Pergamon

Tetrahedron Letters 40 (1999) 71–74

TETRAHEDRON LETTERS

# Solid-Phase Amino-Zinc-Enolate Cyclization for the Synthesis of 3-Substituted Prolines

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Received 16 October 1998; accepted 6 November 1998

**Abstract** : Preparation of 3-substituted prolines was achieved by extension to Solid Phase Organic Synthesis (SPOS) of the amino-zinc-enolate cyclization we have recently described.[1] Functionalizations of proline at C-3 were considered by nucleophilic substitutions of an iodo derivative obtained on the resin.


Combinatorial libraries are now considered as useful tools for the discovery of biologically active compounds.[2] Solid Phase Peptide Synthesis (SPPS) and Solid Phase Organic Synthesis (SPOS) have been widely used for the construction of peptide and non-peptide libraries.[3] However, applications of peptides as drugs are often hampered by poor bioavailability and biodegradation by enzymes.[4] To circumvent these disadvantages, while retaining the biological activity of the original peptide, peptidomimetics of low molecular weight have been developed. A particularly interesting and promising class of peptidomimetics is formed by small heterocycles which can be used as rigid highly functionalized scaffolds.[5] Experience has shown that compounds with biological activity are often derived from heterocyclic structures and several syntheses of heterocycles on solid phase have been reported (benzodiazepines, β-lactams, substituted prolines...).[5] In particular, proline derivatives are largely used for their conformational rigidity to replace natural amino acids in peptides and therefore better understand the bioactive peptide conformation.[6] Furthermore proline derivatives might also be used as scaffold to build up low molecular weight primary screening libraries.[6] Within the proline field, we are interested in the spatial side-chain arrangement of 3-substituted derivatives as peptidomimetics to explore their interactions with G-protein coupled receptors. With this in mind, we required a straightforward method for the onset of a combinatorial library of 3-substituted prolines as pharmacological probes. We have previously described the amino-zinc-enolate cyclization as a new and simple route to obtain 3-substituted prolines[1] and we wish to report here the extension of this strategy to SPOS.

## Results and discussion

The Wang resin[7], suitable for LDA and zinc salt[8] chemistry, was chosen as the solid support to perform the amino-zinc-enolate cyclization. The loading was achieved by transesterification of the chiral ester **3**[1,9] (figure 1). The IR spectra of the loaded resin showed a CO band at 1736 $cm^{-1}$ (figure 1). The diastereoselective

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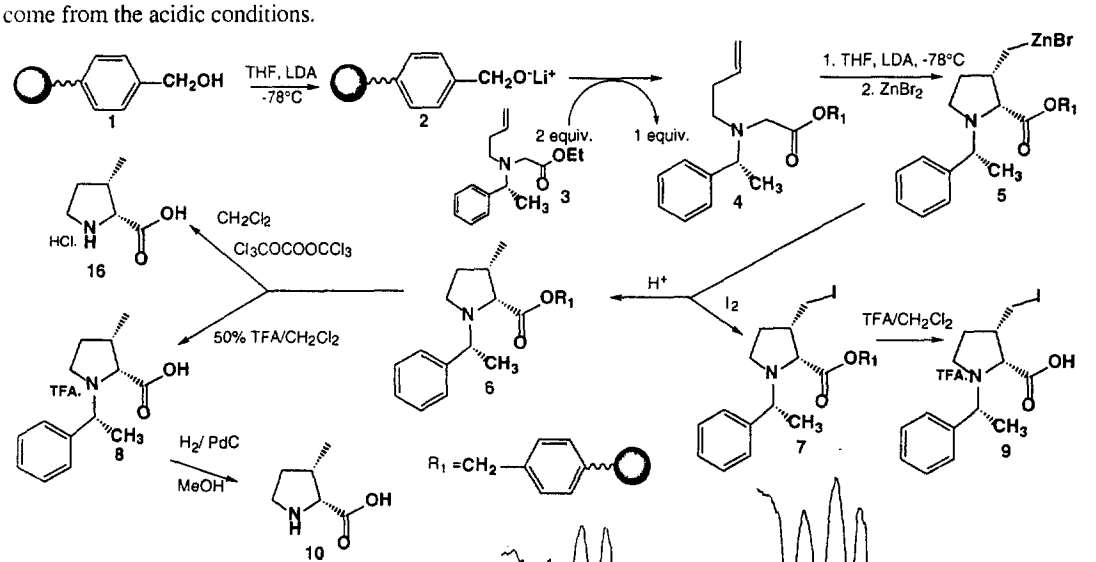
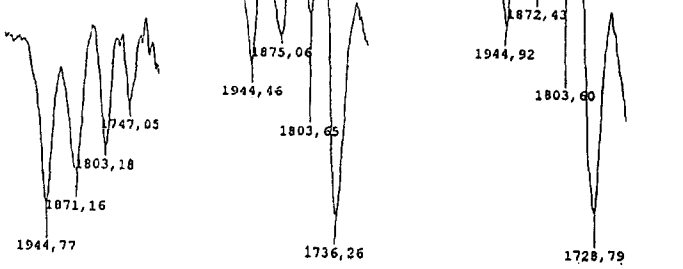
0040-4039/99/$ - see front matter 
*PII:* S0040-4039(98)02373-9

amino-zinc-enolate cyclization (THF, LDA 3 equiv., $ZnBr_2$ 5 equiv.)[10] was performed on the loaded resin **4**. The cyclic organozinc derivative **5** was further protonated leading to derivative **6** or iodonolyzed in **7**.[10]After cyclization, a shift of the CO band from 1736 $cm^{-1}$ to 1728 $cm^{-1}$ was observed for derivative **6** (figure 1). The compounds **8** and **9** were characterised by mass spectrometry[11], after cleavage from the resin (50% $TFA/CH_2Cl_2$). Mass spectrometry analysis showed that the amino-zinc-enolate cyclization occurred cleanly on the resin and was virtually quantitative. No by-product resulting from the acyclic ester **4** was detected. Moreover, after iodonolysis and cleavage of **7** from the resin, **9** was the only product resulting from **4** as evidenced by HPLC-mass spectrometry. The functionalization of the cyclic zinc derivative **5** does not affect the asymmetric induction. Thus, we only needed to assign the absolute configuration of the hydrolysed product, after cleavage from the resin and debenzylation. The absolute configuration was assigned by comparison of the optical rotation of **10** with its enantiomer we have previously described.[1] This value showed that the solid support did not affect the direction of the asymmetric induction, the R-(+)-α-methylbenzyl leading to the (2R,3S) absolute configuration.[12] The classical conditions reported for the cleavage from the Wang-resin (TFA/$CH_2Cl_2$) yielded the N-benzyl free carboxylic acid **8**. The fully deprotected compound **16** was obtained using triphosgene for the N-debenzylation.[13] The cleavage from the resin with ten equivalents of triphosgene may come from the acidic conditions.




**Characteristic areas of IR spectra :**




**a. Wang resin (1)** **b. Loaded Wang resin (4)** **c. Resin after cyclization (6)**

**Figure 1**

The next point we have examined is the functionalization of the iodo derivative **7**. This compound was subjected to nucleophilic substitutions (figure 2) using three kinds of nucleophiles : i) sodium thiophenate, ii) tryptamine and iii) p-nitrophenol.

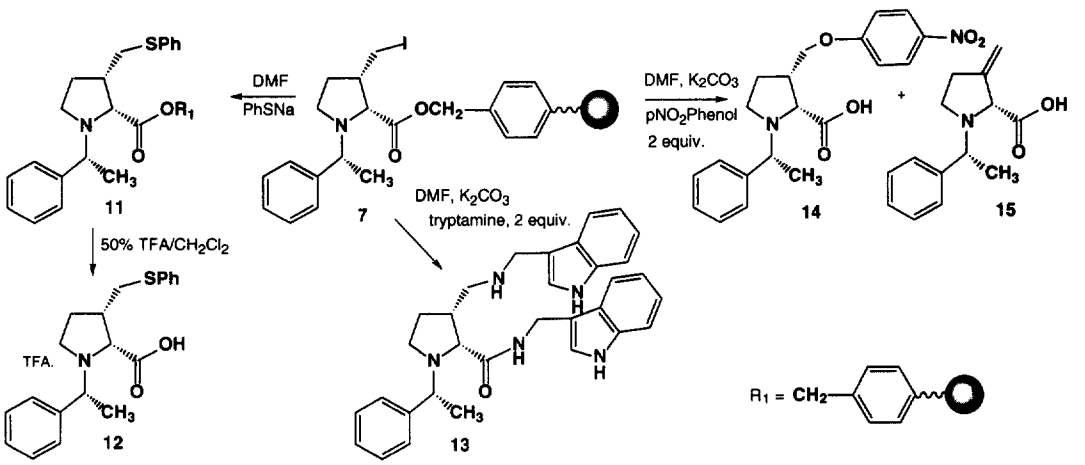



**Figure 2**

The nucleophilic substitutions were performed in DMF, at 50°C. With sodium thiophenate, the derivative **12** was characterised by mass spectroscopy after cleavage of **11** from the resin. No by-product resulting from the iodo derivative **7** was detected in that case. In the reaction involving tryptamine and p-nitrophenol, less reactive, two equivalents of nucleophile were used in the presence of a base ($K_2CO_3$). In these conditions, the reaction resulted not only in the nucleophilic substitution of the iodine but also in the cleavage of the product from the resin. The formation of the compound **14** and the one resulting from β-elimination of iodine, namely **15**, could be explained by basic conditions during the work-up, leading to the cleavage of the p-nitrophenol ester.

In conclusion, we have demonstrated that the amino-zinca-ene enolate cyclization can be applied to the SPOS, allowing to build up a 3-substituted proline library. Further studies for the functionalization at C-3 are under investigation.

**Acknowledgements**

Philippe Karoyan wishes to acknowledge Pr. Solange Lavielle and Dr. Sandrine Sagan for the editing of this manuscript.

**References and Notes**

All reactions were monitored by IR and mass spectrometry analyses.

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9. General condition for transesterification : LDA (1.1 equiv.) was added to a suspension of Wang resin in dry THF at -78°C. The solution was stirred for five minutes at this temperature as two equivalents of the ester **3** were added. The reaction mixture was stirred overnight at room temperature, filtered off over a fritted-funnel. The resin was washed with $CH_2Cl_2$ (3x), EtOH (3x), $CH_2Cl_2$ (3x) and dried *under vacuo*.
10. General conditions for cyclization : The resin was washed with dry THF prior to use. LDA (3 equiv.) was added at -78°C under nitrogen to a dry THF solution of the loaded resin **4**. The temperature was raised to 0°C and then brought back to - 78°C as 1M etheral dry solution of Zinc Bromide (5 equiv.) was added. The reaction mixture was stirred for 6 hours at room temperature and then hydrolysed with 10% citric acid aqueous solution or iodonolyzed at 0°C by addition of iodine (5 equiv.). In that case, the reaction mixture was further stirred for two hours. The reaction mixture was filtered off over a fritted-funnel. The resin was washed with 10% citric acid (3x, to remove the zinc salts), acetone (3x), $CH_2Cl_2$ (3x), EtOH (3x), $CH_2Cl_2$ (3x) and dried *under vacuo*.
11. Mass spectrometry : analyses were performed either by direct infusion of pure samples (flow rate 5µL/min, about 10 µg/mL dissolved in 1:1 acetonitrile/10mM aqueous ammonium acetate) or HPLC-MS of reaction mixtures (column: Hypersil ODS 6 cm, int. diam. 4.6 mm, particle size 3 µm; mobile phase A: 2:8 acetonitrile/10mM aqueous ammonium acetate ; mobile phase B: acetonitrile ; gradient : from 0 to 95% B in 10 min ; injection : 5 µL) by positive-ion electrospray using a quadrupole ion trap mass spectrometer (LCQ, Finnigan). **8** : $[M+H]^+$ m/z 234; **9** $[M+H]^+$ m/z 360; **10** : $[M+H]^+$ m/z 130; **12** $[M+H]^+$ m/z 342; **13** : $[M+H]^+$ m/z 534.3; **14** $[M+H]^+$ m/z 371; **15** $[M+H]^+$ m/z 232.
12. (2R,3S)-ß-methyl proline; $[\alpha]_D^{25}$ 63 (*c* 1, $H_2O$), mp 230-232°C,.Lit $[\alpha]_D^{25}$ 69.8 (*c* 1, $H_2O$).[14]
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