*First International Electronic Conference on Synthetic Organic Chemistry (ECSOC-1), www.mdpi.org/ecsoc/, September 1-30, 1997*

[A0036]

# Site-Selective Incorporation of Thioamide-Linkages into a Growing Peptide via Variation of the 'Azirine/Oxazolone Method'

**Jürg Lehmann, Anthony Linden, and Heinz Heimgartner***

Organisch-chemisches Institut der Universität Zürich, Zürich, E-mail: heimgart@oci.unizh.ch

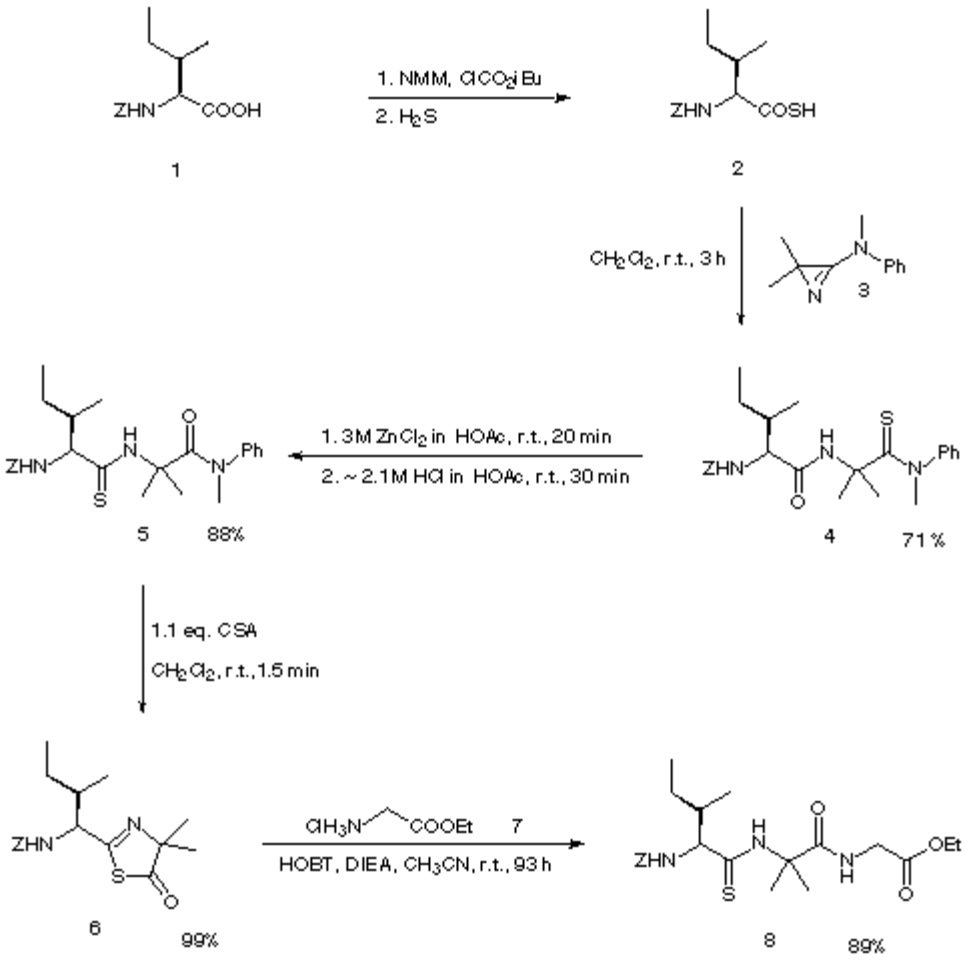
*Received: 25 August 1997 / Uploaded: 27 August 1997*

## 1. Introduction.

Several structural factors are known to restrict the conformational flexibility of peptides, *e. g*. thioamide groups, α- or N-substitution, etc. For many years we have been interested in the constraints introduced by the presence of α-methylated α-amino acids, and with the 'azirine/oxazolone method' we have developed a convenient synthetic access to such peptides. 3-Amino-2*H*-azirines proved to be useful synthons for the introduction of α-substituted α-amino acids [1]. Conversion of 3-amino-2*H*-azirines with thiobenzoic acid, which leads to the corresponding thioamides, has shown the possibility of using α-amino thioacids in the 'azirine/oxazolone method' to sythesize endothiopeptides [2,3].

## 2. Results and Discussion

The principle of the novel methodology, in which a thioamide group is site-selectively introduced next to the bulky 2-methylalanine (α-aminoisobutyric acid, Aib) of a growing peptide, is shown in Scheme 1.




**Scheme 1.**

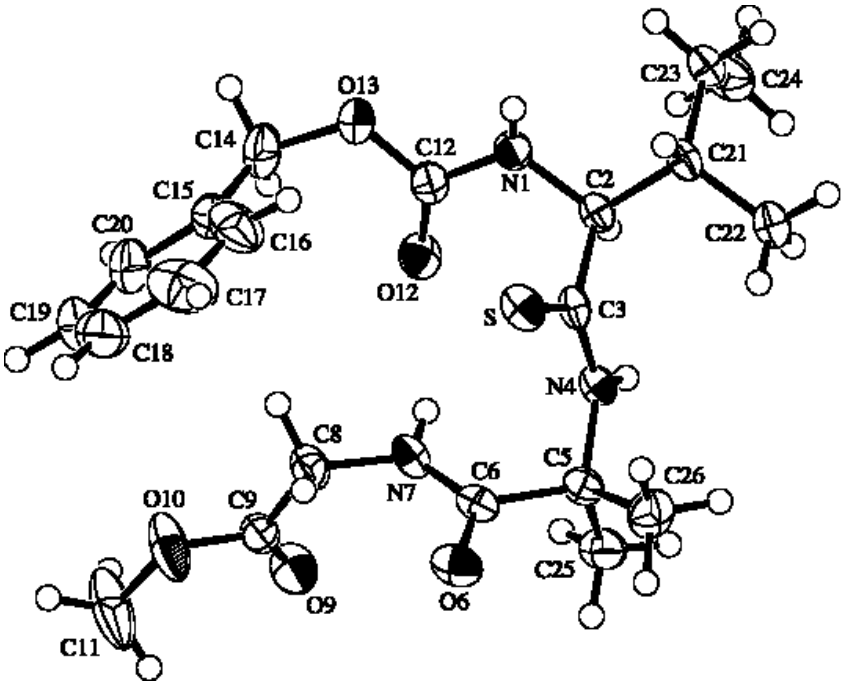
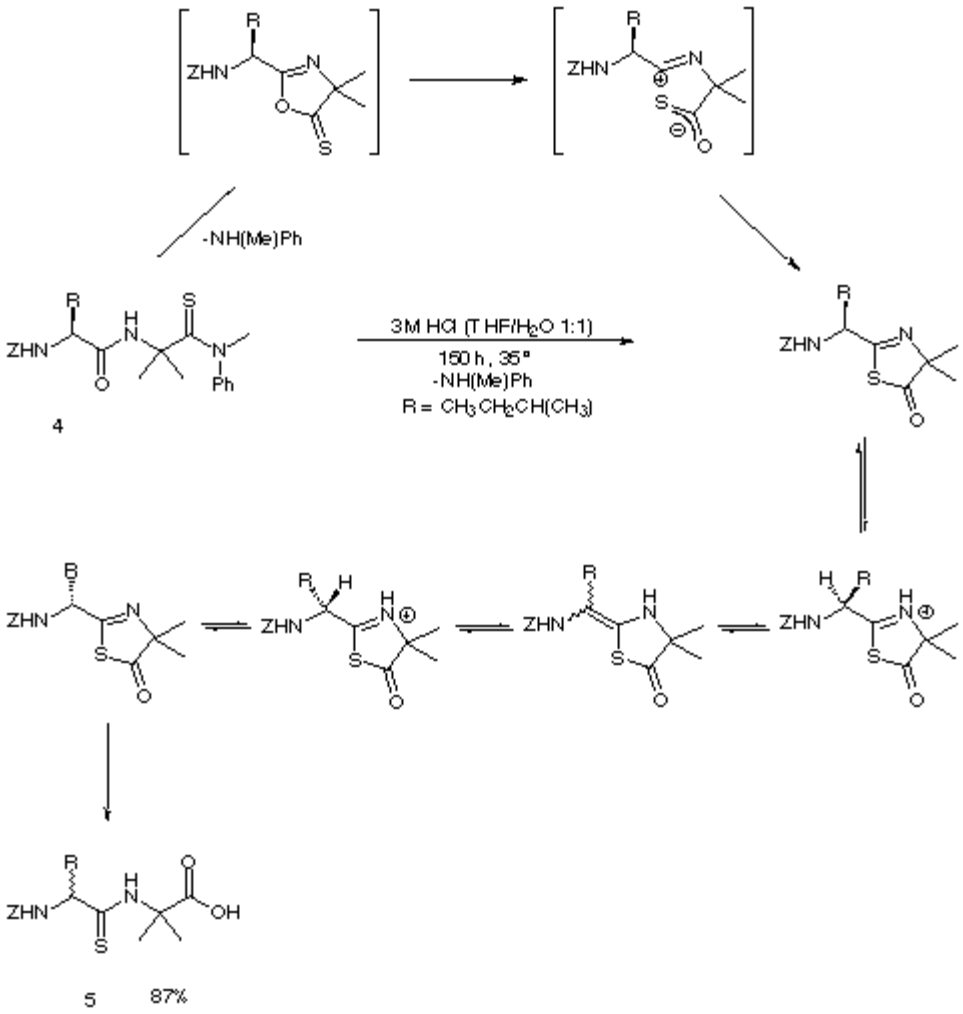



**Figure 1.** ORTEP Plot of the molecular structure of **8**.

The formation occurs via a variation of the 'azirine/oxazolone method': reaction of an N-protected a-amino thioacid (*e.g.* **2**) with 2,2-dimethyl-3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**3**) yields a dipeptide thioamide (*e.g.* **4**). In contrast to the corresponding dipeptide amides, hydrolysis of the terminal thioamide group

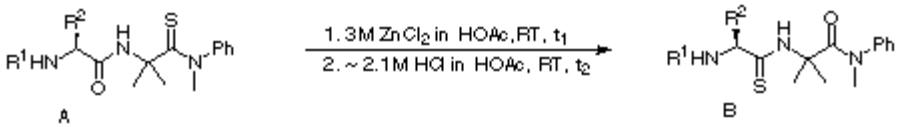
under the conditions of the 'azirine/oxazolone method' (3M HCl in THF/$H_2O$ 1:1, 35deg.) leads, apart from the extraordinary long reaction time and the shift of the S-atom, to complete epimerisation (*Scheme 2*).




**Scheme 2.**

By using $ZnCl_2$ in acetic acid, conditions were established under which the transformation **A to B** (*e.g.* **4 to 5**) proceeds without any epimerisation and in high yields (Table). A possible mechanism of this novel isomerization is shown in *Scheme 3*. The $ZnCl_2$ activated thiocarbonyl group in **A** is intramolecularly attacked by the O-atom of the carbonyl group. The produced *Lewis* acid stabilised amphoteric ion forms a bicyclic system which converts to the thioamide **B**; the probably essential function of the acetic acid is not expressed in this mechanism.

**Table.** Transformation of **A** to **B**.

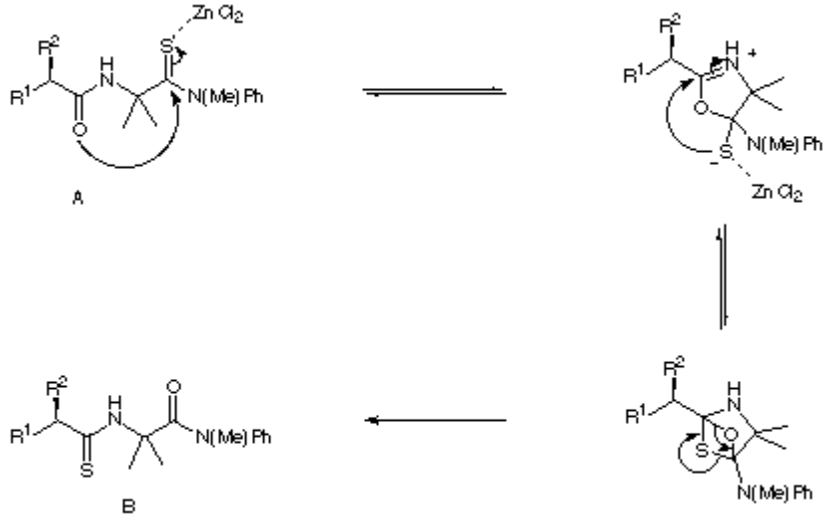



A B

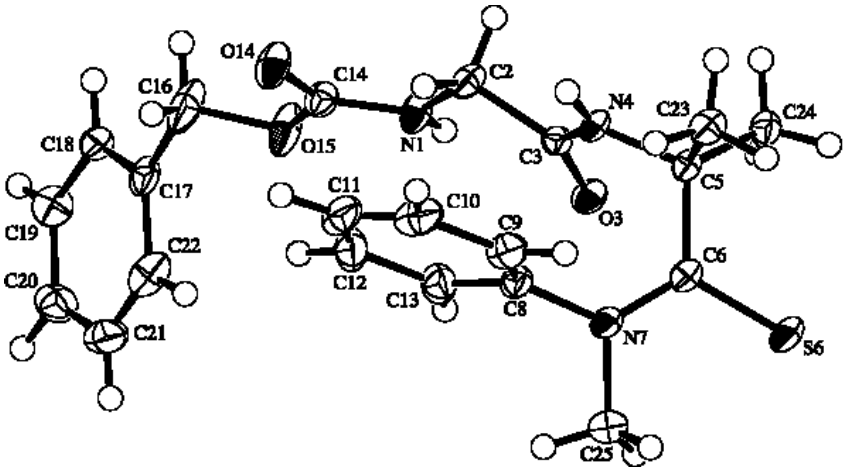
| $R_1$ | $R_2$ | $t_1$(min) | $t_2$(min) | yield(%) |
|---|---|---|---|---|
| Z | $CH_3CH_2CH(CH_3)$, (S) | 20 | 30 | 88 |
| Z | H | 50 | 15 | 96 |
| Z | $PhCH_2$ | 20 | 30 | 94[1)] |
| NVOC | $CH_3CH_2CH(CH_3)$, (S) | 20 | 30 | 92 |

| | | | | |
|---|---|---|---|---|
| FMOC | $CH_3CH_2CH(CH_3)$, (S) | 20 | 30 | 96 |
| FMOC | $(CH_3)_2CH$ | 15 | 20 | 86 |
| FMOC | $CH_3$ | 1.5 | 2 | 94[2)] |

Z = Benzyloxycarbonyl, FMOC = 9-Fluorenylmethoxycarbonyl,
NVOC = 6-Nitroveratryloxycarbonyl
1) ~10 % (R)-enantiomer, 2) 1.5 % (R)-enantiomer




**Scheme 3.**



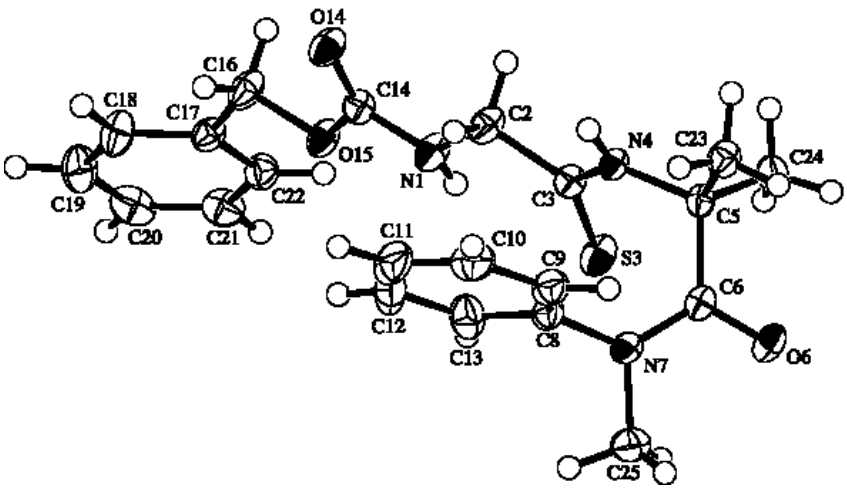
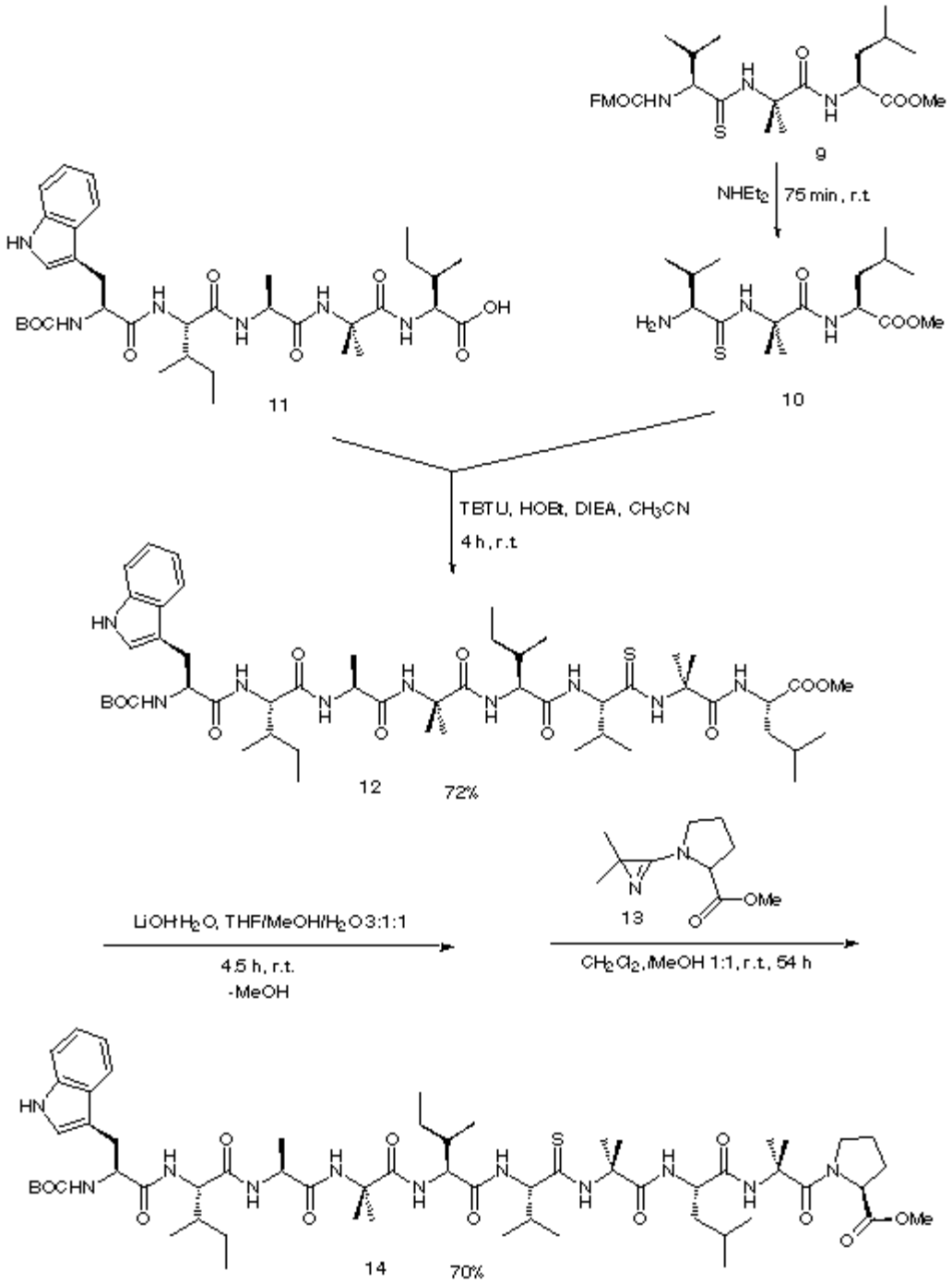



**Figure 2.** ORTEP Plots of the molecular structures of Z-Gly-Aib$^t$-N($CH_3$)Ph (above) and Z-Gly$^t$-Aib-N($CH_3$)Ph (below).

The acid catalyzed conversion of endothiopeptides of type **B** (*e.g*. **5** in *Scheme 1*) into the corresponding 1,3-thiazol-5(4*H*)-ones (*e.g.* **6**) and direct coupling with a C-protected a-amino acid (*e.g*. **7**) yields endothiotripeptides (*e.g*. **8**) in high yields, without epimerisation, and with the specific position of the thioamide group.

With this novel methodology, we succeeded in producing the decaendothiopeptide **14** (*Scheme 4*). Removal of the FMOC-group in **9** and coupling of the two segments **10** and **11** with TBTU yielded the octaendothiopeptide **12**. After C-terminal deprotection in **12** and reaction with the 3-amino-2*H*-azirine **13**, we obtained the decaendothiopeptide **14** without epimerisation.




**Scheme 4.**

## References

[1] H. Heimgartner, *Angew. Chem.* **1991**, *103*, 271.

[2] C. Jenny, H. Heimgartner, *Helv. Chim. Acta* **1986**, *69*, 374.

[3] D. Obrecht, H. Heimgartner, *Chimia* **1982**, *36*, 78.

---

## Comments

During 1-30 September 1997, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with **A0036** as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author(s).

---