Molecular Medicinal Chemistry
IDECEFYN
vol 13 May-August 2007, **45-46** http://www.idecefyn.com.ar ISSN 1666-888X

New strategies for solid-phase synthesis of polysubstituted 2-azetidinones

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Introduction

Combinatorial chemistry is defined as a set of methodologies for the synthesis of a large number of structurally different molecules in rapid and simultaneous way (Mata, 1997 a,b; Terrett, 1998).

This set of compounds (libraries) can then be evaluated using methodologies of biological high-throughput screening (HTS). This concept has had a substantial impact on the progress of research programs, increasing the studies on structure-activity relationships and increasing the number of leader compounds as well as candidate compounds for clinical trials.

The main method for the generation of combinatorial libraries is the solid phase organic synthesis (SPOS) (Burgess, 2000; Seneci, 2000; Zaragoza Dörwald, 2000; Czarnik, 2001) since it greatly simplifies the most complex and slow phase of the process of synthesis of new compounds: the isolation and purification stage, as the excess of reagents and/or secondary products can be easily removed by a simple filtration because of not being bound, unlike the target compound, to the solid and insoluble support.

On the other hand, the problem of bacterial resistance to antibiotics is one of the great challenges of the medicine of our time. Therefore, it is interesting the possibility to generate by combinatorial chemistry β-lactamic compounds libraries to address current need to develop new and more potent antibiotics and/or enzyme inhibitors to combat such resistance.

Based on our previous experience in solid-phase synthesis of polysubstituted β-lactams (Delpiccolo *et al.*, 2005), we tried to create a different strategy in terms of binding to the solid support. In this case the formation of the azetidinone ring is achieved by a Staudinger reaction, ketene being bound to the polymeric support, thus obtaining immobilized β-lactams at position 3.

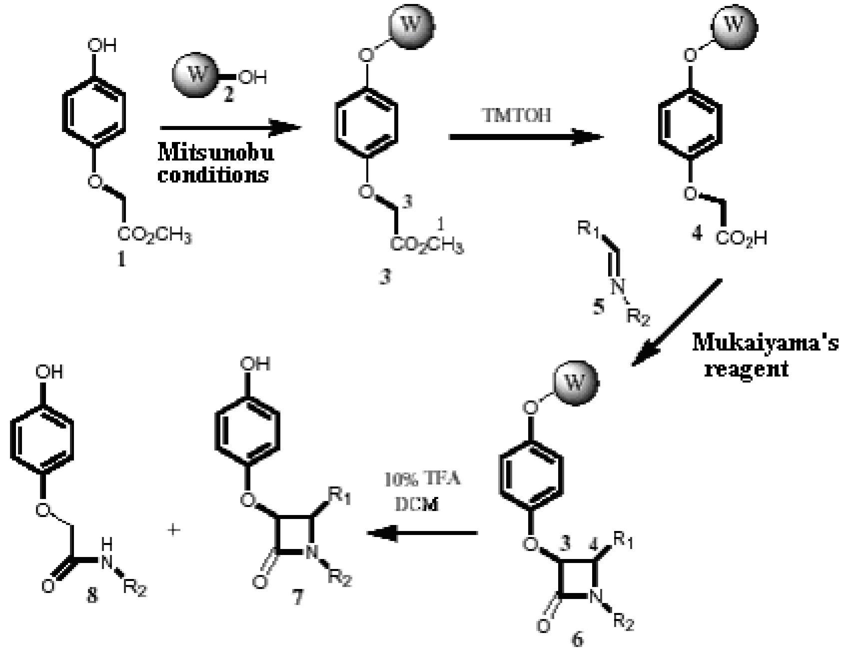
Methodology

In this work the strategy shown in Scheme 1 was designed . The binding of the methyl ester of 4-hydroxyphenoxyacetic acid (**1**) to Wang resin is achieved by Mitsunobu reaction. The effectiveness of this reaction is checked by the appearance in the IR spectrum of the resin of the signal for stretching carbonyl group (1730 cm^{-1}) and by ^{13}C-NMR in gel phase (C-1 = 52 ppm, C-3 = 66 ppm).

The next step was the hydrolysis of the methyl ester **3**. The literature for this type of solid-phase reaction is rather scarce and unreliable. We found that trimethyltin hydroxide is a useful reagent for the hydrolysis of ester **3**. The formation of **4** is corroborated by the ^{13}C-NMR signal disappearance accounting for the methyl ester (52 ppm).

The resin-bound acid (**4**) is subjected to Staudinger reaction conditions, using Mukaiyama's reagent as activator of the carboxylic acid.

The formation of the azetidinone ring is supported by the appearance in the IR spectrum of the β-lactamic carbonyl stretching signal (1740 cm^{-1}) and by ^{13}C-NMR in gel phase (C-3 = 83 ppm, C-4 = 61 ppm). Product release from the resin is achieved by treatment with a 10% trifluoroacetic acid solution in dichloromethane by stirring for 1 hour.



Scheme 1

Results

Applying this synthetic sequence the β-lactams (**7**) were obtained in good to very good yields for the four steps of synthesis, taking as base the original charge of the starting resin.

In all cases, besides obtaining the expected β-lactam, the acyclic subproduct **8** is obtained, which would derive from the hydrolysis of the intermediate generated in the Staudinger reaction, this subproduct being separated from the β-lactam **7** by column chromatographic purification.

Conclusions

This work accounts for the development of an original strategy in terms of solid support linking for solid-phase synthesis of β-lactamic compounds. The discovery of this new methodology will give the opportunity to study still unexplored alternatives to the solid-phase synthesis of bicyclic β-lactams.

Acknowledgements

We appreciate the financial support of CONICET, National Agency for Scientific and Technologic Promotion, Josefina Prats Foundation, Universidad Nacional de Rosario (Argentina).

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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