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A convenient synthesis of medium-sized lactams through RCM reaction of oxyoxazolidinones

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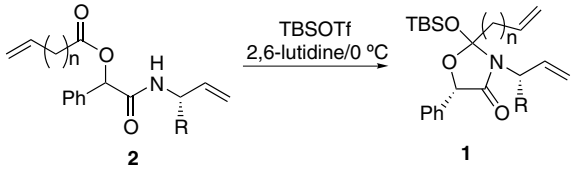
Abstract—Oxyoxazolidinones, which are prepared from secondary *O*-acylmandelamides by treatment with TBSOTf, underwent the RCM reaction in the presence of Grubbs catalyst to give oxazoloazepines or oxazoloazecines, which were readily converted into N-unsubstituted seven-membered or eight-membered lactams by the reductive treatment.

Recently, we have discovered a new type of heterocyclic compounds, oxyoxazolidinones, which are readily prepared from *O*-acylmandelamides on treatment with TBSOTf.[1] The formation of the ring takes place in a stereoselective manner and they are usually isolated as a single diastereomer. These compounds have sufficient stability toward chromatographic purification as well as further transformation, despite the structure which is isoelectronic to orthoester in most cases which are labile on touch with aqueous media.[2] We have succeeded in providing a new method to prepare N-unsubstituted pyrrolidinones and piperidinones through *trans*-selective radical cyclization between the side chains of oxyoxazolidinones.[3] Medium-sized lactams sometimes give rise to difficulties in their preparation[4] for which so many useful methods have been devised so far.[5] Recently, the ring closing metathesis (RCM) reaction attracted synthetic chemists toward the construction of medium-sized rings.[6] In this letter, we describe the RCM reaction between the side chains of oxyoxazolidinones, followed by reductive treatment to provide a useful method for the preparation of medium-sized N-unsubstituted lactams.[7]

Preparation of precursors **1** was performed by the method reported before (Scheme 1). The results are summarized in Table 1. Treatment of *O*-acylmandelamide **2** with TBSOTf in the presence of 2,6-lutidine smoothly afforded oxyoxazolidinone **1** in good yields, except for the preparation of 2-(3-butenyl)oxyoxazolidine **2b**. This is probably due to the isomerization of the alkenyl part toward a conjugated system which predominated before the cyclization reaction took place.



Scheme 1.

Table 1. Preparation of oxyoxazolidinone **1**

Entry	**2**	*n*	R	**1**	Yield[a] (%)
1	**2a**	0	H	**1a**	60
2	**2b**	1	H	**1b**	0
3	**2c**	2	H	**1c**	93
4	**2d**	2	*i*-Pr	**1d**	83
5	**2e**	2	*i*-Bu	**1e**	87
6	**2f**	2	Ph	**1f**	85
7	**2g**	3	H	**1g**	95
8	**2h**	4	H	**1h**	95

[a] Isolated yields.

We next examined the RCM reaction for **1** (Scheme 2). The results are summarized in Table 2. Two types of Grubbs catalysts were employed in the reaction. Treatment of **3a** with catalyst **A** failed to form the desired bicyclic compound **3a** due to steric hindrance caused at the C2-position of oxyoxazolidinone (entry 1), while compound **1c** underwent smooth ring closure

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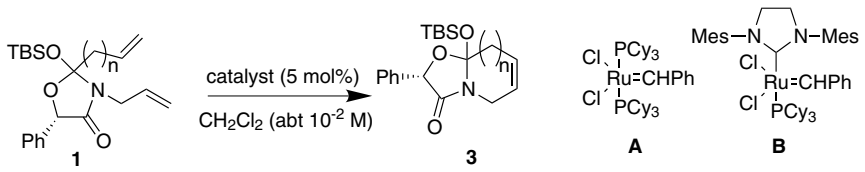


Scheme 2.

Table 2. RCM reaction of **1**

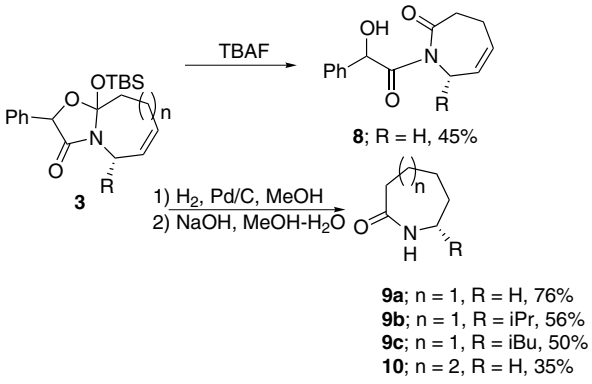
Entry	1	*n*	R	Catalyst	3	Yield[a] (%)
1	**1a**	0	H	**A**	**3a**	0
2	**1c**	2	H	**A**	**3c**	91
3	**1d**	2	*i*-Pr	**A**	**3d**	79
4	**1e**	2	*i*-Bu	**B**	**3e**	78
5	**1f**	2	Ph	**B**	**3f**	66
6	**1g**	3	H	**A**	**3g**	0
7	**1g**	3	H	**B**	**3g**	98
8	**1h**	4	H	**B**	**3h**	0

[a] Isolated yields.

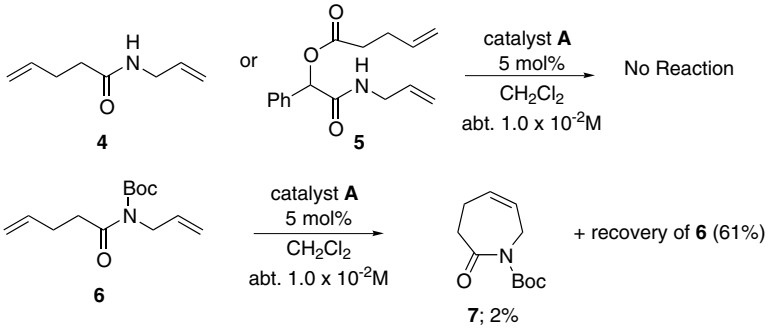
metathesis reaction to give **3c** in 91% yield (entry 2). Other oxazoloazepines **3d** to **3f** were also prepared in good yields. Some starting materials were required to use catalyst **B** to achieve high yields from the RCM reaction (entries 3–5). The reaction was not sensitive to reaction concentrations of the range from 5×10^{-3} to 2×10^{-2} M, and the RCM products were obtained in good yields. The formation of oxazoloazecine **3g** could not be achieved by the reaction catalyzed by catalyst **A** and precursor **1g** was recovered (entry 6). Exposure of **1g** to catalyst **B**, on the other hand, successfully resulted in the formation of eight-membered ring **3g** in 98% yield (entry 7), while compound **1h** never gave oxazoloazonine **3h**.

The merit of the present method is well demonstrated by the fact that neither of the noncyclic compounds **4**, **5**, and **6** gave the corresponding cyclized products efficiently under the same RCM conditions (Scheme 3). For example, no trace amounts of cyclized product was observed in the reaction mixture of **4** and **5**. Even Boc group at the nitrogen atom afforded insufficient bias for the cyclization because the exposure of *N*-Boc derivative **6** under the same reaction conditions gave only 2% of cyclized product **7**; most of **6** was recovered after the reaction. These results were in contrast to the fact that compound **1c** smoothly underwent the RCM reaction to give **3c** in 91% yield (Table 2, entry 1). Thus, the oxyoxazolidinone ring offers an excellent bias to proceed the cyclization of medium-sized rings, through the RCM reaction, that are usually hard to form.

To remove the mandelic unit, treatment of **3** with TBAF was examined. To our surprise, the obtained product still contained mandelic amide unit and the formation of N-free azepine was not observed. The obtained imide **8** was reluctant to hydrolysis under usual conditions. Thus, simple removal of mandelic unit by treatment with TBAF, which was achieved in the formation of pyrrolidinone, never occurred in this case. After several efforts to seek a method to remove the mandelic unit, we finally succeeded under hydrogenation conditions (Scheme 4).[8] Under these conditions, N-unsubstituted azepinones **9** or azecinones **10** were successfully isolated (Scheme 4), although the alkene unit in the ring disappeared during the reductive conversion.



Scheme 4.



Scheme 3.

In conclusion, we have succeeded in providing a new method to prepare N-unsubstituted medium-sized lactams through the RCM reaction of oxyoxazolidinones. These unique heterocyclic compounds are prepared easily from *O*-acylmandelamides and effectively offer steric bias for the RCM reaction to give seven- or eight-membered ring. This is in contrast to the fact that secondary amides never form cyclized products due to favorable conformation of an amide moiety. Further application of the present method is now underway in our laboratory.

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