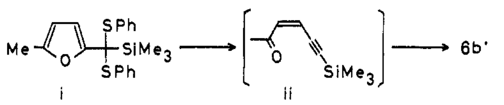
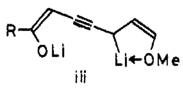
(10) **8a** (R = H): bp 115–118 °C at 0.06 mmHg; IR (neat) 3005, 1875, 1636, 1618, 1250, 1110, 845 cm^{-1}; NMR (CCl_4) δ 0.10 (9 H, s), 0.14 (9 H, s), 0.23 (9 H, s), 4.61 (1 H, d, J = 6.0 Hz), 6.24 (1 H, d, J = 6.0 Hz), 7.0–7.4 (5 H, m); M$^+$ at *m/e* 374.

(11) On treatment with metallic sodium and chlorotrimethylsilane, the diphenyl dithioacetal of 5-methyl-2-furoylsilane (i) was converted into **6b′** (R = CH_3) via unsaturated ketone ii.[3] In this case, one phenylthio group was considered to behave as a leaving group from the enolate of type **3** (X = SC_6H_5).



(12) Both of the olefinic bonds were confirmed to have the *Z* configuration. The internally coordinated metalocycle iii appears to be a probable intermediate.[15]



(13) See, for example, H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95,** 3310 (1973); G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39,** 3459 (1974).

(14) All of the reactions were carried out at −40 °C. After usual workup, acetylenic and allenic ketones were usually obtained as mixtures. The former were converted easily into the latter on treatment with silica gel.

(15) (a) D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96,** 5560 (1974); W. C. Still and T. L. Macdonald, *ibid.*, **96,** 5561 (1974); (c) W. C. Still and T. L. Macdonald, *J. Org. Chem.*, **41,** 3620 (1976).

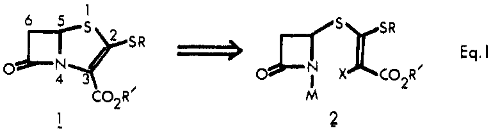
Kunio Atsumi, Isao Kuwajima*
Department of Chemistry, Tokyo Institute of Technology
Ookayama, Meguro-ku, Tokyo 152, Japan
Received October 17, 1978

Penems. 1. Penem Formation via a Novel Oxidative Addition Process Mediated by Copper(I)

Sir:

The total synthesis of naturally occurring β-lactam antibiotics, and in particular derivatives and nuclear analogues thereof, has received considerable attention in recent years as a means to produce potentially more effective antibacterial agents by rational design. Traditionally the synthetic methodology for the construction of bicyclic β-lactams possessing an α,β-unsaturated carboxylate moiety in the ring fused to the azetidinone has centered on the use of the Wittig reaction or its modifications, at some stage of development. The versatility of this approach has been exemplified by the elegant syntheses of cephems,[1] oxadethiacephems,[2] carbadethiacephems,[2b,3] and most recently penems[4] and carbadethiapenems.[5] In this report we present a new annulation procedure which provides a facile entry into the synthesis of 2-thioalkyl-substituted penems **1.**

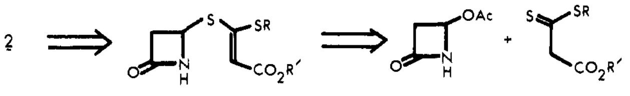
In considering synthetic approaches to **1** we were intrigued by the possibility that a metal-assisted oxidative addition reaction of a halodithioketene acetal azetidinone derivative **2** (M = metal, X = halogen) might be feasible (eq 1). Although



1 2

there is no apparent, directly applicable literature precedent for such a process, it has been documented that similar anionic nitrogen species undergo related coupling and annulation reactions in the presence of cuprous halides.[6] In addition to these copper(I)-promoted transformations, it has also been shown that α-bromoacrylates undergo facile, stereospecific self-coupling in the presence of bis(1,5-cyclooctadiene)nickel(0).[7]

We were further attracted to this proposal since the requisite fully functionalized secolactam **2** (M = H) was found to be readily available via halogenation of lactam derivative **3,** obtained from a displacement reaction of 4-acetoxyazetidin-2-one (**4**)[8] and the appropriate 1,1-dithiomalonate diester **5**[9] as outlined in eq 2. The following account describes our experimental findings by which this strategy was successfully realized.



3 4 5 Eq. 2

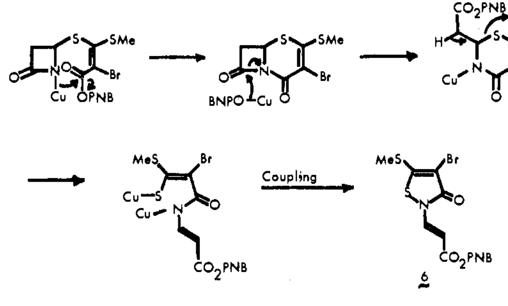
Treatment of stoichiometric amounts of **4** and *p*-nitrobenzyl methyl 1,1-dithiomalonate (**5**)[12] (R = Me; R′ = $CH_2C_6H_4$-*p*-NO_2 ≡ PNB) with methanolic sodium methoxide (25 °C, 67 h) afforded the expected secolactam **3**[13] in 74% yield as a 1:1 mixture of *Z* and *E* isomers. Exposure of the mixture **3** to *N*-bromosuccinimide (1.1 equiv) in the presence of HMPA (1 equiv) in THF (25 °C, 0.5 h) provided a 78% yield of the desired bromodithioketene acetal derivative **2**[13] (M = H) as a mixture of isomers (*Z*/*E* = 2.4).[14] Reaction of the *Z* bromide **2** with lithium diisopropylamide (1.0 equiv) in the presence of CuI·PBu_3[15] (1.0 equiv) in THF at −78 °C (1 h) followed by warming to −25 °C (5 h) gave penem **1** (R = Me; R′ = PNB, mp 165–166.5 °C) in 43% yield.[16] The spectral properties exhibited by penem **1** were in accord with those reported by Woodward and co-workers[4] which appear to be characteristically definitive for this nucleus: IR ($CHCl_3$) 1795, 1689 cm^{-1}; λ_{max} (dioxane) 268 nm (ϵ 16 931), 317 (11 053). The NMR spectrum was unexceptional: δ ($CDCl_3$) 2.47 (s, SMe), 3.2 (dd, J = 2.5, 16 Hz, H-6β), 3.8 (dd, J = 5, 16 Hz, H-6α), 5.17 (dd, J = 2.5, 5.0 Hz, H-5), 5.27 (s, CO_2CH_2Ar), 7.47 (d, J = 9 Hz, ArH), 8.2 (d, J = 9 Hz, ArH).

The fact that the annulation reaction was indeed mediated by cuprous ion was readily ascertained, for in its absence the identical process yielded no detectable lactam products. The stereospecificity of the reaction was demonstrated at an early stage of development in which a mixture of bromides **2**[18] (*E*/*Z* = 1.6) treated successively with LDA (1.0 equiv) and CuI (1.1 equiv) in THF at −78 °C followed by warming to −5 °C over 2 h resulted in the isolation of **1** (4%) and 8% of a material whose structure was designated as **6** on the basis of mechanistic considerations and the following spectroscopic data: IR ($CHCl_3$) 1724, 1695, 1637 cm^{-1}; NMR ($CDCl_3$) δ 2.6 (s, SMe), 5.3 (s, CO_2CH_2Ar), 5.61 (d, J = 14 Hz, C=C*H*CO_2PNB), 7.5 (d, J = 9 Hz, ArH), 8.2 (d, J = 9 Hz, ArH), 8.33 (d, J = 14 Hz, NCH=C); *m/e* 432, 430 (M$^+$). In an identical reaction of only the *Z* bromide **2,** the same yield of penem **1** was obtained and **6** was not detected.

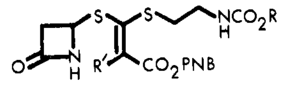
A mechanism by which **6** may be formed, for which there is some precedent,[19] is given in Scheme I.

Having demonstrated the viability of this approach for the construction of a simple 2-thioalkylpenem, we sought to elaborate the method for the synthesis of penems possessing an appropriately N-protected 2-cysteaminyl substituent, a moiety common to the highly potent, naturally occurring antibiotic thienamycin and related substances.[20] Similarly then, a mixture of secolactams **7a**[13] was obtained from the reaction

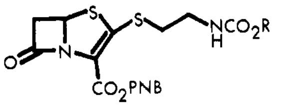
Scheme I



0002-7863/79/1501-2210$01.00/0



7a R′ = H, R = PNB
7b R′ = H, R = CH_2CCl_3
8a R′ = Br, R = PNB
8b R′ = Br, R = CH_2CCl_3



9a R = PNB
9b R = CH_2CCl_3

of **4** and *p*-nitrobenzyl-*N*-*p*-nitrobenzyloxycarbonylcysteaminyl-1,1-dithiomalonate[12] with sodium methoxide in methanol (25 °C, 24 h, 84%). Bromination of **7a** with NBS (1.1 equiv) (1 equiv of HMPA, THF, 25 °C, 0.3 h, 44%) afforded only the desired *Z* isomer **8a**.[13] Cyclization as before (1.1 equiv of LDA, 3.3 equiv. of CuBr·SMe$_2$, THF, −78 to 0 °C, 3.0 h) gave penem **9a** in 55% yield: mp 151–153 °C; IR (CHCl$_3$) 1795, 1720 (br), 1690 (sh) cm^{-1}; NMR (CDCl$_3$) δ 3.1 (m, SCH$_2$), 3.27 (dd, J = 2, 16 Hz, H-6β), 3.56 (m, NCH$_2$), 3.84 (dd, J = 5, 16 Hz, H-6α), 5.19 (dd, J = 2, 5 Hz, H-5), 5.23 (s, CO$_2$CH$_2$Ar), 5.28 (br m, NH), 5.32 (s, CO$_2$CH$_2$Ar), 7.57 (m, ArH), 8.28 (m, ArH); λ_{max} (dioxane) 268 nm (ϵ 24 752), 318 (10 080).

The analogous sequence could also be conducted with the cysteamine nitrogen protected with the trichloroethyloxycarbonyl group. Thus **7b** was obtained analogously in 70% yield and brominated (1.1 equiv of NBS, 6 equiv of HMPA, THF, −78 to −20 °C, 1 h) to **8b**[13] in 70% yield (*Z*/*E* = 9). Cyclization of **8b** to **9b**[13] was best accomplished (52%) employing CuI·PBu$_3$ (1 equiv) at −78 to −20 °C over a period of 5 h.

In conclusion, it has been demonstrated that a highly strained bicyclic β-lactam nucleus can be readily constructed in the presence of diverse functional groups utilizing a mild, facile, stereospecific oxidative addition reaction mediated by Cu(I) as the key transformation. The further application of this methodology for the synthesis of novel antibiotics will be reported in due course.

Acknowledgment. We are indebted to Professor Barry M. Trost for many fruitful discussions, to Mr. J. Smith and Mr. H. Flynn for mass spectral measurements, to Dr. B. Arison and Mr. H. Flynn for obtaining the 300-MHz NMR spectra, to Dr. J. A. McCauley and his associates for UV measurements, and to Mr. J. P. Gilbert and his staff for microanalytical determinations.

Supplementary Material Available: List of physical and spectroscopic properties of all new β-lactams (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, **55**, 408 (1972); (b) R. Scartazzini and H. Bickel, *ibid.*, **55**, 423 (1972); (c) R. Scartazzini, J. Gostell, H. Bickel, and R. B. Woodward, *ibid.*, **55**, 2567 (1972); (d) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4649 (1973); (e) *ibid.*, 4653 (1973); (f) N. G. Steinberg, R. W. Ratcliffe, and B. G. Christensen, *ibid.*, 3567 (1974); (g) R. A. Firestone, N. S. Maciejewicz, and B. G. Christensen, *J. Org. Chem.*, **39**, 3384 (1974); (h) D. Borman, *Justus Liebigs Ann. Chem.*, 1391 (1974); (i) J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J. Chem. Soc.*, *Perkin Trans. 1*, 1615 (1976); (j) R. B. Woodward, K. Heusler, I. Ernest, K. Burri, R. J. Friary, F. Haviv, W. Oppolzer, R. Paioni, K. Syhora, R. Wenger, and J. K. Whitesell, *Nouv. J. Chem.*, **1**, 85 (1977); (k) D. I. C. Scopes, A. F. Kluge, and J. A. Edwards, *J. Org. Chem.* **42**, 376 (1977); (l) S. Yamamoto, N. Haga, T. Aoki, S. Hayashi, H. Tanida, and W. Nagata, *Heterocycles*, **8**, 283 (1977); (m) R. Scartazzini and H. Bickel, *ibid.*, **7**, 1165 (1977).

(2) (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974); (b) R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, G. S. Patel, and B. G. Christensen, *J. Med. Chem.*, **20**, 551 (1977); (c) M. Narisada, H. Onoue, and W. Nagata, *Heterocycles*, **7**, 839 (1977); (d) Y. Hamashima, M. Narisada, M. Yoshioka, S. Uyeo, T. Tsuji, I. Kikkawa, and W. Nagata, Abstracts of the 176th National Meeting of the American Chemical Society, Miami Beach, Fla., Sept 1978, No. 14, Medicinal Chemistry.

(3) (a) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem.* Soc., **96**, 7584 (1974); (b) J. Finkelstein, K. G. Holden, and C. D. Perchonock, *Tetrahedron Lett.*, 1629 (1978).

(4) I. Ernest, J. Gostell, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978), and references therein.

(5) (a) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 8006 (1978); (b) M. Narisada, S. Uyeo, and W. Nagata. Abstracts of the 176th National Meeting of the American Chemical Society, Miami Beach, Fla., Sept 1978, No. 13, Medicinal Chemistry.

(6) For example, R. G. R. Bacon and A. Karim, *J. Chem. Soc.*, *Perkin Trans. 1*, 272, 278 (1973), have reported the effective coupling of potassium phthalimide with both aryl and vinyl halides catalyzed by cuprous ions, and T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *ibid.*, 389 (1976), have reported a novel, intramolecular cyclization of a copper(I) enamide and an aromatic bromide, and similarly with a pyrrole anion: T. Kametani, T. Ohsawa, M. Ihara, and K. Fukumoto, *ibid.*, 460 (1978).

(7) M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Am. Chem. Soc.*, **94**, 9234 (1972).

(8) K. Clauss, D. Grimm, and G. Prossel, *Justus Liebigs Ann. Chem.*, 539 (1974).

(9) By analogy to the works of the Hoechst group[8,10] in which **4** was found to undergo facile displacements with sulfur nucleophiles and, more significantly, with a highly enolizable carbonyl compound, it was anticipated that thionomalonate **5** would also succeed, since compounds of this type readily form thiolate anions owing to the lower difference in dissociation energy between C═S and C—S (45 kcal/mol^{-1}) as compared with that between C═O and C—O (73 kcal/mol^{-1}).[11]

(10) H. W. Schnabel, D. Grimm, and H. Jensen, *Justus Liebigs Ann. Chem.*, 477 (1974).

(11) W. O. Foye, *J. Chem. Educ.*, **46**, 841 (1969).

(12) F. DiNinno and E. Linek, a manuscript describing the preparation of these and related compounds has been submitted for publication.

(13) All new compounds gave satisfactory spectroscopic analyses.

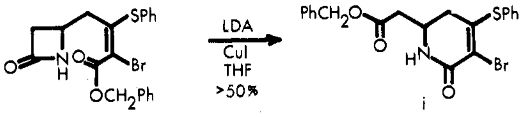
(14) It was found that in the absence of HMPA the undesired *E* bromide predominated (*Z*/*E* = 0.47).

(15) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7**, 9 (1963).

(16) Alternatively, penem **1** could be prepared in 52% yield when CuBr·SMe$_2$[17] (2 equiv) was substituted for CuI·PBu$_3$.

(17) H. O. House, C.-Y. Chu, M. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40**, 1460 (1975).

(18) It was not possible to obtain a pure sample of the *E* bromide owing to its instability toward silica gel plate layer chromatography. The result of this decomposition was a deposition of *p*-nitrobenzyl alcohol, as the only identifiable substance, which presumably arises from an acid-catalyzed process similar to that indicated initially in Scheme I. Based on this finding, which was observed for all of the bromodithioketal azetidinone derivatives reported herein, the *E* and *Z* configurations were assigned. Diagnostically then was the uniformly downfield H-4 resonance of the *Z* bromide relative to the *E* bromide in the NMR spectrum, which allowed for the determination of the *E*/*Z* ratio prior to and after purification.



i

(19) T. N. Salzmann, unpublished results. In a related system depicted below, it was shown that compound i was the only product from the analogous reaction.

(20) (a) G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978), and references therein; (b) K. Okamura, S. Hirata, Y. Okamura, Y. Fukagawa, Y. Shimauchi, K. Kouno, T. Ishikura, and J. Lein, *J. Antibiot.*, **31**, 480 (1978).

Frank DiNinno,* Ernest V. Linek, B. G. Christensen
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065

Received December 4, 1978

Derivatives of Heteropolyanions. 2. Metal–Metal-Bonded Derivatives

Sir:

We recently reported the preparation of several series of organic derivatives of the Keggin-structure (Figure 1) heteropolyanions $W_{12}SiO_{40}{}^{4-}$, $Mo_{12}SiO_{40}{}^{4-}$, and $W_{12}PO_{40}{}^{3-}$.[1] Extension of this work has led to the first heteropolyanions which contain metal–metal bonds, including $CpFe(CO)_2SnW_{11}PO_{39}{}^{4-}$ ($Cp = \pi\text{-}C_5H_5$), $(OC)_3Co(SnW_{11}SiO_{39})_2{}^{11-}$, $\pi\text{-}C_3H_5Pd(SnW_{11}SiO_{39})_2{}^{11-}$, and a high molecular weight completely inorganic polymer, $[(OC)_3CoGe_2W_{11}SiO_{40}{}^{5-}]_n$. Alternatively, these anions and the others reported here can be viewed as transition-metal complexes which contain heteropolyanion ligands.

These anions are prepared by reacting the "unsaturated" Keggin fragments $W_{11}SiO_{39}{}^{8-}$, $Mo_{11}SiO_{39}{}^{8-}$, or $W_{11}PO_{39}{}^{7-}$,

0002-7863/79/1501-2211$01.00/0