

Solid-Phase Organic Chemistry: Synthesis of 2 β -(Heterocyclylthiomethyl)Penam Derivatives on Solid Support

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Abstract: The synthesis of 2 β -(heterocyclylthiomethyl)penam derivatives on solid support has been developed. Compounds are obtained in good to high yields (based on loading of the original resin). The key step is the solid-phase double rearrangement of the corresponding penicillin sulfoxide.

Introduction

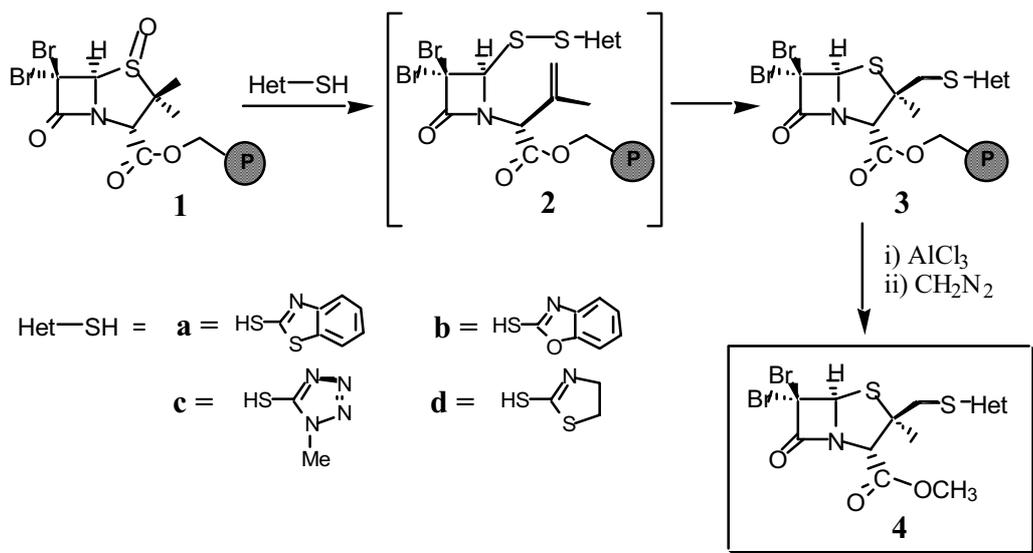
The impact of combinatorial chemistry of small molecules on the drug discovery process is now widely recognized by the scientific community [1]. Solid-phase organic synthesis (SPOS) is a valuable tool for the generation of structurally diverse compounds for combinatorial libraries.

In our work dealing with the solid-phase synthesis of biologically interested compounds, we have developed methodologies for tethering functionalized polystyrene resins to penicillin derivatives. Our research has also established a new, mild and efficient procedure for the removal of sensitive molecules from Merrifield and Wang resins, using aluminum chloride (AlCl₃) [2].

Results and discussion

Heterocyclic thio substituents have been identified as pharmacophores in β -lactam chemistry, particularly with activity against methicillin-resistant *staphylococcus aureus* (MRSA) [3]. Thus, we considered the solid-phase synthesis of 2 β -(heterocyclylthio)methyl substituted penicillins as a rapid and efficient method for the generation of combinatorial libraries.

The key step of this synthesis of the double rearrangement of sulfoxide **1** (Scheme 1). The thermal rearrangement of **1** generates the sulfenic acid which is trapped by the corresponding heterocyclic thiol (Het-SH) to give the disulfide intermediate **2**. Then, a new rearrangement rebuilds the thiazolidine ring to obtain the 2 β -(heterocyclylthio)methyl penams (**3**).



This work began with the immobilization of penam derivative onto Merrifield resin and oxidation with *m*-chloroperbenzoic acid (MCPBA, 1.4 equiv.) to obtain the resin-bound sulfoxide **1**. These reactions were monitored by FT-IR. In the case of the reaction of sulfoxide **1** with 2-mercaptobenzothiazole (2-MBT) (**a**) in the presence of catalytic amounts of *p*-toluenesulfonic acid, the resin-bound 2 β -(benzothiazol-2-yl)thiomethyl derivative (**3a**) was obtained. After cleavage with AlCl₃ and esterification with diazomethane, compound **4a** was obtained with an overall yield of 45% (based on initial loading of the Merrifield resin).

The versatility of this methodology has been demonstrated by the synthesis of different 2 β -(heterocyclylthio)methyl penams. For example, using 2-mercaptobenzoxazole (**b**), the Merrifield resin-bound 2 β -(benzoxazol-2-yl)thiomethyl derivative (**3b**) was obtained. After cleavage and esterification, compound **3b** was transformed into the ester **4b** (overall yield: 50%). Similarly, a series of closely related derivatives have been prepared with overall yields ranging from 45 to 55% .

Acknowledgments: Financial support from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina; The Royal Society of Chemistry (U.K.); Agencia de Cooperación Iberoamericana (Spain); Fundación Antorchas (Argentina); Universidad Nacional de Rosario (Argentina) and Asociación Prociencia de Rosario (Argentina) is gratefully acknowledged.

References and Notes

- (a) *A Practical Guide to Combinatorial Chemistry*; DeWitt, S.H; Czarnik, A.W., Eds.; ACS Books: Washington, 1997; (b) Bunin, B.A. *The Combinatorial Index*; Academic Press: San Diego, 1998.
- Mata, E.G. *Tetrahedron Lett.* **1997**, *38*, 6335.
- Hecker, S.J. *Journal of Antibiot.* **1998**, *51*, 722.