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Synthesis of γ,δ-unsaturated quaternary α-alkylamino acids using umpolung reaction and Claisen rearrangement

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ABSTRACT

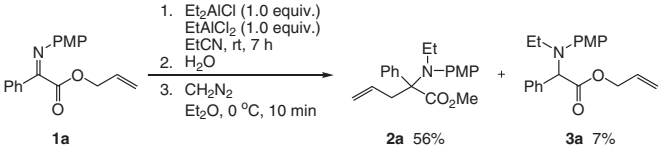
A new synthesis of γ,δ-unsaturated quaternary α-amino acid derivatives was developed utilizing N-alkylation and Claisen rearrangement of allyl α-iminocarboxylates.

α-Amino acids containing quaternary carbons α to the carbonyl constitute an interesting class of nonproteinogenic acids and are used to construct novel peptidic sequences with enhanced properties in various physiologically active peptides and proteins which have become a major concern in the area of bioorganic chemistry.[1] Quaternary α-amino acids are also powerful enzyme inhibitors,[2] and their synthesis has been achieved using several methods so far.[3] In general, γ,δ-unsaturated α-amino acids are not always popular but can be important intermediates for complex peptides.[4] The first synthesis of α-allyl-α-amino acids by the Claisen rearrangement was described by Steglich who utilized an oxazole intermediate in 1975.[5,6] In 1982 the Ireland-Claisen rearrangement of glycine allylic ester was reported by Bartlett.[7] Kazmaier reported diastereoselective synthesis of γ,δ-unsaturated amino acids using the ester enolate Claisen rearrangement.[8–10] Most of their methods use dianion enolates mediated Claisen rearrangement, while there are only a few examples in which monoanion species are involved.[11a] Since application of new synthetic methods has developed the chemistry of amino acids and related fields,[11] the search for more efficient tools is still a worthwhile goal.

An umpolung of α-imino ester is difficult to take place due to the electronegativity of the imino functionality,[12] and therefore, only limited examples are available.[13] We have studied umpolung reactions of α-imino esters and have already reported N-alkylation-coupling reactions of the imines derived from glyoxylates.[14,15] Although three component coupling of α-imino esters was reported using umpolung addition of organometals, there still appears to remain an important issue regarding enhancement of the reactivity of the intermediary enolates.[13b] Herein, we report a one-pot tandem synthesis of γ,δ-unsaturated amino ester using N-alkylation followed by a monoanion mediated enolate Claisen rearrangement.

As an initial reaction, allyl 2-(4-methoxyphenylimino)-2-phenylacetate **1a** was first reacted with diethylaluminum chloride and ethylaluminum dichloride in EtCN followed by treatment with CH_2N_2 in diethyl ether at 0 °C for 10 min (Scheme 1). The reaction proceeded as expected to give the desired rearranged product **2a** in a 56% yield.

In order to find optimum reaction conditions, we next screened solvents, temperatures, reaction times, and additives, and the results are summarized in Table 1. As shown in Table 1, dichloromethane, 1,4-dioxane, and THF were not suitable for the reaction (entries 2–4). Using diethyl ether as the solvent, the yield of **2a** was improved slightly (entry 5). When dimethoxyethane (DME)



Scheme 1. Initial examination of the umpolung reaction followed by Claisen rearrangement.

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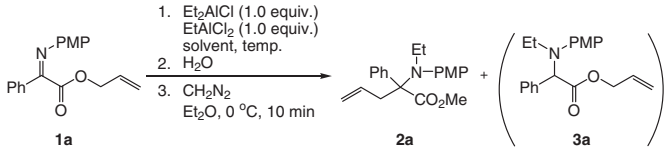
Table 1
Examination of the optimum conditions



Entry	Solvent	Temp.	Time (h)	Yield of **2a** (%)	Yield of **3a** (%)
1	EtCN	rt	7	56	7
2[a]	CH_2Cl_2	rt	6	15	0
3	1,4-Dioxane	rt	6	3	18
4	THF	rt	6	4	41
5	Et_2O	rt	6	37	9
6	DME	rt	6	52	6
7	DME	rt	44	23	9
8	EtCN	rt	44	42	8
9[b]	DME	rt	6	49	12
10	DME	40 °C	6	60	5
11[c]	DME	40 °C	6	57	0
12	DME	50 °C	6	58	6
13[d]	DME	50 °C	6	0	62
14	EtCN	50 °C	6	3	26
15[e]	DME	60 °C	6	31	4
16[f]	DME	82 °C	6	0	0

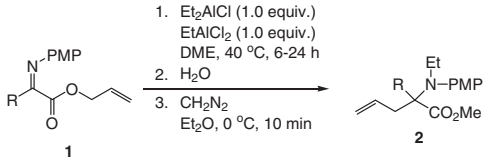
[a] *N*-Ethyl-4-methoxybenzenamine was obtained in a 20% yield.
[B] Compound **1a** was added to the aluminum reagents.
[c] Et_2AlCl (2.0 equiv) was used.
[d] In the presence of MS 4 Å.
[e] *N*-Ethyl-4-methoxybenzenamine was obtained in a 30% yield.
[f] *N*-Ethyl-4-methoxybenzenamine was obtained in a 34% yield.

was used, the yield was as good as in the case of EtCN (entry 6). Extending the reaction time decreased the product yields (entries 7 and 8). Changing the order of the addition in which the imino ester **1a** was added to the aluminum reagents solution did not noticeably improve the yield (entry 9). The reaction temperature was next examined (entries 10–16). The reactions in DME at 40 or 50 °C gave the product in good yields (entries 10 and 12), while more elevated temperatures such as 60 and 82 °C decreased the product yields and gave *N*-ethyl-4-methoxybenzenamine formed by hydrolysis of the iminium salt which was derived from oxidation of the aluminum enolate (entries 15 and 16).[14c] Interestingly, the presence of molecular sieves 4 Å as an additive prevented the Claisen rearrangement to afford the initial N-ethylated product **3a** solely in a good yield (entry 13). On the other hand, raising the reaction temperature in EtCN did not afford the desired product **2a** at all (entry 14). The optimized reaction conditions were thus found to be conducive to DME as solvent at 40 °C for 6 h.

The scope of substrates was next examined, and the results are summarized in Table 2. Aromatic groups having either electron-donating or electron-withdrawing *meta*- or *para*-substituents underwent the desired reaction to give the products (entries 1-5) except for the *p*-methoxyphenyl derivative (entry 6). In the case of 4-methoxyphenyl derivative, hydrolyzed *N*-ethyl-4-methoxybenzenamine is the major by-product, which indicates that the electron-donating *para*-methoxy group may decrease the reactivity of the intermediary iminium salt, whereas such an effect is not prominent for *meta*-methoxy derivative due to the less effective electron-donating ability for the *meta*-position as compared with the *para*-counterpart. The use of thienyl derivative afforded the rearrangement product in a low yield (entry 7), while the substrate substituted by a cyclohexyl group derivative gave the product in a moderate yield (entry 8). However, the bulky *tert*-butyl derivative gave no adduct (entry 9).

The allyl moiety was next examined, and the results are summarized in Table 3. The reactions of methallyl and 2-butenyl esters proceeded to give the desired products in good yields in which no

Table 2
Examination of the substituent



Entry	R	Yield (%)
1	Ph	60
2[a,b]	3-F-C_6H_4	76
3[a]	4-F-C_6H_4	65
4[c]	4-Cl-C_6H_4	58
5	3-MeO-C_6H_4	79
6[a,d]	4-MeO-C_6H_4	0
7[e,f]	2-Thienyl	30
8[a]	*c*-Hex	40
9	*t*-Bu	0

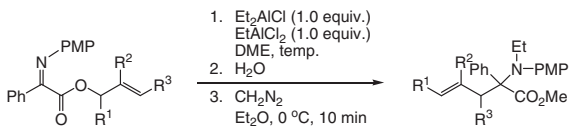
[a] Et_2AlCl (2.0 equiv) was used.
[b] *N*-Ethyl-4-methoxybenzenamine was obtained in a 23% yield.
[c] At room temperature.
[d] *N*-Ethyl-4-methoxybenzenamine was obtained in a 95% yield.
[e] At 0 °C.
[f] *N*-Ethyl-4-methoxybenzenamine was obtained in a 70% yield.

diastereoselectivity of the product was observed (entry 1), while that of crotyl ester gave no rearrangement product, and only N-ethylated product was obtained in a low yield (entries 1,2 vs 3). The rearranged product was not obtained using α-imino cinnamyl ester, either.

Moreover, examination into other alkylating reagent revealed that the reaction was sensitive to the bulk of the reagent (Scheme 2).

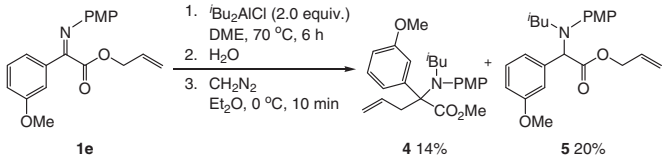
A proposed reaction mechanism is shown in Scheme 3. First, ethylaluminum dichloride that is a stronger Lewis acid than diethylaluminum chloride coordinates with the carbonyl oxygen atom followed by N-ethylation of diethylaluminum chloride to give an intermediary aluminum enolate,[16] Then Claisen rearrangement takes place to give the amino acid derivative which is methylated with diazomethane. Selectivity of the product geometry may be explained in terms of two possible enolates. The (*Z*)-enolate leads to the conformation **6a** possessing the R^1 group in an equatorial arrangement to afford the (*E*)- alkene, while the (*E*)-counterpart takes the conformation **7b**, with an axial R^1 substituent, which seems to be unfavorable in the six-membered chair-like transition state. However, the conformer with an oxygen coordinated to the bulky organoaluminum reagent would be favored over **7b** in view of the 1,2-steric interaction between R^1 and the coordinated aluminum moiety in **7a**, leading to the preferential formation of (Z)-alkene.[5] Regarding the substrate having a terminal methyl group,

Table 3
Examination of allyl moiety

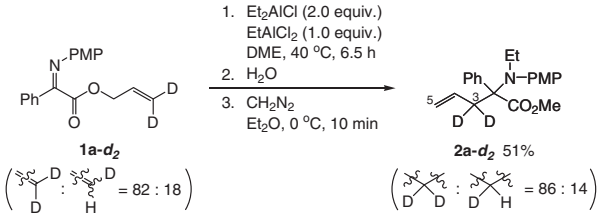


Entry	R^1	R^2	R^3	Temp. (C°)	Time (h)	Yield of **2** (%)
1[a]	Me	H	H	40	12	62[b,c]
2	H	Me	H	0	24	73
3	H	H	Me	50	6	—[d]

[a] Et_2AlCl (2.0 equiv) was used.
[b] *E*/*Z* = 59:41.
[c] *N*-Ethylated product was obtained in a 9% yield.
[d] *N*-Ethylated product was obtained in a 26% yield.



Scheme 2. Reaction using diisobutyl aluminum chloride.

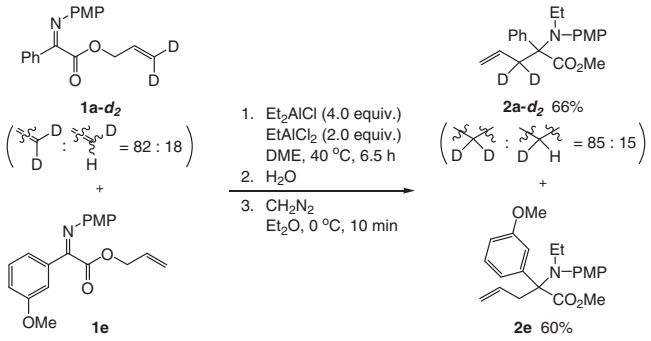


Scheme 4. Isotopic labeling experiment.

although it is possible that the intramolecular rearrangement also occurs with this kind of disubstituted olefin, the rearranged product is not obtained (Table 3, entry 3). This result suggests that an intermolecular C–C bond formation might not be excluded.[17]

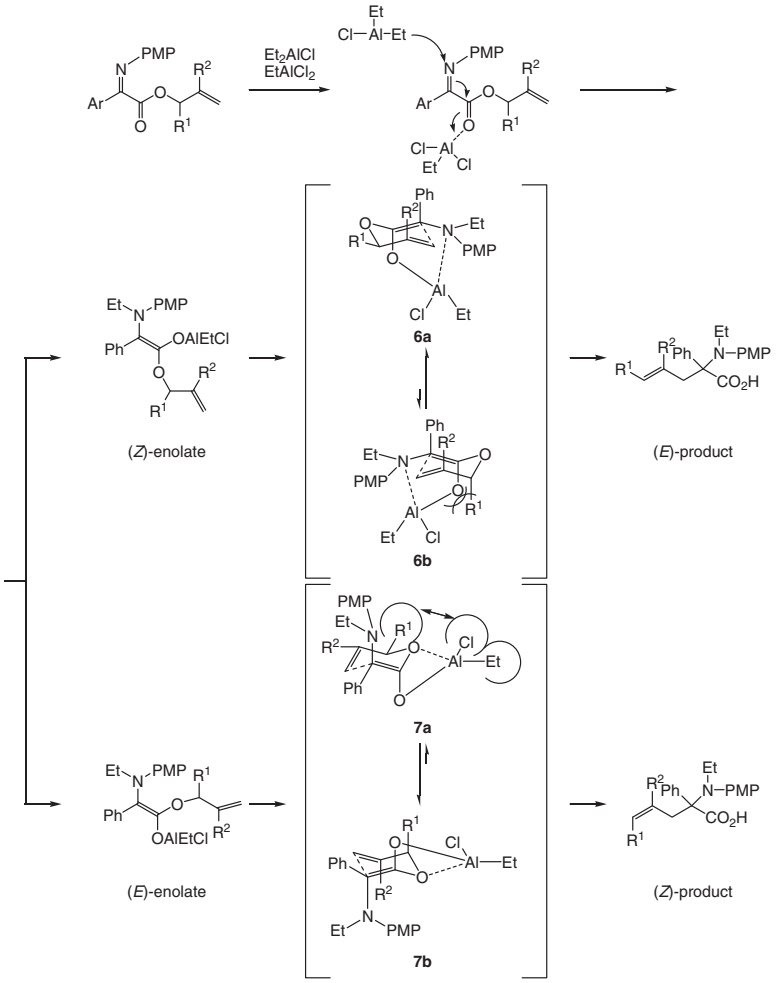
In order to clarify the reaction mechanism in more detail, a deuterium labeling experiment was carried out (Scheme 4). The α-imino ester **1a-*d*$_2$** was prepared according to the reported method.[18] The rearrangement gave only the product **2a-*d*$_2$** (86% D incorporation at C3), and there was no deuterium scrambling at other positions. This result indicates that the present reaction most probably proceeds via a [3,3]-sigmatropic rearrangement to give the product.

Moreover, a crossover experiment was carried out with two different imino esters **1a-*d*$_2$** and **1e** (Scheme 5). The intramolecular reaction products **2a-*d*$_2$** (85% D incorporation at C3) and **2e** were obtained in 66% and 60% yields, respectively, while an intermolecular reaction product was not obtained at all. This result also supports the proposed [3,3]-sigmatropic rearrangement.



Scheme 5. A crossover experiment.

In conclusion, we have found a new one-pot synthesis of α-amino acid derivatives having an α-quaternary carbon utilizing



Scheme 3. Proposed reaction mechanism.

a monoanion enolate Claisen rearrangement of the aluminum enolate prepared by umpolung reaction in moderate to good yields. This reaction provides a useful addition to existing methods for the synthesis of biologically active nitrogen-containing compounds having a quaternary carbon.

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.2012.01.133.

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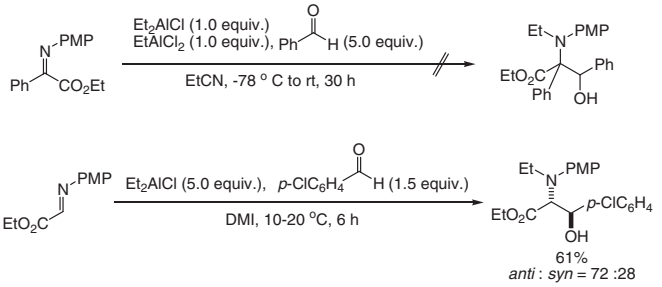
16. It is not very clear which ethyl group is delivered from $EtAlCl_2$ or Et_2AlCl. However, it is presumed that initially a stronger Lewis acid $EtAlCl_2$ may activate the α-imino ester followed by the ethylation with Et_2AlCl, in which a mixture of (*E*)-and (*Z*)-enolates may be formed.
17. We found that the aluminum enolate from the imino ester derived from ethyl benzoylformate reacted with electrophiles sluggishly, while the one derived from ethyl glyoxylate reacted more easily.



18. See the Supplementary data.