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Pyrrole synthesis using a tandem Grubbs' carbene–$RuCl_3$ catalytic system

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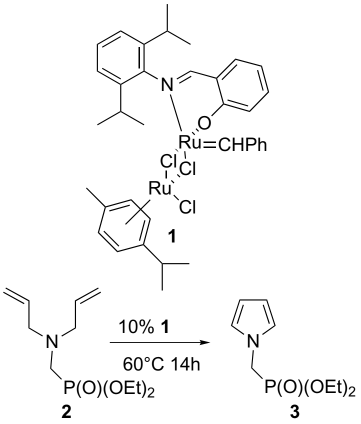
Abstract—A straightforward pyrrole synthesis from diallylamines is developed by using a tandem catalyst system leading to ring-closing metathesis with the second generation Grubbs' catalyst (10%) followed by dehydrogenation in the presence of $RuCl_3 \times H_2O$ (2%).

In view of the wide range of physiological activities, α-aminophosphonic acids have received a lot of attention by several research groups. Several of these derivatives have proven to be enzyme inhibitors,[1,2] herbicides (e.g., glyphosate) or neurotransmitters.[3,4] During our efforts to evaluate new azaheterocyclic phosphonates for agricultural applications,[5–7] the possibility of ring-closing metathesis with new ruthenium catalysts was explored. During one of our experiments using the novel bimetallic catalyst **1**[8] on aminophosphonate **2**, we were surprised to isolate pyrrole **3** instead of the expected corresponding 3-pyrroline, suggesting that not only ring closing took place but also isomerization[9] and dehydrogenation (Scheme 1).



Scheme 1.

Literature study revealed that pyrrole formation was reported only twice as a side reaction during ring-closing metathesis. Evans et al.[10] mentioned the observation of some pyrrole formation in a single experiment using first generation Grubbs' catalyst at elevated temperature. Yang et al.[11] prepared some pyrroles under microwave conditions using second generation Grubbs' catalyst. Neither of these articles however provided a more general method of preparing pyrroles from the corresponding amines. Since the importance of the pyrrole nucleus is proven by its presence in both natural and synthetic biologically active compounds,[12] we decided to further investigate this phenomenon in order to develop a new synthetic approach to this heterocycle. However, when more reactions were evaluated, it proved impossible to achieve similar results. It even proved to be impossible to repeat our results formerly obtained. Because of this, we evaluated some other Ru-species that could catalyze the formation of pyrroles since use of the second generation Grubbs' catalyst

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Keywords: Ring-closing metathesis; Pyrrole synthesis.

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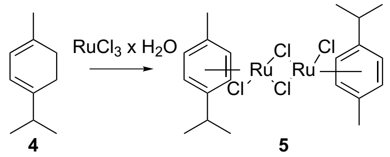
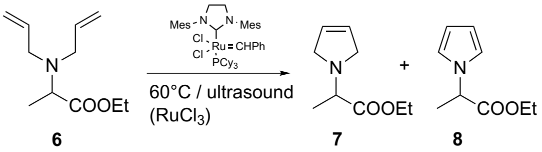


Scheme 2.



Scheme 3.

alone at high temperatures resulted only in the formation of small amounts of the pyrroles (maximal 30% in the crude reaction mixture). Rationalizing our observations in combination with the fact that it is known that several transition metal compounds can catalyze both hydrogenation and dehydrogenation,[13] we deduced that maybe trace amounts of $RuCl_3$ were present during our initial experiments, thus favouring the pyrrole formation. This compound was used to synthesize Ru-dimer **5** from **4**,[14] by a dehydrogenation (Scheme 2). This dimer was then used in the synthesis of **1**.

In a quick test 10% second generation Grubbs' catalyst and some $RuCl_3 \times H_2O$ was added to a solution of **6** in chlorobenzene and the mixture was heated at 60 °C overnight. It was found that the ^1H NMR spectrum only showed the presence of **8** and not the corresponding 3-pyrroline **7**. However, a strong signal in the aromatic region was also observed, showing that a large portion of the product had polymerized. The latter might be explained by the fact that pyrrole could be polymerized thermally or is unstable in the presence of a large quantity of $RuCl_3 \times H_2O$. After evaluation of different solvents (chlorobenzene, dichloromethane and 1,2-dichloroethane), different time–temperature conditions and variable amounts of $RuCl_3 \times H_2O$, the best results were achieved using 10% second generation Grubbs' catalyst with 2% $RuCl_3 \times H_2O$ (both added in two portions within a 2 h period) in 1,2-dichloroethane at 60 °C in an ultrasonic bath. The beneficial influence of the ultrasonic bath is probably due to the formation of a fine dispersion of the $RuCl_3 \times H_2O$ in the reaction mixture, thus greatly increasing its active surface. Following these conditions **6** was converted to **8** in more than 90% as followed by ^1H NMR. In order to exclude the possibility that the pyrrole formation was solely by the action of the second generation Grubbs' catalyst, a comparative study was performed in which the ring closing and dehydrogenation of the alanine derivative **6** was followed by ^1H NMR with and without $RuCl_3 \times H_2O$. In both cases the formation of the corresponding pyrroline **7** and pyrrole **8** was observed, but the pyrrole formation was greatly favoured in the presence of 2% $RuCl_3 \times H_2O$ (Scheme 3). As shown in Figure 1, the initial rate of pyrrole formation is about the same in both cases. However, in the presence of 2% $RuCl_3 \times H_2O$, the relative amount of **7** never exceeds the relative amount of **8**. After 12 h at 60 °C the amount of **7** has dropped to about 20% at which time there is still about 45% left in the case without $RuCl_3 \times H_2O$. When second generation Grubbs' is used at lower temperatures, no pyrrole formation is observed. This might suggest that at higher temperatures, some other Ru-species are formed, due to the decomposition of the catalyst, which catalyze the dehydrogenation.

In order to test the general applicability of this reaction, we applied the same methodology on a number of substrates and were able to produce a variety of pyrroles in good to excellent yields although a great loss was often observed during purification (Table 1).[15] An extreme example is entry j, since no pyrrole could be isolated and only decomposition products were recovered. Elevating the reaction temperature increased the speed of dehydrogenation, however several pyrroles proved to be unstable when subjected to elevated temperatures (above 70 °C) in the presence of both Grubbs' second generation catalyst and $RuCl_3 \times H_2O$ for a long period of time. Amines with an electron withdrawing group on the N-atom (Tos, Boc, Ac) did not dehydrogenate to the pyrrole but gave the expected pyrrolines in excellent yields (>95% within minutes) as also observed by other groups.[16] This proves that the basicity of the N-atom plays a crucial role in the dehydrogenation and might suggest that coordination between the N-atom and a Ru species initiates the reaction.

Although RCM on vinyl chlorides has been reported before,[17] we were unable to produce a Cl-substituted pyrrole (entry h). Even upon lowering the concentration only dimer was isolated.

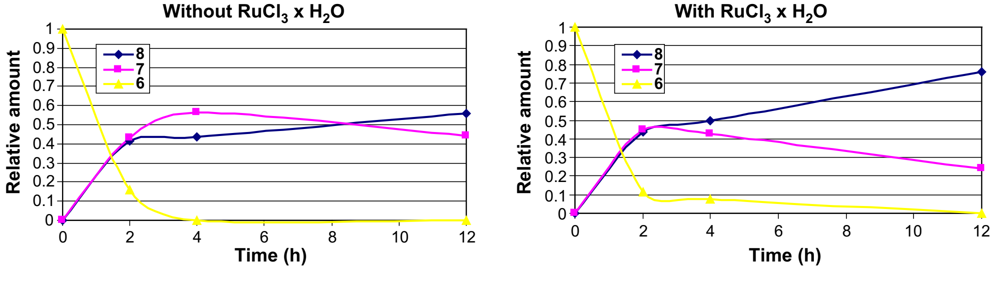
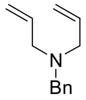
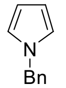
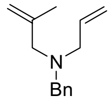
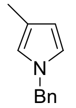
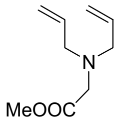
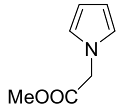
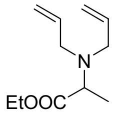
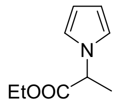
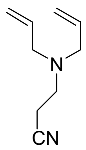
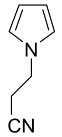
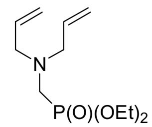
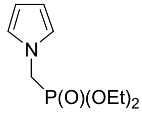
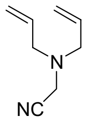
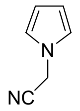
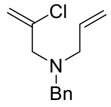
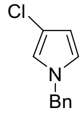
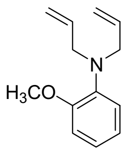
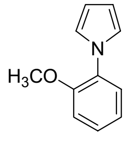
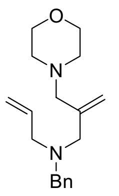
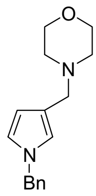


Figure 1. Comparison of pyrrole formation catalyzed by the second generation Grubbs' catalyst with and without $RuCl_3 \times H_2O$.

Table 1. Synthesis of different pyrroles using second generation Grubbs' catalyst in combination with $RuCl_3 \times H_2O$

Entry	Substrate	Pyrrole	Conversion[a] (%)	Yield[b] (%)
a			74	55
b			69	50
c			91	63
d			78	57
e			44	30
f			71	60
g			30	0
h			0	0
i			95	74
j			82	0

[a] Conversion determined by ^1H NMR on the crude reaction mixture.

[b] Yield after purification by flash chromatography.

In summary, a straightforward pyrrole synthesis from diallylamines was developed by a tandem ring closure–dehydrogenation reaction using a combination of Grubbs' catalyst and ruthenium(III)chloride. Further research on this catalytic couple for the synthesis of more challenging pyrroles and other heterocyclic systems as well as research towards the reaction mechanism is currently under investigation.

Acknowledgements

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15. Representative experimental procedure: In a dry reaction tube, 50mg of diallylamine is weighed and dissolved in 1,2-dichloroethane (0.05M). To this solution, 5mol% of Grubbs' second generation catalyst and 1mol% of $RuCl_3 \times H_2O$ is added. The tube is sealed and placed in an ultrasonic bath at 60–65°C. After 2h, the tube is removed from the ultrasonic bath, reopened and 5mol% of Grubbs' second generation catalyst and 1mol% of $RuCl_3 \times H_2O$ is added for a second time. The tube is placed back in the ultrasonic bath for an additional 10h. To check the conversion, 0.5mL of the reaction mixture is put into a small flask and the solvent is removed in vacuo. The residue is redissolved in $CDCl_3$ and a ^1H NMR spectrum is taken. If the spectrum shows the presence of remaining starting material, this is removed by an acid–base extraction (CH_2Cl_2). The combined solutions (in $CDCl_3$ and 1,2-dichloroethane) are coated on silica-gel and further purified by flash-chromatography (using an appropriate mixture of hexanes/ethylacetate as eluent).

The purity was checked by quantitative GC analysis (Agilent 6890 Series. Phase EC-5, length 30 m, ID 0.25 mm, film thickness 0.25 µm, FID-detector, carrier gas N_2, detector gas H_2).

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