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Communications

Azomethine Ylide Generation via the Rhodium(II)-Induced Cyclization Reaction of Oximino α-Diazo Ketones

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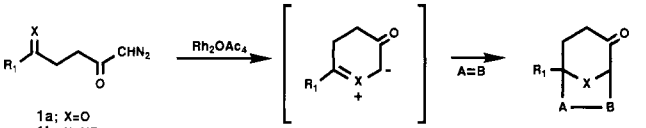
Summary: The rhodium(II)-catalyzed reaction of α-diazo ketones with a neighboring oxime ether generates cyclic azomethine ylides which undergo ready 1,3-dipolar cycloaddition.

The reaction of keto carbenoids with heteroatoms which possess a lone pair of electrons is rapidly gaining prominence as an efficient method for heterocyclic synthesis.[1-8] Previous papers from these laboratories have described a route to oxapolycyclic ring systems which involves the tandem cyclization–cycloaddition reaction of a rhodium carbenoid intermediate.[8] In an effort to increase the versatility of the method, we were led to examine hetero π-systems other than carbonyl groups. Of most immediate concern was the feasibility of employing γ-imino diazo ketones to access cyclic azomethine ylides. Cycloaddition reaction of these 1,3-dipoles should provide the 8-azabicyclo[3.2.1]octane framework found in a number



1a; X=O
1b; X=NR$_2$
1c; X=NOCH$_3$

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of potent CNS-active agents such as cocaine and anatoxin-a.[9] In this paper we report the successful implementation of this approach to azomethine ylides utilizing oxime ethers as the hetero π-functionality.

Our initial efforts focused on the preparation of imino diazo ketones such as **1b** (R_1 = Ph, R_2 = CH_2Ph). Unfortunately, all attempts to convert the iminobutyric acid to **1b** failed to give product of acceptable purity. A less problematic alternative was found in the use of methyl oxime derivative **1c**. In this case, conversion of the acid to the desired diazo ketone **1c** (R_1 = Ph) was accomplished in 65% yield using the standard diazomethane acylation protocol. Treatment of this compound with various dipolarophiles in the presence of a rhodium(II) catalyst, however, failed to give any sign of the desired cycloadduct.[10] A possible explanation for the apparent lack of cyclization to the azomethine ylide is that the oxime ether exists in the anti configuration. In the absence of any in situ isomerization to the syn isomer, the nitrogen lone pair of electrons would be incapable of interacting with the rhodium carbenoid. In order to avoid this complication, we elected to investigate the isoxazoline analogue **5** which was readily prepared from methyl 4-nitrobutyrate in three steps.[11] Consistent with the above rationale, the

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(10) No characterizable products could be isolated from this reaction.
(11) A synthetic sequence similar to that used by Pollini and coworkers was employed to prepare **5**; see: Pollini, G. P.; Barco, A.; Benetti, S.; Veronesi, B. *Synth. Commun.* **1978**, *8*, 219.

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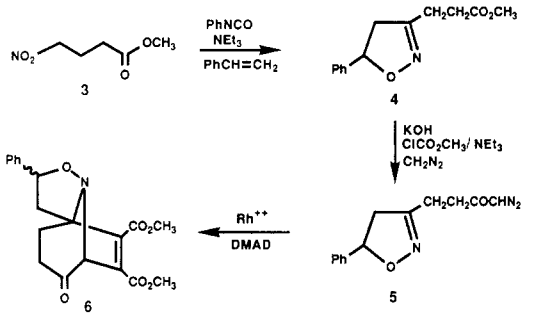
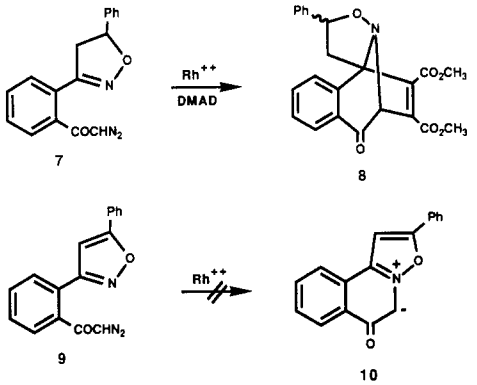
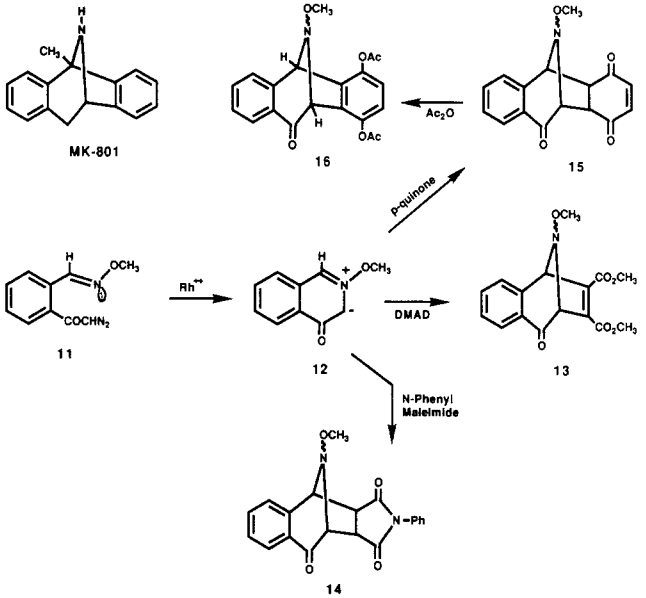
rhodium(II) octanoate[12] catalyzed reaction of **5** and dimethyl acetylenedicarboxylate (DMAD) afforded the azomethine ylide derived cycloadduct **6** as a 4:1 mixture of diastereomers in 65% yield.[13]



A similar transformation occurred using the α-diazoacetophenone derivative **7**[14] to produce isoxazolo[3,2-*a*]isoquinoline **8** as a 2:1 mixture of diasteromers in 82% yield. As a means of probing the effect of an aromatic heteroatom on the rhodium(II)-mediated cyclization step, the closely related isoxazole **9** was prepared. In this case, no cycloadduct was formed under the standard reaction conditions.[10] This observation suggests that the low basisity of the isoxazole nitrogen lone pair may preclude cyclization to the azomethine ylide dipole.[15]



The success of the isoxazoline derivatives, which incorporates the correct nitrogen lone pair orientation for cyclization, suggests that acyclic oxime ethers which exist in the proper configuration would also function as suitable azomethine ylide precursors. In this vein, 2-(diazoacetyl)benzaldehyde *O*-methyl oxime (**11**) was prepared as a single stereoisomer and is assumed to exist in the more stable anti configuration. Indeed, addition of a catalytic amount of rhodium(II) octanoate in the presence of a slight excess of either DMAD or *N*-phenylmaleimide provided cycloadducts **13**[16] and **14** in 80 and 64% yield, respectively. In the case of cycloadduct **14**, a 1:1 mixture of exo:endo diasteromers was obtained and easily separated by flash chromatography.[19] The cycloaddition was also performed



using *p*-quinone as the dipolarophile to give cycloadduct **15** in high yield. Treatment of this material with excess acetic anhydride in pyridine afforded diacetate **16** in 67% overall yield from **11**. This latter cycloadduct incorporates the basic dibenzo[a,d]cyclohepten-5,10-imine skeleton found in MK-801,[20] which is a selective ligand for brain cyclidine (PCP) receptors that has attracted considerable recent attention as a potent anticonvulsive and neuroprotective agent.[21,22]

In summary, the results reported here demonstrate for the first time the ability of imine derivatives to undergo the rhodium(II)-induced cyclization with α-diazo ketones to generate cyclic azomethine ylides. The results of further studies and application of this new methodology for alkaloid synthesis will be reported at a future date.

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(12) We have found Rh(II) octanoate to be a more effective catalyst in comparison to rhodium(II) acetate due to its greater solubility and homogeneous nature in most organic solvents.

(13) Satisfactory analyses were obtained for all new compounds reported. Complete spectroscopic and degradative details will be given in our full publication. Compound **6** (major diastereomer): NMR ($CDCl_3$, 300 MHz) δ 2.07 (m, 1 H), 2.40 (m, 3 H), 2.69 (m, 1 H), 3.20 (dd, 1 H, *J* = 12.9 and 7.6 Hz), 3.80 (s, 3 H), 3.96 (s, 3 H), 4.78 (s, 1 H), 5.30 (dd, 1 H, *J* = 8.0 and 7.6 Hz), and 7.38 (m, 5 H).

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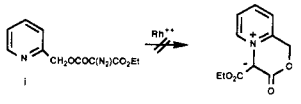
(15) Another example of a heteroaromatic system that was investigated involved pyridine diazoester i which failed to cyclize upon treatment with rhodium(II) octanoate.



(16) The 8-azabicyclo[3.2.1]octadiene ring system **13** has a sufficiently high nitrogen barrier so that both invertomers are seen at 25 °C. The NMR spectrum of **13** contains two distinct sets of chemical shifts for the bridgehead protons and methoxylamine hydrogens. The effects of ring strain, heteroatom substitution and restriction of the CNC angle by the bicyclic ring in raising the barrier to inversion are well known.[17,18]

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(19) The stereochemical assignment was facilitated by the appearance of the bridgehead protons of the exo isomer of **14** as a set of singlets in accord with a predicted dihedral angle of 90° for this diastereomer.

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