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REGIOSELECTIVE SYNTHESIS OF EITHER α- OR γ- AMINO ACID DERIVATIVES VIA Li, Sn-MASKED, AND/OR Ge-MASKED DIENOLATES

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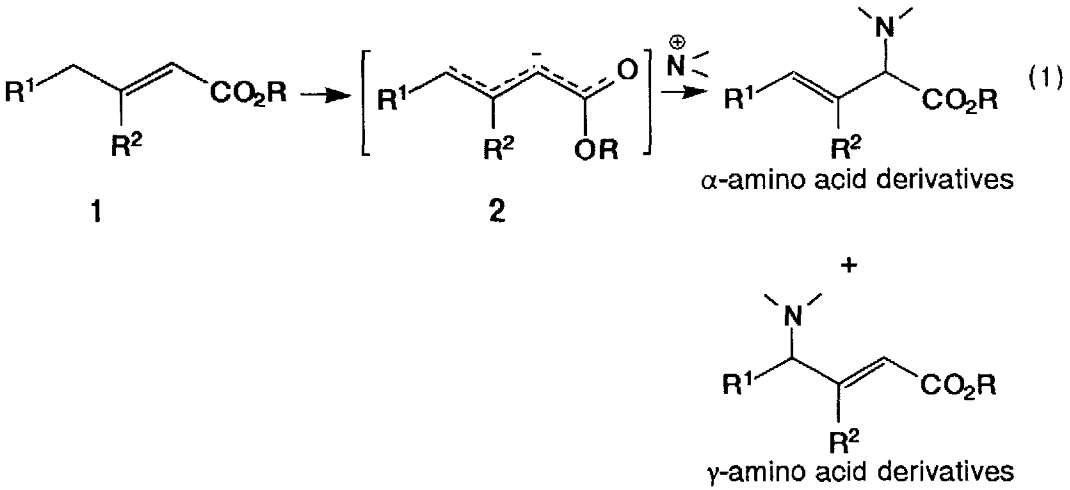
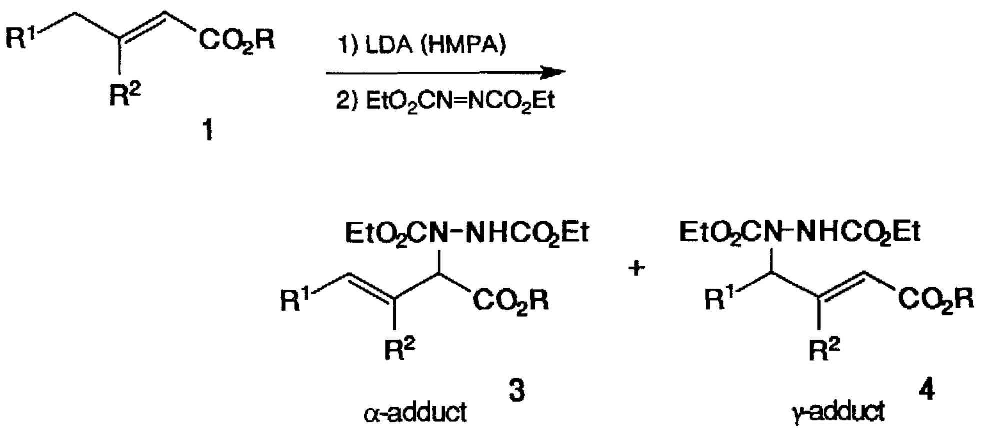
Summary: Either the α- (**3**) or γ-amino acid derivatives (**4**) can be prepared with very high regioselectivity by treating diethyl azodicarboxylate (DEAD) with (i) lithium dienolates themselves (**2**) in certain cases, (ii) Sn-masked dienolates (**5**), or (iii) Ge-masked dienolates (**6**).

The amination reaction of lithium dienolates often produces a mixture of α- and γ-amino acid derivatives (eq 1). For example, treatment of the lithium dienolate of β,β-dimethylacryloyl imide with DBAD(di-t-butyl azodicarboxylate) affords a 51% of the α-adduct along with 42% of the γ-isomer.[1]



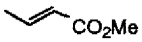
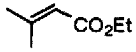
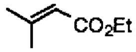
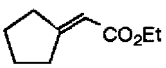
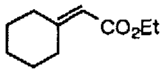
Regiocontrolled synthesis has been required in our group, since such functional groups are frequently found in important biologically active natural products, like vinyl glycine,[2] statine,[3] and anthopleurine.[3] We report that highly regioselective synthesis of either α- or γ-amino acid derivatives is realized via the reaction of DEAD(diethyl azodicarboxylate) with certain lithium dienolates or with Sn- and Ge-masked dienolates.

First, we examined the reaction of the lithium dienolates (**2**) prepared by treatment of the corresponding enoates (**1**) with LDA in HMPA-THF or in THF alone (eq 2). The results are summarized in Table 1.

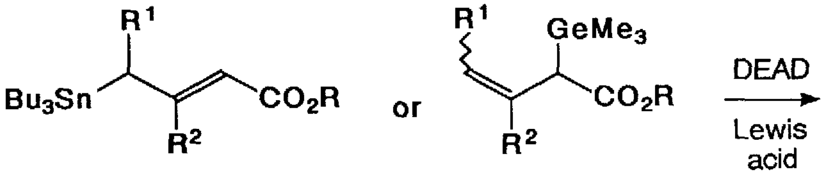


(2)

Table 1. Reaction of Lithium Dienolates with DEAD[a]

entry	substrate	conditions	product ratio α : γ (E/Z of γ) (3 : 4)	total isolated yield, %
1		A	1 : > 99 (> 99/1)	64
2		A	1 : > 99 (> 99/1)	71
3		B	1 : 10 (1/1)	78
4		A	1 : 5 (2/1)	75
5		B	1 : 3 (1/2)	87
6		B	4 : 1 (1/1.5)	69

[a] Lithium dienolates (2) were prepared as described previously.[4] Condition A; 1(2mmol), LDA(1.1 eq) in HMPA (1.3 eq)-THF, -78°C, 30min. Condition B; 1(2mmol), LDA(1.1 eq) in THF, -78°C, 30min. To this solution, DEAD(1.1 eq) in CH_2Cl_2 was added at -78°C and then the reaction was quenched at 0°C. The isomer ratio was determined by 270 MHz ^1H NMR. The product was isolated through a silica-gel column chromatography.

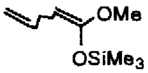
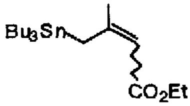
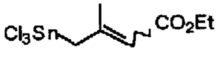
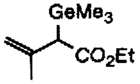
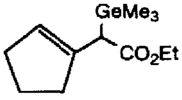
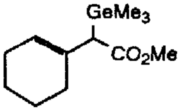


(3)

5
Sn-masked dienolate

6
Ge-masked dienolate

Table 2. Lewis Acid Mediated Reaction of Sn- and Ge-Masked Dienolates with DEAD[a]

entry	masked dienolate	Lewis acid	temp (°C) reaction time	product ratio $\alpha:\gamma$ (3 : 4) (E/Z of γ)	total isolated yield, %
1		$TiCl_4$	-78, 30min	1 : 4 (> 99/1)	85
2		$ZnCl_2$	-78 → 0 40min	15 : 1	80
3		b	-10, 100min	10 : 1	28
4		b	-10, 30min	10 : 1	58
5		$TiCl_4$	-78 → r. t. 2h	1 : > 99 (3/1)	71
6		$TiCl_4$	-78 → 5 40min	1 : > 99 (8/1)	88
7		$TiCl_4$	-78 → 0 30min	1 : > 99 (6/1)	55

[a] To a CH_2Cl_2 solution of DEAD(2 mmol), $TiCl_4$(1 eq)-CH_2Cl_2 or $ZnCl_2$(1 eq)-CH_2Cl_2 was added at -78°C except entries 3 and 4. The masked dienolates (1.2 eq) in CH_2Cl_2 were added and the reaction was quenched at the indicated temperature. [b] In entries 3 and 4, the lithium dienolates were trapped with 1.1 eq $SnCl_4$ at -78°C and then DEAD was added to this mixture (in situ method).

In contrast to the lithium dienolate derived from the α,β-unsaturated imide,[1] the dienolates from enoates gave the γ-amino acid derivatives (**4**) either exclusively (entries 1 and 2) or very predominantly (entry 3). The γ-selectivity decreased in the presence of HMPA (cf. entry 3 and 4). An interesting contrast was observed in the cyclic systems: the five membered derivative gave the γ-isomer predominantly while the six membered derivative produced the α-isomer preferentially (entries 5 and 6). No isomerization took place between the α- and γ-isomers under the reaction conditions, and thus the regioisomers (**3** and **4**) are produced under kinetic control.

It is clear that certain γ-amino acids are obtained with very high regioselectivity by simply treating dienolates with DEAD. However, the α-isomers in entries 1-5 and the γ-isomer in entry 6 are not available. We next examined the Lewis acid mediated reaction of Sn- and Ge-masked dienolates (eq 3), and the results are summarized in Table 2.

As expected, the γ-Sn masked dienolates (**5**) gave the α-adducts with high regioselectivity (entries 2-4) and the α-Ge masked dienolates (**6**) produced the γ-adducts exclusively (entries 5-7). The well-known silyl dienol ether afforded the γ-isomer predominantly but the selectivity was not so high (entry1, cf. entry 1 of Table 1). The in situ method seems to be convenient (entries 3 and 4), since the isolation of the masked enolate is no necessary and further use of Lewis acid is not required.

It is known that the reaction of azodicarboxylates with lithium enolates[5,6] or with ketene silyl acetals[7,8] produces the amino acid derivatives in high yields. However, the regiocontrol on the amination reaction of dienolates has not been achieved. The present results clearly indicate that either the α- or γ-amino acid derivatives can be prepared with very high regioselectivity by treating DEAD with (1) lithium dienolates themselves in certain cases, (2) Sn-masked dienolates, or (3) Ge-masked dienolates. We are now extending this methodology to the synthesis of some useful γ- and α-amino acids.

References and Notes

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