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Microwave-promoted tandem reactions for the synthesis of bicyclic γ-lactams

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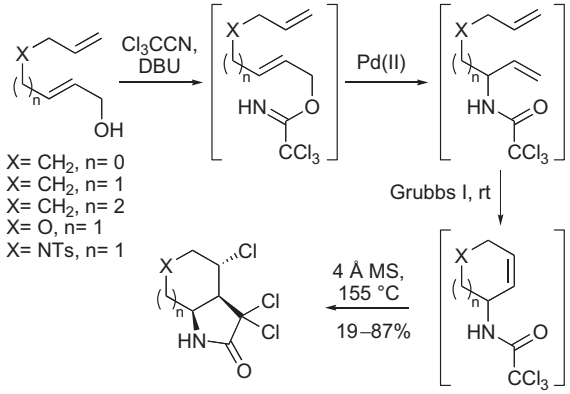
ABSTRACT

A microwave-promoted three-step tandem process for the synthesis of bicyclic γ-lactams is developed. In all cases examined this led to significantly faster tandem processes producing the bicyclic γ-lactams more cleanly and reproducibly compared to standard thermal conditions.

The use of microwaves to heat chemical reactions has become a very popular and useful approach in organic synthesis.[1] This non-conventional energy source is based on the ability of some reagents and solvents to transform electromagnetic energy into heat by 'microwave dielectric heating' effects.[2] Its use can lead to a spectacular acceleration of reactions, resulting in shorter reaction times, a reduction in side reactions, higher yields, milder reaction conditions and an improvement in reproducibility. More recently, the combination of microwave technology with the principles of green chemistry have produced a range of relatively sustainable and environmentally benign procedures involving solvent-free conditions, supported reagents or reusable catalysts for the synthesis of biologically-active compounds and fine chemicals.[3]

Our own research into green chemistry has focused on the development of one-pot tandem processes for the multi-step synthesis of functionalised carbocyclic amides.[4] These processes involved the use of the Overman rearrangement of allylic trichloroacetimidates[5] in combination with ring closing metathesis (RCM) reactions of the resulting trichloroacetamide derived dienes to give carbocyclic amides of various ring sizes. An asymmetric variant was also developed and used for the synthesis of the tropane alkaloid, (+)-physoperuvine.[6] More recently, we reported a one-pot tandem process for the synthesis of bicyclic [3.3.0], [4.3.0] and [5.3.0] γ-lactams from allylic alcohols.[7] This process involved a palladium(II)-catalysed Overman rearrangement followed by a RCM reaction and a Kharasch cyclisation,[8] both mediated by Grubbs 1st generation catalyst (Scheme 1).[9] While this process gave high yields (60–87% over four steps) for bicyclic γ-lactams derived from allylic alcohols with an all carbon side chain, more modest yields (19–36%) were observed for substrates bearing a side-chain heteroatom. The yields for these compounds could be improved (39–52%) by employing a thermal Overman rearrangement[10] during the first stage of the tandem process. However, using thermal conditions rather than a palladium(II)-catalyst resulted in long reactions times (72 h for X = O, 136 h for X = NTs).

As all three steps of this tandem process can be accelerated by heat, it was proposed that the application of microwave energy would allow a more rapid and efficient synthesis of the bicyclic γ-lactams. In this Letter, we now report a one-pot tandem process



Scheme 1. Tandem synthesis of bicyclic γ-lactams.

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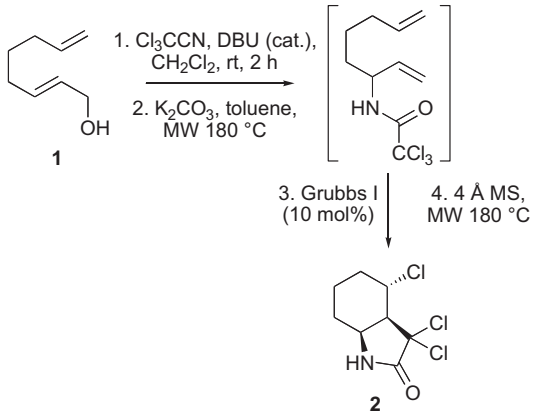
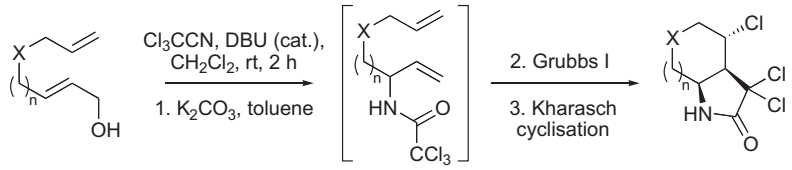
Table 1
Development of the microwave-promoted tandem process

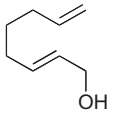
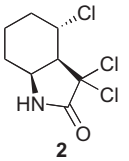
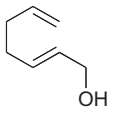
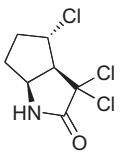
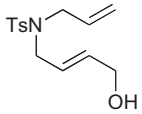
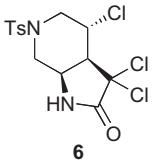
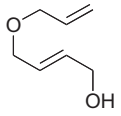
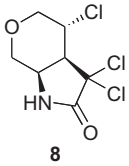


Entry	Overman rearrangement	RCM reaction	Kharasch cyclisation	Yield[a] (%)
1	MeCN (10%), 0.5 h	rt, 3 h	0.5 h	24
2	SiC PHE, 1 h	rt, 1 h	0.5 h	42
3	SiC PHE, 1 h	MW 60 °C, 0.75 h	0.5 h	44
4	SiC PHE, 1 h	MW 60 °C, 0.25 h	0.75 h	64

[a] Isolated yield from (2*E*)-octa-2,7-dien-1-ol (**1**).

Table 2
Comparison of microwave-promoted and thermal tandem processes



Entry	Allylic alcohol	Bicyclic γ-lactam	Reaction conditions: (1) Overman rearrangement; (2) RCM; (3) Kharasch cyclisation	Yield[a] (%)
1	 **1**	 **2**	(1) MW 180 °C, 1 h; (2) MW 60 °C, 0.25 h; (3) MW 180 °C, 0.75 h[b]	64
			(1) Δ, 140 °C, 18 h; (2) rt, 1 h; (3) Δ, 155 °C, 4 Å MS, 2 h[c]	61
2	 **3**	 **4**	(1) MW 180 °C, 1 h; (2) MW 60 °C, 0.25 h; (3) MW 180 °C, 1.25 h[b]	50
			(1) Δ, 140 °C, 18 h; (2) rt, 1 h; (3) Δ, 155 °C, 4 Å MS, 4 h[c]	48
3	 **5**	 **6**	(1) MW 180 °C, 1.5 h; (2) MW 60 °C, 0.5 h; (3) MW 180 °C, 1 h[b]	44
			(1) Δ, 140 °C, 136 h; (2) rt, 1 h; (3) Δ, 155 °C, 4 Å MS, 3 h[c]	39
4	 **7**	 **8**	(1) MW 180 °C, 1 h; (2) MW 60 °C, 0.5 h; (3) MW 180 °C, 5 h[b,d]	43
			(1) Δ, 140 °C, 72 h; (2) rt, 1.5 h; (3) Δ, 155 °C, 4 Å MS, 3 h[c,d]	45

[a] Isolated yields from allylic alcohols.
[b] All steps were promoted by microwave heating using a SiC passive heating element.
[c] Overman rearrangement and Kharasch cyclisation were carried out under standard thermal conditions.
[d] RCM and Kharasch steps were accomplished using the Hoveyda–Grubbs 2nd generation catalyst.

for the synthesis of bicyclic γ-lactams in which all three-steps are accelerated using microwave heating. For comparison, the synthesis of these compounds under standard thermal conditions is also described.

The development of a microwave-assisted tandem process was initially studied using (2*E*)-octa-2,7-dien-1-ol (**1**) (Table 1).[11] This was converted into the allylic trichloroacetimidate using trichloroacetonitrile and DBU under standard conditions.[12] Our previous tandem process for the synthesis of bicyclic γ-lactams used toluene as the solvent. However, toluene is an example of a microwave transparent solvent due to its inability to absorb effectively the microwave energy (low tan δ value).[2] Thus, our initial attempt involved using more polar acetonitrile as a co-solvent (entry 1). The Overman rearrangement was carried out at 180 °C in a microwave reactor and was complete in 0.5 h. The reaction vessel was cooled to room temperature and Grubbs 1st generation catalyst (10 mol %) was added. After 3 h, molecular sieves were added[13] and the microwave reactor was again heated to 180 °C. Although the three steps were complete in only 4 h, (1*S**,5*S**,6*S**)-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**2**) was isolated in only 24% overall yield from allylic alcohol **1**.[14]

Other co-solvents that are known to absorb microwave energy more efficiently such as DMSO, acetic acid and chlorobenzene were briefly investigated but all interfered with the various steps of the tandem process resulting in low yields of **2**. Kremsner and Kappe showed that microwave-assisted reactions could be done in non-polar solvents using silicon carbide bars as passive heating elements (PHE).[15] This chemically inert and strongly microwave absorbing material can transfer thermal energy to the reaction mixture via conduction phenomena. Thus, a second attempt at the microwave-assisted synthesis of bicyclic γ-lactam **2** was carried out in toluene using silicon carbide PHE throughout (entry 2). Under these conditions both the Overman rearrangement and the RCM step were complete in one hour, producing bicyclic γ-lactam **2** after the Kharasch cyclisation in a much-improved 42% yield. The next attempt then investigated the use of microwave heating (at 60 °C) of the RCM step (entry 3). This gave bicyclic γ-lactam **2** in a slightly improved 44% yield. Using NMR spectroscopy to investigate the progress of the tandem process under these conditions, it was found that the RCM reaction could be completed more rapidly, while the Kharasch cyclisation required slightly more time for complete conversion (entry 4). These optimised conditions allowed the isolation of bicyclic γ-lactam **2** after only 2 h in 64% overall yield.

With these optimised conditions in hand, a number of other allylic alcohols were subjected to the microwave-assisted tandem process (Table 2).[16] For comparison, the three-step tandem process for each substrate was also performed under standard thermal conditions. In all cases, the bicyclic γ-lactams were isolated much more cleanly using the microwave-promoted process than under the standard thermal conditions. However, the most dramatic difference between the two types of reaction conditions is the time required for completion of the tandem process. Bicyclic γ-lactams **2** and **4** could be prepared in 2 and 2.5 h, respectively, under microwave conditions, while requiring nearly one day under standard thermal conditions. The heterocyclic analogues **6** and **8** could be prepared in 3 and 6.5 h, respectively, using the microwave-promoted process while requiring several days under standard thermal conditions. Although the microwave heating of the RCM and Kharasch steps does, in most cases, lead to significant shortening of reaction times,[17] it is the acceleration of the Overman rearrangement that leads to the dramatic differences observed between the microwave and thermal tandem processes.[18] Furthermore, while developing the microwave-promoted tandem processes shown in Table 2, it was found that the short reaction times for the Kharasch cyclisation meant that the addition of molecular sieves was not required.

In summary, a one-pot tandem process where all three-steps are promoted by microwave heating has been developed for the effective synthesis of a series of bicyclic γ-lactams. These new conditions allow the synthesis of the bicyclic γ-lactams more cleanly, more reproducibly and in significantly shorter reaction times compared to standard thermal conditions. In particular, this new approach circumvents the problems and limitations of using palladium(II)-catalysed or thermal Overman rearrangements during the three-step tandem process for the synthesis of heteroatom derived bicyclic γ-lactams.

Acknowledgements

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16. *General procedure:* The allylic alcohol (0.4 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To the solution was added DBU (0.5 equiv) and trichloroacetonitrile (1.5 equiv). The reaction mixture was allowed to warm to room temperature before stirring for 2 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated in vacuo to give the allylic trichloroacetimidate which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (5 mL) and transferred to a microwave vial containing K_2CO_3 (0.02 g) and a silicon carbide (SiC) bar. The vial was then sealed under Ar and the reaction mixture heated in a microwave reactor (Biotage initiator, 300 W) for the required time at 180 °C. Grubbs first-generation catalyst (10 mol %) was added and the mixture was heated at 60 °C until complete. The temperature was then raised to 180 °C and heating continued until the reaction was complete. Purification was carried out by flash column chromatography eluting with petroleum ether/EtOAc to afford the desired bicyclic γ-lactam.
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