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A New Approach to the Synthesis of Non-Racemic Isoindolin-1-one Derivatives

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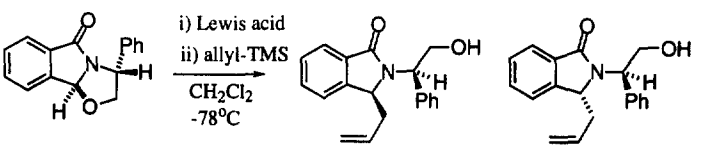
Abstract: A new approach for the synthesis of non-racemic 3-substituted isoindolin-1-one targets has been developed through application of a tricyclic γ-lactam substrate as an *N*-acyliminium ion precursor.

Keywords: Amino alcohols, aminals, stereocontrol, transition states, nitrogen heterocycles

We have recently become interested in the preparation and reactivity of isoindolinones due to the actual and potential biological activities of many derivatives, particularly 3-substituted isoindolin-1-ones.[1] In this current paper we describe our studies towards the stereoselective synthesis of this class of heterocycle through application of a tricyclic lactam substrate as an *N*-acyliminium ion precursor.

The tricyclic lactam (**1**) was prepared as a single diastereoisomer as previously reported,[2] and was subjected to an aminal ring-opening reaction using allyl trimethylsilane as the nucleophile. We first chose to apply titanium (IV) chloride as the Lewis acid activator, and were disappointed to find that although the reaction proceeded in high yield (86%) to give the desired 3-allyl isoindolin-1-one product, analysis of the crude reaction mixture by 270 MHz ^{1}H-NMR showed that the product was formed as a 1:1 mixture of diastereoisomers (**2**) and (**3**). This diastereoselectivity was significantly lower than observed by Meyers using the same combination of Lewis acid and nucleophile with the corresponding phenylglycinol-derived bicyclic lactam (reported diastereoselectivity: >9 : 1).[3]



(**1**) (**2**) (**3**)

Scheme 1.

Variation of the Lewis acid component had little effect on the level of product diastereoselectivity (see Table 1). The relative stereochemistry of the products was confirmed by X-ray crystal analysis of diastereoisomer (**2**).[4]

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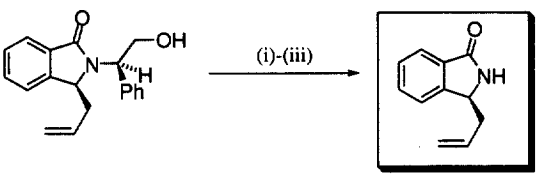
Table 1. Effect of Lewis Acid on Product Diastereoselectivity

Lewis acid	Yield (%)	(2) : (3)
$TiCl_4$	86	1 : 1
$BF_3.OEt_2$	95	1.6 : 1
$SnCl_4$	90	1.5 : 1
TMSOTf	90	2 : 1

In order to gain more insight into the generality of the ring-opening reaction, a range of nucleophiles was investigated with $TiCl_4$ as activator. Yields of the desired products were high and a similar level of diastereoselectivity was observed for all: TMS-CN (95%, 1.5 : 1), indole (84%, 2 : 1) and furan (82%, 1.5 : 1). We also applied vinyl acetate and the silyl enol ether of acetophenone to the aminal ring-opening reaction, but without success.

We were able to demonstrate (Scheme 2) removal of the chiral auxiliary to provide the desired 3-substituted 2*H*-isoindolin-1-one (**4**)[5] in good yield and without loss of stereochemical integrity at the 3-position of the isoindolin-1-one ring using a method recently developed by Vernon and Fains.[6]



d.e. = 33% (*S*)-(+)-(**4**); 33% e.e.

(i) $MeSO_2Cl$, Et_3N (63%); (ii) NaOEt, EtOH, CH_2Cl_2 (74%);
(iii) 3M HCl/EtOH-H_2O, 80 °C (90%)

Scheme 2

Although only a low level of diastereoselectivity was observed on Lewis acid induced ring-opening of the tricyclic lactam substrates with a range of carbon nucleophiles, we have demonstrated a new route to non-racemic 3-substituted-2*H*-isoindolin-1-one targets. A complimentary yet more stereoselective approach to non-racemic 3-substituted isoindolin-1-ones is described in the accompanying paper.

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5. (**4**), $C_{11}H_{11}NO$: m.p. 109-110 °C; $[\alpha]^{D}_{20}$ = +17.81 (c = 0.7, CH_2Cl_2); ν_{max} (nujol, cm^{-1}) 3157, 1691, 1679, 1465, 1376; δ_H (270 MHz, $CDCl_3$) 2.30-2.40 (1H, m), 2.65-2.75 (1H, m), 4.64 (1H, dd, *J* 7.56, 5.4), 5.10-5.17 (2H, m), 5.71-5.87 (1H, m), 7.42-7.58 (3H, m), 7.82-7.85 (1H, m); δ_C ($CDCl_3$) 38.9, 56.2, 119.2, 122.5, 123.7, 128.2, 131.7, 132.0, 132.9, 146.9, 170.9; m/z (CI) 174 (MH^+). Chiral HPLC study carried out using Chiracel-OJ column eluting with a 3% IPA / 97% hexanes solvent mixture. Retention times: major enantiomer, 34.35 mins; minor enantiomer , 44.86 mins.
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