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RHODIUM(II)-CATALYZED DECOMPOSITION OF VINYLDIAZOMETHANES IN THE PRESENCE OF 1,2-DIHYDROPYRIDINES: SYNTHESIS OF THE 6-AZABICYCLO[3.2.2]NONANE NUCLEUS

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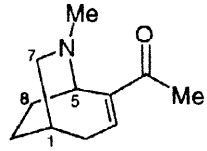
Abstract: *A series of functionalized 6-azabicyclo[3.2.2]nonadienes was synthesized via rhodium(II)-catalyzed decomposition of vinyldiazomethanes in the presence of substituted dihydropyridines. The regioselectivity of the reaction was shown to be highly dependent on the steric bulk of the catalyst as well as the structure of the vinyldiazomethane. Each regioisomer was elaborated into higher homologs of ferruginine (1, 2).*

Azabicyclic systems are common structural units in a vast array of natural products and pharmaceutical agents.[1] Consequently, general synthetic methods to these systems are very useful. We recently reported that functionalized tropanes can be readily prepared from the reaction between vinylcarbenoids and pyrroles.[2] In this communication, we describe the facile synthesis of the 6-azabicyclo[3.2.2]nonane skeleton from the reaction of vinylcarbenoids and protected 1,2-dihydropyridines.[3] A particularly interesting aspect of this chemistry is the dramatic effect of catalyst size on the regioselectivity of the reaction. The utility of this chemistry is demonstrated by the elaboration of these compounds to regioisomeric homologs (**1**, **2**) of the tropane alkaloid ferruginine.[4]



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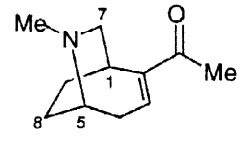

2

Decomposition of the methoxy-substituted vinyldiazomethane **3a** with rhodium(II) octanoate (2 mol%, toluene solution) in the presence of *N*-phenoxycarbonyl-1,2-dihydropyridine **4** (1.25 equiv) produced approximately equal amounts of the regioisomeric azabicyclononadienes **5a** and **6a** in up to 59% combined yield (Table 1).[5] Repeating the reaction using rhodium pivalate resulted in a significant increase in the selectivity for the formation of regioisomer **5a** (4.5 to 1; Table 1, entry 2). This selectivity increased to >15:1 when the extremely bulky rhodium triphenylacetate[6] was used (entry 3). Similar results were obtained with the ethyl ketone-substituted diazomethane **3b** (entries 4 and 5). Decomposition of **3b** with rhodium octanoate resulted in preferential formation of regioisomer **6b** (2.5 to 1) while use of the more bulky rhodium pivalate catalyst resulted in >2:1 selectivity favoring the opposite regioisomer. The moderate yields in these reactions are presumably due to inefficient trapping of the carbenoid as no other by-products from reaction of the carbenoid with the dihydropyridine were observed.

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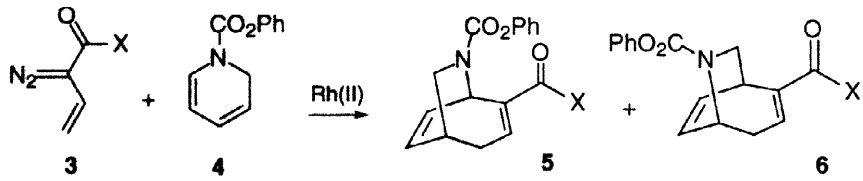
Table 1. Synthesis of 6-Azabicyclo[3.2.2]nonadienes **5** and **6**.

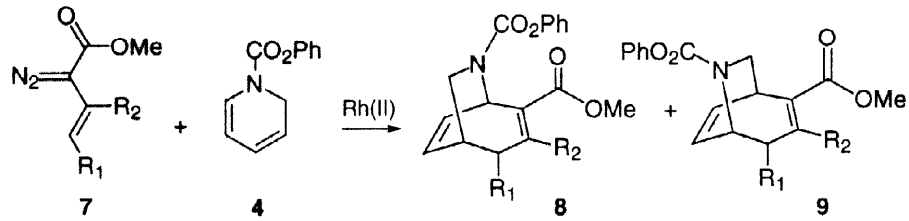


3 4 5 6

entry	diazo	X	catalyst	product	5, yield, %	6, yield, %
1	**3a**	OMe	$Rh_2(OOct)_4$	**a**	30	29
2	**3a**	OMe	$Rh_2(OPiv)_4$	**a**	56	12
3	**3a**	OMe	$Rh_2(TPA)_4$	**a**	50	3
4	**3b**	Et	$Rh_2(OOct)_4$	**b**	11	25
5	**3b**	Et	$Rh_2(OPiv)_4$	**b**	27	12

Vinydiazomethanes substituted on the terminal position of the double bond gave preferential formation of the 4-substituted regioisomers **8** (Table 2). Decomposition of the phenyl-substituted diazomethane **7a** with $Rh_2(OOct)_4$ produced a 3:1 ratio of **8a** and the 2-substituted isomer **9a**. When rhodium pivalate was used, only a trace of **9a** was formed, and **8a** was isolated in 69% yield. Substitution on the internal position of the double bond of the diazomethane gave results similar to that of **3a** (entries 4 and 5, Table 2). Decomposition of the siloxy-vinyldiazomethane **7c** with rhodium octanoate gave a 2:3 ratio of isomers **8c** and **9c** while use of rhodium pivalate shifted the ratio to >10:1 favoring **8c**.

Table 2. Synthesis of 6-Azabicyclononadienes **8** and **9**.

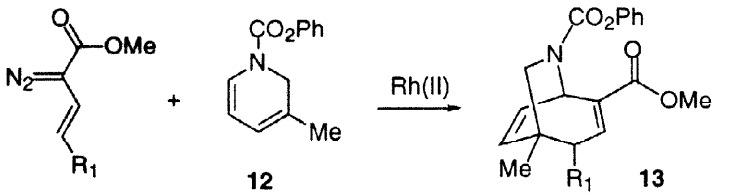


7 4 8 9

entry	diazo	R_1	R_2	catalyst	equiv 4	product	8, yield, %	9, yield, %
1	**7a**	Ph	H	$Rh_2(OOct)_4$	3.0	**a**	30	9
2	**7a**	Ph	H	$Rh_2(OPiv)_4$	3.0	**a**	69	trace
3	**7b**	Me	H	$Rh_2(OPiv)_4$	1.25	**b**	58	3
4	**7c**	H	OTBS	$Rh_2(OOct)_4$	3.0	**c**	17	24
5	**7c**	H	OTBS	$Rh_2(OPiv)_4$	3.0	**c**	34	3

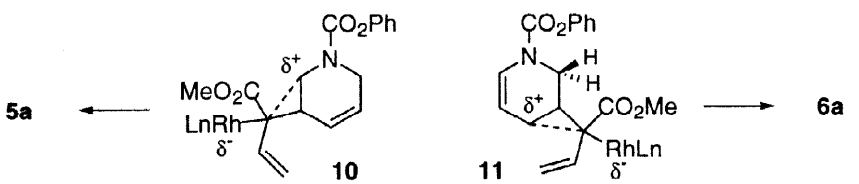
The formation of each regioisomer can be rationalized by a mechanism in which cyclopropanation of either of the two double bonds of the dihydropyridine occurs followed by a Cope rearrangement of the resulting divinylcyclopropane.[7] Since vinylcarbenoid cyclopropanations are considered to occur via a concerted, but non-synchronous mechanism,[8] reasonable transition states for formation of each of the regioisomers are **10** and **11**.

Table 3. Synthesis of 6-Azabicylo[3.2.2]nonadienes **13** from the 3-Methyl-1,2-dihydropyridine **12**.



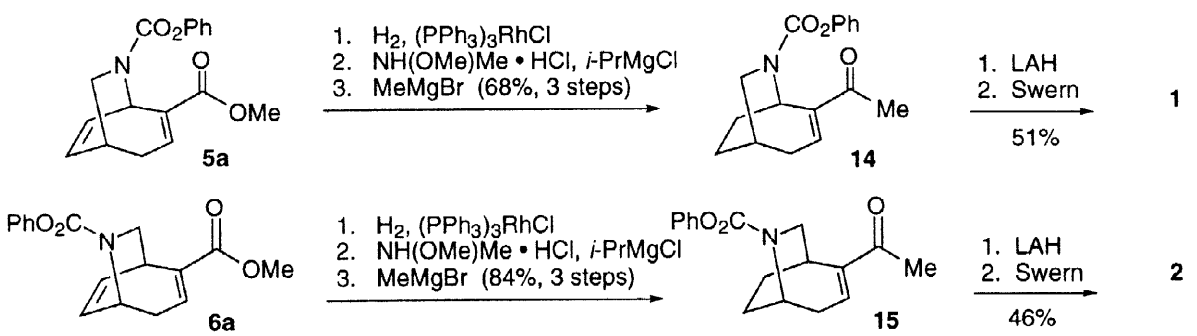
entry	diazo	R_1	catalyst	equiv 12	product	yield, %
1	**3a**	H	$Rh_2(OPiv)_4$	0.5	**13a**	65
2	**7a**	Ph	$Rh_2(OPiv)_4$	1.25	**13b**	71
3	**7b**	Me	$Rh_2(OPiv)_4$	1.25	**13c**	50

While one would anticipate that intermediate **11** would be electronically favored, the vinylcarbenoid complex behaves like a very bulky electrophile and steric influence is often the dominating factor in vinylcarbenoid reactions.[2b] The presence of the sp^3 center adjacent to the site of electrophilic attack in **11** would be expected to be more sterically demanding than the adjacent sp^2 center in intermediate **10**. Consistent with this reasoning is the dramatic shift to the formation of the 4-substituted isomers (e.g. **5** and **8**) with more sterically bulky catalysts. Furthermore, the reaction of vinyldiazomethanes with the 3-methyl-1,2-dihydropyridine **12** resulted in the exclusive formation of a single regioisomer (**13**) of the azabicyclononadiene resulting from cyclopropanation at the less substituted double bond (Table 3).



Both regioisomers **5a** and **6a** were elaborated into racemic ferruginine/anatoxin homologs **1** and **2** (Scheme 1). This was accomplished by hydrogenation of the C(8)-C(9) double bond followed by conversion of the methyl ester to a methyl ketone via the Weinreb amide[9] to give **14** and **15**, respectively. Reduction of the phenoxycarbonyl group followed by reoxidation of the secondary alcohol resulted in the formation of **1** and **2**.

Scheme 1



This communication describes the facile synthesis of two regioisomeric 6-azabicyclo[3.2.2]nonadienes, which have been elaborated into two novel homologs of ferruginine. Control of regioselectivity is achieved by varying the vinyldiazoacetate, catalyst, and substituents on the dihydropyridine. These results further illustrate the high substrate diversity of 3+4 annulations between vinylcarbenoids and alkenes.

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(5) Typical Procedure: A chilled solution of freshly purified **3a** (3.82 g, 30.3 mmol) in 50 mL dry toluene was added dropwise to a solution of **4** (7.61 g, 37.8 mmol) and $Rh_2(OOct)_4$ (476 mg, 0.611 mmol) in 100 mL toluene over 30 min. The reaction was stirred for 1.5 h, and then heated to reflux for 30 min. The reaction mixture was concentrated under reduced pressure and chromatographed (4:1 to 1:1 petroleum ether/Et_2O) to give **5a** (2.69 g, 8.98 mmol, 30%) and **6a** (2.59 g, 8.64 mmol, 29%).

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