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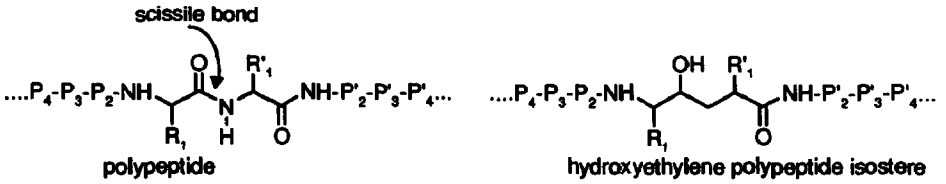
$CrCl_2$ Mediated Allylation of N-Protected α-Amino Aldehydes. A Versatile Synthesis of Polypeptides Containing an Hydroxyethylene Isostere.

Paola Ciapetti, Maurizio Taddei* and Paola Ulivi
Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, Via G. Capponi 9, I-50121 Firenze, Italy

Abstract: *Differently substituted allylic bromides react with N-protected amino aldehydes to give intermediate products for the synthesis of hydroxyethylene dipeptide isosteres. The low stereoselectivity of this reaction can be improved using aldehydes protected with hindered groups. This reaction can be efficiently applied to oligopetide aldehydes. We describe a protocol, for the preparation of peptides containing an hydroxyethylene isostere, which allows a rapid variations of the aminoacid sequence*

During the past decade several research groups have developed novel dipeptide isosteres containing a mimic of the tetrahedral transition state formed during the hydrolysis of the peptidic bond.[1] The hydroxyethylene dipeptide isostere has been one of the most successful modifications which produced highly effective inhibitors of aspartic proteinases such as renin or HIV-1 protease.[2]

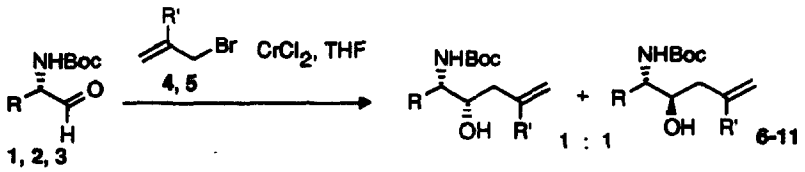


Scheme 1

The common strategy for the synthesis of these isosteres,[3] which are always incorporated into a polypeptidic substrate in place of the scissile P-P' dipeptide, is the preparation of the isostere $H_2NAA_1\Psi[CH(OH)CH_2]AA'_1OH$ and the coupling of this frame with the oligopeptides P_4-P_3-P_2 and P'_2-P'_3.[4] Some reports describe also a methodology for the introduction of an hydroxymethylenamine peptide isostere using a solid phase procedure suitable for a rapid variation of the peptidic sequence.[5]

We speculated that synthetic approaches which allow the formation of the hydroxyethylene isostere directly on oligopeptides aldehydes followed by coupling with the P' part of the product using either liquid or solid phase techniques could be more convenient for the variation of the aminoacid sequence of the peptide itself. In searching for a chemoselective method for the formation of a new Carbon-Carbon bond in oligopeptides, we found that the Hiyama reaction[6] is a very efficient (although not very stereoselective) method to prepare peptides containing hydroxyethylene isosteres.

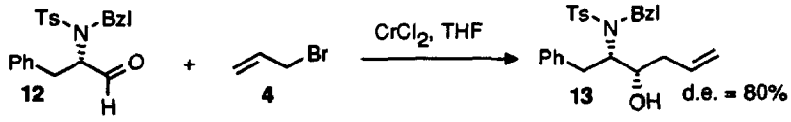
Allylic bromides such as **4** or **5** react cleanly with N-Boc-amino aldehydes **1-3** in the presence of $CrCl_2$ in THF to give amino alcohols **6-11** with good yields (65-80%) but as mixtures of diastereoisomers. (scheme 2)



1 : R = $PhCH_2$. **2** : R = 3-Indolyl-CH_2. **3** : R = $C_2H_5(CH_3)CH$. **4** : R' = H. **5** : R' = COOEt.
6 : R = $PhCH_2$; R' = H. **7** : R = 3-Indolyl-CH_2; R' = H. **8** : R = $C_2H_5(CH_3)CH$; R' = H.
9 : R = $PhCH_2$; R' = COOEt. **10** : R = 3-Indolyl-CH_2; R' = COOEt.
11 : R = $C_2H_5(CH_3)CH$; R' = COOEt

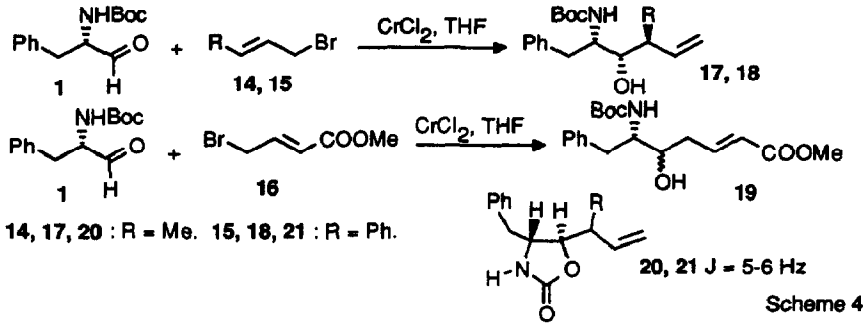
Scheme 2

Different reaction conditions were tried in the effort to increase the stereoselectivity of this reaction. When the solvent was changed from THF to diethyl ether, the allylic Cr(III) reagent did not formed, whereas the use of different ligands for the Cr(III), as PPh_3 or $P(OEt)_3$ did not give any increase of the d.e. Also the attempts to react the allylic Cr(III) reagent with an amino aldehyde precomplexed with a chelating salt, as $MgBr_2$ or $ZnCl_2$ did not improve the stereoselectivity. N-Protected α-amino aldehydes behave as α-alkoxy aldehydes, showing the absence of chelation of the heteroatom on the Cr(III).[7] However aldehyde **12**, derived from N-tosyl-N-benzyl-phenylalanin, reacted with allylbromide **4** to give product **13** in good yield and acceptable d.e. (80%) confirming that the presence of a large substituent on the α carbon of the aldehyde is the predominant factor to influence the stereoselectivity. (scheme 3)



Scheme 3

Crotyl-type bromides react with simple N-Boc amino aldehydes with good stereocontrol. Compounds **14-15** reacted in fact with aldehyde **1** to give the homoallylic alcohols 17–18 with excellent d.e. (> 90% in favour of the isomer reported in scheme 4).

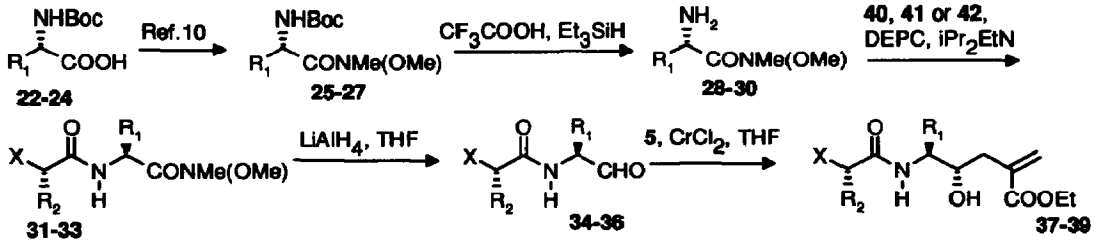


Scheme 4

The stereochemistry of products **17** and **18** was determined by observation of the coupling constants in the ^1H NMR spectra of the corresponding oxazolidinones **20-21**.[8] The unsaturated bromide **16** (having the double

bond conjugated to a COOMe) reacted with **1** without allylic shift (so that the conjugation was not lost) to give product **19** as a 1:1 mixture of diastereoisomers. (scheme 4)

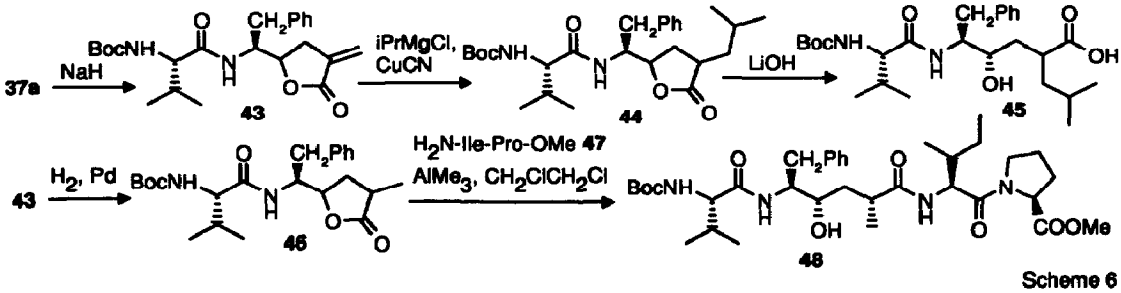
2-Bromoethyl acrylate **5** was the reagent of choice for the synthetic scheme proposed as the objective of this paper. Product **5** reacted in fact, in the presence of $CrCl_2$, with aldehydes **34-36** in good yields but (again) with moderate stereoselectivity.[9] The protocol for the preparation of oligopeptide aldehydes is described in scheme 5. The N-methyl-N-methoxy-amides[10] **28** and **29** were coupled, using DEPC (diethyl phosphorocyanidate) and iPr_2EtN in CH_2Cl_2, respectively with BocValOH (**40**), to give product **31**, and with BocTrpOH (**41**) to give product **32**. The amide **30** was coupled with the tripeptide **42** to give the amide **33**. Reduction of amides **28-30** with $LiAlH_4$ in THF at room temperature followed by acidic work-up ($NaHSO_4$ 10% and extraction in ethyl acetate) gave aldehydes **34-36** in 60-75% yield. These aldehydes reacted with bromide **5** in THF in the presence of $CrCl_2$ at room temperature for 2-6 h to give products **37-39** in 65-80% yield as a 3 : 1 mixture of diastereoisomers (in favour of the *syn* product). In the case of compound **37** the two diastereoisomers were separated by column chromatography on silica gel.



22, 25, 28 : R_1 = $PhCH_2$. **23, 26, 29** : R_1 = Me_2CH. **24, 27, 30** : R_1 = 3-Indolyl-CH_2.
31, 34, 37 : R_1 = $PhCH_2$; R_2 = Me_2CH; X = BocNH. **32, 35, 38** : R_1 = Me_2CH; R_2 = 3-Indolyl-CH_2; X = BocNH
33, 36, 39 : R_1 = 3-Indolyl-CH_2, R_2 = Me_2CHCH_2, X = Boc-Pro-ValNH-.
40 : Boc-Val-OH. **41** : Boc-Trp-OH. **42** : Boc-Pro-Val-Leu-OH

Scheme 5

Hydroxy ester **37** (the *syn* isomer) was lactonized with NaH in THF to give lactone **43** (85%) which underwent Michael addition with iPrMgCl in the presence of CuCN in THF at -25°C, to give product **44** in 75% yield and 80% d.e. Lactone **44** was finally hydrolysed with LiOH in dioxane to give product **45** (Boc-Val-PheΨ[CH(OH)CH_2]LeuOH) in 65% yield. (scheme 6)



Scheme 6

The unsaturated lactone **44** could be also reduced to product **46** (H_2, Pd/C, 90% yield). The saturated lactone was coupled with the dipeptide **47**, using a modification of the Weinreb reaction[11] with $AlMe_3$ in CH_2Cl-CH_2Cl, to give product **48** (BocVal-PheΨ[CH(OH)CH_2]Ala-Ile-ProOMe) in 61% yield. (scheme 6)

We have demonstrated that $CrCl_2$ mediated addition reaction of allylic bromides to protected α-amino aldehyde is an efficient and rapid method to prepare peptide mimetics with an hydroxyethylene isostere. We described here only the synthesis of two isosteres with Leu or Ala as the P' aminoacid, but in principle a large number of mimic of natural aminoacids can be prepared through the Michael addition to lactone **44**. The application of this methodology to a solid phase protocols is currently underway in our laboratories.

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