$Ph_2CHLi$ is a solvent-dependent equilibrium mixture of contact-ion and solvent-separated ion pairs[14] as shown by UV,[15] NMR,[14] conductivity,[15] and kinetic studies.[13,16] Therefore the constants reported in Table I are apparent rate constants or composites of the rate constants $k_c$ and $k_s$ for the two kinds of ion pairs in **4**.[16]

Preliminary attempts to determine rate constants at 0.0 °C for the reaction of **4** with neopentyl iodide in THF gave values that are comparable in magnitude with rates obtained at 25 °C. Presumably this is due to an increase in the proportion of the more reactive solvent-separated ion pair at lower temperatures.[13,16]

Although neopentyl chloride does not react with **1** or **4** to give a coupling product, it does give $Ph_3CH$ and $Ph_2CH_2$ and probably the carbenoid. By contrast neophyl chloride ($PhC(CH_3)_2CH_2Cl$) couples with **4** to give 1,1,3-triphenyl-3-methylbutane (52.6%)[17] without evidence for the presence of a rearranged coupling product.

In summary we conclude that **1** and **4** react with neopentyl bromide, neopentyl iodide, and benzyl fluoride following second-order rate laws and exhibiting $S_N2$-like alkyl group and element effects on coupling reaction rates.

**Acknowledgment:** We gratefully acknowledge the support of the City University's Faculty Research Award Program through a PSC-BHE grant, No. 12290. We also thank Professor K. D. Berlin (Oklahoma State University) for providing data on the properties and synthesis of **3**.

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(4) Aliquots (2.5 mL) of a reaction were quenched with methyl iodide in chilled (0 °C) vials. Unreacted $Ph_3CLi$ is measured as 1,1,1-triphenylethane along with **2**a or **2b** and **3** or **5** by quantitative gas chromatography.

(5) Stilbene probably comes from $\alpha$-fluorobibenzyl either by in situ dehydrohalogenation with $Ph_3CLi$ or by thermal elimination of HF in the injection port of the gas chromatograph.[6] The formation of $\alpha$-fluorobibenzyl occurs by a scheme like that known for benzyl chloride's reaction with *n*-butyllithium.[6]

$$Ph_3CLi + PhCH_2F \rightarrow PhCHFLi \xrightarrow{PhCH_2F} PhCHFCH_2Ph + LiF$$

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(17) Yields have not been optimized nor has a rate been determined.

**H. E. Zieger,* Donald Mathisen**

*The City University of New York, Department of Chemistry*
*Brooklyn College, Brooklyn, New York 11210*

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# A Facile Ring-Opening Reaction of Furfuryl Carbanion. Regioselective Generation of Di- or Trianionic Enolates

*Sir:*

Furan derivatives are well known to undergo ring-opening reactions under acidic conditions and have widely been employed as excellent precursors of 1,4 diketones.[1] However, they are usually quite stable under basic conditions because of the $\pi$-electron excessive character of furan ring.

We have recently reported ring-opening reactions of furan derivatives under the influence of metallic sodium and chlorotrimethylsilane; 2-furancarboxylic esters[2] and 2-furaldehyde diphenyl thioacetals[3] are converted into the corresponding acyclic silyl enol ethers. In these reactions, 2-furfuryl carbanion **2** was postulated to be a key intermediate for ring opening. In the course of mechanistic studies, it has been proved that a facile ring cleavage of furan takes place through **2** to yield allenic enolate **3**[4] on treatment of a furan having an anion stabilizing group with butyllithium. With the resulting enolate **3**, it has also been found that lithiation of the allenic hydrogen[5] is further effected very easily to yield the corresponding dianionic enolate **4**. However, examination of the silylated products revealed a marked contrast; **1a** afforded **5a**[6] as a sole product through selective removal of $\beta$ hydrogen, while the $\delta$ hydrogen was lithiated preferentially to yield **6b**[7] and **6b'**[8] from **1b.**

In each case, the geometry of the enol double bond was confirmed to be *Z* exclusively,[9] as expected from the furan ring. Further, in this successive lithiation reaction, the second step, b, appears to proceed much more rapidly than the lithiation of the starting furan derivative (step a) (Scheme I). For example, an equimolar reaction of 2-benzylfuran (**1a,** R = H) with butyllithium was accompanied by recovery of the starting material (50%), giving disilylated product **5a** (R = H) in 42% yield. The following procedures are illustrative. To a solution of 2-benzylfuran **1a** (R = H) (0.310 g, 2 mmol) was added a solution of butyllithium (4 mmol) at −78 °C. Then the solution was warmed to 0 °C and stirred for 10 min. After the solution was cooled again to −78 °C, chlorotrimethylsilane (0.76 mL, 6 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into an ice-cooled saturated aqueous $NaHCO_3$ solution and this mixture was then extracted with hexane. The crude product was distilled to give 0.513 g (85%) of the *Z* isomer of the silyl enol ether of 5-phenyl-3-trimethylsilyl-4-pentyn-1-al (**5a,** R = H). See Table I.

With 3 equiv of butyllithium, trianionic enolate can also be generated efficiently; silylation and acidic hydrolysis of the

Scheme I

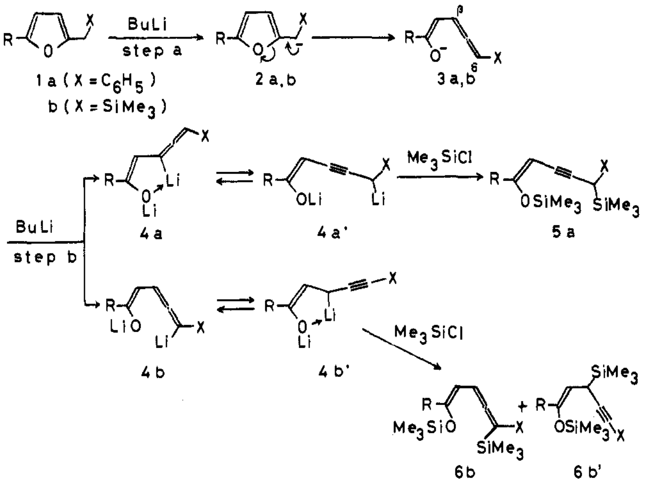

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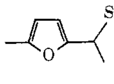
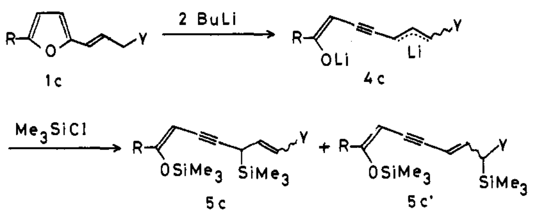
**Table I.** Ring-Opening Reactions of Furans with 2 Equiv of BuLi

| furan | product (% yield) |
|---|---|
| **1a** (R = H) | **5a** (R = H) (85)[a] |
| **1b** (R = $CH_3$) | $MeCOCH_2CH{=}C{=}C(SiMe_3)_2$ (51)[b]<br>$MeCOCH_2C(SiMe_3)HC{\equiv}CSiMe_3$ (12)[b] |
|  | $MeCOCH_2C(SiMe_3){=}C{=}C(CH_3)SiMe_3$ (61)[b,c] |
| **1c** (R = Me; Y = Ph) | **5c** (R = Me; Y = Ph) (93)[a,d] |
| **1c** (R = H; Y = OMe) | **5c** (R = H; Y = OMe) (73)[a] |
| **1c** (R = Me; Y = OMe) | **5c** (R = Me; Y = OMe) (86)[a,e] |
| **1c** (R = Me; Y = SPh) | **5c** (R = Me; Y = SPh) (50)[a]<br>**5c′** (R = Me; Y = SPh) (20)[a] |

[a] Distilled yields. [b] Isolated yields after acidic hydrolysis (HCl–$H_2O$–THF). [c] The starting material was recovered in 16% yield. [d] (*Z*,*E*)-**4c** was formed exclusively. [e] (*Z*,*Z*)-**4c** was formed exclusively.[12]

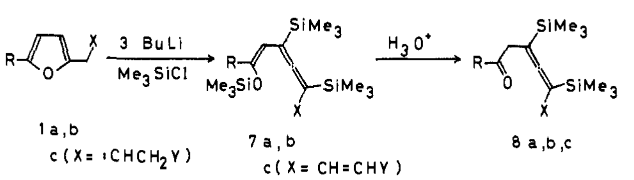
**Table II.** Ring-Opening Reactions of Furans with 3 Equiv of BuLi

| furan | product (% yield) |
|---|---|
| **1a** (R = H) | **7a** (R = H) (92) |
| **1a** (R = Me) | **8a** (R = Me) (80) |
| **1b** (R = Me) | **8b** (R = Me) (75)<br>$MeCOCH_2CHC(SiMe_3){\equiv}CSiMe_3$ (13) |
| **1c** (R = Me; Y = Ph) | **8c** (R = Me; Y = Ph) (86) |



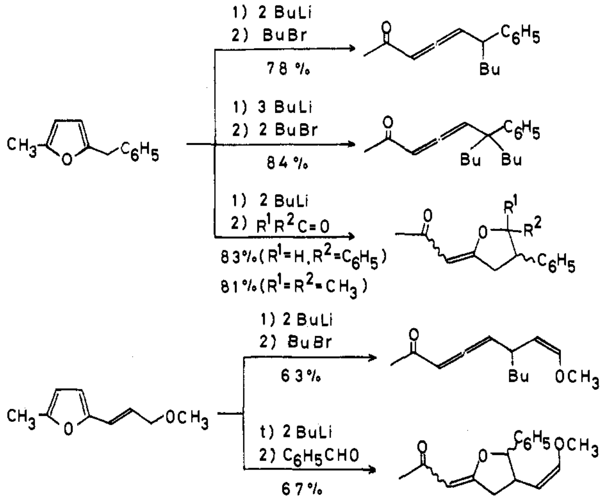
reaction mixture afforded the corresponding disilylated allenic carbonyl compound **8** as the major product.[10] See Table II.

Successful application of this reaction to the ethylenic homologue has broadened the synthetic use of it. It has been shown that furfuridene derivative **1c** having an appropriate substituent Y undergoes similar ring cleavage to yield the corresponding dianionic enolate **4c** under the same conditions. Highly unsaturated silyl enol ether **5c** can be prepared in good yield on treatment with the chlorosilane. With **1** (X = SR), the alkylthio group was expected to behave as a leaving group from the generated enolate **3** to give the corresponding carbonyl compound,[11] RCOCH=CHC≡CH, which should make the reaction much more complex. However, for generation of **4c**, both alkoxy and phenylthio are employable equally well as anion stabilizing group Y, which leads to the formation of **5c** possessing an alkoxyvinyl[12] or phenylthiovinyl group. These products should be especially useful synthetic intermediates because of two types of differently masked carbonyl functionalities.



The high regioselectivity on lithiation of allenic hydrogen is also remarkable with the enolate derived from the furfuridene derivative. Similarly to the case with **3a**, lithiation takes place specifically on the δ hydrogen without any contamination of the regio isomer. With exceptional case **3b**, the origin of the selectivity observed is mostly attributable to anion stabilizing effects of both the acetylenic and phenyl or ethylenic groups as shown in **4a′** or **4c**, although the neighboring effect of the enolate group shown in **4a** cannot be neglected completely.

Scheme II



Carbon chain extension can also be effected via di- or trianionic enolates with high regioselectivity (Scheme II). With both alkyl halides and carbonyl compounds, the reactions usually take place on the δ carbon of the enolate. The following two features are worthy of note: (i) two alkyl groups can also be introduced efficiently on the same carbon via trianionic enolate and (ii) the reaction proceeds on the δ carbon selectively even in reactions with aldehydes which are known to be highly reactive toward the enolate moiety also.[13] The products are isolated as the corresponding allenic ketones through isomerization of the original acetylenic ones.[14] ε-Hydroxy allenic ketones, resulting from the reactions with carbonyl compounds, undergo internal 1,4 addition to yield enones possessing oxacyclopentane ring.

In this opening procedure, furan derivatives are shown to behave as precursors of highly reactive species having two or three kinds of nucleophilic centers.

We are currently studying the synthetic use of these polylithiated intermediates in more details.

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(6) **5**a (R = H): bp 128–131 °C at 0.08 mmHg; IR (neat) 3005, 2198 (w), 1614, 1250, 1092, 845 $cm^{-1}$; NMR ($CCl_4$) δ 0.06 (9 H, s), 0.21 (9 H, s), 3.23 (1 H, d, *J* = 2.5 Hz), 4.68 (1 H, dd, *J* = 6.0, 2.5 Hz), 6.38 (1 H, d, *J* = 6.0 Hz), 7.0–7.4 (5 H, m); $M^+$ at *m/e* 302.

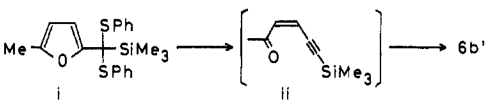
(7) The parent ketone of **6b** (R = $CH_3$): bp 68–71 °C at 0.08 mmHg; IR (neat) 2942, 1912, 1710, 1250, 848 $cm^{-1}$; NMR ($CCl_4$) δ 0.15 (18 H, s), 2.14 (3 H, s), 3.00 (2 H, d, *J* = 3.0 Hz), 4.60 (1 H, t, *J* = 3.0 Hz); $M^+$ at *m/e 240*.

(8) The parent ketone of **6b′** (R = $CH_3$): bp 79–82 °C at 0.1 mmHg; IR (neat) 2942, 2150, 1721, 1250, 845 $cm^{-1}$; NMR ($CCl_4$) δ 0.18 (9 H, s), 0.20 (9 H, s), 2.25 (3 H, s), 2.23–2.70 (3 H, m); $M^+$ *m/e* 240.

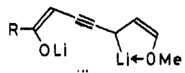
(9) The observed coupling constants of vicinal olefinic hydrogens, 6.0 Hz for **5**a (R = H), **7**a (R = H), and **5c** (R = H; Y = $OCH_3$), agree closely with the reported values, 6.0[9a] and 6.1[9b] Hz, for (*Z*)-silyl enol ethers of aldehydes. (a) D. A. Evans, K. M. Hurst, and J. M. Takacs, *J. Am. Chem. Soc.*, **100**, 3467 (1978); (b) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(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 melalocycle iii appears to be a probable intermediate.[15]



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(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.

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

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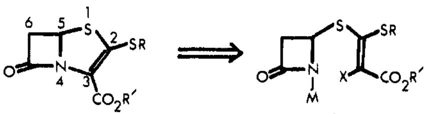
# Penems. 1. Penem Formation via a Novel Oxidative Addition Process Mediated by Copper(I)

*Sir:*

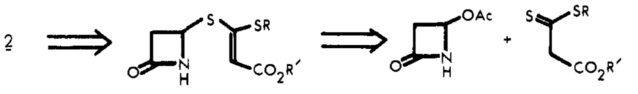
The total synthesis of naturally occurring β-lactam antibiotics, and in particular derivatives and nuclear analogues thereof, has received considerable attention in recent years as a means to produce potentially more effective antibacterial agents by rational design. Traditionally the synthetic methodology 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 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]



1 2 Eq. 1

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

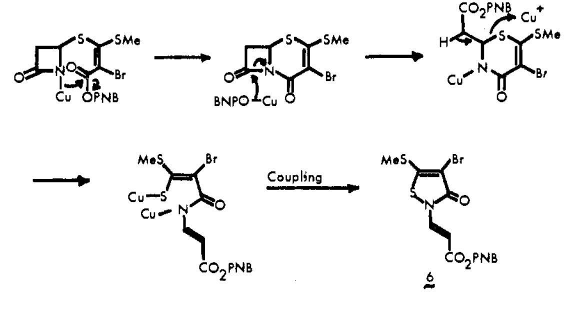
Treatment of stoichiometric amounts of **4** and *p*-nitrobenzyl methyl 1,1-dithiomalonate (**5**)[12] (R = Me; R′ = $CH_2C_6H_4$-*p*-$NO_2$ ≡ PNB) with methanolic sodium methoxide (25 °C, 67 h) afforded the expected secolactam **3**[13] in 74% yield as a 1:1 mixture of *Z* and *E* isomers. Exposure 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 $CuI \cdot PBu_3$[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 $cm^{-1}$; $\lambda_{max}$ (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*$CO_2$PNB), 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



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