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Synthesis of α,β-Unsaturated 4,5-Disubstituted γ-Lactones via Ring-Closing Metathesis Catalyzed by the First-Generation Grubbs' Catalyst

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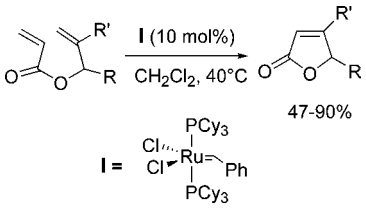
ABSTRACT

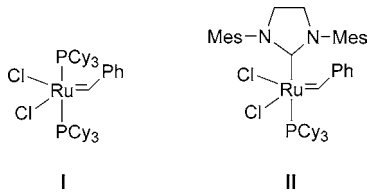


4-Methyl-5-alkyl-2(5*H*)-furanones have been prepared by ruthenium-catalyzed ring-closing metathesis of the suitable methallyl acrylates. Despite the electron deficiency of the conjugated double bond and of the *gem*-disubstitution of the allylic alkene moiety in the starting acrylates, the first-generation Grubbs' catalyst I proved to be an effective promoter for the ring closure, affording the expected butenolides in good to high yields.

The olefin metathesis reaction has become a powerful tool in organic synthesis since the development of well-defined single-component ruthenium and molybdenum alkylidene catalysts.[1] One of its most successful applications is the ring-closing metathesis reaction (RCM) which affords cyclic compounds from diolefinic precursors.[1,2]

Among the different classes of cyclic compounds achievable by RCM, unsaturated lactones of various ring sizes were obtained from α,ω′-diolefinic esters using first- and/or second-generation Grubbs' alkylidene catalysts,[1c,3] indenylidene[4] and cationic allenylidene ruthenium complexes,[5] or $[RuCl_2(p\text{-cymene})]_2$ under neon light.[6]

More specifically, the preparation of α,β unsaturated γ- and δ-lactones through RCM of allyl and homoallyl acrylates have been reported using either the first-generation (**I**) or second-generation (**II**) Grubbs' catalysts (Figure 1).[7]



I II

Figure 1.

In the past few years, we have been involved in the metal-promoted synthesis of five-membered lactones having in-

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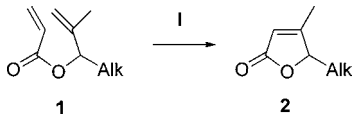
teresting odoriferous properties, and we decided to focus our attention on the preparation of α,β-unsaturated γ-lactones **2**, bearing a methyl group at C-4 and alkyl group at C-5**.** Indeed, compounds **2** are advanced intermediates on the way to naturally occurring important γ-lactones with fragrance properties, like Whisky lactone and Cognac lactone.[8] Thus, we envisaged obtaining compounds **2** through the ring-closing metathesis of the appropriate methallyl acrylates **1** (Scheme 1), as the key step in the synthesis of γ-lactone fragrances.

Scheme 1



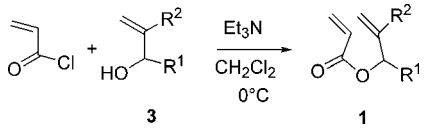
1 **2**

However, the acrylates **1**, characterized by a *gem*-disubstitution of the alkene in the allylic moiety and by an electron-poor conjugated double bond, were expected to be critical substrates for a RCM reaction.[1c−d,3a,9] According to the literature, the reaction would have required the use of one of the catalysts of type **II**, which were reported as the first complexes to induce the formation of trisubstituted olefins in the presence of a deactivating group such as acrylate[1c,d,3b] and to exhibit an efficiency comparable to that of the alkoxyimido molybdenum complexes developed by Schrock in the preparation of cyclic sterically hindered olefins.[1,10]

In this paper, we show how the RCM reaction of substrates **1** can be performed in the presence of commercially available complex **I**, which remains the most attractive catalyst for synthetic applications due to its lower cost.

The starting methallylacrylate esters have been prepared by the reaction of the secondary allyl alcohols **3** with acryloyl chloride, affording the expected products in good yields, except for the case of the isopropyl derivative **3d** (Table 1).

Table 1. Synthesis of Acrylates **1a**−**e**



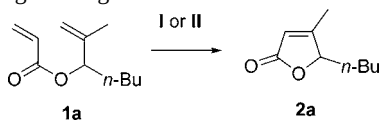
3 **1**

entry	substrate	R^1	R^2	product (yield, %)[a]
1	**3a**	*n*-Bu	Me	**1a** (81)
2	**3b**	*n*-Pn	Me	**1b** (87)
3	**3c**	Cy	Me	**1c** (75)
4	**3d**	*i*-Pr	Me	**1d** (14)
5	**3e**	*n*-Bu	$CH_2OSi(i\text{-}Pr)_3$	**1e** (80)

[a] Isolated yields.

The acrylate ester **1a** was chosen as the model compound to find the best conditions for the RCM reaction using complex **I** as catalyst. The first reactions run on **1a** showed a dependence of the product yield upon the initial concentration of the substrate. Thus, when a solution 0.25 M of **1a** was refluxed for 24 h in CH_2Cl_2 in the presence of the ruthenium complex **I** (10 mol %) under a standard RCM procedure,[11] the expected 4-methyl-5-butyl-2(5H)-furanone **2a**[12] was obtained in 29% yield (entry 1, Table 2). Noteworthy, however, was the finding that the product yields could be raised by working with the same mol % of catalyst but in more dilute solutions of **1a** (entries 2 and 3, Table 2).

Table 2. Ring-Closing Metathesis of **1a**



1a **2a**

entry	concn of **1a** (M)	catalyst (mol %)	yield of **2a**[a] (%)
1	0.25	**I** (10)	29
2	0.11	**I** (10)	48
3	0.01	**I** (10)	59
4	0.01	**I** (5)	53
5	0.04	**II** (5)[b]	55
6	0.01	**I** (5)[c]	60
7	0.01	**I** (10)[c]	70
8	0.01	**I** (10)[d]	85

[a] Isolated yields. [b] Carried out in toluene, 60 °C. [c] From a 0.04 M solution. [d] From a 0.01 M solution added by a syringe pump.

This positive effect of dilution on the reaction yields was not surprising. As reported in the literature,[9] low substrate concentration can indeed minimize the formation of dimeric alkene products, arising from undesired cross-metathesis processes.

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(10) Reaction catalyzed by the molybdenum complex [Mo(CHCMe$_2$Ph)(NAr)(OCMe(CF$_3$)$_2$)$_2$] (Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$): Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324−7325.

(11) After three vacuum/argon cycles performed on the appropriate amount of [RuCl$_2$(PCy$_3$)$_2$(=CHPh)] in a Schlenk tube, a solution of the acrylate ester in anydrous dichloromethane is tranferred via cannula and the reaction mixture kept under reflux for 20−24 h.

An important parameter to be considered is the stability of the catalyst **I** in the reaction mixture. Since the alkylidene ruthenium complexes are known to decompose via second-order pathways, which are obviously concentration dependent,[13] a lower concentration may also imply a longer lifetime of the catalyst. In fact, when the catalyst load was reduced to 5% for [**1a**] = 0.01 M, there was no significant decrease in yield (entry 4, Table 2).

Importantly, when the reaction was performed using the second-generation Grubbs' catalyst **II** (5 mol %) in dichloromethane under conditions identical to those in entry 4, the RCM product was isolated only in 15% yield. A further reaction of **1a** (0.04 M) using catalyst **II** in toluene at 60 °C (entry 5, Table 2) raised the yield to 55%, a value which is comparable to those obtained using complex **I**.[14]

Once we verified the unexpected tendency of the diolefinic acrylic ester **1a** to cyclize in the presence of **I**, we attempted to further optimize the reaction yields by trying to combine beneficial effects from dilution and from a continuous supply of fresh catalyst solution. This has been accomplished by slow addition from a syringe pump of a solution of complex **I** to a refluxing solution of the substrate, both in dichloromethane.[15] When a 0.04 M dichloromethane solution of complex was added to a 0.01 M solution of **1a**, over a period of 6 h, and the reaction mixture kept at reflux for an additional 12 h, the butenolide **2a** was obtained in 60% yield (**I** in 5 mol %) or 70% yield (**I** in 10 mol %), respectively.[16] Upon reducing the concentration of **I** in the syringe to 0.01 M (**I** in 10 mol %), the yield increased to 85%.

Having found appropriate experimental conditions that allowed the RCM of the diolefin **1a** to be performed with excellent yields of isolated product, using the first-generation Grubbs' catalyst, the same procedure outlined in entry 8 of Table 2 was extended successfully to the preparation of butenolides with different alkyl substituents at the 5 position **2b**−**e** (Table 3) in good yields.

Table 3. RCM Reaction of **1a**−**e** Catalyzed by Complex **I**

1 **2**

entry	substrate	R^1	R^2	product (yield, %)[a]
1	**1a**	*n*-Bu	Me	**2a** (85)
2	**1b**	*n*-Pn	Me	**2b** (90)
3	**1c**	Cy	Me	**2c** (78)
4	**1d**	*i*-Pr	Me	**2d** (47)
5	**1e**	*n*-Bu	$CH_2OSi(i\text{-}Pr)_3$	**2e** (57)

[a] Isolated yields.

We also ran the cyclization of compound **1e** (entry 5). This was performed in order to test if the RCM conditions were compatible with a different group on the allylic portion double bond suitable of further manipulation. We chose the triisopropylsilyl ether derivative **5e,** a good substrate for an RCM-based synthetic approach to the 4-hydroxymethyl-5-alkyl-2(5*H*)-furanone structures, which are found in many interesting natural compounds showing bactericide properties.[17]

The procedure presented here shows the effectiveness of the Grubbs' first-generation complex **I** in RCM reaction of diolefins bearing acrylic and *gem*-disubstituted double bonds at the α and ω positions.

So far, the formation of cyclic trisubstituted olefins catalyzed by the first-generation catalyst **I** or related complexes has been reported to occur in the case of methyl-substituted dienes derived from malonic esters or from amides,[1,6,18] in which the *gem*-diester or nitrogen substitution on the hydrocarbon chain backbone favors a substrate conformation suitable for cyclization. Moreover, to the best of our knowledge, the ring-closing metathesis reaction of diolefins derived from acrylic esters either requires assistance by the Lewis acid $Ti(O\text{-}i\text{-}Pr)_4$,[7a−d,19] the use of the more active second-generation Grubbs' catalyst **II**,[3b] or of nitro-substituted Hoveyda−Grubbs ruthenium carbenes.[20] As a matter of fact, the synthesis of unsaturated five-membered heterocycles with alkyl substituents on the double bond is considered to be mainly the domain of the *N*,*N*′-disubstituted heterocyclic alkylidene ruthenium catalysts.[1c,d,3b,21]

In addition to the entropy of reaction, which assists all RCM processes due to the formation of two molecules from the diolefin,[1c,d,3a] it is reasonable to think that the reaction of the specific substrates **1** is favored by the short length of the chain connecting the two reactive double bonds and by the stability of the five-membered lactone products.[22] These and other factors may contribute to overcome the intrinsic low efficiency of catalyst **I** with respect to catalysts of type **II**.

Thus, this work expands the scope of the RCM process in the synthesis of substituted γ-lactones and reinforces the

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(14) The higher reactivity of complex **II** in toluene than in dichloromethane has already been documented; see ref 3b.

(15) Dropwise addition of the title complex has been successfully used by Brown et al. in the preparation of naturally occurring 6-substituted-5,6-dihydro-2*H*-pyran-2-ones via RCM, as reported in ref 7e.

(16) The addition of the catalyst solution can be performed using a dropping funnel or upon slow continuous addition from an infusion pump.

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concept that not one single catalyst is superior to all others in all possible applications.[20]

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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