Organometallics **2006,** *25,* 5852−5853

Tungsten-Promoted Dearomatization of Heterocycles: Uncovering the Latent 2-Azadiene Character of Pyrimidines

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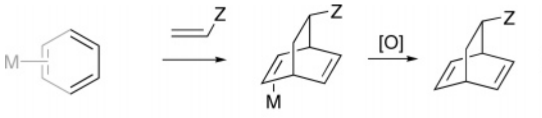
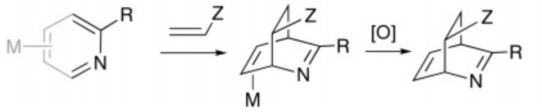
Received October 18, 2006

Summary: A tungsten pyrimidine complex exists in equilibrium with an undetected amount of an η^2-bound isomer, which is found to be a potent diene for Diels−Alder cycloaddition reactions.

The η^2 coordination of benzene by the π-basic metal fragment $\{TpW(NO)(PMe_3)\}$[1] (Tp = hydridotris(pyrazolyl)borate) can render the uncoordinated portion of the ring structurally and chemically similar to a 1,3-diene.[1,2] In this manner, the benzene ligand can be induced to undergo a Diels−Alder cycloaddition with an appropriate dienophile (eq 1) and the thermodynamically unstable bicyclooctadiene can be recovered intact.[1,3] Recently this novel approach to *aromatic cycloaddition reactions* was expanded to pyridines.[4] Since pyridine itself binds $\{TpW(NO)(PMe_3)\}$ through nitrogen, a substituent at the 2-position was required to encourage η^2 coordination. Similar to the case for its carbobicyclic counterpart, oxidative decomplexation of the metal renders an intact azabicyclooctadiene product (eq 2).



(1)



(2)

An analogous η^2-diazine complex could display the chemical behavior of a diene, azadiene, or diazadiene, depending on the position of the metal (Figure 1), and the products of cycloaddition with an alkene could lead to novel diazabicycloctadiene cores. Among these, we considered pyrimidines as particularly worthy of exploration, because of their ubiquitous role in biological systems.[5,6]

Pyrimidine itself is recalcitrant to cycloaddition, owing to its aromatic stability,[7] but we anticipated that its tungsten complex might prove otherwise. Ligand exchange of $TpW(NO)(PMe_3)(\eta^2\text{-benzene})$ (**1**) with the parent pyrimidine yielded a deep blue product (**2**) in 89% yield with spectroscopic features consistent with a formulation of $TpW(NO)(PMe_3)$(pyrimidine-κN). A nitrosyl stretching feature in the infrared absorption spectrum at 1515 cm^{-1} and a chemically reversible couple at $E_{1/2} = -0.66$ V (+/0; 100 mV/s) in a cyclic voltammogram of **2** point to a highly reducing metal center. Similar features are observed for N-coordinated pyridine complexes of $\{TpW(NO)(PMe_3)\}$.[4] Broadened ^{1}H NMR signals for the bound heterocycle indicate a fluxional process at ambient temperature. Dropping the temperature to −80 °C resolves the features of the ring protons and carbons for two rotamers, but no η^2-coordinated isomer could be detected.

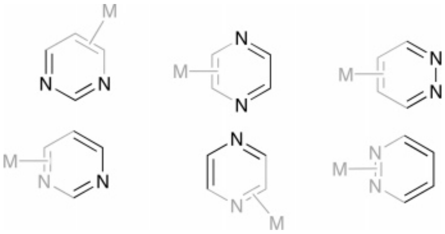


Figure 1. Latent diene, azadiene, and diazadiene functionalities of η^2-coordinated diazine complexes.

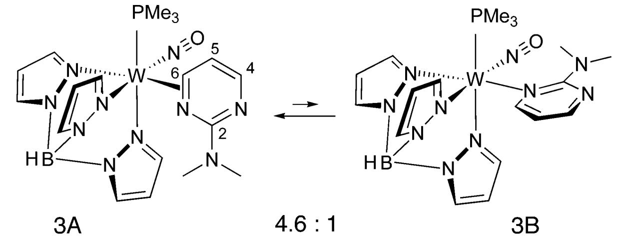


Figure 2. Two isomers of the 2-(dimethylamino)pyrimidine complex **3**.

Pursuing a strategy successfully used for pyridines,[4] we next considered the possibility of blocking the pyrimidine nitrogens with a dimethylamino group. Treatment of **1** with 2-(dimethylamino)pyrimidine gave **3** in 88% yield (Figure 2). This species was found to exist in solution as a 4.6:1 equilibrium ratio of two isomers. While the minor species (**3B**) shows spectral features similar to those of the N-coordinated pyrimidine complex **2**, the major isomer (**3A)** features a blue-shifted NO stretch at 1570 cm^{-1}, an anodic wave at −0.34 V (+/0), and a shielded methine group (^{1}H, 4.81 ppm; ^{13}C, 71.3 ppm), features reminiscent of several known examples of tungsten η^2-pyridine complexes.[4] COSY, HSQC, HMBC, and NOESY data confirmed the structure shown in Figure 2, where the metal is coordinated across C6 and N1.

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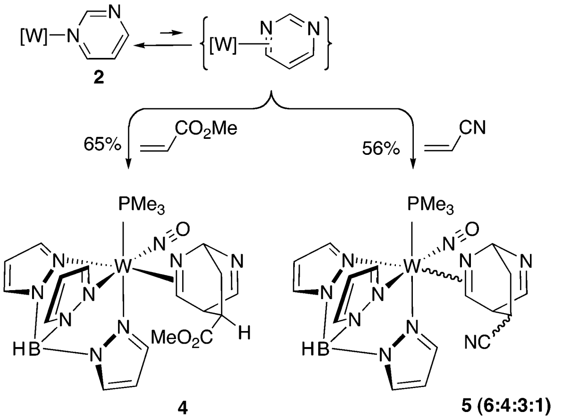
10.1021/om060960f CCC: $33.50

Scheme 1



Reports of η^2-pyrimidines are scarce, but a Ta(III) η^2-pyrimidine complex has been characterized by Wolczanski et al.,[8] and Shepherd et al. have reported evidence for a ruthenium analogue.[9] Unfortunately, while the dimethylamine substituent allowed for the preparation of an η^2-pyrimidine complex, this species failed to exhibit the desired [4 + 2] cycloaddition with *N*-methylmaleimide, methyl acrylate, or methyl vinyl ketone.

We next considered the possibility that the N-bound pyrimidine complex **2** could be in equilibrium with a small amount of an η^2 isomer. Provided that the purported species was sufficiently reactive, cycloaddition with an appropriate dienophile could still be realized. The highly reducing nature of **2** renders it incompatible with highly activated dienophiles such as TCNE, maleimides, quinones, and DMAD. However, treatment of **2** with *singly activated dienophiles* such as methyl acrylate and acrylonitrile yielded the cycloadducts **4** (65%) and **5** (56%), respectively (Scheme 1).

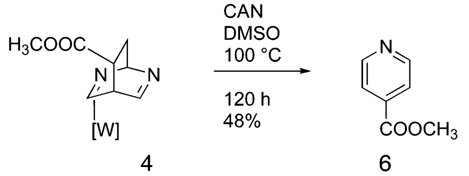
Compound **4** is isolated exclusively with the bicyclic ligand in an exo stereochemistry (EWG away from the original azadiene fragment) and with the coordinated imine nitrogen syn to the PMe_3 ligand. The nitrile analogue **5** is isolated in a 2:5 ratio of exo and endo isomers, each one present as a mixture of two coordination diastereomers. Of note, all isomers of **4** and **5** exhibit the same regiochemistry of cycloaddition, with the electron-withdrawing group distal to the ring nitrogens, and cycloaddition always occurs with the dienophile adding to the uncoordinated face of the pyrimidine.

Key spectroscopic features indicating formation of cycloadducts include, for each complex, a highly shielded methine group and IR and electrochemical data consistent with other η^2 heterocyclic complexes of {TpW(NO)(PMe_3)}.[10,11] NOESY, COSY, HSQC, and HMBC data confirm the assigned structures.

That the bicyclic cores in **4** and **5** are formed from an unsubstituted pyrimidine, without excessive temperatures or pressures, is remarkable. This strongly suggests the presence of an η^2-pyrimidine intermediate, as is shown in Scheme 1. The rate of cycloaddition of **4** was determined to be directly proportional to dienophile concentration. The proposed N to η^2 linkage isomerization prior to cycloaddition does not appear to be rate-limiting under these reaction conditions ([dienophile] $\approx$ 2−10 M). While it remains possible that cycloaddition directly involves the dominant N-bound isomer of **2**, this seems highly unlikely, given that the heterocycle is still aromatic in this binding mode.

The regiochemistry of these cycloadditions is noteworthy in that the β-carbon of the dienophile binds to the *imine carbon* of the 2-azadiene fragment. This is the opposite of what we observed for the analogous cycloadditions with pyridines (eq 2).[4,12] Owing to their chemical instability, examples of unsubstituted 2-azadienes participating in [4 + 2] cycloadditions are virtually unknown. When π substituents are present, their electronic effects, rather than the orientation of azadiene, determine the regiochemical outcome.[7,13] The high degree of regioselectivity observed in the formation of **4** and **5** suggests that the metal not only disrupts the aromatic character of the pyrimidine but also increases the electron density at C2, regardless of whether the coordinated imine nitrogen is syn or anti to the PMe_3 ligand.

Preliminary attempts to liberate the delicate diazabicyclooctadiene from the metal have mostly resulted in recovery of pyrimidine from retrocycloaddition. Given its aromatic nature, this is not surprising. However, when a DMSO solution of **4** with 1 equiv of CAN (*caution!* see ref 14) was held at 100 °C for 120 h, methyl isonicotinate (**6**) was formed in 48% yield.



(3)

Whether its formation is initiated by a retrocycloaddition of hydrogen cyanide (followed by oxidation), or some other mechanism, is under investigation, but we note that DMSO appears to be required for this outcome. The delicate nature of these diazabicyclooctadiene ligands will likely require their chemical modification prior to removal from the metal, and studies in this vein are underway. In this regard, the tungsten serves not only to activate the cycloaddition but also to protect the resulting bicyclic structure from retrocycloaddition.

Pyridines, pyrimidines, imidazoles, and other aromatic nitrogen heterocycles are common ligands for transition-metal complexes. This study demonstrates that seemingly conventional N-bound heterocyclic complexes may be in equilibrium with undetectable, yet highly reactive, isomers featuring π-coordinated heterocycles that may lead to unexpected reactivity patterns.

Acknowledgment. This work was supported by the NIH (NIGMS; R01-GM49236) and the NSF (CHE0116492; UR).

Supporting Information Available: Text giving full synthetic details for the preparation of cycloadducts **2**−**5** and figures giving their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Bassett, K. C.; You, F.; Graham, P. M.; Myers, W. H.; Sabat, M.; Harman, W. D. *Organometallics* **2006**, *25*, 435.

[12] For example, in the acrylonitrile cycloaddition with TpW(NO)(PMe_3)(3,4-η^2-2,6-lutidine), the β carbon binds to C4 of the 2-azadiene, exclusively.

[13] Gonzalez, J.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3031.

[14] Do not heat DMSO with an excess of any powerful oxidant.