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# Microwave enabled external carboxymethyl substituents in the ring-closing metathesis

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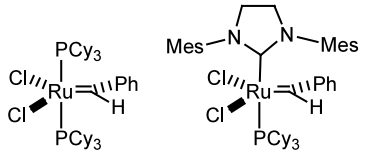
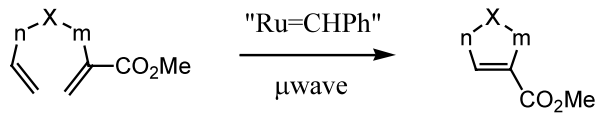
**Abstract**—The ring-closing metathesis of diolefin substrates containing an external carboxymethyl substituent is presented. The reaction is enabled through microwave irradiation allowing greatly enhanced yields and conversion rates. The reaction results in the formation of carboxymethyl substituted dihydropyrroles, dihydrofurans, and cyclopentenes. In certain cases, pyrroles are formed through further in situ oxidation. 

The olefin metathesis reaction resulting in ring formation (ring-closing metathesis or RCM) has become an important and powerful reaction within the field of synthetic organic chemistry.[1] The ruthenium catalysts developed by Grubbs (**1** and **2**, Scheme 1)[2] have been utilized for RCM based ring formation as a key step in numerous natural product synthesis.[3] The reaction is very general in the formation of many ring sizes and types,[4] with notable exceptions in the eight member ring size cases.[5,6] In addition, it is fairly general to functionality that is internal to the new ring system being formed. However, the reaction does show limitations to external substituents.[6] So far, only substituents with little or no steric or electronic bias are compatible (i.e. Me or Et). External groups with an electronic bias ($CO_2Me$, OMe, CN, Br) result in little to no yield of the RCM product.[6,7] Adding additional substitution external to the newly formed double bond would allow the formation of an activated system enabling further unique functionalization.




Grubbs Type I (**1**) Grubbs Type II (**2**)

**Scheme 1.**




**Scheme 2.**

As part of a drug discovery program, we became interested in exploring the carboxymethyl substituent via 2-substituted methacrylate systems (Scheme 2). Although the only report of this system in the ring-closing metathesis resulted in a low conversion (~5%), we extrapolated that we could realize our goal to access this system by applying microwave irradiation to raise the yield and apply this reaction to other systems.[8]

Investigations into the conditions suitable for ring closing metathesis reactions of these substrates under microwave irradiation were initiated. The *N*-*p*-toluenesulfonyl substrate (**4a**, Table 1) with the added carboxymethyl substituent was investigated under a variety of conditions. Treatment with Grubbs type I catalyst (**1**) resulted in only a trace of the desired dehydropyrrolidine product (**5a**). Switching to the Grubbs type II catalyst (**2**) gave slightly better results, and at room temperature the reaction proceeded to about 40% conversion even after prolonged exposure. Heating to 50°C, resulted in conversion to about 75% after 5 h, but proceeded no further. We then investigated irradiation in the microwave, which gave more promising results.[9] Irradiation for 5 min at 50°C gave 85% conversion, and at 150°C for 5 min gave 97% conversion. Further beneficial effects of the microwave can be seen in comparison reaction times and conversions. In condi-

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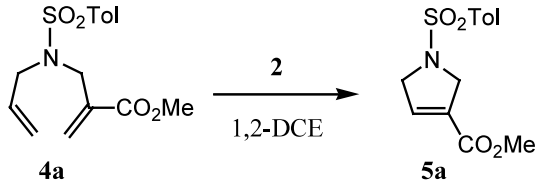
**Table 1.** Conversion of **4a** to **5a** with 3% of **2** in 1,2-DCE[9–11]




**4a** **5a**

| Conditions (0.025 M in **4a**) | Temperature (°C) | % Conversion (time)[a] |
|---|---|---|
| rt | 24 | 6 (5 min) |
| rt | 24 | 30 (6 h) |
| rt | 24 | 37 (20 h) |
| Thermal | 50 | 62 (5 min) |
| Thermal | 50 | 75 (20 min) |
| Thermal | 50 | 75 (5 h) |
| μwave, 0–10 W, 1 psi | 50 | 85 (5 min) |
| μwave, 60–80 W, 60 psi | 150 | 97 (5 min) |

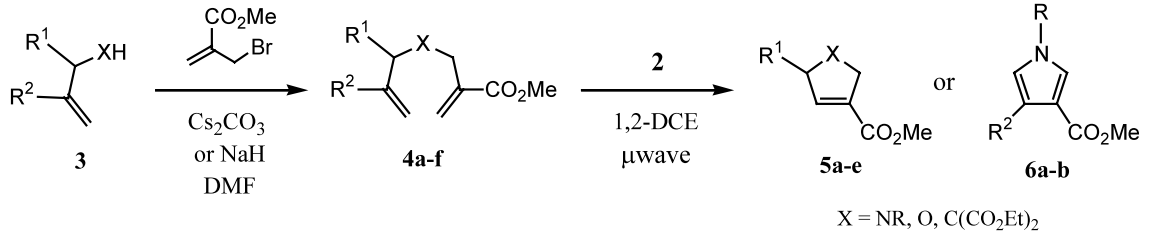
[a] % Conversions determined by $^1$H NMR analysis of the crude reaction mixture.

tions not involving microwave heating, conversion reaches a maximum after several hours, presumably due to lower catalyst turnover or catalyst decomposition. At room temperature the maximum conversion is 37% and at 50°C it is 75%, compared to 85 and 97% after 5 min using the microwave. These results clearly show that microwave heating results in further conversions in shorter time either overcoming catalyst decomposition or increasing catalyst turnover.

With evidence that we were observing a rate acceleration and increase in catalyst efficiency for this ring closure via microwave irradiation we investigated the substrate variability (Scheme 3, Table 2[9–13]). We began our study by preparing carboxymethyl containing substrates based on known analogous bisolefin compounds which give successful ring closing metathesis reactions. We focused on the various five member ring cases.[1,4,6] Alkylations with methyl-2-(bromomethyl) acrylate were carried out with a variety of allylated substrates (**3a–f**, Scheme 3) with carbon, oxygen, and nitrogen nucleophiles in the presence of cesium carbonate or sodium hydride as base. Analogs were prepared that were precursors to dihydropyrrole (**4d–f**), dihydrofuran (**4c**), and cyclopentene (**4b**) systems. We ran reactions at either 100 or 150°C, with a catalyst amount of 3, 6, or 12 mol%, and irradiation times of 5 or 10 min with the goal of obtaining product yields after purification. The *N*-*p*-tosylsulfonamide substrate (**4a**) gave 82% of the dehydropyrrolidine (**5a**).[11,12] The diallyl malonate substrate **4b** followed suit and gave a 100% conversion and 56% isolated yield of the cyclopentene ester **5b** when exposed to the same conditions. The lower isolated yield is due presumably to product volatility. We were gratified to see this conversion, since Grubbs reported that this substrate gave ~5% conversion when using the type I catalyst (1).[6] Finally, the reaction translated to the dihydrofuran system **5c** with bisolefin **4c** in 82% isolated yield under slightly lower temperature (100°C).[12,13]

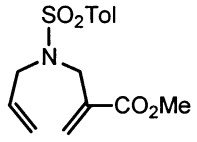
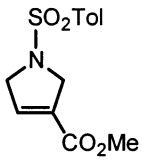
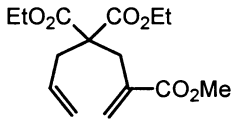
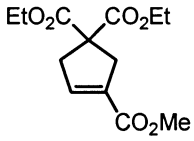
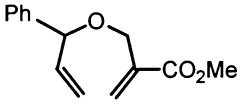
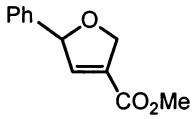
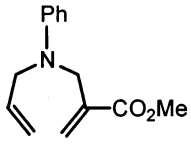
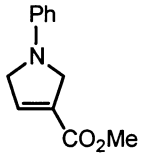
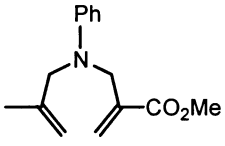
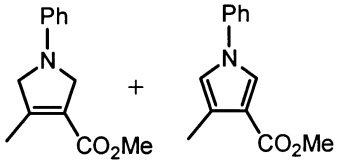
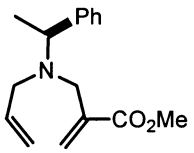
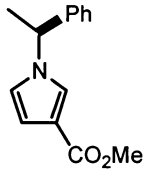
We next considered several nitrogen substrates which would give dehydropyrrolidines with different groups on nitrogen.[12,13] This type of substrate could be incorporated as a 3,4-dehydro-isoproline peptidomimetic scaffold or be utilized as an intermediate to construct alkaloid natural products.[14,15] We were also interested in determining if the basicity would effect the RCM in these systems. We discovered that the reaction was successful, but were surprised to find that we isolated the pyrrole products (**6a**,**b**) along with the expected dehydropyrrolidines. The *N*-phenyl substrate translated cleanly in a similar fashion to the *N*-tosyl result (entry 1) resulting in a 70% yield of the dehydropyrrolidine **5d**. The methallyl-acrylate substrate **4e** was exposed to these conditions and we were intrigued to find that not only did the reaction provide a successful RCM reaction resulting in a tetrasubstituted olefin product **5e** (16%), but also the corresponding 2,3,5-trisubstituted pyrrole **6a** (48%) as the major product.[13] The pyrrole formation can be explained through an RCM followed by an in situ oxidation. The final example, the *N*-(*S*-α-methylbenzyl) substrate **4f** gave the pyrrole product **6b** exclusively in 76% isolated yield.[13] When comparing substrates (**4a** to **4d** to **4f**), it is clear this oxidation is dependent upon the nitrogen basicity.

In conclusion, we have provided an example of the microwave accelerated ring-closing metathesis reaction with an external carboxymethyl substituent forming products with an activated olefin. In the case of five-membered rings, dehydropyrrolidines, dihydrofuran, cyclopentene, and pyrrole substrates are formed in good yields. The microwave allows shorter conversion times and higher conversion rates. *Also, to our knowledge, this is the first reported pyrrole formation utilizing the RCM*. Further progress in these areas will be the subject of future reports.




**Scheme 3.**

**Table 2.**

| Entry | Reactant (4) | Product (5 or 6) | Conditions[a] | Isolated Yield of 5 or 6 (%)[b] |
|---|---|---|---|---|
| 1 |  **4a** |  **5a** | 0.025M in **4a**<br>3 mole % of **2**<br>150°C, 60-80W,<br>60 psi, 10 min. | 82 |
| 2 |  **4b** |  **5b** | 0.05M in **4b**,<br>6 mole % of **2**<br>150°C, 60-80W,<br>60 psi, 5 min. | 56 |
| 3 |  **4c** |  **5c** | 0.025M in **4c**,<br>6 mole % of **2**<br>100°C, 40-60W,<br>40 psi, 5 min. | 78 |
| 4 |  **4d** |  **5d** | 0.05M in **4d**,<br>3 mole % of **2**<br>150°C, 60-80W,<br>60 psi, 5 min. | 70 |
| 5 |  **4e** |  **5e** **6a** | 0.05M in **4e**,<br>12 mole % of **2**<br>150°C, 60-80W,<br>60 psi, 5 min. | 64<br>(**5e**:**6a** 16:48) |
| 6 |  **4f** |  **6b** | 0.025M in **4f**,<br>6 mole % of **2**<br>150°C, 60-80W,<br>60 psi, 5 min. | 76 |

[a]All reactions carried to >97% completion. [b]Yields determined by mass balance on product purified by flash chromatography.


## Acknowledgements

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9. All microwave reactions were performed in the CEM Discover™ unit produced by the CEM Corporation, Mathews, N.C. Settings and readings for power (W), time of irradiation, and pressure were taken from the instrument. Reactions were performed in an 8 mL sealed vessel equipped with a Teflon stir flea. The vessels were sealed with septa and aluminum crimp provided by the vendor.
10. All new RCM products gave satisfactory $^{1}H$ NMR, MS, and $^{13}C$ NMR/DEPT spectra consistent with the structural assignments.
11. Procedure for the ring-closing metathesis of **4a** to give **5a**. Substrate **4a** (31 mg, 0.1 mmol) was dissolved in 4 mL of 1,2-dichloroethane in a pressure tube containing a magnetic stir bar. Grubb's II catalyst (**2**) (2.6 mg, 0.003 mmol) was then added into the pressure tube. The pressure tube was then sealed and heated to 150°C (60–80 W, 60 psi) for 10 min. The solvent was removed by rotary evaporator, and the crude product was purified by flash chromatography (hexane/ethyl acetate = 9/1) to provide **5a** as a white solid (23 mg, 82% yield). Physical data for **5a**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 21.91 ($CH_3$), 52.34 ($CH_3$), 53.9 ($CH_2$), 55.85 ($CH_2$), 127.85 (CH), 130.32 (CH), 136.47 (CH); MS (ESI): 585 (2M+23), 304 (M+23), 282 (M+H).
12. General procedure for microwave-assisted RCM products in Table 2. Substrate (**4a**–**f**) was dissolved in 4 mL of 1,2-dichloroethane in a pressure tube containing a magnetic stir bar to yield solutions with a concentration between 0.025 and 0.05 M. The catalyst (**2**) was then weighed into the pressure tube. The pressure tube was then sealed and heated under selected microwave conditions. The reaction conversion was monitored and analyzed by LC/MS. The solvent was removed by rotary evaporator, and the crude product was purified by flash chromatography (hexane/ethyl acetate = 9/1 for entries 1 and 2; hexane/ethyl acetate = 20/1 for entries 4 and 6; hexane/ethyl acetate = 100/1 for entry 5; methylene chloride for entry 3).
13. $^{13}C$ NMR-DEPT and mass spectral data for all new products in Table 2. Dehydro analogs: **5a**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 21.91 ($CH_3$), 52.34 ($CH_3$), 53.9 ($CH_2$), 55.85 ($CH_2$), 127.85 (CH), 130.32 (CH), 136.47 (CH); MS (ESI): 585 (2M+23), 304 (M+23), 282 (M+H); **5c**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 52.23 ($CH_3$), 74.77 ($CH_2$), 88.93 (CH), 126.75 (CH), 128.71 (CH), 129.11 (CH), 140.9 (CH); MS (ESI): 205 (M+H); **5d**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 52.19 ($CH_3$), 53.83 ($CH_2$), 55.67 ($CH_2$), 111.55 (CH), 116.73 (CH), 129.8 (CH), 138.08 (CH); MS (ESI): 204 (M+H); **5e**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 12.02 ($CH_3$), 52.54 ($CH_3$), 55.53 ($CH_2$), 60.94 ($CH_2$), 111.46 (CH), 116.52 (CH), 120.94 (CH), 129.75 (CH); MS (ESI): 218 (M+H). Pyrroles: **6a**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 12.10 ($CH_3$), 51.20 ($CH_3$), 119.42 (CH), 120.94 (CH), 125.23 (CH), 126.86 (CH), 130.07 (CH); MS (ESI): 238 (M+23), 216 (M+H); **6b**: $^{13}C$ NMR-DEPT (75 MHz, $CDCl_3$): 22.3 ($CH_3$), 51.38 ($CH_3$/CH), 57.36 ($CH_3$/CH), 110.44 (CH), 121.23 (CH), 125.06 (CH), 126.33 (CH), 128.3 (CH), 129.22 (CH); MS (ESI): 481 (2M+23), 230 (M+H).
14. To our knowledge, this system has not been prepared or reported. The pyrrolidine-3-carboxylate has been utilized as a β-turn motif in a GPIIb/IIIa antagonist, see: Hoekstra, W. J.; Maryanoff, B. E.; Damiano, B. P.; Andrade-Gordon, P.; Cohen, J. H.; Costanzo, M. J.; Haertlein, B. J.; Hecker, L. R.; Hulshizer, B. L.; Kauffman, J. A.; Keane, P.; McComsey, D. F.; Mitchell, J. A.; Scott, L.; Shah, R. D.; Yabut, S. C. *J. Med. Chem.* **1999**, *42*, 5254–5265.
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