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Oxazolidinone to succinamide: a novel rearrangement reaction

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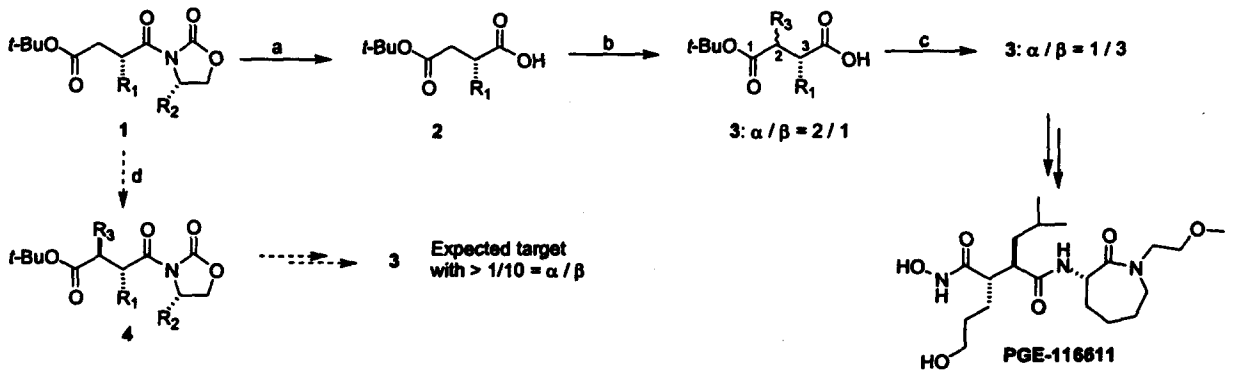
Abstract

During the course of an investigative work with a monosubstituted succinic acid half-ester tethered to a chiral oxazolidinone, an unexpected disubstituted succinimide was obtained with a high degree of stereoselectivity as the major product. Subsequent investigative work confirmed the structure and further defined the scope of this rearrangement reaction.

The design of many novel and selective matrix metalloproteinase (MMP) inhibitors has been based on mono- and disubstituted succinic acid derivatives.[1,2] As shown in Scheme 1, monosubstituted succinates (**2**) can be prepared in high yield using oxazolidinone derived chiral auxiliaries.[3,4] The stereoselective preparation of the corresponding disubstituted succinic esters is, however, quite challenging because of the lack of selectivity observed in the subsequent alkylation step.[5]



Scheme 1. Strategy towards the synthesis of various disubstituted succinic acids. Reagents and conditions: (a) $LiOH/H_2O_2$, THF–water; (b) 2.2 equiv. LDA in THF at −78°C followed by an electrophile; (c) 2.2 equiv. LDA in THF at rt followed by MeOH quench; (d) 1.1 equiv. LDA in THF at −78°C followed by an electrophile

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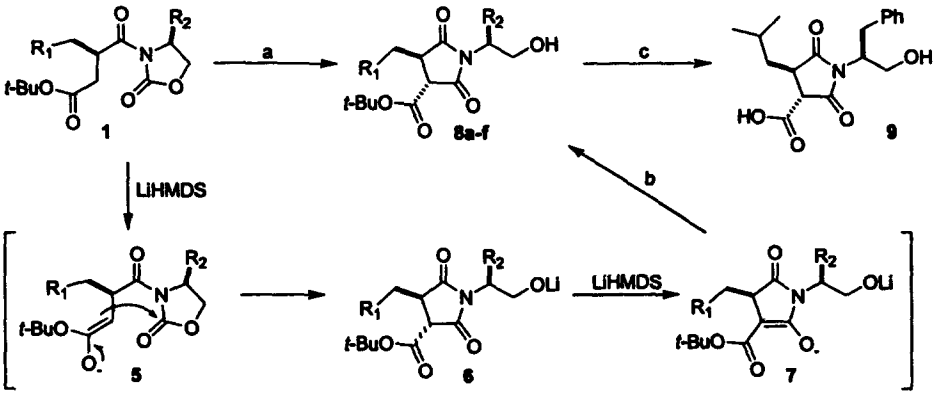
Disubstituted succinic acid derivatives are well known moieties for use in peptidomimetic-based MMP inhibitors. In an attempt to develop a stereoselective approach to these intermediates, we reasoned that the presence of an attached chiral auxiliary may influence the diastereoselectivity of the alkylation step. Several early experiments starting with **1** failed to provide the desired product **4**; instead, a more polar product with a molecular composition resembling that of **8** was isolated. Considering the novelty of this rearrangement reaction, further characterization of the product and optimization of the reaction conditions were performed.



Scheme 2. Possible pathways leading to disubstituted succinimides. Reagents and conditions: (a) overall reaction; 2.2 equiv. $LiN(TMS)_2$ in THF under argon at −78°C to rt; (b) aq. work-up gave least hindered *trans* geometry; (c) **8a** treated with TFA:CH_2Cl_2, 1:1 mixture, left at rt overnight

A typical method involved treatment of the oxazolidinone **1** in THF at −78°C with 2.2 equivalents of $LiN(TMS)_2$. The cooling bath was then removed and the reaction mixture was warmed to room temperature over a 30–45 min period. An aqueous ammonium chloride work-up followed by silica gel column chromatography then provided the desired product **8** in 58–83% yield. Interestingly, it was determined that the addition of excess base to the oxazolidinone **1** during the deprotonation step optimized the yield of the desired product.

HPLC analysis of the crude mixture **8a** indicated that only one diastereomer was formed in the reaction.[6] Several attempts were made to obtain a single crystal for X-ray analysis but were unsuccessful. Deprotection of the *tert*-butyl ester **8a** with TFA:CH_2Cl_2 (1:1) afforded carboxylic acid **9** which produced the desired crystal for X-ray analysis (Fig. 1) verifying the assigned structure as shown in Scheme 2.

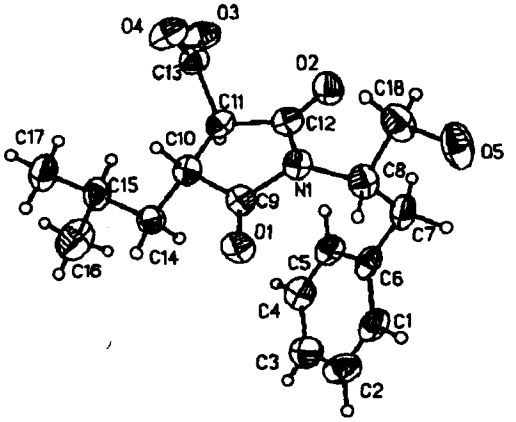


Figure 1. An ORTEP diagram of **9**

Table 1
Yield of various succinimides

Compound	R_1	R_2	yield (%)[†]
8a	*i*-Pr-	$PhCH_2$-	70
8b	*p*-MeOPh-	$PhCH_2$-	75
8c	*n*-C_8H_{17}-	$PhCH_2$-	59
8d	*n*-C_5H_{11}-	$PhCH_2$-	66
8e	$PhCH_2$-	$PhCH_2$-	58
8f	*i*-Pr	*i*-Pr	83

[†]Yield of isolated, purified material. All compounds passed CHN analysis.

A possible mechanism for the reaction is shown in Scheme 2. Abstraction of the least hindered proton on **5** generates an anion which may attack the ring carbonyl of the oxazolidinone leading to succinimide **6**. A second equivalent of base then abstracts the malonate proton to give the enolate **7**. Aqueous work-up then protonates the enolate, providing the observed thermodynamic product **8**. The generality of the rearrangement was examined and the results are shown in Table 1. The rearrangement afforded the desired succinimides in moderate to high yield regardless of the substitution pattern.

In conclusion, we have observed an unexpected rearrangement of an oxazolidinone derivative leading to the formation of a *trans*-disubstituted succinimide. The generality of this rearrangement was demonstrated by the synthesis of a wide variety of disubstituted succinamides with high *trans* selectivity.

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6. TLC shows one major spot/product which was purified by column chromatography and analyzed by HPLC. For **8a**, HPLC analysis shows a single peak.