The Journal of
Organic
Chemistry

VOLUME 54, NUMBER 15 JULY 21, 1989

Communications

Use of Copper(I) Trifluoromethanesulfonate in β-Lactam Synthesis

Nobuhide Miyachi, Fuyuko Kanda, and Masakatsu Shibasaki*

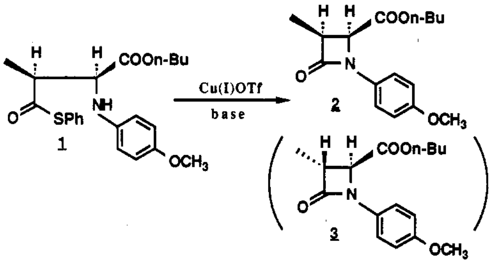
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Received March 7, 1989

Summary: β-Amino thiol esters and β-9-borabicyclo[3.3.1]nonylamino thiol esters were converted to corresponding β-lactams in excellent yields without any epimerization by treatment with Cu(I)OTf and $CaCO_3$ in refluxing toluene or dioxane. And the β-amino thiol ester **21** was transformed into the β-lactam **22** in one pot (55%) just by heating with Cu(I)OTf and $CaCO_3$ in dioxane.

Sir: In recent years metal enolate–imine condensation reactions have been demonstrated to be a useful strategy for the synthesis of β-lactams. Of these reactions the boron enolate–imine[1a–f] and the tin(II) enolate–imine condensation reactions[1g–i] seem to be particularly serviceable in terms of their generality and high stereoselectivity. These coupling reactions, however, result in formation of β-amino thiol esters in good yields without producing β-lactams directly, thus requiring an additional β-lactam-forming reaction. β-Amino thiol esters are generally converted to β-lactams by hydrolysis of a thiol ester followed by Ohno's β-lactam-forming reaction,[2] making those coupling reactions for β-lactam synthesis less efficient. In this paper we report a highly efficient method for the synthesis of β-lactams from either β-amino thiol esters or β-9-borabicyclo[3.3.1]nonylamino thiol esters as well as a one-pot synthesis of the β-lactam **22** from **21**.

Scheme I



We envisioned that safe and cheap Cu(I)OTf[3] with soft acidity would be a useful reagent for the construction of

---

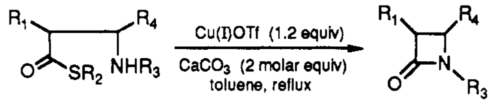
(1) For boron enolates, see: (a) Ohtsuka, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. *Tetrahedron Lett.* **1981**, *22*, 2109. (b) Iimori, T.; Shibasaki, M. *Ibid.* **1985**, *26*, 1523. (c) *Ibid.* **1986**, *27*, 2149. (d) Iimori, T.; Ishida, Y.; Shibasaki, M. *Ibid.* **1986**, *27*, 2153. (e) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488. (f) Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409. For tin(II) enolates, see: (g) Mukaiyama, T.; Suzuki, H.; Yamada, T. *Chem. Lett.* **1986**, 915. (h) Yamasaki, N.; Murakami, M.; Mukaiyama, T. *Ibid.* **1986**, 1013. (i) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Ibid.* **1987**, 293. For zirconium enolates, see: (j) Iwasaki, G.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 3257. For lithium enolates, see: (k) Ha, D.-C.; Hart, D. J.; Yang, T.-K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. (l) Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647. (m) Georg, G. I.; Gill, H. S. *J. Chem. Soc., Chem. Commun.* **1985**, 1433. (n) Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, *26*, 937. (o) Hatanaka, M.; Nitta, H. *Ibid.* **1987**, *28*, 69. For aluminum enolates, see: (p) Iwasaki, G.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 3257. (q) Wada, M.; Aiura, H.; Akiba, K. *Ibid.* **1987**, *28*, 3377. For zinc enolates, see: (r) Iwasaki, G.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 3257. (s) Steen, F. H.; Jastrzebski, J. T. B. H.; Koten, G. *Ibid.* **1988**, *29*, 2467. (t) Oguni, N.; Ohkawa, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1376. For silyl enol ethers, see: (u) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643. (v) Ikeda, K.; Achiwa, K.; Sekiya, M. *Ibid.* **1983**, *24*, 913.

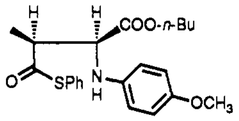
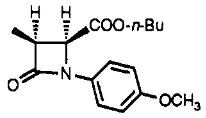
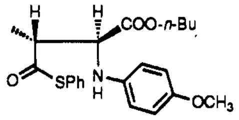
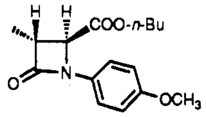
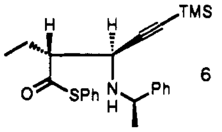
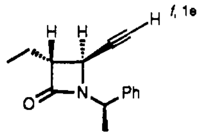
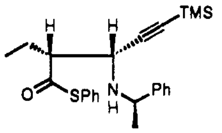
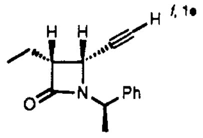
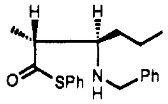
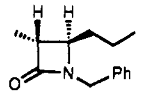
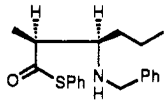
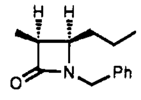
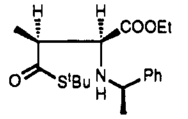
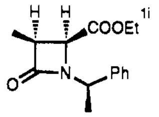
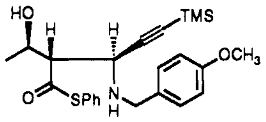
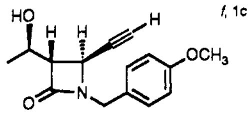
(2) $Hg(OCOCF_3)_2$ was used for the direct synthesis of β-lactams from β-amino thiol esters by Mukaiyama. Unfortunately, this reagent is highly toxic. See: Mukaiyama, T.; Suzuki, H.; Yamada, T. *Chem. Lett.* **1986**, 915. Also *tert*-butylmagnesium chloride was used for the direct synthesis of β-lactams from β-amino thiol esters in our laboratories. This method, however, gives β-lactams in rather low yields (e.g. 7 → 8, 23%). See: Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488.

(3) Cu(I)OTf was first prepared by Salomon and Kochi. See: (a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889. For application to organic synthesis, see: (b) Salomon, R. G.; Folting, K.; Streib, W. E.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 1145. (c) Cohen, T.; Kuhn, D.; Falck, J. R. *Ibid.* **1975**, *97*, 4749. (d) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218. (e) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861. (f) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garrey, D. S. *Ibid.* **1981**, *103*, 1568. (g) Raychandhuri, S. R.; Ghash, S.; Salomon, R. G. *Ibid.* **1982**, *104*, 6841.

0022-3263/89/1954-3511$01.50/0

Table I. Synthesis of β-Lactams from β-Amino Thiol Esters by Cu(I)OTf



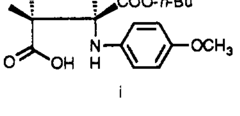
entry	β-amino thiol ester	reaction time, h	product	yield, %
1	 **1**	1.5[a]	 **2**	80[g]
2	 **4**	1.5[a,e]	 **3**	82[g]
3	 **5**	0.7[b]	 **6**	89[h]
4	 **7**	0.6[c]	 **8**	87[h]
5	 **9**	0.5[c]	 **10**	92[g]
6	 **11**	0.5[c]	 **12**	85[g]
7	 **13**	2.4[d]	 **14**	86[h]
8	 **15**	0.4[c]	 **16**	67[h]

[a] Cu(I)OTf was added over a period of 1 h. [b] Cu(I)OTf was added over a period of 0.5 h. [c] Cu(I)OTf was added over a period of 0.25 h. [d] Cu(I)OTf was added over a period of 2 h. [e] Dioxane was used as a solvent. [f] A mixture of the products was treated with n-Bu$_4$NF. [g] Racemic compound was used. [h] Optically active compound was used.

β-lactams from β-amino thiol esters. Thus, (±)-β-amino thiol ester **1** prepared by the boron enolate–imine condensation reaction was treated with Cu(I)OTf (1.2 equiv) and diisopropylethylamine (2 equiv) in refluxing toluene for 26 h, giving the *cis*-β-lactam **2** (57%), R_f value 0.33, silica gel plate, AcOEt–hexane (1:6), two developments, and the *trans*-β-lactam **3** (5%), R_f value 0.39, silica gel plate, AcOEt–hexane (1:6), two developments, together with recovery of the starting β-amino thiol ester **1** (16%) (Scheme I). In order to improve the efficiency of the present reaction many experiments were carried out, and finally we have found that use of CaCO$_3$ (2 molar equiv) instead of diisopropylethylamine provides the satisfactory result, giving only the *cis*-β-lactam **2** (80%) in a short reaction time.[4] We then investigated the scope and limitations of the present methodology for the β-lactam synthesis. The results are summarized in Table I.[5] As shown

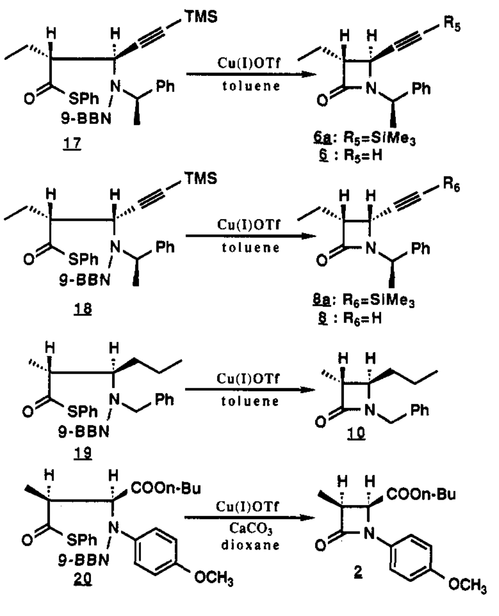
---

[4] Use of CaCO$_3$ gave **2** (27%), **3** (27%), and **i** (48%), and use of K$_2$CO$_3$ afforded **2** (78%) and **3** (4%).

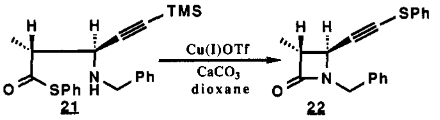


i

Scheme II



Scheme III



in Table I, all the β-amino thiol esters investigated were transformed into the corresponding β-lactams[7] in good to excellent yields without any epimerization of an asymmetric carbon,[8] thereby making the metal enolate–imine condensation methodology for the β-lactam synthesis more efficient. It is noteworthy that the β-lactams **6** and **16** have been already demonstrated to be useful intermediates for PS-5, thienamaycin, and 1β-methylcarbapenem antibiotics.[1b,c,e,f]

Occasionally, hydrolysis of β-9-borabicyclo[3.3.1]-nonylamino thiol esters, such as **17**, **18**, **19**, and **20**, formed by the boron enolate–imine condensation reaction, to β-amino thiol esters requires rather drastic reaction conditions to result in formation of epimerized β-amino thiol esters.[9] It was expected that these stable β-9-borabicyclo[3.3.1]nonylamino thiol esters would be also converted to the β-lactams directly without any epimerization just by treatment with Cu(I)OTf. Indeed, the β-9-borabicyclo[3.3.1]nonylamino thiol esters **17**, **18**, and **19** purified by silica gel column chromatography were treated with Cu(I)OTf (1.2 equiv) in refluxing toluene, providing **6** (83%),[10] 8 (82%),[10] and **10** (85%), respectively.[11] On the other hand, conversion of **20** to **2** (58%) was best carried out by treatment of Cu(I)OTf (1.2 equiv) and $CaCO_3$ (2 molar equiv) in refluxing dioxane.[12] Thus, a much more efficient method for the synthesis of β-lactams using boron enolates and imines has been established.

It is interesting to note that treatment of **21** with Cu(I)OTf (1.2 equiv) and $CaCO_3$ (2 molar equiv) in refluxing dioxane for 5 h afforded the alkynylphenyl sulfide **22** in one pot (55%)[13] (Scheme III). Since alkynylphenyl sulfides of type **22** are useful intermediates for the synthesis of carbapenems,[14] the present reaction has opened a new and efficient way to carbapenem antibiotics. Although the real mechanism of the above reaction is not clear at present, it appears that the copper acetylide formed by Cu(I)OTf plays a key role.[15]

In conclusion, Cu(I)OTf has been found to be an extremely useful reagent for the synthesis of various β-lactams, making the metal enolate–imine condensation reactions for β-lactams much more efficient. Further studies along this line are in progress.

Acknowledgment. Financial support of this project was provided by CIBA-GEIGY Foundation for the Promotion of Science and Takeda Science Foundation.

Supplementary Material Available: Spectral data for compounds 2, 3, 10, 12, and 22 (2 pages). Ordering information is given on any current masthead page.

---

(5) A general procedure follows. To a stirred suspension of **9** (27.4 mg, 0.0837 mmol) and $CaCO_3$ (16.8 mg, 0.167 mmol) in toluene (2.3 mL) was gradually added a suspension of Cu(I)OTf (25.2 mg, 0.1004 mmol) in toluene (1.6 mL) over a period of 0.25 h at refluxing temperature (argon atmosphere). The whole reaction mixture was refluxed with stirring for an additional 0.25 h, quenched with pH 7 phosphate buffer, extracted with AcOEt, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (AcOEt–hexane, 1:3) to give **10** (16.7 mg, 92%) as a colorless oil.

(6) Prepared by the condensation reaction of the boron enolate with the imine derived from 3-(trimethylsilyl)-2-propynal and (*R*)-α-methylbenzylamine followed by acidic hydrolysis. In the paper (*J. Org. Chem.* **1987**, *52*, 3488) we have described (*S*)-α-methylbenzylamine mistakenly.

(7) Authentic samples were prepared according to the literature,[1c,i,e] and their structure was unequivocally determined based on ^{1}H NMR (270 MHz), IR, and MS spectral data. Furthermore, the structure of the new compounds was determined from ^{1}H NMR (270 MHz), IR, MS, and HR-MS spectra as described in the supplementary material.

(8) Stereochemical homogeneity was determined from the ^{1}H NMR (270 MHz) spectrum and the TLC analysis.

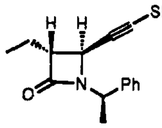
(9) Hydrolysis of a mixture of **17** and **18** (5.8:1) with concentrated HCl in ether–MeOH (2.2:1, 25 °C, 5 h) gave the anti isomer and the syn isomer in a ratio of 5.2:1–2.2:1. In general, β-9-borabicyclo[3.3.1]nonylamino thiol esters are too unstable to be purified by silica gel column chromatography.

(10) A mixture of **6a** (20%) and **6** (63%) was formed, and also a mixture of **8a** (41%) and **8** (41%) was obtained.

(11) A general procedure follows. To a stirred solution of **17** (54.7 mg, 0.103 mmol) in toluene (2.9 mL) was gradually added a suspension of Cu(I)OTf (30.4 mg, 0.121 mmol) in toluene (1.9 mL) over a period of 0.25 h at refluxing temperature (argon atmosphere). The whole reaction mixture was refluxed with stirring for an additional 0.33 h, quenched with pH 7 phosphate buffer, extracted with AcOEt, and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (AcOEt–hexane, 1:7) to give **6a** (6.0 mg, 20%) as a colorless oil and **6** (14.5 mg, 63%) as a colorless oil.

(12) The conditions [Cu(I)OTf in refluxing toluene] gave **2** (11%). On the other hand, the conditions [Cu(I)OTf and $CaCO_3$ in refluxing toluene] afforded **2** (26%).

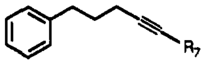
(13) Although the yield is not optimized, **5** was also converted to ii in one pot (34%) under the same reaction conditions.



ii

(14) Maruyama, H.; Shiozaki, M.; Oida, S.; Hiraoka, T. *Tetrahedron Lett.* **1985**, *26*, 4521. Maruyama, H.; Hiraoka, T. *J. Org. Chem.* **1986**, *51*, 399.

(15) A suspension of iii and CuSPh (1.2 equiv) in dioxane was refluxed with stirring for 4 h. However, none of iv was formed. On the other hand, a solution of iii, CuSPh (1.2 equiv) and Cu(I)OTf (2 equiv) in dioxane was refluxed with stirring for 1 h, affording iv in 53% yield.



iii: R_7 = $SiMe_3$
iv: R_7 = SPh