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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.

Contents

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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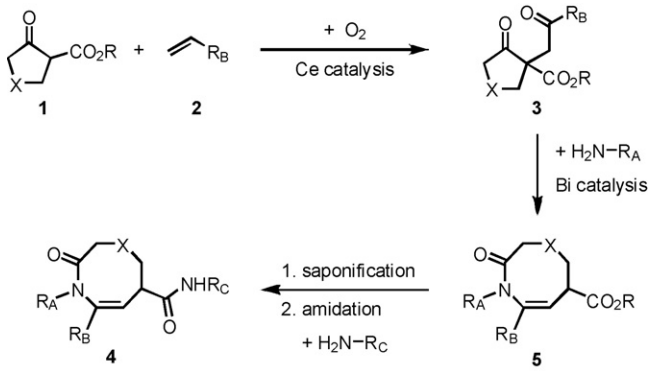


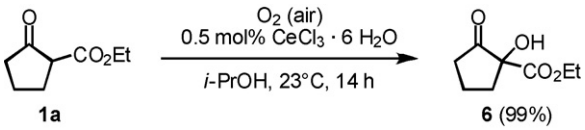
Scheme 1. Eight-membered ring lactams as molecular scaffolds for combinatorial chemistry.

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**.

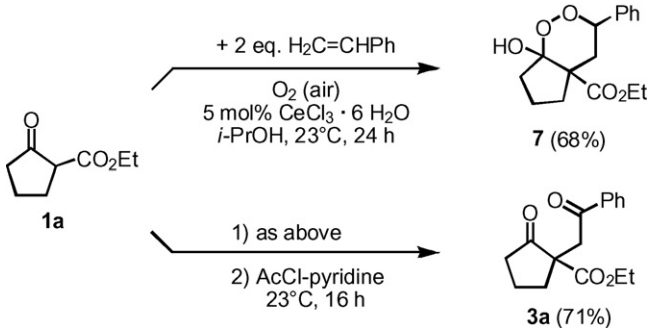
2. Results and discussion

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.



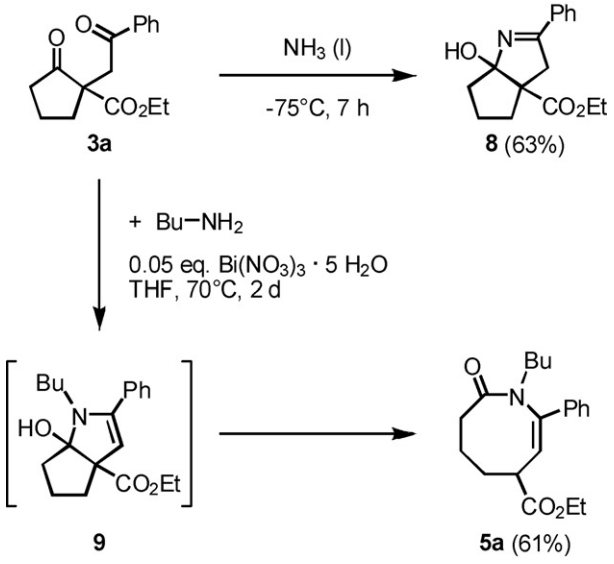
Scheme 2. An example of Ce-catalyzed α-hydroxylation of a β-oxoester **1**.



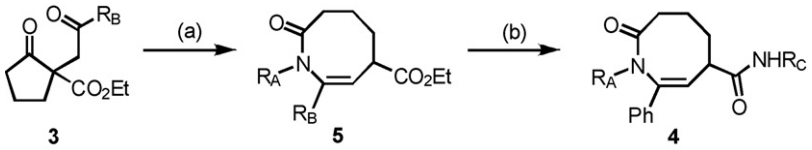
Scheme 3. Ce-catalyzed α-oxidation in the presence of olefins: formation of 1,2-dioxane derivative **7** and its fragmentation furnishing 1,4-diketone **3a**.

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**.

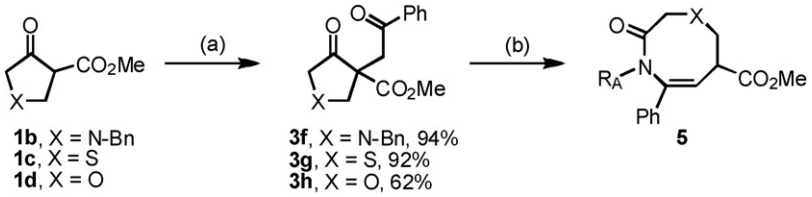
In order to elucidate the scope of this transformation, diketone **3a** (R_B = Ph) was converted with several primary amines R_A–NH_2 (Scheme 5, Table 1) [15]. Reactions were performed in THF at



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



Scheme 5. Preparation of a lactam model library. Conditions: (a) 5–10 equiv. R_A–NH_2, 5–10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, THF, 70–100 °C, 2–4 d, closed reaction vial; for yields and residues R_A, R_B see Table 1. (b) (1) LiOH–H_2O, EtOH, 70 °C, 0.5 h (microwave oven); (2) 1 equiv. R_C–NH_2, 2 equiv. Et*Ni*Pr_2, 1 equiv. HATU, DMF, 23 °C, 1 d; for yields and residues R_A, R_C see Table 2. HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate.



Scheme 6. Synthesis of lactams **5** with an additional heteroatom. Conditions: (a) for **3f** and **3g**: $PhCOCH_2Br$, K_2CO_3, acetone, 65 °C, 1 h; for **3h**: $PhCOCH_2Br$, NaH, THF, 70 °C, 16 h. (b) 2 equiv. R_A–NH_2, 10 mol% $Bi(NO_3)_3{\cdot}5H_2O$, THF, 100 °C, 6 h, closed reaction vial; for yields and residues R_A and X see Table 3.

Table 1
Synthesis of eight-membered ring lactams **5** with R = Et and X = CH_2.

Entry	**3**	R_B	R_A	Yield (**5**)
1	**3a**	Ph	Bu	61% (**5a**)
2	**3a**	Ph	Me	84% (**5b**)
3	**3a**	Ph	Bn	67% (**5c**)
4	**3a**	Ph	4-$MeOC_6H_4CH_2$	57% (**5d**)
5	**3a**	Ph	Allyl	71% (**5e**)
6	**3a**	Ph	Cy	40% (**5f**)
7	**3a**	Ph	*t*$BuO_2CCH_2CH_2$	41% (**5g**)
8	**3b**	4-$MeOC_6H_4$	Me	51% (**5h**)
9	**3c**	2-ClC_6H_4	Me	46% (**5i**)
10	**3d**	2-Thiazolyl	Me	66% (**5j**)
11	**3e**	4-Pyridyl	Bu	45% (**5k**)

70–100 °C for 2–4 d in a closed reaction vial. Bismuth catalyst was used in 5–10 mol%. The best yield was obtained with methyl amine (entry 2), but yields with R_A = Bn, *p*-methoxybenzyl and allyl were also satisfying (entries 3–5). With R_A = Cy the yield drops significantly (entry 6). Entry 7 (conversion of β-alanine ester) shows that the reaction is compatible with amino acid derivatives. With respect to the aromatic residue R_B instead of Ph, also electron rich (entry 8) and sterically hindered (entry 9) phenyl rings can be applied. Moreover, also electron rich, heterocyclic (entry 10) and electron deficient, heterocyclic (entry 11) substituents are compatible with the employed reaction conditions.

For the introduction of residues R_C, ethyl ester groups were submitted to saponification and the resulting carboxylates coupled with amines R_C–NH_2 in the presence of HATU and Et*Ni*Pr_2 to give amides **4**. Four representative examples starting from esters **5a** and **5c** are listed in Table 2. In order to prepare the unsubstituted amide (R_C = H), ammonia was used for the amidation reaction. Actually, residues R_A, R_B, and R_C were randomly chosen for practicability reasons rather than considering their diversity. The latter is anyway a vague concept, which is hardly quantified with a numeric parameter [16].

Table 2
Ester saponification and formation of amides **4** with R_B = Ph and X = CH_2.

Entry	**5**	R_A	R_C	Yield (**4**)
1	**5a**	Bu	2-$ClC_6H_4CH_2CH_2$	87% (**4a**)
2	**5a**	Bu	H	84% (**4b**)
3	**5a**	Bu	2-(1-Piperidinyl)ethyl-	65% (**4c**)
4	**5c**	Bn	Bn	99% (**4d**)

Table 3
Synthesis of eight-membered ring lactams **5** with R = Me and R_B = Ph.

Entry	**3**	X	R_A	Yield (**5**)
1	**3f**	N–Bn	Bn	35% (**5l**)
2	**3f**	N–Bn	Me	20% (**5m**)
3	**3f**	N–Bn	Allyl	31% (**5n**)
4	**3g**	S	Bn	56% (**5o**)
5	**3g**	S	Me	68% (**5p**)
6	**3g**	S	Allyl	51% (**5q**)
7	**3g**	S	Cy	62% (**5r**)
8	**3h**	O	Me	32% (**5s**)[a]

[a] Conditions: 2 equiv. $MeNH_2$, 1 equiv. *p*-TosOH, THF, 80 °C, 16 h.

We further extended the diversity of lactams **4** by introducing a heteroatom X, which however turned out not to be compatible with cerium-catalyzed radical oxidation. Synthesis of starting materials **3f**, **3g**, and **3h** was for this reason accomplished by alkylation of oxoesters **1b**, **1c**, and **1d** with phenylacylbromide (Scheme 6) [17]. Conversion of the compound **3f** (X = N–Bn) gave only poor yields of products **5l**–**5n** (Table 3, entries 1–3). When the reaction of **3f** with Cy–NH_2 was investigated, no unique product could be isolated. In contrast, the reaction of tetrahydrothiophene gave good results, even with R_A = Cy (entry 7). The resulting thiazocines **5o**–**5r** (entries 4–7) were isolated in multigram-amounts. All attempts to prepare oxazocine **5s** by bismuth-catalyzed conversion of tetrahydrofuran derivative **3h** were not fruitful. Also application of other Lewis acids was not successful. To our surprise and after extensive experimentation, we were able to obtain compound **5s** in low yield and together with a byproduct (entry 8). For this reason we conclude, that there will be no efficient access to oxazocines like **5s** from 1,4-diketone **3h**.

3. Conclusion

Bismuth nitrate catalyzed reaction of 1-phenacyl-2-oxocyclopentane-1-carboxylates **1** with primary amines R_A–NH_2 yielded eight-membered ring lactams **5** with one enamide moiety. These lactams **5** define a new type of non-planar molecular scaffold and could be applied as a basis for combinatorial library synthesis. Therefore, we optimized conditions and evaluated scope and limitations of this reaction. The amines R_A–NH_2 and the aromatic ring R_B in the carbonyl compounds **1** have been varied. A mechanistic rationale for the ring expanding transformation considers nucleophilic attack of the amine to both carbonyl groups of the 1,4-diketone moiety under formation of the bicyclic intermediate **9**, as proposed for the Paal–Knorr pyrrole synthesis.

We identified three points of diversification R_A, R_B, and R_C, one resulting from the primary amines R_A–NH_2 applied in the lactam formation and the second being the aromatic residue R_B of the starting carbonyl compound. To address the third spot we cleaved the ethyl ester group with LiOH and coupled the resulting carboxylic acids with HATU and further primary amines R_C–NH_2 to give amides **4**.

When applied to starting materials with a tetrahydrothiophene or pyrrolidine moiety, tetrahydro-2*H*-1,4-thiazocin-3-ones and hexahydro-1,4-diazocin-2-ones are obtained as representatives of these very rare heterocyclic systems. In case of tetrahydrofuran derivatives, other reaction conditions are required and yields of tetrahydro-2*H*-1,4-oxazocin-3-ones are very limited.

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