Pergamon

Tetrahedron Letters 40 (1999) 1281–1284

TETRAHEDRON LETTERS

Stille Coupling Approaches to the Stereospecific Synthesis of 7-[(*E*)-Alkylidene]cephalosporins

John D. Buynak,* Venkata Ramana Doppalapudi, Mohammed Frotan, and Ramon Kumar

Department of Chemistry, Southern Methodist University, Dallas TX 75275-0314
(e-mail: jbuynak@mail.smu.edu)

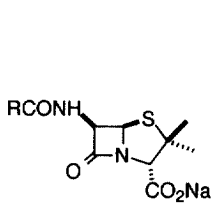
Received 30 October 1998; revised 17 December 1998; accepted 18 December 1998

Abstract

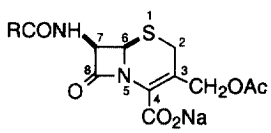
Stille coupling methodology is used to stereospecifically synthesize 7-[(*E*)-alkylidene]cephalosporins, potential enzyme inhibitors which are unavailable *via* other synthetic methodology. Two procedures are described, utilizing either a stannylalkylidene cephem which is then coupled with an organohalide, or a haloalkylidene cephem which is coupled with an organostannane.

Keywords: Tin and compounds, cephalosporins, penicillins, enzyme inhibitors

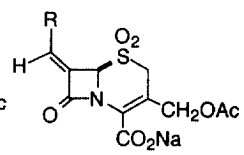
The most common mechanism whereby bacteria develop resistance to β-lactam antibiotics is the acquisition of the ability to produce β-lactamase, which hydrolytically destroys penicillins (**1**) and cephalosporins (**2**). Fortunately, inhibitors of β-lactamase, such as clavulanic acid, sulbactam, and tazobactam, can be coadministered with β-lactam antibiotics to defeat many resistant strains. We recently reported excellent β-lactamase inhibitory activity associated with the cephalosporin-derived compounds **3** (R = α-pyridyl) and **4** (R = COO-*t*-Bu).[1] **3** displays excellent selective inhibition of the class C lactamases, which prefer cephalosporins as substrates, while **4** inhibits the class A enzymes which prefer penams. Other α-alkylidene-β-lactams which have displayed inhibitory activity include penams, such as **5** (R = α-pyridyl)[2] and **6** (R = COONa),[3] as well as the penem **7**.[4,5] We have reported that selected 7-alkylidenecephalosporin esters are inhibitors of human leukocyte elastase, an enzyme which is overactive in selective disease states, including emphysema and rheumatoid arthritis.[6]



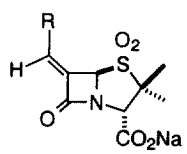
1



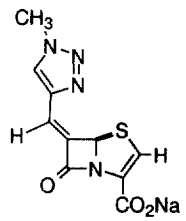
2



3, 4



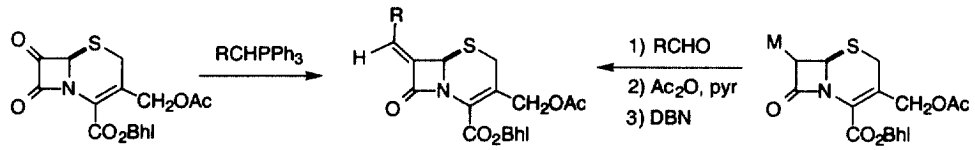
5,6



7

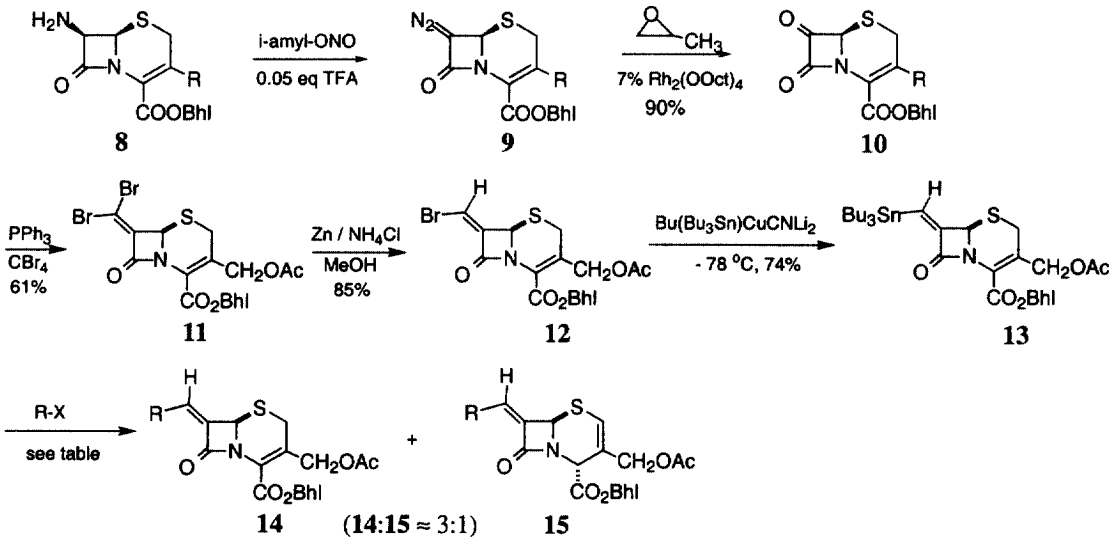
0040-4039/99/$ - see front matter
PII: S0040-4039(98)02691-4

As shown, available synthetic methodology for the preparation of α-alkylidene-β-lactams includes two methods: 1) a Wittig reaction on the corresponding (penam or cephem-derived) α-oxo-β-lactam, or 2) a reaction of the α-metallated-β-lactam with an appropriate aldehyde or ketone, followed by elimination. In either case, the predominant (and, in many cases, selective) stereochemical geometry of the product alkene is *Z*. The aldol method is preferable for the preparation of libraries of potential inhibitors due to the commercial availability of diverse aldehydes and ketones (as contrasted to the need for the Wittig reagents to be individually prepared). The aldol approach can be reasonably synthetically efficient for penams.[7,8] However, in both the cases of the penems[9] and the cephalosporins[10] the requisite anions are difficult to prepare, relatively unstable, and the yields usually poor.



In connection with our inhibitor discovery program, we desired a method for the rapid preparation of potential alkylidene inhibitors. Ideally, this would be achieved by utilizing a single, readily accessible, reactive, β-lactam-containing intermediate which could then be coupled with a commercially available collection of compounds in a stereocontrollable fashion. To expedite the synthesis of new compounds, it would be useful if the new methodology produced stereoisomers different from those available from current methodology. The Stille coupling provides an excellent opportunity for the facile coupling of diverse aryl and vinyl halides with tin-containing substrates.[11] It has already found utility in the preparation of 3-substituted cephems.[12] We now report its usefulness in the preparation of 7-[(*E*)-alkylidene]cephalosporins.

As shown, we have recently reported a mild and efficient method for the preparation of 7-oxocephalosporinate, **10**, from 7-ACA (**8**).[13] This ketone can be converted to the dibromomethylidene cephalosporin, **11**, which can be stereospecifically reduced to the *E*-monobromide **12**.[1] This bromide can then be transformed into vinylstannane **13** by the use of the Lipshutz higher order cuprate.[14,15] Under very mild conditions, this stannane can be stereospecifically coupled with representative aryl and vinyl halides as shown in Table 1.



The reaction is completely stereospecific, with retention of configuration at the 7'-position. However, it is complicated by a concurrent partial isomerization of the dihydrothiazine double bond from the Δ-3,4 (cephalosporin numbering) to the Δ-2,3 position, in each case forming a nearly identical (*ca.* 3:1) mixture of **14** and **15** as shown. The product mixture is, fortunately, shifted quantitatively to the side of the Δ-3,4-isomer upon oxidation to the sulfone (the actual β-lactamase inhibitors are all sulfones). This well known isomerization of cephalosporin sulfides can also be catalyzed by traces of base.[16] In the case of the cephalosporin antibiotics (sulfides), the undesired Δ-2,3 isomer is often removed by the oxidation of the sulfur to the sulfoxide, followed by a subsequent reduction to the sulfide.

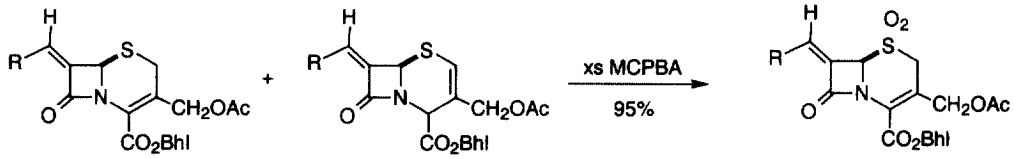
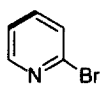
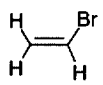
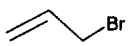
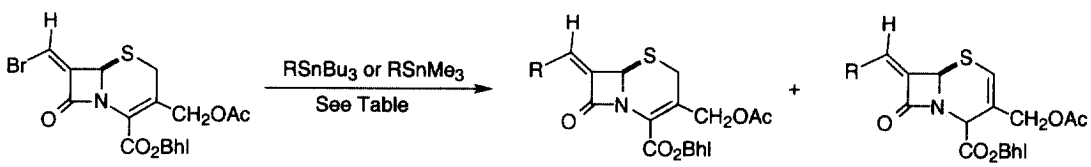


Table 1. Stille coupling of 7-[(*E*)-tributylstannylmethylidene]cephalosporin (**13**) with selected organohalides.

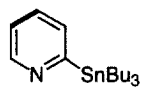
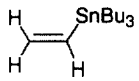
entry	R-X	Conditions	Yield (**14**:**15** ≈ 3:1)
1	Ph-I	10% $Pd_2(dba)_3$, DMF, RT, 6h	92%
2		10% $Pd_2(dba)_3$, DMF, RT, 6h	72%
3		10% $Pd_2(dba)_3$, DMF, RT, 2.5h	87%
4		10% $Pd_2(dba)_3$, DMF, RT, 2h	74%
5		10% $Pd(PPh3)_4$, THF, 70 °C	78%

As an alternative approach, the monobromide **12**, itself, could be coupled with selected organostannanes to produce similar products. The use of hexamethydistannane in this coupling (entry 4) itself represents a convenient alternative to the Lipshutz reagent reported above for the generation of *E*-trialkylstannanes, such as **13**.

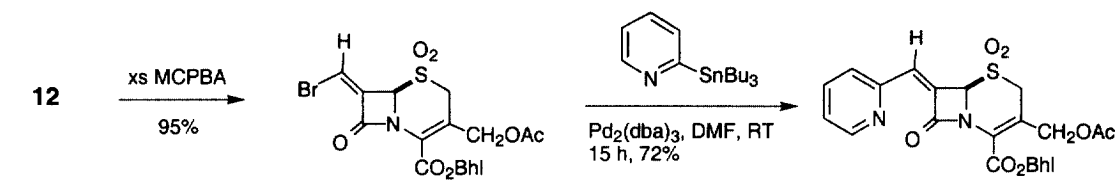


12 **14** (**14**:**15** ≈ 3:1) **15**

Table 2. Stille coupling of 7-[(*E*)-bromomethylidene]cephalosporin (**12**) with selected organostannanes.

Entry	Stannane	Conditions	Yield (**14**:**15** ≈ 3:1)
1	Ph-$SnMe_3$	10% $Pd_2(dba)_3$, DMF, RT, 6h	81%
2		10% $Pd_2(dba)_3$, DMF, RT, 15h	75%
3		10% $Pd_2(dba)_3$, DMF, RT, 15h	80%
4	$Me_3SnSnMe_3$	10% $Pd_2(dba)_3$, DMF, RT, 1h	90%

As shown below, **12** can also be oxidized to its corresponding sulfone, **16**, which is also a suitable partner in the Stille coupling.



16

Acknowledgment. We thank the Robert A. Welch Foundation and the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References

1 Buynak, J. D.; Wu, K.; Bachmann, B.; Khasnis, D.; Hua, L.; Nguyen, H. K.; Carver, C. L. *J. Med. Chem.* **1995**, *38*, 1022-1034.
2 Chen, Y. L.; Chang, C. W.; Hedberg, K.; Guarino, K.; Welch, W. M.; Kiessling, L.; Retsema, J. A.; Haskell, S. L.; Anderson, M.; Manousos, M.; Barrett, J. F. *J. Antibiot.* **1987**, 803-822.
3 Buynak, J. D.; Geng, B.; Bachmann, B.; Hua, L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1513-1518.
4 Farmer, T. H.; Page, J. W.; Payne, D. J.; Knowles, D. J. C. *Biochem. J.* **1994**, *303*, 825-830.
5 For other examples of penem-derived lactamase inhibitors, see: Philips, O. A.; Czajkowski, D. P.; Spevak, P.; Singh, M. P.; Hanehara-Kunugita, C.; Hyodo, A.; Micetich, R. G.; Maiti, S. N. *J. Antibiot.* **1997**, *50*, 350-356.
6 Buynak, J. D.; Rao, A. S.; Ford, G. P.; Carver, C.; Adam, G.; Geng, B.; Bachmann, B.; Shobassy, S.; Lackey, S. *J. Med. Chem.* **1997**, *40*, 3423-3433.
7 Brown, B. B.; Volkmann, R. A. *Tetrahedron Lett.* **1986**, *27*, 1545-1548.
8 Aimetti, J. A.; Kellogg, M. S. *Tetrahedron Lett.* **1979**, 3805-3808.
9 Osborne, N. F.; Broom, N. J. P.; Coulton, S.; Harbridge, J. B.; Harris, M. A.; Stirling-Francois, I.; Walker, G. *J. Chem. Soc. Chem. Commun.* **1989**, 371-373.
10 DiNinno, F.; Beattie, T. R.; Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960-2965.
11 Farina, V; Krishnamurthy, V.; Scott, W. J. in Organic Reactions; Paquette, L. A., Ed.; Wiley: New York, **1979**, Vol. 50, 1-651.
12 Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833-5847.
13 Buynak, J. D.; Rao, A. S.; Nidamarthy, S. D. *Tetrahedron Lett.* **1998**, *39*, 4945-4946.
14 Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065-2068.
15 Jarosz, S. *Tetrahedron Lett.* **1996**, *37*, 3063-3066.
16 Murphy, C. F.; Webber, J. A. In *Cephalosporins and Penicillins, Chemistry and Biology*; Flynn, E. H. Ed.; Academic Press: New York, **1972**; pp 171-176.