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Microwave-Accelerated Ruthenium-Catalyzed Olefin Metathesis

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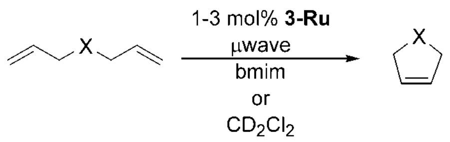
ABSTRACT



Microwave heating is an efficient method for the acceleration of ring-closing metathesis reactions using ruthenium-based catalysts. The reaction can be rapidly conducted in either ionic liquids, such as 1-butyl-3-methylimidazolium tetrafluoroborate (bmim), or in a microwave transparent solvent (MTS) such as dichloromethane.

During the past decade, ring-closing metathesis (RCM) has emerged as a powerful tool for the construction of small, medium, and macrocyclic ring systems.[1] A large part of the success of this reaction has been due to the availability of well-defined catalysts such as those developed by Shrock[2] (**1-Mo**) and Grubbs[3] (**2-Ru**, **3-Ru**) (Figure 1). However, the catalysts developed by Grubbs have proven to be more useful in synthetic transformations due to their low sensitivity to air and moisture, as well as their tolerance of a variety of common organic functional groups.[4]

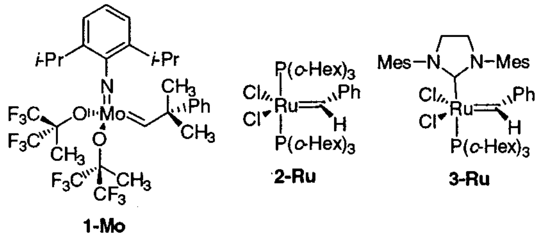


Figure 1.

Recently, this laboratory has focused on the application of microwave heating in organic synthesis. The initial investigations centered on the utility of microwave heating in the synthesis of several types of organophosphorus compounds.[5] Carrying out reactions using microwave heating, as opposed to conventional heating, has the major advantage of shorter reaction times because of the rapid core heating associated with microwaves. Consequently, reactions exhibit cleaner products and more facile workup procedures. Our interest in this area has prompted us to explore its application in reactions other than the synthesis of organophosphorus compounds. Herein, we report a systematic analysis of the effect of microwave heating in ring-closing metathesis reactions using Grubbs catalysts.[6]

Our initial goal was to investigate the use of room temperature ionic liquids as environmentally friendly solvents in microwave heating reactions. The ionic liquids seemed advantageous since they would couple with microwaves

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(1) For recent reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (d) Fhrstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(2) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(3) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(4) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(5) (a) Kiddle, J. J.; Gurley, A. F. *Phosphorus, Sulfur, Silicon* **2000**, *160*, 195. (b) Kiddle, J. J. *Tetrahedron Lett.* **2000**, *41*, 1339.

(6) For the first example of RCM under microwave activation, see: Varray, S.; Gauzy, C.; Lamaty, F. *J. Org. Chem.* **2000**, *65*, 6787.

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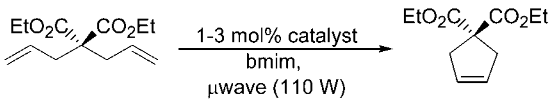
through a dielectric heating mechanism,[7] were reasonably polar, can dissolve organic compounds, have relatively high boiling points (>200 °C), and a low volatility.[8] The low volatility of the ionic liquids was of particular importance since our microwave reactions were conducted in sealed Teflon-capped pressure tubes. We thought this would not be compatible with the typical RCM solvent dichloromethane; however, upon further investigation we have found that this is not the case.

As a first step, we examined the RCM reaction of diethyl diallylmalonate in 1-butyl-3-methylimidazolium tetrafluoroborate (bmim) with three ruthenium-based catalysts to determine which one would be most effective in an ionic liquid (Table 1).

Table 1. Microwave-Accelerated RCM with Grubbs Catalysts in Ionic Liquids

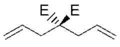
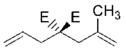
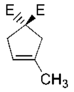
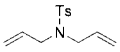
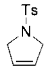
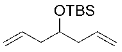
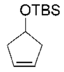
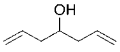
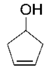
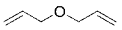
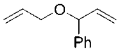
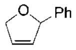


Catalyst	Conversion (%)[a] time [s]
2-Ru	80 [60]
Ⓟ—**2-Ru**[b]	40 [60]
3-Ru	100 [15]

[a] Determined from ^{1}H NMR. [b] Bound to vinyl polystyrene.

The results from the model study in Table 1 were not surprising since catalyst **3-Ru** has been reported to be more active than **2-Ru** in RCM reactions.[3b] In addition, the lower conversion with the polymer-bound Grubbs catalyst has been previously reported to be about 2 orders of magnitude less reactive than the homogeneous analogue **2-Ru** which is similar to our results.[9] Although the reactivity profile of the catalysts was not unexpected, the extremely short reaction time suggested that RCM reactions could easily be accelerated by microwave heating. In addition, the fact that no other precautions were taken in the reaction (i.e., exclusion of air/moisture) demonstrated that the typical RCM reaction could also be easily adapted to microwave heating.

Table 2. Microwave-Accelerated RCM in bmim

entry	substrate[a]	product	time (s)	microwave conversion (%)[b]	thermal conversion (%)[c]
a			15	100	3
b			15	100	0
c			15	100	0
d			45	100	12
e			30	55	0
f			60	no product	2
g			15	100	4

[a] E = CO$_2$Et, 0.02−0.04 M, 2−3 mol % **3-Ru**. [b] Determined from ^{1}H NMR. [c] Thermal reactions were conducted under conditions identical to those used in the microwave experiments. The temperature used in the thermal reactions was the highest temperature observed in the microwave reactions (33 °C except entries **d** and **e** which were 54 and 61 °C, respectively).

We then turned our attention to a more comprehensive examination of RCM reactions using **3-Ru** in bmim as solvent, the results of which are shown in Table 2.[10] In all cases the RCM reactions were complete in 60 s or less, often with 100% conversion. To determine the efficiency of microwave heating in RCM reactions, control experiments were conducted using thermal heating under identical reaction conditions. In all but two cases, the rate of the reaction under microwave heating was significantly greater than those performed under identical thermal conditions, providing clear evidence for an acceleration of RCM reactions through microwave activation. The low conversion of 1,6-heptadien-4-ol (entry **e**) was unexpected since previous work by Grubbs showed a quantitative conversion to the product using **3-Ru**. However, those reactions were conducted in CD$_2$Cl$_2$ and may account for the difference in conversion. In the case of the allyl ether (entry **f**), no product was formed possibly due to vaporization of the ether (bp 94 °C) caused by the rapid heating associated with microwave energy. Recently, a report has appeared in the literature concerning the use of ruthenium catalysts in ionic liquids for olefin metathesis.[11] The authors reported reaction times of 1 h at 80 °C to achieve 100% conversion of the same substrate in entries **a** and **c** (Table 2) that required only 15 s each under microwave heating. Although this suggests a significant reduction in reaction time using microwave heating, it should be noted that the authors utilized the less reactive catalyst **2-Ru** in their experiments. In addition, the ionic liquid used had a different anion (hexafluorophosphate vs tetrafluoroborate) than ours. It is, however, unlikely that these differences would have a major impact on the reactions and account for the dramatic reduction in reaction time seen with microwave heating.

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(7) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213.

(8) Welton, T. *Chem. Rev.* **1999**, *99*, 2071.

(9) Nguyen, S. T.; Grubbs, R. H. *J. Organomet. Chem.* **1995**, *497*, 195.

(10) **General procedure for microwave-accelerated RCM**: ***Caution***! It is hazardous to heat organic reactions in closed vessels by either conventional or microwave means. Therefore, caution should be exercised when conducting reactions of this type. Substrate and 1 mL of solvent (bmim or CD$_2$Cl$_2$) were combined in a pressure tube to yield solutions with a concentration between 0.02 and 0.04 M. Next, the catalyst was weighed into the pressure tube that is immediately sealed finger tight with a threaded Teflon cap. The pressure tube was put into a beaker and then placed in the center of a Panasonic 1100W microwave oven (Model NN-S758). The reaction mixture is then heated for the appropriate time on a power setting of 10% (approximately 110 W). Once the heating cycle is complete, the reaction mixture is either extracted with ethyl acetate (bmim) or used directly to determine the conversion by ^{1}H NMR.

(11) Buijsman, R. C.; van Vuuren, E.; Sterrenburg, J. G. *Org. Lett.* **2001**, *3*, 3785.

Although the RCM reactions in ionic liquids under microwave heating were very successful, we were concerned about the limited data to which we could compare our results. Therefore, we decided to extend our investigation to further validate the utility of microwave heating in RCM reactions. To this end, we next focused our attention on using dichloromethane as a solvent for our microwave-accelerated RCM reactions.

Initially, the use of dichloromethane was not considered since the reactions are carried out in sealed tubes and it was prudent to avoid low-boiling solvents under these conditions. However, the dielectric constant (ϵ_S) of dichloromethane is 9.1 and we hypothesized that it might be transparent to microwave energy and thus show little or no heating when subjected to microwaves. These conditions would then allow the direct coupling of the microwave energy to the reactants in the mixture.

To test this hypothesis, it was first necessary to determine the microwave heating profile of dichloromethane. Figure 2 shows the microwave heating profile of dichloromethane over a period of 3 min. The graph clearly shows that dichloromethane is reasonably transparent to microwave energy and in fact does not reach its boiling point (40 °C) within the time of the experiment. For comparison, methanol will reach its boiling point (65 °C) in less than 1 min of microwave heating.[6]

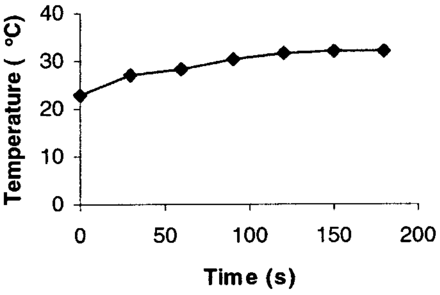
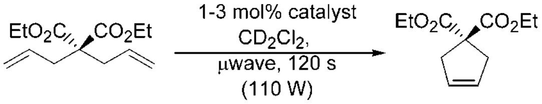


Figure 2. Microwave heating profile of dichloromethane.

Following confirmation that dichloromethane was indeed a transparent solvent in microwave heating, we then sought to establish the most effective catalyst for the microwave-accelerated RCM reactions in dichloromethane. Not surprisingly, catalyst **3-Ru** proved to be superior to the other two catalysts as was previously noted in the reactions utilizing ionic liquids as solvents (Table 3). Also, during the course of this model study it was found that for the complete conversion of diethyl diallylmalonate to the cycloalkene using **3-Ru** required 120 s in dichloromethane. This time was established as a baseline for comparison of the microwave heating data.

Table 3. Microwave-Accelerated RCM with Grubbs Catalysts in Dichloromethane

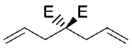
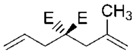
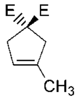
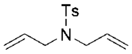
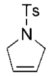
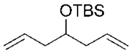
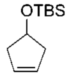
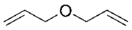
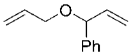
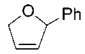


Catalyst	Conversion (%)[a]
2-Ru	75
Ⓟ—**2-Ru**[b]	36
3-Ru	100

[a] Determined from ^{1}H NMR. [b] Bound to vinyl polystyrene.

With the most effective catalyst and a standard reaction time determined, we then examined the microwave-accelerated RCM reaction of several substrates in dichloromethane (Table 4).

Table 4. Microwave-Accelerated RCM in Dichloromethane

entry	substrate[a]	product	microwave conversion (%)[b]	thermal conversion (%)[c]
h			100	21
i			79	9
j			91	45
k			64	7
l			85	4
m			86	7

[a] E = CO_2Et, 0.02−0.04 M, 2−3 mol % **3-Ru**, 120 s. [b] Determined from ^{1}H NMR. [c] Thermal reactions were conducted under conditions identical to those used in the microwave experiments. The temperature used in the thermal reactions was the highest temperature observed in the microwave reactions (33 °C).

As illustrated in Table 4, the extension of the microwave heating methodology to RCM reactions in dichloromethane behaved in a fashion similar to those in ionic liquids. The reaction times were reduced, but not to the extent seen with the ionic liquids. However, in comparison to the thermal control experiments under identical conditions, the microwave reactions did show enhanced conversions with every substrate. In addition to the evidence of a rate enhancement seen by comparing the microwave experiments to the controls, Grubbs and co-workers have reported the complete thermal conversion of the substrates in entries **h** and **i** to products after 10 min in refluxing dichloromethane.[8] In our microwave experiments, the substrate in entry **h** shows complete conversion in one-fifth the time required in the experiments conducted by Grubbs. In addition, although the substrate in entry **i** showed only a 79% conversion after 120 s, the substrate could be completely converted to product by heating for an additional 60 s (180 s total) in comparison to the 10 min necessary in the thermal reaction described above. Although there was not a dramatic reduction in reaction time using dichloromethane as the solvent, it is important to note that none of the microwave reactions exceeded 33 °C. This fact suggests that the microwave energy is producing nonthermal effects that may involve direct coupling to one of the two or both reactants in these transformations. However, in preliminary experiments it has not been possible to ascertain which component(s) are coupling with the microwave energy or if other factors related to the medium are influencing the microwave heating.[12] Even without a clear understanding of the heating mechanism, one practical consideration would be that RCM reactions carried out under microwave heating would be more useful for substrates which were sensitive to prolonged exposure to heat.

In conclusion, we have reported an effective and efficient method to accelerate ring-closing metathesis reactions in both ionic liquids and dichloromethane through microwave heating. Although, the reactions in dichloromethane are not significantly more rapid than those of similarly reported model studies under thermal heating, they do provide an alternative method that does not necessitate heating the substrate at reflux. Further research will be directed toward a better understanding of the mechanisms involved in microwave heating of organic reactions.

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(12) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.