

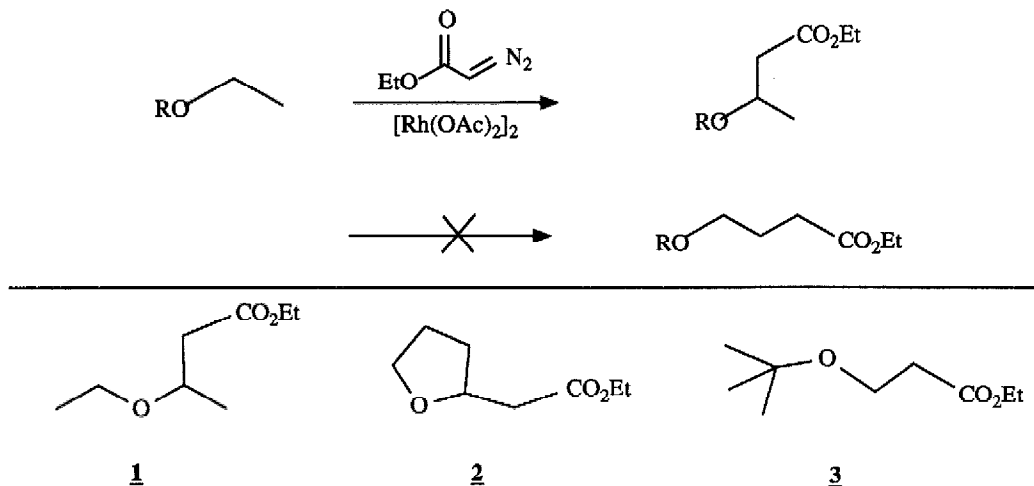
Rhodium Acetate Catalyzes the Addition of Carbenoids α - to Ether Oxygens

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Summary: Diazo-carbonyl compounds, when catalyzed by rhodium acetate, insert preferentially adjacent to ether oxygens. This phenomenon was exploited to develop a synthesis of 3(2H)-furanones.

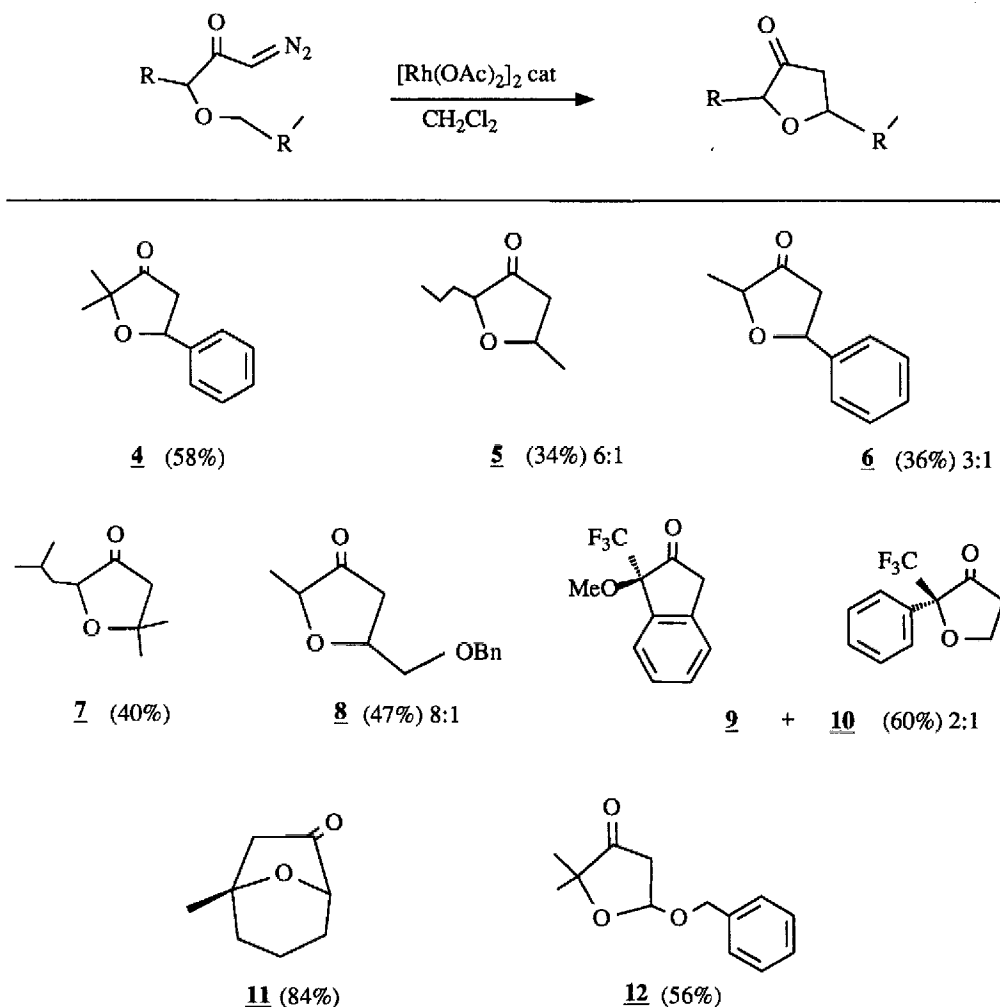
The insertion of carbenes derived from diazo-carbonyl compounds into unactivated aliphatic C-H bonds has been well documented.¹ This reaction has been particularly useful in the intramolecular sense to produce preferentially five-membered rings.² During the course of our studies we have found that the presence of an ether oxygen promotes this insertion and the carbon-hydrogen bond adjacent to the ether oxygen is the preferred site of reaction, compared to a normal aliphatic carbon-hydrogen bond. This reaction was examined for both the inter- and intramolecular routes. Herein we present a synthesis of furanones from 2-alkoxy carboxylic acids.

Initially, we explored the $[\text{Rh}(\text{OAc})_2]_2$ catalyzed reaction of ethyl diazoacetate with aliphatic ethers. Reactions were performed at room temperature, using ether as the solvent. The amount of catalyst required was 1 weight % based on the diazo-ester. Reaction times were 10-30 minutes and yields of compounds **1-3** ranged between 20-40%. Products were isolated by column chromatography on silica gel, or by bulb to bulb distillation³. Although there were detectable amounts of maleate and fumarate as a result of carbene dimerization, the amounts formed were less than 2%. Insertion of the carbene into a C-H bond distal to the ether was not observed.



Owing to the limited utility of the intermolecular process, we turned our attentions to the intramolecular version of this reaction. The rhodium acetate catalyzed reaction of β -alkoxy diazoketones was previously examined by Roskamp and Johnson⁴ and C-O insertion with alkyl migration to produce cyclobutanones was the major course of reaction. Bearing this in mind, we chose to study the reactivity of diazoketones derived from α -alkoxy carboxylic acids.

The diazoketones were prepared in a standard manner from the corresponding carboxylic acids in a 2 step sequence. The acids were converted to their acid chlorides using oxalyl chloride, then treated with an excess of diazomethane to furnish good yields of the diazoketones. Treatment of the alkoxy diazoketones with the rhodium II catalyst (1 weight %) at room temperature in CH_2Cl_2 at medium dilution (0.01-0.05M) afforded 3(2H)-furanones. A sample of the furanones prepared in this manner are shown below.

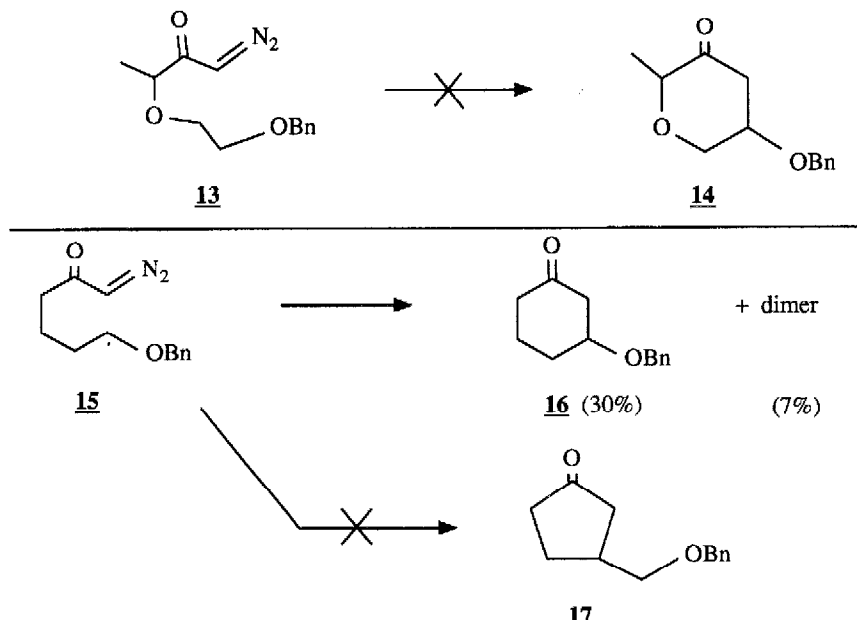


While the reactions appeared to be very clean (as judged by tlc and gc analysis) the yields tended to be rather low, particularly when the diazoketone contained acidic α -hydrogens. This poor recovery of product

furanone is still not well understood. As the carbenoid intermediates are highly reactive, we suspect that some decomposition (as yet uncharacterized) occurs during the course of the reaction. Examination of the crude product by ^1H NMR spectroscopy indicated additional aliphatic signals accounting for the decomposition products. The regioselection of the reaction is absolute since no cyclopentanone formation was detected as a result of C-H insertion into an unactivated aliphatic chain. Where possible, the cyclization was stereoselective, affording the 2,5 -cis disubstituted 3(2H)-furanones as the major isomer.⁵ The reaction proceeded well in a trans-annular sense (cf compound **11**).⁶ Though in modest yield, furanone **12** was produced as a result of ether-acetal C-H insertion.

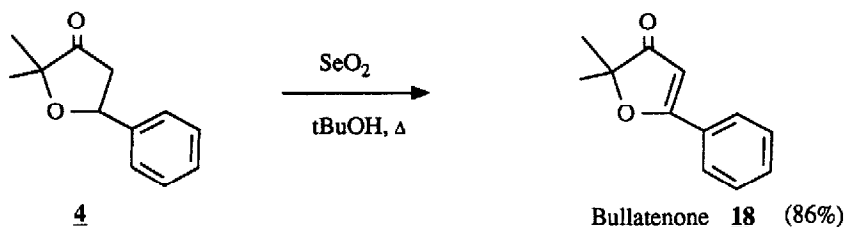
A deviation from the normal exclusive C-H insertion adjacent to ethers was observed with the diazoketone derived from α -methoxy- α -(trifluoromethyl) phenyl acetic acid (Mosher's acid). A 2:1 mixture of **9** to **10** was obtained with apparent insertion into the aromatic ring predominating.⁷

While intramolecular C-H insertion to form 5-membered rings is the preferred process, both steric and electronic influences play important roles in the outcome of the reaction.^{8,9} Competition experiments were designed to test the directing influence exerted by the ether oxygen compared with the propensity for 5-membered ring formation. Furanone **8** illustrated the clear preference for the 5-membered ring when two ether oxygens were present to activate the C-H bonds leading to either the 5- or the 6-membered rings. None of the 6-membered, **14**, ring was observed. However, when a carba analog of diazoketone **13** was cyclized, the dominating factor of ether activation prevailed and only the 6-membered ring, **16**, was formed together with the carbene derived dimer.^{10,11}



The synthetic utility of this approach to furanones was employed to prepare the natural product bullatenone, a plant metabolite of *Myrtus bullata*. Oxidation of furanone **4** with SeO_2 according to the procedure of Smith et. al. provided bullatenone.¹²

The ether activation of C-H bonds towards carbenoid insertion serves as further indication that electronic



factors play an important role in this reaction. This electronic activation complements the findings of Stork and Nakatani who recently reported the effect of deactivation of C-H insertion by proximal electron withdrawing esters.⁹

In conclusion, we believe that the route described can be of practical utility in the preparation of 3(2H)-furanone derivatives and provides a viable alternative to published syntheses.¹³

References and Notes:

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