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Novel anti-β-functionalized γ,δ-unsaturated amino acids via a thio–Claisen rearrangement

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ABSTRACT

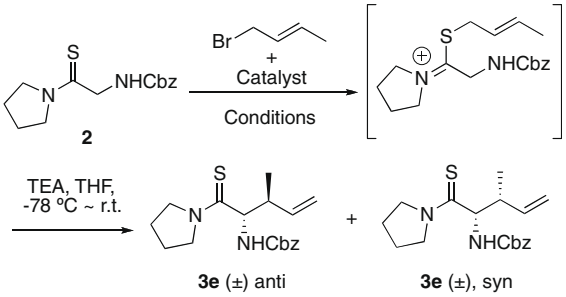
A significantly improved thio–Claisen rearrangement method was developed for preparing anti-β-functionalized γ,δ-unsaturated amino acids, which are extremely useful nonproteinogenic amino acids used in chemistry and biology research. The mild reaction condition successfully introduced base labile functional groups into the amino acids with excellent anti/syn selectivities.

Nonproteinogenic amino acids are among the most useful small molecules in modern biology, chemistry, and drug discovery.[1–3] Design and synthesis of unnatural amino acids with novel functional groups for different chemical and pharmacological applications are in great demand, especially since peptides have emerged as a reliable resource for new drug development.[4–7] β-Functionalized γ,δ-unsaturated amino acids have drawn significant research interest[8,9] for two main reasons: first, the β-functionalization allows the introduction of pharmaceutically interesting side chain groups and second, the orthogonal reactivity of the terminal double bond during peptide synthesis provides access to further chemical modification. These amino acids have also been observed to occur naturally and have enzyme inhibition activities.[10,11]

Several synthetic methodologies have been developed for the construction of these molecules,[12–18] among which the Claisen rearrangement is the most often used. Chelation–Claisen rearrangement has proven to be effective in producing syn-β-functionalized γ,δ-unsaturated amino acids,[14,15] but the corresponding anti amino acids were not readily available with high enantiopurities until we introduced the Eschenmoser–Claisen rearrangement and the thio–Claisen rearrangement methods.[16–18] Despite these successes, the amino acids produced were generally limited to those having only hydrocarbon groups in the β-position. This can be attributed to the harsh reaction conditions that were employed in the above-mentioned syntheses: usually requiring strong base treatment to form the enolate dianion (or equivalent) for the alkylation. Since nature uses much more than just hydrophobic amino acids, such as glutamic acid and glutamine, therefore, it is of great importance to develop a general and mild method to provide more versatile amino acid derivatives. We report here a greatly improved thio–Claisen rearrangement reaction, which features a $FeBr_3$-catalyzed allylation. Base labile functional groups were readily introduced into the β-position with excellent anti/syn selectivities for the first time. Upon removing the auxiliaries from the thioamides, novel, biologically interesting amino acids were prepared.

Since a mild and efficient condition to form the Claisen rearrangement precursor is the critical step to expand functional group compatibility, we hypothesized that using the thioamide as a nucleophile to react with the electrophilic allylic bromide would be a viable solution.[19] This is because the resulting thioiminium

Table 1
Allylation condition screening for thio–Claisen rearrangement



Entry	Catalyst	Conditions	Solvent	Yield[a]
1	No catalyst	Rt, 24 h	CH_2Cl_2	0
2	No Catalyst	Rt, 24 h	THF	0
3	No catalyst	Rt, 24 h	MeCN	10
4	No catalyst	45 °C, 24 h	MeCN	32
5	20 mol % $ZnBr_2$	45 °C, 12 h	MeCN	41
6	20 mol % $ZnBr_2$	45 °C, 24 h	MeCN	64
7	20 mol % $FeBr_3$	45 °C, 24 h	MeCN	74
8	20 mol % $FeBr_3$	45 °C, 48 h	MeCN	76

[a] Isolated yield of total isomers.

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ion formed should increase the acidity of the α-proton significantly, making it more acidic than the NH proton. Therefore, only one equivalent of a weak base should be sufficient to deprotonate the α-proton and trigger the rearrangement as compared to the multi equivalents of strong base used previously. Fortunately, by monitoring the reaction of just mixing the thioamide **3** and crotyl bromide in dry MeCN at ambient temperatures, the reaction proceeded based on the consumption of the thioamide. Upon adding TEA as the base to deprotonate the resulting thioiminium cation and initiate the rearrangement, we successfully isolated the thio–Claisen rearrangement product **3e** (Table 1). Despite the low yield of this reaction, we were encouraged by this result and optimized the reaction conditions by varying the temperatures and solvents (Table 1, entries 1–4). We found that heating and the use of a polar aprotic solvent accelerated the allylation process. We also envisioned that facilitating C–Br bond breaking should improve the allylation yield and hence the rearrangement yield. Indeed, both $ZnBr_2$ and $FeBr_3$ gave significantly improved yields via a Friedel–Crafts alkylation type reaction (Table 1, entries 5–8), with $FeBr_3$ providing somewhat better results.

Several more examples were studied with pyrrolidine as the auxiliary, and the benzyloxycarbonyl group was selected as the N^{α}-protecting group. The thioamide **2** was prepared from the amide **1** by using Lawesson's reagent.[20] **2** was allylated using the optimized conditions illustrated in entry 7 (Table 1). All reactions proceeded smoothly giving the desired thio–Claisen rearrangement products (**3a**–**h**). The results are summarized in Table 2. The good to excellent anti/syn ratios were as expected, when considering the formation of the favored *Z*-thioenol ether after deprotonation[21] and the chair-like six-membered ring transition state[18,22] (**A** in Fig. 1) of the Claisen rearrangement. Most noticeably, ester groups were successfully introduced into the β-position for the first time. Thus, this mild reaction condition has expanded the variety of functional groups which can be introduced at the β-position. Moreover, compound **3g** and **3h** were obtained as diastereopure products. We attribute these excellent results to a possible bicyclic transition state model: the ester carbonyl group would

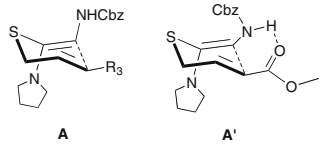
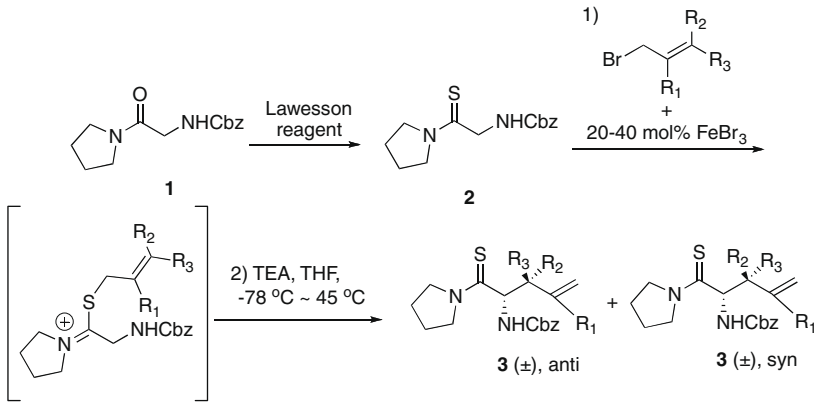
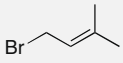
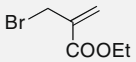
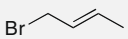
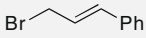
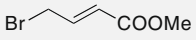
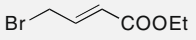


Figure 1. Proposed transition state models for thio–Claisen rearrangement.

Table 2
Results of thio–Claisen rearrangement

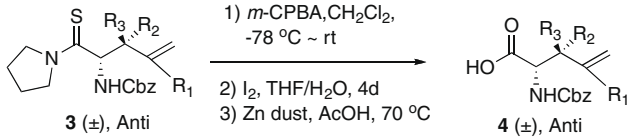


3a. R_1, R_2, R_3 = H
3b. R_1 = Me; R_2, R_3 = H
3c. R_1 = H; R_2, R_3 = Me
3d. R_1 = COOEt; R_2, R_3 = H
3e. R_1, R_2 = H; R_3 = Me
3f. R_1, R_2 = H; R_3 = Ph
3g. R_1, R_2 = H; R_3 = COOMe
3h. R_1, R_2 = H; R_3 = COOEt

Pdt	Allylation reagent	Anti/syn	Yields[a]
3a		n/a	68
3b		n/a	69
3c		n/a	42
3d		n/a	72
3e		10:1[b]	74
3f		8:1[b]	51
3g		>49:1[b]	82
3h		>49:1[b]	72

[a] Isolated yield of total isomers.
[b] Determined by ^1H NMR.

Table 3
Results of amino acid generation



Entry	R_1, R_2, R_3	Anti/syn	Yields[a]
4d	COOEt, H, H	n/a	78
4e	H, H, Me	10:1[b]	76
4g	H, H, COOMe	>49:1[b]	82
4h	H, H, COOEt	>49:1[b]	83

[a] Isolated yield of total isomers.
[b] Determined by ^{1}H NMR.

establish a hydrogen bond with the α-amino group, forming a second six-membered ring to further stabilize the transition state (**A′** in Fig. 1).

The final step of converting the thioamide into the carboxylic acid is always a challenge, especially when our compounds carry the ester functional groups and two acidic α-protons at two stereogenic centers. The previously reported one-pot alkylation–reduction–oxidation method was found not to be appropriate due to the reactivity of the β-ester functional group. Therefore, an oxidation–iodolactonization–reduction method was used instead. The thioamides **3** were first converted to the amides[23] and used without purification to form the iodolactones,[24] which were subjected to a reductive elimination reaction with zinc to open the lactone ring and form both the carboxylic acid and the terminal double bond simultaneously.[25] Results are presented in Table 3, showing that little or no epimerization happened during the reaction.

In conclusion, we have disclosed a significantly improved thio–Claisen rearrangement method for preparing novel anti-β-functionalized γ,δ-unsaturated amino acids. The mild reaction conditions not only offered good to excellent anti/syn selectivities in high yield but also make it possible to greatly expand the functional group availability in these amino acids. Further investigation of the enantioselective synthesis of these novel amino acids, the scope of this synthetic methodology, and the applications of these synthesized novel amino acids to drug design is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.102.

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