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CYCLIC CARBONYL YLIDE FORMATION FROM THE RHODIUM (II) ACETATE CATALYZED REACTION OF 1-DIAZOALKANEDIONES

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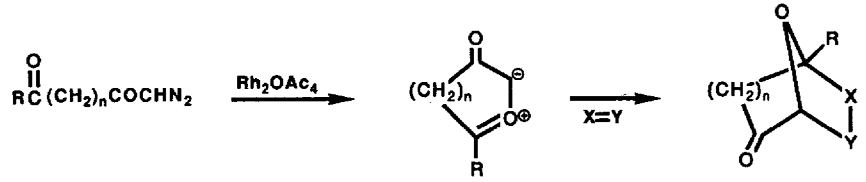
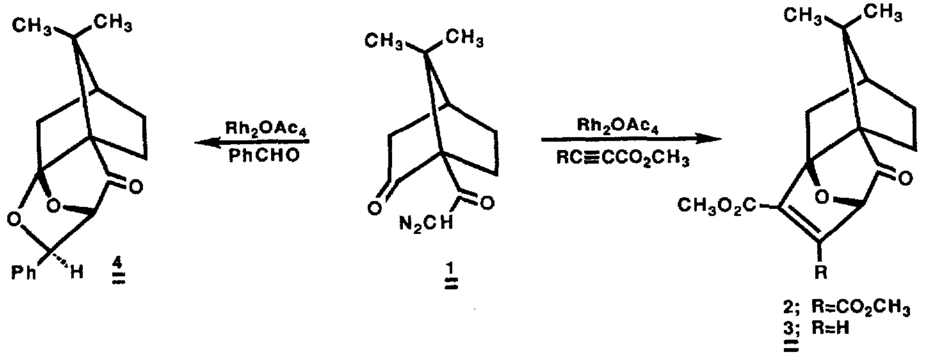
Abstract: Treatment of 1-diazoalkanediones with rhodium (II) acetate results in cyclization of the intermediate rhodium carbenoid to give a cyclic carbonyl ylide which readily undergoes bimolecular dipolar cycloaddition with various dipolarophiles.

α-Diazoketones are valuable synthetic intermediates, with considerable utility in the preparation of a variety of cyclic and acyclic organic molecules.[1-8] We have recently reported that the rhodium metal induced reaction of 1-diazo-2,5-pentanediones in the presence of various dipolarophiles results in carbonyl ylide formation followed by 1,3-dipolar cycloaddition.[9] Of the many unexplored questions concerning the factors that govern the formation of carbonyl ylides by this method, one that is very easy to formulate focuses upon the course of the reaction as a function of the length of the tether that links the carbonyl and diazoketone functionalities. Until now, the tether length has been restricted to cases where n=2 (i.e. 6-ring formation).[10] In this communication, we report that a similar tandem cyclization-cycloaddition sequence occurs with both 5 and 7-ring cyclic carbonyl ylides.



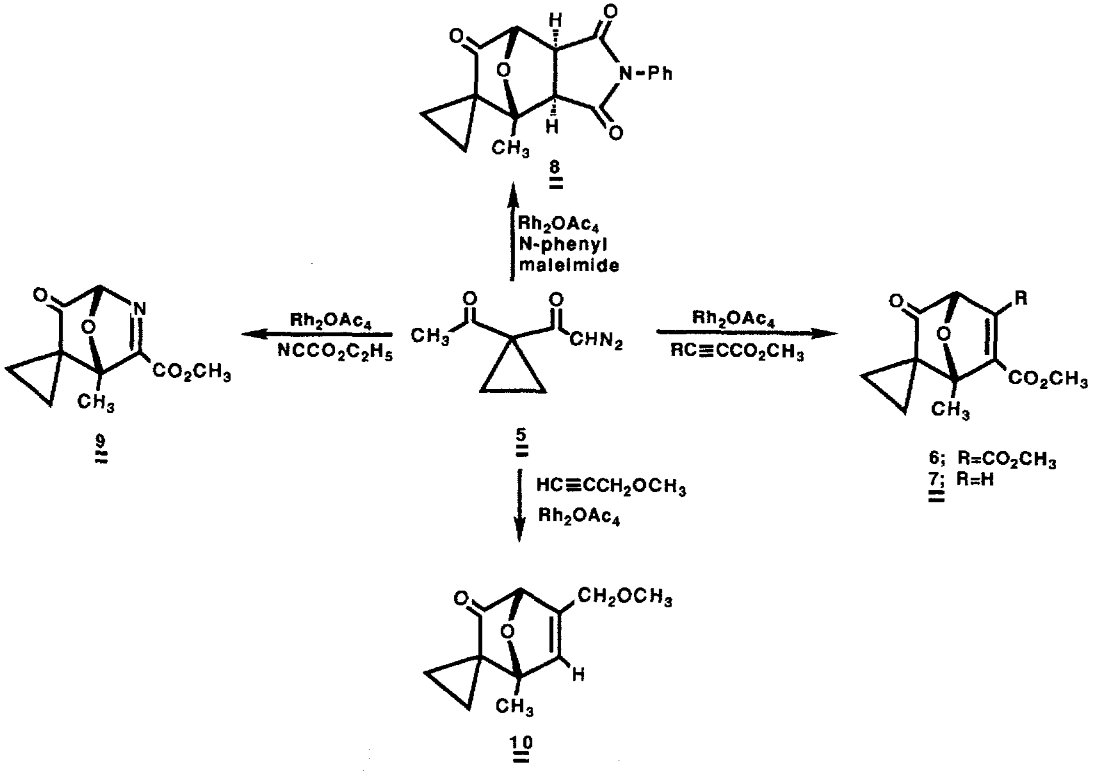
As a consequence of the ready availability of ketopinic acid,[11] 6-diazoketo-7,7-dimethylbicyclo[2.2.1]heptane (1) was the initial system selected for study. Treatment of **1** with a catalytic amount of rhodium (II) acetate at 25°C in benzene with dimethyl acetylenedicarboxylate (10% mol excess) afforded cycloadduct **2**, mp 83-84°C, in 85% yield.[12] The cycloaddition proceeded with complete diastereofacial selectivity. We believe that approach from the α-face of the dipole is the preferred process as a consequence of the severe steric interaction with the bridgehead gem dimethyl group associated with β-attack. Similar treatment of **1** with methyl propiolate produced cycloadduct **3** in 72% isolated yield as the exclusive cycloadduct, mp 80-81°C.[12] This result clearly demonstrates the high degree of regioselectivity possible in these reactions. In addition to the high facial and regioselectivity of the cycloaddition, diazoketone **1** also exhibits a high level of stereoselectivity. Cycloaddition of the metallocarbenoid derived from **1** was



4, 1, 2; R=CO$_2$CH$_3$, 3; R=H

carried out in the presence of benzaldehyde. Bicyclic ketal 4 was the only product isolated in 66% overall yield. The stereochemical assignment (exo-phenyl group) was made on the basis of its characteristic NMR spectrum which showed the absence of coupling of the bridgehead hydrogen (NMR (CDCl$_3$, 300 MHz) δ 1.08 (s, 3H), 1.17 (s, 3H), 1.4 (m, 1H), 1.8-2.1 (m, 5H), 2.6 (td, 1H, J=14.5 and 2.9 Hz), 4.33 (s, 1H), 4.71 (s, 1H) and 7.2-7.4 (m, 5H).

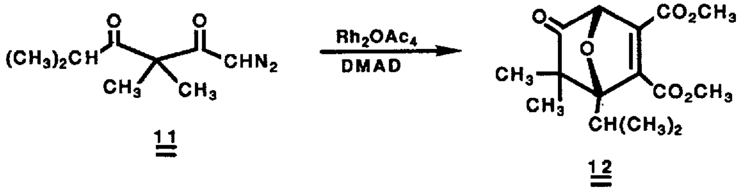
We also studied the cyclization-cycloaddition chemistry of the cyclopropyl substituted diazoketone 5. Treatment of this material with rhodium (II) acetate at 25°C in deuteriochloroform with DMAD afforded the expected cycloadduct 6 in 97% yield. In order to further explore the scope



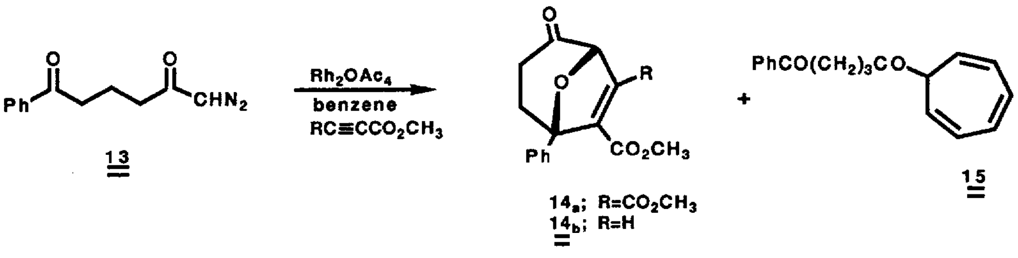
8, 9, 5, 6; R=CO$_2$CH$_3$, 7; R=H, 10

of the reaction, diazoketone **5** was reacted with methyl propiolate, N-phenylmaleimide, ethyl cyanoformate and methyl propargyl ether to give cycloadducts **7-10** in high yield. The complete regiochemical crossover encountered with methyl propargyl ether[13] can be rationalized on the basis of FMO considerations. Of the three categories described by Sustmann,[14] type II is particularly common for carbonyl ylides since they possess one of the smallest HOMO-LUMO energy gaps of the common 1,3-dipoles.[15] For carbonyl ylides, the HOMO of the dipole is dominant for reactions with electron-deficient dipolarophiles such as methyl propiolate, while the LUMO becomes important for cycloaddition to more electron rich species such as propargyl ethers. MNDO calculations on the carbonyl ylide derived from **5** clearly indicate that the largest coefficient in the LUMO resides on the carbon bearing the methyl group.[16] This site becomes linked with the less substituted carbon of the acetylenic group thereby accounting for the regiochemical results.

Extension of the carbenoid cyclization-cycloaddition sequence to an acyclic 1,3-keto diazoketone system was next investigated. To this end, diazoketone **11** was prepared and treated with rhodium (II) acetate at 25°C in the presence of DMAD. Under these conditions cycloadduct **12** was isolated in 63% yield (NMR ($CDCl_3$, 300 MHz) δ 1.06 (d, 3H, J=6.8 Hz), 1.17 (d, 3H, J=6.8 Hz), 1.22 (s, 3H), 1.31 (s, 3H), 2.36 (sept, 1H, J=6.8 Hz), 3.77 (s, 3H), 3.87 (s, 3H) and 4.93 (s, 1H).



The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting centers should be sufficiently close so that effective overlap of the lone pair of electrons on the carbonyl group with the metallocarbenoid center can occur. In view of the stringent spatial requirements associated with the process, we thought it worthwhile to consider what effect a variation in the spatial proximity between the diazoketone and carbonyl group would have on the course of the reaction. To this end we investigated the rhodium (II)-catalyzed reaction of 1-diazo-6-phenyl-2,6-hexanedione **13** with DMAD and methyl propiolate in benzene as the solvent. In both cases a 2:1 mixture of products was formed. The major product corresponds to the expected cycloadduct **14**. The minor component was assigned as cycloheptatriene **15** and is derived from a bimolecular addition of the rhodium carbenoid to benzene followed by ring



tautomerization. The formation of a mixture of products in this case indicates that the additional methylene groups in **13** has sufficiently retarded the rate of intramolecular cyclization so as to allow the bimolecular reaction with benzene to occur.[17]

In conclusion, the facility with which the rhodium catalyzed cyclization-cycloaddition reaction of a variety of 1-diazoalkanediones occurs makes this process particularly attractive for the preparation of complex polyoxacyclic ring systems. We are continuing to explore the scope and mechanistic details of these rhodium catalyzed reactions of 1-diazoalkanediones and will report additional findings at a later date.

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12. All new compounds were characterized by ^{1}H and ^{13}C-NMR and by high resolution mass spectra; NMR **2** (CDCl$_3$, 300 MHz) δ 1.14 (s, 3H), 1.21 (s, 3H), 1.3-1.4 (m, 2H), 1.85-1.95 (m, 1H), 2.0-2.2 (m, 3H), 2.39 (dt, 1H, J=15.0 and 3.0 Hz), 3.78 (s, 3H), 3.86 (s, 3H) and 4.85 (s, 1H); NMR **3** (CDCl$_3$, 360 MHz): δ 0.78 (ddd, 1H, J=13.0, 9.2 and 3.6 Hz), 1.07 (s, 3H), 1.17 (s, 3H), 1.57 (ddd, 1H, J=13.0, 9.2 and 4.7 Hz), 1.82 (m, 1H), 1.99 (dd, 1H, J=4.7 and 4.1 Hz), 2.05 (ddd, 1H, J=13.0, 11.7 and 4.7 Hz), 2.25 (ddd, 1H, J=14.3, 3.3 and 3.1 Hz), 2.64 (d, 1H, J=14.3 Hz), 3.71 (s, 3H), 4.59 (d, 1H, J=2.38 Hz) and 7.28 (d, 1H, J=2.38 Hz).
13. NMR **10** (CDCl$_3$, 300 MHz) δ 0.53-1.31 (m, 4H), 1.34 (s, 3H), 3.32 (s, 3H), 4.09 (dd, 1H, J=12.0 and 1.6 Hz), 4.17 (dd, 1H, J=12.0 and 1.6 Hz), 4.68 (s, 1H) and 6.37 (t, 1H, J=1.6 Hz).
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16. Calculations were performed with the Ampac program (QCPE 506) using the AMI Hamiltonian. The calculations show that the LUMO is located at -0.93 eV and the HOMO at -10.47 eV for the carbonyl ylide drived from **5** with coefficients of -0.62 (C$_4$) and -.37 (C$_2$) in the LUMO.
17. No characterizable compound was obtained from the reaction of **13** with Rh$_2$OAc$_4$ in chloroform or methylene chloride.

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