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## The stereoselective formation of $\beta$ -lactams with acyl ketenes generated from 5-acyl-Meldrum's acids<sup>†</sup>

Anna Zakaszewska, Ewelina Najda and Sławomir Makowiec\*

**Acyl ketenes formed during thermal decomposition of 5-acyl-2,2-dimethyl-1,3-dioxo-4,6-diones undergo stereoselective [2+2] cycloaddition to chiral aldimines. We report the first example of optically active 3-acyl- $\beta$ -lactam formation from Meldrum's acid derivatives.**

The development of methods for the formation of the 2-azetidone system is an ongoing task in organic synthesis. Since the first preparation of  $\beta$ -lactam by Staudinger in 1903 based on [2+2] cycloaddition, many new methods for the formation of these valuable target molecules have been developed. These methods are based on various approaches such as radical cyclization,<sup>1</sup> dehydration of  $\beta$ -amino acids,<sup>2</sup> Rh-catalyzed insertion of carbene into a C–H bond,<sup>3</sup> ester enolate–imine cyclocondensation<sup>4</sup> or malonate activated cyclization.<sup>5</sup> Nevertheless, the classical [2+2] cycloaddition of ketenes to imines is still the method of choice in many cases.<sup>6</sup> Usually these methods need an activation of carboxylic acids for ketenes generation; the most popular are acid chlorides,<sup>7</sup> Mukaiyama reagent<sup>8</sup> and carbonyldiimidazole.<sup>9</sup>

In 1980, Watanabe<sup>10</sup> and his co-workers proposed an alternative method for the generation of ketenes in the synthesis of 2-azetidones. This approach was based on the thermal decomposition of 5-acyl-2,2-dimethyl-1,3-dioxo-4,6-diones as a convenient source of ketenes.<sup>11</sup> In 2010 we successfully adopted this approach for the preparation of 3-carbamoyl-2-azetidones.<sup>12</sup> In both cases, the azetidones were obtained as a racemic mixture of two *trans* diastereoisomers. To the best of our knowledge, there have been no reports of any successfully stereocontrolled preparation of 2-azetidones using derivatives of Meldrum's acid as a source of ketenes,<sup>13</sup> in contrast to a situation where classical methods have been used to generate the ketenes.<sup>14</sup> However, in 2005 Almqvist and his co-workers published a paper describing the stereoselective

reaction of 5-acyl Meldrum's acid with 2-thiazolines, which according to the authors should lead to the synthesis of optically active  $\beta$ -lactams.<sup>15</sup> Nevertheless, a later insightful structure elucidation revealed incorrect structure assignment: the obtained product turned out to be a six-membered ring instead of a four-membered ring.<sup>16</sup>

In this paper, we would like to present the first example of stereoselective formation of 2-azetidone from 5-acyl Meldrum's acid as a ketene source and chiral imines. As a source of asymmetric induction we have used chiral imines, which were easily formed from commercially available optically pure amines: (*R*)-(+)-1-phenylethylamine, (*R*)-(+)-1-(1-naphthyl)ethylamine, (*R*)-(+)-1-(2-naphthyl)ethylamine or racemic *sec*-butylamine.

The first experiment was performed between 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione **1a** and (*R*)-*N*-benzylidene-1-phenylethylamine **2aa** in boiling DCE saturated with gaseous HCl (entry 2, Table 1). After the reaction workup, we isolated a mixture of two diastereoisomers: (3*S*,4*S*)-3-benzoyl-1-((*R*)-1-phenylethyl)-4-(*p*-tolyl)azetid-2-one and (3*R*,4*R*)-3-benzoyl-1-((*R*)-1-phenylethyl)-4-(*p*-tolyl)azetid-2-one **3aaa** and **4aaa** with only 15% isolated yields. The most important variable in the case of our reaction is the type of solvent and its boiling range, which has a direct influence on the rate and reactivity of generated ketenes. We have observed that increasing the temperature of the process resulted in slightly higher yields of 2-azetidones with the maximum at 131 °C for chlorobenzene as a solvent (Table 1). Chlorobenzene has one advantage over hydrocarbons with a similar boiling point: a higher dipole moment, which allows the iminium salt to remain dissolved during thermolysis. The second variable we tested was the reagent ratio. Experiments with (*R*)-*N*-benzylidene-1-phenylethylamine as well as with racemic *N*-benzylidenebutan-2-amine demonstrated that higher yields of 2-azetidones are obtained when 1.5 eq. of imine is used in boiling chlorobenzene.

Despite optimization, yields for 2-azetidones formed from 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxo-4,6-dione did not exceed 32%. It has to be added that during the reaction, we observed the formation of a significant amount of polar tar, which was separated during flash chromatography. Additionally, in all

Department of Organic Chemistry, Faculty of Chemistry,  
Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland.  
E-mail: mak@pg.gda.pl; Fax: +48-58-347-2694; Tel: +48-58-347-2883

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