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Formal [4+1] annulation of α,α-dialkyl β-oxo amides and dimethylsulfoxonium methylide: a synthetic route to β-hydroxy-γ-lactams†

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A facile and efficient one-pot synthesis of β-hydroxy-γ-lactams from α,α-dialkyl β-oxo amides and trimethylsulfoxonium iodide in the presence of sodium hydride *via* a tandem Corey–Chaykovsky reaction and an intramolecular lactamization process is developed.

Many biomedicinal natural products, including (+)-lactacystin[1] and (−)-pramanicin[2] (Fig. 1), contain a γ-lactam ring.[1–3] In addition, functionalized γ-lactams and their benzo-/hetero-fused analogues serve as versatile intermediates in the synthesis of a variety of bioactive compounds[4] and valuable monomers for the preparation of heteroatomic polymers[5] as well. Extensive work has generated many synthetic methods for γ-lactams, involving ring expansion of β-lactams,[6] metal carbine intramolecular C–H insertion,[7] formal [3+2] annulations,[8] and other cycloaddition reactions.[9] It remains of interest to develop efficient methods for the construction of γ-lactam skeletons, especially those with wide general applicability to achieve more elaborate and flexible substitution patterns.

On the other hand, dimethylsulfoxonium methylide (DSM), also known as a Corey–Chaykovsky reagent,[10] has been extensively used as a methylene-transfer reagent in the synthesis of epoxides,[11] cyclopropanes,[12] aziridines,[13] extension of esters,[14] diolefination of cycloalkanones,[15] and ring transformation.[16] Its efficient utilization in the transition-metal-free transformations relies on the extremely mild reaction conditions required and the easy handling capability of reaction systems.[17]

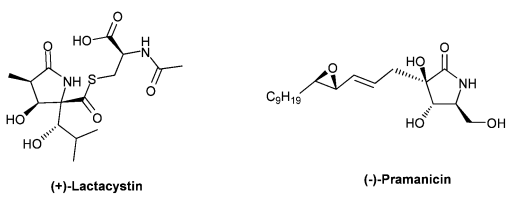

Fig. 1 Examples of substituted γ-lactam derivatives.

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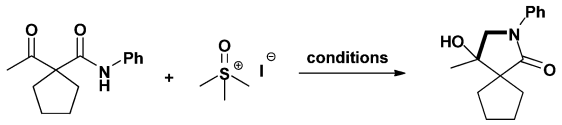
During the course of our studies on the synthesis and application of β-oxo amides and their derivatives, we developed a one-pot synthesis of pyridin-2(1*H*)-ones,[18] isoxazoles,[19] spiro-fused pyrazolin-5-ones,[20] and spiro-fused pyrazolin-5-one *N*-oxides.[21] Inspired by these results and in continuation with our research interest in the synthesis of highly valuable heterocycles, we investigated the reaction of β-oxo amides with DSM generated *in situ* from trimethylsulfoxonium iodide in the presence of NaH. As a result, we developed a formal [4+1] annulation for a facile and efficient synthesis of β-hydroxy-γ-lactams under very mild conditions. Herein, we report our experimental results and present a proposed mechanism involved in the cyclization.

The substrates, 1-acyl-1-carbamoyl cycloalkanes **1**, were prepared by the reaction of β-oxo amides with 1,4-dibromobutane or 1,2-dibromoethane in the presence of K_2CO_3 in DMF at room temperature in high yields (up to 95%).[18a] We then selected 1-acetyl-*N*-phenylcyclopentanecarboxamide **1a** as a model compound to examine its reaction behavior towards the Corey–Chaykovsky reagent. Thus, the reaction of **1a** and trimethyl sulfoxonium iodide **2** (1.2 equiv.) in the presence of NaH (4.0 equiv.) was first attempted in toluene at room temperature, but no reaction occurred as indicated by TLC (Table 1, entry 1). When **1a**, **2** (1.2 equiv.) and NaH (4.0 equiv.) were subjected to CH_3CN at room temperature for 12.0 h, the reaction proceeded and furnished a product (in 27% yield), which was characterized as 4-hydroxy-4-methyl-2-phenyl-2-azaspiro [4.4] nonan-1-one **3a** based on its spectral and analytical data (Table 1, entry 2).

The optimization of the reaction conditions, including bases, solvents and reaction temperature, was then investigated. When **1a** and **2** (1.2 equiv.) were subjected to aqueous NaOH or NaOEt–EtOH at room temperature, no reaction was observed (Table 1, entries 3 and 4). Treatment of **1a** and **2** with NaH in DMF at room temperature afforded **3a** in 78% yield (Table 1, entry 5). When the reaction of **1a** and **2** was performed with NaH in DMSO at room temperature, the yield of **3a** could reach 82% (Table 1, entry 6). An increase in the reaction temperature could speed up the reaction, while had no significant influence on the yield of **3a** (Table 1, entry 7).

Table 1 Optimization of the reaction conditions for the synthesis of **3a**[a]



1a 2 3a

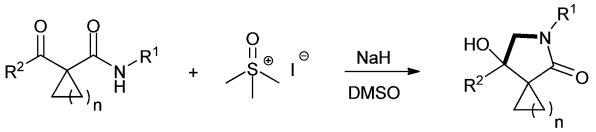
Entry	Base (equiv.)	Solvent	T (°C)	Time (h)	Yield[b] (%)
1	NaH(4.0)	Toluene	rt	12.0	NR[c]
2	NaH(4.0)	CH_3CN	rt	12.0	27[d]
3	NaOEt(4.0)	EtOH	rt	12.0	NR[c]
4	NaOH(4.0)	H_2O	rt	12.0	NR[c]
5	NaH(4.0)	DMF	rt	12.0	78
6	**NaH(4.0)**	**DMSO**	**rt**	**6.0**	**82**
7	NaH(4.0)	DMSO	110	3.0	79
8	NaOH(4.0)	DMSO	rt	12.0	65
9	DBU(4.0)	DMSO	rt	12.0	46

[a] Reagents and conditions: **1a** (1.0 mmol), **2** (1.2 mmol), and a base (4.0 mmol) in 5.0 mL of solvent. [b] Isolated yield of **3a**. [c] No reaction. [d] 62% of **1a** was recovered.

The employment of other bases, such as DBU and NaOH, can result in lower yield of **3a** (Table 1, entries 8 and 9).

Having established the optimal conditions for the synthesis of γ-lactams, we intended to determine its scope with respect to the amide motif. Thus, a series of reactions of 1-acetyl, 1-carbamoyl cyclopentanes **1b–o** and **2** were carried out under identical conditions to those for **1a** in Table 1, entry 6, and some of the results are summarized in Table 2. It was found that the reactions of **1b–k** bearing varied electron-donating and electron-withdrawing arylamide groups or heteroarylamide groups could proceed efficiently to afford the corresponding 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **2b–k** in moderate to good yields (Table 1, entries 2–11). In the cases of substrates **1l** and **1m** bearing a benzylamide group, no desired γ-lactam was obtained and the decomposition of substrates was

Table 2 Synthesis of γ-lactams **3**[a]



1 2 3

Entry	1	R^1	R^2	n	3	Yield[b] (%)
1	**1a**	Ph	Me	3	**3a**	82
2	**1b**	4-MeC_6H_4	Me	3	**3b**	85
3	**1c**	4-ClC_6H_4	Me	3	**3c**	84
4	**1d**	4-$MeOC_6H_4$	Me	3	**3d**	86
5	**1e**	2,4-$Me_2C_6H_3$	Me	3	**3e**	72
6	**1f**	3-ClC_6H_4	Me	3	**3f**	82
7	**1g**	3-MeC_6H_4	Me	3	**3g**	81
8	**1h**	3-$NO_2C_6H_4$	Me	3	**3h**	89
9	**1i**	4-$CF_3C_6H_4$	Me	3	**3i**	91
10	**1j**	1-Naph	Me	3	**3j**	52
11	**1k**	2-Py	Me	3	**3k**	85
12	**1l**	Bn	Me	3	**3l**	—[c]
13	**1m**	Bn	Ph	3	**3m**	—[c]
14	**1n**	Ph	Ph	3	**3n**	48
15	**1o**	4-MeC_6H_4	Ph	3	**3o**	47
16	**1p**	4-MeC_6H_4	Me	1	**3p**	86
17	**1q**	4-ClC_6H_4	Me	1	**3q**	83

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.2 mmol), and NaH (4.0 mmol) in 5.0 mL of DMSO, rt, 6.0 h. [b] Isolated yield of **3**. [c] Not detected.

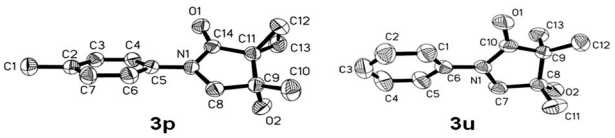
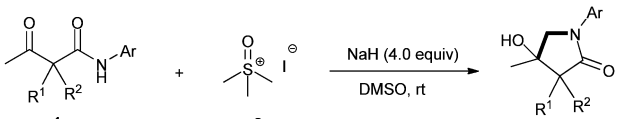


Fig. 2 ORTEP drawing of **3p** and **3u**.

detected (Table 2, entries 12 and 13). The versatility of this γ-lactam synthesis was further evaluated by performing the reaction of **1n** and **1o** containing benzoyl group COR^2 under the identical conditions (Table 1, entries 14 and 15). The formal [4+1] annulation proved to be suitable for 1-acetyl, 1-carbamoylcyclopropanes **1p** and **1q**, affording the corresponding spiro-fused cyclopropyl-γ-lactams of type **2** in high yields (Table 1, entries 16 and 17). The products **3** were characterized by NMR spectra, and the structure of **3p** was further elucidated by X-ray diffraction analysis as shown in Fig. 2.

To expand the general applicability of the synthesis of γ-lactams, we next investigated the effect of α-substituents of the β-oxo amides on the formal [4+1] annulation. Thus, the reactions of β-oxo amides **1r–1w** and **2** were conducted under identical conditions as described above, and the results are summarized in Table 3. In the cases of α-unsubstituted β-oxo amide **1r** and α-monosubstituted β-oxo amides **1s** and **1t**, an unidentified mixture was formed (Table 3, entries 1–3). To our delight, α,α-dialkyl β-oxo amides **1u–w** could undergo the formal [4+1] annulation smoothly to furnish the corresponding γ-lactams **3** in good yields (Table 3, entries 4–6). The structure of **3u** was elucidated by means of the X-ray single crystal analysis (Fig. 2).[22] It should be noted that **3w** was obtained as an inseparable mixture of two diastereoisomers (Table 3, entry 6). The NOESY NMR studies indicate that the relative configuration of the major diastereoisomer is *trans* (see ESI†).[23] The above results reveal that a quaternary carbon at the α position of β-oxo amides **1** is essential for the formal [4+1] annulation and the annulation proceeds in a diastereoselective manner. The quaternary carbon with α,α-dialkyl substituents may facilitate stabilization of the betaine intermediate derived from the ketone carbonyl during the reaction process, forming a favorable conformation of the intermediate for the successive intramolecular lactamization. Therefore, we developed a facile and efficient method for the synthesis of β-hydroxy-γ-lactams **3** under very mild conditions.

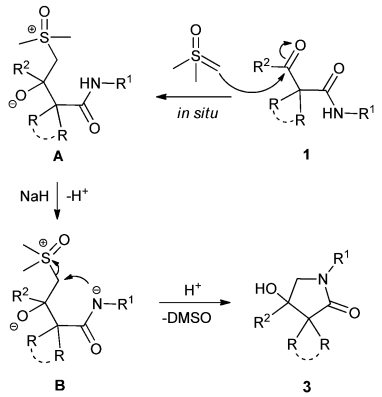
Table 3 Expansion of the applicable scope of the γ-lactam synthesis[a]



1 2 3

Entry	1	Ar	R^1	R^2	3	Yield[b] (%)
1	**1r**	Ph	H	H	**3r**	—[c]
2	**1s**	Ph	H	Me	**3s**	—[c]
3	**1t**	Ph	H	Bn	**3t**	—[c]
4	**1u**	Ph	Me	Me	**3u**	86
5	**1v**	4-ClC_6H_4	Me	Me	**3v**	72
6	**1w**	Ph	Me	Et	**3w**	81[d]

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.2 mmol), and NaH (4.0 mmol) in 5.0 mL of DMSO, rt, 6.0 h. [b] Isolated yield of **3**. [c] Unidentified mixture. [d] Overall yield of diastereoisomers **3w**; dr = 8 : 1 (determined by ^{1}H NMR analysis).



Scheme 1 Plausible mechanism for the synthesis of γ-lactams **3**.

Corey–Chaykovsky reaction[10] was established based on the stoichiometric sulfur ylide-mediated epoxidation reported in 1958 by Johnson and LaCount.[24] Since then, many improvements have been made to this reaction. It is widely known that such reaction involves the attack of an ylide on a carbonyl group, which yields a betaine intermediate that collapses to give an epoxide and a sulfide.[25] In contrast to these reports, Kumar and co-workers recently investigated Corey–Chaykovsky reaction of aldehydes and revealed that no epoxide intermediate was formed during the reaction process.[26] Actually, such an epoxide intermediate was not detectable within our reaction system.

On the basis of the reported literature and our obtained results, a mechanism was proposed for the synthesis of γ-lactams **3** as depicted in Scheme 1. In the presence of sodium hydride, trimethylsulfoxonium iodide **2** is converted into sulfur ylide, *i.e.* Corey–Chaykovsky reagent.[25c] The attack of the *in situ* generated sulfur ylide on the carbonyl group of **1** gives rise to a betaine intermediate **A**, which is in turn followed by facile proton exchange from the carbamate nitrogen to the basic oxide ion to afford the stable species **B**.[26,27] The final product, γ-lactams **3**, is formed after the intramolecular lactamization of **B** with the elimination of DMSO.[26,28]

In summary, a facile and efficient synthesis of β-hydroxy-γ-lactams **3** from readily available α,α-dialkyl β-oxo amides **1** and trimethylsulfoxonium iodide **2** *via* a tandem Corey–Chaykovsky reaction and an intramolecular lactamization process has been developed. The ready availability of substrates, mild reaction conditions, simplicity of execution, high yields and synthetic potential of the products make this protocol much attractive. Further work on the utilization and extension of the scope of the protocol is currently underway in our laboratory.

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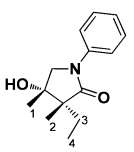
22 For the X-ray diffraction analysis of **3p** and **3u**, see ESI†.
23 The relative stereochemistry of the major diastereoisomer of **3w** was confirmed by NOESY NMR studies. A significant NOESY correlation was observed between H_{C_1} and H_{C_2}, and the correlation between H_{C_1} and H_{C_3} was not detected, both suggesting the *syn* relationship between C_1 and C_2 (see below).



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