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Efficient synthesis of 4-vinyl α,β-unsaturated γ-lactams by ring-closing enyne metathesis reactions

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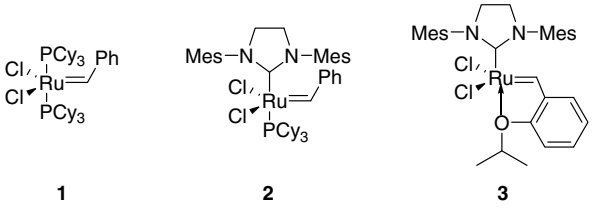
ABSTRACT

The ring-closing enyne metathesis reaction of alkyl 2-substituted-2-(*N*-alkynyl acrylamido)esters using the first-generation Grubbs' catalyst afforded five-membered lactams bearing a 1,3-diene moiety in high isolated yields. In the reaction process, the presence of ethylene gas is essential.

Unsaturated γ-lactams and their derivatives are pharmacologically active materials that are important synthons for the preparation of γ-amino acids,[1] various alkaloids,[2] and natural products.[3] Some of these five-membered ring compounds exhibit significant antitumor properties,[4] as well as inhibition of COX-2[5] and HIV-1 protease.[6] In this regard, the γ-lactam framework has been identified as a 'privileged' structure or pharmacaphore. The versatility of unsaturated γ-lactams can be extended to their vinyl derivatives. The incorporation of a vinyl group at the C-4 position of pyrrolinones is useful for further functionalization, including but not limited to, Diels–Alder reactions, epoxidation, and dihydroxylation, to afford more complex N-containing compounds for drug discovery.[7] Accordingly, the development of synthetic methods to efficiently construct this class of molecules is a desirable goal in organic chemistry. Few methods are described in the literature to prepare unsaturated γ-lactams containing a conjugated diene moiety. To our knowledge, only two publication reporting their preparation have appeared by means of palladium-catalyzed cross-coupling of 4-stannylated α,β-unsaturated γ-lactams with suitable vinyl iodoles.[8]

Recently, diene[9] and enyne[10] ring-closing metathesis reactions have emerged as powerful methods for the construction of many functionalized carbocycles and heterocycles from acyclic diene or enyne precursors, especially as a result of the development of well-defined Ru-catalysts **1**, **2**, and **3** (Scheme 1).

Along these lines, we reported a method for the preparation of pyrrolidine derivatives by Lewis acid-assisted direct ring-closing metathesis (RCM) of diallylamine substrates[11] and ring-closing enyne metathesis (RCEM) of enynes containing a basic N-atom in the absence of ethylene gas.[12] The 1,3-diene structure in vinyl unsaturated γ-lactams suggests that RCEM can be an effective tool for their synthesis.[10] Indeed, it was found that a dumbbell-type bicycle vinyl lactam was formed as a by-product in the group selective reaction of a N-containing enyne in the presence of the second-generation Grubbs' catalyst **2**.[13] We thus envisioned that the RCEM reaction of simple *N*-(2-alkynyl) acrylamides should allow a direct construction of the corresponding vinyl unsaturated γ-lactams. We now report the results of our investigation of this synthetic methodology.



1 **2** **3**

Scheme 1. Widely used Ru-catalysts.

The synthesis of enyne precursors was based on a known procedure[14] starting with commercially available racemic α-amino acids and is shown in Scheme 2. To examine the feasibility of this approach, the RCEM reaction of enyne **6a** was chosen as a model reaction and several Grubbs-type Ru-catalysts (Scheme 1) were tested under various conditions. First, the reaction of **6a** was performed using 7 mol % of **1** in refluxing CH_2Cl_2. Surprisingly, the desired product was not isolated, although the starting material was totally consumed after 3 h. We then treated **6a** with 7 mol % of **2** or **3** in toluene, 1,2-dichloroethane or benzene at higher temperature, again without success.

Possible reaction pathways for RCEM might include the so-called 'yne-then-ene pathway' or/and 'ene-then-yne pathway'.[10,15] In both cases, a ruthenium carbene complex, $Ru{=}CH_2$, plays an important role in the initiation of the reaction.[10] On the 'ene-then-yne' mechanism, ruthenium catalysts **1**, **2**, or **3** could

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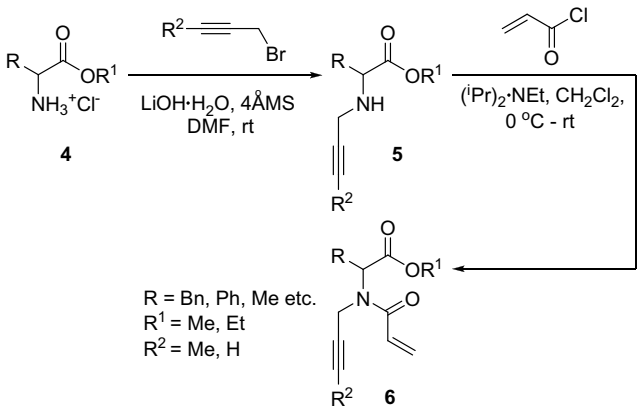


Scheme 2. Synthesis of enyne substrates.

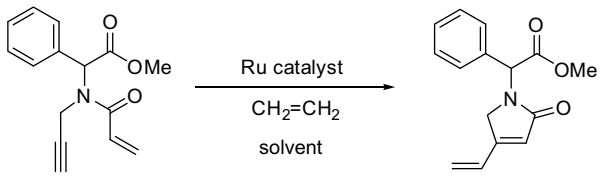
first react with the olefinic moiety of the substrate to initiate the reaction and generate Ru=CH_2 for the catalytic cycle.[12] On the other hand, if the RCEM proceeds by an 'yne-then-ene' pathway, the in situ generation of Ru=CH_2 will be essential for methylene transfer with the alkynyl part of the substrate. We envisioned that, in the case of **6**, the electron-withdrawing character of the amide group might reduce the possibility of the 'ene-then-yne' pathway, and the generation of Ru=CH_2 would be key for the efficient RCEM of substrates such as **6**.

Mori et al. demonstrated that ethylene gas is beneficial for the RCEM of propargyl tosylamides to produce 1-tosyl-5-vinyl-tetrahydropyridines.[16] Mechanistically, it was proposed that Ru=CH_2 first reacted with the alkyne and then ring closed onto the pendant alkene. Therefore, we ran the reaction of **6a** under an ethylene atmosphere, along with Grubbs' first- and second-generation catalysts, and the results are summarized in Table 1. Exposure of **6a** to ethylene in the presence of **1** in CH_2Cl_2 did indeed provide the desired 4-vinyl α,β-unsaturated γ-lactam **7a** in 65% isolated yield (Table 1, entry 1). Further evaluation of Grubbs' catalysts revealed that the second-generation catalyst **2** gave almost the same results as the first-generation catalyst **1** (Table 1, entries 1 and 2). A survey of reaction media (Table 1, entries 1 and 2 vs entries 3 and 4) demonstrated that toluene was the optimal solvent (entry 3, 76% yield).

The scope of α-substituted alkyl 2-[*N*-(prop-2-ynyl)acrylamido]acetates for this RCEM reaction was examined under the optimal reaction conditions. α-Substituents of the substrates, including phenyl, benzyl, isopropyl, and ω-ester groups, are readily tolerated (Table 2, 69–83% yields). Changing the alkoxyl groups from MeO to EtO has little impact on the reaction (Table 2, entry 6).

To expand the scope of this RCEM reaction and verify the influence of ethylene gas, several other substrates **6g–j** were prepared. According to Mori's results of the RCEM of propargyl tosylamides, enynes with an internal alkynyl unit smoothly undergoes the RCEM reaction without the use of ethylene gas.[16] Thus, the reaction of an internal alkynyl substrate **6g** was run on a 1 mmol scale, using 7 mol % of **1** as the catalyst, in 25 mL of toluene at 80 °C under N_2 for 14 h. To our surprise, the reaction only afforded the expected product **7g** in 10% yield (Table 3, entry 1). Using ethylene instead of N_2, the yield of **7g** increased appreciably to 54% (Table 3, entry 2), which demonstrated that the presence of ethylene is crucial for the RCEM reaction for such substrates. When the catalyst loading was increased to 10 mol %, the reaction of **6g** went to completion in 4 h, and the yield of **7g** could be further improved to 75% (Table 3, entry 3). Other α-substituted 2-[*N*-(but-2-ynyl)acrylamido] acetates were also tested, and the results are presented in Table

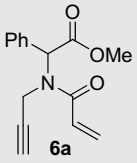
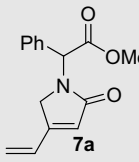
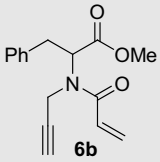
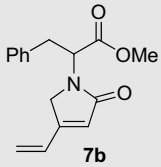
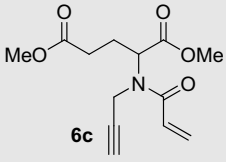
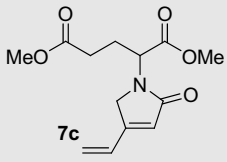
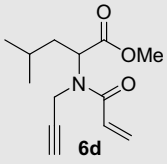
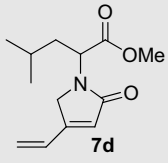
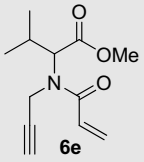
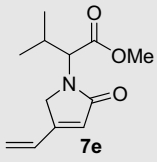
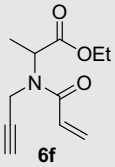
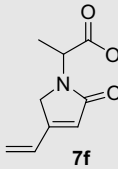
Table 1
The RCEM reaction of **6a** in the presence of ethylene gas[a]



Entry	Catalyst	Solvent	Temperature (°C)	Yield[b] (%)
1	**1**	CH_2Cl_2	40	65
2	**2**	CH_2Cl_2	40	63
3	**1**	Toluene	80	76
4	**2**	Toluene	80	73

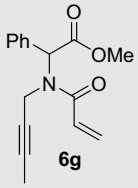
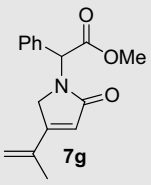
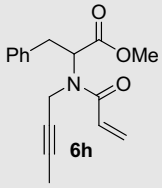
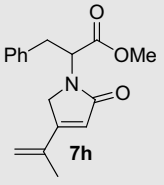
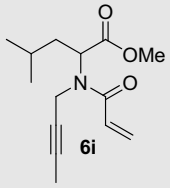
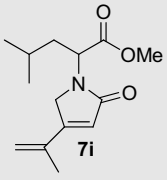
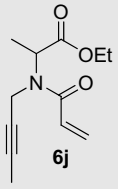
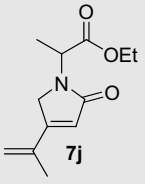
[a] Reaction conditions: **6a** (1 mmol), cat. **1** or **2** (0.07 mmol), CH_2Cl_2 or toluene (25 mL), 40 or 80 °C, 3 h.
[b] Isolated yield.

Table 2
RCEM reaction of α-substituted alkyl 2-[*N*-(prop-2-ynyl)acrylamido]acetates under an atmosphere of ethylene[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)
1	 **6a**	3	 **7a**	76
2	 **6b**	3	 **7b**	83
3	 **6c**	4.5	 **7c**	69
4	 **6d**	4	 **7d**	73
5	 **6e**	4	 **7e**	76
6	 **6f**	3.5	 **7f**	71

[a] Reaction conditions: enynes (1 mmol), **1** (0.07 mmol), toluene (25 mL), 80 °C.
[b] Isolated yield.

Table 3
RCEM reaction of α-substituted alkyl 2-[*N*-(but-2-ynyl)acrylamido]acetates under an atmosphere of ethylene[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)
1[c,d]	 **6g**	14	 **7g**	10
2[d]	**6g**	14	**7g**	54
3	**6g**	4	**7g**	75
4	 **6h**	9	 **7h**	79
5	 **6i**	6	 **7i**	83
6	 **6j**	8	 **7j**	74

[a] Reaction conditions: enynes (1 mmol), **1** (0.1 mmol), toluene (25 mL), 80 °C.
[b] Isolated yield.
[c] The reaction was performed under N_2 instead of ethylene.
[d] The catalyst loading was 7 mol %.

3. It can be concluded that this RCEM reaction is quite general with respect to the enyne architecture and good isolated yields of the corresponding products were obtained in all cases.

In conclusion, we have evaluated the RCEM reaction of various α-substituted alkyl 2-[*N*-(alk-2-ynyl)acrylamido]acetates by the use of Grubbs' first-generation catalyst in the presence of ethylene under mild conditions.[17] This new procedure can be used to prepare a diverse series of 4-vinyl α,β-unsaturated γ-lactams in good yields. We are currently examining further variations of this methodology, and applications to the synthesis of other heterocyclic compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.051.

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17. A general procedure for the ring-closing enyne metathesis is as follows: precursor enyne (1 mmol) was dissolved in freshly distilled and degassed toluene (15 mL) under nitrogen. After stirring for 10 min at room temperature, ethylene gas was purged into the flask instead of the nitrogen. After 20 min, the ruthenium catalyst **1** (41.2 mg, 0.05 mmol) was added quickly. After 3–9 h of reflux, the reaction was complete as indicated by TLC. The solution was concentrated via rotavapor under reduced atmosphere, and the residue was separated by flash column chromatography affording the corresponding five-membered lactam derivatives **7**. (2-Oxo-4-vinyl-2,5-dihydro-pyrrol-1-yl)-phenyl-acetic acid methyl ester **7a**. Product **7a** was obtained in 76% yield from **6a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.28 (m, 5H), 6.58 (dd, 1H, J = 17.6 and 10.8 Hz), 6.13 (s, 1H), 6.01 (s, 1H), 5.42 (d, 1H, J = 17.6 Hz), 5.35 (d, 1H, J = 10.8 Hz), 4.51 (d, 1H, J = 18.4 Hz), 3.78 (s, 3H), 3.65 (d, 1H, J = 18.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 171.0, 154.5, 134.6, 129.7, 129.1, 128.7, 128.4, 122.6, 119.8, 57.2, 52.4, 48.7; HRMS (EI) m/z calcd for $C_{15}H_{15}NO_3$ (M^+) 257.1052, found 257.1032.