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Tetrahedron Letters 46 (2005) 7389–7392

Tetrahedron Letters

Microwave-accelerated cross-metathesis reactions of *N*-allyl amino acid substrates

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Received 7 June 2005; revised 18 August 2005; accepted 23 August 2005
Available online 9 September 2005

Abstract—Microwave heating has been utilised for the cross-metathesis reaction of *N*-allyl amino acid substrates to generate olefin homodimers. Remarkable acceleration of the cross-metathesis reaction (minutes compared to hours) over conventional reflux heating was observed. In addition, improved reaction yields and similar *E*/*Z* ratios for the cross-metathesis products were achieved.

Olefin metathesis using the carbene ruthenium catalysts developed by Grubbs is well studied in conventional organic chemistry, where reactions are most likely directed towards high yields and selective products (Fig. 1).[1] The cross-metathesis (CM) variant of the olefin metathesis reaction in general exhibits unpredictability in both these respects and consequently has much less representation in the organic synthesis literature when compared to the ring-opening metathesis polymerisation (ROMP) and ring-closing metathesis (RCM) variants. A general model of the selectivity of the CM reaction has recently been described by Grubbs and co-workers.[2] The model was derived from the propensity of olefin homodimers, rather than the terminal olefins themselves, to undergo CM, with the underlying premise to circumvent many of the complexities of a system in which both primary (from the terminal olefin counterpart) and secondary (from the olefin dimer) metathesis pathways participate and compete.

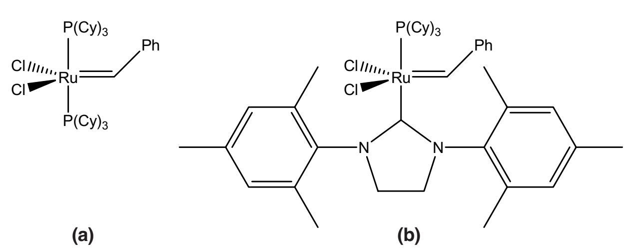
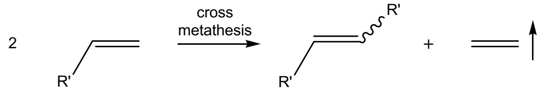


Figure 1. Grubbs first-generation catalyst (a) and Grubbs second-generation catalyst (b).

As part of our ongoing investigation into the development of newly modified amino acid building blocks for application of the metathesis reaction to dynamic combinatorial chemistry (DCC), we needed to synthesise amino acid building blocks containing a terminal olefin. *N*-Allyl amino acid precursors were chosen and synthesised; however, to simplify the complexity of the DCC system, it was decided to prepare the corresponding olefin homodimers for building blocks by CM, Scheme 1. We investigated both the Grubbs first- and second-generation catalysts. This manuscript reports the results with a number of our building blocks.

The synthesis of the *N*-allyl substituted amino acid precursors **2a–c** from commercially available amino acid methyl esters is outlined in Scheme 2.[3] The synthesis utilises the 2-nitrobenzene sulfonamide (*o*NBS) group for the concomitant protection and activation of the amino acid nitrogen. The electron withdrawing nature of the *o*NBS group increases the acidity of the amino acid N*H* proton improving the susceptibility for substitution



Scheme 1. CM reaction for the preparation of olefin homodimers.

Keywords: Olefin; Cross-metathesis; Microwave; Amino acids; *N*-Allylation.

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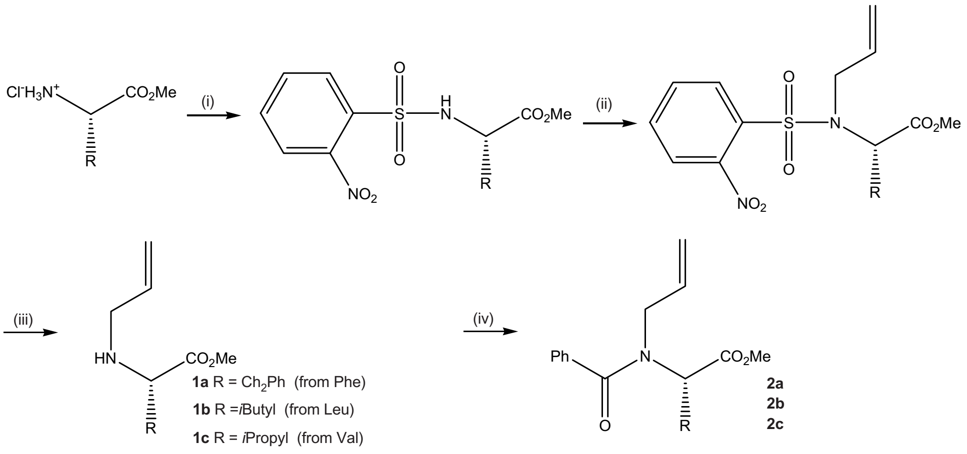
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.08.126

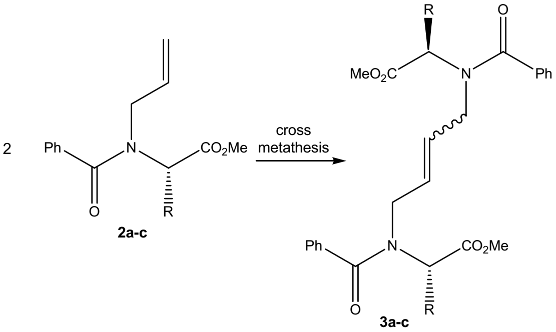


Scheme 2. General synthesis of *N*-allyl substituted amino acid precursors **2a**–**c**: (i) *o*NBSCl, Et_3N, CH_2Cl_2, rt, 16 h, 80–97%; (ii) K_2CO_3, DMF, allyl bromide, rt, 16 h, 83–85%; (iii) PhS^-Na^+, K_2CO_3 or LiOH, mercaptoacetic acid; DMF, rt, 2–3 h, 57–94%; (iv) BzCl, Et_3N, CH_2Cl_2, rt, 2 h, 65–72%.

with allyl bromide. Following allylation, the *o*NBS group is removed by either phenyl thiolate or mercaptoacetic acid. Finally, amide formation with benzoyl chloride generates the olefin precursors **2a**–**c**.[4]

With the three precursors **2a**–**c** in hand, the CM reaction for the preparation of the corresponding olefin homodimer building blocks **3a**–**c** was investigated, Scheme 3.[5] Initial studies with Grubbs first-generation catalyst failed to generate any CM product, even with varying reaction times either at room temperature or at elevated temperatures: refluxing CH_2Cl_2 (40 °C) or refluxing 1,2-dichloroethane (1,2-DCE) (80 °C). Analogues of α-allyl amino acid methyl esters (allylglycines) have undergone CM at room temperature with Grubbs first-generation catalyst,[6] so our results demonstrate the severely reduced efficiency of participation of *N*-allyl amino acid substrates in the CM reaction.

Grubbs second-generation catalyst is reported to have higher activity in the CM reaction[7] and an investigation with substrates **2a**–**c** was undertaken (Table 1). The second-generation catalyst was also not sufficient for CM of our substrates at room temperature (Table 1 entries 1, 2, 6 and 9). The use of refluxing 1,2-DCE for an extended period (18–72 h) was required to facilitate the thermal reaction, albeit with moderate yields (Table 1, entries 3, 4, 7 and 10).



Scheme 3. Synthesis of olefin homodimers **3a**–**c** from precursors **2a**–**c** by CM.

In an attempt to increase the CM yield and shorten the reaction time, microwave (MW) irradiation, in place of conventional heating, was investigated. Thermally driven organic transformations can take place by conventional heating or MW-accelerated heating. MW irradiation, using either a domestic microwave oven or mono-mode reactors, has become a powerful tool for the preparation of organic compounds.[8] The premise for this investigation was the reported success of MW irradiation in the promotion of the RCM variant of the olefin metathesis reaction.[9] In RCM applications, MW irradiation has demonstrated improved yields, substantially reduced reaction times, and reduced thermal degradation of the ruthenium catalyst. It is believed that these improvements arise from the more effective and efficient heating compared to conventional thermal reactions. We could find only one reported example where MW irradiation has been applied to promote the CM variant of the metathesis reaction (in a RCM–CM domino reaction).[10] CM is, therefore, unexplored with respect to the application of MW irradiation and so presented itself as an ideal candidate reaction for the investigation of the effects of MW irradiation on reaction time and product yield. Herein, we report a systematic analysis of the effect of MW heating on the CM reaction on olefin substrates **2a**–**c**.[†]

[†] In the CEM Discover microwave system used in this study, a circular single-mode cavity directs the microwave energy into a defined area, resulting in a homogenous field pattern surrounding the sample and an instantaneous coupling to all polar and ionic components in the sample, leading to a rapid rise in temperature. This microwave can accommodate a single 10 mL 25 bar pressure rated sealed reaction vial. The system incorporates both temperature and pressure feedback systems for control of the reaction conditions. The temperature feedback system uses an infrared temperature sensor positioned below the reaction vessel to permit reproducible temperature control. The reactions were quenched following heating by forced gas cooling with nitrogen gas.