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A Rhodium(II) Catalytic Approach to the Synthesis of Ethers of a Minor Component in a Tautomeric Set

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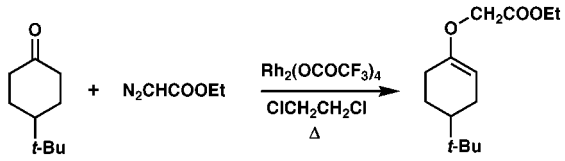
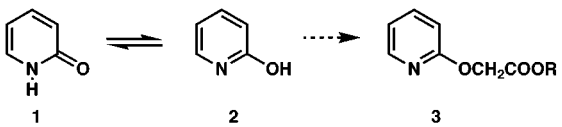
ABSTRACT



The Rh(II)-catalyzed reaction of diazoacetic esters with various carbonyl compounds is an effective method for the synthesis of acetic ester ethers of the corresponding enol forms.

The synthesis of ethers of a minor component in a tautomeric set can be problematic using conventional synthetic procedures. For example, in the case of the 2-pyridone (**1**)−2-hydroxypyridine (**2**) tautomeric set (for which the former predominates in aqueous solution and the later in the gas phase),[1] efficient selective attachment of a group at the 2-oxygen has been elusive. In connection with studies on enantioselective alkylation reactions, we required ester **3**, R = *t*-Bu but were unable to obtain it in more than a few percent yield by alkylation of the 2-pyridone conjugate base with *tert*-butyl bromoacetate, the major product being the *N*-alkylated isomer of **3**. This finding was consistent with literature reports that *N*-attack predominates in such anion alkylation reactions. The formation of **3** by reaction of

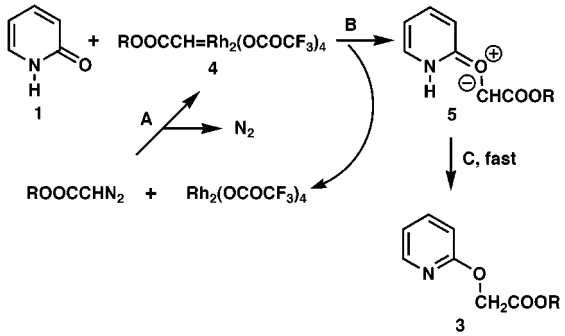


2-bromopyridine with the conjugate base of *tert*-butyl hydroxyacetate was also unsatisfactory as a preparative method.

It occurred to us that Rh(II)-catalyzed etherification of **1** with *tert*-butyl diazoacetate might provide a satisfactory route to **3**. Indeed, when this experiment was conducted, **3**, R = *t*-Bu was readily obtained in 84% yield in 1,2-dichloroethane (DCE) at reflux, 2 mol % of $Rh_2(OCOCF_3)_4$, and 0.9 equiv of the diazoester which was added slowly to the reaction mixture. Similarly, ethyl diazoacetate converted 2-pyridone to ester **3**, R = OEt in 87% yield (see Table 1).

A reasonable mechanistic interpretation of these results is shown in Scheme 1. Step A is the familiar reaction of the diazoester with the catalyst $Rh_2(OCOCF_3)_4$ to form a transient

Scheme 1



(1) (a) Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186. (b) Beak, P.; Fry, F. S., Jr.; Lee, J.; Steele, F. *J. Am. Chem. Soc.* **1976**, *98*, 171.

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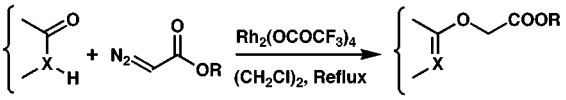
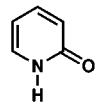
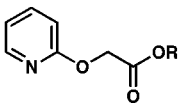
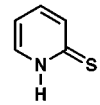
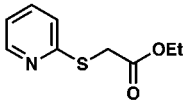
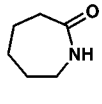
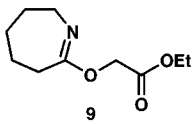
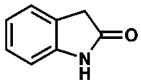
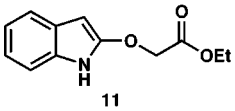
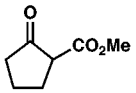
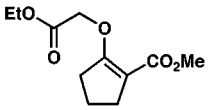
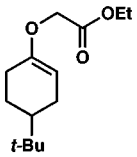
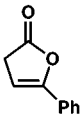
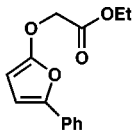
Table 1



substrate	product[a]	yield (%)
 1	 3	84 R = *t*-Bu[b] 87 R = Et
 6	 7	91
 8	 9	82[c]
 10	 11	71[d]
 12	 13	76
 14	 15	69
 16	 17	21

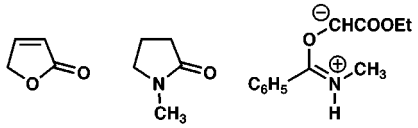
(a) unless otherwise noted all reactions were conducted on a 2 mmol scale in refluxing $(CH_2Cl)_2$ using 1.3 eq of diazoacetate and 2 mol % of $Rh_2(OCOCF_3)_4$ as catalyst. (b) 0.9 eq of diazoacetate was used. (c) reaction was conducted in refluxing CH_2Cl_2. (d) *ca.* 7% of the isomeric indoline was also formed.

Rh(II)−carbene complex (**4**). Transfer of the carbene from rhodium to the oxygen of 2-pyridone generates the oxygen ylide **5** (step B) which upon 1,4-hydrogen shift forms the product **3** (step C).

As shown in Table 1, 2-thiopyridone (**6**) reacts smoothly with Rh(II) and ethyl diazoacetate to form in 91% yield the corresponding thioether **7**, paralleling the behavior of 2-pyridone. ϵ-Caprolactam (**8**) reacts smoothly with ethyl diazoacetate in CH_2Cl_2 at reflux to give the corresponding imino ether **9** in 82% yield, even though negligible amounts of the enol tautomer of the lactam can exist at equilibrium. Similarly, benzpyrrolidone **10** was converted via the imino ether to indole **11** in 71% yield.

The Rh(II)-catalyzed etherification was also applied successfully to ketonic substrates. 2-Methoxycarbonylcyclopentanone (**12**) was transformed into enol ether **13** (76%). Reaction of 4-*tert*-butylcyclohexanone (**14**) with ethyl diazoacetate and a catalytic amount of $Rh_2(OCOCF_3)_4$ in DCE at reflux afforded enol ether **15** in 69% yield.

β,γ-Unsaturated γ-lactone **16** was converted under the standard conditions into furan **17**, as anticipated, but the yield of **17** was only modest. A number of byproducts were formed, possibly as the result of competing C=C addition and C−H insertion pathways. In contrast to **16**, α,β-butenolide **18** was recovered unchanged, consistent with the mechanistic pathway outlined in Scheme 1.



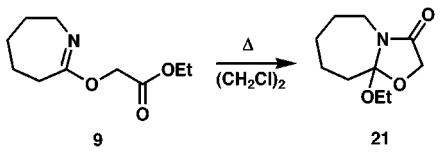
18 19 20

N-Methylpyrrolidine (**19**) was unaffected by heating with ethyl diazoacetate and Rh(II) catalyst at reflux in DCE, presumably because the carbonyl ylide from **19** is insufficiently reactive to abstract hydrogen from either the *N*-methyl or α-CH_2 group and reacts instead with ethyl diazoacetate to form diethyl fumarate. Surprisingly, *N*-methylbenzamide was also recovered unchanged under the standard conditions, a result which could mean that the carbonyl ylide is formed in the *Z* geometry, as shown in **20**, which cannot undergo N → C hydrogen migration to form the imino ether.

To test the mechanistic pathway shown in Scheme 1, a 1:1 mixture of ϵ-caprolactam **8** and *N*-deuterated **8** was treated $Rh_2(OCOCF_3)_4$ catalyst and 10 mol % of N_2-CHCOOEt in CH_2Cl_2 at reflux. Analysis of the reaction product **9** by mass spectroscopy revealed a 1:1 mixture of **9** and monodeuterated **9** (label in the OCHDCCOEt subunit by ^{1}H NMR analysis), indicating the absence of a primary ^{1}H/^{2}H kinetic isotope effect, as expected for the mechanism shown in Scheme 1 with step A or B rate limiting.

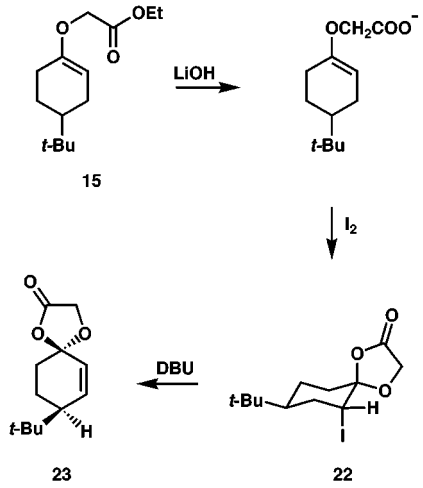
The reaction products **3**, **7**, **9**, **11**, **13**, and **15** are useful intermediates for synthesis and undergo interesting chemical transformations. For instance, when imino ether **9** is heated at reflux in DCE with a catalytic amount of ethanol for 14 h, it undergoes isomerization into the ketal−lactam **21** (82%), which was also formed directly from **8**, N_2CHCOOEt, and Rh(II) when the reaction was conducted in DCE at reflux.

Enol ether **15** was transformed smoothly and stereospecifically into ketal lactone **22** (81%) in one flask by the sequence: (1) saponification with 1:1 aqueous LiOH−THF at 23 °C to produce a solution of the corresponding lithium

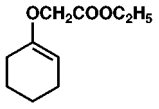


9 21

carboxylate, (2) adjustment of the pH of the carboxylate salt solution to 9−10 by addition of $NaHSO_4$, and (3) reaction with I_2 at 0 °C for 90 min. Treatment of **22** with 1,8-diazabicyclo[5.4.0]undec-5-ene (DBU) in benzene at 50 °C smoothly effected elimination of the elements of HI to form exclusively cyclohexenone ketal **23**. The stereochemistry of the intermediate iodolactone **22** was clear from the ^{1}H NMR spectrum (axial iodine substituent) and the usual trans addition pathway for iodolactonization. The sequence **14** → **15** → **22** → **23** represents a novel method for the conversion of a ketone to a ketal of the corresponding α,β-enone which could be generally useful.



Nearly 50 years ago, Kharasch et al.[2] reported that a mixture of several products (not separated) was obtained when cyclohexanone and ethyl diazoacetate were heated at 90 °C in the presence of copper powder. One component of the mixture (43%) was enol ether **24**. In view of the results described above, it seems reasonable that **24** may be formed by a mechanistic process involving a copper carbenoid which is analogous to that shown in Scheme 1. A thermal (140 °C) reaction has also been described for the transformation of 2-pyridone to the 2-pyridyl ether **3**, R = Et, in modest yield using ethyl diazoacetate.[3,4]



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The procedures for the synthesis of **3**[5] and **11**[6] are illustrative.

Acknowledgment. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

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(2) Kharasch; M. S.; Rudy, T.; Nudenberg, W.; Büchi, G. *J. Org. Chem.* **1953**, *18*, 1030.

(3) Maas, J.; DeGraaf, G. B. R.; Den Hertog, H. J. *Recl. Trav. Chim Pays-Bas* **1955**, *74*, 175.

(4) For a recent review of catalytic reactions of Rh(II) and diazo compounds, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley: New York, 1998.

(5) **Synthesis of 3, R = *t*-Bu:** A solution of 2-pyridone (190 mg, 2.00 mmol) in 4.5 mL $(CH_2Cl)_2$ was dried over 4 Å molecular sieves and transferred via cannula to a two-neck round-bottom flask equipped with a condenser and an elongated, septum-equipped side arm. $Rh_2(OCOCF_3)_4$ (12 mg, 2 mol %) was added, and the reaction mixture was heated at reflux. *tert*-Butyl diazoacetate (0.25 mL, 1.80 mmol), was added from a gastight syringe, over 6 h, using a syring pump. Initially, the reaction mixture was green but it quickly turned to light red. After the addition was completed, the reaction mixture was refluxed for an additional 2 h, allowed to cool to room temperature, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 3 × 10 mL of CH_2Cl_2, and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the crude product was passed through a plug of silica gel with 1:2 ethyl acetate−hexanes for elution to give 316 mg (84% yield) of **3**, R = *t*-Bu, (colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 5.0, 1.8 Hz, 1H), 7.56 (ddd, J = 8.4, 7.0, 1.8 Hz, 1H), 6.86 (dd, J = 7.0, 5.0 Hz, 1H), 6.83(d, J = 8.4 Hz, 1H), 4.76 (s, 2H), 1.43 (s, 9H) ppm; FTIR (film) ν 3004, 2980, 1755, 1598, 1436, 1369, 1290, 1223, 1158 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 162.3, 146.3, 138.6, 117.2, 110.9, 81.6, 62.8, 28.0 ppm; CIMS (ammonia) 210 (100) $[M + H]^+$, 209, 154; HRMS calcd for $C_{11}H_{16}NO_3$ 210.1130, found 210.1132.

(6) **Synthesis of 11:** Oxindole (297 mg, 2.23 mmol) (dried azeotropically with toluene) was dissolved in 5 mL of $(CH_2Cl)_2$, and the solution was transferred to the reaction vessel described above. Following addition of $Rh_2(OCOCF_3)_4$ (14 mg, 2 mol %), the reaction mixture was heated to reflux and ethyl diazoacetate (0.30 mL, 2.88 mmol) was added over 6 h. Following the addition, the reaction mixture was heated at reflux for a further 6 h and the solvent was removed in vacuo under an inert atmosphere. The residue was purified by flash column chromatography on silica gel, eluting with 1:2 ethyl acetate−hexanes to afford 345 mg (71% yield) of indole **11** (colorless, somewhat air-sensitive solid): mp 120−21 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.43−7.41 (m, 1H), 7.22−7.20 (m, 1H), 7.10−7.06 (m, 2H), 5.57 (d, J = 2.2 Hz, 1H), 4.69 (s, 2H), 4.30 (q, J = 7.3 Hz, 2H), 1.32 (t, J = 7.3 Hz, 3H) ppm; FTIR (film) ν 3352, 2990, 1740, 1586, 1463, 1211 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 152.0, 130.9, 127.7, 120.2, 119.9, 118.9, 110.0, 78.0, 67.2, 61.7, 14.3 ppm; EIMS 219 $[M]^+$, 132 (100); HRMS calcd for $C_{12}H_{13}NO_3$ 219.0896, found 219.0901.