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Regiospecific Control of Rh(II) Carbenoids in the C-H Insertion Reaction

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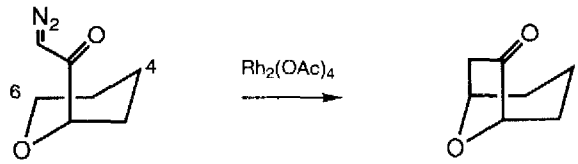
Abstract: *Electronic and conformational effects of Rh(II) catalyzed intramolecular C-H insertions of 2-diazoketo tetrahydropyrans* ***5a-e*** *were studied. The C-6H/C-4H insertion ratio was modulated by the electron withdrawing or donating capacity of the substituted oxygen at C-4.*

During the course of our studies involving the C-H insertion process of α-ketocarbenes, derived from the Rh(II) catalyzed reaction of diazoketones, we had identified stereoelectronic effects responsible for the enhanced susceptibility of C-H bonds adjacent to ether oxygens.[1] One particular system examined was the trans-annular cyclization of 2-diazoketo tetrahydropyran to produce exclusively a bicyclic furanone, resulting from C-H insertion at C-6 (Scheme I). No C-H insertion at the C-4H to form a cyclopentanone was detected. We undertook to examine the formation of the bicyclic furanone ring system in greater detail as it is an integral structural feature in a number of natural products,[2] and is a useful intermediate in the preparation of hydroxy substituted seven-membered rings. [3]

Scheme I

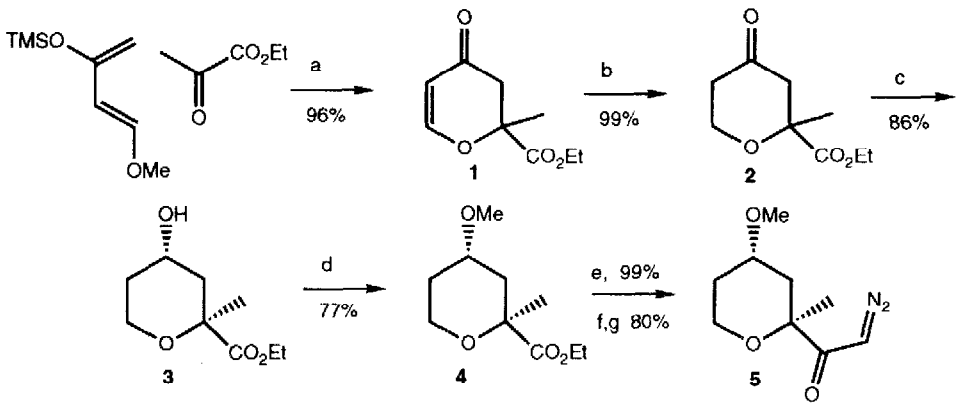


We sought to construct diazoketone precursors with equatorial oxygen substituents at C-4 in order to determine the influence in regioselectivity of the insertion reaction on the tetrahydropyran ring. Specifically, the electronic contribution of substituents on oxygen at C-4 was of interest. With both C-4 and C-6 activated by a neighboring oxygen substituent, it was anticipated that either of these two pathways would be preferred over the formation of the more strained 6,4-fused rings resulting from insertion at C-3H.

The desired ring system was prepared according to the route shown in Scheme II. The tetrahydropyran ring system was constructed by a $ZnCl_2$-catalyzed Diels Alder reaction using Danishefsky's diene[4] and ethyl pyruvate, followed by acidic hydrolysis of the intermediate TMS enol ether to afford enone **1**. Hydrogenation of the olefin and low temperature $NaBH_4$ reduction of the ketone afforded **3** as the major product with an equatorial hydroxy group.

Methylation of the C-4 hydroxyl proved to be difficult, as standard methodology using NaH and MeI in THF or DMF gave poor conversion of alkylated product **4**. Using Ag_2O in neat MeI, we obtained the desired methylated product but the reaction was very slow and failed to go to completion. We found that the methylation could be performed in good yield (77%) and reasonable reaction time (8h) with MeOTf and 2,6-di-*t*-butylpyridine in refluxing CH_2Cl_2. The synthesis of the α-diazoketone was completed by saponification of the ethyl ester with LiOH followed by converstion to an acid chloride and treatment with excess diazomethane to afford **5a**.

Scheme II



Reagents and Conditions: (a) $ZnCl_2$, benzene, RT, 2h then .005M HCl, RT, 20 min. (b) H_2 balloon, 10% Pd/C, EtOH (c) $NaBH_4$, EtOH, -40°C, .5h (d) MeOTf, 2,6-di-t-butyl-4-methylpyridine CH_2Cl_2, reflux, 8h (e) LiOH, MeOH/H_2O, 3:1, RT, 2 days (f) $(COCl)_2$, cat. DMF, CH_2Cl_2, 0°C to RT, 1.5h (g) CH_2N_2, Et_2O, 0°C to RT, overnight.

The 4-siloxydiazoketone **5b** was prepared by silylation of the hydroxyester **3** (TBDPSCl, DMF, imidazole) follwed by DIBAL reduction of the ester (CH_2Cl_2, 0°C,1h) to the corresponding primary alcohol. Oxidation of the alcohol to the carboxylic acid was accomplished in two steps, PCC oxidation to the aldehyde (CH_2Cl_2, NaOAc, RT, 2.5h) followed by $NaClO_2$ oxidation to the carboxylic acid (t-BuOH, H_2O, NaH_2PO_4, 2-methyl-2-butene, 0°C).[5] Conversion of the carboxylic acid to the diazoketone **5b** was accomplished using our standard methodology.

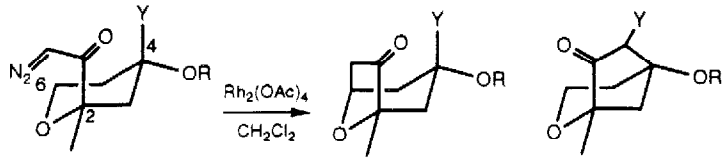
The 4-acetoxydiazoketone **5c** was prepared by saponification of the hydroxyester **3** with LiOH in MeOH and H_2O, neutralized, concentrated then treated with Ac_2O and pyridine (RT, overnight). An aqueous workup provided the 4-acetoxy-2-carboxylic acid which was converted to the diazoketone by formation of a mixed anhydride ($ClCO_2Et$, Et_3N, 0°C, 1h) followed by treatment with diazomethane.

Before describing the C-H insertion experiments, it should be pointed out that the tetrahydropyran ring possesses a bias which favors reaction at the C-6 hydrogen. Examination of molecular models revealed that the reacting carbene carbon is closer to the axial C-6H than to the C-4H by virtue of the short endocyclic ether bond. We were concerned that the interatomic distances alone could completely

determine the regioselectivity and override any electronic effects of the C-4 oxygen substituents. Alternatively, we considered possible dipolar and stereoelectronic effects of the lone pairs on the endocyclic ether oxygen which might also direct the insertion reaction at C-6H.[6]

The first substrate chosen for cyclization was the 4-methoxy substituted diazoketone **5a**. Rh(II) catalyzed decompostion of diazoketone **5a** ($Rh_2(OAc)_4$, CH_2Cl_2, RT) afforded **6a** as the major product. Examination ot the GC-MS of the crude reaction mixture indicated that the ratio of C-6/C-4 hydrogen insertion was 24:1(Table I). Similar reactions using the silyloxy and the acetoxy derivatives **5b** and **5c** also demonstrated preferential C-6H insertion with ratios of 75:1 and >99:1 respectively. We noted a correlation between the electron withdrawing capacity of the R group at C-4 and a preference for C-6H insertion.

Table I



5	R	Y	6	7	Ratio[9] 6/7
a	Me	H	a	a	24:1
b	TBDPS	H	b	b	76:1
c	Ac	H	c	c	>99:1
d	H	H	d	d	5.9:1
e	H	D	e	e	5.7:1

Having determined that electron withdrawing groups influence the chemoselectivity of the C-H insertion reaction, it was necessary to demonstrate that an electron donating substituent at C-4 would enhance insertion at that site. According to the work of Hoz and Wolk[7] we expected that a free hydroxyl would be substantially more electron donating than a methoxyl, therefore the C-4 substituted hydroxy diazoketone **5d** was prepared by hydrolysis of the acetoxy diazoketone **5c** with K_2CO_3 in MeOH and THF at RT. When the diazoketone **5d** was subjected to the same Rh(II) catalyzed carbenoid formation we observed a 5.9:1 ratio of C-6H/C-4H bicyclic products. A plausible mechanism for the C-H insertion process has been proposed by Taber[8] which invokes hydrogen transfer to rhodium followed by reductive elimination and C-C bond formation. The precise mechanism by which hydrogen is transferred to rhodium is unknown and we suggest that the C-H insertion process may involve the transfer of hydride to rhodium. Our results support this mechanism in that an electron donating group facilitates the process of hydride transfer, whereas an electron withdrawing group produces the opposite effect. The ratios observed in products **6a-d** and **7a-d** reflect the electronic effects of the C-4 substituent on oxygen.

If hydride transfer is occurring and is rate determining, the reaction of **5e** bearing a deuterium at

C-4 instead of a hydrogen (prepared by $NaBD_4$ reduction of **2**) might exhibit a kinetic isotope effect and a ratio of >5.9:1 of C-6H/C-4H insertion products would be observed. This was not the case as a similar ratio of 5.7:1 was observed for the isotopically labelled diazoketone **5e**. We speculate that the transition state occurs relatively late along the reaction coordinate and that the rate determining step occurs prior to C-H insertion.

In summary we have demonstrated that stereoelectronic factors in the C-H insertion reaction can influence regiospecificity. We are currently working to expand the scope of the directed C-H insertion of rhodium carbenoids by studying additional substituent effects and by investigating applications to other ring systems.

Acknowledgements: We thank Mr. R. Dinallo and Mr. Keith McKellop for GC-MS determinations.

References and Notes

1. (a) Adams, J., Poupart, M. A., Grenier, L., Schaller, C., Quimet, N. *Tetrahedron Lett.*, **1989**, *30*, 1749. (b) Adams, J., Poupart, M. A., Grenier, L. *Tetrahedron Lett.*, **1989**, *30*, 1753. (c) For a review of Rh(II) catalyzed reactions of diazocarbonyl compounds see Adams, J., Spero, D. M. *Tetrahedron*, **1991**, *47*, 1765. (d) Doyle, M. P., Pieters, R. J., Taunton, J., Pho, H. Q., and Padwa, A., Hertzog, D. L., Precedo, L. *J. Org. Chem.*, **1991**, *56*, 820.
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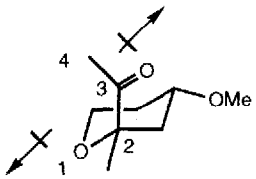
5. All attempts to directly saponify the ester to the carboxylic acid in the presence of the 4-siloxy group failed.
6. Conformational studies on a related model system using molecular mechanics (MM2 force field) indicate that the carbonyl oxygen adopts an anti orientation to the pyran oxygen, serving to minimize the dipole/dipole interaction.



Torsional angle 1,2,3,4=50°

7. Hoz, S., Wolk, T. L. *Tetrahedron Lett.*, **1990**, *31*, 4085.
8. Taber, D. F., Ruckle Jr., R. E. *J. Am. Chem. Soc.*, **1986**, *108*, 7686.
9. All rhodium catalyzed cyclizations were carried out on an analytical scale. Isolation of the minor C-4 insertion product was carried out only in the cyclization of diazoketone **5d**. Ratios of products were determined by GC-MS.

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