One-Step Synthesis of β-Lactams with Retro-Amide Side Chain

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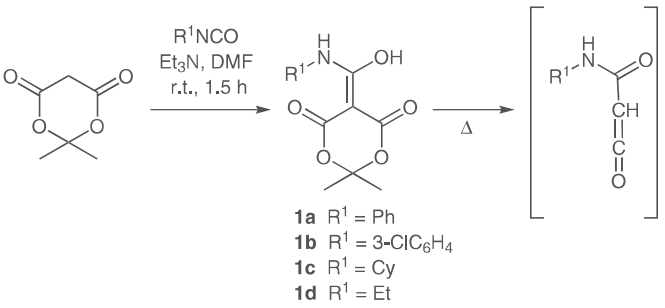
Received 6 September 2010; revised 14 October 2010

Abstract: A one-pot synthesis for the preparation of 1,4-disubstituted 2-oxoazetidine-3-carboxylic acid amides was developed. 5-[(N-substituted-amino)(hydroxy)methylene] Meldrum's acids act as a source of ketenes that react with aldimines in boiling toluene to give β-lactams with a retro-amide side chain.

Key words: lactams, cycloaddition, amides, ketenes, Meldrum's acid

Compounds containing a β-lactam fragment are still the subject of unremitting interest to organic chemists. The main reason for this interest is clear, of course, due to their wide application as a chemotherapeutic. In almost seventy years since the first application of penicillin, β-lactam antibiotics are still the most commonly used drugs in bacterial infections. Although the biotechnological method to obtain multiple antibiotics has been refined,[1] there still remains a lot of work for organic chemists due to the need for modifications in the biotechnologically derived substrates, e.g., semisynthetic cefalosoryn,[1,2] or in the case of some β-lactam antibiotics like aztreonam,[3] total chemical synthesis has proved to be more efficient. In addition, β-lactams are valuable synthetic intermediates. The β-Lactam Synthon Method developed by Ojima uses β-lactams as the starting material for the synthesis of amino acids,[4] hydroxy acids,[5] and peptides.[6] Also chiral β-lactams can be used for asymmetric induction.[7]

Despite the development of many unconventional ways to create a β-lactam system, the Staudinger ketene-imine cycloaddition remains the most popular method for the formation of four-membered lactams. Many methods for the activation of carboxylic acid have been developed.[8] One unusual method for the generation of ketenes is the thermal decomposition of Meldrum's acid derivatives. Yamamoto used acylketenes formed in this way in reaction with aldimines for the preparation of monocyclic β-lactams.[9] Almqvist tried without success to use a modification of this method to obtain 6-acylpenams in the cycloaddition reaction of ketenes with Δ^2-thiazolines. Instead of the expected β-lactams they obtained bicyclic 1,3-oxazinones.[10,11] On the other hand 5-[(N-substituted-amino)(methoxy)methylene] or 5-[(N-substituted-amino)(methylthio)methylene] Meldrum's acid derivatives were explored as a source of ketenes[12] and also 5-[(N-substituted-amino)(hydroxy)methylene] Meldrum's acids **1** were used as a carbamoyl synthon for the preparation of malonic acid derivatives;[13] **1** is simply prepared by the reaction of Meldrum's acid with isocyanate in the presence of triethylamine.[13,14] Thermal decomposition of **1** led to formation of carbamoylketenes, which are able to react with various nucleophilic reagents (Scheme 1).



Scheme 1

In the course of our studies, we decided to check whether it is possible to obtain the β-lactam moiety with a retro-amide side chain by the reaction of carbamoylketenes generated from **1** with aldimines **2**. β-Lactams containing retro-amide side chain are interesting as a unnatural inhibitors of β-lactamases.[15] However, known methods for the preparation of β-lactams with an inverted amide bond in the α-position, which can be applied as a key step in the Wolff rearrangement[16] or Rapoport rearrangement of α-keto-γ-lactams,[17] require multistep syntheses.

In this paper we present a one-step synthesis of β-lactams **3** with a retro-amide side chain based on the reaction of **1** with aldimines **2** (Table 1).

As a first experiment we performed the reaction of **1a** with *N*-benzylideneisopropylamine (**2a**) in benzene saturated with hydrogen chloride (Table 1, entry 1); after purification we obtained 1,4-disubstituted 2-oxoazetidine-3-carboxylic acid amide **3aa** in 54% yield. We chose benzene as a reaction medium based on the experiments of Yamamoto[9] where he generated acylketenes from acyl Meldrum's acids. However, it turned out that 5-[(N-substituted-amino)(hydroxy)methylene] Meldrum's acids **1** decomposes much more slowly than acyl Meldrum's acids and the total disappearance of the substrate followed after 28 hours. We optimized the temperature of the reaction and found the maximum yield in an acceptable reaction time when the reaction was carried out in toluene (entry 3). In addition, we have examined how the stoichiometry affects the yield of the reaction. The use of excess of ketene precursor slightly decreased the yield (entry 4),

SYNTHESIS 2011, No. 1, pp 0069–0072
Advanced online publication: 09.11.2010
DOI: 10.1055/s-0030-1258966; Art ID: P13810SS