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An efficient synthesis of nitrogen-containing heterocycles via a tandem carbenoid N–H insertion/ring-closing metathesis sequence

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ABSTRACT

A series of five- to eight-membered nitrogen-containing heterocycles were prepared via a general and efficient one-pot, two-component sequence featuring rhodium-catalyzed insertion of a vinyl-substituted α-diazocarbonyls into the N–H bond of a series of *tert*-butoxycarbonyl-(Boc)-protected amines, followed by ring-closing metathesis catalyzed by ruthenium benzylidene complexes. This methodology allows easy and convenient access to highly functionalized azacycloalkenes in moderate yields and excellent chemoselectivity in a single transformation.

Heterocyclic systems of the general type shown in Figure 1 are common structural motifs present in a variety of alkaloids[1] and so the development of new methods for their synthesis is of considerable interest to organic and medicinal chemists. A number of approaches for the synthesis of *N*-containing heterocycles have been developed, most lead to the formation of five- and six-membered ring systems, while the construction of eight- and nine-membered heterocycles is still quite limited.[2] One reaction class that has received considerable attention in recent years for the synthesis of oxygen and nitrogen heterocycles is ring-closing olefin metathesis (RCM).[3] For example, syntheses of medium-sized bicyclic lactams and six- to seven-membered oxoazacycloalkenes are known via this methodology.[4] Moreover, exceptional progress has been observed in the development of new synthetic methodologies for the construction of heterocyclic systems based on the chemistry of rhodium(II)-stabilized carbenoid intermediates.[5] Thus, by utilizing the ability of an α-diazocarbonyl moiety to insert regioselectively into the N–H bonds of amines, amides, or carbamates a variety of α-amino ketones, α-amino esters and nitrogen-containing heterocycles have been prepared.[6] In this report, we have applied an α-diazocarbonyl N–H insertion reaction in tandem with ring-closing metathesis to develop a general and efficient strategy for the construction of heterocycles containing various combinations of five- to eight-membered rings.

Synthesis of azacycles via a sequential two-step procedure: The methyl ester of commercially available *trans*-styryl acetic acid was used successfully as a substrate for the transfer of a diazo moiety with *p*-ABSA as a diazo transfer reagent and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base yielding the corresponding methyl styryldiazoacetate **1**.[7] This type of electron acceptor/electron donor substituted diazocarbon is less stable at room temperature than comparable acceptor/acceptor substrates and is more reactive in metal-catalyzed decomposition.[5d] Freshly prepared styryldiazoacetate **1** (Scheme 1) was immediately used in the N–H insertion reaction in order to minimize the electrocyclization of the α-diazocarbonyl and pendent olefin to the corresponding 3*H*-pyrazole[8] and to ensure the effective formation of a styrylcarbenoid intermediate. In addition, an excess of the carbamate trapping agent was used to ensure the effective capture of the rhodium-stabilized carbenoid intermediate.[9] The chemical yields of the insertion products of styryldiazoacetate **1** into the N–H bond of a series of carbamates were modest to good (Table 1). Screening of alternative dirhodium catalysts ($Rh_2(pfb)_4$, $Rh_2(OAc)_4$) and solvents (hexane, pentane, and benzene) did not have any significant effect on the reaction outcome. Additionally, when the Boc-protected alkenyl amines were used as limiting reagents, complex mixtures of products were obtained. Thus, it became apparent that the more stable and thus more selective

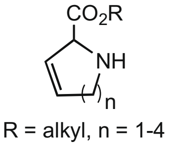

Figure 1. Nitrogen-containing heterocyclic systems.

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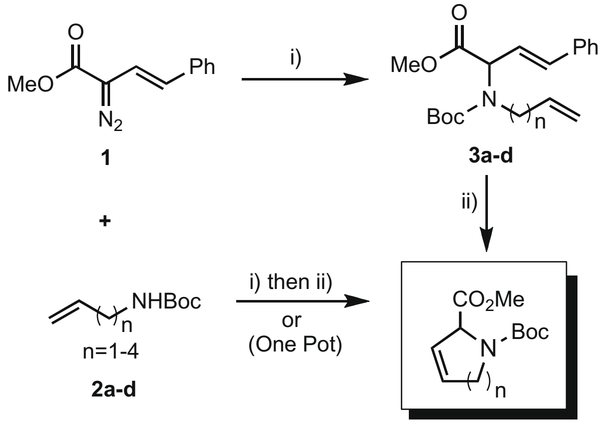
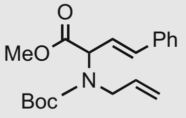
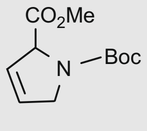
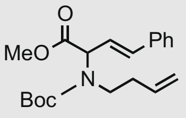
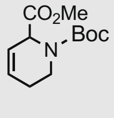
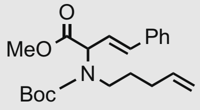
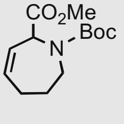
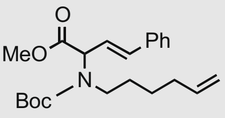
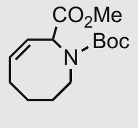


Scheme 1. General Strategy for the Synthesis of Azacycles. Reagents and conditions: (i) 1 mol% $Rh_2(S\text{-}DOSP)_4$, DCE, rt, 0.5 h; (ii) 8–10 mol% Grubbs or Hoveyda-Grubbs 2nd Generation, DCM, reflux, 1.5–3.5 h.

rhodium styrylcarbenoid was not electrophilic enough to insert efficiently into the N–H bond of an alkenyl carbamate, but did provide a usable chemical yield of insertion product. Fortunately, no cyclopropanation of the mono-substituted double bond was observed with carbenoids of this type, and this unique chemoselectivity allowed us to utilize the pendent olefin in the subsequent metathesis. Grubbs second generation catalyst or Hoveyda-Grubbs ruthenium benzylidene complexes were found to be suitable catalysts for the metathesis of the nitrogen-tethered dienes leading to the unsaturated monocyclic azacycles (Table 1). Each of the five- to eight-membered azacycloalkenes was isolated as a mixture of Boc-rotamers in excellent yields. A small decrease in yield was observed for the ring-closing metathesis of the eight-membered azacycle.

Table 1
N–H insertion/RCM of styryl diazoacetate **1** with N-Boc amines **2a–d**

Entry	N–H insertion product (yield %)[a]	RCM product (yield %)[a]
1	 **3a** (55%)	 **4a** (88%)
2	 **3b** (51%)	 **4b** (94%)
3	 **3c** (45%)	 **4c** (80%)
4	 **3d** (50%)	 **4d** (65%)

[a] Isolated yield after chromatography.

Table 2
Comparison of the two-step process and the one-pot approach

Substrate	Two-step (yield %)[a]	One pot (yield %)[a]
4a	48%	42%
4b	48%	57%
4c	36%	31%
4d	32%	30%

[a] Isolated yield after chromatography.

Synthesis of azacycles via a'one pot' tandem N–H insertion/RCM sequence: Having found reaction conditions for the rhodium-catalyzed N–H insertion and subsequent RCM that provided a good yield of the azacycle, we turned our attention to developing a protocol for a one-pot process. Tandem reactions are recognized as industrially applicable and highly atom economical transformations[10] so the extension of this methodology toward the multistep one-pot process was particularly appealing. In a recent example, Davies and co-workers have developed an enyne metathesis/Rh-catalyzed [4+3]-cycloaddition coupling strategy for the enantioselective synthesis of highly functionalized cycloheptadienes.[11] Similarly, Hodgson has shown that a one-pot cross metathesis reaction in tandem with carbonyl ylide formation/intramolecular cycloadditon can be executed with unsaturated 2-diazo-3,6-diketoesters.[12]

This study appears to be the first example of combining the N–H insertion/RCM reactions in a one-pot procedure for the construction of the nitrogen-containing monocycles. To ensure the success of the tandem process, several factors needed to be considered. For example, the initial N–H insertion must be chemoselective at low catalyst loading, in the presence of minimal quantities of the trapping reagent. In addition, reaction conditions of each step in the sequence had to be tuned carefully to minimize any byproduct formation that could suppress the subsequent metathesis step in the sequence. For this reason, 1 mol % or less of the rhodium catalyst was used, while the optimum loading of the corresponding *t*-boc alkenyl amine was determined to be 1.5 mol equiv based on methyl styryldiazoacetate **1**. The progress of the N–H insertion reaction was monitored by TLC and following the disappearance of methyl styryldiazoacetate **1**; Grubbs catalyst was added to the reaction mixture. Unfortunately, under these conditions no metathesis products were isolated, prompting us to consider an alternative of adding a solution containing rhodium catalyst and the N–H insertion products to a solution of the Grubbs catalyst. Thus, the subsequent carbamate tethered-diene products **3a**–**d** were added via cannula to a solution of the Grubbs catalyst at reflux and the reaction mixture was continued at reflux until the disappearance of the starting material was seen, as monitored by TLC. Gratifyingly, this tactic was successful, resulting in the formation of azaheterocycles **4a**–**d** in yields comparable to, or in one case better than the sequential process (Table 2). It is noteworthy to mention that the procedure developed by Diver and co-workers.[13] for work-up ($CNCH_2CO_2K$, 6 equiv in MeOH) was utilized to quench the reaction mixture followed by removal of the inactive polar metathesis catalyst via filtration through a short plug of silica.

In conclusion, a general synthetic strategy has been developed to construct five- to eight-membered azacycloalkenes. The newly devised methodology is a one-pot, two-component coupling process, consisting of the intermolecular N–H insertion of rhodium(II)-stabilized carbenoids in the presence of an olefin, followed by ring-closing metathesis of the corresponding acyclic azo-tethered diene. The isolated yield of the one pot process is comparable to that of the sequential reactions and thus, this protocol is applicable to the construction of biologically interesting heterocycles. Enantioselective N–H insertion and metathesis reactions are currently being developed for the synthesis of corresponding azacycles using newly developed copper complexes of chiral spiro-bisoxazolines.[14]

Acknowledgments

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Supplementary data

Detailed experimental procedures and characterization data for new compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.085.

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