Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3627-3630, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00686-2

A Highly Diastereoselective Synthesis of Tricyclic Lactams and their Application as Novel *N*-Acyl Iminium Ion Precursors in the Synthesis of Isoindolinone Derivatives.

Steven M. Allin,*[a] Christopher J. Northfield,[b] Michael I. Page*[b] and Alexandra M. Z. Slawin[a]

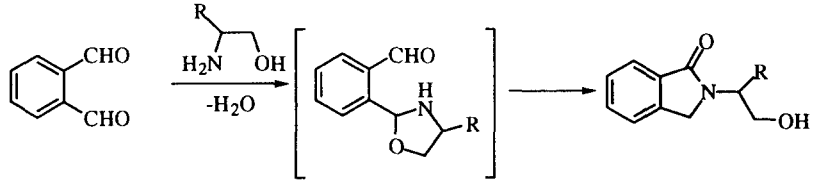
[a]Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, England.

[b]Department of Chemical & Biological Sciences, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, England.

Abstract: Condensation of 2-formylbenzoic acid with α–amino alcohol substrates proceeds with extremely high diastereoselectivity to produce tricyclic γ-lactam products. The relative stereochemistry of the major diastereoisomer has been determined by X-ray crystal analysis and a mechanism suggested to explain the stereochemical outcome. Further, we report that this class of heterocycle can act as an *N*-acyl iminium ion precursor in the synthesis of substituted isoindolinone derivatives.

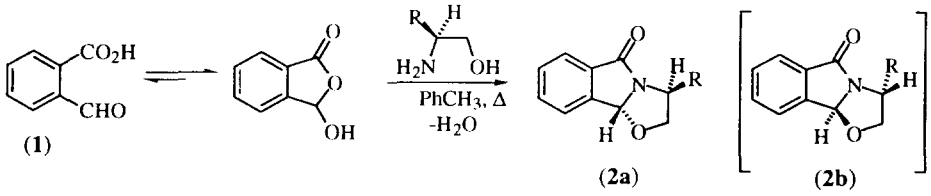
There have been several attempts to design isosteres of β-lactams which are not four-membered rings. Most of these mimics have been γ-lactams, particularly pyrazolidinones, imidazolidinones, cycloserines, and hydantoins.[1] We report here a novel synthesis of a series of tricyclic γ-lactams based on the isoindolinone ring system.

Our group has recently reported the preparation of isoindolinone derivatives by direct condensation of *ortho*-phthaladehyde with amino alcohols.[2] The presence of any other external "synthetic auxiliary" was found to be unnecessary and we have proposed a mechanism involving neighbouring group assistance by the alcohol functional group (Scheme 1).



Scheme 1

As part of an ongoing investigation into the preparation and reactivity of the isoindolinone ring system we have studied the reaction of α-amino alcohols with 2-formylbenzoic acid (**1**) (Scheme 2, Table 1). In general, equimolar amounts of the substrates were heated at reflux under Dean-Stark conditions in toluene solvent for 12 hours. Analysis of the crude product mixture by 270 MHz ^{1}H-nmr spectroscopy showed clean and efficient conversion to the desired tricyclic γ-lactam products (**2**). In each case, only one diastereoisomer of the product was observed. Purification was achieved by flash column chromatography (diethyl ether/light petroleum ether mixtures as eluent); yields quoted in Table 1 are of isolated materials.



Scheme 2

Table 1. Preparation of tricyclic lactams through condensation of α-amino alcohols with 2-formylbenzoic acid.

Substrate	R	yield (%)	diastereoselectivity	$[\alpha]_D$
(+/-) valinol	^{i}Pr	92	exclusive[a]	-
(*S*) phenylglycinol	Ph	70	(**2a**), exclusive	+130.10 [c = 2.70, CH_2Cl_2]
(*R*) phenylglycinol	Ph	70	(**2b**), exclusive	-137.10 [c = 2.20, CH_2Cl_2]
(*S*) phenylalaninol	$PhCH_2$	72	(**2a**), exclusive	+43.94 [c = 2.00, CH_2Cl_2]
(*R*) phenylalaninol	$PhCH_2$	71	(**2b**), exclusive	-44.21 [c = 3.48, CH_2Cl_2]

[a] determined by 270 MHz ^{1}H-nmr spectroscopy

Others have reported high diastereoselectivity in the formation of bicyclic lactams derived from amino alcohol substrates and have confirmed the relative stereochemistry of the major diastereoisomer to be *trans* with respect to the hydrogen atoms at positions C(3) and C(1a) (see Figure 1).[3] Consequently, we expected the single diastereoisomer obtained in our study to have the *trans* stereochemistry highlighted in Scheme 2. Product (**2a**) represents the *trans* tricyclic lactam expected for the (*S*) amino alcohol substrates used, whereas (**2b**) is the major product isomer isolated from the (*R*) enantiomers. This stereochemical prediction was confirmed by X-ray crystal analysis of the (*S*) phenylglycinol derived product (Figure 1).[4]

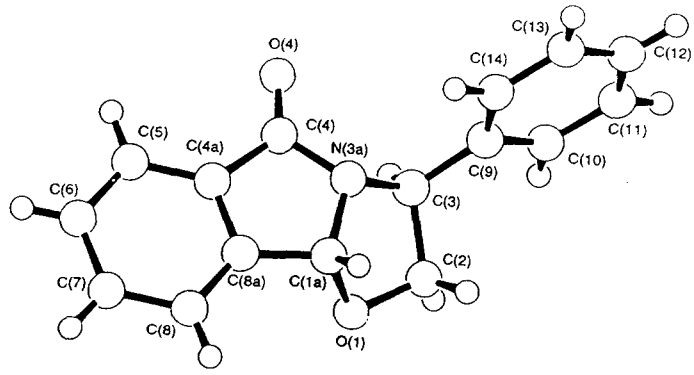
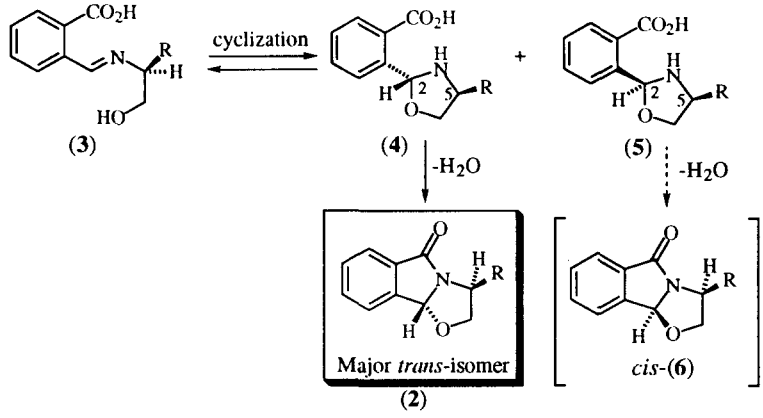


Figure 1.

As can be seen from Figure 1, the favoured *trans* product adopts a "bowl-like" shape, with the bulky phenyl substituent lying on the outer (convex) face. The alternative diastereoisomer, the *cis* product, appears from simple molecular models, to be highly disfavoured due to steric constraints.

In view of our interest[5] in making γ-lactam mimics of the β-lactam antibiotics it is of interest to note that the *N*-atom is pyramidal and 0.4Å out of the plane defined by its three substituents. The *N*-atom of penicillins and cephalosporins is commonly 0.2 to 0.4Å from the plane.[6] Our novel route to yield exclusively the *trans* product compliments that of Takacs who has reported[7] the synthesis of racemic tricyclic lactams *via* mercuric acetate promoted cyclization of *N*-acyl amidals which selectively produces the *cis* product.

Based on our earlier work,[2] we propose a mechanism to explain the stereochemical outcome of the reaction outlined in Scheme 2 which involves initial formation of an hydroxyimine/oxazolidine intermediate (Scheme 3).



Scheme 3

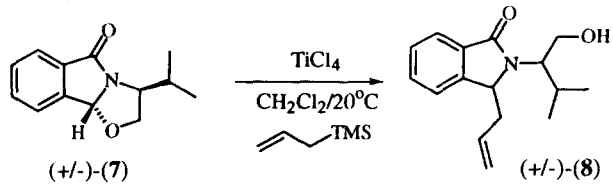
Condensation of an α-amino alcohol with an aldehyde is known to give a product which exists, in solution, as a mixture of the expected imine and the corresponding ring-closed oxazolidine.[2, 8]

Interestingly, previous studies by others[9] have shown (by X-ray analysis) that, for ephedrine-derived oxazolidines, the *cis* oxazolidine (referring to the stereochemistry at positions 2 and 5) is the thermodynamically more stable isomer. However, with aromatic aldehydes bearing electron withdrawing *p*-substituents, the kinetic (*trans*) product can be favoured under certain reaction conditions.[10]

In our study, reversible cyclization of the hydroxyimine (**3**) could produce both the *trans* oxazolidine (**4**) and the *cis* oxazolidine (**5**). Ring closure of (**4**) with concomitant loss of water yields the observed *trans* tricyclic lactam product (**2**). In the case of (**5**) however, cyclization to (**6**) appears from simple molecular models to be highly disfavoured due to remote orientation of the reactive functional groups. The course of the reaction in $CDCl_3$ over molecular sieves has been followed by nmr spectroscopy; the reaction was found to be complete after 10 minutes at room temperature. Tricyclic lactam (**2**) appears to be the thermodynamically more favourable product isomer. No interconversion from (**2**) to (**6**) is observed by nmr spectroscopy on stirring a solution of (**2**) at room temperature for 7 days.

The synthetic potential of *N*-acyl iminium species is now well documented.[11] Bicyclic lactams have been investigated by the groups of Meyers[3a,b] and others[3c,d] as *N*-acyl iminium ion precursors for the synthesis of a wide range of chiral products. We have sought to demonstrate the potential of the tricyclic lactam (**2**) as an *N*-acyl iminium ion precursor for the synthesis of substituted isoindolinone derivatives; the preparation of such compounds is of interest since many derivatives display interesting biological activity.[12]

The (+/-)-valinol derived tricyclic lactam (**7**) was treated with titanium tetrachloride at room temperature in dichloromethane prior to addition of allyl trimethylsilane[3a] to yield the desired substituted isoindolinone (**8**) in 96% isolated yield (Scheme 4).



Scheme 4.

In summary, we report a new synthesis of tricyclic lactams and demonstrate the potential for the synthesis of chiral isoindolinone derivatives through their application as *N*-acyl iminium ion precursors. Further work is underway to develop an enantioselective approach to the synthesis of substituted isoindolinones; our results will be reported in due course.

Acknowledgements: We would like to thank Professor Harry Heaney (Loughborough) for helpful discussions, the University of Huddersfield for financial support and Dr. Neil McLay (Huddersfield) for assistance with nmr studies.

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(*Received in UK* 18 *March* 1997; *revised* 9 *April* 1997; *accepted* 10 *April* 1997)