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NOVEL ENTRY TO THE TROPANE SYSTEM BY REACTION OF RHODIUM(II) ACETATE STABILIZED VINYLCARBENOIDS WITH PYRROLES

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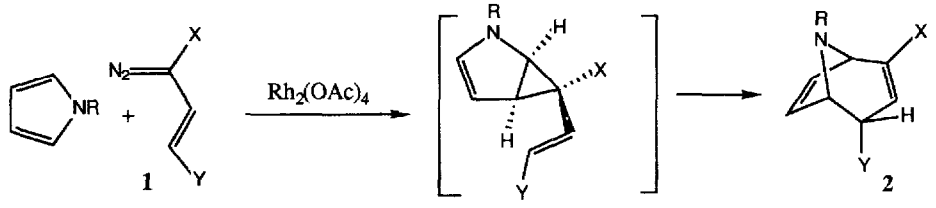
Abstract: *Rhodium(II) acetate catalyzed decomposition of vinyldiazomethanes in the presence of N-alkoxycarbonylpyrroles provides a direct entry to the skeleton of tropane alkaloids. Similar reactions with N-alkylpyrroles result in the formation of alkylation products.*

The tropane alkaloids constitute an important class of natural products because of their extensive biological properties.[1,2] A potentially attractive way to prepare such compounds would be through the reaction of vinylcarbenoids with pyrroles as shown in Scheme 1. We have previously reported that rhodium(II) acetate stabilized vinylcarbenoids undergo a formal 3 + 4 cycloaddition with a range of dienes, both inter- and intramolecularly to generate seven-membered rings in a stereodefined manner.[3] Although the reaction could be considered in terms of a concerted process, a tandem cyclopropanation/Cope rearrangement mechanism has been shown to occur in these reactions.[3a] In this paper, we describe our studies to widen the scope of this chemistry by using pyrroles as the diene component.

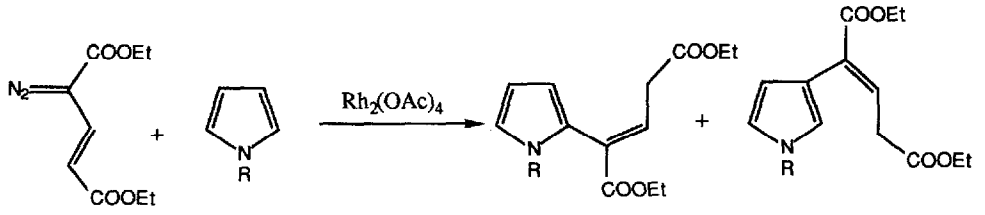
Scheme 1



Decomposition of diethyl diazopentenedioate (**1a**) by rhodium(II) acetate in the presence of five equivalents of pyrrole failed to generate the bicyclic system **2**. Instead the alkylated product **3a** was formed in 71% yield. The pyrrole substitution and double

bond configuration were assigned based on distinctive proton chemical shifts for a 2-substituted pyrrole and a strong nOe enhancement between the methylene and the pyrrole protons. Similarly, with N-methylpyrrole, a mixture of alkylated products, **3b** (78%) and **4b** (8%) were formed. These results are consistent with those observed by Maryanoff in the metal-catalyzed decomposition of ethyl diazoacetate[4a] and diethyl diazomalonate[4b] in the presence of alkylpyrroles. Substitution products are presumably formed because the electron-releasing ability of the nitrogen stabilizes a zwitterionic intermediate and consequently, cyclopropanation does not occur.

Scheme 2



1a **3** **4**

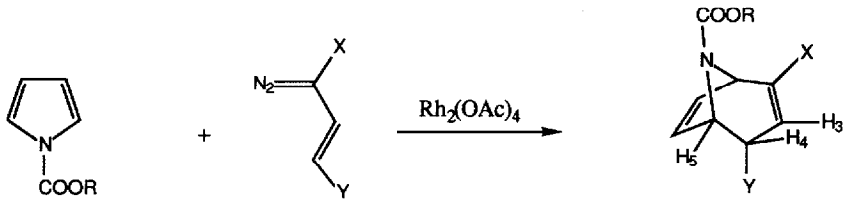
a, R = H; **b**, R = CH_3

Pyrroles can be made to more closely resemble the reactivity of dienes with carbenoids if electron-withdrawing functionality is introduced at the nitrogen.[5] Consequently, the decomposition of **1a** in the presence of N-ethoxycarbonylpyrrole was examined and under these conditions the desired annulation product **2a** was formed. The initial product formed was exclusively the *endo* isomer but on purification by silica gel chromatography, partial isomerization to the *exo* isomer occurred. The reaction was extended to a range of vinylcarbenoids as shown in the Table. In all cases the *endo* isomers were the initially formed products but with the rather acidic systems **2b-d** partial isomerization occurred during the chromatographic purification.

Broadening of the proton NMR signals of **2** was observed at room temperature and this is presumably due to hindered rotation about the amide bond. 7-Azabicyclo[2.2.1]-hept-2-enes exhibit similar behavior and have been studied in detail.[6] Sharp proton NMR spectra were obtained at 95°C in toluene-d_8 and the *exo* and *endo* isomers were readily distinguished by the characteristics of the signal for H_4.[3a] For the *endo* isomer, the signal is broad at room temperature with $J_{H_4\text{-}H_5}$ = ~5 Hz and $J_{H_4\text{-}H_3}$ = ~2.8 Hz, while for the *exo* isomer, the signal is sharp with $J_{H_4\text{-}H_5}$ = ~0 Hz and $J_{H_4\text{-}H_3}$ = ~4.0 Hz and occurs further upfield by about 1 ppm.

An intriguing product was formed in the reaction of N-ethoxycarbonylpyrrole with the vinyldiazomethane **1f** as shown in Scheme 3. Instead of the expected cycloadduct, the dicyclopropanated product **5** was formed in 33% yield. The assigned

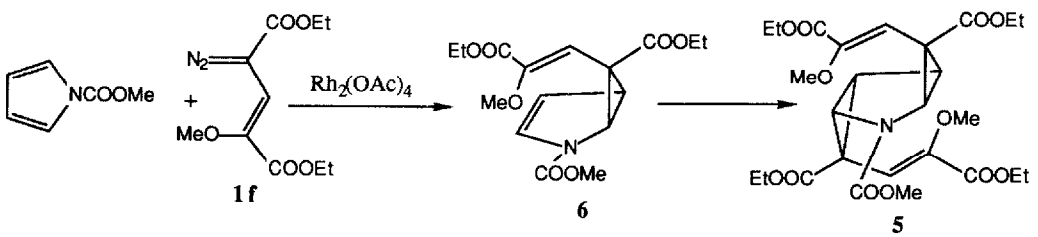
Table: Synthesis of azabicyclooctadienes through reaction of vinylcarbenoids with pyrroles.



R		X	Y	2 (yield, %)
Me	**1a**	COOEt	COOEt	**2a** (62)
Et	**1a**	COOEt	COOEt	**2b** (54)
CH_2CH_2TMS	**1a**	COOEt	COOEt	**2c** (71)
Me	**1b**	COOEt	SO_2Ph	**2d** (61)
Me	**1c**	COOMe	Ph	**2e** (53)
Me	**1d**	COOEt	CH=CHPh	**2f** (18)
Me	**1e**	COOMe	H	**2g** (21)

stereochemistry of **5** was based on the evident lack of symmetry as seen in its proton and carbon NMR and the distinctive nOe enhancements between the vinyl and the cyclopropane protons. Double cyclopropanation of N-ethoxycarbonylpyrrole with ethyl diazoacetate has previously been reported as a minor side reaction.[5a] The formation of **5** in this case can be rationalized based on the observation that sterically congested divinylcyclopropanes undergo a Cope rearrangement rather sluggishly.[3a,7] Presumably this would be the case with the pyrrolocyclopropane **6**, which would then accumulate under the reaction conditions. Due to the reactive enamine functionality in **6**, a second cyclopropanation to form **5** would be very favorable. The generation of only one isomer of **5** attests to the remarkable *endo* selectivity of cyclopropanations with vinylcarbenoids.[3]

Scheme 3



The reaction of vinylcarbenoids with pyrroles offers a very direct stereoselective synthesis of 8-azabicyclo[3.2.1]octa-2,6-dienes. Further studies are in progress to develop enantioselective processes to these compounds and to apply this chemistry to the synthesis of actual tropane natural products.

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