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Ring Closing Metathesis of Vinyl Glycine Derivatives

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Dedicated to Professor Gottfried Heinisch on the occasion of his 60th birthday

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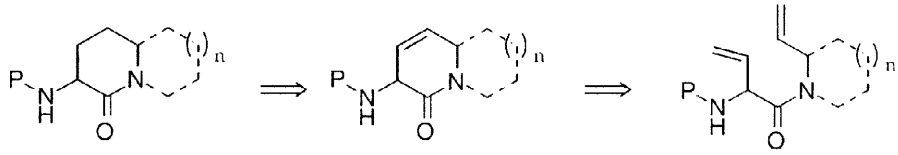
Abstract : Ring closing metathesis of vinyl glycine derivatives using Grubbs' ruthenium catalyst has been performed successfully. The reaction works well with N-allyl amides derived from N-protected vinyl glycines. The use of a trityl protecting group allows the reaction to be performed successfully with the otherwise unreactive N-allyl vinyl glycine ester. © 1998 Elsevier Science Ltd. All rights reserved.

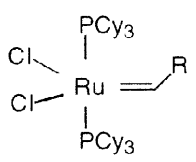
Ring closing metathesis (RCM) has become a very powerful method for the construction of carbocycles and heterocycles.[1,2] This fairly recent development has been boosted by the discovery of efficient ruthenium alkylidene catalysts which show a high tolerance towards many functional groups.[3] As part of a study of new conformationally restricted peptidomimetics **1**, we became interested in RCM reactions of vinyl glycinamides **2** which should be readily prepared from a protected vinyl glycine derivative and an allylic amine (Scheme 1).



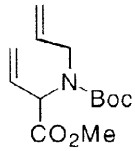
1 (P = Protecting Group) **2**

Scheme 1

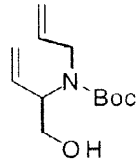
In a recent study,[2g] Grubbs and co-workers found that N-allyl vinyl glycine ester **4** did not undergo the RCM reaction after exposure to the ruthenium catalyst **3a**. This lack of reactivity was assigned to the presence of an acidic proton at Cα. Indeed the corresponding glycinol derivative **5** underwent the RCM reaction.[4]



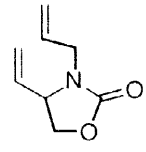
catalysts: **3a** (R = Ph); **3b** (R=CH=CH-Ph)



4 (unreactive)



5 (reactive)



6 (unreactive)

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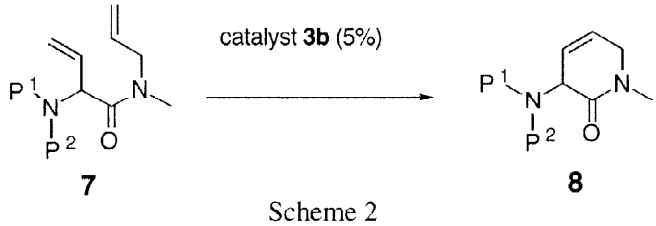
However, a cyclized derivative of vinyl glycinol **6** was also unreactive.[4] This suggested to us that the inertness of **4** and **6** probably resulted from a conformationally dependent electronic effect which deactivates the double bond of vinyl glycine.

In compounds **7**, the carbonyl group is part of an amide group which is less electron-withdrawing than the ester function of **4**. Accordingly, **7a** underwent the RCM reaction in refluxing benzene (Scheme 2, Table 1). Replacement of the hydrogen atom by a benzyl group increased the yield to 60 %. However when the amine substituent was sufficiently nucleophilic, as in **7c**, the RCM reaction was completely suppressed. This is probably due to the coordination of the amine group to the ruthenium complex.[5]

Coordination to the metal could be suppressed by protonation of the amine group as in **7d** or by the use of a bulky group as in **7e**. Indeed, in both cases the RCM reactions took place, yielding compounds **8d** and **8e** respectively in 45 % and 65 % yield.



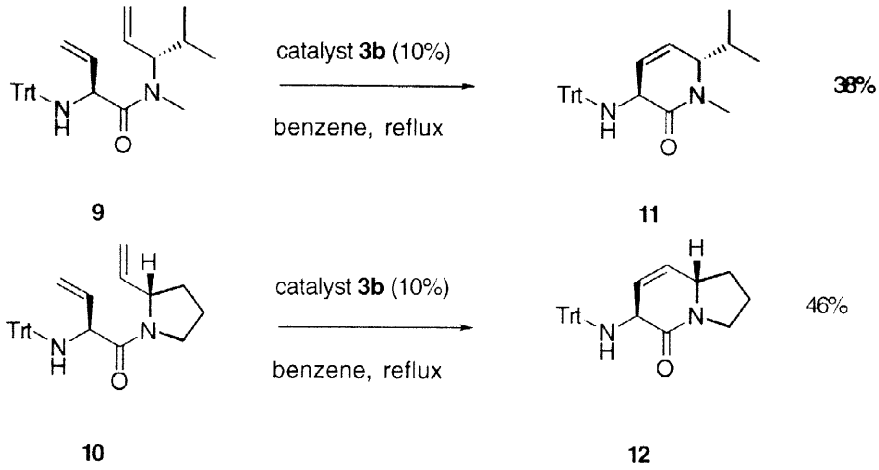
7 **8**

Scheme 2

Table 1 : RCM reactions of **7** in the presence of catalyst **3b**

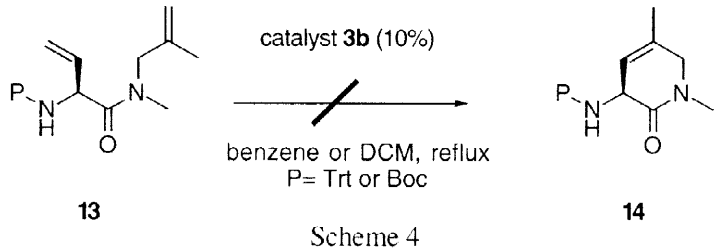
Compound	P1	P2	Conditions	Yield of **8** (%)	Yield of **7** (%)
7a	Boc	H	benzene, reflux	41	-
7b	Boc	$PhCH_2$	benzene, reflux	60	-
7c	H	$PhCH_2$	benzene, reflux	-	58
7d	H	$PhCH_2$	CF_3CO_2H (1 equiv.) benzene, reflux	45	23
7e	H	Trt	benzene, reflux DCM, reflux	65 67	- 15

The use of a trityl protecting group was also beneficial to the RCM reactions of the more substituted vinyl glycinamides **9** and **10** : compounds **11** and **12** were obtained respectively in 38 and 46 % yield (Scheme 3).



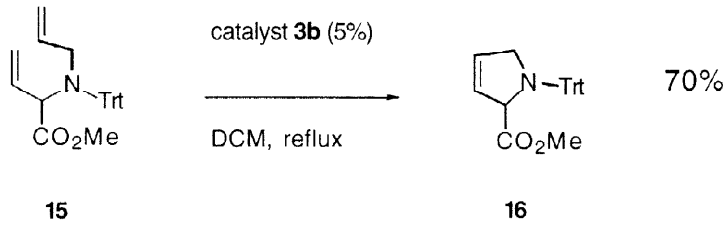
Scheme 3

However the substituted olefins **13** (P = Boc or P = Trt) did not undergo any RCM reactions and in both cases the starting material was recovered quantitatively.



Scheme 4

Our observations also apply to the RCM reactions of vinyl glycine ester of type **4**. As mentioned earlier, the Boc-protected derivative did not undergo the RCM reactions.[2g] We found that the N-trityl protected derivative **15** gave the dehydroproline **16** in a gratifying 70 % yield (Scheme 5).



Scheme 5

This study has thus removed one notable limitation of the RCM strategy which is now applicable to vinyl glycine derivatives. These findings are now being extended to other substrates and applied to the synthesis of new classes of peptidomimetics.

ACKNOWLEDGMENTS

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6. Typical procedure (compound **12**) :
   Under argon atmosphere, to a solution of compound **10** (41 mg, 0,1 mmol) in 1 ml of degassed benzene, was added 11 mg (10 %) of Grubbs' catalyst **3** (R= Ph). The solution was refluxed overnight and after cooling to room temperature the solvent was removed *in vacuo*. The crude compound was directly chromatographied on silicagel (cyclohexane - ethyl acetate 10 : 1 → 2 : 1) to give 18 mg of compound **12** (46 %) and 11 mg of unreacted starting material **10**.
   HMRS (Fab +) : calculated for $C_{27}H_{27}N_2O$: 395.2123; found : 395,2119 (Δ = 1,1 ppm).
   ^1H (500 MHz) and ^{13}C NMR (125 MHz) :