A Facile Conversion of the Phenylthio Group to Acetoxy by Copper Reagents for a Practical Synthesis of 4-Acetoxyazetidin-2-one Derivatives from (*R*)-Butane-1,3-diol

Takashi Nakatsuka, Hiromitsu Iwata, Rie Tanaka, Seiichi Imajo and Masaji Ishiguro*

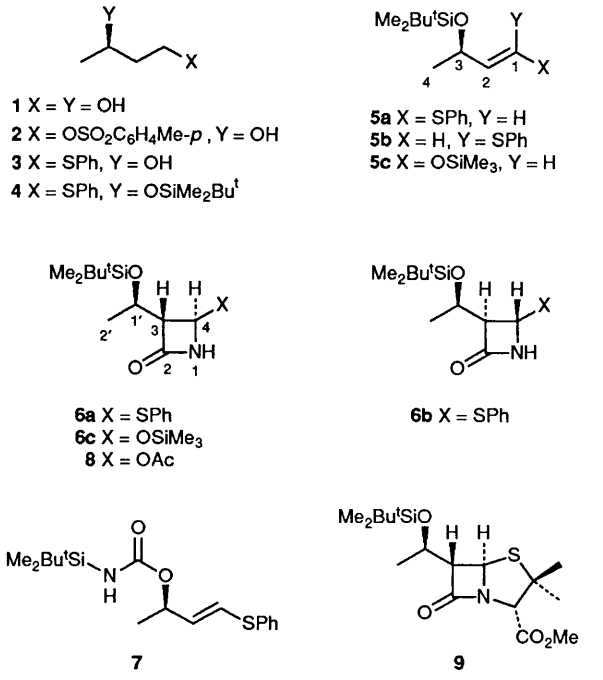
Suntory Institute for Biomedical Research, Shimamoto, Osaka 618 Japan

(3*S*,4*R*,1′*R*)-4-Acetoxy-3-(1′-*tert*-butyldimethylsilyloxyethyl)-azetidin-2-one **8**, an important intermediate for the synthesis of penem and carbapenem antibiotics, was synthesized from (*R*)-butane-1,3-diol **1**, using chlorosulphonyl isocyanate for the formation of β-lactam ring in which a significant solvent effect on the ratio of diastereoisomers **6a** and **6b** was observed; copper(II) acetate rather than the poisonous mercury(II) acetate was used to convert the phenylthio group of compound **6a** to acetoxy.

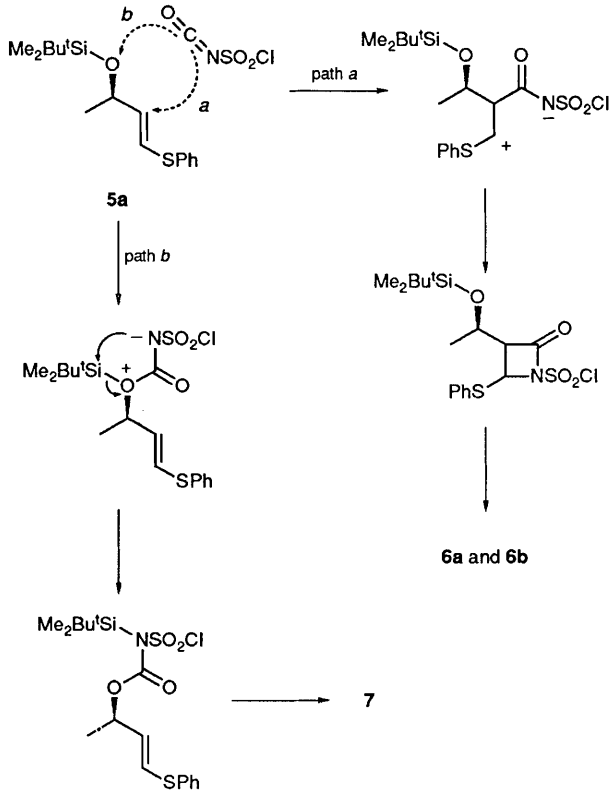
In view of the focus on penems and carbapenems as a new generation of potent antibiotics,[1] (3*S*,4*R*,1′*R*)-4-acetoxy-3-(1′-*tert*-butyldimethylsilyloxyethyl)azetidin-2-one **8** or its equivalents have become key intermediates for the synthesis of these β-lactams. Although there are many methods for synthesizing such intermediates using optically active natural sources such as L-threonine,[2] L-aspartic acid,[3] 6-aminopenicillanic acid,[4] (*S*)-ethyl lactate[5] and (*R*)-methyl 3-hydroxybutyrate,[6–9] simple and practical methods are still required.

(3*S*,4*R*,1′*R*)-4-Phenylthio-3-(1′-*tert*-butyldimethylsilyloxyethyl)azetidin-2-one **6a** is readily accessible starting from several optically active materials such as (*R*)-methyl 3-hydroxybutyrate,[10] 6-aminopenicillanic acid[11] or (*R*)-4-phenylthioazetidine-2-one.[12] However, the conversion of the rather inactive phenylthio group to nucleophilic substitutions at C-4 *via* the active acetoxy substituent requires the use of the poisonous mercury(II) acetate[11] and an alternative oxidative conversion gives the phenylsulphonyl group which is less reactive than acetoxy towards nucleophiles.[11] Here we report a simple method for this conversion using a copper reagent, together with a practical route for production of 4-acetoxyazetidinone **8** starting from (*R*)-butane-1,3-diol, which is now available in large quantity by microbial transformation. We also describe significant solvent effects which govern the chemo- and stereo-selectivity of the chlorosulphonyl isocyanate coupling reaction with *E*- and *Z*-vinyl sulphides **5a** and **5b**, which will be essential for a further optimization of this reaction.

4-Phenylthioazetidinone was synthesized from (*R*)-butane-1,3-diol **1** in 6 steps. Conversion of (*R*)-butane-1,3-diol **1** to the mono-*p*-toluenesulphonate **2** by reaction with toluene-*p*-sulphonyl chloride in 2,6-lutidine followed by treatment of the *p*-toluenesulphonate **2** with sodium benzenethiolate, followed by protection of the hydroxy group of **3** by the *tert*-butyldimethylsilyl group gave **4** in about 90% yield. This protected phenyl sulphide **4** was then converted to a 2.5 : 1 mixture of *E*- and *Z*-vinyl sulphides **5a** and **5b** in 85% yield by a two-step procedure: chlorination with *N*-chlorosuccinimide and subsequent dehydrochlorination using lithium carbonate in dimethylformamide at 80 °C. Since the *E*- and *Z*-vinyl sulphides afford **6a** as the major product in diisopropyl ether as shown in Table 1, this mixture was treated in this solvent at 25 °C with chlorosulphonyl isocyanate (1.1 equiv.) to give a 2 : 1 mixture of phenylthioazetidinones **6a** and **6b** after removal of the *N*-chlorosulphonyl group of the adduct by treatment with thioacetic *S*-acid and then pyridine in ethyl



Scheme 1



Scheme 2

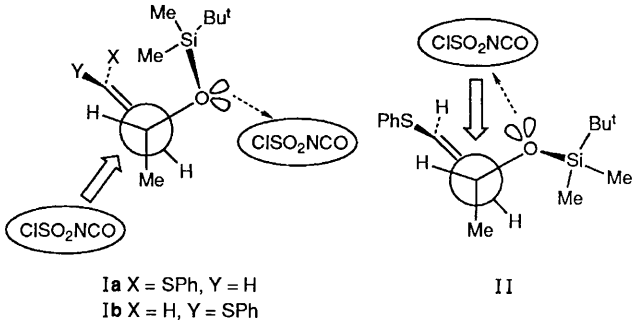


Fig. 1 Major conformers for *E*-vinyl sulphide **I** and *Z*-vinyl sulphide **II** obtained by a conformational search using MM2 energy calculations. Thick arrows indicate the direction of the attack of the reagent whereas dotted arrows indicate the direction of coordination of the oxygen lone pair.

Table 1 Solvent effect on ratio (**6a/6b**) and yield of β-lactams **6a** and **6b**

	E-Isomer		*Z*-Isomer	
Solvent	**6a/6b**	Yield (%)[a]	**6a/6b**	Yield (%)[a]
CH_2Cl_2	2.46	17	0.33	46
$CHCl_3$	—	0	0.69	38
Et_2O	2.17	61	1.00	65
Pr^i_2O	2.55	65	1.27	46
Hexane	4.33	39	2.06	35
Toluene	2.74	37	1.00	53

[a] Isolated yield of **6a** and **6b** after removal of chlorosulphonyl group.

acetate. A reaction temperature lower than 25 °C for this coupling reaction decreased the yield without any appreciable improvement of stereoselectivity. This crude mixture was cleanly separated by washing with *n*-hexane in only one operation to give crystalline **6a** which was thus obtained in 40% yield from the vinyl sulphides **5a** and **5b**.

The solvolytic conversion of the phenylthio group of **6a** to acetoxy is facilitated by mercury(II) acetate as a consequence of its high affinity towards sulphur. Since the affinity of copper reagents for sulphur is also well documented, for example, in the hydrolysis of a thioketal to a keto group using a combination of copper(II) oxide and copper(II) chloride at high temperatures,[13] copper reagents were expected to accelerate the conversion of **6a** to **8**. Thus, copper(II) acetate or its hydrate (0.5 equiv.) was found to facilitate the conversion in acetic acid at 100 °C for 45 min to afford 4-acetoxyazetidinone **8** in almost quantitative yield. A catalytic amount of trifluoroacetic acid enhanced this reaction and lowered the reaction temperature (80 °C). Copper-(I) or -(II) oxide were also effective for this solvolytic conversion while copper(I) iodide or copper(II) chloride did not give the desired product under the same conditions. 4-Methylthioazetidinone **6a** (X = SMe) was also converted to compound **8** in 64% yield while the penam derivative **9** was unreactive under these conditions. This suggests an important role of the hydrogen atom at N-1 for this reaction.

Although a high stereoselectivity[7] has been observed in the reaction of *E*-vinyl silyl ether **5c** at low temperature (−50 °C) to give **6c**, the chemoselectivity and stereoselectivity of the electrophilic addition of chlorosulphonyl isocyanate to acyclic allylic alcohol isomers such as **5a** and **5b** have not been widely investigated in spite of the extensive studies of reactions of chlorosulphonyl isocyanate with various alkene groups.[14–17] The *E*- and *Z*-isomers **5a** or **5b** could be easily separated by silica gel column chromatography and were treated at 25 °C with chlorosulphonyl isocyanate in the various solvents indicated in Table 1.

The failure to form the 3,4-*cis*-product from the *Z*-isomer **5b** indicated a stepwise β-lactam ring formation in this coupling reaction (Scheme 2, path *a*). Reaction of chlorosulphonyl isocyanate with the *E*-isomer in chloroform gave the *N*-silylated carbamate derivative **7** in high yield. This provided direct evidence for the interaction of chlorosulphonyl isocyanate

with the allylic oxygen in halogenated solvents (Scheme 2, path *b*). This chemoselectivity in halogenated solvents for the *E*-isomer can be accounted for in terms of the participation of the oxygen lone pair of the predominant conformer **1a** (>99%). On the other hand, a significant proportion (20%) of the conformer **II** for the *Z*-isomer in addition to the conformer **1b** may contribute to the different chemo- and stereo-selectivity (Fig. 1). The preference of **6a** for the *E*-isomer **5a** can be interpreted by means of the staggered conformation model in transition states proposed by Houk *et al.*[19] Thus, the reaction of the *E*-isomer **5a** in less polar solvents gave better selectivity for the preparation of the desired β-lactam compound **6a**. The alternative stereoselective preparation of the optically active *E*-isomer **5a** will be reported in due course.

Received, 3rd December 1990; Com. 0/05435F

References

1 A. Afonso, A. K. Ganguly, V. Girijavallabhan and S. McCombie, in *Recent Advances in β-lactam Antibiotics*, Spec. Publ. No. 52, ed., A. G. Brown and S. M. Roberts, p. 266, The Royal Society of Chemistry, London, 1985.
2 M. Shiozaki, N. Ishida, T. Hiraoka and H. Yanagisawa, *Tetrahedron Lett.*, 1981, **22**, 5205.
3 T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161.
4 F. DiNinno, T. R. Beattie and B. G. Christensen, *J. Org. Chem.*, 1977, **42**, 2960.
5 Y. Ito, T. Kawabata and S. Terashima, *Tetrahedron Lett.*, 1986, **27**, 5751.
6 M. Ishiguro, H. Iwata, T. Nakatsuka and M. Okitsu, *Jpn. Kokai*, 1986, 207373 (*Chem. Abstr.*, **107**, 23171y).
7 T. Ohashi, K. Suga, I. Sada, T. Miyama and K. Watanabe, *Jpn. Kokai*, 1986, 18791 (*Chem. Abstr.*, **105**, 60469f).
8 E. Hungerbühler, E.P.A. 259268, March 9, 1988 (*Chem. Abstr.*, **109**, 173244m).
9 Y. Ito, Y. Kobayashi and S. Terashima, *Tetrahedron Lett.*, 1989, **30**, 5631.
10 M. Ishiguro, H. Iwata, T. Nakatsuka, R. Tanaka, Y. Maeda, T. Nishihara and T. Noguchi, *J. Antibiotics*, 1988, **41**, 1685.
11 A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, *Chem. Pharm. Bull.*, 1981, **29**, 2899.
12 M. Shibasaki, A. Nishida and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 1982, 1324.
13 K. Narasaka, T. Sakashita and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3724.
14 K. Clauss, D. Grimm and G. Prossel, *Liebigs Ann. Chem.*, 1974, 539.
15 K. Hirai, H. Matsuda and Y. Kishida, *Chem. Pharm. Bull.*, 1973, **21**, 1090.
16 G. Schmid, E.P.A. 179318, April 30, 1986 (*Chem. Abstr.*, **105**, 172174n).
17 J. D. Buynak, J. Mathew, M. M. Rao, E. Haley, C. George and U. Siriwardane, *J. Chem. Soc., Chem. Commun.*, 1987, 735.
18 K. Clauss, *Liebigs Ann. Chem.*, 1969, **722**, 110.
19 K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li and R. J. Loncharich, *Science*, 1986, **231**, 1108.