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Coupling Reactions of Cephalosporin Sulfones: A Stable 3-Stannylated Cephem

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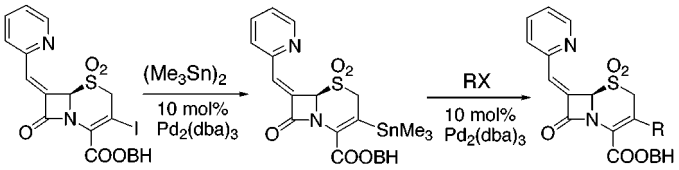
ABSTRACT



The first stable 3-metalated cephalosporin is reported and shown to be an excellent synthetic precursor to a number of prospective *β*-lactamase inhibitors.

One highly effective method for countering antibiotic-resistant microorganisms is the co-administration of an antibiotic and a *β*-lactamase inhibitor.[1] *β*-Lactamase represents a collection of bacterial enzymes (classes A, B, C, and D) that effectively hydrolyze *β*-lactam antibiotics. Historically, the most clinically important of these were the plasmid-mediated class A enzymes.[2] However, in recent years, bacterial resistance mediated by class B, C, and D enzymes has become increasingly significant.[3] Current commercial inhibitors target only class A *β*-lactamases.[1] Our group has recently described classes of compounds that simultaneously inhibit both class A and class C *β*-lactamases.[4] We have designed new inhibitors both of the penicillin and of the cephalosporin skeleton. Unlike the corresponding penicillin and cephalosporin antibiotics, however, these new compounds have the sulfur in the sulfone oxidation state and have an alkylidene side chain in place of the more common acylamido side chain at C6 (penam) or C7 (cephem). Some examples are shown in Figure 1.

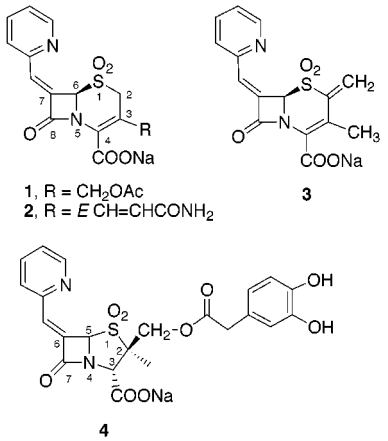


Figure 1. Representative *β*-lactamase inhibitors containing an α-alkylidene-*β*-lactam substructure.

We have recently reported crystallographic evidence that these altered structural features are mechanistically important to the inhibition, leading to the production of a stabilized

(1) Maiti, S. N.; Phillips, O. A.; Micetich, R. G.; Livermore, D. M. *Curr. Med. Chem.* **1998**, *5*, 441−456.
(2) Bush, K.; Mobashery, S. Resolving the Antibiotic Paradox. *Adv. Exp. Med. Biol.* **1998**, *456*, 71−98.
(3) Medeiros, A. A. *Clin. Infect. Dis.* **1997**, *24* (Suppl. 1), S19−S45.
(4) a) Buynak, J. D.; Wu, K.; Bachmann, B.; Khasnis, D.; Hua, L.; Nguyen, H. K.; Carver, C. L. *J. Med. Chem.* **1995**, *38*, 1022−1034. (b) Buynak, J. D.; Rao, A. S.; Doppalapudi, V. R.; Adam, G.; Nidamarthy, S. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1997−2002. (c) Buynak, J. D.; Doppalapudi, V. R.; Rao, A. S.; Nidamarthy, S. D.; Adam, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 847−851. (d) Buynak, J. D.; Doppalapudi, V. R.; Adam, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 853−857.

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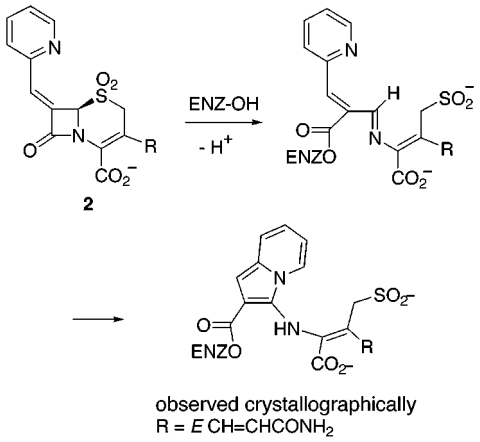
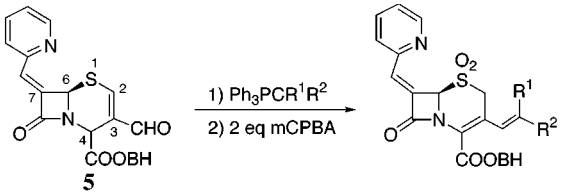
acyl-enzyme after reaction with the active site serine hydroxyl as shown in Scheme 1.[5]

Scheme 1. Mechanistic Pathway Leading to a Stabilized Acyl Enzyme Intermediate



In the process of preparing these new inhibitors, it became necessary for us to devise methodology for the synthesis of C3 functionalized cephalosporins. In particular, we desired a method for the preparation of a structurally diverse collection of side chains from an appropriate late-stage C3-substituted synthetic precursor. As shown in Scheme 2, we

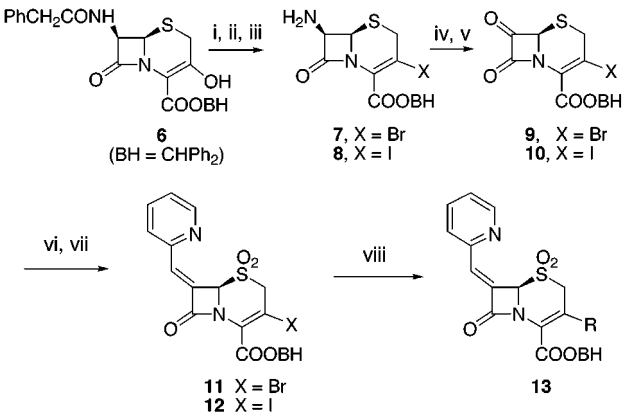
Scheme 2. Previous Route to 3-Substituted 7-Alkylidenecephem Sulfones



had earlier reported a route to such compounds employing aldehyde **5**.[4d] However, the suitability of this earlier route to the preparation of libraries of inhibitors is limited by both the unexpectedly low reactivity of aldehyde **5** and the need for the use of a separate Wittig reagent in the preparation of each new inhibitor.

Farina had earlier reported the synthesis of substituted cephalosporins through a versatile Stille-coupling of the 3-position cephalosporin triflates with organostannanes.[6] Effective utilization of such a catalytic coupling in the generation of new β-lactamase inhibitors in this series of molecules would require an appropriately C3 functionalized cephalosporin. The commercially available[7] 3-hydroxycephem **6** seemed a promising precursor for the generation of such materials. Reasoning that it was probably not possible to subject a reactive C3 triflate to the reaction conditions needed to prepare the appropriate C7 alkylidene analogues, we initially attempted to use O-protected derivatives. However, we found that such intermediates were prone to double bond isomerization (i.e., migration of the double bond from the Δ-3,4 position to the Δ-2,3 position), and we settled on the 3-halocephalosporin sulfones as potential alternatives. Our synthesis of key precursors **11** and **12** is shown in Scheme 3.

Scheme 3. New Synthetic Route Employing 3-Halo-7-alkylidenecephem Sulfones[a]



[a] Reagents: (i) Tf_2O, DIPEA, DCM −78 °C, 85%; (ii) LiBr or LiI (2.5 equiv), THF, rt 36 h, 88% or 72%; (iii) PCl_5, py, DCM/MeOH, 0 °C, 74%; (iv) *i*-prONO, cat. TFA, EtOAc; (v) propylene oxide, cat. $Rh_2(OOct)_4$, C_6H_6; (vi) α-py-CH_2-PPh_3Cl, KO-*t*-Bu, THF/DCM (30% overall for steps iv, v, and vi); (vii) MCPBA (2.5 equiv), DCM, rt, 30 min, 90%; (viii) R'_3SnR, cat. $Pd_2(dba)_3$, DMF or THF (see Table 1).

Thus the enol **6** was readily converted to the corresponding triflate using triflic anhydride in the presence of Hunig's base. Subsequent treatment of the triflate with anhydrous LiX in dry THF produced the corresponding vinyl halides in good yield. Removal of the phenylacetyl group using PCl_5 produced the corresponding amines **7** and **8**, which were then converted to the 7-oxocephalosporins **9** and **10**, respectively, using our reported procedure.[8] These ketones were then used directly in the following Wittig reaction, and the alkylidene products were selectively oxidized to the corresponding sulfones **11** and **12**.

As demonstrated in Table 1, the vinyl iodide **12**, in particular, was an excellent precursor to a number of (previously unavailable) C3-functionalized 7-(*Z*-pyridylmethylidene)cephalosporin sulfones, **13**. As shown by entry 4, we were able to prepare the benzhydryl ester of the 3′*Z* stereoisomer of our highly potent inhibitor **2** from the 3*Z*-

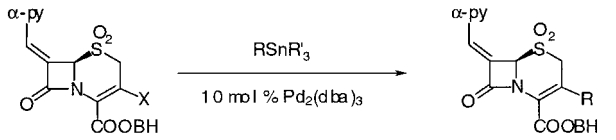
(5) a) Crichlow, G. V.; Nukaga, M.; Buynak, J. D.; Knox, J. R. *Biochemistry* **2001**, *40*, 6233−6239. (b) Strynadka, N.; Buynak, J. D. Unpublished results.

(6) Farina, V.; Baker, S.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 6043−6046. (b) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962−4966.

(7) Otsuka Chemical Co.

(8) Buynak, J. D.; Rao, A. S.; Nidamarthy, S. D. *Tetrahedron Lett.* **1998**, *39*, 4945−4946. Ketones **9** and **10** are not purified because of their instability.

Table 1. Coupling Reactions of **11** and **12** with Organostannanes

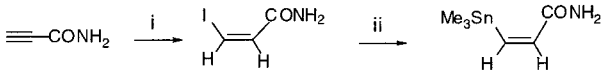


11 (X = Br), **12** (X = I) **13**

entry	X	stannane	product (cmpd #) R	solvent/ time/temp	yield %
1	Br	$SnBu_3$	(**13a**) C_2H_3	DMF/2 h/rt	71
2	I	$PhSnBu_3$	(**13b**) Ph	DMF/2 h/rt	56
3	I	$SnBu_3$	(**13c**) C_4H_3S	DMF/2 h/rt	78
4	I	Me_3Sn $CONH_2$ H H **15**	$CONH_2$ H H (**13d**)	THF/2.5 h / 60 °C	78
5	Br	$(Me_3Sn)_2$	--	DMF/12 h/rt	no rxn
6	I	$(Me_3Sn)_2$	(**13e**) $SnMe_3$	THF/1.5 h/rt	60
7	I	*n*-Bu_3SnOAc	(**13f**) *n*-Bu	DMF/2 h/rt	63
8	I	Bu_3SnSPh	(**13g**) S-Ph	DMF/1 h/rt	72
9	I	$Bu_3SnC{\equiv}CH$	(**13h**) C_2H	DMF/1 h/rt	62

(trimethylstanyl)propenamide **15**, which is itself prepared from 3*Z*-iodopropenamide[9] as shown in Scheme 4.

Scheme 4. Synthesis of 3*Z*-(Trimethylstannyl)-propenamide (**15**)[a]



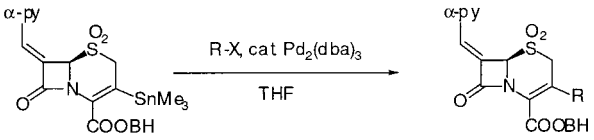
14 **15**

[a] Reagents: (i) LiI, CH_3COOH, 90 °C, 8 h, 85%; (ii) $(Me_3Sn)_2$, 10 mol % $Pd_2(dba)_3$, DMF, rt, 1 h, 59%.

Second, as shown in entry 7, attempted transfer of oxygen from tributyltin acetate instead resulted in the unusually facile transfer of a butyl group from tin to carbon. This result contrasts with a recent report that tributyltin acetate can be an effective reagent for the transfer of acetate to aryl halides.[10] Given the relative ease of migration of the alkyl group in the present case, our results indicate that such trialkyltin esters may be of use in transfer of alkyl groups to other vinylic halides.

Most importantly, coupling of iodide **12** with hexamethyldistannane produced trimethylstannane **13e** as shown in entry 6; **13e** represents the first stable C3 metalated cephem.[11] As shown in Table 2, this stannane is a versatile precursor

Table 2. Coupling Reactions of Stannane **13e** with Organohalides



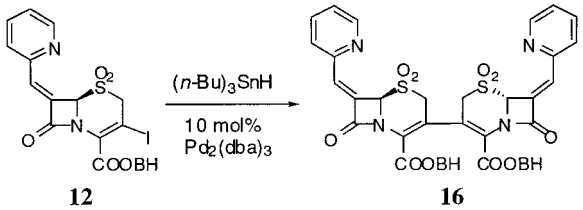
13e

entry	halide	product	product R	time/temp	yield %
1	I	**13a**	C_2H_3	1.5 h / 50 °C	61
2	I-Ph	**13b**	Ph	2 h / 50 °C	55
3	*p*-I-$C_6H_4NO_2$	**13i**	*p*-$C_6H_4NO_2$	2 h / 50 °C	65

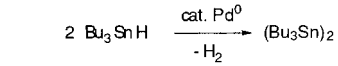
to a number of new cephalosporins. Unlike the vinyl iodide **12** and the C3 cephalosporin triflates, which both must be coupled with organostannanes, the cephalosporin stannane **13e** is suitable for the preparation of a library of prospective inhibitors through coupling with the large number of commercially available vinyl- and arylhalides.

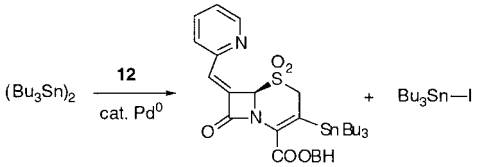
As shown in Scheme 5, an initial attempt to reduce iodide **12** with tributyltin hydride unexpectely resulted in formation of dimer **16**. We believe that this product was produced

Scheme 5. Reaction of **12** with Tributyltin Hydride

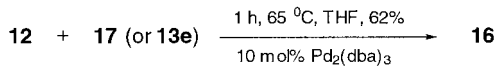


12 **16**





17



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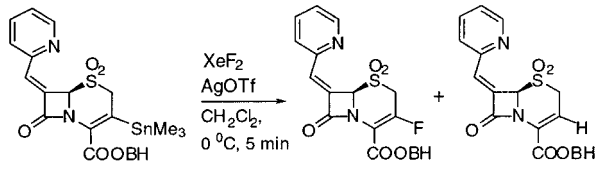
through the intermediacy of the 3-(tributylstanylated)cephem **17**, which itself was likely produced as a result of conversion of the tributyltin hydride to hexabutyldistannane under the influence of the catalyst as shown.[12] In confirmation of this mechanism, we observed that the dimer **16** could also be synthesized through direct coupling of iodide **12** and 3-(trimethylstannanyl)cephem **13e**.

Stannane **13e** also proved to be synthetically useful in the preparation of the 3-fluorocephem **13j** as shown in Scheme 6. Using conditions previously described by Tius in the

Scheme 6. Fluorination of **13e**



13e **13j** **13k**

preparation of unrelated vinyl fluorides,[13] treatment of **13e** with XeF_2 in the presence of silver triflate afforded fluoride **13j** (42%) and reduced compound **13k** (28%).[14] The preparation of 3-fluoro cephems has previously been possible only in extremely low (<5%) yield.[15]

In summary, we have employed organotin reagents to facilitate the preparation of new cephalosporins. In the process, we have described a number of novel and potentially useful synthetic transformations. These include the preparation of Z-vinylstannane **15** and its coupling with **12** to stereospecifically produce **13d**, the rapid transfer of the butyl group from tributyltin acetate, and the preparation of the first 3-stannylcephem, **13e**. This stannylcephem, in turn, was extremely useful in preparing other, previously unavailable, cephalosporins, including cephalosporin dimer **16** and 3-fluorinated cephalosporin **13j**. Stannylcephem **13e** appears well suited to the preparation of cephalosporin-derived β-lactamase inhibitor libraries.

Acknowledgment. We thank the Robert A. Welch Foundation, the Texas Higher Education Coordinating Board, and the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank Otsuka Chemical Co. for a generous gift of compound **6**.

Supporting Information Available: Experimental procedures for the preparation of **13d** and **13e** and spectral data for compounds **12**, **13b**−**h**, **13j**, **13k**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016142V

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(14) The production of **13k** is presumably caused by adventitious amounts of HF in the reaction.

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