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Efficient microwave-assisted formation of functionalized 2,5-dihydropyrroles using ruthenium-catalyzed ring-closing metathesis

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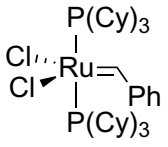
Abstract—A rapid method for the formation of functionalized 2,5-dihydropyrroles using ruthenium-catalyzed ring-closing metathesis under microwave irradiation is presented. The diene substrates were efficiently prepared from aza-Baylis–Hillman adducts.

Ring-closing metathesis (RCM) has become one of the most powerful and versatile methods for the formation of cyclic organic structures.[1] The increasing popularity of this technique can be traced to the development of efficient, commercially available air-stable ruthenium catalysts (**1**, **2**), which show high tolerance towards a wide variety of functional groups.[2] The increased thermal stability of the Grubbs' second generation catalysts, here exemplified by **2**, further improved the usefulness of this method and allowed for efficient performance of reactions at elevated temperatures. The latter is particularly important for the formation of heavily substituted olefins (tri- and tetra-substituted) carrying electron-withdrawing groups, since these substrates typically result in low conversion when reactions are performed at room temperature.



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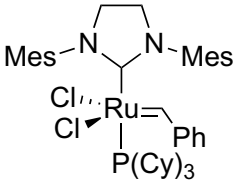
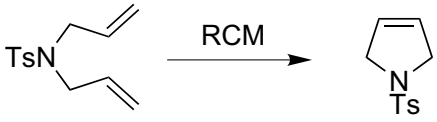


2

The formation of heterocyclic compounds represents one of many applications where RCM has been successfully employed.[3] One particular transformation, the ring closure of *N*,*N*-diallyl *p*-toluensulfonamide yielding *N*-tosyl-2,5-dihydropyrrole, is often used as a model reaction in the evaluation of novel RCM catalysts (Scheme 1).[4] However, the formation of substituted 2,5-dihydropyrrole derivatives using RCM has so far been limited to a few examples. This is further accentuated when it comes to the formation of compounds containing electron-withdrawing substituents.[5]

Naturally, one of the limiting factors for the preparation of heterocyclic compounds using RCM, is the availability of the appropriate dienes as starting materials. One such class of dienes can be obtained easily using Baylis–Hillman chemistry.[6] The Baylis–Hillman reaction as well as its aza-analog, is a powerful method for the formation of highly functionalized compounds.[7,8] Herein we report on the efficient use of aza-Baylis–Hillman adducts for the formation of 2,5-dihydropyrroles using ring-closing metathesis.



Scheme 1.

Keywords: Ring-closing metathesis; 2,5-Dihydropyrroles; Aza-Baylis–Hillman reaction; Microwave assisted synthesis.
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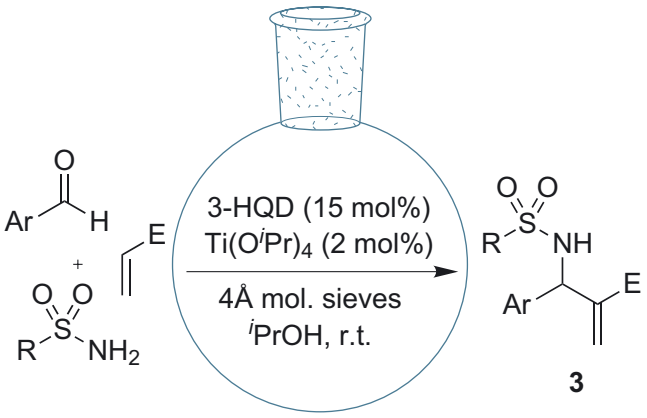
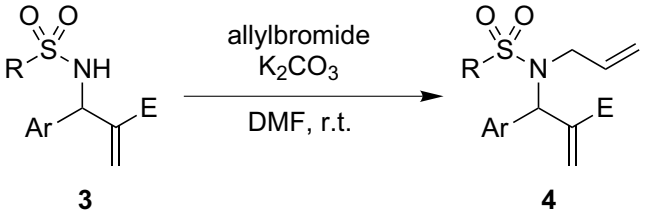


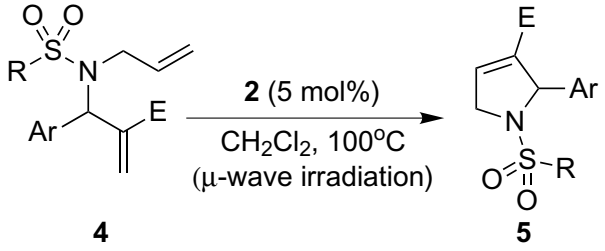
Scheme 2.

We have recently developed an efficient and reliable one-pot protocol for the aza-Baylis–Hillman (aza-BH) reaction (Scheme 2).[9] In this combined Lewis acid- and base-catalyzed three-component reaction we successfully and selectively formed α-methylene-β-amino acid derivatives starting from arylaldehydes, sulfonamides and various Michael acceptors. With the aza-BH adducts in hand, we realized that these compounds, properly functionalized, would serve as ideal building blocks for the preparation of 2,5-dihydropyrroles using RCM. Thus, treating the adducts **3** with allyl bromide under basic conditions gave the corresponding N-allylated compounds **4** in a 'spot to spot' reaction, and after simple extractive workup, the diene-products were isolated in high yields (Scheme 3).[10]

These diene-substrates were subsequently submitted to the RCM reaction employing catalyst **2**. In an initial ring-closing experiment, the allylated aza-BH adduct **4a** and catalyst **2** (5 mol%) were dissolved in dichloromethane (0.05 M substrate concentration), and the solution was heated to 125 °C for 10 min using microwave irradiation. The resulting reaction mixture was evaporated under reduced pressure and the crude product was analyzed by ^{1}H NMR spectroscopy. The spectrum obtained revealed no traces of starting material and the 2,5-dihydropyrrole-derivative **5a** was the only observable compound. In an optimization of this reaction we found that increasing the substrate



Scheme 3.



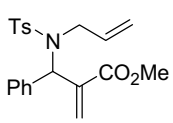
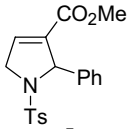
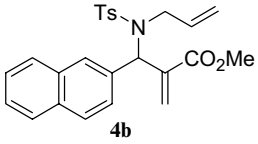
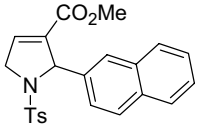
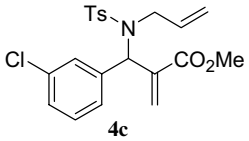
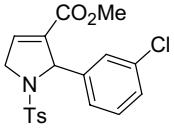
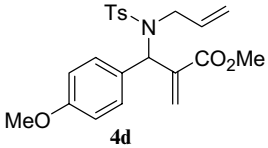
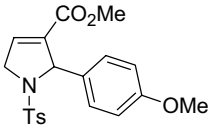
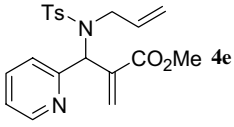
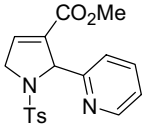
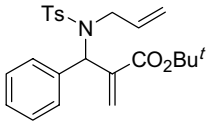
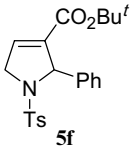
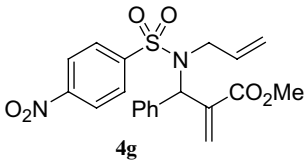
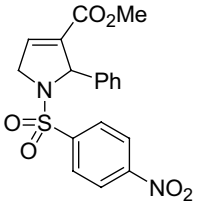
Scheme 4.

concentration to 0.1 M and performing the reaction at 100 °C resulted in full conversion of the starting material into **5a** in 60 s (Scheme 4). The use of microwave irradiation has proven to be particularly effective in a number of chemical transformations.[11] Although nonthermal microwave effects have been claimed to operate in the RCM reaction,[12] Kappe and co-workers recently showed that the reaction progresses equally well independently of the type of heating used.[13,14] In fact, for simple substrates, the RCM reaction works sufficiently well even at room temperature. In our case, however, heating turned out to be crucial for the reactivity. Performing the RCM reaction of the electron-deficient substrate **4a** at room temperature resulted in the formation of a small amount of product **5a**, however, after 48 h there was still a considerable amount of starting material left unreacted.

With the optimized conditions in hand, we submitted a number of allylated aza-BH adducts (**4a**–**g**) to the RCM reaction and the results are presented in Table 1,[15] which shows that most substrates were converted into the desired ring-closed products (**5a**–**g**)[16] within 1 min reaction time. The only exception was the RCM reaction of the sterically more congested *tert*-butyl ester **4f**, which required an additional 60 s for full conversion (entry 6). In addition, the 4-nitrosulfonyl derivative **4g** reacted smoothly and furnished the nosyl-functionalized 2,5-dihydropyrrole **5g** in good yield (entry 7). There are good opportunities for further synthetic manipulations of this particular compound since the conditions required for nosyl removal are significantly milder then those available for *N*-tosyl deprotection.[17]

In conclusion, we have demonstrated how N-allylated aza-Baylis–Hillman adducts can be efficiently transformed into functionalized 2,5-dihydropyrrole-derivatives using ring-closing metathesis under microwave irradiation. The 2,5-dihydropyrrole products were isolated in high yields after simple filtration of the reaction mixture to remove the catalyst followed by evaporation of the solvent. Hence, from a practical point of view, this is a rapid, convenient and simple method for the formation of this particular class of heterocyclic compounds.

Table 1. Efficient formation of 2,5-dihydropyrrole-derivatives catalyzed by **2**[a]

Entry	Diene	Product	Time (s)	Yield[b] (%)
1	 **4a**	 **5a**	60	92
2	 **4b**	 **5b**	60	95
3	 **4c**	 **5c**	60	91
4	 **4d**	 **5d**	60	78
5	 **4e**	 **5e**	60	95
6	 **4f**	 **5f**	120	90
7	 **4g**	 **5g**	60	90

[a] Reaction conditions: a solution of diene **4** (0.5 mmol) and catalyst **2** (5 mol %) in CH_2Cl_2 (5 mL; [**4**]=0.1 M) were microwave irradiated in a sealed tube for 60 s with the temperature set to reach 100 °C.
[b] Isolated yields.

Acknowledgements

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15. *General experimental procedure* exemplified for the formation of **5a**. A solution of diene **4a** (0.5 mmol) and catalyst **2** (5 mol %) in CH_2Cl_2 (5 mL) was microwave irradiated in a sealed tube for 60 s at 100 °C (temperature control, fixed hold time off, normal absorption mode) using an Emry's™ Creator. The reaction mixture was filtered through a short plug of silica, followed by evaporation of the solvent to yield 165 mg (92%) of the pure product (as white crystals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, $J = 8.3$ Hz, 2H), 7.22–7.25 (m, 5H), 7.14 (d, $J = 8.3$ Hz, 2H), 6.78 (dd, $J = 4.1$, 2.4 Hz, 1H), 5.72–5.76 (m, 1H), 4.51 (dt, $J = 17.0$, 2.4 Hz, 1H), 4.38 (ddd, $J = 17.0$, 5.7, 1.9 Hz, 1H), 3.58 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 143.3, 139.4, 135.8, 135.6, 135.5, 129.5, 128.3, 128.0, 127.8, 127.1, 69.0, 55.0, 51.8, 21.5; MS (MALDI-TOF) (m/z) 396.29 (MK^+) 380.28 (MNa^+) 358.28 (MH^+).
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