Pergamon

Tetrahedron Letters, Vol. 37, No. 33, pp. 5967-5970, 1996

0040-4039/96 \$15.00 + 0.00

PII: S0040-4039(96)01289-0

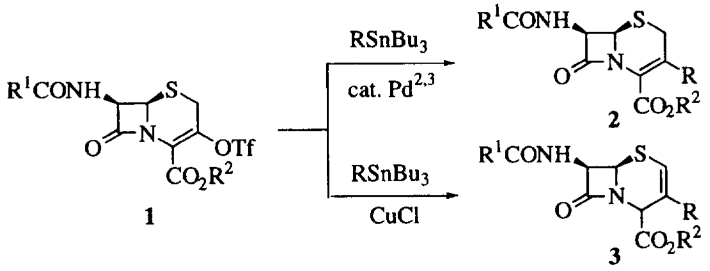
Synthesis of 3-Alkenyl-Δ^2-cephems by Copper(I) Chloride-Promoted Alkenylation of 3-Trifluoromethylsulfonyloxy-Δ^3-cephem with Alkenyltributyltins

Hideo Tanaka, Shin-ichi Sumida, and Sigeru Torii*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima-Naka, Okayama, 700, Japan

***Abstract*:** Synthesis of 3-alkenyl-Δ^2-cephems **3** was performed in regioselective manner by copper(I) chloride-promoted alkenylation of 3-trifluoromethylsulfonyloxy-Δ^3-cephem **1** with alkenyltributyltins. Subsequent Diels-Alder reaction of the 3-vinyl-Δ^2-cephem **3a** with acrolein opened a new access to C(2)-C(3) fused tricyclic cephalosporin **9**. Copyright © 1996 Elsevier Science Ltd

Palladium-catalyzed cross-coupling reaction of alkenyl halides or triflates with organotin compounds, the so-called Stille coupling[1], has been well recognized to offer a promising methodology for stereoselective synthesis of substituted alkenes. Farina[2] and Munroe[3] reported a straightforward synthesis of 3-alkenyl-Δ^3-cephems **2** through the palladium-catalyzed Stille cross-coupling reaction of the 3-trifluoromethylsulfonyloxy-Δ^3-cephems (triflate) **1** with organotin compounds. It is known that the presence of copper(I) salts in the Stille coupling dramatically enhances the reaction rate.[4,5] On the other hand, our group[6], Kyler[7], Piers[8], Quayle[9], Takeda[10], and Falck[11] independently reported that some intra- and inter-molecular Stille-type coupling reactions could be performed by the aid of copper(I) salt alone without palladium catalysts. In this connection, we investigated copper(I) chloride-promoted alkenylation of the triflate **1** with alkenyltributyltins and found that the reaction proceeded in a different fashion to give Δ^2-isomers **3**, exclusively (Scheme 1). Herein, we describe the copper(I) chloride-promoted alkenylation of the triflate **1** together with further transformation of the resulting 3-vinyl-Δ^2-cephem **3a**, opening a new synthetic route to C(2)-C(3) fused tricyclic cephalosporin **9**.



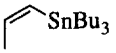
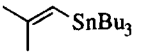
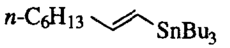
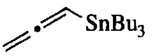
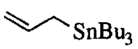
$R^1 = PhCH_2$
$R^2 = p\text{-}MeOC_6H_4CH_2$
R = Alkenyl, Allyl etc

Scheme 1

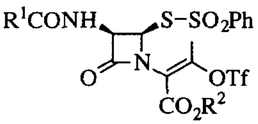
Upon treatment of **1**[12] with tributylvinyltin (1.5 equiv.) in *N*-methylpyrrolidone (NMP) in the presence of copper(I) chloride (1.5 equiv.) at ambient temperature for 6 h, 3-vinyl-Δ^2-cephem **3a** (R = vinyl) was obtained in 74% yield without any detectable amount of 3-vinyl-Δ^3-cephem **2a** (R = vinyl). The presence of copper(I) chloride is indispensable since the lack of copper(I) chloride resulted in the recovery of **1** (91%). In place of copper(I) chloride, copper(II) chloride was also used effectively to give **3a** in 65% yield, while $AgNO_3$ and $NiCl_2(bpy)$ could not effect the coupling reaction, resulting in the recovery of **1** in 76 and 81% yields, respectively. Isomerization of 3-vinyl-Δ^3-cephem **2a** into the Δ^2-isomer **3a** did not occur under identical conditions, suggesting that the Δ^3-cephem **2a** is a primary product and not a secondary product derived from isomerization of the Δ^2-isomer **3a**.

The copper(I) chloride-promoted alkenylation of the triflate **1** with other alkenyltins was performed in a similar manner to afford the corresponding 3-alkenyl-Δ^2-cephems **3** without any detectable amount of the Δ^3-isomers **2** (entries 2-4 in Table 1). 3-Allenyl- and 3-allyl-Δ^2-cephems **3e** and **3f** were also obtained in 47 and 50% yields, respectively, by use of allenyltributyltin and allyltributyltin (entries 5 and 6).

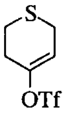
Table 1. Copper(I) Chloride-Promoted Reaction of 3-Trifluoromethylsulfonyloxy-Δ^3-cephem **1** with Various Alkenyltributyltins.

Entry	$RSnBu_3$	Time/h	Isolated Yield/%
1		6	74 (**3a**)
2		7	64 (**3b**)
3		3.5	71 (**3c**)
4		5	51 (**3d**)
5		6	47 (**3e**)
6		4.5	50 (**3f**)

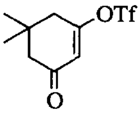
In order to gain a mechanistic insight into the copper(I) chloride-promoted alkenylation, the reaction of alkenyltriflates **4**, **5**, and **6** with tributylvinyltin (1.2 equiv.) in NMP containing copper(I) chloride (1.2 equiv.) was carried out. In all entries, however, no appreciable alkenylation took place, resulting in the recovery of **4** (88%) and **5** (89%) or decomposition of **6**.[13] The failure suggests that the copper(I) chloride-promoted alkenylation reaction is not a simple addition/elimination reaction,[14] and, in turn, leads us to a plausible mechanism involving six-membered allenic compound **7** (Scheme 2).



4

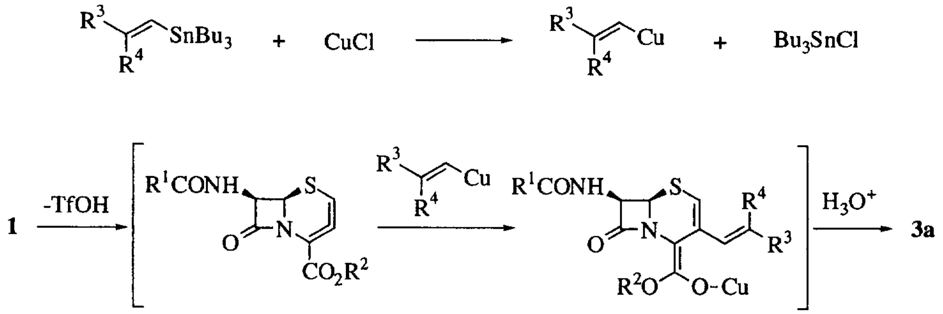


5



6

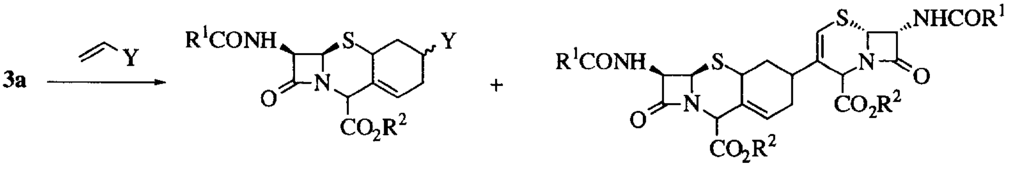
In the initial stage of the reaction, the six-membered allenic intermediate **7** would be formed by 1,2-elimination reaction of the triflate **1**,[15,16] while transmetallation of tributylvinyltin with copper(I) chloride would give a vinylcopper species[5]. In the second stage, Michael addition of **7** with the vinylcopper species would take place to afford the 3-vinyl-Δ^2-cephem **3a** through an intermediate **8** (Scheme 2). The sequential elimination/addition is in accordance with the fact of the exclusive formation of the Δ^2-isomer **3a**.



7 **8**

Scheme 2

Incidentally, C(2)-C(3) fused tricyclic cephalosporins have received considerable attention as a new candidate for β-lactam antibiotics. Procedures explored so far for the formation of the C(2)-C(3) fused ring rely on the Aldol/Wittig reaction of 3'-triphenylphosphonium ylide-Δ^3-cephems with glyoxal[17], Diels-Alder reaction of 2,3-di-*exo*-methylenecephem with dienophiles[18], and [2+2] cycloaddition of *in situ* generated allenic compound **7** with olefins[15]. A new access to the C(2)-C(3) fused tricyclic cephalosporins based on Diels-Alder reaction of **3a** was demonstrated by further transformation of **3a** into **9** (Scheme 3).



9 **10**

Scheme 3

The Diels-Alder reaction of 3-vinyl-Δ^2-cephem **3a** with acrolein (4 equiv.) in dichloromethane at ambient temperature for 21 h afforded the tricyclic cephalosporin **9** (Y = CHO, 77%) together with a dimer **10** (7%). The formation of the dimer **10** was performed more effectively (92%) by heating **3a** alone in dichloromethane at 40 °C for 5 days. These facts suggest that **3a** can work not only as a diene but also as a dienophile in the Diels-Alder reaction. Further application of the alkenyl-Δ^2-cephems **3** to the synthetic useful β-lactam antibiotics is in progress.

We acknowledge financial support by a Grant-in-Aid for Scientific Research (06453140, 05403025) from The Ministry of Education, Science, and Culture of Japan. Thanks are due to the SC-NMR Laboratory of Okayama University for obtaining NMR spectra.

REFERENCES AND NOTES

1. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508-524. Mitchell, T. N. *Synthesis* **1992**, 803-815.
2. Farina, V.; Baker, S. R.; Sapino, C. *Tetrahedron Lett.* **1988**, 29, 6043-6046. Baker, S. R.; Roth, G. P.; Sapino, C. *Synth. Commun.* **1990**, 20, 2185-2189. Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, 55, 5833-5847. Farina, V.; Kant, J. *Synlett* **1994**, 565-574.
3. Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H.; Munroe, J. E. *J. Org. Chem.* **1989**, 54, 5828-5830.
4. Liebeskind, L. S.; Fegel, R. W. *J. Org. Chem.* **1990**, 55, 5359-5364. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, 33, 919-922. Ye, J.; Bhatt, R. K.; Falck, J. P. *J. Am. Chem. Soc.* **1994**, 116, 1-5. For other application of the copper effect", see references cited therein.
5. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, 59, 5905-5911.
6. Tanaka, H.; Kameyama, Y.; Sumida, S-i.; Torii, S. *Tetrahedron Lett.* **1992**, 33, 7029-7030.
7. Ghosal, S.; Luke, G. P.; Kyler, K. S. *J. Org. Chem.* **1987**, 52, 4296-4298.
8. Piers, E.; Wong, T. *J. Org. Chem.* **1993**, 58, 3609-3610. Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, 60, 2322-2323. Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, 37, 1173-1176.
9. Beddoes, R. L.; Cheeseright. T.; Wang, J.; Quayle, P. *Tetrahedron Lett.* **1995**, 36, 283-286.
10. Takeda, T.; Matsunaga, K.; Kabasawa, Y.; Fujiwara, T. *Chem. Lett.* **1995**, 771-772.
11. Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, 117, 5973-5982.
12. Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, 54, 4962-4966.
13. The alkenylation of **4** with tributylvinyltin in the presence of a palladium catalyst afforded the desired coupling compound in 72% yield. Tanaka, H.; Kameyama, Y.; Sumida, S-i.; Shiroi, T.; Sasaoka, M.; Taniguchi, M.; Torii, S. *Synlett* **1992**, 351-353.
14. Kant reported that the addition/elimination reaction of the triflate **1** (R^1 = $PhOCH_2$, R^2 = $CHPh_2$) with various organocuprate afforded 3-alkyl- and 3-alkenyl-Δ^3-cephems **2** (R^1 = $PhOCH_2$, R^2 = $CHPh_2$ R = Alkyl, Alkenyl etc.). Kant, J.; Sapino Jr, C.; Baker, S. R. *Tetrahedron Lett.* **1990**, 31, 3389-3392. Kant, J. *J. Org. Chem.* **1993**, 58, 2296-2301.
15. Elliot, R. L.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1993**, 58, 6954-6955. Elliot, R. L.; Nicholson, N. H.; Peaker, F. E.; Takle, A. K.; Tyler, J. W.; White, J. *J. Org. Chem.* **1994**, 59, 1606-1607.
16. Cainelli, G.; Contento, M.; Panunzio, M.; Sandri, S.; Umani-Ronchi, A.; Col, M. D. *Synlett* **1994**, 243-244.
17. Hatanaka, M.; Yamamoto, Y.; Ishimaru, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1705-1706. Hatanaka, M.; Yamamoto, Y.; Ishimaru, T.; Takai, Y. *Chem. Lett.* **1985**, 183-186.
18. Gunda, T. E.; Kover, K. E. *Liebigs Ann. Chem.* **1991**, 1349-1351.

(*Received in Japan* 29 *May* 1996; *revised* 26 *June* 1996; *accepted* 28 *June* 1996)