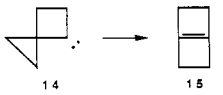
which has been shown to occur with retention of configuration at the migrating carbon center.[20] Finally, the directly analogous hydrocarbon carbene **14** is known to isomerize to **15**.[21]



**14** **15**

(20) Guarino, A.; Wolf, A. P. *Tetrahedron Lett.* **1969**, 655.

Further studies are currently underway to further develop our understanding of the ozonolysis of allenes and to test the mechanistic hypotheses put forth.

**Acknowledgment.** Support for this work was generously provided by the National Institute of Health (Grant GM 39988).

(21) Wiberg, K. B.; Burgmaier, G. J.; Warner, P. *J. Am. Chem. Soc.* **1971**, *93*, 246.

# A Method for the Synthesis of Alkynyl Phenyl Sulfides from Alkynyltrimethylsilanes. A Novel, Efficient Synthesis of the Thienamycin Intermediate from 3(*R*)-Hydroxybutyric Acid

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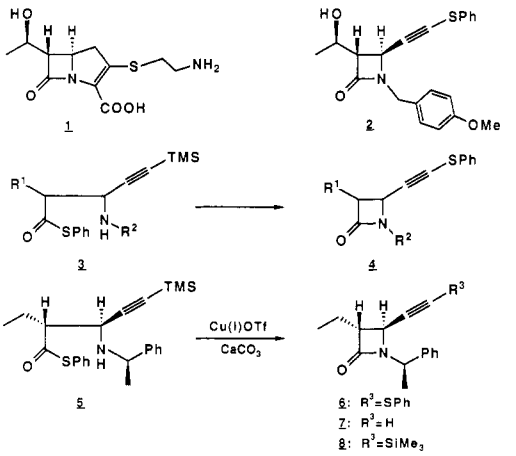
*Summary:* The mechanism of the one-pot conversion of β-amino thiol esters of type **3** to β-lactams of type **4** has been clarified, and it is proposed that the actual active species is a PhSSPh–CuOTf complex. Through the use of this novel reaction, an efficient synthesis of the thienamycin intermediate **2**, starting with 3(*R*)-hydroxybutyric acid, has been achieved. Furthermore, the combined reagents (PhSSPh–CuOTf) have been demonstrated to be a powerful source of $PhS^+$ through the conversion of several alkynyltrimethylsilanes to alkynyl phenyl sulfides.

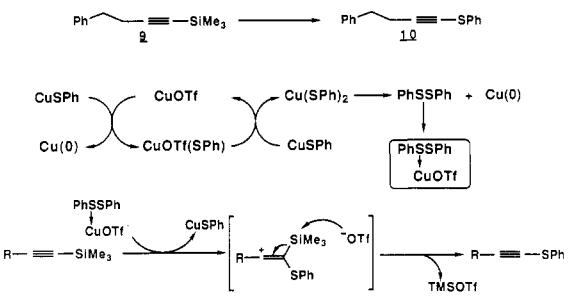
The carbapenem skeleton can be constructed efficiently via two synthetic routes. One uses an intramolecular carbene insertion reaction,[1] and the other proceeds via an intramolecular Wittig reaction.[2] The key synthetic intermediate for the synthesis of (+)-thienamycin (**1**) utilizing the latter process is the alkynyl phenyl sulfide **2**,[2c,d] whose novel and efficient synthesis starting with 3(*R*)-hydroxybutyric acid is reported herein. In addition, the detailed mechanism of the direct conversion of β-amino thiol esters of type **3** to β-lactams of type **4** and the method for the synthesis of alkynyl phenyl sulfides from alkynyltrimethylsilanes are also described (Scheme I).

We have recently found that treatment of the β-amino thiol ester **5** with CuOTf (1.2 equiv) and $CaCO_3$ (2 molar equiv) in refluxing dioxane for 5 h affords the alkynyl phenyl sulfide **6** in one pot (34%), together with **7** (28%). On the other hand, using toluene instead of dioxane provided none of **6**, giving instead a mixture of **7** and **8** in 89% yield.[3] We decided to initiate mechanistic studies on the conversion of **5** to **6**, because alkynyl phenyl sulfides of type **4** are known to be useful intermediates for the synthesis of carbapenem antibiotics.[2] The reagents which appeared to play a key role in the above transformation were CuOTf, $CaCO_3$, and CuSPh, formed by reaction of CuOTf with the β-amino thiol ester. It was found that treatment of the simple model compound **9** with CuSPh (1.2 equiv) afforded

**Scheme I**




**Scheme II**




none of **10**. On the other hand, treatment of **9** with the combined reagents (1.2 equiv of CuSPh and 1.2 equiv of CuOTf) in refluxing dioxane provided **10** in 30% yield, indicating that both reagents are essential in the conversion of alkynyltrimethylsilanes to alkynyl phenyl sulfides. When the above reaction was carried out at 45 °C, phenyl disulfide was formed in 100% yield and no **10** was produced. These results implied that the actual reagent for the above transformation is phenyl disulfide. After several attempts, it was found that treatment of **9** with 1.2 equiv of phenyl disulfide, 1.2 equiv of CuOTf, and 2.0 molar equiv of $CaCO_3$ in refluxing dioxane gave **10** in 82% yield.[4]

(1) (a) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. (b) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Ibid.* **1980**, *21*, 2783.

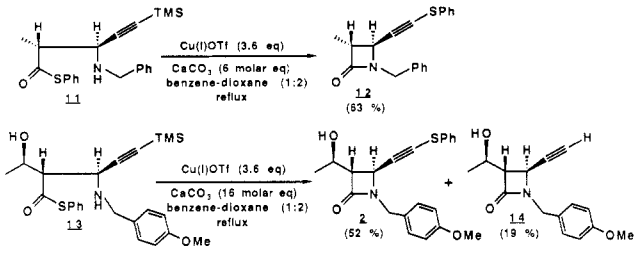
(2) (a) Ponsford, R. J.; Roberts, P. M.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 847. (b) Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1984**, *25*, 2793. (c) Maruyama, H.; Shiozaki, M.; Oida, S.; Hiraoka, T. *Ibid.* **1985**, *26*, 4521. (d) Maruyama, H.; Hiraoka, T. *J. Org. Chem.* **1986**, *51*, 399.

(3) Miyachi, N.; Kanda, F.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3511.

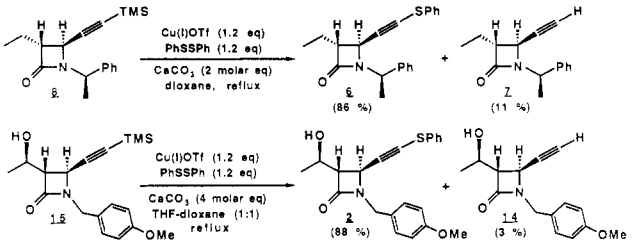
(4) Exposure of **9** to phenyl disulfide only afforded none of **10**.

0022-3263/90/1955-1975$02.50/0 

**Scheme III**




**Scheme IV**




The following experiments were conducted in order to clarify the mechanism by which alkynyltrimethylsilanes are converted to alkynyl phenyl sulfides by the combined reagents. First, reaction of **9** with benzenesulfenyl triflate[5] (apparently produced from phenyl disulfide and CuOTf) in the presence of $CaCO_3$ was carried out, giving none of **10**. Second, the copper acetylide,[6] apparently formed from the alkynyltrimethylsilane and CuOTf, was treated with phenyl disulfide in the presence of $CaCO_3$. No **10**, however, was obtained, suggesting that the actual active species for the sulfenylation reaction is the PhSSPh–CuOTf complex, as shown in Scheme II.[7] Next, the mechanism of the formation of phenyl disulfide was carefully investigated. When CuSPh was heated in dioxane at 55 °C for 16 h, phenyl disulfide was formed in 10% yield. On the other hand, treatment with CuSPh with CuOTf in dioxane at 55 °C for 16 h afforded phenyl disulfide in 95% yield. These results highlighted the crucial role played by CuOTf in the facile formation of phenyl disulfide. Furthermore, the solvent effect on the formation of phenyl disulfide was also examined. Although phenyl disulfide was formed in nearly quantitative yield by treatment of CuSPh with CuOTf in dioxane, the reaction in toluene under the same conditions afforded phenyl disulfide in only 8% yield. This result explained why the transformation of **5** to **6** did not proceed in toluene solvent. On the basis of the experimental results described above, a proposed reaction mechanism for the transformation of **3** to **4** is shown in Scheme II.

With this possible mechanism in hand, we next attempted to improve the efficiency of the conversion (**3** → **4**). The mechanism shown in Scheme II indicated that at least 2 equiv of CuOTf is necessary for the efficient conversion of **3** to **4**.[8] Therefore, several combinations of reaction conditions were examined, and we have now found that treatment of **5** with 3.6 equiv of CuOTf and 6 molar equiv of $CaCO_3$ in benzene–dioxane (1:4) at reflux temperature provided the desired product **6** in 63% yield, together with **7** (9%). Likewise, **11** was converted to **12** in 63% yield by treatment with CuOTf (3.6 equiv) and $CaCO_3$ (6 molar equiv) in benzene–dioxane (1:2) at reflux temperature (Scheme III). Next, the methodology described above was successfully applied to yield a novel and efficient synthesis of the thienamycin intermediate **2**, starting with 3(*R*)-hydroxybutyric acid. Exposure of the β-*p*-methoxybenzylamino thiol ester **13**, obtainable from 3(*R*)-hydroxybutyric acid in a highly stereoselective manner (ca. 60% overall yield),[9] to CuOTf (3.6 equiv) and $CaCO_3$ (16 molar equiv) in benzene–dioxane (1:2) at reflux temperature[10] gave the key intermediate **2**, $[\alpha]^{20}_D$ −86° (*c* 1.32, $CHCl_3$), in 52% yield together with **14** (19%), whose spectral data were in accord with those of an authentic sample.[2c,d]

Moreover, in order to demonstrate the synthetic utility of the combined reagents (PhSSPh–CuOTf) as a powerful source of $PhS^+$, reactions using several trimethylsilylalkynes were carried out. Treatment of **8** with phenyl disulfide (1.2 equiv), CuOTf (1.2 equiv), and $CaCO_3$ (2 molar equiv) in refluxing dioxane afforded **6** in 86% yield together with a small amount of **7** (11%). Likewise, **15** was transformed into **2** (88%) together with **14** (3%) on exposure to phenyl disulfide (1.2 equiv), CuOTf (1.2 equiv), and $CaCO_3$ (4 molar equiv) in THF–dioxane (1:1) at reflux temperature[11] (Scheme IV).

In conclusion, the mechanism of the transformation of **3** to **4** has been elucidated, making possible a novel and efficient synthesis of the thienamycin intermediate **2** starting from 3(*R*)-hydroxybutyric acid. Furthermore, the combined reagents (PhSSPh–CuOTf) have been shown to be a powerful source of $PhS^+$, whose further synthetic application is currently under investigation.

**Acknowledgment**. Financial support of this project was provided by The Akiyama Foundation.

(5) Prepared according to the literature. See: Effenberger, F.; Russ, W. *Chem. Ber.* **1982**, *115*, 3719.

(6) Prepared from the lithium acetylide and copper(I) iodide.

(7) In order to detect the complex, the $^1H$ NMR spectra of a mixture of phenyl disulfide and CuOTf in dioxane-$d_8$ were taken at various temperatures. However, positive results could not be obtained. Alternatively, the mechanism shown below is also plausible.

$$PhSSPh + CuOTf \rightarrow [PhSSPh]^{\cdot+} + Cu(0) + {}^-OTf$$

$$[PhSSPh]^{\cdot+} + Cu(0) + {}^-OTf \xrightarrow[RC\equiv CSiMe_3]{} RC\equiv CSPh + \tfrac{1}{2}PhSSPh + Me_3SiOTf + Cu(0)$$

See: (a) Pandery, G.; Jayathirtha, R. V.; Bhalerao, U. T. *J. Chem. Soc., Chem. Commun.* **1989**, 416. (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Bartoli, D. *Tetrahedron Lett.* **1989**, *30*, 1417.

(8) Formation of CuOTf and PhSTMS from CuSPh and TMSOTf is excluded, because treatment of **9** with PhSTMS and CuOTf in the presence of CaCO3 (dioxane, reflux) did not produce **10**.

(9) (a) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523. (b) *Ibid.* **1986**, *27*, 2149.

(10) A general procedure follows: To a stirred suspension of **13** (36.6 mg, 0.0828 mmol) and $CaCO_3$ (132.6 mg, 1.33 mmol) in benzene–dioxane (1:2, 2.2 mL) was gradually added $(CuOTf)_2$-benzene (25 mg, 0.0500 mmol) in benzene–dioxane (1:2, 1.5 mL) over a period of 0.5 h at reflux temperature (argon atmosphere), and the reaction mixture was refluxed with stirring for 5 min. To the resulting suspension was then added $(CuOTf)_2$-benzene (50 mg, 0.0993 mmol) in dioxane (1.5 mL) over a period of 0.5 h at reflux temperature. After being stirred at the same temperature for 10 min, the reaction mixture was cooled to room temperature and quenched with pH 7 phosphate buffer (4 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine. Concentration of the dried solvent ($Na_2SO_4$) afforded a pale brown oil, which was purified by silica gel column chromatography (ethyl acetate–hexane, 1:1) to give **2** as a yellow oil (15.8 mg, 52%) and **14** (4.0 mg, 19%) as colorless needles.

(11) A general procedure follows: To a stirred suspension of **15** (22.0 mg, 0.0662 mmol), $CaCO_3$ (26.5 mg, 0.265 mmol), and phenyl disulfide (17.4 mg, 0.0795 mmol) in THF–dioxane (1:1, 1.8 mL) was gradually added $(CuOTf)_2$-benzene (20.0 mg, 0.0397 mmol) in THF–dioxane (1:1, 1.2 mL) over a period of 0.5 h at reflux temperature (argon atmosphere). After being stirred for 1.8 h under the same conditions, the reaction mixture was cooled to room temperature and quenched with pH 7 phosphate buffer (3 mL). The aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with brine. Concentration of the dried solvent ($Na_2SO_4$) afforded a pale brown oil, which was purified by silica gel column chromatography (ethyl acetate–hexane, 1:1) to give **2** (21.4 mg, 88%) as a yellow oil and **14** (0.5 mg, 3%) as colorless needles.