NJC

RSC Publishing

LETTER

View Article Online
View Journal | View Issue

Simple and novel synthesis of 3-(thio)phosphoryl-β-lactams by radical cyclization†

Cite this: *New J. Chem.*, 2013, **37**, 2254

Received (in Montpellier, France) 19th February 2013, Accepted 14th May 2013

DOI: 10.1039/c3nj00192j

www.rsc.org/njc

Paweł Punda and Sławomir Makowiec*

Radical cyclization of phosphono-acetenamides promoted by manganese(III) acetate leads exclusively to the formation of 3-phosphoryl-β-lactams. The thiophosphoryl analogues were also prepared using this method. In particular, the presented protocol does not require the use of noble metals, while comparable methods do.

Modification of the β-lactam ring is still the focus of organic chemists, mainly due to the well-known antimicrobial activity of this class of compounds.[1] However, this is not only the biological activity of azetidones that attracts attention; β-lactams also exhibit cholesterol absorption activity,[2] anti-cancer activity,[3] muscarinic agonist properties[4] or inhibition of human leukocyte elastase responsible for autoimmune diseases.[5] In light of the β-lactam synthon method developed by Ojima *et al.*, synthetic applications of azetidones have shown increasing importance in synthetic organic chemistry.[6] Recently we have focused on the carbamoyl and thiocarbamoyl modification of the azetidone ring at position 3, based on Meldrum's acid derivative type of Staudinger cycloaddition.[7] As an extension of this topic we have undertaken attempts to develop a similar method for the preparation of 3-phosphoryl-β-lactams. In the chemical literature, three methods can be found for the preparation of 3-phosphoryl-β-lactams: first, the simplest involving direct metalation of the α-position in 3-unsubstituted β-lactams followed by reaction with three coordinated phosphorus electrophiles and oxidation to five coordinated phosphorus. However, this process sometimes leads to a mixture of mono- and di-phosphorylated products;[2c,8] another promising method is a Staudinger type cycloaddition of imines with ketenes generated from the phosphono-acetates activated with CDI.[9] Despite the attractive simplicity of this method, it is limited only to reaction with *N*-aryl imines. The last known method for the preparation of 3-phosphoryl-β-lactams is based on rhodium catalysed intramolecular C–H insertion of carbenes generated from diazo-compounds.[10] However, the carbene insertion process usually leads to formation of a mixture of five- and four-membered lactams and selectively 3-phosphoryl-β-lactams can be obtained only when specific substituents on nitrogen are present.[11]

In the light of our own experience[7] it seemed obvious that a convenient alternative approach for the synthesis of 3-phosphoryl-β-lactams should assume the use of 5-phosphoryl-2,2-dimethyl-1,3-dioxane-4,6-diones as a source for thermal generation of phosphorylketenes and subsequently their cycloaddition to aldimines. However, no example of preparation and reactivity of phosphoryl Meldrum's acid is known in the literature.

Hence we performed a systematic study of the preparation of any 5-phosphoryl-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**); unfortunately, the reactions with five coordinated phosphorus electrophiles did not give the desired product, while reaction with a three coordinated derivative, diphenyl chlorophosphine, led to an unstable compound, which decomposed during purification to phosphine oxide and Meldrum's acid (Scheme 1). These unpublished and unsatisfactory attempts at preparation of 5-phosphoryl-2,2-dimethyl-1,3-dioxane-4,6-dione forced us to search for a new strategy for the synthesis of 3-phosphoryl-β-lactams. On the other hand, an alternative to the typical Staudinger method of construction of a β-lactam ring involves the oxidation and radical cyclization of derivatives of acetyl acetenamides.[12] However, to the best of our knowledge, this type of reaction was never tested for the preparation of 3-phosphoryl-β-lactams from phosphonoacetenamides, which due to different position of the keto–enol equilibrium, may cause problems during oxidation.

In this paper we wish to report the application of manganese(III) acetate as a reagent for the cyclization of phosphono-acetenamides to β-lactams. The key substrate **3** was obtained in the classic

Department of Organic Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Narutowicza 11/12, 80-233 Gdańsk, Poland. E-mail: mak@pg.gda.pl; Fax: +48-58-347-2694; Tel: +48-58-347-1724

† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of compounds **3a–f**, **4a–f**, **5f** and **6a** and their spectroscopic characterization. See DOI: 10.1039/c3nj00192j

