Tetrahedron, **29**, 1629 (1973).
(17) Iron was inserted by the $FeSO_4$/HOAc method. J. E. Falk, "Porphyrins and Metalloporphyrins," Elsevier, New York, N.Y., 1964, p 135.
(18) N-Substituted imidazoles were prepared by refluxing silver imidazolide with 2-bromobutane and triphenylmethyl chloride in xylene, respectively: 1-isobutylimidazole, $bp^{0.1}$ 70–80 °C; 1-triphenylmethylimidazole, mp 219–220 °C.
(19) Simple hemes under similar conditions would only give incomplete oxygenation and are oxidized totally in less than 30 s. The enhanced O_2 binding ability and stability of the "crowned" heme implies a weaker than normal bonding between the iron and the imidazole under the "crown", presumably for steric reasons.
(20) The bimolecular oxidation apparently is the principal mechanism by which all Fe(II) porphyrins oxidize. This has been demonstrated by recent hemoglobin and myoglobin model compound studies. See for example: (a) F. Basolo, B. M. Hoffman, and J. A. Ibers, *Acc. Chem. Res.*, **8**, 384 (1975); (b) T. G. Traylor in "Bioorganic Chemistry," Vol. 4, E. van Tamelen, Ed., Academic Press, New York, N.Y., in press; (c) B. R. James in "The Porphyrins," Vol. 2, Part C, D. Dolphin, Ed., Academic Press, New York, N.Y., in press.
(21) Estimated with the aid of CPK models.

C. K. Chang
Department of Chemistry, Michigan State University
East Lansing, Michigan 48824
Received January 17, 1977

The Conversion of 3-*exo*-Methylenecephalosporin to 3-Halomethylcephems; a Convenient Synthesis of 3′-Substituted Cephalosporins from Penicillins

Sir:

Recently, Kukolja and co-workers reported a novel conversion of penicillin sulfoxide (**1**) to 3-*exo*-methylenecephem sulfoxide (**2**).[1] The unusual functionality at C_3 (i.e., exo-olefin) presented a potential route to 3-halomethylcephems (**3** → **5**).

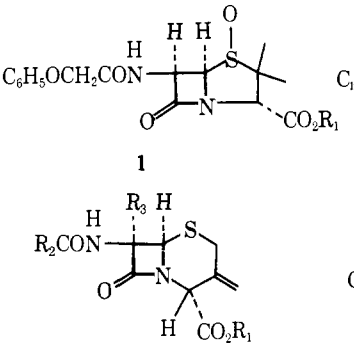
Surprisingly, the 3-*exo*-methylene olefin does not add halogens under usual conditions.[2] We have found, however, a new method to convert the 3-*exo*-methylenecephems to the 3-halomethyl system. This process depends on the activation of the 3-*exo*-methylene by conversion to an allylic anion, A. This anion is subsequently trapped with an electrophile to give a halomethylcephem, **5**.[3]

The observation that led us to this new process was that treatment of **3a** with lithium methoxide and 2 equiv of *tert*-butyl hypochlorite in tetrahydrofuran (THF) at 80 °C afforded **5a** in 40% yield: IR ($CHCl_3$) 1786, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (bs, 2, C_2-H), 3.46 (s, 3, C_7-OCH_3), 3.82 (s, 2, side chain CH_2), 4.34 (s, 2, C_3-CH_2Cl), 5.04 (s, 1, C_6-H), and 6.8–7.6 (ArH).[4,5]

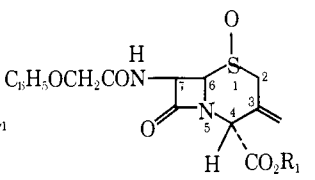
This reaction of the usually inert 3-*exo*-methylene functionality can be explained if we presume that the double bond was activated by conversion to the allylic anion, A (R_3 = H or OCH_3), which was subsequently intercepted with chlorine at the γ-carbon.[6] We theorized that if a base-electrophile combination could be found that would be specific for the C_4 hydrogen-C_3-*exo*-methylene, then a conversion of the 3-*exo*-methylene to the 3-halomethylcephem could be carried out without concomitant oxidation at C_7. When cephem **3b** was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and bromine in tetrahydrofuran over a temperature range of −80 to 0 °C, there was obtained upon workup **5b** in 80% yield: IR ($CHCl_3$) 1785, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.6 (bs, 2, C_2-H), 4.46 (bs, 2, C_3-CH_2Br), 4.58 (s, 2, side chain CH_2), 5.05 (d, 1, J = 5 Hz, C_6-H), 5.40 (s, 2, ester CH_2), 5.95 (q, 1, J = 5 and 9 Hz, C_7-H), and 6.8–8.3 (ArH).[7]

This reaction obviously supports our suppositions. Further support was obtained from modifications of this reaction.

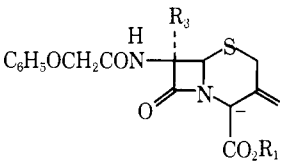
When cephem **3a** was treated as above with DBU–bromine followed by quenching with trimethyl phosphite at 0 °C, there was obtained upon workup **5c** in 63% yield: IR ($CHCl_3$) 1785, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 3.50 (bs, 2, C_2-H), 3.84 (s, 2, side chain CH_2), 4.30 (s, 2, C_3-CH_2Br), 4.98 (d, 1, J = 4.5 Hz, C_6-H), 5.86 (q, 1, J = 4.5 and 9 Hz, C_7-H), 6.84 (d, 1, J = 9 Hz, side chain NH), and 7.0–7.6 (ArH).[8]



1

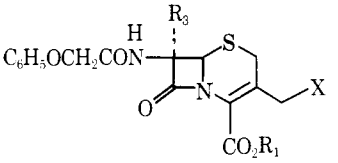


2



3a, R_1 = benzhydryl
R_2 = 2-thienylmethyl
R_3 = H
b, R_1 = *p*-nitrobenzyl
R_2 = phenoxymethyl
R_3 = H

A



5a, R_1 = benzhydryl; R_2 = thienyl methyl; R_3 = OCH_3; X = Cl
b, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = Br
c, R_1 = benzhydryl; R_2 = 2-thienylmethyl; R_3 = H; X = Br
d, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = I
e, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = OAc
f, R_1 = *p*-nitrobenzyl; R_2 = phenoxymethyl; R_3 = H; X = *N*-methylthiotetrazole

The general versatility of this method was further demonstrated by the reaction of cephem **3b** with DBU–I_2 in THF from −80 to 0 °C to give the 3-iodomethylcephem **5d**, IR ($CHCl_3$) 1785, 1745, 1703 cm^{-1}; NMR ($CDCl_3$) δ 3.44 and 3.82 (ABq, 2, J = 18 Hz, C_2-H), 4.40 (s, 2, C_3-CH_2I), 4.54 (s, 2, side chain CH_2), 4.98 (d, 1, J = 5 Hz, C_6-H), 5.34 (s, 2, ester CH_2), 5.82 (q, 1, J = 5 and 9 Hz, C_7-H), and 6.8–8.4 (ArH).[9]

Since we had the halomethylcephems in hand, we treated them with appropriate 3′-nucleophilic reagents to form 3′-substituted cephems. These reactions provide a conversion of penicillin to biologically important cephems. Treatment of **5b** with silver acetate in acetic acid afforded **5e** in 30% yield.[10] Similarly, the reaction of **5b** with 1.2 equiv of *N*-methylthiotetrazole in dimethylformamide afforded cephem **5f** in 97% yield: IR ($CHCl_3$) 1785, 1745, 1705 cm^{-1}; NMR ($CDCl_3$) δ 6.0 (d, 1, J = 5 Hz, C_7-H), 5.5 (s, 2, ester CH_2), 5.1 (d, 1, J = 5 Hz, C_6-H), 4.0 (s, 3 H, N-CH_3).[11]

These are examples of the utilization of the 3-*exo*-methylenecephem in the synthesis of biologically important cephems.

Acknowledgments. The authors wish to express their gratitude to Dr. J. Greene, Dr. A. Katner, Dr. J. A. Webber, Mr. S. Bogard, and Ms. L. Smirz for their scientific contribution.

References and Notes

(1) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **98**, 5040 (1976).
(2) We found the 3-*exo*-methylene olefin of both the cephem sulfoxide or the corresponding sulfide afforded starting material or decomposition products

upon reaction with bromine under a variety of conditions.
(3) This investigation has been reported at a recent symposium. See G. A. Koppel, "Recent Advances in β-Lactam Chemistry," Cambridge, England, 1976.
(4) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973).
(5) All new compounds were characterized by satisfactory mass spectral and elemental analyses.
(6) It has not been demonstrated whether or not C_7 oxidation precedes or is competitive with the C_3-olefin chlorination.
(7) Cephem was obtained from the corresponding cephem sulfoxide (prepared from penicillin by the Kukolja rearrangement, see ref 1) in 92–95% yield by reduction with PCl_3–DMF.
(8) In contrast, the reaction of cephem with bromine in THF at 0 °C affords a quantitative yield of 5-bromothienyl-3-*exo*-methylenecephem sulfide.
(9) Formerly, the only source of 3-iodomethyl was the iodide exchange with the 3-halomethylcephem. See Belgian Patent 755256.
(10) Cephem **5e** is identical with that made from 7-ACA.
(11) C. F. Murphy, R. E. Koehler, and C. W. Ryan, Abstracts, 14th Interscience Conference on Antimicrobial Agents and Chemotherapy, 425 (1974).

G. A. Koppel,* M. D. Kinnick, L. J. Nummy
The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46206
Received October 18, 1976

A New Synthesis of β-Lactams

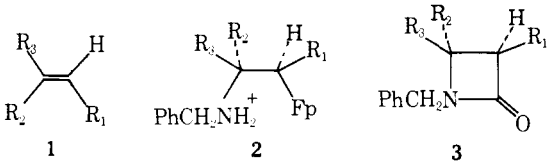
Sir:

We recently reported the regiospecific addition of heteroatomic nucleophiles to a number of Fp(olefin) cations[1] (Fp = η^5-$C_5H_5Fe(CO)_2$). Furthermore, it has been shown that oxidatively induced ligand transfer in FpR complexes (R-Fe-CO → FeCOR) leads to carboxylation of R with retention of configuration at the migrating carbon center.[2] We now show that an appropriate combination of these processes provides a facile and stereospecific synthesis of mono- and bicyclic β-lactams from olefins.

The readily available propylene complex (**1b**)[3] adds benzylamine at −25 °C to give the ammonium salt (**2b**)[1] in high yield. This on oxidation at −78 °C in methylene chloride solution with Cl_2, followed by addition of triethylamine gives the β-lactam (**3b**)[4,5] in 47% yield: IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5, Ph), 4.65, 4.06 (2d, 2, J = 15 H, $PhCH_2$), 3.56 (m, 1, CHN), 3.05 (dd, 1, J = 4.9, 14.5 Hz, CH_2CO), 2.48 (dd, 1, J = 2.5, 14.5 Hz, CH_2CO), 1.17 (d, 3, J = 6 Hz, CH_3).

This sequence, which proceeds through the β-amino acid chloride,[2b] is particularly well suited for the conversion of unstable Fp(olefin)-amine adducts, derived from disubstituted olefins. These also provide useful substrates for examining the stereochemistry and stereospecificity of the sequence. Thus, the addition of an equivalent of benzylamine to a solution of the *cis*-2-butene complex (**1d**) in nitromethane-chloroform (3:1) at −24 °C affords a mixture of the adduct (**2d**, 45%), displacement product ($FpNH_2CH_2Ph$)(BF_4) (40%), and unreacted olefin complex. Oxidation of this solution at −78 °C with chlorine gave *trans*-3,4-dimethylazetidinone (**3d**)[5] as the single isomer (GLC analysis) in 34% yield based on **2d**; IR (neat) 1745 cm^{-1}; NMR δ 7.28 (s, 5, Ph), 4.62, 4.05 (2d, 2, J = 15 Hz, CH_2Ph), 3.16 (dq, 1, J = 6, 2 Hz NCH), 2.74 (dq, 1, J = 6, 2 Hz, CHCO), 1.25, 1.17 (2d, 6, J = 6 Hz, CH_3).

Similar experiments with the *trans*-2-butene complex (**1c**), gave only the *cis*-3,4-dimethylazetidinone (**3c**) in approximately 10% yield: NMR δ ($CDCl_3$) 7.23 (m, 5, Ph), 4.52, 4.0 (d, 2, J = 15.5 Hz, CH_2Ph), 3.51 (m, 1, J = 6.3, 6.0 Hz, CHN), 3.13 (m, 1, J = 7.5, 6.0 Hz, CHCO), 1.11 (d, 3, J = 7.5 Hz, CH_3), 1.01 (d, 3, J = 6.3 Hz, CH_3).



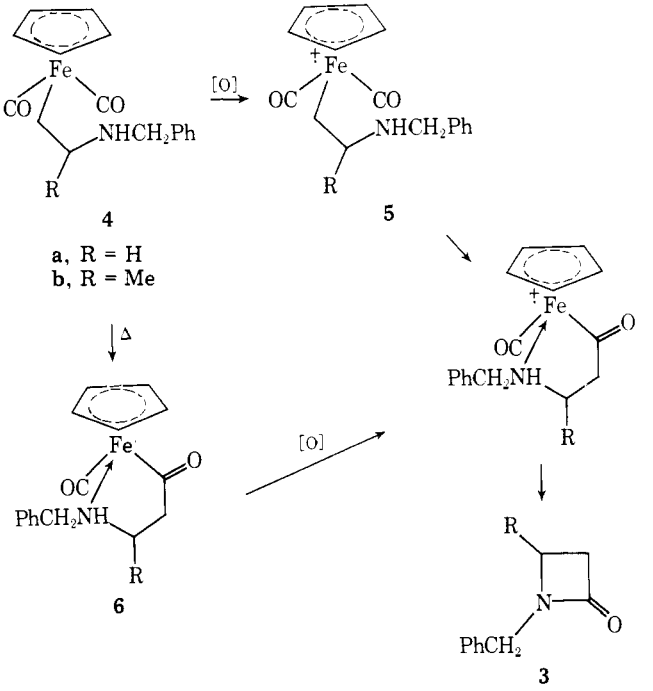
1 2 3

a, R_1,R_2,R_3 = H
b, R_1,R_2 = H; R_3 = Me
c, R_1,R_3 = Me; R_2 = H
d, R_1,R_2 = Me; R_3 = H

These results are in accord with a stereochemical sequence involving trans addition to the olefin complex,[6] followed by carboxamidation with retention of configuration at the C-Fe bond.[2]

Milder oxidizing reagents such as Cu^{2+} and Ag^+ are without effect on the benzylammonium salts, but the free amine, (**4b**) obtained from **2b** by treatment at 0 °C with 1 N NaOH solution, was smoothly transformed to the β-lactam (69%) by freshly prepared lead dioxide[7] or by silver oxide in THF solution (25 °C, 16 h). Similarly, oxidation of the free amine derived by deprotonation of **2a**, gave the β-lactam (**3a**)[5,8] in 30% yield:[9] IR (neat) 1745 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (s, 5, Ph), 4.36 (s, 2, CH_2), 3.25–2.75 (m, 4, CH_2CH_2).

These changes may be depicted in terms of a mechanism involving initial oxidation at the metal atom.[2a,10] Alkyl ligand transfer in the resulting radical cation (**5**) is apparently rapid and is probably promoted by decreased electron density at the metal and hence also at the carbonyl carbon.[11] Ligand transfer in the uncharged alkylamino complex **4**, which affords the stable chelate **6**[12] (ν_{CO}(THF) 1920, 1620 cm^{-1}), is by contrast relatively slow. Hence **6** cannot be an intermediate in the oxidative conversion of the alkylamino complexes to β-lactam.



Nevertheless, these chelate complexes constitute alternative and advantageous intermediates since their conversion to β-lactams, on exposure to PbO_2 or Ag_2O, is even more facile than the corresponding β-aminoalkyl complexes. This sequence is particularly advantageous with heat sensitive β-lactams. Thus, rearrangement of **2a** to **6a** (CH_3CN, 70 °C, 20 h) in the presence of 10% PBu_3, followed by oxidation with Ag_2O (70 °C, 1 h) gave β-lactam (**3a**) in 59% yield.

Similarly **2b** is converted to **6b** by heating in THF solution (70 °C, 5 h, 10% Bu_3P), and then by the addition of Ag_2O to the β-lactam in 82% yield.

The synthetic sequence may readily be extended to the construction of fused ring β-lactams starting with amino olefins. Complex **7b** is obtained in 80% yield from the exchange reaction involving 1-hexenylammonium tetrafluoroborate and Fp(isobutene) tetrafluoroborate. Successive deprotonation