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SYNTHESIS OF AZA SUBSTITUTED POLYCYCLES VIA RHODIUM (II) CARBOXYLATE INDUCED CYCLIZATION OF DIAZOIMIDES

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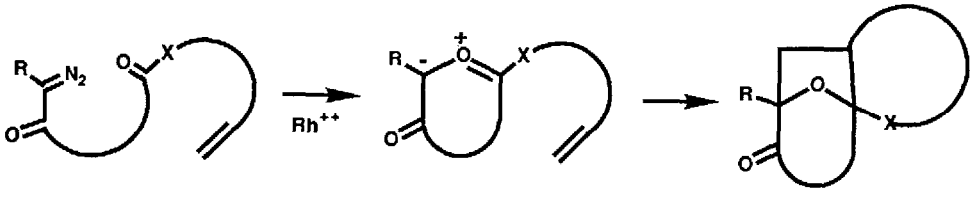
Abstract: Treatment of several substituted diazoimide derivatives with rhodium (II) carboxylates results in nitrogen-containing cyclic carbonyl ylide formation followed by 1,3-dipolar cycloaddition.

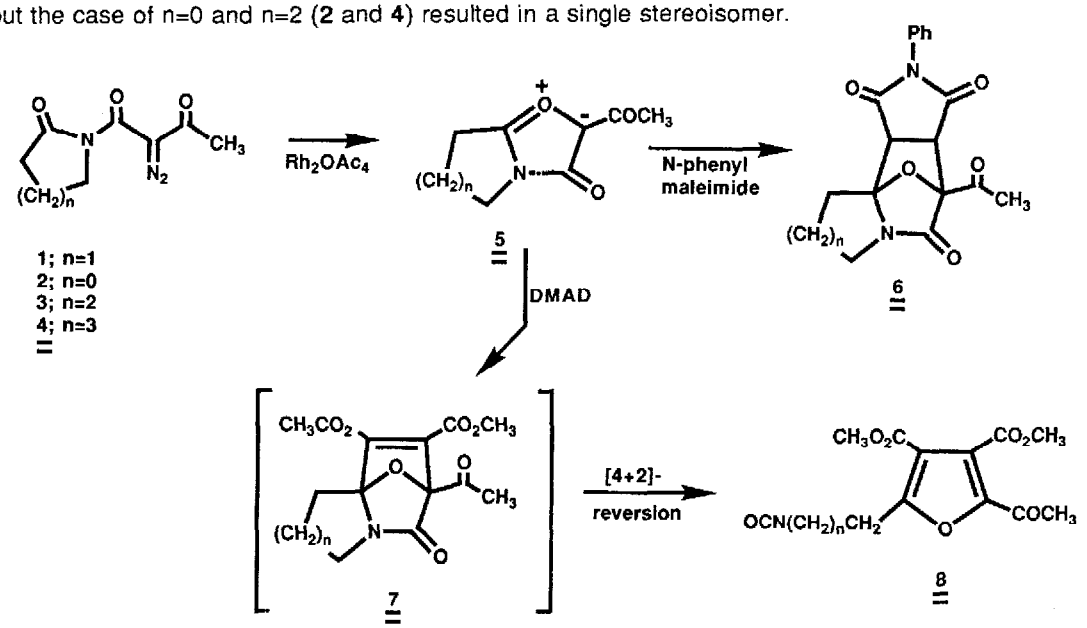
α-Diazoketones have found numerous applications in organic synthesis, and their use in either hetero or carbocyclic ring formation is well documented.[1-6] Recently, we described the formation of bridged oxabicyclo compounds from the rhodium (II) acetate catalyzed reaction of 1-diazo alkanediones.[7] The reaction involves the formation of a rhodium carbenoid, subsequent transannular cyclization of the electrophilic carbon onto the adjacent keto group to generate a cyclic carbonyl ylide followed by 1,3-dipolar cycloaddition.[8,9] The inclusion of a nitrogen atom



within the cyclic dipole holds potential promise as an easy entry into various alkaloid natural product skeletons.[10] Consideration of the extension of this protocol to the synthesis of nitrogen containing natural products suggested the need for clarifying several relevant questions: (1) will a nucleophilic amide or imide functionality cyclize more efficiently than the keto group to give the 1,3-dipole; (2) to what extent will the cyclization be dependent on the length of the tether separating the carbenoid center and the neighboring carbonyl group; (3) since diazoketones are reactive dipoles, will the presence of an activated pi-bond be subject to uncontrollable cycloaddition across the diazo group to produce a pyrazoline cycloadduct? In this manuscript, we describe some recent observations dealing with the above questions.

Our investigation began with the cyclic diazoimides **1-4** which were of interest in our long range goal of planned synthesis of alkaloids. These compounds were easily prepared in high yield by heating the appropriate cyclic amide with 2,2,6-trimethyl-4H-1,3-dioxen-4-one[11] in xylene at 140°C. The resulting N-(acetoacetyl)amide was treated with mesyl azide/triethylamine in the usual way to give the diazoimides.[12] A sample of cyclic diazoimide **1** was allowed to react with rhodium

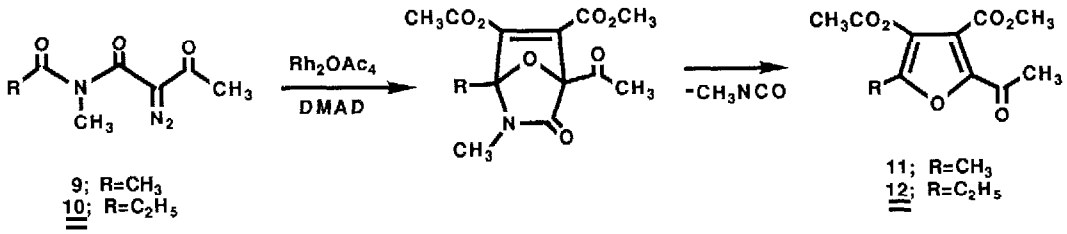
acetate (80°C) in benzene and the initially formed rhodium carbenoid cyclized onto the adjacent imide carbonyl group to produce an isomunchnone dipole (**5**).[13] This species undergoes ready 1,3-dipolar cycloaddition with N-phenylmaleimide to afford the expected dipolar cycloadduct **6** as a 1.2:1 mixture of *exo* and *endo* isomers in 78% yield. The generality of the method was demonstrated by varying the cyclic imide so as to probe any geometric effects of ring size on the outcome of the cyclization-cycloaddition reaction. The ring size was reduced to a four-membered ring (**2**; n=0) (61%) and enlarged to a six (**3**; n=2) (85%) and seven (**4**; n=3) (75%) membered ring. In all cases, high yields of the expected cycloadduct derived from N-phenylmaleimide was obtained. Interestingly, the cyclic cases where n=1 and n=3 (i.e. **1** and **4**) showed little *exo*/*endo* selectivity, but the case of n=0 and n=2 (**2** and **4**) resulted in a single stereoisomer.



When dimethyl acetylenedicarboxylate was used as the trapping dipolarophile, the expected cycloadduct was not isolated. Instead, furanoisocyanate **8** (n=2) was the only product formed in 85% yield. This is the result of a subsequent [4+2]-cycloreversion of the initially formed cycloadduct under the reaction conditions. Isocyanate **8** was characterized as its urethane derivative by reaction with methanol.[14]

The conformational rigidity imposed by the cyclic imide ring was demonstrated to be inconsequential by carrying out the tandem cyclization-cycloaddition sequence using acyclic imides **9** and **10**. Both substrates readily reacted with rhodium acetate in the presence of dimethyl acetylenedicarboxylate to give cycloadducts **11** and **12** in 82% and 86% yield, respectively.

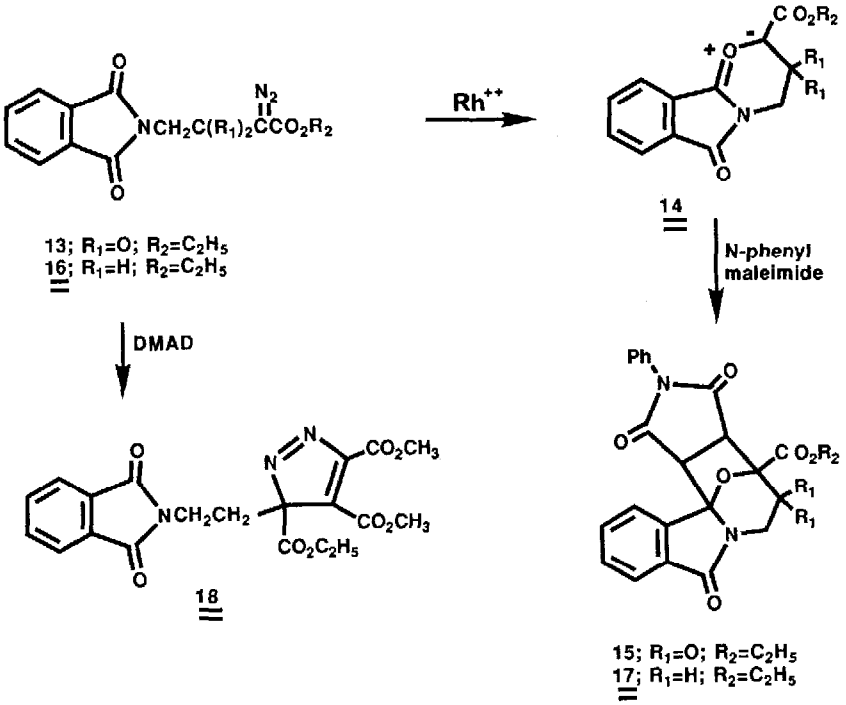
We also thought it worthwhile to consider what effect a variation in the spatial proximity between the diazoketo group and the imide functionality would have on the course of the reaction. To this end, we investigated the rhodium (II)-catalyzed reaction of the diazophthalimide derivative **13**.[15] Cyclization in this case would lead to a six-ring dipole. Indeed, when **13** was treated with N-



9; R=CH_3
10; R=C_2H_5

11; R=CH_3
12; R=C_2H_5

phenylmaleimide in the presence of Rh_2OAc_4 in refluxing benzene, cycloadduct **15** was obtained as the exclusive product in 87% yield.[16] Similar treatment of the less activated diazo phthalimidoester **16** with rhodium (II) octanoate at 25°C with N-phenylmaleimide also afforded cycloadduct **17** (92%) derived from the six-ring dipole.[17] This observation indicates, that at



13; R_1=O; R_2=C_2H_5
16; R_1=H; R_2=C_2H_5

14

18

15; R_1=O; R_2=C_2H_5
17; R_1=H; R_2=C_2H_5

least in this situation, both the mono and diacyl substituted carbenoids (derived from **16** and **13**, respectively) exhibit comparable reactivity.[18] In the absence of a catalyst, **16** undergoes facile dipolar cycloaddition with DMAD across the diazo group to give 3H-pyrazole **18** in high yield.

In conclusion, the facility with which the rhodium (II) acetate catalyzed cyclization-cycloaddition reaction of N-(diazoacetoacetyl)amides occurs makes this process particularly attractive for the synthesis of aza-substituted polycycles. We are continuing to explore the scope and mechanistic details of these rhodium catalyzed processes and will report additional findings at a later date.

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14. NMR **8** ($CDCl_3$, 300 MHz) δ 1.85-2.00(m, 2H), 2.45 (s, 3H), 3.07 (t, 2H, J=7.4 Hz), 3.15-3.25 (m, 2H), 3.68 (s, 3H), 3.82 (s, 3H), 3.95 (s, 3H) and 5.0-5.18 (bs, 1H).
15. Experiments in these labs suggest that substituted amides are unsuitable as nucleophilic carbonyl functionalities in the carbene cyclization.
16. NMR **15** δ 1.30 (t, 3H, J=7.1 Hz), 3.36 (d, 1H, J=14.5 Hz), 3.68 (d, 1H, J=7.4 Hz), 4.31 (d, 1H, J= 7.4 Hz), 4.34 (q, 2H, J=7.1 Hz), 4.45 (d, 1H, J=14.5 Hz) and 7.20-7.85 (m, 9H).
17. NMR **17** δ 1.31 (t, 3H, J=7.1 Hz), 2.13 (ddd, 1H, J=13.7, 12.1 and 6.8 Hz), 2.42 (dd, 1H, J=13.7 and 4.8 Hz), 3.38 (ddd, 1H, J=14.5, 12.1 and 4.8 Hz), 3.63 (d, 1H, J=7.5 Hz), 3.86 (d, 1H, J=7.5 Hz), 4.30 (q, 2H, J= 7.1 Hz), 4.51 (dd, 1H, J=14.5 and 6.8 Hz) and 7.3-7.8 (m, 9H).
18. An earlier report by Maier and Evertz[10] indicated that the rhodium carbenoid derived from a 2-diazo-1,3-dicarbonyl amide was significantly more effective in the cyclization-cycloaddition reaction than a mono substituted diazocarbonyl amide.

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