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Solid Phase Synthesis of Aziridine 2-Carboxylates

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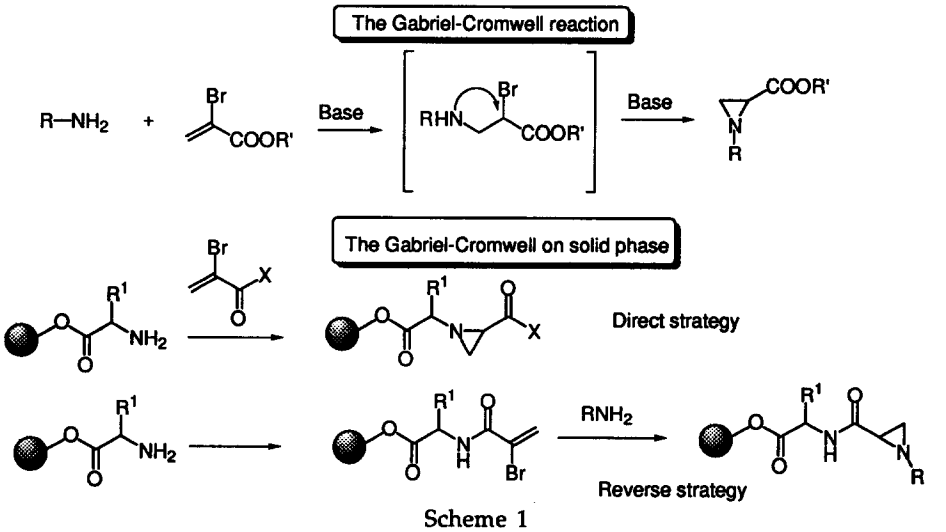
Abstract

Several oligopeptides and amino acids containing an aziridine 2-carboxylate group were prepared using a solid phase version of the Gabriel-Cromwell reaction. Wang resin loaded with different Fmoc amino acids was employed as the substrates and two different strategies were explored. Aziridine oligopeptides were prepared by addition of resin containing NH_2 groups to α-bromoacrylates and α-acrylamides or by addition of different primary amines to bromoacrylates loaded on the resin.

Keywords: Solid phase synthesis; aziridine; peptides and oligopeptides.

Aziridines are important heterocycles in organic and medicinal chemistry. The use of reactive aziridine derivatives as intermediates in the synthesis of several classes of compounds has been widely explored[1] and several methods have been developed for their synthesis.[2] Moreover several aziridine containing peptidomimetics have shown interesting properties as enzyme inhibitors[3] or mimetics of basic amino acids.[4]

We recently described the synthesis of aziridine 2-carboxylate peptidomimetics through the Gabriel-Cromwell addition of amino acid esters to α-bromoacrylates and acrylamides.[5]



Scheme 1

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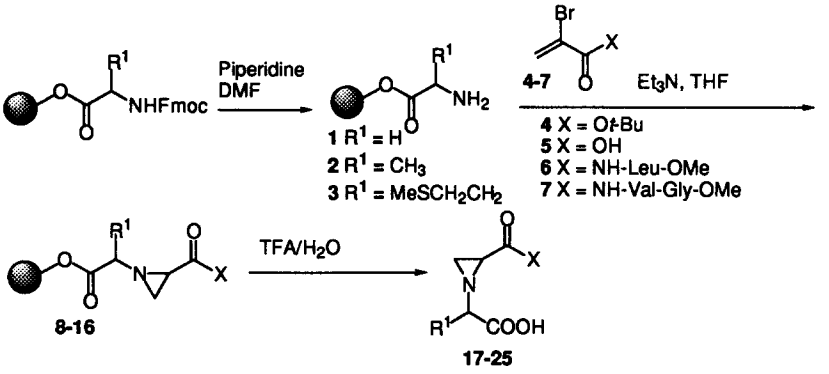
As the synthetic procedure of this reaction is very simple, we envisioned the possibility that the Gabriel-Cromwell reaction would be an useful addition to the arsenal of organic transformations performed on a resin bound substrate as recently described for other Michael-type reactions.[6]

The addition of a primary amine to α-bromoacrylate on solid phase can be carried out following two different strategies:

- a direct strategy where the NH_2 is loaded on the resin and the Michael acceptor added in solution;
- a "reverse" strategy where the α-bromoacrylate is built on the resin and the amine added in solution.

For the first approach we started with a Wang resin loaded with *N*-Fmoc-glycine. After deprotection of the nitrogen with DMF and piperidine, followed by several washings of the resin with DMF, the resin was dispersed in THF and a solution of *tert*-butyl bromoacrylate and Et_3N in THF was added and the mixture was stirred overnight at room temperature (all the reactions described here were carried out in a manual peptide synthesis vessel constructed from a sintered glass funnel, using nitrogen for agitation). The complete conversion of the reaction was monitored directly on the resin with the Kaiser test.[7] When no more free NH_2 was present on the resin, the solvent was discarded and the resin washed several times with THF, DMF and THF. The aziridine peptides were then cleaved from the resin using standard conditions (TFA/H_2O: 95/5) and the products were purified by crystallization from diethyl ether. Products **17-25** were obtained in good yields and almost pure (^1H NMR and MS analysis).

The same protocol was carried out using α-bromoacrylic acid **5** generated in situ from 2,3-dibromopropionic acid and Et_3N) and several α-bromoacrylamides derived from natural amino acids or peptides (**6-7**).

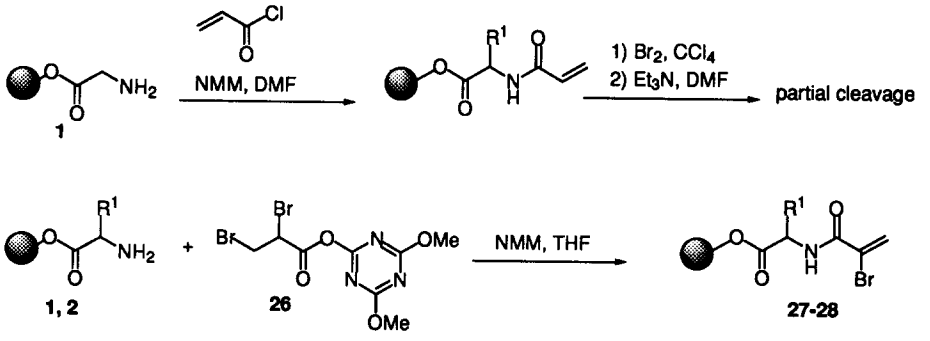


8, 17 R^1 = H, X = Ot-Bu. **9, 18** R^1 = H, X = H. **10,19** R^1 = H X = OH. **11, 20** R^1 = H, X = NH-Leu-OMe. **12, 21** R^1 = H, X = NH-Val-Gly-OMe. **13, 22** R^1 = CH_3, X = NH-Leu-OMe. **14, 23** R^1 = CH_3, X = NH-Val-Gly-OMe. **15, 24** R^1 = $MeSCH_2CH_2$, X = NH-Leu-OMe. **16, 25** R^1 = $MeSCH_2CH_2$, X = NH-Val-Gly-OMe.

Scheme 2

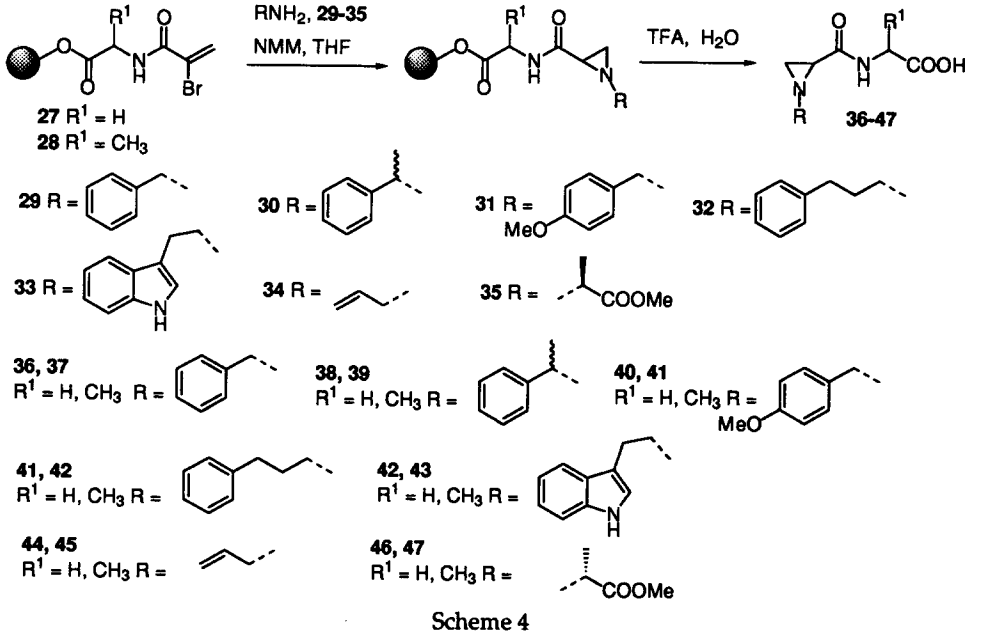
Analogously the second "reverse" strategy could be accomplished starting from a Wang type resin. At first we tried to prepare the α-bromoacrylamide on the resin loading acryloyl chloride on a NH_2-Gly-Wang resin followed by addition of bromine and elimination of HBr mediated by Et_3N.

Although the first reaction was carried out successfully (as monitored by the Kaiser test and FT-IR analysis of the beads), the additon of Br_2 followed by basic elimination could not be carried out completely as we observed the formation of variable amounts of the product resulting from partial cleavage of the organic frame from the resin. Consequently we decided to react the amino acid loaded on the resin with 2,3-bromopropanoic acid in the presence of a peptidic coupling agent. Amongst several methods employed, the best result was obtained by reaction of 2,3-dibromopropanoic acid activated as the 4,6-dimethoxy-1,3,5-triazinyl- ester (**26**) prepared from the corresponding acid and 2-chloro-4,6-dimethoxy-1,3,5-triazine.[8]



Scheme 3

The coupling of NH_2-Gly-Wang resin with 2.5 equiv. of **26** in THF and in the presence of 3 equiv. of NMM gave directly the α-bromoacrylamide loaded on the beads, as showed by FT-IR analysis. This product was then reacted with different amines in THF and in the presence of NMM to give the corresponding aziridine in good to acceptable yields.



Scheme 4

This procedure could be successfully applied to "simple" primary amines and to amines derived from amino acids or peptides. In the last step we observed a strong influence of the solvent employed on the yields. Best results were obtained using THF or CH_2Cl_2; when DMF was used only small amounts of products were obtained. All products prepared with this protocol were finally cleaved from the resin using TFA/H_2O to give the aziridine carboxylic acids **36-47.**

The procedure described in this paper was very simple and allowed the preparation of a series of unprotected aziridine oligopetides that are more difficult to prepare using the "normal" approach. Moreover the level of diversity of products that can be reached is relatively high and the sequence can be applied to a split & recombine protocol for a combinatorial approach.

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