Pergamon

Tetrahedron Letters 39 (1998) 4905–4908

TETRAHEDRON LETTERS

A Facile and Highly Stereoselective Approach to a Polycyclic Isoindolinone Ring System *via* an *N*-Acyliminium Ion Cyclization Reaction

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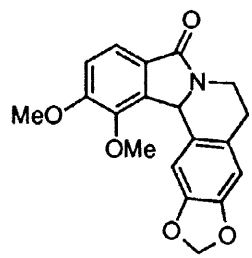
Received 1 April 1998; accepted 27 April 1998

Abstract: A highly diastereoselective synthesis of chiral ring-fused isoindolinone products, the skeleton of which is common to many naturally occurring and biologically active compounds, is achieved in only two synthetic steps from readily available precursors *via* an *N*-acyliminium ion cyclization reaction of an isoindolinone substrate.

The synthetic potential of *N*-acyliminium species is now well documented. Such compounds exhibit a broad versatility resulting in a range of synthetic applications.[1] There has been much recent interest in the synthesis of ring-fused heterocyclic systems *via* *N*-acyliminium ion cyclization as the key ring-forming step.[2] Several research groups have reported the synthesis of chiral ring-fused isoindolinone targets *via* *N*-acyliminium ion cyclization without addressing the question of stereocontrol during the reaction.[2] The isoindolinone ring system is interesting due to the actual and potential biological activities of many derivatives.[3] In addition, several naturally occurring chiral alkaloids contain a ring-fused isoindolinone moiety, including neuvamine **1**[4] and lennoxamine **2**.[4b, 5]



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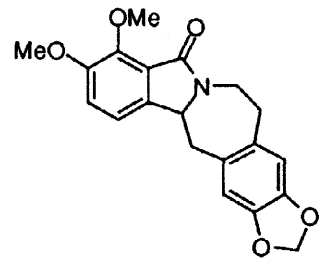

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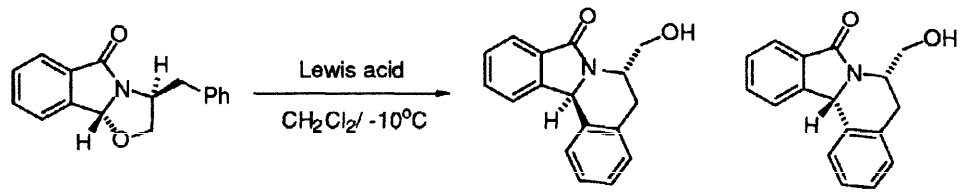
Herein we report a facile new procedure which allows the synthesis of chiral ring-fused isoindolinone products in only two synthetic steps with extremely high levels of diastereoselectivity, from readily available precursors.

We have recently reported the preparation of a novel series of tricyclic γ-lactams and their potential for use as *N*-acyliminium ion precursors in the synthesis of 3-substituted isoindolin-1-one derivatives.[6] We subsequently recognised that suitable substrates could serve as valuable intermediates in the synthesis of non-racemic ring-fused isoindolinones through Lewis acid mediated formation of an *N*-acyliminium intermediate followed by intramolecular nucleophilic addition of a proximate, electron-rich aromatic substituent.

0040-4039/98/$19.00
PII: S0040-4039(98)00892-2

The diastereoisomerically pure *N*-acyliminium ion precursor **3** required for the initial study was prepared directly from the corresponding enantiomerically pure amino alcohol substrate, (*S*)-phenylalaninol, in 87% isolated yield by our usual method.[6] The relative *trans*-stereochemistry of the tricyclic lactam products has been verified by single crystal X-ray analysis.[6]

Substrate **3** was expected to undergo *N*-acyliminium ion formation on treatment with a Lewis acid activator (1.5 equivalents, -10°C, CH_2Cl_2), allowing cyclization of the aromatic substituent to form the desired tetracyclic isoindolinone target as a mixture of two possible diastereoisomers, **4a** and **4b**, as highlighted in Scheme 1.



3 **Scheme 1.** **4a** **4b**

This was indeed found to be the case and, as can be appreciated from Table 1, an extremely high degree of diastereoselectivity can be achieved in this reaction, particularly on using trimethylsilyl triflate as the Lewis acid activator (Table 1, entry e, **4a** : **4b** = ≥49 : 1).

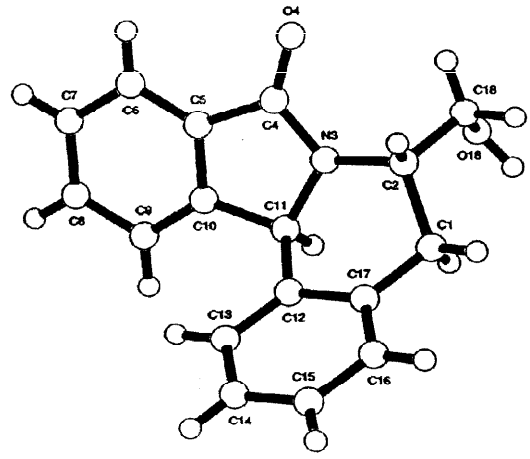
Table 1. ***N*-Acyliminium Cyclization Reaction of Tricyclic Lactam, 3**

Entry	Activator	Yield, 4 (%)	4a : 4b[#]
a	$SnCl_4$	98	2 : 1
b	$TiCl_4$	93	2 : 1
c	$BF_3.OEt_2$	99	3 : 1
d	H_2SO_4	80	6 : 1
e	TMSOTf	97	≥49 : 1

[#]determined by 270 MHz ^{1}H NMR spectroscopy

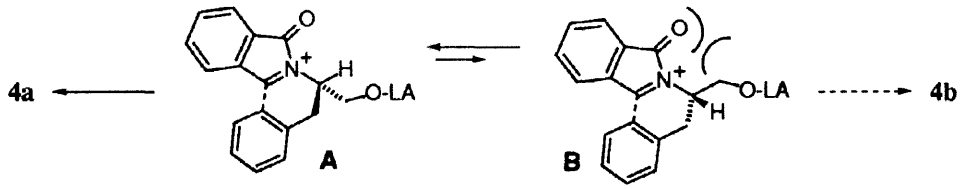
In all cases the cyclization reaction proceeded cleanly and in excellent yield. The major diastereoisomer was isolated by fractional crystallisation from dichloromethane and hexanes, and the relative stereochemistry of the major diastereoisomer was established to be **4a** by single crystal X-ray analysis (Figure 1).[7] No epimerisation of **4b** to **4a** (or *vice-versa*) was observed on treating the reaction mixtures with a Lewis acid (TMSOTf) in dichloromethane at room temperature over 24 hours.

Figure 1.



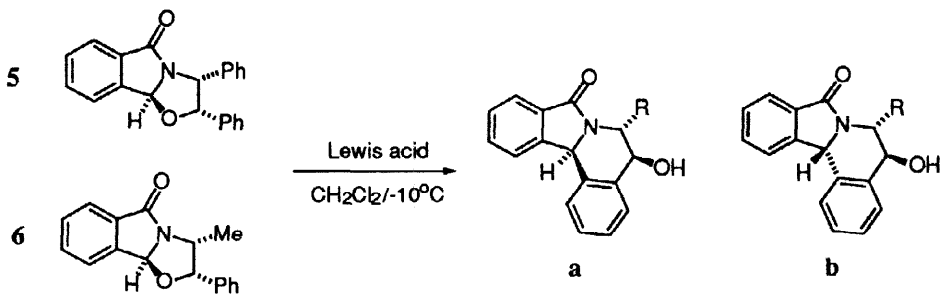
We have rationalised the stereochemical outcome of the reaction by invoking the transition state models highlighted in Scheme 2. We believe that stereocontrol in the intramolecular cyclization reaction results not from a chelation control mechanism, as previously suggested by others to explain diastereoselective nucleophilic addition to similar *N*-acyliminium ion species,[8] but from acyclic stereocontrol resulting from a 1,3-interaction between the amide carbonyl group and the substituent at the chiral centre of the amino alcohol component.[9]

In transition state **A** (Scheme 2), leading to the favoured product **4a**, the carbonyl moiety would be "eclipsed" in a 1,3-fashion by the hydrogen atom at the chiral centre. In the alternative transition state **B** however, leading to the minor product diastereoisomer **4b**, an unfavourable 1,3-interaction between the carbonyl group and the more bulky Lewis acid-complexed oxymethyl group exists. This conformation may initially appear to be more favourable due to the possibility of chelation of both the amide oxygen atom and the alkoxy- group with a metal counter-ion; such an interaction would lead to formation of a 7-membered chelate. However, from consideration of the results shown in Table 1, it is clear that if chelation is taking place it is resulting in a *lower* level of diastereoselection: the Lewis acids used in our study that are capable of multi-point co-ordination actually lead to lower levels of product diastereoselectivity (Table 1, entries a-c); probably due to an increased contribution of a chelated transition state similar in structure to **B**.



Scheme 2. Transition State Models for Diastereoselective *N*-Acyliminium Ion Cyclization of 3

We were pleased to find that the above protocol could be applied to other, more substituted, substrate systems. The corresponding tricyclic lactams **5** (98% yield) and **6** (93% yield) were prepared by our usual method,[6] as single diastereoisomers, from 1*S*,2*R*-2-amino-1,2-diphenylethanol and 1*S*,2*R*-norephedrine respectively. Results for the cyclization reaction (Scheme 3) are presented in Table 2.



Scheme 3

Substrate **5** proved to be less reactive than **3** and **6**, proceeding only under the influence of $TiCl_4$ to yield the desired tetracyclic product in excellent yield. Substrate **6** underwent cyclization with TMS-triflate as the Lewis acid activator in almost quantitative yield. The relative stereochemistry of the major product

diastereoisomer was confirmed in both cases by single crystal X-ray analysis. Again, excellent levels of product diastereoselectivity were observed for the cyclization reactions.

Table 2. *N*-Acyliminium Cyclization Reaction of Tricyclic Lactams, 5 and 6

Substrate	R	Lewis acid	Yield (%)	Ratio (a:b)#
5	Ph	TMSOTf	no reaction	-
5	Ph	$TiCl_4$	94	14 : 1
6	Me	TMSOTf	99	26 : 1

#determined by 270 MHz ^{1}H NMR spectroscopy

These results further support our proposal that the induced diastereoselectivity arises from acyclic stereocontrol resulting from a 1,3-interaction between the amide carbonyl group and the substituent at the chiral centre of the amino alcohol component and not *via* chelation control, since with substrates **5** and **6** the alcohol functionality would be more remotely oriented in the transition state and therefore unavailable for co-ordination to the amide carbonyl group. Transition state model **A**, proposed in Scheme 2, can be applied successfully to rationalise the stereochemical outcome of the cyclization reaction of substrates **5** and **6**.

In summary, we have identified a novel and highly stereoselective route to the ring-fused chiral isoindolinone ring system, the skeleton of which is common to many naturally occurring and biologically active compounds. In only two synthetic steps we have prepared the ring-fused heterocyclic system with almost complete stereocontrol. Work is underway to further elaborate the structures of ring-fused products prepared by this protocol. Our results will be reported in due course.

Acknowledgements: We thank the Universities of Huddersfield & Loughborough for facilities and financial support. We also thank Dr. Neil McLay (Huddersfield) and Dr. Tim Smith (Loughborough) for NMR assistance, and Professor Harry Heaney (Loughborough) for helpful discussions.

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