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Microwave-assisted ruthenium-catalyzed olefin metathesis under solvent-free conditions

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Abstract—An efficient method for ring-closing metathesis under solvent-free conditions and by microwave activation was established. Non-thermal microwave specific effects were evident.

Ring-closing metathesis (RCM) has been established as a powerful and efficient synthetic method for carbon–carbon bond formation leading to carbocycles or heterocycles.[1] Many useful transformations have been reported for industrial applications as well as for the synthesis of complex molecules. Widely used, well-defined alkylidene–metal complexes for this transformation include the alkoxy imido molybdenum complex **1**[2] and the benzylidene ruthenium complexes **2** and **3**[3] (Fig. 1). However, the ruthenium catalyst **2** and derivatives thereof developed by Grubbs et al. 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.[1f] They have also been widely utilized for RCM as a key step in numerous natural product syntheses.[4] Microwave (MW) activation as a non-conventional energy source has emerged as a powerful technique to promote a variety of chemical reactions and has become a very popular and useful technique in organic chemistry.[5] The combination of solvent-free conditions and microwave irradiation leads to large reduction in reaction times, enhancements in conversions and, sometimes, in selectivity with several advantages of the eco-friendly approach, termed green chemistry.[6]

In continuation of our program aimed at the study of MW effects in organic synthesis under green chemistry conditions, we report here our study on solvent-free microwave-assisted ruthenium-catalyzed olefin ring-closing metathesis.

It is noted that the RCM under MW irradiation has already been described in the literature by Kiddle et al.[7] Reactions were performed using a domestic MW oven (Panasonic 1100 W, operating on a power setting of 10%, i.e. only under effective MW irradiation for 10% of the time at full power) in the presence of CD_2Cl_2 or

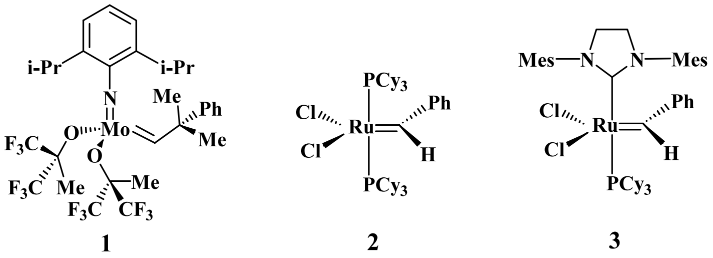

Figure 1.

Keywords: olefin metathesis; microwave irradiation; solvent-free conditions.

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1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]-BF_4) as solvents. Important MW effects on the conversions of the reactions were observed in comparison with classical activation systems. However, unfortunately no yields were reported in this paper. It should also be noted that, with a domestic MW reactor, realistic power and temperature controls during the reaction could not be achieved. In this way, the comparison of the two activation systems reported by Kiddle et al. seems not to be reliable.

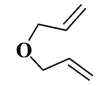
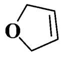
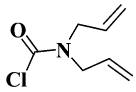
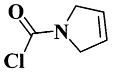
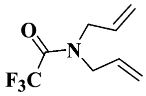
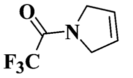
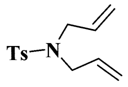
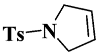
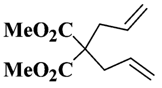
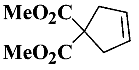
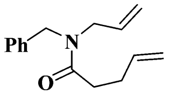
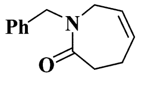
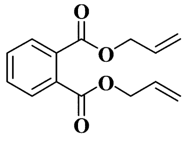
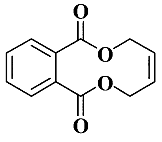
Recently, Wilson et al.[8] described the synthesis of pyrroles and derivatives by microwave-accelerated ring-closing metathesis. All reactions were performed using the CEM-Discover system in the presence of dichloroethane as solvent. Beneficial MW effects were reported with respect to both reaction times and conversions. However, no study of MW specific effects was realized due to the lack of consideration of comparative conditions with conventional heating.

The aim of our study was to underline the potential of coupling a solvent-free reaction with focused MW activation and further to demonstrate non-thermal MW specific effects by comparing the results obtained with conventional heating under similar conditions.

In our initial studies, we attempted to optimize the reaction conditions for olefin ring-closing metathesis. A series of carbon-, oxygen- and nitrogen-containing acyclic dienes were tested. All reactions were performed in the CEM-Discover monomode system in closed vessels in the presence of dichloromethane or dichloroethane as solvent or under solvent-free conditions. The optimized results are summarized in Table 1.

Typically, metathesis reactions were carried out in degassed solvents (dichloromethane or benzene) in the presence of 5–10% ruthenium catalyst **2** at concentrations ranging from 0.004 to 0.05 M. High-dilution concentrations were employed to minimize the forma-

Table 1. RCM catalyzed by **2** (4 mol% catalyst) in closed vessels under monomode MW irradiation (CEM-Discover system)

Entry	Substrate	Product	Time (min.)	Temperature[e] (°C)	Yield (%)[a]	
					Solvent[b]	No solvent
1			3	50	100 (98)	96 (94)
2			5	50	98 (95)	67
3			0.5 3	50 50	93 (90) 78[c]	95 92 (90)
4			0.5	50	100	100
5			3 1	80 80	92 85	85 80
6			30	50	98 (92)	(70)
7			30	150	79[d]	71

[a] Yield estimated by GC using an internal standard, isolated yields are given in brackets.

[b] Solvent CH_2Cl_2 (c=2 M).

[c] 1 mol% catalyst **2**.

[d] 8 mol% catalyst **2** using $ClCH_2CH_2Cl$ as solvent.

[e] Temperature, evaluated by infrared detection, is maintained constant all along the reaction by modulation of emitted MW power.

tion of dimer, resulting from cross-metathesis when the reaction rates were slow. The data in Table 1 indicate that, under MW irradiation, only a slight difference in yield was detected when the reaction was conducted in the absence of any solvent. It is important to note that when the ruthenium complex **2** is soluble in the substrate, the addition of solvent is unnecessary. RCM, in this case, can be carried out more easily under solvent-free conditions.

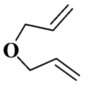
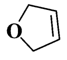
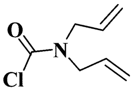
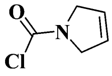
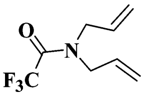
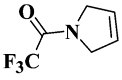
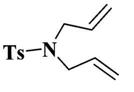
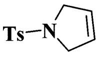
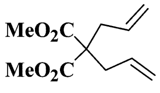
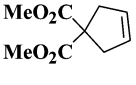
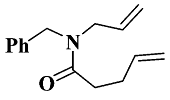
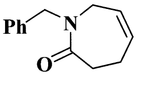
When compared to conventional syntheses in refluxing dichloromethane, improvements are noticeable, for example in entry 6, where refluxing for 4 hours is necessary to obtain similar yields.[9] It is much more evident in the case of the allyl ether (entry 1) where we obtained quantitative yields whereas Kiddle[7] observed 'no product', possibly due to vaporization of the reagent. Once again, it is obvious that focused microwave activation using the monomode system presents significant advantages when compared to a domestic microwave oven.[6a]

We then turned our attention to a more comprehensive MW-specific effect on RCM. For the sake of comparison and in order to check the efficiency of MW activation in RCM reactions as well as the possible intervention of non-thermal MW-specific effects, control experiments were conducted using a thermostatted oil bath (Δ = conventional heating) under identical reaction conditions (time, temperature, vessel, temperature ramp). The main results are given in Table 2.

As illustrated in Table 2, non-thermal MW specific effects were revealed except in the case of entry 4 (the reactivity of the system being too high and thus masking any possible MW effect). These effects are increased in magnitude with the less reactive systems (entry 6>2>1). They can be related to the polarity increases as the reaction progresses consistent with the mechanism, i.e. the involvement of polar metallacyclobutanes with polar carbon–metal bonds. MW irradiation can therefore improve this reaction by enhancement of the dipole–dipole stabilization of the transition state when compared to the ground state.[5c]

In conclusion, we have reported an efficient method for olefin ring-closing metathesis using solvent-free reaction and microwave activation under green chemistry conditions. Such a conclusion was already possible from a preliminary study by Lamaty et al. during their synthesis of cyclic amino acid derivatives via RCM on a polyethyleneglycol-supported substrate.[11] Non-thermal MW specific effects were also demonstrated. Efforts to extend this method to enyne ring-closing metathesis reactions are in progress. Further research will be directed towards a better understanding of the mechanisms involved in microwave-assisted ring-closing metathesis.

Table 2. Comparison of thermal versus microwave irradiation on RCM in closed vessels catalyzed by ruthenium complex **2** (4 mol%) under solvent-free conditions[10]

Entry	Substrate	Product	Time (min.)	Temperature (°C)	Isolated yield (%)	
					MW	Δ
1			3	50	94	78
2			5	50	67[a]	48[a]
3			3	50	90	74
4			0.5	50	100	100
5			1	80	80[b]	60[b]
6			30	50	70	44

[a] Yield estimated by GC using an internal standard.

[b] 1 mol% catalyst **2**.

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10. Typical procedure for ring-closing metathesis using the CEM-Discover monomode system under solvent-free conditions: Acyclic olefin (2 mmol) and Grubbs' catalyst **2** (10 mol%) were mixed in the absence of any organic solvent and then submitted to MW irradiation for a period of time and temperature (see Tables 1 and 2). After cooling, the crude product was purified by flash chromatography to afford the corresponding cyclic olefin. All products are already described in the literature.[1,9]
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