CHEMISTRY LETTERS, pp. 1867-1868, 1990.

A Facile Access to 3-Hydroxycephems from Penicillin G through Bi/Sn or Ti/Sn Redox-Promoted Cyclization of 4-(Phenylsulfonylthio)azetidinones[1)]

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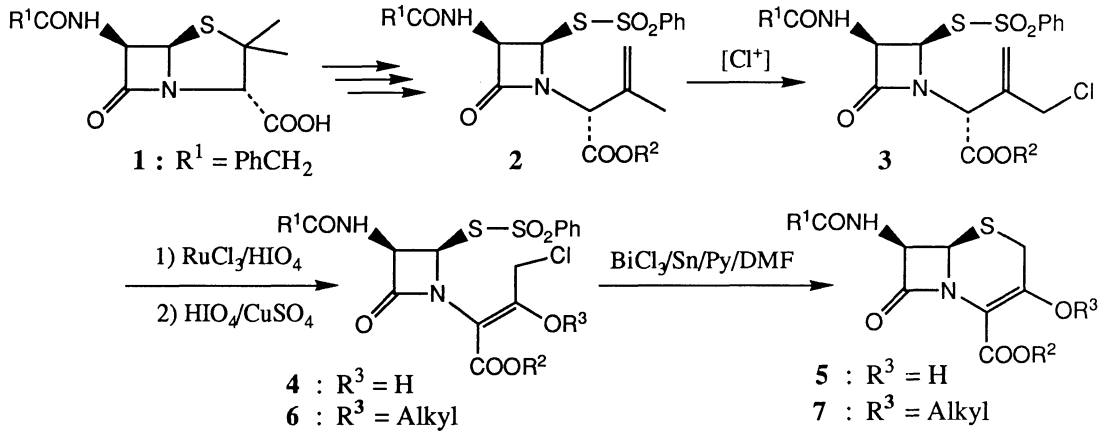
Direct conversion of 1-(3-chloro-2-hydroxy-1-*p*-methoxybenzyloxycarbonyl-1-propenyl)-4-(phenylsulfonylthio)azetidinones derived from penicillin G into 3-hydroxycephems was performed successfully by the action with $BiCl_4$/Sn or $TiCl_4$/Sn bimetal redox couples in DMF containing pyridine.

3-Hydroxycephems **5** are versatile intermediates for the synthesis of a series of orally active cephalosporin antibiotics having hydrogen or hetero atom substituents, *e.g.*, chloro and methoxy groups, attached directly to the C(3)-position of the Δ^3-cephem skeleton.[2)] Synthesis of **5** has been performed by manipulation of the C(3)-acetoxymethyl group of cephalosporanic acid derivatives.[3)] On the other hand, conversion of readily available penicillins **1** into **5** has also been a subject of intensive studies as an economical base.[4)] In the previous papers,[5)] we have reported a straightforward penicillin-cephalosporin conversion involving the ene-type chlorination of azetidinones **2** derived from penicillin **1** leading to **3**. Herein, we describe that the C=C bond fission of thus obtained **3** and subsequent reductive cyclization in a newly devised $BiCl_3$/Sn or $TiCl_4$/Sn bimetal redox system may open a short cut route to the 3-hydroxycephems **5** from **1** (Scheme 1).



Scheme 1.

A typical experimental procedure is as follow: Reaction of **3** (R^2 = *p*-$MeOC_6H_4CH_2$) with $RuCl_3$ (0.03 equiv.) and HIO_4 (2 equiv.) in dioxane/H_2O (2/1) at 15 °C for 1 h and then with HIO_4 (2.1 equiv.) and $CuSO_4$ (2.7 equiv.) in acetone/H_2O (5/2) for 2.5 h afforded enol **4** (80%). Subsequently, a mixture of **4**, $BiCl_3$, and Sn (1: 0.1: 2.5) in DMF containing pyridine (5 vol/vol %) was stirred at room temperature for 2 h. The mixture was poured into aqueous 10% HCl and extractive workup with ethyl acetate followed by column chromatography (SiO_2, MeOH/CH_2Cl_2: 1/100) afforded **5** (85%). In place of the $BiCl_3$/Sn combination, $TiCl_4$/Sn an be used without significant change affording **5** (80%).

The presence of a catalytic amount of $BiCl_3$ or $TiCl_4$ under the combination with tin metal is essential for this reaction since in the absence of the metal salts, no appreciable reaction occured. Although the role of the metal salts is still ambiguous, it is likely that low valent bismuth "Bi(0)" or titanium "Ti(0)" generated *in situ* by reduction of Bi(III) or Ti(IV) with tin metal works as a promoter of the cyclization reaction. Other metal salt/metal combinations, so far investigated, were less effective; metal salt/metal (yields of **5**): $SbCl_3$/Sn (28%), $BiCl_3$/Zn (15%), $BiCl_3$/Al (13%), $PbBr_2$/Sn (trace).

Cyclization of the protected enols **6**, easily derived from **4**, was also achieved in a similar fashion by proper choice of the metal salt/metal combination; for example, the reaction of **6** in a $PbBr_2$/Al/DMF system (2 h) afforded **7** ($R^2 = R^3 = Ph_2CH$, 77%; R^2 = *p*-$MeOC_6H_4CH_2$, R^3 = Me, 49%).

Further applications to the cyclization of various monocyclic azetidinone derivatives into cephems and the verification of the electron relay mechanism of bimetal redox systems will be discussed in due course.

The authors are grateful to the SC-NMR Laboratory of Okayama University for the mesurement of 500 MHz ^1H NMR spectra.

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(Received July 26, 1990)