Pergamon

Tetrahedron Letters, Vol. 37, No. 45, pp. 8249-8252, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01881-3

Solid Phase Ring-Closing Metathesis: Cyclization/Cleavage Approach towards a seven membered Cycloolefin

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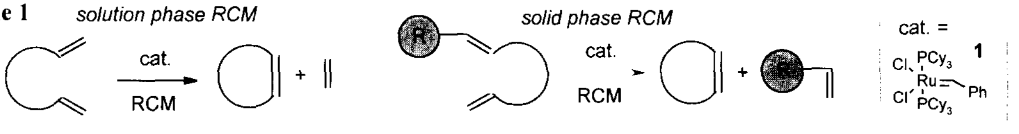
Abstract: The application of solid phase ring-closing metathesis (RCM) in a cyclization/cleavage strategy was demonstrated for the first time by the successful synthesis of the seven membered cycloolefin **4**. Probably due to intermolecular metathetical dimerizations at the resin, **4** could not be obtained in higher yields than 54%. Copyright © 1996 Elsevier Science Ltd

In conjunction with the rapidly growing interest in combinatorial chemistry, solid phase mediated organic synthesis is under intensive investigation now.[1] Solid-supported reactions are characterized by simple filtration/washing steps, thus allowing the use of large excess reagents to drive reactions to completion. Furthermore, solid-supported reactions can be automated rather easily. Anchoring of the first building block at a solid support is usually done via a functional group present in the target structure such as a carboxylate, alcohol, etc. This functional group at the first building block is covalently bound to a linker which may be regarded as an immobilized protective group. After completion of the synthesis cleavage from the resin (deprotection) liberates the product, bearing the functional group by which it was attached. In certain cases, the presence of such an anchoring functional group is undesired. Recently, two examples of "traceless" linkers, *i.e.* leaving a proton behind, have been described.[2] A different concept to avoid undesired functionalities, after solid phase synthesis, is the cyclization/cleavage approach. This concept is well known for the solid supported synthesis of lactams and lactones, formed after intramolecular aminolysis or transesterification of an ester linkage.[3] A second advantage of a well designed cyclization/cleavage strategy is the high purity of the detached final products; if the required functionality for cyclization is introduced with the last building block, only the anticipated products will cleave from the resin.

In this communication we describe the application of solid phase ring-closing metathesis (RCM) in the cyclization/cleavage approach towards cycloolefins.[4] With the recently discovered versatile ruthenium carbene complex catalyst **1** by Grubbs and co-workers[5], RCM seems to be the most practical method for (macro)cyclizations.[6] RCM of a bis terminal diene gives a cycloolefin with loss of a molecule of ethylene (Scheme 1).

Scheme 1



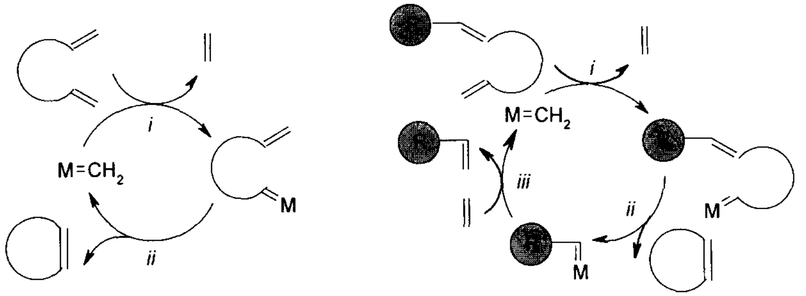
RCM of a diene attached at one end to a solid support, as demonstrated in Scheme 1, liberates a cycloolefin and gives a terminal olefin at the resin. Close examination of the accepted reaction mechanism reveals that after RCM the catalyst is immobilized at the resin (Scheme 2). As a consequence, the catalyst is not available for other immobilized substrates (due to the infinite dilution effect of the resin). Therefore, with solid-supported RCM addition of a terminal olefin such as ethylene will be necessary to detach the catalyst, thus closing the catalytic cycle again (step *iii* in Scheme 2).

We tested the solid phase RCM cyclization/cleavage concept by the synthesis of the 7-membered cycloolefin **4**, which serves as a model compound, from diene **2** (R=1% DVB polystyrene) (Scheme 3).[7]

To prove that the anticipated linking strategy[8] for attachment to the resin would still allow efficient RCM, initial experiments were carried out in solution with diene **3** (R=Et).

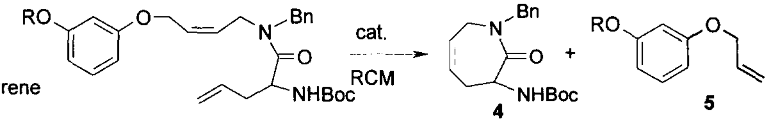
Scheme 2.

Solution and solid phase RCM catalytic cycles



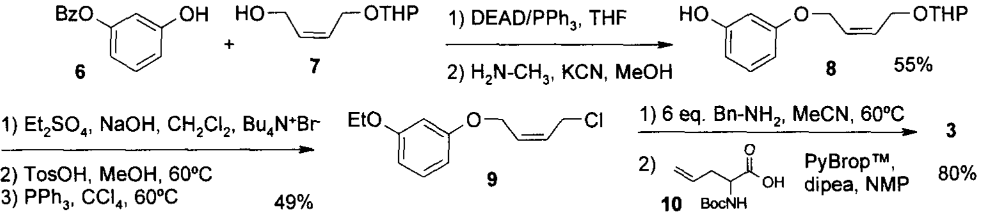
Scheme 3

2: R=1% crosslinked methylene polystyrene
3: R=Et



The synthesis of the solution phase RCM precursor **3** started by Mitsunobu etherification of mono resorcinol ester **6** with allylic alcohol **7** followed by removal of the benzoate protective group to give mono resorcinol ether **8** in 55% overall yield (Scheme 4).

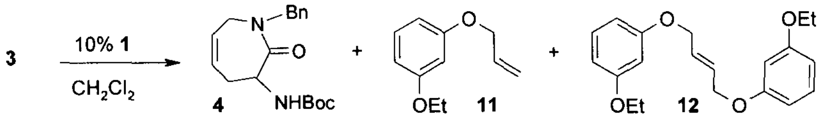
Scheme 4



Etherification of phenol **8** with diethylsulfate under phase transfer conditions and subsequent removal of the THP protective group, followed by treatment of the alcohol with PPh_3 in CCl_4 gave allylic chloride **9** in 49% overall yield. Nucleophilic substitution of the chloride with benzylamine followed by PyBrop™ mediated acylation of the obtained 2° amine with *rac* *N*-Boc-allylglycine **10** gave solution phase RCM precursor **3** in 80% overall yield.[9]

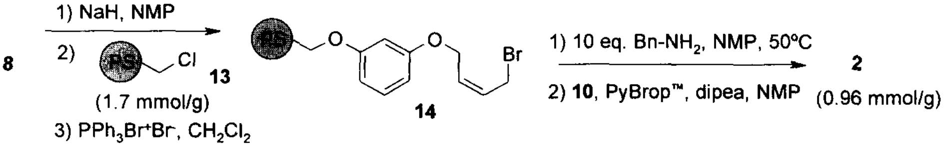
RCM of **3** in CH_2Cl_2 (0.02 M) using 10 Mol % of **1** at 25°C under a nitrogen atmosphere for 20 h gave 97% of the expected cycloolefin **4**[10], after purification by column chromatography (Scheme 5).[11]

Scheme 5



Also resorcinol ether **11** was isolated together with **12**, resulting from metathetical dimerization (cross metathesis), in a total yield of 98% in a 1.5:1 ratio. After the successful application of the linker strategy in solution the solid phase RCM precursor **2** was prepared from chloromethylated (Merrifield) resin **13** (Scheme 6).

Scheme 6



Alkylation of the sodium phenolate of **8** with 1% DVB Merrifield polystyrene **13** (loading 1.7 mmol/g) in N-methyl pyrrolidinone (NMP) resulted in 84% yield (yield determined by weight).[12] Allylic bromide **14** was synthesized in one step from the corresponding THP ether by treatment with $PPh_3Br^+Br^-$ in CH_2Cl_2.[13] Substitution of the allylic bromide with benzylamine in NMP at 50°C, followed by PyBrop™ mediated acylation of the 2° amine with *rac* *N*-Boc-allylglycine **10** gave the solid phase RCM precursor **2** with a final loading of 0.96 mmol/g (determined by weight).[14] Subsequent synthetic steps were analyzed by comparing the microIR spectra of the functionalized resins (Scheme 6) with those of the corresponding compounds in solution (Scheme 4).[15] Besides microIR, also HR MAS NMR[16] has been applied for the final characterization of **2** (see figure).

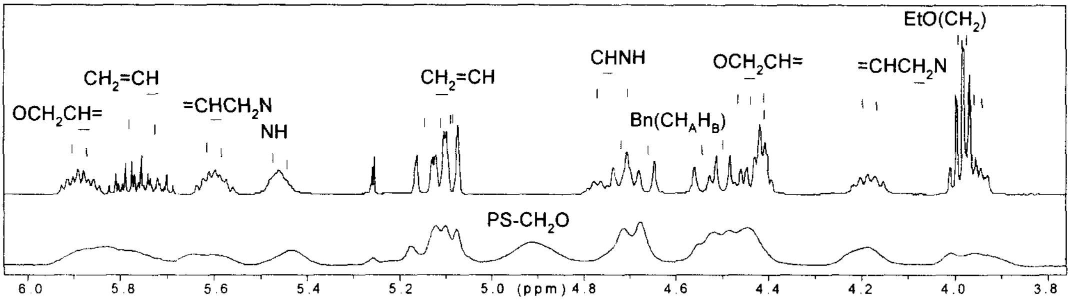
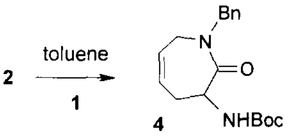


Figure. *HR MAS 400 MHz ^1H NMR spectrum (bottom) of* **2** *(swollen in CD_2Cl_2) compared with the fully assigned 500 MHz ^1H NMR spectrum of* **3** *(selected regions only). Two conformers are observed. For more details (including 2D NMR results) see ref. 15c.*

Solid phase RCM was performed using several conditions.[17] We have varied the amount of catalyst, temperature and the reaction time. After stirring for 7 days using 14% catalyst and ethylene as a cofactor only 5% of **4** was isolated (Scheme 7).[18]

Scheme 7



entry	% cat. **1**	cofactor	T(°C)	reac. time	yield **4**
1	14	ethylene	23	7 days	5%
2	30	,,	23	2 days	44%
3	12	1-octene	23	7 days	32%
4	12	,,	50	2 hours	37%
5	100	-	50	16 hours	54%

Despite the low yield we were pleased to find that indeed metathetical cyclization/cleavage could be accomplished. MicroIR analysis of the residual resin only revealed starting material. Increasing the amount of catalyst to 30% (entry 2) gave a 9-fold higher yield (5% → 44%). This observation suggests that catalyst recycling by ethylene addition proceeds sluggishly. Indeed, substitution of ethylene for 1-octene (entry 3) gave a 6-fold better yield (three catalytic cycles completed). Application of higher temperatures only resulted in shorter reaction times. The highest obtainable yield is already reached after 2 hours at 50°C (entry 4). Because we assumed that the moderate yields were mainly the result of irreversible immobilization of the ruthenium carbene complex an experiment was performed using 100% of **1** (entry 5). Unexpectedly, after allowing the reaction to stir for 16 hours at 50°C only 54% of **4** was isolated. Again, microIR of the residual resin only revealed starting material (although with a lower loading). A second RCM experiment with the residual resin from entry 5 only gave trace amounts of product. These observations suggest that intermolecular metathetical dimerizations at the resin had occurred, giving immobilized macrocyclic structures. With the high capacity Merrifield resin used (1.7 mmol/g) and the powerful metathesis macrocyclization reaction, dimerization is likely to occur. However, this subtle transformation cannot be detected by microIR spectroscopy. Experiments to liberate the residual material by BBr_3 mediated ether cleavage only gave complex mixtures which could not be further characterized.

In summary, with the successful solid phase synthesis of **4** we have demonstrated the application of RCM in the cyclization/cleavage approach towards cycloolefins.

Work is now in progress using lower capacity resins which may prevent intermolecular reactions, due to the higher pseudo dilution effect. Alternative olefin cofactors for catalyst recycling will be considered to optimize the catalyst turnover number. Finally, we will apply solid phase cyclization/cleavage RCM for the synthesis of combinatorial cycloolefin libraries.

Acknowledgement: We thank Dr. Hans Meissner, Dr. Wouter Iwema Bakker (Solvay Pharmaceuticals, Weesp) and Dr. Rint Sybesma (Technical University of Eindhoven) for their helpful and stimulating discussions. Drs. John Reichwein (University of Utrecht) is acknowledged for his accurate experimental contribution.

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3 Smith, A.L.; Thomson, C.G.; Leeson, P.D. *Bioorg.Med.Chem.Lett.* **1996**, 6, 1483-1486, and references cited therein.

4 The following paper, which has been published after completion of our manuscript, describes solid phase RCM and cross metathesis yielding immobilized cycloolefins and asymmetric *vic*-disubstituted olefins, respectively; Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew.Chem.* **1996**, 108, 2111-2112.

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6 For excellent reviews, see: a) Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc.Chem.Res.* **1995**, 28, 446-452. b) Schmalz, H.G. *Angew.Chem.Int.Ed.Engl.* **1995**, 34, 1833-1836. See also: Fürstner, A.; Langemann, K. *J.Org.Chem.* **1996**, 61, 3942-3943.

7 Miller, S.J.; Grubbs, R.H. *J.Am.Chem.Soc.* **1995**, 117, 5855-5856.

8 The additional resorcinol unit introduces the synthetically versatile phenol moiety which allows etherification by the mild Mitsunobu reaction. This method was initially chosen for attachment of **8** at alcohol type resins (see ref. 12).

9 **3**; R_f 0.45 (EtOAc/hexanes=1/2). ^{1}H NMR ($CDCl_3$) see figure. EIMS, *m/z* (relative intensity) 494 ($[M]^+$, 1), 357 ($[M\text{-}EtOPhO]^+$, 70), 91 ($[C_7H_7]^+$, 100). FTIR (film) ν (cm^{-1}) 3420 and 3305 (NH), 2980 (CH_3), 1705 (C=O, carbamate), 1640 (C=O, 3° amide), 1180 (C-O).

10 **4**: R_f 0.35 (EtOAc/hexanes=1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H, PhH_5), 5.90 (d, 1H, J=7 Hz, NH), 5.75-5.69 and 5.64-5.57 (2xm, 2H, HC=CH), 4.96 (ddd, 1H, J=12 Hz, J=7 Hz and J=4 Hz, α-H), 4.71 and 4.61 (AB, 2H, J_{AB}=15 Hz, CH_2Ph), 4.34-4.26 (m, 1H, C=CH-CH$\underline{H}$-N), 3.35 (dd, 1H, J=17 Hz and J=8 Hz, C=CH-C$\underline{H}$H-N), 2.72-2.64 (m, 1H, C=CH-CH$\underline{H}$-C), 2.32-2.23 (m, 1H, C=CH-C$\underline{H}$H-C), 1.46 (s, 9H, $C(CH_3)_3$). EIMS, *m/z* (relative intensity) 316 ($[M]^+$, 5), 260 ($[M\text{-}C_4H_8]^+$, 55), 91 ($[C_7H_7]^+$, 100).

11 Grubbs *et al.* (see ref. 7) described RCM of a bis terminal diolefin to give a similar seven membered lactam in only 50% yield. The lower yield obtained by Grubbs *et al.* (50% *vs.* 97%) might be explained by the fact that in our approach only one terminal olefin is present at which initial metallation occurs preferably. Probably, efficient product formation is only possible by initial reaction at the allyl glycine double bond.

12 Mitsunobu type etherification of resorcinol monoether **8** with 1% DVB hydroxyethyl polystyrene or TentaGel® S-OH using several conditions failed. MicroIR analysis on both resin types revealed the presence of urethane carbonyls, presumably originating from 1,2-diethoxycarbonyl hydrazide fragments.

13 Schwarz, M.; Oliver, J.E.; Sonnet, P.E. *J.Org.Chem.* **1975**, 40, 2410-2411. Synthesis of the allylic chloride via the allyl alcohol, as performed in solution, failed. Removal of the THP group proceeded quantitatively, but transformation into the allylic chloride, using the same conditions as for the synthesis of **9**, could not be accomplished.

14 **2**: ^{1}H NMR ($CDCl_3$) see figure. FTIR microspectroscopy (Nicolet Magna 550 FTIR coupled with Nic-Plan IR microscope in transmission mode) ν (cm^{-1}) 3420 and 3295 (NH), 2975 (CH_3), 1710 (C=O, carbamate), 1650 (C=O, 3° amide), 1175 (C-O); polystyrene at 3060, 3025, 2850 and 700.

15 With FTIR microspectroscopy only *one* 90μm bead is analyzed. One analysis only takes 10 min. (including sample preparation). Due to the high loading it was even necessary to flatten the beads (with a diamond anvil cell) to avoid too intensive absorptions. See: Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, 52, 843-848.

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17 All solid phase RCM reactions were carried out on a 0.5 g resin scale in capped 10 mL V-vials, loaded with a small magnetic stirring bar. Heating was performed by placing the vials in a temperature controlled oil bath. Ethylene, as used in entries 1 and 2, was added by passing a gentle stream through the suspension for 10 minutes at room temperature followed by addition of the catalyst and capping of the vial. Work-up was accomplished by filtration followed by subsequent washings with 5 mL CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, Et_2O and CH_2Cl_2. The resin was allowed to swell/shrink for 5 min. before each filtration. The combined filtrates were concentrated *in vacuo* followed by passing the residue through a short path of silica (hexanes/EtOAc=4/1), to remove the catalyst remainings. In entries 3 and 4 also 7-tetradecene was isolated in yields of 40% and 62%, respectively, resulting from metathetical dimerization of 1-octene.

18 It was ruled out that the formed product gave ring-opening metathesis with ethylene. Stirring of **4** with catalyst **1** in an ethylene atmosphere in toluene at room temperature for 2 days did not show any conversion.

(*Received in UK* 5 *September* 1996; *accepted* 20 *September* 1996)