nucleus, with a *cis* ring junction, in moderate yield. Although the *exo:endo* selectivity was in most cases poor, these isomers are readily separated by flash chromatography. The functionality tolerated at both C2 and C7 should allow further elaboration to Martinelline

Pyrroloquinolines form the core structure unit of a number of biologically interesting molecules. For example, the potent gastric (H^+/K^+) ATPase reversible inhibitor **1**[1] and the recently isolated natural product martinelline **2**,[2] a non-peptide Brady inhibitor contain this entity. Many approaches to this ring system involve dimerisations[3] or the use of symmetrical substrates[4] which greatly reduces the versatility and applicability of this chemistry. Recently, intramolecular 1,3-dipolar cycloaddition,[5] free radical[6] and transition metal catalysed cyclisations[7] of aryl halides have been employed to obtain pyrroloquinolines, with the last two methods being specifically targeted to martinelline.



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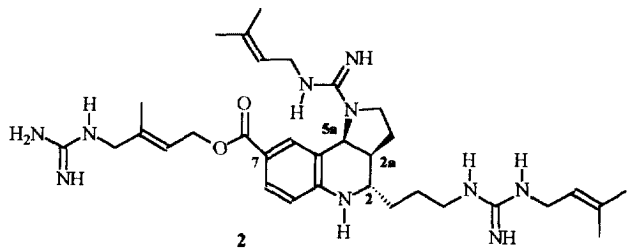

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In recent studies directed towards synthesis of martinelline **2** and analogues thereof, we required a stereoselective synthesis of the heterocyclic pyrroloquinoline core. This proved more difficult than initially anticipated due to the tendency of the benzylic amine to eliminate and give fully aromatic quinoline products.[8] Therefore, a mild procedure was required for obtaining this ring system. One particularly attractive option was an imino Diels-Alder reaction using a cyclic enamide as the dienophile. This would guarantee the correct regiochemistry at the tri-substituted aromatic ring if a *para*-substituted aniline was employed. Thermal imino Diels-Alder reactions with acyclic enamide substrates are documented.[9]

The indium trichloride catalysed Diels-Alder reaction of imines of aromatic amines with both electron rich[10] and deficient alkenes[11] is emerging as a useful method for the synthesis of substituted quinolines. We now

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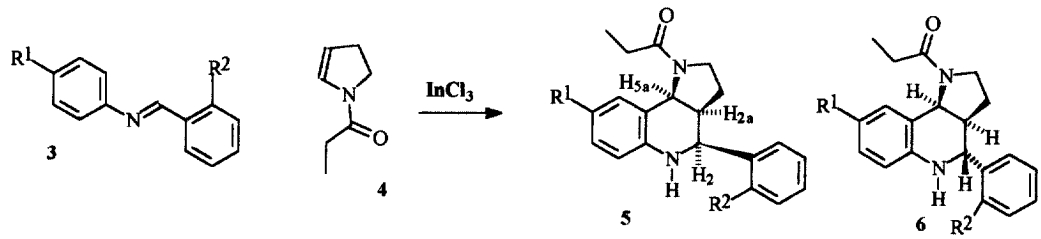
report our findings on the use of cyclic enamides as dienophiles in this reaction which regioselectively gave the required pyrroloquinolines with a *cis* ring junction in workable yields **Scheme 1, Table 1.**

Imines **3** were readily available by condensing the corresponding amines with the aromatic aldehydes and the cyclic enamide **4** was prepared by condensing the corresponding imine with propionyl chloride.[12] The Diels-Alder reaction of imines **3** with enamide **4** took place rapidly at room temperature in acetonitrile containing a catalytic quantity of indium trichloride and gave the *endo/exo* cycloadducts **5** and **6** respectively in moderate overall yield **Table 1.**[13] This reaction is regioselective giving predominantly the benzylic amine isomers shown and the *endo* and *exo* stereoisomers were readily separated by flash chromatography. In all cases the *endo* isomer **5** had the higher R_f value. Cycloaddition works equally well for substrates containing either electron donating or withdrawing substituents *para* to the imine nitrogen **Table 1** entries b and d respectively.



Scheme 1

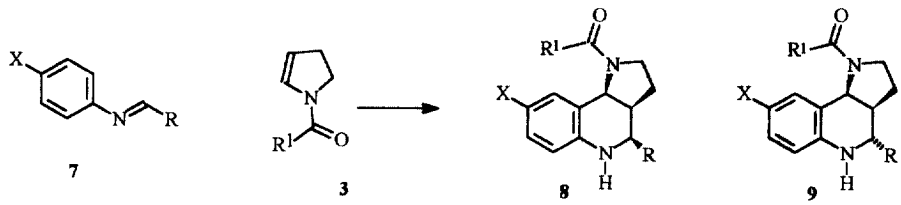
Table 1

Substrate	R^1	R^2	Ratio **5:6**	Yield %
3a	H	H	1:1	41
3b	OMe	H	1: 0.8	50
3c	H	NO_2	2:1	50
3d	CO_2Me	H	1:1	48

The proton NMR spectra for diasteroisomers **5a** and **6a** had very similar coupling constants $J_{H5a\,H2a}$ (6.1 and 6.7Hz) and $J_{H2a\,H2}$ (2.7, 2.5Hz) respectively for the diagnostic hydrogens H_2, H_{2a} and H_{5a} attached to the three contiguous chiral centres.[14] The 6Hz coupling constants are much too small to be *trans* diaxial and are consistent with an axial-equatorial arrangement in which the dihedral angle between the two protons is deformed to approximately 40°. This corresponds to a *cis* ring junction in both stereoisomers. Coupling constants $J_{H2a\,H2}$ are diagnostic of axial equatorial and equatorial equatorial hydrogens, but the difference between the two is too small to make a reliable assignment. It is gratifying that these coupling constants are very similar to those reported for martinelline of $J_{H5a\,H2a}$ 6.2Hz and $J_{H2a\,H2}$ of 'less than 2Hz' based on the absence of a cross peak in a COSY spectrum. Saturation of proton H_{5a} in the *endo* adduct **5a** gave an nOe enhancement on H_2 of 2.3% and H_{2a} of 6% confirming the ring junction was *cis* and that protons H_{5a} and H_2 were *cis*. With *exo* isomer **6a**,

saturation of H_{5a} again gave a strong nOe onto H_{2a} of 6.8% confirming a *cis* ring junction. The absence of an nOe enhancement to the benzylic hydrogen H_2, along with an nOe enhancement to the distant aromatic ring of 2%,[15] confirmed that H_{5a} and H_2 were *trans* with the phenyl ring axial. In the *exo* isomer, two of the alkyl groups are pseudo axial and the amino group is pseudo equatorial.

For this reaction to be of maximum benefit then it is necessary to have an alkyl chain attached at C2, preferably *exo*, and a group attached to nitrogen which was easily removable. However, the reaction was unsuccessful with imines derived from simple aliphatic aldehydes with only intractable materials being formed. The imines derived from methyl glyoxylate underwent cyclo-addition with enamide **3** and gave a separable mixtures of *endo/exo* isomers **8a,b** and **9a,b**, ratio 2:1, in disappointing 20% and 31% combined yields respectively **Scheme 2**. The poorer yields and the preference for *endo* adducts **8** make this chemistry less attractive. With the imine derived from cinnamaldehyde **7c**, cyclo-addition was more efficient, giving substrates **8c:9c** (1:1) in 52% combined yield. Substrates **8c:9c** contain a potentially cleavable double bond which should allow further, more useful functionalisation on this side chain. Finally, the reaction tolerated a CBz group incorporated into the cyclic enamide, giving products **8d:9d** in 45% combined yield, ratio 1:1.



a X=OMe; R=CO_2Me; R^1 =Et.
b X=Me; R=CO_2Me; R^1 =Et.
c X=H; R=CH=CHPh; R^1 =Et.
d X=OMe; R=CO_2Et; R^1 =OBn.

Scheme 2

The ready availability of starting materials and convenience of this procedure make it ideal for preparing precursors for martinelline and analogues thereof.

General procedure. Anhydrous indium trichloride (0.16mmol) was added to a solution of imine (**3,** 0.8mmol) and cyclic enamide (**4,** 0.8mmol) in dry acetonitrile (7ml) at room temperature. After 30 min tlc analysis indicated consumption of enamide **4**. Saturated sodium bicarbonate 2ml was then added and the mixture was extracted with methylene chloride 2x10ml, dried over magnesium sulphate and concentrated. Flash chromatography on the residue gave *endo exo* pyrroloquinolines **5** and **6** in the yields indicated in **Table 1**.

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12. Kraus, G.A.; Neuenschwander, K. *J. Org. Chem.* 1981, **46**, 4791-4792.
13. In the absence of indium trichloride no reaction took place, even in boiling acetonitrile.
14. This is the same numbering as introduced by Witherup see reference 2.
15. Although the NMR signals for aromatic protons in the quinoline ring were readily assigned, the *ortho meta and para* protons in the pendant aromatic overlapped, even at 500MHz. It was therefore not possible to see which protons were being specifically enhanced. The value of 2% is the total enhancement for all five protons making the actual value very small indeed. However the quality of the difference spectrum was excellent and this is a 'real' nOe supporting the proposed stereochemistry.