Chemistry of *O*-Silylated Ketene Acetals[1]: A Synthesis of β-Lactam Antibiotics

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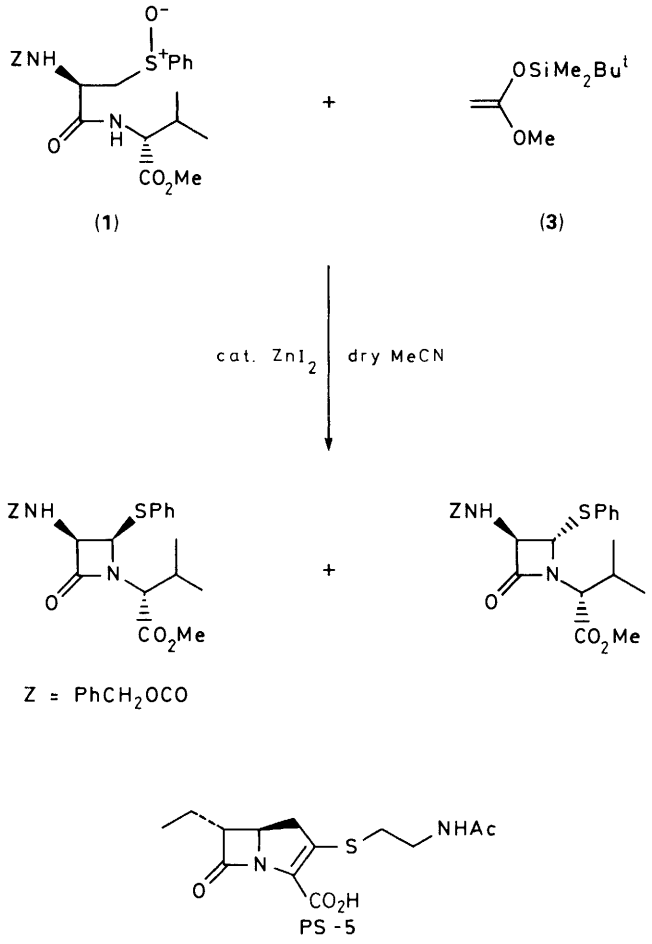
β-Amido sulphoxides (**2**) react with the *O*-silylated ketene acetal (**3**) to give the 4-phenylthioazetidin-2-ones (**4**), which are converted into azetidin-2-one esters (**5**), known precursors of various types of carbapenem antibiotics.

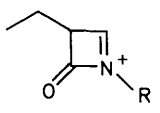
Since the discovery of non-classical β-lactam antibiotics such as thienamycin and PS-5, much attention has been focused on the exploration of a synthetic strategy for these naturally occurring carbapenem antibiotics.[2] Of the many routes to the azetidin-2-one ring, the biomimetic β-lactam synthesis is an attractive area.[3] In a recent communication, we described[4] a biomimetic approach to the penicillin synthesis from the Arnstein tripeptide analogue (**1**) by our silicon-induced Pummerer-type rearrangement (Scheme 1).[5] We now apply the method to a synthesis of carbapenem antibiotics involving PS-5 from readily obtained β-amido sulphoxides (**2**).

The sulphoxides (**2a**—**i**)† were treated with 1-(dimethyl-t-butylsiloxy)-1-methoxyethylene (**3**) to give the corresponding 4-phenylthioazetidin-2-ones (**4a**—**i**) (Table 1). A typical procedure is as follows. To a solution of (**2a**) (102 mg, 0.52 mmol) and zinc iodide (8.3 mg, 0.026 mmol) in dry acetonitrile (5 ml) was added (**3**) (294 mg, 1.56 mmol) at room temperature, and the mixture was stirred for 1 h. After removal of the solvent, the residue was subjected to column chromatography on silica gel to give (**4a**) (135 mg, 88%).‡ The generality of this reaction is indicated by the finding that both *N*-substituted and *N*-unsubstituted (**2**) reacted readily with (**3**) to give (**4a**—**i**) in high yields. The latter were characterised on the basis of ^{1}H n.m.r. and accurate mass spectra results; the *cis*/*trans* assignments and the ratio of these for the 3,4-disubstituted azetidin-2-ones (**4e**—**i**) was made by both 500 MHz ^{1}H n.m.r. spectrometric measurements and h.p.l.c.

Although a number of methods have appeared[2] for carbon–carbon bond formation at the C-4 position of azetidin-2-one, most of the methods start from 4-acetoxy- and 4-chloroazetidin-2-ones and involve either strongly basic and acidic conditions or require low temperature. We have now found a versatile and practical method for carbon–carbon bond formation by using 4-arylsulphinylazetidin-2-ones obtained from 4-arylthioazetidin-2-ones. Oxidation of (**4a**—**d**), with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene dichloride followed by reaction with (**3**) in the presence of a catalytic amount of zinc iodide in dry acetonitrile at room temperature for 0.5—1.5 h afforded the azetidin-2-one esters (**5a**—**d**), respectively in high yields. Similarly, 3-ethyl-4-phenylthioazetidin-2-ones, (**4g**—**i**) were oxidised with *m*-CPBA to the 4-sulphinyl compounds, which were successfully treated with (**3**) to give the mixtures of the corresponding *cis*- and *trans*-azetidin-2-one esters (**5g**—**i**) (Table 2). The *trans*-azetidin-2-one esters (**5g**—**i**) were produced selectively even if *trans*-4-phenylthioazetidin-2-ones were used as the starting materials. Therefore, it is presumed that carbon–carbon bond formation in the reaction of 4-phenylthioazetidin-2-ones with (**3**) proceeds *via* a nucleophilic attack of the ester enolate anion on the iminium intermediates (**A**) to give the *trans*-azetidin-2-one esters (**5g**—**i**). To our knowledge, this is the first example of the substitution of a sulphinyl group by an enol ester equivalent at the 4-position of azetidin-2-one.§



Scheme 1.



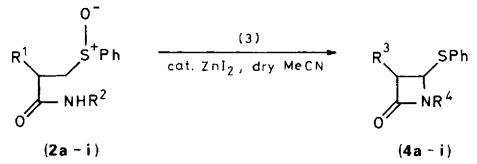
(**A**)

† The previously unknown sulphoxides (**2b**—**d** and **2f**—**i**) were prepared from the appropriate α,β-unsaturated amides or esters and details of their preparation will be published in the full paper.

‡ The *N*-desilylated compounds of (**4a**) (Bu_4NF AcOH in THF, 0 °C, 0.5 h, 99%) was known to be utilised for the synthesis of various types of β-lactam antibiotics, carbapenems, penems, oxapenems, and monobactams.[6]

§ Substitution of a sulphinyl group by an allyl group at the 4-position of azetidin-2-one was accomplished by the reaction with allyl stannane.[7]

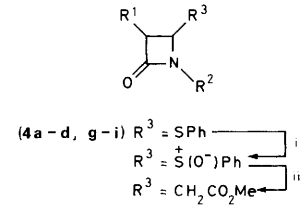
Table 1. The synthesis of the β-lactams (**4a**—i)



Entry	Sulphoxide R¹	Sulphoxide R²	Reaction conditions[a]	Product R³	Product R⁴	Yield[b] (%)	Ratio[c] *cis*:*trans*
1	(**2a**) H	H	R.t. 1 h	(**4a**) H	$SiMe_2Bu^t$	88	
2	(**2b**) H	CH_2Ph	R.t. 6 h	(**4b**) H	CH_2Ph	73	
3	(**2c**) H	CH(Me)Ph	R.t. 4 h	(**4c**) H	CH(Me)Ph	85[d]	
4	(**2d**) H	$CHPh_2$	R.t. 3 h	(**4d**) H	$CHPh_2$	93	
5	(**2e**) Me	H	R.t. 3 days	(**4e**) Me	$SiMe_2Bu^t$	77	72:28
6	(**2f**) Me	CH_2Ph	R.t. ⟶ 65 °C 5 h	(**4f**) Me	CH_2Ph	77	71:29
7	(**2g**) Et	H	R.t. ⟶ 50 °C 14 h	(**4g**) Et	$SiMe_2Bu^t$	75	63:37
8	(**2h**) Et	CH_2Ph	R.t. 1 day	(**4h**) Et	CH_2Ph	63	59:41
9	(**2i**) Et	$CHPh_2$	R.t. ⟶ 50 °C 6 h	(**4i**) Et	$CHPh_2$	78	44:56

[a] The reactions were carried out on 0.1—1 mmol scale of sulphoxides with 3—5 equiv. of (**3**) in the presence of a catalytic amount (0.05—0.1 equiv.) of ZnI_2. [b] Isolated yields by column chromatography (silica gel) are given. [c] The ratios were determined by ^1H n.m.r. and h.p.l.c. [d] 1:1 Mixture of diastereoisomers.

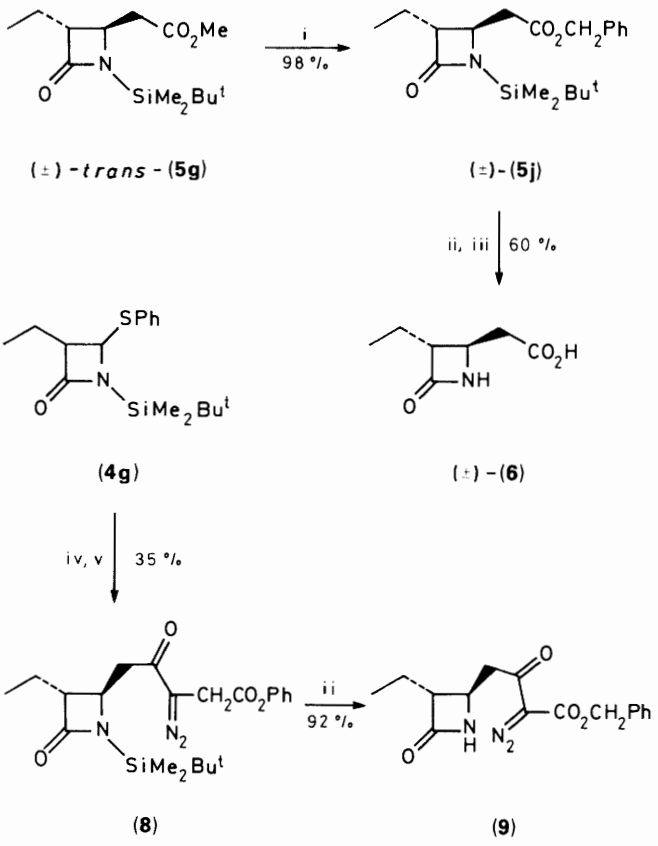
Table 2. Carbon–carbon bond formation at the 4-position of azetidin-2-one



Entry	β-Lactam R¹	β-Lactam R²	Reaction conditions[a]	Product	Yield[b] (%)	Ratio[c] *trans*:*cis*
1	(**4a**) H	$SiMe_2Bu^t$	R.t. 30 min	(**5a**)	86	
2	(**4b**) H	CH_2Ph	R.t. 1 h	(**5b**)	48	
3	(**4c**) H	CH(Me)Ph	R.t. 1 h	(**5c**)	75[d]	
4	(**4d**) H	$CHPh_2$	R.t. 10 min	(**5d**)	60	
5	(**4g**) Et (*cis*:*trans* = 63:37)	$SiMe_2Bu^t$	−20 °C 1h	(**5g**)	67	94:6
6	(**4h**) Et (*cis*:*trans* = 59:41)	CH_2Ph	−20 °C 10 min	(**5h**)	45	89:11
7	(**4i**) Et (*cis*:*trans* = 44:56)	$CHPh_2$	−20 °C 1 h	(**5i**)	62	91:9

[a] The reactions were carried out on 0.05—0.2 mmol scale of sulphoxides with 2 equiv. of (**3**) in the pesence of a catalytic amount (0.05—0.1 equiv.) of ZnI_2. [b] Isolated yields [from (**4**)] by column chromatography on silica gel are given. [c] The ratios were determined by 500 MHz ^1H n.m.r. [d] 1:1 Mixture of diastereoisomers.

Finally, our attention was focused on the synthesis of the carbapenem antibiotic, PS-5. The *trans*-azetidin-2-one methyl ester (**5g**) was transesterified[8] with benzyl alcohol to give the *trans*-azetidin-2-one benzyl ester (**5j**) (98%). Desilylation of (**5j**) with Bu_4NF and AcOH in THF followed by reductive debenzylation on 10% Pd–C in ethanol gave the *trans*-4-carboxy-3-ethylazetidin-2-one (**6**) (60% overall yield) [m.p. 105—108 °C, lit.,[9] 105—108 °C], which is known as an intermediate of PS-5. Furthermore, reaction of 3-ethyl-4-phenylthioazetidin-2-one (**4g**) (*cis*/*trans* = 63:37) with *m*-CPBA in methylene dichloride gave the 4-sulphinyl compound, which was treated with the silyl enol ether (**7**) to give the *trans*-azetidin-2-one-diazo ester (**8**) directly in 35% overall yield. The ester (**8**) was treated with Bu_4NF and AcOH in THF to give the desilylated diazo ester (**9**)[9,10] (92%), which was characterised on the basis of ^1H n.m.r., i.r., and mass spectral data.



Scheme 2. *Reagents:* i, $PhCH_2OH$, $Ti(OPr^i)_4$, 80 °C, 2h; ii, Bu_4NF, AcOH–THF, 0 °C, 30 min; iii, $[H_2]$, 10% Pd–C/EtOH, room temp., 10 min; iv, *m*-CPBA/CH_2Cl_2, 0 °C, 1 h; v, $Bu^tMe_2SiOC(=CH_2)$-$C(=N_2)CO_2CH_2Ph$ (**7**), cat. ZnI_2, dry MeCN, room temp., 15 min.

Application of this methodology to an asymmetric synthesis of (+)-PS-5 starting from optically active 3-hydroxybutyrate is under investigation.

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Received 29*th March* 1989
(*Accepted* 29*th June* 1989); *Paper* 9/02755F