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Continuous flow ring-closing metathesis, an environmentally-friendly access to 2,5-dihydro-1*H*-pyrrole-3-carboxylates

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2,5-dihydro-1H-pyrrole-3-carboxylates are important building blocks for the synthesis of high value pyrroles and pyrroloquinoline derivatives with interesting biological activities. The use of continuous flow allowed to perform a key synthetic step, namely ruthenium-catalyzed ring-closing metathesis, with a residence time of 1 min at 120°C. Dimethyl carbonate, a green solvent, was demonstrated for the first time to be excellent for this reaction in continuous flow. The continuous flow conditions proved general and scale-up of this reaction was not only possible, but also highly efficient. Conversion of 10 grams of diene was realized in 37 minutes under continuous flow, yielding the desired heterocycle in 91% yield.

Introduction

Olefin metathesis is becoming more and more used at the industrial level for the synthesis of API (Active Pharmaceutical Ingredients).[1] For example, ring-closing metathesis (RCM) was applied to the synthesis of ciluprevir (BILN-2061), a pseudopeptide inhibitor of HCV NS3 protease (Figure 1).[2] Vaniprevir (MH-7009), a ciluprevir analog which synthesis also requires a RCM step, is now evaluated in phase III clinical trials.[3] The six-membered ring oseltamivir phosphate, also known as Tamiflu, and used in the treatment of influenza, could also be synthesized thanks to a RCM process.[4] The seven-membered heterocyclic ring in SB-462795, a cathepsin K inhibitor for the treatment of osteoporosis, was also obtained using RCM as a key step.[5]

In this context, beside our general interest in olefin metathesis, specifically using greener solvents such as poly(ethylene)glycol, glycerol and water,[6] we recently demonstrated that 2,5-dihydro-1*H*-pyrrole-3-carboxylates could be obtained via ring-closing metathesis (RCM) using

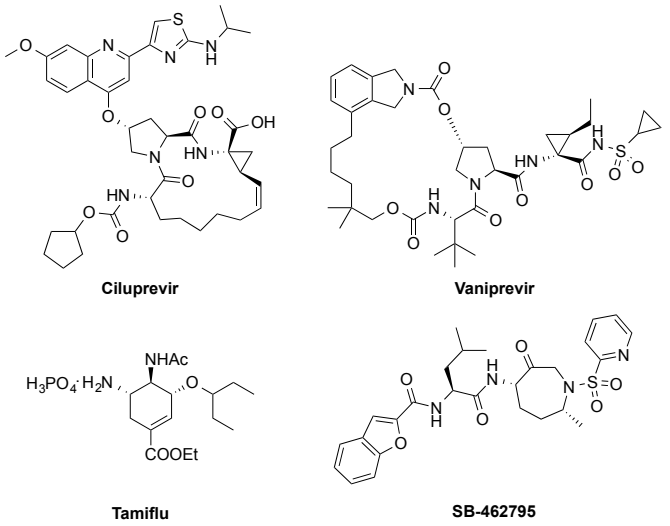

Figure 1. Pharmaceutical drugs synthesized using olefin metathesis

ethyl acetate as a solvent, and 1 mol% of **NO_2-Grela**[7] as catalyst (Figure 2). These compounds were then converted efficiently into the corresponding pyrroles, which are highly versatile building blocks for biologically active compounds (Scheme 1).[8] We also demonstrated that the 2,5-dihydro-1*H*-pyrrole-3-carboxylate **2a** was a highly significant intermediate in the synthesis of pyrroloquinolines,[9] which behave as 5-HT_6 receptor neutral antagonists. These compounds, displaying pro-cognitive properties, might be useful in the treatment of cognitive decline associated with Alzheimer's disease and cognitive disorders caused by genetic abnormalities.[9a, 10] Ring-closing metathesis on substrates similar to **1a**, bearing an

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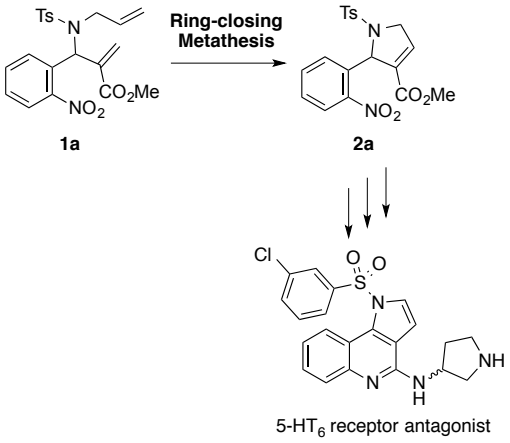


Scheme 1. Synthesis of high value molecules through metathesis[9a]

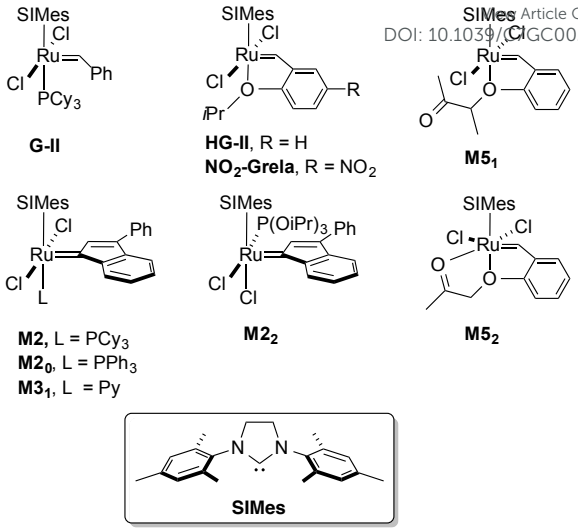
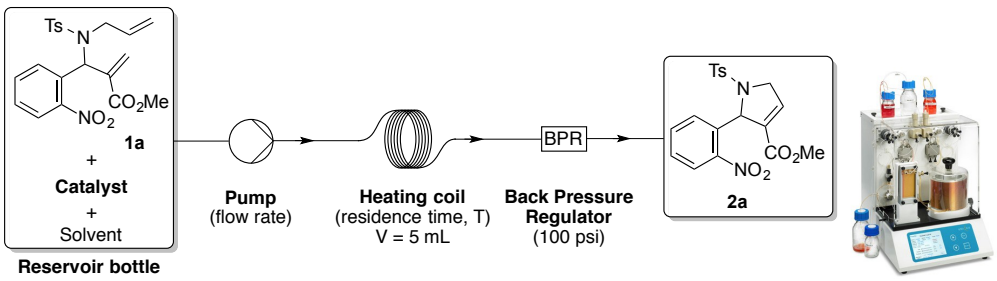


Figure 2. Structure of the catalysts screened in this study

electron-withdrawing group on the olefin, is usually more difficult than RCM of benchmark substrates such as diallyltosyl amine.[11] An improvement of the method consisted in performing the reaction under microwave activation, which allowed to reduce the reaction time to 5 min.[9c, 11b, g, h] However, scalability of the microwave conditions still represents a huge challenge for this method. One efficient way to circumvent this issue would be to use continuous flow chemistry. Indeed, high temperature microwave synthesis could be easily translated to continuous flow synthesis, since both techniques allow efficient heating/cooling and generation of a superheated solvent.[12] In order to obtain reaction conditions that could be applicable on even a larger scale, we decided to focus on the RCM of **1a** using continuous flow chemistry. Continuous flow is more and more prevalent in organic chemistry,[13] providing several advantages over batch synthesis.[14] As low quantities of reagents are in contact with each other in microfluidic systems, a perfect control of stoichiometry,[15] important for the selectivity of reactions, as well as the control of exothermic reactions,[16] could be envisaged. In addition, versatile conditions, in terms of temperature, pressure and flow rates, could be applied, to facilitate optimisation process.

The literature reports dealing with ruthenium-catalyzed metathesis under continuous flow conditions remain scarce[17] and they focus mostly on the development of heterogeneous catalysts.[18] Since, for the moment, most heterogeneous catalysts showed limited recyclability, our approach was to focus on the development of environmentally friendly conditions using easily available homogeneous catalysts.

Table 1. Optimization of the RCM continuous flow conditions[a]



Entry	Solvent	T (°C)	Res. Time (min.)	HPLC Conv. (%)								
				G-II	NO_2-Grela	HG-II	$M5_1$	$M5_2$	M2	$M2_0$	$M3_1$	$M2_2$
1	CH_2Cl_2	90	30	72	74	94	96	14	98 (84)[b]	94	25	35
2	AcOEt	90	30	75	73	95	85	22	23	60	23	88
3	DMC	90	30	74	84	94	82	10	98	50	21	75
4		110	5	76	85	94	78	7	98	57	11	77
5	DMC	120	1	71	73	85	69	5	96	46	19	53
6		130	5									92

[a] Reaction conditions: **1a** (0.125 mmol), catalyst (3 mol%), solvent (1 mL), T, residence time; HPLC conversions of **1a** into **2a** are given. See Table S1 in SI for the complete optimization. [b] 2 mol% catalyst were used.

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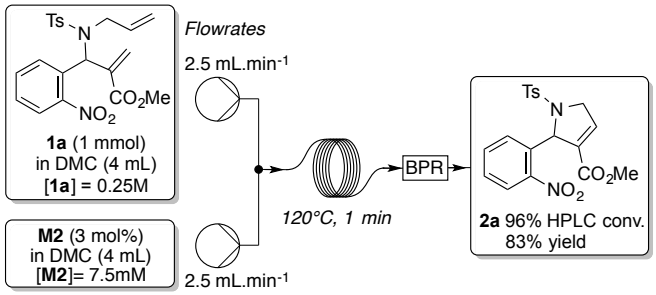
Results and discussion

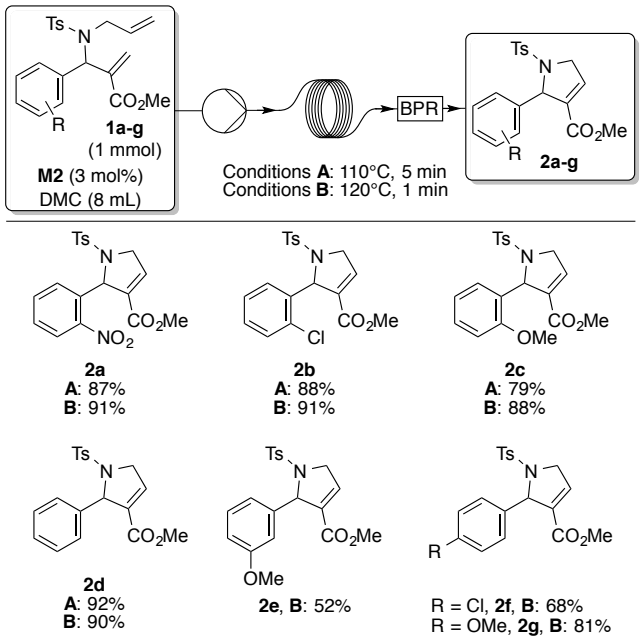
Reactions were performed using a Uniqsis Flowsyn system, and reagents (substrates and catalyst) were dissolved together in a single reservoir bottle prior to pumping into the residence coil. To make sure that this methodology could be robust and practically scalable, reactions were performed in air using ACS Grade solvents, without degassing or drying. Second generation commercially available catalysts, bearing *N*,*N*'-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene (IMes) as NHC ligand, from different families, were tested (Figure 2). Benzylidene (**G-II**[19]), boomerang-type (**HG-II**[20] and **NO_2-Grela**[7]), "Scorpio"[21] (**$M5_1$**[22] and **$M5_2$**[23]) and robust indenylidene[24] (**M2**,[25] **$M2_0$**, **$M3_1$**, **$M2_2$**[26]) catalysts were screened in the RCM of compound **1a**, with an *o*-NO_2 phenyl ring, in dichloromethane as solvent, at 90°C, with a residence time of 30 min and 3 mol% of ruthenium catalyst (Table 1, entry 1). Pre-catalysts **$M5_1$**, **HG-II**, **M2** and **$M2_0$**, which are more resistant to temperature than **G-II**, **NO_2-Grela**, **$M5_2$** and **$M3_1$**, gave the best HPLC conversions (up to 98%). Using **M2** as catalyst, reducing the catalyst loading from 3 to 2 mol% was detrimental to the reaction. While decreasing the residence time to 20 min at 90°C resulted in a lower conversion, a concomitant increase of temperature to 110°C allowed to obtain 94% conversion in only 5 min.[27] It is important to note that traces (up to 5%) of isomerization of **1a**, resulting from the formation of a ruthenium hydride species,[6f] were detected in the crude reaction mixtures; interestingly, the amount of isomerization was below 1% when **$M5_2$**, **M2**, **$M2_0$** and **$M3_1$** were used.[27]

Although those conditions could be suitable for efficient RCM, in a continuous effort to find environmentally friendly conditions,[6a-e] we decided to search for a greener solvent than dichloromethane. Previous studies in batch showed that ethyl acetate and dimethyl carbonate (DMC) could be suitable solvents for RCM.[28] In addition, these solvents were classified as non-toxic for the industrial synthesis of API.[29] Since it was an appropriate solvent for the RCM of **1a** in batch,[8] ethyl acetate was first tested (Table 1, entry 2). Reactions using **HG-II**, **$M5_1$** and **$M2_2$** gave interesting HPLC conversions (>85%) in AcOEt, but results were not better than in dichloromethane. DMC was then evaluated for the first time, to the best of our knowledge, in continuous flow RCM. To our delight, catalysts **HG-II** and **M2** gave excellent results in the conditions tested. Catalyst **M2**, which is a highly stable indenylidene-type pre-catalyst, allowed to reach almost full conversion when reactions were performed at 110°C for 5 min or at 120°C for 1 min (Table 1, entries 6-8). However, **HG-II** gave a lower conversion at 120°C, probably because of a slightly lower thermal stability. Additionally, isomerisation of **1a** was observed when **HG-II** was used (up to 5%). Finally, a third interesting set of conditions was found with catalyst **$M2_2$**, which has a latent character that already proved to be useful in RCM and polymerisation reactions.[26, 30] At 130°C, catalyst **$M2_2$** gave 92% conversion within only 5 min reaction (Table 1, entry 6).



Scheme 2. Continuous flow RCM of **1a** using 2 pumps

As stated above, reactions were run using one solution that was pumped into the residence coil. Since catalyst decomposition could occur rapidly when the catalyst is in the presence of alkene substrate, through the formation of a ruthenium methylidene species,[31] reactions were also performed using two separate solutions, one containing the substrate **1a**, the other one the catalyst. Catalysts **M2**, which is temperature stable and gave the best results in DMC, and **$M3_1$**, which activates faster and is thus more prone to decomposition, were tested. Then, the substrate and catalyst solutions were pumped at the same flow rate and mixed in a coil heated at 120°C. After a residence time of 1 min, as for Table 1, entry 5, conversions reached 96% and 19% with **M2** and **$M3_1$** resp., similar to the ones obtained in the one pump experiments. This is demonstrating that decomposition, if happening, does not distort the results obtained in Table 1 using a single reservoir bottle. Performed on a 1 mmol scale, conditions with **M2** using two separate solutions gave, after 1 min residence time at 120°C, filtration over silica, evaporation and precipitation from diethyl ether, cyclized compound **2a** in 83% yield (Scheme 2). Such result permits to envision the use of an automated system, allowing the screening of substrates or catalysts.



Scheme 3. Continuous flow metathesis of substrates **1a-g**. Reaction conditions: **1a-g** (1.0 mmol), **M2** (3 mol%), DMC (8 mL), 110°C, 5 min (conditions **A**) or 120°C, 1 min (conditions **B**). Isolated yields are given.

In the next step, we investigated the utility of the developed method for the RCM of compounds **1b-g**, bearing different substituents on the phenyl ring (Scheme 3). Two sets of experimental conditions (A: 110°C for 5 min and B: 120°C for 1 min) were compared using substrates **1a-d** to select the one that would give the best results. Compounds **2a-d**, bearing respectively a nitro group, a chlorine atom, a methoxy group or a hydrogen atom in *ortho* position of the phenyl ring were obtained through RCM, after evaporation and precipitation from diethyl ether. Experimental conditions B resulted in shorter reaction time and provided slightly better yields. Conditions B were thus selected and applied to substrates **2e-g**, bearing a chlorine atom or a methoxy group either in *meta* or *para* position of the phenyl ring. Compound **2e, 2f** and **2g** were isolated in 52%, 68% and 81% yield, respectively. In all the cases, conversion was almost complete and neither degradation nor intermolecular unwanted side reaction that would have given dimer side-products were observed. Moderate yields were mainly due to incomplete precipitation during product isolation.[27]

Continuous flow is an innovative technology since, once optimal conditions are found, they can be directly applied to reaction scale-up. The RCM of 10g (23 mmol) of compound **1a** was thus attempted, using 3 mol% of **M2** catalyst in DMC, with a reaction coil heated at 120°C and a flow rate to ensure a 1 min residence time. Gratifyingly, 10g of substrate were pumped into the continuous flow system within 37 min and the cyclized dihydropyrrole **2a** could be isolated in 91% yield, which is exactly the same yield as obtained on a 1 mmol scale (Scheme 4). In comparison, RCM of 15g of **1a** in batch gave less satisfying results.[8] To confirm that the RCM reaction proceeded in the reaction coil and not in the reservoir bottle before pumping into the coil, the conversion was checked, in the reservoir solution, after 37 min. Less than 5% conversion was measured, demonstrating that the RCM process required heating at 120°C in continuous flow.

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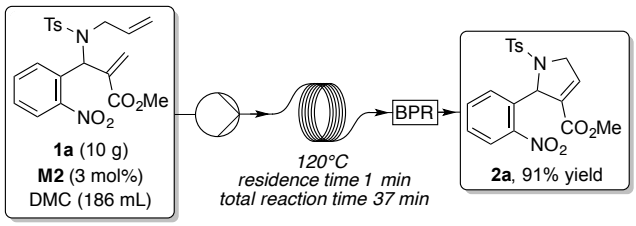

Scheme 4. Continuous flow RCM of 10g of **1a** in 37 min.

Since **HG-II** is one of the most used catalyst for API synthesis, it was also evaluated on larger scale using conditions from Table 1, entry 4. Thus, on a 2 mmol scale with a residence time of 5 min at 110°C in DMC, cyclized compound **2a** was isolated in 92% yield. Total reaction time was 16 min in this case. **HG-II** is thus a good candidate for large scale RCM, even though, on the same scale, total reaction time would be longer than with **M2**. In addition, isomerization of **1a** also occurred on this scale; the undesired isomer was separated from **2a** upon precipitation, and then isolated and fully characterized.[27]

Conclusions

We reported in this study a highly efficient continuous flow protocol allowing the ring-closing metathesis of dienes **1a-g** to obtain 2,5-dihydro-1*H*-pyrroles **2a-g**. We demonstrated that dimethyl carbonate, an environmentally friendly solvent, was an excellent solvent for the metathesis reaction in flow, which could be completed within 1 min at 120°C. In addition, scaling-up the reaction using continuous flow, from 1 to 23 mmol, did not change the outcome of the ring-closing metathesis, and yielded the cyclized compound **2a** in 91% yield after 37 min.

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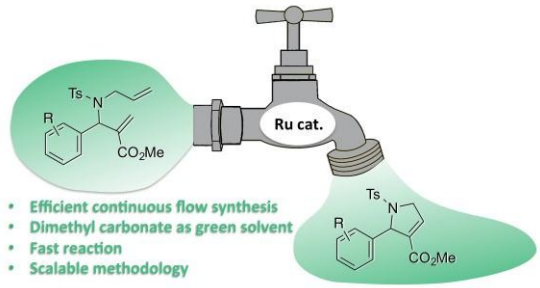

Ring-closing metathesis, realized for continuous flow using dimethyl carbonate as solvent, allowed to convert up to 10g of dienes into important building blocks.