Send Orders for Reprints to reprints@benthamscience.ae

Letters in Organic Chemistry, 2017, *14*, 000-000

RESEARCH ARTICLE

Manganese(III) Promoted Cyclization of *N*-alkenyl-*N*-(2-hydroxyethyl) amides to Iso-Oxacepham Potent β-Lactamase Inhibitors

Paweł Punda[1], Marta Schielmann[2] and Sławomir Makowiec[1,*]

[1]*Department of Organic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80 233 Gdańsk, Poland;* [2]*Department of Pharmaceutical Technology and Biochemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland*

ARTICLE HISTORY

Received: August 31, 2016
Revised: October 24, 2016
Accepted: March 01, 2017

DOI:
10.2174/1570178614666170321123252

Abstract: ***Background***: β-Lactams are still a subject of interest of organic chemists. The main reason for this interest is due to their application as a chemotherapeutic. β-Lactam antibiotics are still the most commonly used drugs in bacterial infections.

Method: Methods using 4-exo-trig radical cyclization leading to β-lactams are an alternative to classical Staudinger`s β-Lactams formation. We prepared *N*-alkenyl-*N*-(2-hydroxyethyl)amides to check the action of internal nucleophile. In the next step, with use of $Mn(OAc)_3$ promoted radical cyclization 3-carbamoyl, 3-tiocarbamoyl and 3-phosphoryl β-lactams containing intramolecular nucleophile were prepared. These intermediates were able to induce the second ring closing through a carbocation trapping.

Results: Iso-oxacepham derivatives were synthesized by the 4-exo-trig radical cyclization as innovative one-pot approach. Subsequent cyclization process of *N*-alkenyl-(2-hydroxyethyl)amides to 7-substituted iso-oxacephams was described. Influence of carbamoyl, thiocarbamoyl and phosphoryl moieties located on C-7 position of iso-oxacephamic scaffold on β-lactamase inhibitory activity was confirmed on bacterial β-lactamases from group C.

Conclusion: In this paper, we describe alternative approach for the synthesis of 7-substituted iso-oxacepham. The hypothetic reaction mechanism for the second ring closing was confirmed. The β-lactamase inhibition was observed in case of four synthesized compounds.

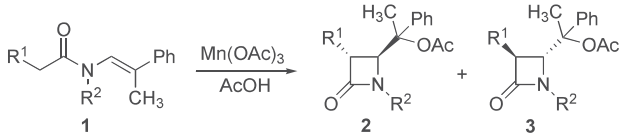
Keywords: β-lactams, β-lactamase inhibitors, iso-oxacephams, radical cyclizations, *N*-alkenylamides, cyclization.

1. INTRODUCTION

Through the decades, research aimed at the synthesis of new antibacterial agents has focused mainly on the preparation of β-lactams. The increasing number of drug-resistant bacteria causes the necessity to seek for new modified structures. One approach to overcome bacterial resistance, is a modification of the core of antibiotics molecule. Classical penam/penem or cepham/cephem core could be replaced by oxa- or carba- analogs. Good examples of such a strategy are oxacephems antibiotics Flomoxef, and Latamoxef. Similarly, iso-oxacephems gained the attention due to their antibacterial activity [1, 2].

Taking into account the reports concerning carbamoyl β-lactams as inhibitors of bacterial β-lactamases [3], we focused our efforts on development of an easy route providing 7-substituted-iso-oxacephams. Previously we presented synthetic approach to form 3-carbamoyl-monobactams, based on modification of Staudinger ketene-imine cycloaddition [4].

Methods using 4-exo-trig radical cyclization leading to β-lactams are an alternative to classical Staudinger`s method [5]. Our research group has also made certain progress in this topic, as we developed method for preparation of *N*-alkyl/arylacarbamoyl-β-lactams **2**, **3** and their sulfur analogues based on radical cyclization [6]. Moreover, we applied $Mn(OAc)_3$ promoted radical cyclization to synthesis of difficult to achieve 3-phosphoryl and 3-thio phosphoryl-β-lactams (Scheme **1**) [7].



R^1 = RNHC(O), RNHC(S), $(RO)_2P(O)$, $(RO)_2P(S)$
R^2 = Alkyl

Scheme (1). Synthesis of 3-substituted monobactams *via* radical cyclization of *N*-alkenylamides.

*Address correspondence to this author at the Department of Organic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80 233 Gdańsk, Poland; Tel/Fax: +48-58-347-2883; E-mail: mak@pg.gda.pl

1570-1786/17 $58.00+.00 © 2017 Bentham Science Publishers