Tetrahedron Letters, Vol.32, No.37, pp 4969-4972, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A SIMPLE SYNTHESIS OF ψ[(*E*)CH=CH]Gly DIPEPTIDE ISOSTERES VIA REDUCTIVE ELIMINATION OF γ-OXYGENATED α,β-ENOATES WITH ALKENYLCOPPER REAGENTS

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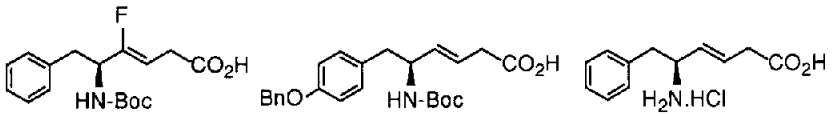
Key Words: dipeptide isosteres; ψ[(*E*)CH=CH]Gly; γ-mesyloxy-α,β-enoates; alkenylcopper reagents; reductive elimination

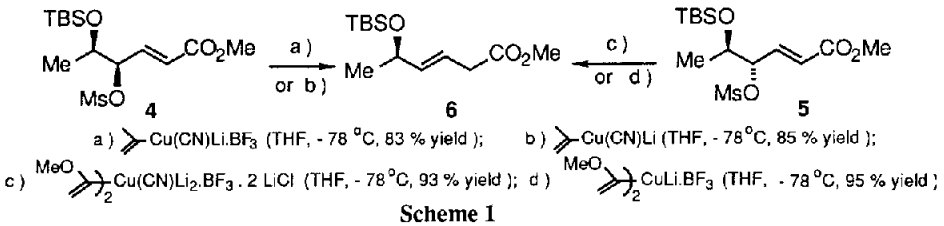
Abstract: *Readily available protected forms of δ-amino-γ-mesyloxy-α,β-enoates can be converted to protected dipeptide isosteres, ψ[(E)CH=CH]Gly, in high yields by reduction with alkenylcopper reagents.*

A recent major advance in the development of protease inhibitors was the replacement of the scissile peptide bond with "transition-state mimics".[1] It has also recently been suggested that the backbone modification of the amide bond of a peptide with an (*E*)-double bond might provide "(*E*)-CH=CH isosteres" possessing high lipophilicity as well as enhanced resistance to biodegradation.[2] The (*E*)-CH=CH- bond closely resembles the three-dimensional shape of the parent amide bond.[3] One avenue, which has not been exploited for the synthesis of ψ[(*E*)CH=CH]Gly, is via efficient reductive elimination of various types of γ-oxygenated α,β-unsaturated esters.[4] Two recent independent publications, describing the synthesis of (*E*)-alkene isosteres, ψ[(*E*)CF=CH]Gly **1**, by Ciba-Geigy [5] and of ψ[(*E*)CH=CH]Gly **2** by Merck, Sharp and Dohme,[6] prompt us to report our results (*e.g.*, synthesis of **3**) in this area.



1 **2** **3**

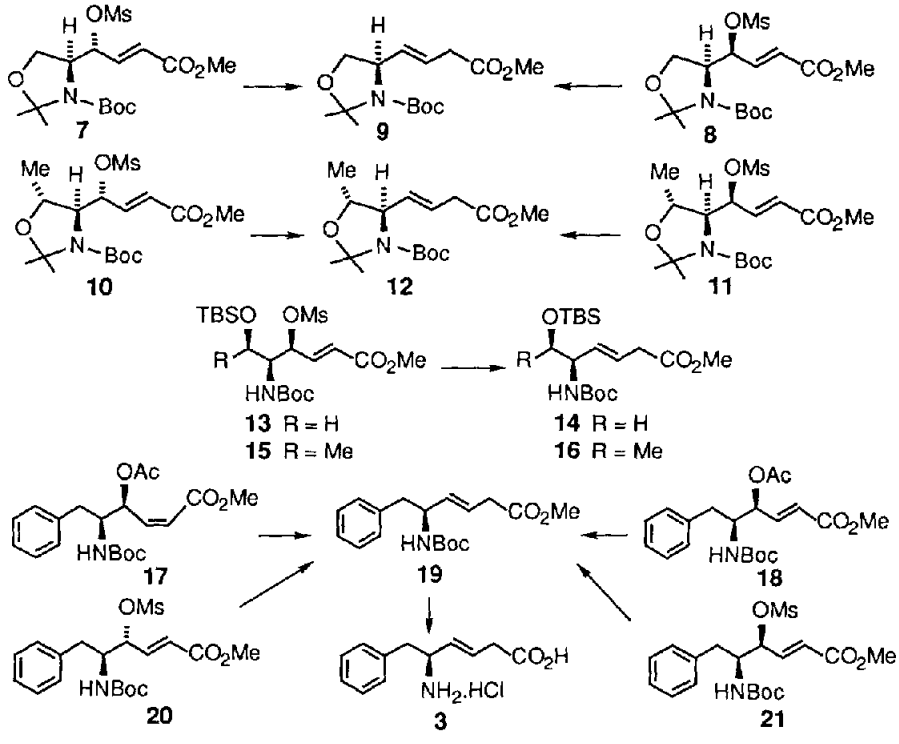
Our synthetic strategy for the synthesis of ψ[(*E*)CH=CH]Gly is based on the observation that γ-mesyloxy-α,β-unsaturated esters **4**[7b] and **5**[7b] were readily converted into the β,γ-unsaturated ester **6** in high yields by treatment with alkenylcopper reagents as shown in **Scheme 1**. Reaction times of 5 ~ 30 min at - 78 °C were sufficient for conversion of the mesylates into the corresponding β,γ-unsaturated ester. The olefinic geometry at the β,γ-position in **6** was exclusively desired *trans*.



Scheme 1

This reductive elimination has been successfully applied to the synthesis of *trans*-alkene isosteres,

ψ[(*E*)CH=CH]Gly.[8] The results in **Scheme 2** and **Table 1** show that alkenylcopper reagents give ψ[(*E*)CH=CH]Gly isosteres from corresponding γ-oxygenated-α,β-enoates in satisfactory yields.[9]



Scheme 2

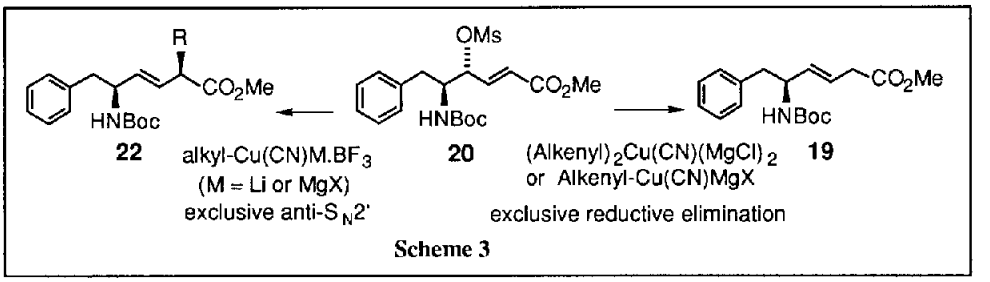
Reaction of both γ-mesyloxy-α,β-enoates **7** and **8** with either the lower order or the higher order alkenylcyanocuprate gave the (*E*)-alkene isostere **9** in high yields (**Table 1**, entries 1 ~ 4).[10] Likewise, both (*Z*) and (*E*)-γ-acetoxy-α,β-enoates **17** and **18** could be converted to Boc-Phe-ψ[(*E*)-CH=CH]Gly-OMe **19** by reaction with the Gilman type reagent (**Table 1**, entries 10 and 13) or the higher order reagent (**Table 1**, entries 11 and 12) in acceptable yields. The desired (*E*)-stereochemistry of the products was inferred from the ca. 15.6 Hz coupling constant of the two olefinic protons. The presence of a HNBoc group at the δ-position in the substrates **17**, **18**, **20**, and **21** does not exert any influence on the course of the reductive elimination.

It has recently been reported[5] that (*E*)-CH=CH isosteres easily undergo isomerization of the double bond at the β,γ-position to yield α,β-unsaturated carbonyl compounds. However, in our study, the reaction and work-up conditions used did not cause double bond isomerization to the α,β-position. Homochiral α-alkyl-(*E*)-β,γ-enoates,[7] dipeptide isosteres,[11] and ψ[(*E*)-CH=CH]Gly-OMe, are usually stable up to at least at 160 °C (1 mm Hg). Consequently, protected dipeptide isosteres such as **9**, **12**, **13**, and **15** could be Kügelrohr distilled without any double bond migration to the α,β-position. Treatment of the protected isostere **19** with 3N-HCl under reflux for 6 h gave the amino acid hydrochloride **3**, mp 134 - 135 °C (recrystallized from a mixture of THF-Me_2CO). No sign of isomerization of the double bond in **3** was detected by ^1H NMR (in CD_3OD).

Table 1. Synthesis of Protected ψ[(*E*)-CH=CH]Gly Isosteres by Reductive Elimination of δ-Aminated γ-Mesyloxy or γ-Acetoxy-α,β-unsaturated Esters with Alkenylcopper Reagents [a)]

Entry	Substrate	Reagent	Product	Yield(%)
1	**7**	(vinyl)Cu(CN)MgCl	*N,O*-Isopropylidene Boc-Ser-Ψ[(*E*)CH=CH]Gly-OMe **9**	99
2	**7**	(*iso*-propenyl)Cu(CN)MgBr	*N,O*-Isopropylidene Boc-Ser-Ψ[(*E*)CH=CH]Gly-OMe **9**	91
3	**7**	$(vinyl)_2Cu(CN)(MgCl)_2$	*N,O*-Isopropylidene Boc-Ser-Ψ[(*E*)CH=CH]Gly-OMe **9**	91
4	**8**	$(vinyl)_2Cu(CN)(MgCl)_2$	*N,O*-Isopropylidene Boc-Ser-Ψ[(*E*)CH=CH]Gly-OMe **9**	93
5	**10**	$(vinyl)_2Cu(CN)(MgCl)_2$	*N,O*-Isopropylidene Boc-Thr-Ψ[(*E*)CH=CH]Gly-OMe **12**	92
6	**11**	$(vinyl)_2Cu(CN)(MgCl)_2$	*N,O*-Isopropylidene Boc-Thr-Ψ[(*E*)CH=CH]Gly-OMe **12**	90
7	**13**	$(vinyl)_2Cu(CN)(MgCl)_2$	*O*-TBS *N*-Boc-Ser-Ψ[(*E*)CH=CH]Gly-OMe **14**	75
8	**15**	$(vinyl)_2Cu(CN)(MgCl)_2$	*O*-TBS *N*-Boc-Thr-Ψ[(*E*)CH=CH]Gly-OMe **16**	89
9	**15**	(*iso*-propenyl)Cu(CN)MgBr	*O*-TBS *N*-Boc-Thr-Ψ[(*E*)CH=CH]Gly-OMe **16**	86
10	**17**	$(vinyl)_2CuMgCl.MgI(Cl)$	Boc-Phe-Ψ[(*E*)CH=CH]Gly-OMe **19**	86
11	**17**	$(vinyl)_2Cu(CN)(MgCl)_2$	Boc-Phe-Ψ[(*E*)CH=CH]Gly-OMe **19**	78
12	**18**	$(vinyl)_2Cu(CN)(MgCl)_2$	Boc-Phe-Ψ[(*E*)CH=CH]Gly-OMe **19**	73
13	**18**	$(vinyl)_2CuMgCl.MgI(Cl)$	Boc-Phe-Ψ[(*E*)CH=CH]Gly-OMe **19**	78
14	**20**	$(vinyl)_2Cu(CN)(MgCl)_2$	Boc-Phe-Ψ[(*E*)CH=CH]Gly-OMe **19**	97
15	**21**	$(vinyl)_2Cu(CN)(MgCl)_2$	Boc-Phe-Ψ[(*E*)CH=CH]Gly-OMe **19**	96

a) All reactions were carried out in THF at - 78 °C for 30 min with 3 to 4 molar equivalents of alkenylcopper reagents. Reported yields refer to chromatographically purified and spectroscopically pure compounds.



Scheme 3

Of particular interest was comparison of alkyl (sp3)- and alkenyl (sp2)-copper reagents (**Scheme 3**). Whereas alkyl-Cu(CN)M.BF_3 (alkyl = primary, secondary, and tertiary; M = Li or MgX) readily reacted with the mesylate **20** to yield the alkylated isosteres **22** in high yields via an anti-S_N2' pathway,[11] alkenylcoppers such as alkenyl-Cu(CN)MgX (the lower order reagents), $(alkenyl)_2Cu(CN)(MgX)_2$ (the higher order reagents), and $(alkenyl)_2CuMgX$ (the Gilman type reagents) rapidly reacted with **20** at - 78 °C to afford the reductive elimination product **19** as the sole product in high yield.

In summary, the present methodology for the synthesis of ψ[(*E*)CH=CH]Gly isosteres using alkenylcopper

reagents has several advantages in terms of (*E*)-stereoselectivity, efficiency and convenience.

The following procedure is typical for the reductive elimination **(Table 1**, entry 8). To a stirred suspension of CuCN (90 mg, 1 mmol) in dry THF (4 mL) under argon at - 78 °C was added by syringe 0.91 mL (2 mmol) of freshly prepared 2.2 M vinylmagnesium chloride in THF. The mixture was allowed to warm to 0 °C and then stirred at this temperature for 10 min. A solution of mesylate **15** (120 mg, 0.25 mmol) in dry THF (2 mL) was added to the above reagent at -78 °C with stirring. The stirring was continued for 30 min followed by quenching with 3 mL of a 2 : 1 saturated NH_4Cl - 28 % NH_4OH solution. After the usual work-up, the product was purified by flash chromatography over silica gel with *n*-hexane - EtOAc (4 : 1) to give **16** (86 mg, 89 % yield) as a colorless oil of better than 99 % purity (capillary GC and ^1H NMR). Kügelrohr distillation was at 160 °C (1 mm Hg); $[\alpha]^{18}_D$ + 7.44° (c 0.941, $CHCl_3$). The synthesized protected isostere **16** exhibited ^1H NMR (in $CDCl_3$) and IR (in $CHCl_3$) consistent with the assigned structure. Anal. C, H, N.

Acknowledgment: A part of this work was supported by the Grant-in-Aid from the Ministry of Education, Science and Culture (Japan).

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(Received in Japan 15 April 1991)