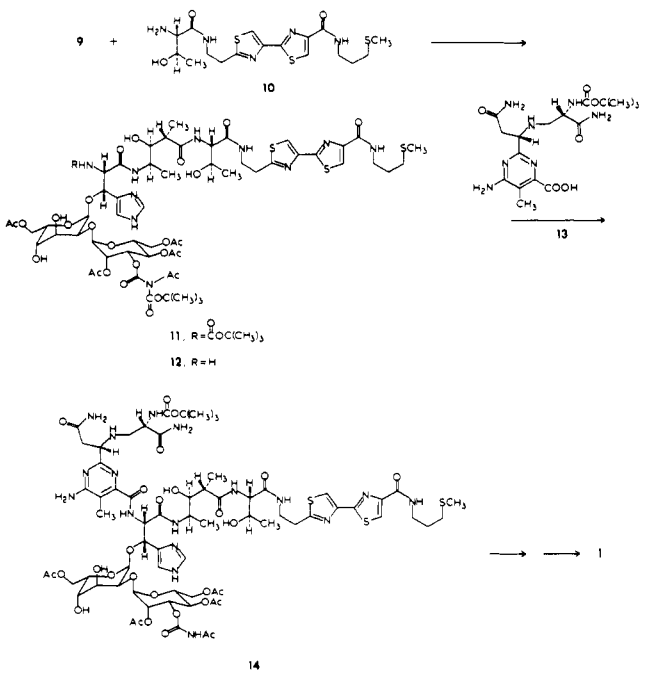
Scheme I



zylation of the ester was effected; free carboxylate **7** was isolated as a white foam in ~75–80% yield, $[\alpha]^{24}_D$ −9.3° (*c* 0.37, $CHCl_3$).

Condensation of **7** and benzyl (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvalerate[9] was carried out in CH_2Cl_2 (DCC, 1-hydroxybenzotriazole) at 25 °C for 3 h. The oily residue obtained after extractive workup was purified by flash chromatography, affording dipeptide analogue **8** as a white foam in 77% yield, $[\alpha]^{24}_D$ −12.2° (*c*, 2.3, C_2H_5OH), R_f 0.45 (silica gel TLC; 1:1 $CHCl_3$–EtOAc). Benzyl ester **8** was then dissolved in ethanol and hydrogenated over palladium black (1 atm of H_2, 55 °C) for 24 h, which effected removal of the benzyl groups and solvolysis of the N^{im}–BOC protecting group. The product (**9**)[10] was obtained in quantitative yield ($[\alpha]^{24}_D$ −0.3° (*c* 1.0, CH_3OH)) and in a good state of purity, as judged by silica gel TLC; it was used directly for condensation with "tripeptide S" derivative **10**[11] (DCC, 1-hydroxybenzotriazole) in DMF at 25° for 24 h (Scheme I). The pale yellow glass obtained after extractive workup of the reaction mixture was purified by chromatography on silica gel (elution with 5:1 $CHCl_3$–methanol). Compound **11** was obtained as a colorless glass in 61% yield. Removal of the BOC protecting groups (3:5 dimethyl sulfide–trifluoroacetic acid, 0 °C, 1 h) provided **12** in 59% yield as a colorless glass.

The final coupling of **12** (24 mg) with BOC–pyrimidoblamic acid (**13**)[12] (12 mg, 1.5 equiv) was effected via the agency of diphenylphosphoryl azide (DMF, 25 °C, 48 h). Following extractive workup (EtOAc–H_2O), deblocking of **14** was accomplished by successive treatments with 0.1 M NaOH (0 °C, 22 h) and 1:2 CH_3SCH_3–CF_3COOH (0 °C, 1 h). Chromatography on XAD-2 provided 21 mg of crude product, a portion of which provided pure bleomycin demethyl A_2 after chromatography on CM-Sephadex C-25. The purified sample, obtained as a colorless glass, was found to have chromatographic properties identical with authentic bleomycin demethyl A_2[13] on CM-Sephadex C-25 and silica TLC in several solvent systems. The synthetic and authentic samples also had identical 360-MHz ^1H NMR spectra. Bleomycin has recently been shown to effect epoxidation of *cis*-stilbene in the presence of Fe(III) and iodosobenzene;[14] the synthetic and authentic samples of bleomycin demethyl A_2 were both found to mediate this transformation. Moreover, the synthetic bleomycin demethyl A_2 solubilized radioactivity from [^3H]thymine-labeled *E. coli* DNA[15] to precisely the same extent as the authentic material. Conversion of synthetic bleomycin demethyl A_2 to bleomycin A_2 was carried out as described[16] and provided material identical with authentic bleomycin A_2 (**1**) in all respects. Bleomycin demethyl A_2 can be converted efficiently to bleomycinic acid[13] and therefore provides facile synthetic access to all of the naturally occurring bleomycins.

Acknowledgment. We thank Guy Ehrenfeld and Dr. Natesan Murugesan for carrying out the biochemical comparisons of synthetic and authentic bleomycins. Authentic bleomycin was obtained through the courtesy of Dr. William Bradner, Bristol Laboratories. This work was supported by PHS Research Grant CA27603, awarded by the National Cancer Institute, DHHS.

Supplementary Material Available: Listing of ^1H NMR spectral data for all new compounds prepared (1 page). Ordering information is given on any current masthead page.

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Synthesis of β-Lactams by the Photolytic Reaction of Chromium Carbene Complexes with Imines

Michael A. McGuire and Louis S. Hegedus*

Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

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Pentacarbonyl(methoxyalkyl- or -arylcarbene)chromium complexes are readily prepared by the reaction of chromium hexacarbonyl with alkyl- or aryllithium reagents, followed by alkylation with trimethyloxonium tetrafluoroborate.[1] Since the methoxy group can readily be replaced by nitrogen,[2] sulfur,[3] and carbon[4] nucleophiles, a wide range of differently substituted carbene complexes is readily available. Although the reactions of chromium carbene complexes have been extensively studied,[5] they have found only limited use in organic synthesis.[6] Recently chromium carbene complexes have been used in the synthesis of silyl-substituted vinylketenes,[7] cyclopropanes,[8] ketenimines,[9] indenones,[10] and naphthoquinones.[11]

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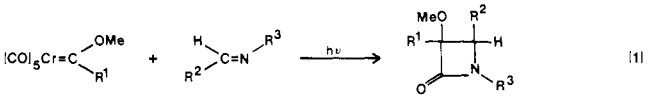
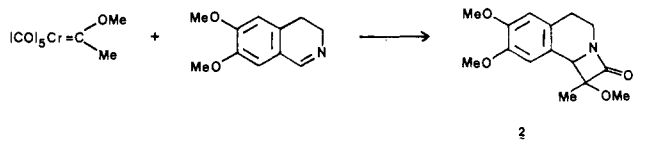
Imines were reported to react with pentacarbonyl(methoxymethyl and -phenylcarbene)chromium complexes to produce iminocarbene complexes, by nucleophilic displacement of the methoxy group by the nitrogen of the imine.[12] We report herein that sunlight irradiation of hexane or ether solutions of imines and chromium carbene complexes produced β-lactams in fair to good yield (eq 1–3). The *N*-methylimine of benzaldehyde was the most



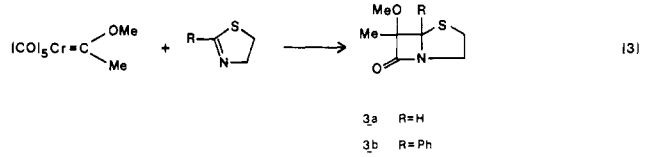
[1]

1a $R^1 = R^3 = Me$, $R^2 = Ph$
1b $R^1 = Me$, $R^2 = R^3 = Ph$
1c $R^1 = R^2 = Ph$, $R^3 = Me$

[2]



2



[3]

3a R=H
3b R=Ph

efficient substrate, reacting with both the methoxymethyl- (product **1a**) and the methoxyphenyl- (product **1c**) carbene complex in essentially quantitative yield. (The lower isolated yields reflect losses during purification.) Benzaldehyde *N*-phenylimine (product **1b**) and the phenylthiazoline (product **3b**) reacted with the methoxymethylcarbene complexes with only ≈60% conversion. Even in the presence of excess carbene complex 30–40% of the starting imine was recovered after the consumption of all of the carbene complex. The isoquinoline substrate similarly was not entirely consumed, with 50% crude yields being obtained. Further, this material (product **2**) slowly decomposed upon purification. In contrast, the unsubstituted thiazoline reacted cleanly, in high yield, producing the penam ring system (product **3a**). The reaction appears to be general. A number of imine/carbene complex combinations are under investigation.

Sunlight photolysis was required for β-lactam formation. When heat was used in place of sunlight the reaction took a different, as yet not understood, course. The reactions were run by the addition of the imine (1 equiv) to the chromium carbene complex (1 equiv) in hexane or diethyl ether (depending on the solubility of the imine) (10 mL/mmol) in an Airlessware flask under an argon atmosphere. The contents were thoroughly mixed, and the flask was exposed to bright sunlight on the roof of the chemistry building for 1–3 h at ambient temperatures (10–20 °C). (The reaction proceeds, although more slowly, when irradiated with a 275-W Westinghouse sunlamp.) The original yellow solution turned either clear or red (depending on substrate) and deposited a brown precipitate. When no further change in appearance was noted, the mixture was exposed to air while irradiation was continued. After 1–3 h the supernatant was colorless, and the solid was green. Filtration followed by evaporation of the solvent gave the crude β-lactam, which was purified by recrystallization from hexane–chloroform mixtures (**1a–c**, **3a,b**, physical data in Table I) or by preparative layer chromatography (**2**, basic alumina, ethyl acetate, R_f 0.6).

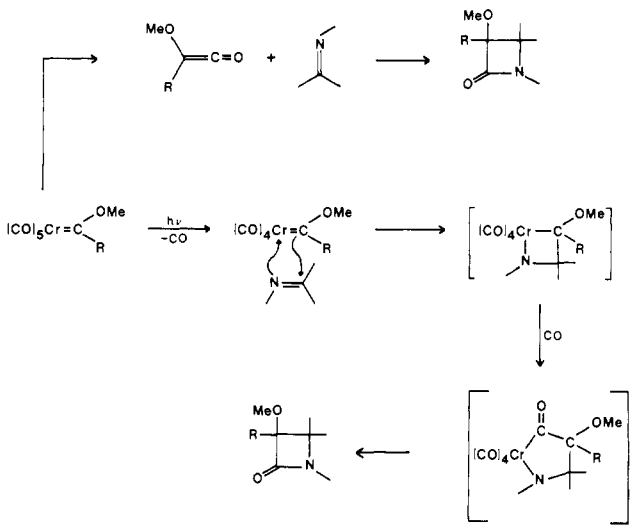
The mechanism of this β-lactam-forming reactions is unknown at present. Two plausible paths are shown in Scheme I. The

Table I. Physical Data for Compounds 1-3

compd	yield, %[a]	mp, °C[b]	ν_{CO}, cm^{-1}	^1H NMR, δ[c]
1a	76	74–75	1750	1.60 (s, 3, CH_3), 2.80 (s, 3, NCH_3), 3.00 (s, 3, OCH_3), 4.15 (s, 1, CH), 7.25 (s, 5, Ar H)
1b	52	155–156	1758	1.70 (s, 3, CH_3), 3.10 (s, 3, OCH_3), 4.90 (s, 1, CH), 7.3 (m, 10, Ar H)[d]
1c	72	91–92	1750	2.82 (s, 3, NCH_3), 3, 18 (s, 3, OCH_3), 4.62 (s, 1, CH), 7.21 (m, 10, Ar H)
2	38	106–107	1760	1.05 (s, 3, CH_3), 2.8–3 (m, 3), 4.1 (m, 1, CH_2CH_2), 3.60 (s, 3, OCH_3), 3.86 (s, 6, Ar OCH_3), 4.70 (s, 1, CH), 6.56 (s, 1, Ar H), 6.62 (s, 1, Ar H)[e]
3a	81	29	1770	1.38 (s, 3, CH_3), 2.76, 2.85, 3.06, 4.18 (m, 1 each, CH_2CH_2), 3.48 (s, 3, OCH_3), 5.02 (s, 1, CH)[e]
3b	52	105–106	1755	1.63 (s, 3, CH_3), 3.00 (s, 3, OCH_3), 3.15 (m, 2), 3.20, 4.16 (m, 1 each, CH_2CH_2), 7.3 (m, 5, Ar H)

[a] Reported yields are for isolated, purified (by crystallization or alumina chromatography) material. [b] Satisfactory elemental analyses (C, H, N (S)) were obtained for all products. [c] $CDCl_3$ solvent with Me_4Si as internal standard. [d] Mass spectrum, *m/e* 267 (parent), 181 (PhNCHPh), 148 (PhCHC(OMe)Me). [e] Spectra recorded at 360 MHz.

Scheme I



first involves photolytic ejection of one carbon monoxide, creating a vacant coordination site and permitting coordination of the imine nitrogen. (This is necessary to prevent attack of this nitrogen on the electrophilic carbene carbon.[12]) Cycloaddition followed by CO insertion and reductive elimination generates the β-lactam. Chromium carbene complexes lose carbon monoxide much more readily than other chromium carbonyls.[13] The subsequent cycloaddition/insertion/elimination process is analogous to that proposed in the reaction of chromium carbene complexes with alkynes and ynamines to form cyclobutenones.[14] Alternatively, the reaction may involve photolytic production of the ketene followed by cycloaddition of the ketene to the imine. (Production

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of ketenes from chromium carbene complexes at 80 °C and 150 atm CO pressure has been claimed.[15,16]) Which, if either, of these mechanisms is in operation is currently under study, as is the application of this method to the synthesis of biologically active β-lactams.

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Registry No. 1a, 82918-98-7; **1b**, 82918-99-8; **1c**, 82919-00-4; **2**, 82919-01-5; **3a**, 82919-02-6; **3b**, 82919-03-7; $(CO)_5Cr{=}C(Me)OMe$, 20540-69-6; $(CO)_5Cr{=}C(Ph)OMe$, 27436-93-7; PhCH=NMe, 622-29-7; PhCH=NPh, 538-51-2; 3,4-dihydro-6,7-dimethoxyisoquinoline, 3382-18-1; 2-thiazoline, 504-79-0; 2-phenyl-2-thiazoline, 2722-34-1.

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Use of Two-Dimensional NMR in the Study of a Double-Stranded DNA Decamer

J. Feigon, J. M. Wright, W. Leupin, W. A. Denny,† and D. R. Kearns*

Department of Chemistry
University of California, San Diego
La Jolla, California 92093
Received June 7, 1982

The recent development of two-dimensional (2-D) NMR techniques represents a major advance in the use of NMR for the study of biological molecules.[1-5] The usefulness of these techniques in studies of small proteins has already been demonstrated,[6,7] but applications to oligonucleotides have been limited.[8,9] In this communication we present the first application[10] of 2-D NOE (NOESY)[11] and 2-D homonuclear *J*-correlated (COSY)[12] spectroscopy to a double-stranded DNA, the synthetic DNA decamer $d(A_1T_2A_3T_4C_5G_6A_7T_8A_9T_{10})_2$.[13] The results obtained provide information on the conformation of the helix, dynamic properties, and assignments of the resonances, which would have been difficult or impossible to obtain by conventional NMR methods.

The 500-MHz one-dimensional proton NMR spectrum of $d(ATATCGATAT)_2$ at 27 °C is shown in Figure 1A, along with assignments to proton type. The majority of the aromatic resonances were assigned on the basis of various one-dimensional NMR techniques described elsewhere.[10] A stacked plot of a 2-D NOE experiment on $d(ATATCGATAT)_2$ at 27 °C with mixing time τ_m = 350 ms is shown in Figure 1B. The intense diagonal spectrum arises from protons that did not cross relax with other protons during τ_m.[5] The main features of interest, however, are the relatively small off-diagonal cross peaks that arise from dipole–dipole cross relaxation during τ_m.[11,12,14] The long mixing time (τ_m = 350 ms) coupled with the phase-cycling scheme used in these experiments suppresses any *J*-coupling contribution to

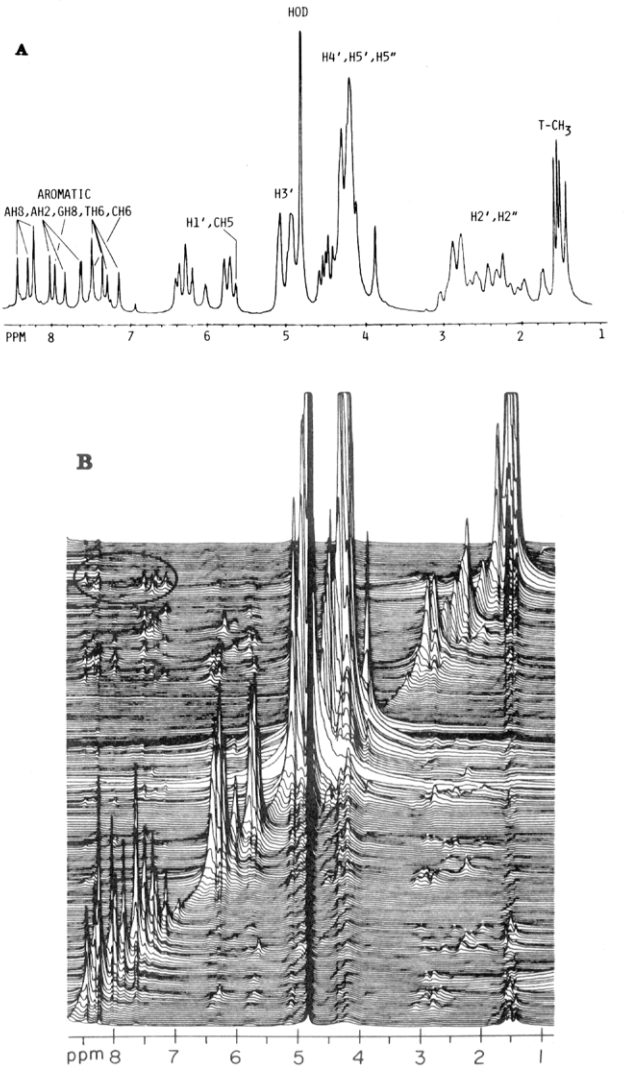

Figure 1. (A) 500-MHz ^{1}H NMR spectrum of the nonexchangeable proton resonances in $d(A_1T_2A_3T_4C_5G_6A_7T_8A_9T_{10})_2$ at 27 °C. Approximately 120 μL of a sample of 3 mM in duplex in 10 mM sodium phosphate, pH 7.0, 0.1 M NaCl, was contained in a Wilmad 508-cp microcell. Samples were repeatedly evaporated to dryness in the NMR tube and redissolved in 99.996% D_2O. Assignments to general proton type are given above the appropriate spectral regions. (B) 500-MHz NOESY spectrum (stacked plot) of $d(ATATCGATAT)_2$ at 27 °C with τ_m = 350 ms. The spectral width was ±2000 Hz. The data set consisted of 1024 points in the t_2 dimension and 128 points in the t_1 dimension. 32 FIDs were accumulated for each value of t_1, with a 4-s delay between acquisitions, and the total accumulation time was 5.3 h. Spectra were collected by using quadrature-phase detection with the carrier at the center of the spectrum. A 32-step phase-cycling routine was used to suppress axial ridges and cancel out components of transverse magnetization after the second 90° pulse (details of the phase cycling will be published elsewhere). The resulting data matrix was processed with an exponential broadening of 6 Hz in both dimensions and was zero-filled in the f_1 dimension. The absolute value mode is used. The nonsymmetrical appearance of the cross peaks is a result of the method of data collection and processing. Cross peaks between the thymine methyl and the AH8 and TH6 resonances are circled at the top left.

†Cancer Chemotherapy Research Laboratory, University of Auckland, School of Medicine, Private Bag, Auckland, New Zealand.
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