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PHOTOLYTIC REACTION OF CHROMIUM AND MOLYBDENUM CARBENE COMPLEXES WITH IMINES

SYNTHESIS OF CEPHAM, OXAPENAM, AND OXACEPHAM DERIVATIVES

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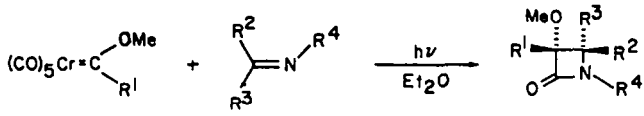
Abstract—A variety of substituted β-lactams, including a cepham analog, were synthesized by the photochemical reaction of [(methoxy)(methyl)carbene]chromium complexes with substituted imines. Oxazines and oxazolines were inert towards chromium carbene complexes. Oxazines were converted to bicyclic β-lactams by the photolytic reaction of molybdenum carbene complexes. Oxazolines were considerably less reactive and produced only low yields of β-lactam product and an equivalent amount of the corresponding oxazinone, incorporating two (MeO)(Me)C(CO) groups.

The synthesis of both naturally occurring and unnatural β-lactams has been an important area of research for over forty years, primarily because of the biological activity displayed by this class of compounds. In addition to continuing efforts using classical organic synthetic methodology, a number of new β-lactam syntheses involving the use of transition metals have recently been developed. These include the rhodium(I) catalyzed carbonylation of aziridines,[1] the reaction of allylic epoxides with iron pentacarbonyl,[2] the carbonylation of aminoolefins by iron carbonyl complexes,[3] and the Pd-catalyzed carbonylation of azirines.[4] We have recently reported a new synthesis of β-lactams from the photolytic reaction of imines with chromium carbene complexes (Eq. (1))[5] and have used it to synthesize a number of mono- and bicyclic β-lactams, including a penicillin analog.[6] Herein we report the extension of this chemistry to the synthesis of cephalosporin analogs, functionalized monocyclic β-lactams, and oxapenam and oxacepham derivatives.



(1)

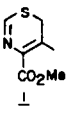
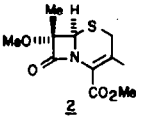
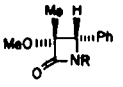
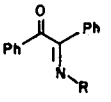
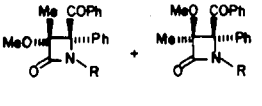
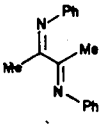
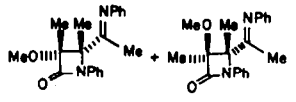
RESULTS AND DISCUSSION

The results of the reaction of pentacarbonyl [(methoxy)(methyl)carbene]chromium with a variety of substituted imines are displayed in Table 1. Thiazine **1** was converted in fair yield to cephalosporin analog **2**. As is typical for this β-lactam-forming reaction, a single diastereoisomer, as shown, was obtained. There was no evidence of the other diastereoisomer even in the crude reaction mixture prior to purification. The stereochemistry shown was assigned based on a comparison of the ^{1}H-NMR chemical shift of the OMe group (δ 3.50 in **2**) with those of very similar compounds produced from thiazolines (δ 3.50 and δ 3.48) and characterized by single crystal X-ray diffraction studies.[6]

Several N-substituted imines were converted to monocyclic β-lactams in fair to excellent yield. Imines **3** and **5**, containing phosphonate groups, were intermediates in the synthesis of thiazine **1**. These were converted, in high yield, to the corresponding β-lactams **4** and **6**. Enamine imine **7** was converted to the N-vinyl β-lactam in somewhat lower overall yield, although this particular reaction has not been optimized. As is the usual case with this imine/chromium carbene reaction, the reactions were stereospecific producing the single diastereoisomer of the product shown, in which the O-methyl and phenyl groups were *cis*. (This stereochemistry was deduced from the ^{1}H-NMR chemical shifts of the O–Me groups which appeared at δ 3.06, 3.10, and 3.06 for **4**, **6**, and **8**, typical for O–Me groups *cis* to a phenyl group.[6,7] Other O–Me groups in these β-lactams normally appear in the δ 3.5–3.7 region.) Since imine **5** has a chiral center, and racemic **5** was used in the reaction to produce **6**, compound **6** was a mixture of the two diastereoisomers at that center.

α-Ketoimines (**9**, **11**) and α-diimine (**13**) behaved somewhat differently. Both the N–Me and N-phenyl monoimines of benzil underwent reaction to produce a mixture of diastereoisomers, the ratio of which depended on the N-substituent. Again, stereochemistry was easily assigned from the ^{1}H-NMR chemical shift of the O–Me group. The diimine of biacetyl also underwent reaction to produce both possible diastereoisomers. In this case, the stereochemistry of the products was more difficult to assign. It was assumed that the compound having the higher field ^{1}H-NMR absorption for the O–Me group (δ 3.56) was **14a**, while that having the lower field absorption (δ 3.61) was **14b**. However, there is no clear precedent for the effect of a *cis* N-phenylimino group on the chemical shift of an adjacent O–Me group, so the stereochemical assignment of these diastereoisomers remains uncertain. Diimine **13** could not be converted to the *bis* β-lactam,

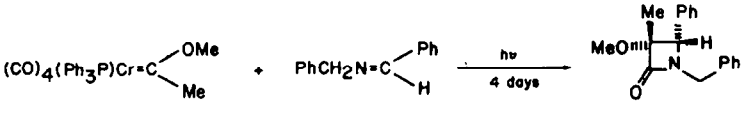
Table 1. β-Lactams from imines and [(methoxy)(methyl)carbene]chromium complexes (Eq. (1))

IMINE	PRODUCT	YIELD%[a]
 1	 2	52
PhCH=NR 3, R=$CH_2P(O)(OEt)_2$ 5, R=$CH(CO_2Me)P(O)(OEt)_2$ 7, R=$CH=CH_2$	 4, R=$CH_2P(O)(OEt)_2$ 6, R=$CH(CO_2Me)P(O)(OEt)_2$ 8, R=$CH=CH_2$	 90 80 41[b]
 9, R=Ph 11, R=Me	 10A 12A	10B, R=Ph 12B, R=Me 52[b] (A/B=2) 52[b] (A/B=1.15)
 13	 14A 14B	40[b] (A/B=0.25)

[a] Reported yields are for isolated, analytically pure product.
[b] Yields are not optimized.

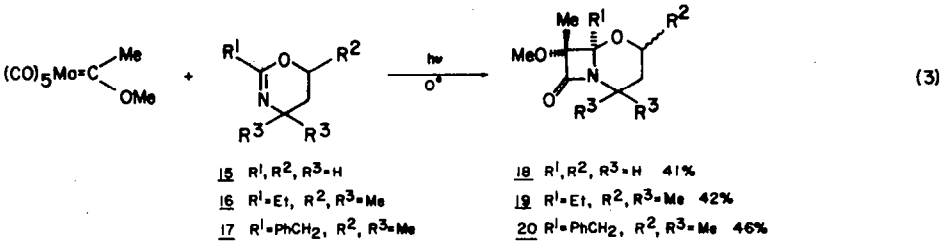
even in the presence of excess chromium carbene complex. Further, treatment of the isolated mono-β-lactam **14** with additional chromium carbene complex failed to introduce an additional β-lactam group, and **14** was recovered unchanged.

The reactivity of organometallic complexes can often be altered by changing one or more of the "innocent" (those not directly involved in the process) ligands. With the intent of both adjusting the reactivity of the carbene complex, and ultimately, of inducing chirality in the β-lactam formed, the monotriphenylphosphine complex of pentacarbonyl[(methoxy)(methyl)carbene]-chromium was prepared by a simple ligand substitution process.[8] Irradiation of this complex and the N-benzyl imine of benzaldehyde produced the desired β-lactam (Eq. (2)) in fair yield (53%), although the reaction was somewhat slow (4 days). Further studies of this complex are in progress.



(2)

With the intent of preparing oxapenam and oxacepham analogs, oxazines and oxazolines were photolyzed with pentacarbonyl[(methoxy)(methyl)-carbene]chromium. Under a variety of conditions, no conversion to the β-lactam was observed. Rather, the carbene complex decomposed slowly, and the oxazine or oxazoline was recovered unchanged. *No* product containing the carbene moiety in any form was observed. Similar results were obtained when the corresponding, more stable, tungsten carbene complex was used in place of the chromium complex. In contrast, irradiation of a mixture of the less stable pentacarbonyl[(methoxy)(methyl)carbene]-molybdenum complex and oxazines **15–17** at 0° produced bicyclic β-lactams **18–20** in fair yield (Eq. (3)). The reaction was stereospecific, producing only one of the two possible diastereoisomers at the two asymmetric centers formed during this reaction. Since oxazines **16** and **17** have a chiral center, and since racemic material was used in the reaction, products **19** and **20** are mixtures of diastereoisomers at that center alone. This molybdenum carbene complex reacted with the N–Me and the N-benzylimines of benzaldehyde to give β-lactams having the same stereochemistry as was



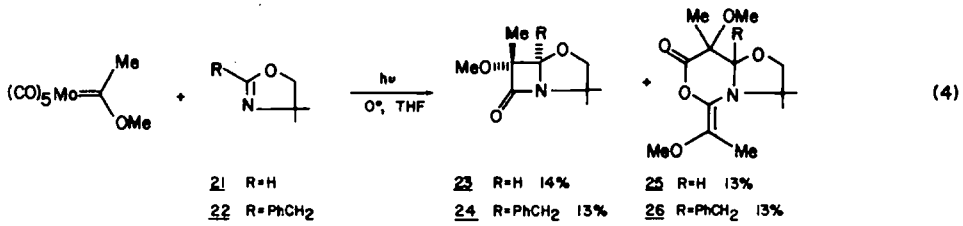
15 R¹, R², R³=H
16 R¹=Et, R², R³=Me
17 R¹=PhCH₂, R², R³=Me

18 R¹, R², R³=H 41%
19 R¹=Et, R², R³=Me 42%
20 R¹=PhCH₂, R², R³=Me 46%

(3)

obtained using the corresponding chromium carbene complex (Eq. (2)). Thus the stereochemistry of β-lactams **18–20** are assigned by analogy.

Oxazolines behaved in yet a different manner (Eq. (4)). They were significantly less reactive than the oxazines, and 25–50% of the starting oxazoline was recovered after complete consumption of a 1.5 molar excess of the carbene complex. A low yield of the desired β-lactam was obtained, again as a single diastereoisomer. An equal amount of product containing the oxazoline and *two* (MeO)(Me)C(CO) fragments was also obtained, again as a single isomer (by high field (360 MHz) ^{1}H-NMR spectroscopy). Its stereo-



21 R=H
22 R=PhCH₂

23 R=H 14%
24 R=PhCH₂ 13%

25 R=H 13%
26 R=PhCH₂ 13%

(4)

chemistry could not be assigned. This material was shown to be a dihydrooxazinone, both by spectroscopy and by literature analogy. Oxazinones are the major products from the reaction between free ketenes and a wide range of imines.[9] The fact that they are formed, as in Eq. (4), in a reaction which involves extensive decomposition of the relatively unstable molybdenum carbene complex, coupled with the observation that unstable diphenylcarbene complexes of group VI metals can decompose to produce both coordinated and free diphenyl ketene under certain conditions[10] suggest that **25** and **26** may result from the reaction of oxazolines **21** and **22** with (methoxy)(methyl)ketene (free or coordinated) produced from the decomposition of the molybdenum carbene complex. However, decomposition of the corresponding chromium carbene complex in the presence of oxazolines **21** and **22** led to *no* β-lactam or oxazinone products, but rather the oxazoline was recovered unchanged (*vide supra*). Thus the role of free ketenes in this reaction remains unresolved. Both the stereospecificity and the lack of ketene-type products in the other Cr and Mo carbene complex chemistry presented here and elsewhere make the general intermediacy of free ketene in these reactions unlikely.

EXPERIMENTAL

General procedures. All m.ps were obtained with a Mel-Temp m.p. apparatus and are uncorrected. IR spectra were recorded on a Beckmann 4200 spectrophotometer. All 60 MHz ^{1}H-NMR spectra were recorded on either a Varian Model EM360 or a Varian Model T-60 spectrometer using Me_4Si as an internal standard and are reported in δ. All ^{13}C-NMR spectra were recorded on a JEOL JNM FX-100 Fourier Transform spectrometer. High field NMR spectra were recorded on a Nicolet NT360 spectrometer or an IBM 270 NMR spectrometer. Mass spectra were recorded on a V.G. Micromass 16F spectrometer.

All chromatographic isolations were accomplished by radial-layer chromatography, using a Chromatotron Model 7924 with Kiesel gel 60 PF silica gel.

Analyses were performed by M–H–W Laboratories, Phoenix, Arizona.

Materials. All solvents were freshly distilled and stored under argon. Immediately before use they were degassed and saturated with argon. THF (Fischer, Spectra Grade) was predried over Na wire, heated at reflux over Na wire with benzophenone, and distilled at atmospheric pressure under N_2. Diethyl ether (Fischer, Reagent Grade) was predried over $MgSO_4$, heated at reflux over Na with benzophenone, and distilled at atmospheric pressure under N_2. Petroleum ether (Skelly solve F, petroleum naphtha) was heated at reflux over CaH_2 and distilled at atmospheric pressure under N_2. MeLi was purchased from Aldrich as a 1.4 M soln in Et_2O. Trimethyloxonium tetrafluoroborate was obtained from Alfa and was used without further purification. Chromium hexacarbonyl was purchased from Strem Chemicals and was finely ground in a mortar and pestle before use. [(Methoxy)-(methyl)carbene]pentacarbonylchromium(0) and -molybdenum(0) were synthesized by literature procedures.[11,12] Thiazine **1** and imines **3** and **5** were synthesized by the procedure of Ratcliffe and Christensen.[13] N-Vinylimine **7**,[14] benzil mono anils **9** and **11**,[15] and diimine **13**[16] were also prepared by literature procedures, as were oxazines **15–17**[17] and oxazolines **21** and **22**.[18]

General procedure for the synthesis of β-lactams through the photolytic reaction of imines with chromium or molybdenum carbenes

$(CO)_5M{=}C(OMe)(Me)$ (1 equiv.) was weighed into a Pyrex 100-ml Erlenmeyer flask which was then sealed with a rubber serum cap. The reaction vessel was evacuated and filled with argon (3 cycles). (If the imine was a solid it was introduced into the reaction vessel before the vessel was sealed.) Solvent (40–100 ml/mmol) was added by means of a cannula. When the imine was a liquid it was introduced (1 equiv.) by syringe. The reaction vessel was then either placed in a sunny spot outdoors at ambient temp or irradiated with six 20-W Vitalite fluorescent tubes. After x hr the soln became heterogeneous, cloudy, and often changed and darkened in color. The end point was determined to be when no more color changes in the

soln could be observed. Isolation consisted of filtration and removal of solvent *in vacuo* to yield a colored oil. The oil in several cases was nearly pure β-lactam but in most cases the oil contained small amounts of starting imine plus Cr by-products. These by-products were eliminated by dissolving the oil in a nonprotic solvent. The soln was then exposed to air in the same light used for irradiation. After *x* hr a great deal of ppt formed and the soln was clear and colorless. Filtration and removal of solvent *in vacuo* yielded the desired β-lactam along with starting material. Purification was accomplished by recrystallization or by chromatography.

Synthesis of 1 - *diethylphosphonomethyl* - 2 - *phenyl* - 3 - *methoxy* - 3 - *methyl* β-*azetidinone* (**4**)

Chromium carbene complex (250 mg, 1.0 mmol) and **3** (255 mg, 1.0 mmol) were combined in the usual manner in CH_2Cl_2 (50 ml) and irradiated under Vitalites until no starting material was detected by TLC (12 hr). After air oxidation, filtration, and solvent removal, the residue was evaporatively distilled (200°/50 mm Hg) to give **4** as a colorless oil (307 mg, 90%).

^{1}H-NMR (270 MHz) ($CDCl_3$): δ 1.30 (m, 6, 2-$CH_2C\underline{H}_3$), 1.65 (s, 3, —CH_3), 3.06 (s, 3, —OCH_3), 4.11 (m, 6, —$C\underline{H}_2P$, 2-$OC\underline{H}_2CH_3$), 4.70 (d, 1, J_{HP} = 2.2 Hz, PhC$\underline{H}$N), 7.36 (m, 5, ArH). IR (neat): 1760 (s, C=O) cm^{-1}. (Found: C, 56.04; H, 7.01; N, 4.00. Calc for $C_{16}H_{24}NO_5P$: C, 56.31; H, 7.04; N, 4.11%.)

Synthesis of 1 - *diethylphosphonomethoxycarbonylmethyl* - 2 - *phenyl* - 3 - *methoxy* - 3 - *methyl* - β - *azetidinone* (**6**)

Using the procedure described above the chromium carbene complex (250 mg, 1.0 mmol) and **5** (313 mg, 1.0 mmol) produced 320 mg (80%) of **6** as a mixture of diastereoisomers after evaporative distillation (200°/50 mm Hg).

^{1}H-NMR (270 MHz) ($CDCl_3$): δ 1.30 (m, 6, 2-$CH_2C\underline{H}_3$), 1.66 and 1.70 (s, 3, —CH_3), 3.10 and 3.14 (s, 3, —OCH_3), 3.48 and 3.88 (s, 3, CO_2CH_3), 4.05 (m, 1, —CHP), 4.22 (m, 4, 2-$OC\underline{H}_2CH_3$), 4.82 (m, 1, —PhCHN), 7.36 (m, 5, ArH). IR (neat): 1741 (s, C=O), 1766 (s, C=O) cm^{-1}. (Found: C, 54.36; H, 6.52; N, 3.59. Calc for $C_{18}H_{26}NO_7P$: C, 54.14; H, 6.52; N, 3.51%.)

Synthesis of methyl 3 - *methyl* - 7 - *methoxy* - 7 - *methylceph* - 3 - *em* - 4 - *carboxylate* (**2**)

Using the procedure described above, the chromium carbene complex (250 mg, 1.0 mmol) and methyl 5-methyl-6H-1,3-thiazine-4-carboxylate (171 mg, 1.0 mmol) produced an orange oil which was purified by Chromatotron (silica gel, 3:1 hexane/ether) and recrystallized from hexane to give **2** (157 mg, 50%) m.p. 72–73°.

^{1}H-NMR (270 MHz) ($CDCl_3$): δ 1.54 (s, 3, CH_3), 2.10 (s, 3, =C$C\underline{H}_3$), AB system, δ_A = 3.14, δ_B = 3.41, J_{AB} = 17 Hz (2, $C\underline{H}_2$s), 3.50 (s, 3, OCH_3), 3.86 (s, 3, CO_2CH_3), 4.85 (s, 1, CHS). IR (CCl_4): 1740 (s, C=O), 1780 (s, C=O) cm^{-1}. (Found: C, 51.28; H, 6.02; N, 5.45. Calc for $C_{11}H_{15}NO_3S$: C, 51.38; H, 5.83; N, 5.44%.)

Synthesis of 1 - *vinyl* - 3 - *methyl* - 3 - *methoxy* - 4 - *phenyl* - β - *azetidinone* (**8**)

By the procedure described above, the carbene complex (250 mg, 1.0 mmol) and N-vinylbenzylideneimine (131 mg, 1.0 mmol) were irradiated in a diethyl ether soln under argon. After 3 days, the brown heterogeneous soln was allowed to air oxidize. Standard isolation and purification by Chromatotron (2 mm silica gel, 1:1 petroleum ether/ether) afforded 89 mg (41%) of **8** as a white solid (m.p. 71–73°).

^{1}H-NMR (270 MHz) ($CDCl_3$): δ 1.66 (s, 3H, CH_3), 3.06 (s, 3H, OCH_3), 4.31 (d, 1H, J = 11.9 Hz, C=CH_2), 4.42 (d, 1H, J = 6.5 Hz, C=CH_2), 4.67 (s, 1H, CH), 6.78 (dd, 1H, J = 11.9 Hz, J = 6.5 Hz, N—CH=C), 7.32–7.36 (m, 5H, Ph). IR ($CDCl_3$): 1760 (C=O), 1639 (C=C) cm^{-1}. (Found: C, 72.04; H, 6.95; N, 6.37. Calc for $C_{12}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45%.)

Synthesis of 1,4 - *diphenyl* - 3 - *methoxy* - 3 - *methyl* - 4 - *benzoyl* - β - *azetidinone* (**10a,b**)

By the procedure described above, the carbene complex (250 mg, 1.0 mmol) and N-phenyl ketoimine of benzil (285 mg, 1.0 mmol) were irradiated in a diethyl ether (60 ml) soln under argon. After 4 days the dark red soln was allowed to air oxidize. Standard isolation and purification by Chromatotron (2 mm silica gel, 1:1 petroleum ether/ether) afforded 193 mg (52%) of **10** containing two isomers in a ratio of 2:1. These isomers were not separable on silica gel.

Isomer A: ^{1}H-NMR (60 MHz) ($CDCl_3$): δ 1.50 (s, 3H, CH_3), 3.48 (s, 3H, OCH_3), 7.0–8.1 (m, 15H, Ph). *Isomer* B: ^{1}H-NMR (60 MHz) ($CDCl_3$): δ 1.50 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 7.0–8.1 (m, 15H, Ph). IR ($CDCl_3$): 1745 (C=O), 1685 (C=O) cm^{-1}. (Found: C, 77.36; H, 5.61; N, 3.69. Calc for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77%.)

Synthesis of 1,3 - *dimethyl* - 3 - *methoxy* - 4 - *phenyl* - 4 - *benzoyl* - β - *azetidinone* (**12a,b**)

By the procedure described above the carbene complex (250 mg, 1.0 mmol) and the N-methyl ketoimine of benzil (223 mg, 1.0 mmol) were irradiated with sunlight or the Vitalites for 48 hr in 60 ml of diethyl ether. Oxidation in ether with light, filtration, and concentration on the rotary evaporator gave 270 mg of a white semi-solid. Purification by Chromatotron (2 mm silica gel, 1:1 petroleum ether/diethyl ether) gave 172 mg (52%) of **12** containing two isomers in a ratio of 1.15:1.

Isomer A: ^{1}H-NMR (60 MHz) ($CDCl_3$): δ 1.51 (s, 3H, CH_3), 2.93 (s, 3H, N—Me), 3.33 (s, 3H, OCH_3), 7.20 (s, 5H, Ph), 7.5–8.0 (m, 5H, Ph). *Isomer* B: ^{1}H-NMR (60 MHz) ($CDCl_3$): δ 1.43 (s, 3H, CH_3), 2.78 (s, 3H, N—Me), 3.65 (s, 3H, OCH_3), 7.25 (s, 5H, Ph), 7.40–8.0 (m, 5H, Ph). IR ($CDCl_3$): 1760 (C=O), 1685 (C=O) cm^{-1}. (Found: C, 73.81; H, 6.08; N, 4.44. Calc for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53%.)

Synthesis of 1 - *phenyl* - 3,4 - *dimethyl* - 3 - *methoxy* - 4 - *acetanil* - β - *azetidinone* (**14a,b**)

By the procedure described above, the carbene complex (250 mg, 1.0 mmol) and the N-phenyldiimine of 2,3-butanedione (236 mg, 1.0 mmol) were irradiated in a CH_2Cl_2 (50 ml) soln under argon. After 3 hr, the soln had turned deep purple. Oxidation after 2.5 days of irradiation, filtration, and concentration on a rotary evaporator gave 188 mg of a yellow solid. Purification by Chromatotron (2 mm silica gel, 1:1 petroleum ether/ether) gave 144 mg (45%) of **14** containing two isomers in a ratio of (A = 0.25 : B = 1.0).

Isomer A: R_f = 0.52 (40% ether/hexane; silica gel). ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.62 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 6.74, 7.05–7.55 (m, 10H, Ph). *Isomer* B: R_f = 0.36. ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.58 (s, 3H, CH_3), 1.86 (s, 6H, CH_3), 3.61 (s, 3H, OCH_3), 6.65, 7.05–7.55 (m, 10H, Ph). IR ($CDCl_3$): 1745 (C=O), 1650 (C=N) cm^{-1}. (Found: C, 74.54; H, 6.71; N, 8.61. Calc for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69%.)

Synthesis of 1 - *benzyl* - 3 - *methoxy* - 3 - *methyl* - 4 - *phenyl* - β - *azetidinone*

The tetracarbonyl(methoxy(methyl)carbene)(triphenylphosphine)chromium(0) complex was prepared according to the method of Fischer and Fischer.[8] The carbene complex (190 mg, 0.39 mmol) was weighed into a quartz tube. The tube was sealed with a rubber serum cap, evacuated, and filled with argon (4 cycles). Diethyl ether (40 ml) and N-benzylbenzylidene imine (76 mg, 0.39 mmol) were added, and the soln was irradiated for 4 days. After oxidation, standard isolation and purification by Chromatotron (2 mm silica gel, 1:1 petroleum ether/ether) afforded 58 mg (53%) of the β-lactam as a colorless oil.

^{1}H-NMR (60 MHz) ($CDCl_3$): δ 1.61 (s, 3H, CH_3), 3.15 (s, 3H, OCH_3), 3.95 (d, 1H, J = 16.8 Hz, CH_2Ph), 4.28 (s, 1H, CH), 4.97 (d, 1H, J = 16.8 Hz, CH_2Ph), 7.45–7.55 (m, 10H, Ph). IR ($CDCl_3$): 1753 (C=O) cm^{-1}. (Found: C, 76.59; H, 6.76; N, 4.90. Calc for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98%.)

Synthesis of 7-*(methoxy, methyl)*-O-*cepham* (**18**)

To a soln of [(methoxy)(methyl)carbene]pentacarbonylmolybdenum(0) (295 mg, 1.0 mmol) in dry THF (50 ml) in a pyrex jacketed tube cooled by pumping −5° MeOH/H_2O from a constant temp bath through it under argon at 0° was added 85 mg (1.0 mmol) of **15**. The reaction tube was irradiated in a Rayonet with 3000 A and 3500 A lamps (6 of each) for 72 hr. Air oxidation in hexane, EtOAc, filtration, and concentration afforded 188.9 mg of a yellow oil. Purification by Chromatotron (1 mm silica gel, hexane/EtOAc 9 : 2) afforded 69.0 mg (40.4%) of the β-lactam. Crystallization of β-lactam from pentane afforded white crystals (m.p. 54–55°).

^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.44 (s, 3H, CH_3), 1.55 (m, 1H, $NCH_2C\underline{H}_2CH_2O$), 1.83 (m, 1H, $NCH_2C\underline{H}_2CH_2O$), 3.09 (d of t, 1H, J's = 4.6, 12.2 Hz, $NC\underline{H}_2$), 3.43 (s, 3H, OCH_3), 3.70 (t, 1H, J = 12.0 Hz, $OC\underline{H}_2$), 3.90 (dd, 1H, J's = 5.8, 13.5 Hz, $NC\underline{H}_2$), 4.11 (d, 1H, J = 12.0 Hz, $OC\underline{H}_2$), 4.90 (s, 1H, OCHN). IR (CCl_4): 1770 (C=O) cm^{-1}. (Found: C, 56.00; H, 7.73; N, 7.99. Calc for $C_8H_{13}NO_3$: C, 56.15; H, 7.60; N, 8.18%.)

Synthesis of 2,4,4-*trimethyl*-6-*ethyl*-7-*(methoxy, methyl)*-O-*cepham* (**19**)

To a soln of [(methoxy)(methyl)carbene]pentacarbonylmolybdenum(0) (295 mg, 1.0 mmol) in dry THF (50 ml) in a pyrex cold jacket tube under argon at 0° was added 155 mg (1.0 mmol) of **16**. The reaction tube was irradiated in a rayonet with 3000 A and 3500 A lamps for 48 hr. Air oxidation in hexane, EtOAc, filtration, and concentration afforded 164.3 mg of a yellow oil. Purification by Chromatotron (1 mm alumina petroleum ether/ether 1 : 1) afforded 102.0 mg (42.3%) of the β-lactam containing two inseparable isomers.

Isomer A: ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 0.98 (t, 3H, J = 7.3 Hz, $CH_2C\underline{H}_3$), 1.21 (d, 3H, J = 6.1 Hz, $C\underline{H}_3CHO$), 1.34 (s, 3H, gem dimethyl), 1.39 (s, 3H, $C\underline{H}_3COCH_3$), 1.47 (m, 2H, CH_2), 1.55 (s, 3H, gem dimethyl), 1.97 (m, 2H, $C\underline{H}_2CH_3$), 3.49 (s, 3H, OCH_3), 3.89 (m, 1H, C—H). *Isomer* B: ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 0.92 (t, 3H, J = 7.4 Hz, $CH_2C\underline{H}_3$), 1.21 (d, 3H, J = 6.1 Hz, $C\underline{H}_3CHO$), 1.27 (s, 3H, gem dimethyl), 1.39 (s, 3H, $C\underline{H}_3COCH_3$), 1.48 (m, 2H, $C\underline{H}_2$), 1.57 (s, 3H, gem dimethyl), 1.89 (m, 2H, $C\underline{H}_2CH_3$), 3.51 (s, 3H, OCH_3), 4.02 (m, 1H, C—H). IR ($CDCl_3$): 1745 (C=O) cm^{-1}. (Found: C, 64.40; H, 9.27; N, 5.59. Calc for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.54; N, 5.81%.)

Synthesis of 2,4,4 - *trimethyl* - 6 - *benzyl* - 7 - *(methoxy,methyl)* - O - *cepham* (**20**)

To a soln of [(methoxy)(methyl)carbene]pentacarbonylmolybdenum(0) (295 mg, 1.0 mmol) in dry THF (50 ml) in a pyrex cold jacket tube under argon at 0° was added 217 mg (1.0 mmol) of **17**. The reaction tube was irradiated in a Rayonet with 3000 A and 3500 A lamps for 72 hr. Air oxidation in hexane, ethyl acetate, filtration, and concentration afforded 270 mg of a yellow oil. Purification by Chromatotron (1 mm alumina, petroleum ether/ether 1 : 1) afforded 138.0 mg (45.5%) of the β-lactam containing two isomers.

Isomer A: ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.21 (d, 3H, J = 6.1 Hz, $C\underline{H}_3CHO$), 1.25 (s, 3H, gem dimethyl), 1.36 (s, 3H, $C\underline{H}_3COCH_3$), 1.38 (m, 2H, $C\underline{H}_2$), 1.53 (s, 3H, gem dimethyl), 3.05 (d, 1H, J = 14.0 Hz, $PhC\underline{H}_2$), 3.31 (d, 1H, J = 14.0 Hz, $PhC\underline{H}_2$), 3.48 (s, 3H, OCH_3), 3.92 (m, 1H, CH), 7.19–7.38 (m, 5H, Ph). *Isomer* B: ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.21 (d, 3H, J = 6.1 Hz, $C\underline{H}_3CHO$), 1.27 (s, 3H, gem dimethyl), 1.37 (s, 3H, $C\underline{H}_3COCH_3$), 1.38 (d, 2H, J = 4.3 Hz, $C\underline{H}_2$), 1.62 (s, 3H, gem dimethyl), 3.05 (d, 1H, J = 14.0 Hz, $PhC\underline{H}_2$), 3.31 (d, 1H, J = 14.0 Hz, $PhC\underline{H}_2$), 3.46 (s, 3H, OCH_3), 4.3 (m, 1H, CH), 7.19–7.38 (m, 5H). IR ($CDCl_3$): 1750 (C=O) cm^{-1}. (Found: C, 71.12; H, 8.12; N, 4.52. Calc for $C_{18}H_{25}NO_3$: C, 71.30; H, 8.25; N, 4.62%.)

Synthesis of 6-*(methoxy,methyl)*-3,3-*dimethyl*-7-*oxo*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane* (**23**)

To a soln of [(methoxy)(methyl)carbene]pentacarbonylmolybdenum(0) (442.5 mg, 1.5 mmol) in dry THF (50 ml) in a pyrex cold jacket tube under argon at 0° was added 148.5 mg (1.5 mmol) of 4,4-dimethyl-2-oxazoline. The reaction tube was irradiated in a Rayonet with 3000 A and 3500 A lamps for 72 hr. Air oxidation, filtration, followed by concentration on a rotovap afforded 179.1 mg of crude mixture. Purification by Chromatotron (1 mm silica gel, hexane/EtOAc9 : 2) afforded 51.0 mg (13%) of oxazinone plus 40.0 mg (14%) of oxapenam.

Oxapenam **23**: ^{1}H-NMR (270 MHz) ($CDCl_3$): δ 1.15 (s, 3H, $(C\underline{H}_3)_2C$), 1.27 (s, 3H, $C\underline{H}_3COCH_3$), 1.51 (s, 3H, $(C\underline{H}_3)_2C$), 3.39 (s, 3H, OCH_3), 3.49 (d, 1H, J = 7.8 Hz, CH_2), 3.82 (d, 1H, J = 7.8 Hz, CH_2), 5.14 (s, 1H, CH). IR ($CDCl_3$): 1760 (C=O) cm^{-1}. (Found: C, 58.12; H, 8.28; N, 7.80. Calc for $C_9H_{15}NO_3$: C, 58.40; H, 8.10; N, 7.57%.)

Oxazinone **25**: ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.20 (s, 3H, $(C\underline{H}_3)_2C$), 1.32 (s, 3H, $(C\underline{H}_3)_2C$), 1.47 (s, 3H, $C\underline{H}_3COCH_3$), 1.98 (s, 3H, $C\underline{H}_3C$=), 3.25 (s, 3H, $C\underline{H}_3OC$=), 3.44 (d, 1H, J = 7.6 Hz, $C\underline{H}_2O$), 3.58 (d, 1H, J = 7.6 Hz, $C\underline{H}_2O$), 3.61 (s, 3H, OCH_3), 4.88 (s, 1H, CH). IR ($CDCl_3$): 1760, 1720 (C=O) cm^{-1}. (Found: C, 57.47; H, 7.60; N, 4.97. Calc for $C_{13}H_{21}NO_5$: C, 57.59; H, 7.74; N, 5.17%.)

Synthesis of 6-*(methoxy,methyl)*-5-*benzyl*-3,3-*dimethyl*-7-*oxo*-4-*oxa*-1-*azabicyclo*[3.2.0]*heptane* (**24**)

To a soln of [(methoxy(methyl)carbene]pentacarbonylmolybdenum(0) (442.5 mg, 1.5 mmol) in dry THF (50 ml) in a pyrex cold jacket tube under argon at 0° was added 283.5 mg (1.5 mmol) of 2-benzyl-4,4-dimethyl-2-oxazoline. The reaction tube was irradiated in a Rayonet with 3000 A and 3500 A lamps for 72 hr. Air oxidation, filtration, followed by concentration afforded 275 mg of crude mixture. Purification by Chromatotron (1 mm silica gel, hexane/EtOAc 9:2) afforded 68.5 mg (13%) of oxazinone plus 53.0 mg (13%) of oxapenam.

Oxapenam (**24**): ^{1}H-NMR (270 MHz) ($CDCl_3$): δ 1.13 (s, 3H, $(C\underline{H}_3)_2C$), 1.29 (s, 3H, $C\underline{H}_3COCH_3$), 1.52 (s, 3H, $(C\underline{H}_3)_2C$), 3.10 (d, 1H, J = 14.1 Hz, CH_2—Ph), 3.41 (d, 1H, J = 14.1 Hz, CH_2—Ph), 3.54 (s, 3H, OCH_3), 3.68 (d, 1H, J = 8.1 Hz, CH_2), 3.92 (d, 1H, J = 8.1 Hz, CH_2), 7.33–7.37 (m, 5H, Ph). IR (CCl_4): 1775 (C=O) cm^{-1}. (Found: C, 69.60; H, 7.80; N, 4.83. Calc for $C_{16}H_{21}NO_3$: C, 69.83; H, 7.63; N, 5.09%.)

Oxazinone (**26**): ^{1}H-NMR (360 MHz) ($CDCl_3$): δ 1.02 (s, 3H, $(C\underline{H}_3)_2C$), 1.10 (s, 3H, $(C\underline{H}_3)_2C$), 1.19 (s, 3H, $C\underline{H}_3COCH_3$), 1.96 (s, 3H, $C\underline{H}_3C$=), 3.07 (d, 1H, J = 14.0 Hz, CH_2Ph), 3.17 (d, 1H, J = 8.3 Hz, CH_2Ph), 3.22 (s, 3H, $\underline{H}_3COC$=), 3.31 (d, 1H, J = 8.3 Hz, $C\underline{H}_2O$), 3.49 (d, 1H, J = 8.3 Hz, CH_2O), 3.68 (s, 3H, OCH_3), 7.21–7.38 (m, 5H, Ph). IR (neat): 1765, 1720 (C=O) cm^{-1}. (Found: C, 66.75; H, 7.90; N, 3.76. Calc for $C_{20}H_{27}NO_5$: C, 66.51; H, 7.48; N, 3.88%.)

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