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SYNTHESIS OF β-LACTAMS FROM CHROMIUM CARBENES AND IMINES

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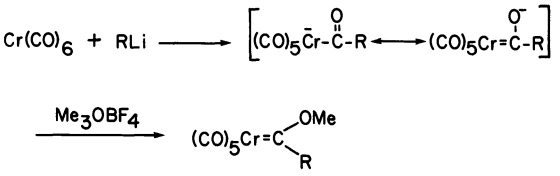
Abstract - Chromium carbene complexes react with imines when irradiated with visible light. A wide range of imines react, giving rise to a variety of substituted β-lactams. The reaction is regio and stereospecific and has been used to synthesize penicillin analogues. Under thermal conditions, chemistry of the α-carbon of the carbene complex predominates, resulting in the production of unusual new chromium carbene complexes.

INTRODUCTION

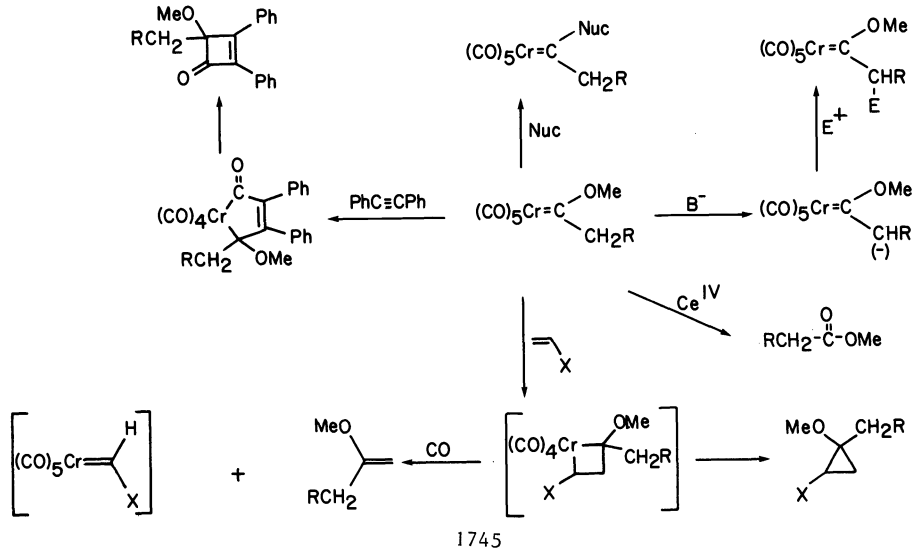
Heteroatom-stabilized chromium carbene complexes are readily prepared by treatment of chromium hexacarbonyl with an organolithium reagent, followed by alkylation of the thus-formed "ate" complex with trimethyloxonium tetrafluoroborate (equation 1) [1]. The chemistry of these types of complexes has been extensively studied [2], and some of the more important



(1)

reactions are summarized in Scheme 1. Of particular interest are the reactions with alkenes and alkynes, which are assumed to proceed via cycloaddition reactions involving metallacyclic intermediates [3]. Should reactions of this type occur with imines as substrates, aziridines, β-lactams (α-azetidinones) or β-azetidinones would result (equation 2), depending on the direction of addition of the imine to the chromium carbene complex. Herein we summarize our studies in this area.

SCHEME I. Reactions of Chromium Carbene Complexes



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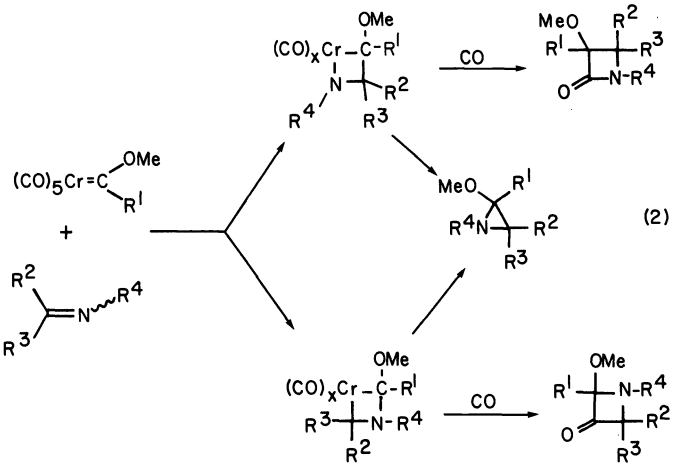
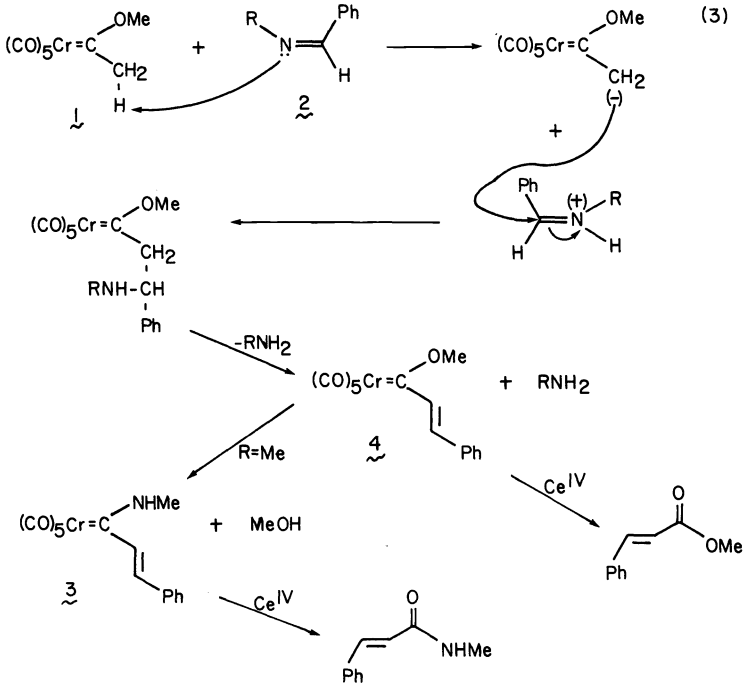


(2)

RESULTS AND DISCUSSION [4]

Initial studies focused on the thermal reactions of imines with chromium carbene complexes. Treatment of [(methyl)(methoxy)carbene]pentacarbonyl chromium 1 with the N-methyl imine of benzaldehyde 2 at 50° for 2 hrs produced a new carbene complex 3 which, when oxidized, gave N-methyl cinnamide. When the reaction was repeated using the corresponding N-phenylimine, methyl cinnamate was ultimately obtained. This reaction was thought to proceed as in equation 3. Deprotonation of the acidic α-carbon of the carbene by the imine followed by condensation of the iminium salt with the carbene carbanion produced a β-amino carbene complex. Loss of amine generated the unsaturated carbene complex 4. N-Methylamine was sufficiently basic to displace the methoxy group to give 3, whereas aniline was not.

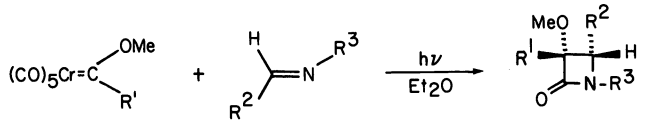


(3)

Results with other imines confirmed that, under thermal conditions, carbene complex α-carbon chemistry was the major reaction process observed. There was no evidence that a metallacyclic intermediate had ever formed, or that any reaction had taken place at the chromium center of the carbene complex.

In order for cycloaddition to occur, the nitrogen (or carbon) of the imine must, at some point, coordinate to the chromium center, which, in the starting carbene complex, is coordinatively saturated. It was (naively) thought that creation of a vacant site on chromium would facilitate the desired reaction of imines. Carbene complexes are known to undergo

facile photo dissociation of a CO ligand upon irradiation [5]. Thus the reaction of chromium carbene complexes with imines was attempted using sunlight photolysis to promote the reaction. Exposure of an ether solution of complex 1 and a variety of imines to sunlight for 2 hr resulted in the production of β-lactams in fair to excellent yield (equation 4). (In climates lacking significant sunlight, these reactions can be carried out using six 20 watt "vitalite" fluorescent tubes which have a spectral distribution similar to sunlight.)



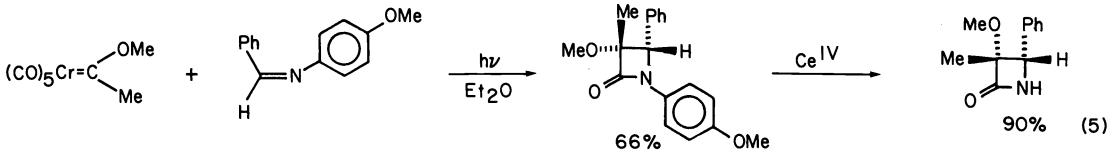
(4)

$R^1 = R^3 = Me,\ R^2 = Ph$ 76%

$R^1 = Me,\ R^2, R^3 = Ph$ 52%

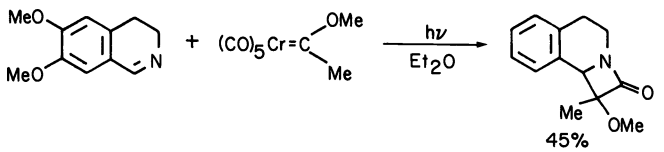
$R^1 = R^2 = Ph,\ R^3 = Me$ 72%

The reaction is restricted to imines having N-substitution since imines having free N-H groups exchange with the methoxy group on the carbene [6]. However, N-unsubstituted β-lactams were available from this reaction by using N-paramethoxyphenyl imines as substrates, and cleaving the N-aryl group from the β-lactam using aqueous Ce^{IV} (equation 5) [7].

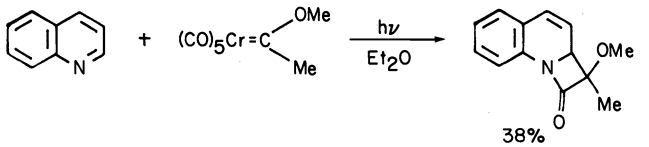


66% 90% (5)

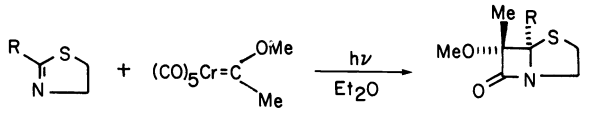
Cyclic imines including dihydroisoquinolines (equation 6), quinoline itself (equation 7), thiazolines (equation 8), and benzothiazines [8] (equation 9) reacted as well, giving bicyclic β-lactams in good yields. All reactions were stereospecific, giving a single isomer of the product β-lactam. With aromatic imines, the phenyl and O-methyl groups were always cis to each other in the β-lactam product (as shown by nmr spectroscopy and, in one case, X-ray diffraction). With imines of chiral amines, up to 58% diastereomeric excess (by 360 MHz nmr spectroscopy) was obtained. With chiral thiazoline 5 as substrate, a single isomer of the β-lactam product 6 was obtained ($[\alpha]_D = +145.4°$). Its absolute stereochemistry is currently being determined.



45% (6)

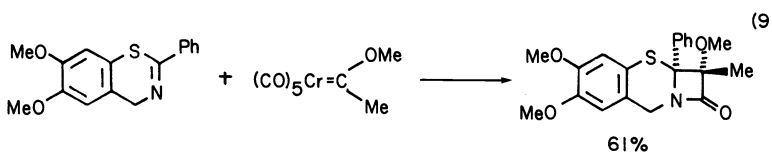


38% (7)

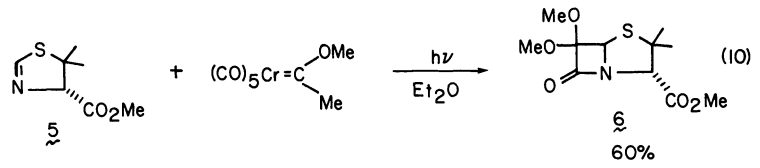


R=H 81%

R=Ph 52% (8)

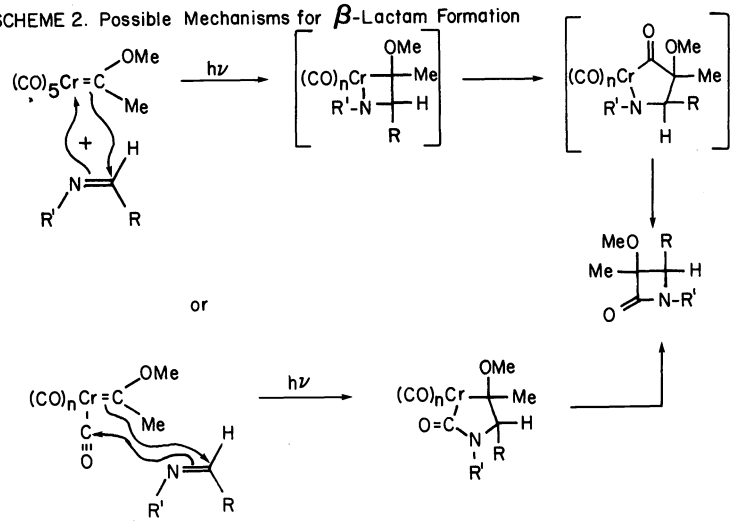


61% (9)



A reasonable mechanism for the β-lactam-forming reaction is shown in Scheme 2. It involves initial (photo) cycloaddition of an imine to the chromium-carbene to give the four-membered metallacycle. Insertion of carbon monoxide, followed by reductive eliminate produces the β-lactam. Alternatively, the initial cycloaddition may occur at the carbene carbon and an adjacent carbon monoxide, giving an acyl complex directly. Reductive elimination would then form the observed β-lactam [9]. Studies are currently underway to elucidate this mechanism, and to determine the scope and synthetic utility of this new β-lactam synthesis.

SCHEME 2. Possible Mechanisms for β-Lactam Formation



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8. We thank Dr. Lajos Fodor, Department of Laboratory Medicine, County Hospital, Gyula, Hungary, for providing the benzothiazines used in this study.

9. We thank Professor J. Schwartz for suggesting a mechanism of this general type.