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SELECTIVITY IN THE LACTONE FORMATION VIA C-H INSERTION REACTION OF DIAZOMALONATES

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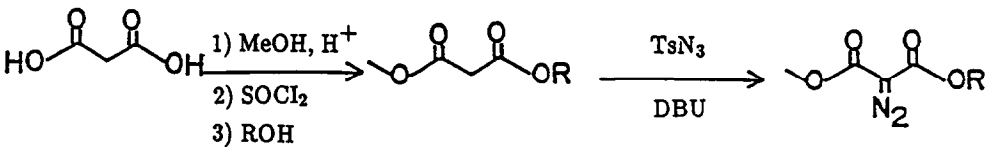
Summary: Rhodium(II)-acetate mediated intramolecular C-H insertion reactions of alkyl methyl diazomalonates result in the formation of β- and γ-lactones. The selectivity depends on both the substitution pattern of insertion centers and the conformational bias of metallocarbenes.

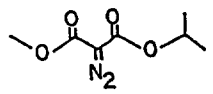
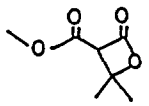
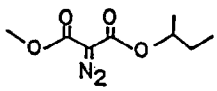
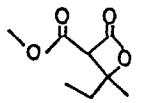
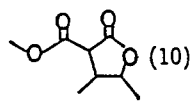
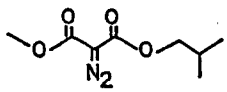
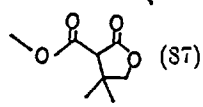
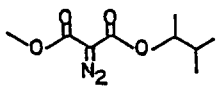
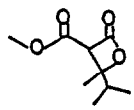
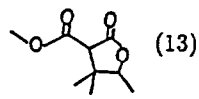
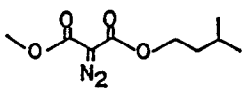
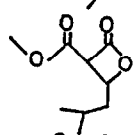
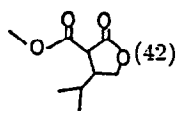
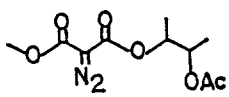
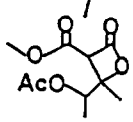
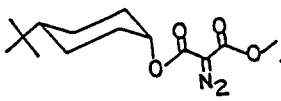
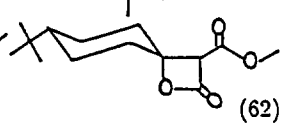
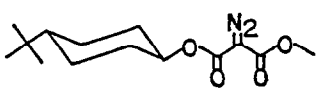
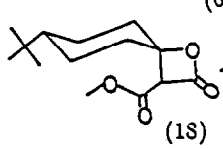
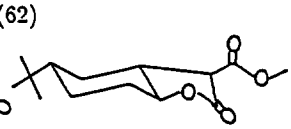
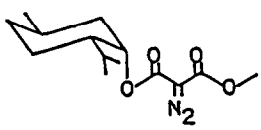
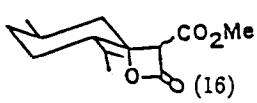
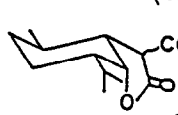
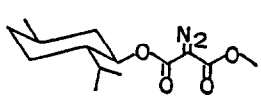
Intramolecular C-H insertion reactions[1] are unique in the formation of ring systems in that unactivated carbon centers are utilized in annulations. Preferred formation of five-membered ring carbocycles from methyl esters of α-diazo-β-keto carboxylic acids is well documented[2]. Four-membered ring β-lactams are apparently the favored products from the C-H insertion reactions of various α-diazoacetoacetic amides[3]. Despite scattered examples[4] of successful application of the C-H insertion reactions for the formation of oxygen-containing ring systems, systematic studies on the selectivity of lactone formation via intramolecular C-H insertion reactions are not yet reported. We wish to communicate here results of our recent experiments on rhodium(II)-acetate catalyzed intramolecular C-H insertion reactions of various alkyl methyl diazomalonates.

Alkyl methyl diazomalonates were routinely prepared from malonic acid via formation of the mono methyl ester in methanol-sulfuric acid, conversion to the acid chloride in thionyl chloride, esterification with various alcohols in the presence of base, and diazo transfer reaction under standard conditions[5].



Insertion reactions were performed in dichloromethane at room temperature using rhodium(II)-acetate as the catalyst. Moisture was strictly forbidden to prevent accumulation of O-H insertion products. Results of the reactions are summarized in the table.

(Table) Insertion Reaction of Diazomalonates Catalyzed by $Rh_2(OAc)_4$[a]

Entry	Starting Materials[b]	Products (yield,%)[c] β-lactones[d]	γ-lactones[e]	Diastereomeric ratios[f]
1		 (67)		
2		 (50)	 (10)	β- 2.5 : 1 γ-[g]
3			 (87)	
4		 (40)	 (13)	β- 10 : 1 γ- 1.5 : 1
5		 (20)	 (42)	
6		 (50)		
7[h]		 (62)		
8[i]		 (18)	 (24)	γ- 6 : 1
9		 (16)	 (50)	β- one isomer γ- one isomer
10			 (80)	γ- 6 : 1

Notes : a. Reaction conditions : 0.01–0.03 M in dry CH_2Cl_2 under N_2 atmosphere at r.t., cat. $Rh_2(OAc)_4$, 15 hours. b. The characteristic IR absorption of the diazo functionality; 2140 cm^{-1}. c. Isolated yields. All products were identified by NMR, IR and mass spectra. d. IR spectra exhibited the β-lactone carbonyl absorptions at 1840 cm^{-1}. e. IR spectra showed the γ-lactone carbonyl absorptions at 1780 cm^{-1}. f. Each ratio was determined by high resolution NMR analysis (100, 200, and 300 MHz). g. Almost equal amount of four diastereomers. h. 4-t-Butylcyclohexanone was also isolated in 22% yield. i. Like entry 7, 4-t-butylcyclohexanone was obtained in 50% yield.

Isopropyl methyl diazomalonate (entry 1) produced a reasonably high yield of the β-lactone product. The reaction of the corresponding 2-butyl ester (entry 2) also resulted in the predominant formation of a β-lactone mixture. The γ-lactone products were isolated in much smaller amounts. Isobutyl methyl diazomalonate (entry 3), on the other hand, produced only the γ-lactone in high yield; but 3-methyl-2-butyl ester (entry 4) was transformed into the β-lactone and γ-lactone products in a 3:1 ratio. To check the feasibility of the δ-lactone formation, isoamyl methyl diazomalonate (entry 5) was reacted and a 1:2 mixture of the β-lactone and γ-lactone products was isolated. No δ-lactone product was formed under the standard conditions. Finally, 3-acetoxy-2-butyl methyl diazomalonate (entry 6) yielded only the β-lactone products; surprisingly, no γ-lactones were found from the reaction mixture.

The following generalizations for acyclic alkyl esters can be made from the results described above. β-Lactone formation is the preferred process when methine C-H bonds are available for the insertion to form four-membered rings (entries 1,2,4,6). When the methine C-H bond is available only for the five-membered ring formation, high yield of the γ-lactone products is obtained (entry 3). β-Lactones are preferred products when formation of both β-lactones and γ-lactones is possible with insertions into different methine C-H bonds within the same molecule (entries 4,6). In spite of the reports on the related diazoacetate insertion reactions[4a], δ-lactone formation is not a preferred process even when methine C-H bonds are available for the insertion reaction. In case of the isoamyl ester, only β- and γ-lactones were formed even though they are products of methylene C-H bond insertions (entry 5). The trend is best explained by two independent factors: the high reactivity of methine C-H bonds in insertion reactions and the intrinsic conformational bias of metallocarbenoid species formed from diazomalonates to prefer four-membered ring formation. The preference for methine C-H insertion is amply discussed by Taber in his report[6] on cyclopentanone construction by rhodium acetate-mediated intramolecular C-H insertion of α-diazo-β-keto esters. It is argued that alkyl groups are inductively electron donating and so increase the electron density of the C-H bond, making it more susceptible to attack by the electrophilic rhodium-carbene species. In the same context, it should be reminded that the rate of diazoketone insertion into methylene C-H bonds which are α or β to a carbonyl function is reported[7] to be greatly reduced. The preferred β-lactone formation over γ-lactone construction (both via methine C-H insertion) calls for more careful analysis. Preferential diazoketone insertion into C-H bonds adjacent to ether oxygens was reported and it was viewed by the authors as an example of electronic activation.[8] This may be extrapolated to explain four-membered ring preference via insertion into C-H bonds adjacent to ester oxygens. But only β-lactone products were produced from the reaction of 3-acetoxy-2-butyl methyl diazomalonate (entry 6) and γ-lactones were not formed even though two methine C-H bonds must be electronically nearly identical. It can thus be argued that preferred β-lactone formation is the result of conformational bias of metallocarbenoid species formed from diazomalonate rather than the consequence of electronic activation. β-Lactam formation via carbene insertion reaction of α-diazo amides has already been attributed to a conformational effect by others.[9]

Next various cyclohexyl methyl diazomalonates were tested to delineate more subtle aspects in the insertion reactions. cis-4-t-Butylcyclohexyl methyl diazomalonate (entry 7) yielded only the β-lactone product in a reasonable yield. However, trans-4-t-butylcyclohexyl ester (entry 8) was transformed into a mixture slightly favoring γ-lactones over the β-lactones. The results can be interpreted in terms of more favorable participation of equatorial C-H bonds in the insertion reactions.

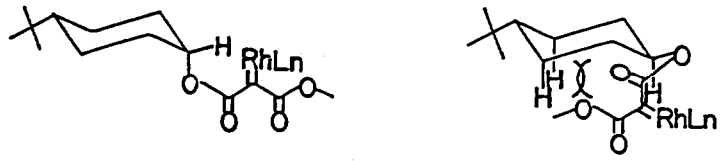


Figure 1

This equatorial C-H insertion preference can be explained by steric considerations; i. e., axial C-H bonds are relatively more hindered than equatorial ones (see Figure 1). Steric effects of neighboring substituents were also quite substantial. For example, neomenthyl methyl diazomalonate (entry 9) was converted into a mixture of a β-lactone and a γ-lactone in a 1:3 ratio. The corresponding menthyl ester (entry 10) yielded only γ-lactones in high yield. In both cases, the neighboring isopropyl group provided enough steric bias toward the formation of γ-lactones. It is remarkable that all β- and γ-lactone products in the menthyl and neomenthyl ester series resulted from insertions on equatorial C-H bonds (entries 9,10). It is thus apparent that in insertion reactions of cyclohexyl methyl diazomalonates steric factors could override the preference for the four-membered ring formation via methine C-H bond participation. Steric factors in the regiocontrolled methylene insertion in preference to methine insertion is well described by Ikegami.[10] General steric effects in the insertion reaction is also discussed by Taber.[6]

Comparison studies on selectivities of C-H insertions of alkyl diazoacetates and diazoacetoacetates are in progress and the results will be reported in due course.

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