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Synthesis of Polyheterocyclic Ring Compounds by the Intramolecular Cycloaddition of N-Alkenyl Substituted Diazoimides

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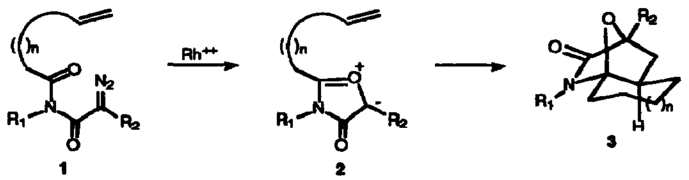
Abstract: Rhodium(II) catalysis of various diazoimides containing tethered π-systems attached to the nitrogen atom results in isomünchnone dipole formation followed by intramolecular dipolar-cycloaddition.

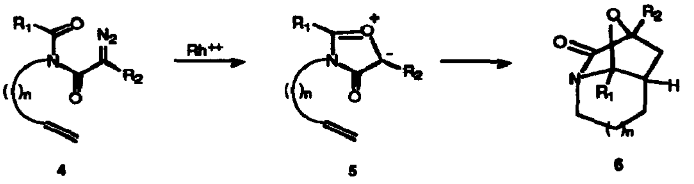
Cycloaddition reactions of 1,3-dipoles with carbon-carbon multiple bonds are of considerable importance in heterocyclic synthesis.[1] Intramolecular dipolar cycloadditions have been particularly useful in natural product synthesis, since this reaction results in the formation of an extra ring and exhibits increased reactivity due to entropic factors.[2-4] The regiochemistry of the process is complicated by a complex interplay of factors such as the nature of the 1,3-dipole, alkene polarity, ring strain, and other nonbonded interactions. In general, the intramolecular situation can be assessed as a competition between bridged and fused modes of cycloaddition.

In previous papers from this laboratory we have outlined a strategy for the synthesis of polyheterocyclic ring systems wherein heterocycle **3** is prepared by an intramolecular dipolar cycloaddition of an isomünchnone dipole **2**.[5] As shown below, the mesoionic dipole **2** was generated by treating a diazoimide containing a carbon-tethered alkenyl group with Rh(II) acetate.[5-10] Two basic structural variations can be achieved by altering the point of attachment of the alkenyl tether. We refer to these as *type I* and *type II* internal cycloaddition routes. To date, all of our studies have dealt with *type I* cycloadditions.[5] From a synthetic standpoint, we were struck by the ease with which the

Type I

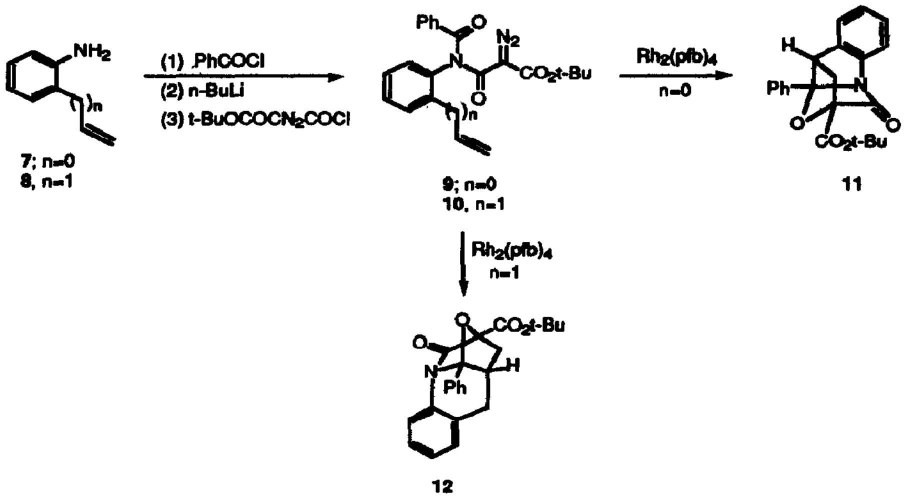


Type II



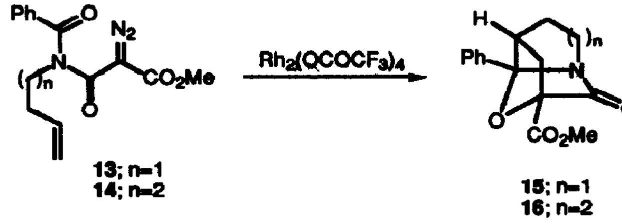
type II reaction would allow for the preparation of complicated N-hetero tricyclic compounds such as 6. Provided with this stimulus, we have investigated the Rh(II) catalyzed behavior of a series of N-alkenyl substituted diazoimides. The results reported below summarize various aspects of this study.

The systems that we initially studied were ultimately derived from *ortho*-substituted anilines, such that the tethered alkene was attached to the benzene backbone. This arrangement provides interatomic distances and bond angles that are ideal for dipole formation. Diazoimides 9 and 10 were prepared by reaction of the appropriately substituted *ortho*-anilines with benzoyl chloride followed by the sequential treatment of the amide with n-butyllithium and t-butyl 2-diazomalonyl chloride.[11] Exposure of diazoimides 9 and 10 to a catalytic quantity of Rh(II) perfluorobutyrate at 25°C afforded the polyheterocyclic systems 11 and 12 in excellent yield (93%, 95%) and with complete diastereospecificity. The structure of 12 was unambiguously determined through an X-ray crystallography study. Assignment of the stereochemistry of the closely related cycloadduct 11 is based on its spectroscopic properties and by analogy to 12.

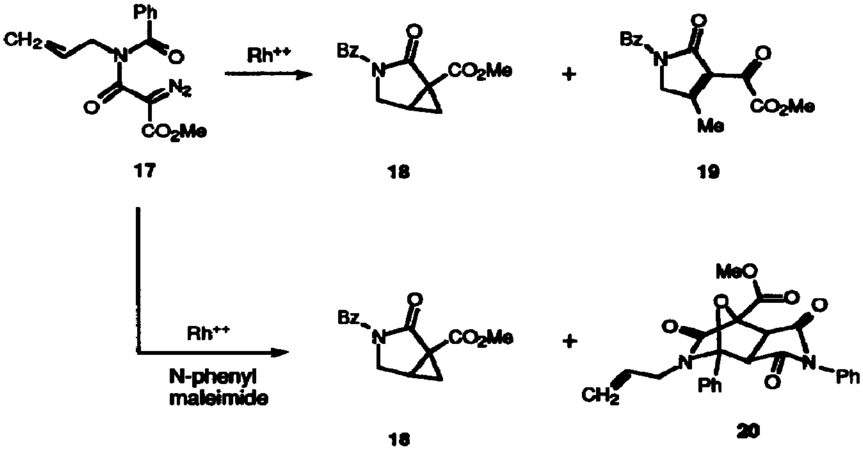


Diazoimides where the alkenyl substituent was tethered onto the N-atom by a simple methylene chain were also observed to undergo cycloaddition across the isomünchnone dipole. Thus, treatment of diazoimides 13 and 14 with a catalytic quantity of rhodium(II) trifluoroacetate in benzene (80°C) gave cycloadducts 15 and 16 in high yield (>95%) as single diastereomers. Their spectroscopic properties as well as molecular mechanics calculations support the stereochemical assignment of cycloadducts 15 and 16 as being the result of *exo* cycloaddition with respect to the dipole. The structural assignment of 15 was unequivocally established by an X-ray crystal analysis.

The facility of an intramolecular cycloaddition reaction depends on the length and nature of the tether connecting the dipole and dipolarophile functionalities. The activation energy of the process will also reflect the strain energy of the ring to be formed and the stereoelectronic interactions in the transition state. In order to probe the limits of tether length on the intramolecular cycloaddition of



these N-alkenyl substituted isomünchnones, we examined the Rh(II) catalyzed behavior of diazoimide 1 7. Exposure of 1 7 to a refluxing mixture of $Rh_2(OAc)_4$ in benzene did not produce any detectable quantities of an intramolecular cycloaddition product. Instead, the reaction afforded the intramolecular cyclopropanation product 1 8 (60%) as well as pyrrolone 1 9 (17%). The formation of 1 9 involves an initial 1,3-dipolar cycloaddition of the diazo group across the neighboring π-bond followed by nitrogen extrusion and diradical reorganization.[12-14] This same rearranged dihydro-1H-pyrrole 1 9 is also formed upon heating diazoimide 1 7 in benzene in the absence of $Rh_2(OAc)_4$.



	18	20
$Rh_2(OAc)_4$	40%	60%
$Rh_2(tfa)_4$	0%	100%

When the reaction of 1 7 was carried out in the presence of N-phenyl maleimide, a mixture of 1 9 as well as the bimolecular cycloadduct 2 0 was obtained. Interestingly, a variation in product ratio was observed when the catalyst ligand was changed to the more electron withdrawing trifluoroacetamide group ($Rh_2(tfa)_4$). With this catalyst, only the bimolecular cycloadduct 2 0 was found. The chemoselectivity encountered presumably reflects the differences in electrophilicity between the various rhodium carbenoid intermediates, implying involvement of the metal and its ligands during the formation of the isomünchnone dipole.[15-18] The fact that no dipolar cycloaddition occurs in the absence of a trapping agent suggests that ring strain of the resulting intramolecular cycloadduct is sufficiently reflected in the transition state of cycloaddition so that a substantial kinetic barrier to this process exists.

In conclusion, isomünchnone dipoles generated from the Rh(II) catalyzed reaction of diazoimides undergo successful intramolecular dipolar-cycloaddition across alkenyl π-systems tethered to the nitrogen atom of the imide. The facility of the cycloaddition is critically dependent on conformational factors in the transition state. Further work in this area is in progress and will be reported in due course.

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