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Mini-review

Cerium and bismuth catalysis hand in hand—Synthesis of a eight-membered ring lactam library

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ABSTRACT

Cerium-catalyzed C–C coupling of 1,3-dicarbonyl compounds with styrene derivatives and oxygen yielded compounds with a 1,4-dicarbonyl moiety after base induced Kornblum–DeLaMare fragmentation. Further conversion of these 1,4-diketones with primary amines in a bismuth-catalyzed reaction gave eight-membered ring lactams, which are a new and promising molecular scaffold for medicinal chemistry. Further derivatization was achieved by saponification of esters to their corresponding carboxylic acids and followed by amidation with primary amines with a coupling reagent. We furthermore investigated the synthesis of cogeners with an additional O, S, or N atom in the eight-membered ring, thus extending the diversity of our scaffold.

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1. Introduction

In contrast to their congeners with smaller ring size, eight-membered ring lactams (2-azocanones) are extraordinary rare structural motifs in natural products [1]. However, these heterocycles are nevertheless found more often in a medicinal chemistry context. Tailored biologically active compounds of this type are mostly benzo-annulated or fused with other heterocycles [2]. Containing at least one endocyclic C–C double bond, i.e. hexahydroazocinones, they adopt a conformation, which makes them attractive peptide building blocks, since they are known to mimic a dipeptide β-turn [3]. This mini-review summarizes our recent advances in the synthesis of eight-membered ring lactams.

We have recently observed a new, elegant and relatively simple route to prepare unsaturated 2-azocanone derivatives **5** (1,4,5,6,7,8-hexahydroazocin-8-ones, Scheme 1) by transformation of readily available starting materials **3** and primary amines R_A–NH_2 with bismuth compounds as catalysts. This finding was a result of attempted synthesis of pyrrole derivatives from 1,4-diketones **3** and these amines R_A–NH_2 (Paal–Knorr synthesis) [4]. Our interest in 1,4-diketones of type **3** resulted from our research on cerium-catalyzed oxidation reaction of β-oxoesters **1** in the presence of olefins **2**, for example styrene (R_B = Ph).

Since hexahydroazocinones were reported to exist in a folded conformation [5], compounds **5** are representing an attractive molecular scaffold for combinatorial chemistry. In our continuing efforts to identify sophisticated structural motifs as a basis for combinatorial library synthesis in drug discovery we are interested in such non-planar and easily accessible scaffolds that provide several points of diversification. Such three-dimensional scaffolds open additional opportunities for adapting the shape of drug molecules to the requirements of binding sites on biological targets. Therefore, we have explored scaffolds **5** as the basis of library synthesis. Two points of diversity in structures **5** are the residues R_A at N-1 and R_B at C-2 originating from diketones **3** and primary amines, respectively. As an additional site for further diversifying functionalization (R_C) we considered the carboxylate moiety at C-4,

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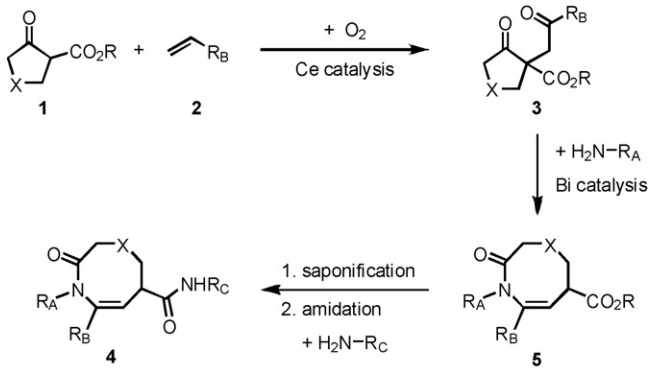


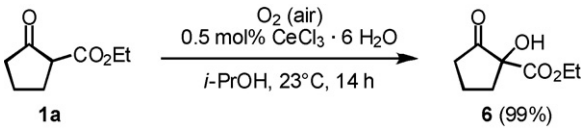
Scheme 1. Eight-membered ring lactams as molecular scaffolds for combinatorial chemistry.

which could be converted with another amine R_C–NH_2 to carboxamides after saponification. Furthermore, besides carbocyclic starting materials **1** and **3** (with X = CH_2), we considered heterocyclic oxoesters **1** with X = N–R_D, S and O to result in diazocane, thiazocane or oxazocane scaffolds **4** and **5**.

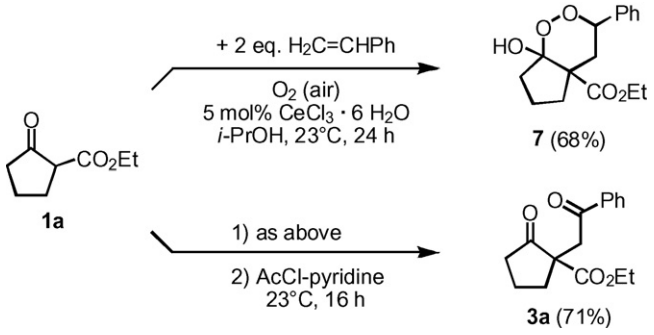
2. Results and discussion

Ce(IV) compounds, in particular CAN, are stoichiometric reagents for the α-oxidation of carbonyl compounds [6]. For the use of Ce salts in catalytic amounts, Ce(III) must be reoxidized to Ce(IV) under reaction conditions. Molecular oxygen (air) would be the optimal oxidant for this purpose with respect to economical and ecological considerations, but the redox potentials do not fit to such requirements. A couple of years ago we made however the observation, that β-dicarbonyl compounds are α-oxidized by air in the presence of Ce salts [7]. Products of this transformation are α-hydroxy-compounds [8]. Scheme 2 gives an example: product **6** is formed from oxoester **1a** in almost quantitative yield under an atmosphere of air and with only 1 mol% of $CeCl_3 \cdot 7H_2O$ as catalyst.

The β-dicarbonyl compounds **1** play a twofold role in this transformation: they are of course substrates for this reaction, but also shift the redox potential of Ce(III)/Ce(IV) by coordination to Ce ions under formation of β-diketonato complexes. Studies into the mechanism of this process have been performed, and indeed, we presume an α-radical to be formed under the employed reaction conditions [9]. In the presence of styrene, this α-radical was trapped and 1,2-dioxane derivatives like compound **7** were formed [10]. Since 1,2-dioxane derivatives can be transformed by Kornblum–DeLaMare fragmentation [11] with acetic anhydride–pyridine furnishing 1,4-diketones [12], we developed a two-step one-pot protocol for the conversion of β-ketoesters by α-oxidation, olefin insertion and fragmentation giving the 1,4-diketones **3** [13]. Whereas compounds **7** (with three stereogenic centers) are obtained as mixtures of several diastereoisomers, products **3** possess only one stereocenter and are of course racemates. Several cyclic and acyclic β-oxoesters, β-diketones as well as α-acetyl-lactams and -lactones can be submitted to this transformation. Scheme 3 gives an example when staring with ketoester **1a**. Product **3a** is isolated after chromatographic purification in 71% yield in the case of the one-pot protocol.



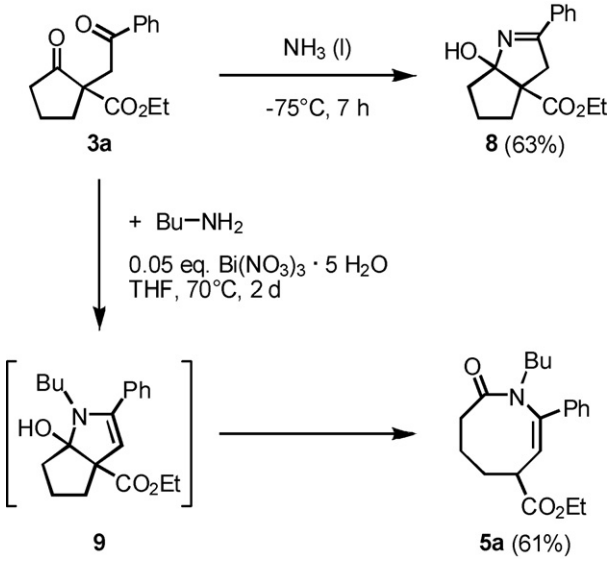
Scheme 2. An example of Ce-catalyzed α-hydroxylation of a β-oxoester **1**.



Scheme 3. Ce-catalyzed α-oxidation in the presence of olefins: formation of 1,2-dioxane derivative **7** and its fragmentation furnishing 1,4-diketone **3a**.

Since the 1,4-dicarbonyl moiety in compounds **3** is the most important starting point for the preparation of pyrrole derivatives, we aimed to prove the utility of our products **3** in this context and tried to convert them into highly substituted dihydropyrrole derivatives containing at least one quaternary carbon atom within the five-membered ring. But when reacting starting material **3a** with ammonia under acidic conditions, only complex reaction mixtures were obtained. However, when performing the conversion of diketone **3a** in liquid ammonia at low temperature, a single and unique product **8** was obtained; its constitution was established by X-ray single crystal structure analysis (Scheme 4) [13a]. After experimentation with several Brönsted and Lewis acidic catalysts, we were able to identify another optimized protocol using $Bi(NO_3)_3 \cdot 5H_2O$, which gave also a unique product **5a** in the reaction with butylamine in 61% yield [14]. Formation of this eight-membered ring lactam **5a** can be understood from the constitution of 2-azabicyclo[3.3.0]octane derivative **8**: the primary amine Bu–NH_2 seemed to react with both ketone moieties of diketone **3a** and formed a bicyclic hemiacetal-enamine **9** as a reaction intermediate with the C–C double bond in a fixed (*Z*)-configuration. A subsequent retro-Claisen reaction cleaved the central bond of bicycle **9** and formed a monocyclic eight-membered ring product **5a**.

In order to elucidate the scope of this transformation, diketone **3a** (R_B = Ph) was converted with several primary amines R_A–NH_2 (Scheme 5, Table 1) [15]. Reactions were performed in THF at



Scheme 4. Attempts on dihydropyrrol synthesis and formation of eight-membered ring lactams **5**.