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Synthesis of β-lactams on solid support using Aminoacids as chiral auxiliary

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Introduction

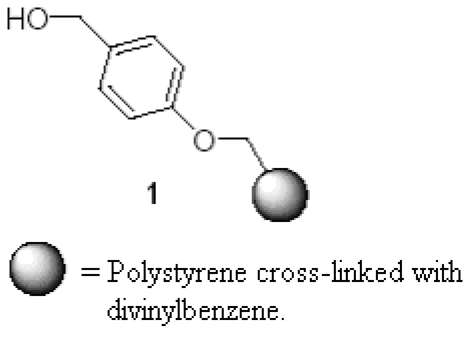
An economical way to obtain optically active β-lactam derivatives is the use of amino acids as chiral auxiliaries in Staudinger reaction (Bose *et al*., 1985). This strategy has been used for asymmetric synthesis of bicyclic β-lactam compounds, such as 2-isocephems, from threonine (Tenneson and Belleau, 1980). In addition, β-lactams obtained by this method are useful as versatile intermediates for the preparation of α-aminoacids and derivatives and, in general, as synthon for peptide synthesis (Ojima, 1993).

However, this interesting approach has been little explored in the field of solid phase organic synthesis (SPOS). In recent years SPOS methodologies have received increasing attention due to its importance as main tool leading to generation of combinatorial libraries. Undoubtedly, the interest in the synthesis of optically active β-lactam derivatives via amino acids as chiral auxiliaries, requires further investigation on the posibilities of applying solid phase chemistry.

In this communication results obtained with different resins and several α-aminoacids for achieving the formation of different β-lactam derivatives will be shown.

Methodology

For immobilization of the starting material, Fmoc-aminoacid, both Wang resin as well as Janda Jel resin were used. Wang resin (**1**) consists of a basic structure of polystyrene cross-linked with divinylbenzene, and a 4-hydroxybenzyl group as *linker*. "Janda Jel" resin (**2**) (Toy and Janda, 1999) is an interesting alternative since polymer matrix is a polyestyrene resin cross-linked with 1,4-*bis*(vinylphenoxy)butane, which increases twice its swelling capacity with respect to common resins. This increase in swelling capacity implies a better contact between reagents and substrate linked to the resin.



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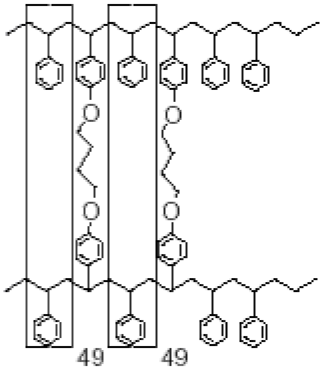

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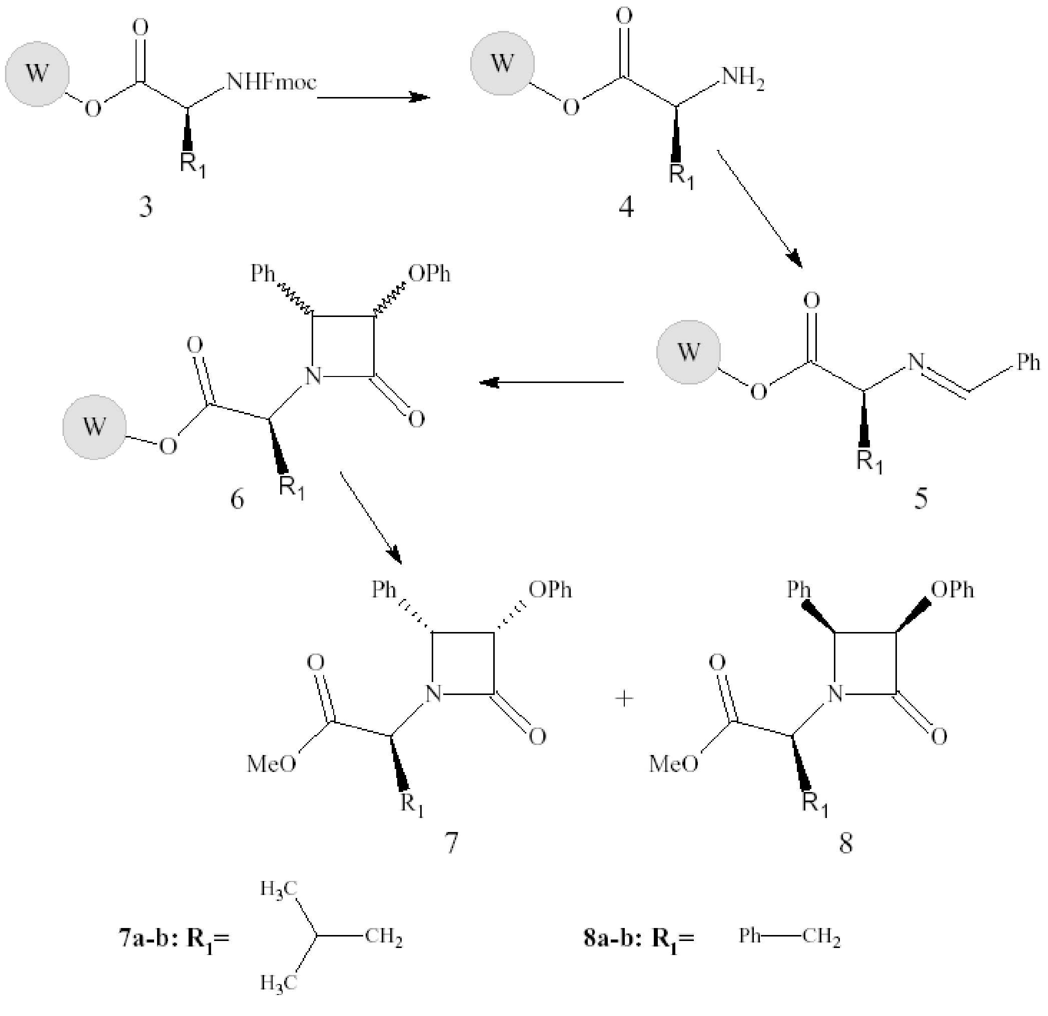
The used methodology is based on the application of the Staudinger reaction to chemistry on solid support. Therefore, Fmoc-amino acid is immobilized on solid support, and then the amino group is deprotected, usually with 30% piperidine in DMF. The amino group release can be monitored by the Kaiser test (Kaiser *et al*., 1970). The amine linked to solid support is transformed in an imine by condensation with an aldehyde in a 1% v/v AcOH solution. Afterwards, β-lactamic ring formation is carried out by the Staudinger methodology, which involves the reaction of imine linked to the solid support with a ketene, *in situ* generated from an acid chloride and triethylamine as base. Infrared spectrum of solid phase product shows a peak at approx. 1770 cm^{-1}, accounting for a β-lactam carbonyl. Finally, resin separation depends on the *linker* that connects the polymer matrix and the substrate. In the case of using Wang resin, β-lactam is released using a 10% v/v trifluoracetic acid (TFA) solution in dichloromethane. The acid obtained was methylated with diazomethane.



Results

This procedure was also used to generate β-lactams derived from different Fmoc-amino acids, such as Fmoc-leucine, Fmoc-phenylalanine, Fmoc-(O*t*Bu)-serine, Fmoc(Boc)-lysine and Fmoc(Boc)-aspartic acid.

With Fmoc-Leu-Wang resin as starting material, a mixture of diastereisomeric β-lactams **7a-b** is obtained, characterized by NMR, ^1H, ^{13}C, HMQC and HMBC, with 1:1.5 diastereoisomeric ratio, and overall yield of 75%. Also from Fmoc-Phe-Wang resin a mixture of diastereisomeric β-lactams **8a-b** is obtained, with 1:1.3 ratio, and a yield of 70%.

A very interesting result was obtained in the case of Fmoc-(O*t*Bu)Ser-Wang resin. Selectively one of the diastereoisomers suffers from hydroxyl deprotection under separation conditions of the substrate from the resin (10% TFA in dichloromethane). Meanwhile the other remains unchanged, and is obtained as *ter*-butyl ether. This result as well as the assignation of diastereisomers is the aim of this study at the

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time of submission of this communication.

Regarding the use of other resins, such as Janda Jel, two strategies were carried out: (a) use a Merrifield resin-type *linker*, known as Janda Jel-Merrifield, or (b) use a Wang resin-type *linker*, known as Janda Jel-Wang.

In the case of strategy (a) well results were not obtained, which is in agreement with the results obtained with classical Merrifield resin (Delpiccolo *et al*., 2005). However, strategy (b) was successful, thus achieving the synthesis of the corresponding β-lactam using glycine as starting amino acid. Actually, studies are being carried out with various aminoacids in order to determine the scope of this methodology.

Conclusions

This communication deals with results achieved in the use of chiral α - aminoacids for solid-phase preparation of β-lactam derivatives, performing a comparative study of the different synthetic strategies used, in particular the efficiency of different solid supports.

Acknowledgements

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