Pergamon

Tetrahedron Letters 43 (2002) 4067–4069

TETRAHEDRON LETTERS

Short synthesis of protease inhibitors via modified Passerini condensation of *N*-Boc-α-aminoaldehydes

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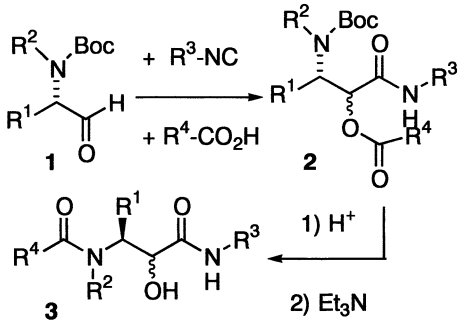
Received 28 March 2002; revised 12 April 2002; accepted 15 April 2002

Abstract—Extension of the previously reported modification of Passerini multicomponent reaction (involving condensation with *N*-Boc-α-aminoaldehydes followed by a deprotection–transacylation step) to α-aminoacid derived carboxylic or isocyanide components, allowed the highly convergent and short synthesis of complex peptidomimetic structures, including known potent inhibitors of serine proteases.

Oligopeptides containing the α-hydroxy-β-aminoamide or the α-oxo-β-aminoamide structures have demonstrated in many cases to be very useful as 'transition-state analog' protease inhibitors. In particular, the α-hydroxy-β-aminoamides seem well suited for aspartic proteases,[1] while the α-oxo-β-hydroxyamides are more successful for cysteine[2] and serine proteases.[3]. Recently we[4,5] and others[6,7] have disclosed a new variation of the old Passerini multicomponent reaction,[8] allowing a short entry into various members of these two classes of peptidomimetics. This methodology is based on a Passerini condensation of *N*-Boc-α-aminoaldehydes followed by smooth deprotection–transacylation to afford a three-unit peptidomimetic incorporating an α-hydroxy-β-aminoamide (Scheme 1). The three units derive from the three components of the Passerini reaction.



Scheme 1.

Keywords: Passerini reaction; protease inhibitors; peptidomimetic; multicomponent reactions; isocyanides; oxoamides.

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In order to obtain higher oligopeptides and, at the same time, to further increase the number of diversity factors in the final products, we have now extended the methodology to functionalised carboxylic acids and/or isocyanides derived from α-aminoacids.[9] In this way four or even five factors of diversity may be introduced in a 3–4 step linear sequence to give 4 or 5-unit peptidomimetics.

For example, four different inputs may be introduced in the synthetic scheme by employing a *N*-Boc-α-aminoacid as carboxylic component as shown in Scheme 2.[10] After Passerini reaction[11] (that took place without epimerisation at the stereogenic centres of the aldehyde and of the acid), treatment with CF_3CO_2H cleaved both Boc groups. Then, upon basification, the acyl group migrated exclusively on the aldehyde derived amino group. The remaining free amine in **6** could be coupled with another carboxylic acid (the fourth factor of diversity) to give tetrapeptide **7** in three steps and with an overall yield of 59% (Scheme 3).

A similar strategy was employed in the synthesis of α-oxoamides **12**[15] and **17**,[16] known to be potent inhibitors of two important serine proteases: prolyl endopeptidase and *Cytomegalovirus* protease, respectively. In these cases, the synthesis was completed by a final oxidation with sodium hypochlorite and catalytic TEMPO radical.[17] The synthesis of *Cytomegalovirus* protease inhibitor **17**[18] is particularly noteworthy since in this case a complex structure formed by five fragments joined trough four amide bonds was prepared convergently in only three steps and with an overall yield of 35%.

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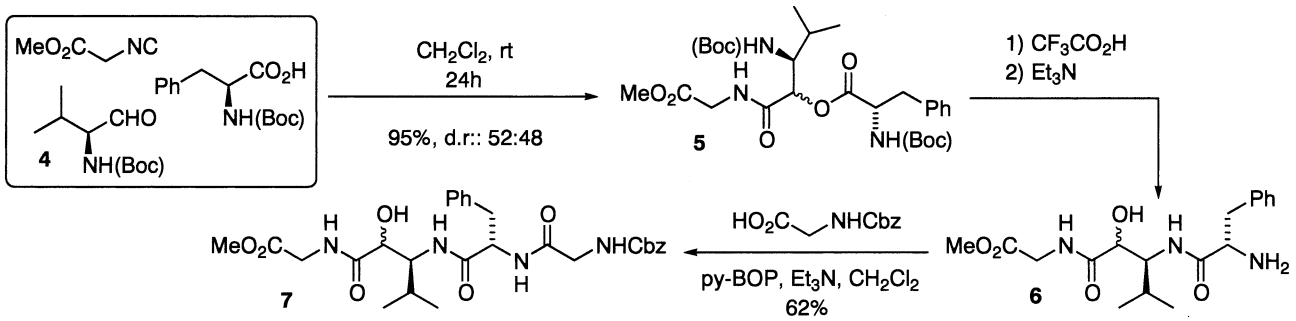
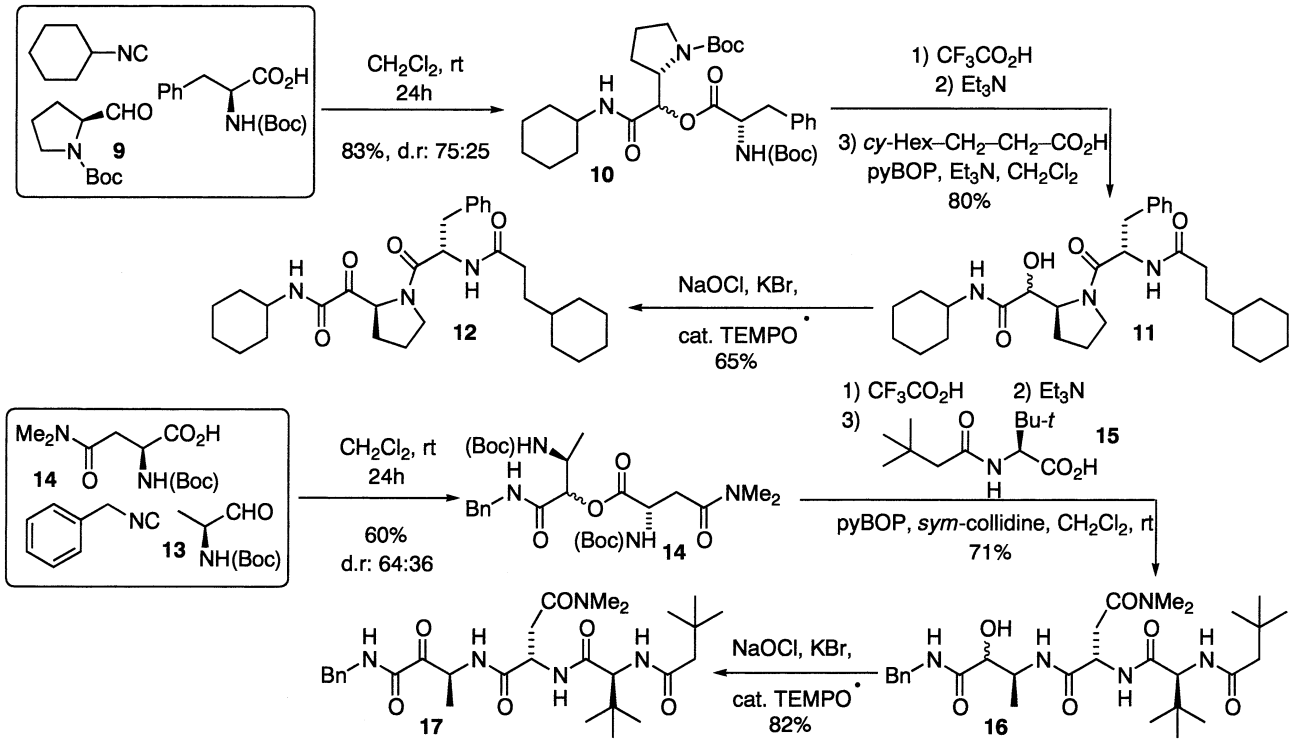
PII: S0040-4039(02)00728-1



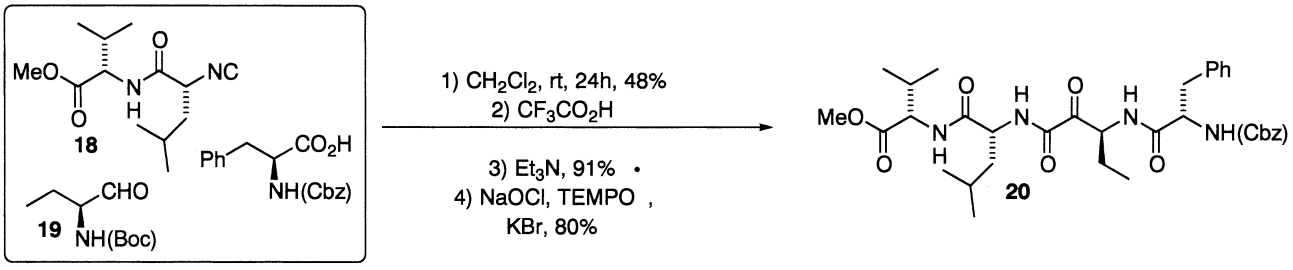
Scheme 2.



Scheme 3.

Another way to increase the complexity of the α-oxoamides prepared by our methodology is to employ a dipeptidic isocyanide, such as compound **18**[19] (Scheme 4). In this way, α-oxoamide **20**, which is the methyl ester of a known potent inhibitor of prolyl endopeptidase,[21] could be prepared in three steps and 35% overall yield. This compound is formed by four different units joined by amide bonds.

The high convergency of the synthetic pathways shown in this communication definitely compensates for the fact that the yields of Passerini condensations, in some cases, were not as good as when simple monofunctionalised components were used.[4] When employing *N*-Boc-α-aminoacids as the carboxylic component, we often detected the formation of variable amounts of the corresponding α-hydroxyamides, formally derived from



Scheme 4.

coupling of the isocyanides with the aldehydes without inclusion of the carboxylic component. For example, during the synthesis of **14**, the desired adduct **14** was also accompanied by a 32% yield of the corresponding α-hydroxyamides.[22] Subtle differences in the structure of the three components seem to be important in determining the yields. The worst case found so far by us is represented by the condensation of isocyanide **18** with aldehyde **19** and (Boc)-L-valine, that gave the expected Passerini product (an intermediate for the synthesis of poststatine[24]) in only 30% yield. However, simply by using aldehyde **9** instead of **19**, the yield was raised to an acceptable 62%.

In conclusion we have shown here that a very concise and convergent assembly of complex peptidomimetics containing an α-hydroxyamide or an α-oxoamide unit can be achieved by using *N*-Boc-α-aminoacids (as carboxylic components) or peptidic isocyanides as substrates in the previously reported variation of Passerini condensation.[4] The utility of this methodology is particularly evident in the field of protease inhibitors, as demonstrated by the examples reported here as well as by the recently published synthesis of a fragment of cyclotheonamide.[7]

Acknowledgements

We wish to thank C.N.R., the University of Genoa, and M.U.R.S.T. (COFIN 00) for financial assistance, and Miss Sabrina De Biase for her help in this work.

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10. All new compounds have been fully characterised by ^{1}H, ^{13}C NMR, IR, elemental analysis; pyBOP = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate.
11. Aldehyde **13** was prepared by $LiAlH_4$ reduction of the corresponding Weinreb hydroxamates following the procedure reported in Ref. 12 (80% overall yield from Boc-L-alanine). In our hands, no appreciable racemisation was observed upon chromatography (see Ref. 13). Aldehydes **4**, **9** and **19** were prepared from the corresponding (Boc) aminoacids by reduction with $BH_3{\cdot}Me_2S$ (Ref. 14) (62, 94 and 93% yield) followed by Swern oxidation (quantitative).
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18. Compound **14** was prepared in 74% overall yield from *N*-Boc-L-aspartic acid α benzyl ester: (1) Et_3N, $ClCO_2Et$, THF; (2) $Me_2NH{\cdot}HCl$, Et_3N; (3) H_2, Pd/C, *i*PrOH. Compound **15** was prepared from L-*N*-Boc-*tert*-leucine in five steps (54% overall yield): (1) Boc-ON, Et_3N, 1,4-dioxane; (2) BnOH, *N*-ethyl-*N*(3-dimethylaminopropyl)-carbodiimide (EDCI), 4-dimethylaminopyridine, CH_2Cl_2, 0°C, 80% (two steps); (3) CF_3CO_2H, CH_2Cl_2; (4) *t*-$BuCH_2CO_2H$, *N*-hydroxybenzotriazole, EDCI, *N*-methylmorpholine, CH_2Cl_2, 75% (two steps); (5) H_2, Pd–C, *i*-PrOH, 91%.
19. Isocyanide **18** was prepared from D-leucine in three steps (47.5% overall yield): (1) HCO_2H, Ac_2O, rt, 78% (Ref. 20); (2) L-Val–OMe·HCl, DCC, *N*-hydroxybenzotriazole, *N*-methylmorpholine, 87%; (3) $POCl_3$, Et_3N, CH_2Cl_2, 70%.
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22. It is worth noting that in a recent work by Semple (Ref. 7) a Passerini condensation involving a Boc aminoaldehyde and a protected α-aminoacid proceeded in 59% yield. It is possible that also in that case formation of α-hydroxyamides may account for the yield not very high. The concurrent formation of α-hydroxyamides does not seem to depend upon the presence of water in the reaction medium, nor to the reaction times. A similar behaviour was observed recently using formic acid (Ref. 23). Experiments directed toward elucidation of this interesting aspect of Passerini reaction are in progress.
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