Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4899–4901

TETRAHEDRON LETTERS

Synthesis of Δ^3-pyrrolines and Δ^3-tetrahydropyridines via microwave-accelerated ring-closing metathesis

Ronald Grigg,[a,*] William Martin,[b] James Morris[a] and Visuvanthar Sridharan[a]

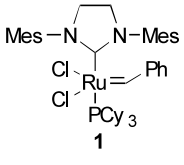
[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK*

[b]*Process Research and Development, GlaxoSmithKline, Stevenage SG1 2NY, UK*

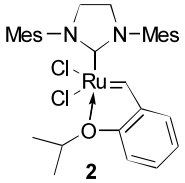
Received 4 March 2003; revised 15 April 2003; accepted 25 April 2003

Abstract—Microwave irradiation effects ring-closing metathesis of electron-deficient and sterically conjested double bonds with a drastic reduction in reaction time and reduced catalyst loading.

Ring-closing metathesis (RCM) has emerged as a powerful synthetic method for the construction of small, medium and macrocyclic ring systems.[1] The development of second-generation air-stable Ru catalysts such as **1** and **2**[2–4] which exhibit higher thermal stability, wider functional group tolerance and accommodate a higher density of substitution on the double bond formed in RCM opened up new synthetic opportunities.[5] However, RCM has its limitations with respect to substitution patterns on the double bond. Formation of tri- and tetra-substituted cyclic alkenes with external electron-withdrawing substituents (CO_2Me) via RCM normally results in low yields.[6,7]



1



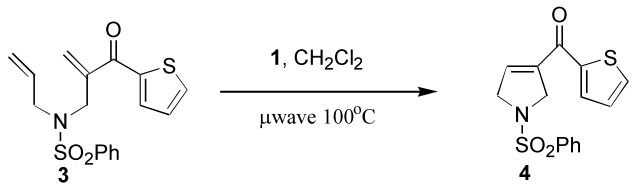
2

Microwave irradiation, as opposed to conventional heating, results in major rate increases due to instantaneous heating and there is no physical contact between the energy source and the reaction vessel.[8] The technique thus facilitates the rapid exploration of 'chemistry space'. Tri- and tetra-substituted heterocyclic alkenes, with electron-withdrawing substituents on the double bond, are potential dienophiles/dipolarophiles for Diels–Alder and 1,3-dipolar cycloaddition reactions. Our ongoing interest in RCM in the synthesis of such compounds led us to explore the use of microwave irradiation in RCM to access such heterocyclic alkenes.

Initially we studied the microwave-accelerated RCM of **3** (Scheme 1) which we prepared by a four-component palladium catalysed cascade carbonylation/allenylation/amination process.[9] DCM was the solvent of choice owing to its microwave transparency[10] thus allowing the maximum uptake of irradiated microwave energy by the substrate and catalyst. A target temperature of 100°C was set and the catalyst loading and concentration of **3** varied to find the optimum reaction conditions. The results are summarised in Table 1.[11]

The best set of conditions (Table 1, entry 3) furnished **3** in 86% yield. Next we studied the formation of a range of 3-substituted five- and six-membered heterocyclic alkenes via microwave induced RCM by varying the aryl/heteroaryl acyl group (Table 2).[12]

Microwave heating results in shorter reaction times and lower catalyst loadings. Wilson et al. have recently reported a closely related process.[13]



Scheme 1.

* Corresponding author. Tel.:+44-113-343-6501; fax: +44-113-343-6530; e-mail: r.grigg@chem.leeds.ac.uk

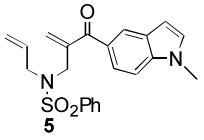
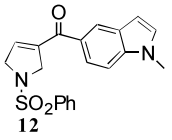
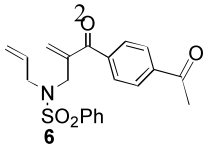
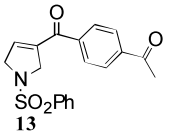
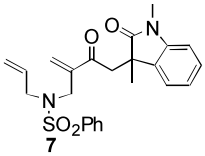
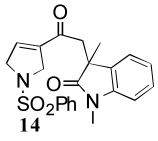
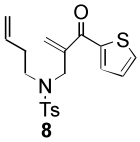
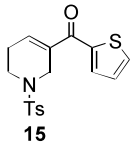
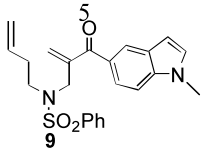
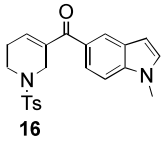
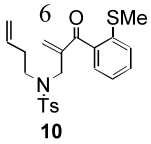
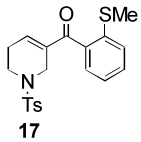
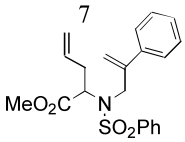
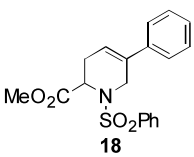
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)01080-3

Table 1. Optimisation of reaction conditions

Entry[a]	Time (min)	Conc. (mM)	Catalyst loading (mol%)	Conversion (%)
1	5	15	5	100
2	1	15	5	100
3	**1**	**15**	**2.5**	**100**
4	1	30	2.5	90
5	2	30	1	88
6	1	30	1	88
7[b]	1	30	2.5	80

[a] The temperature was set to reach a maximum of 100°C in all cases.
[b] Catalyst **2** used.

Table 2.

Entry	Starting Material[a]	Catalyst Loading (mol%)	Product	Conversion (%)	Yield (%)[b,c]
1	 **5**	2.5	 **12**	93	80
2	 **6**	2.5	 **13**	100	87
3	 **7**	1	 **14**	100	90
4	 **8**	2.5	 **15**	100	86
5	 **9**	5	 **16**	92	77
6	 **10**	2.5	 **17**	92	78
7	 **11**	2.5	 **18**	100	88

a) Substrates **5-11** were synthesised via a cascade palladium catalysed carbonylation/allenylation/ amination process.[9]
b) Yields refer to isolated yields.
c) Corresponding thermal reactions were carried out in toluene at 70°C for 2-5h using 5 mol% of **1** and resulted in comparable yields. [9]

In conclusion, we report an efficient method of accelerating the RCM of electron-deficient, sterically encumbered dienes in DCM through microwave irradiation.

Acknowledgements

We thank the University of Leeds, the EPSRC and GlaxoSmithKline for their support.

References

1. For recent metathesis reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, 371; (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.
2. Scholl, M.; Irnka, T. N.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.
3. Jafarapour, L.; Nolan, S. *Organometallics* **2000**, *191*, 2055–2057.
4. Furstner, A.; Theil, O. R.; Ackemann, L.; Schant, H. J.; Nolan, S. *J. Org. Chem.* **2000**, *105*, 2204–2207.
5. (a) Liu, D.; Kozmin, S. A. *Org. Lett.* **2002**, *4*, 3005–3007; (b) Maleczka, K. E.; Terrel, L. K.; Geng, F.; Ward, J. S. *Org. Lett.* **2002**, *4*, 2891–2899.
6. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318.
7. Basu Cabral, J. A.; Paquette, L. A. *Tetrahedron Lett.* **2002**, *43*, 5453–5456.
8. Lidstrom, P. *Tetrahedron* **2001**, *59*, 9268–9283.
9. Grigg, R.; Hodgeson, A.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *49*, 1023–1026.
10. Nayo, K. G.; Hearhoof, E. H.; Leiddle, J. J. *Org. Lett.* **2002**, *4*, 1567–1570.
11. *General proceedure for microwave RCM*: Substrate (**3**, **5–11**) and CH_2Cl_2 (4 ml) were combined in a microwave pressure vial, containing a small magnetic stirrer bar, to afford solutions of either 1.5 or 3.0 mM. Catalyst was then added to this solution and the pressure vial immediately sealed and subjected to microwave irradiation (Smith Creator model). The solvent was then removed and the product conversion measured by 500 MHz NMR analysis. Passing the crude product through a small pad of silica, eluting with ether/petrol, afforded the product.
12. All new compounds have been fully characterised (^1H, ^{13}C, IR, MS and elemental analysis).
13. Yang, C.; Murray, W.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783–1786.