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ONE-STEP SYNTHESIS OF OXAZOLINOAZETIDINONES FROM PENICILLIN SULFOXIDES: POTENTIAL INTERMEDIATES FOR 1-OXACEPHEM SYNTHESIS†

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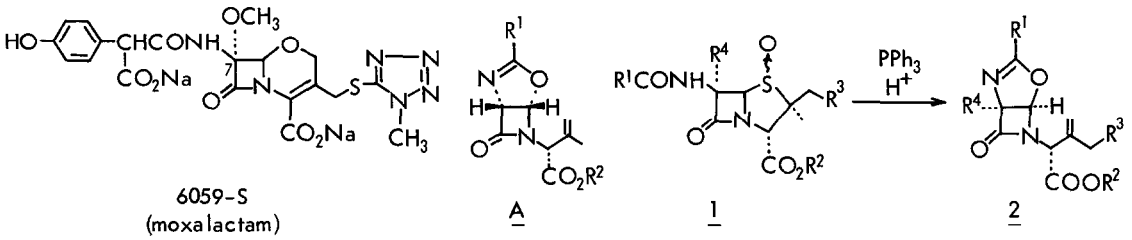
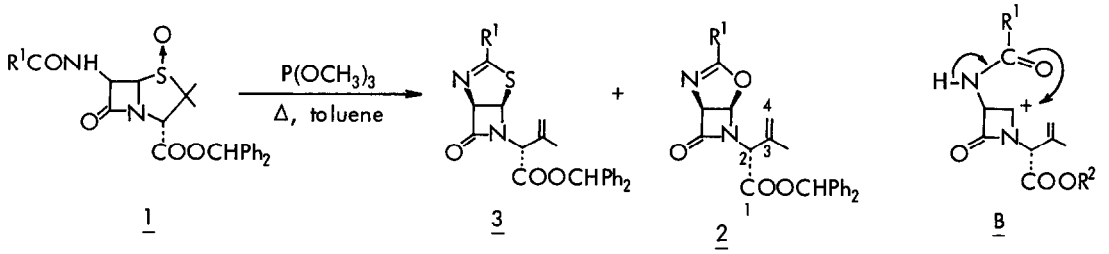
Summary Reaction of penicillin sulfoxides with a tervalent phosphorous compound in the presence of a catalytic amount of squaric acid gave oxazolinoazetidinones, potential intermediates for synthesis of 1-oxacephems, in good yields. 2β-Chloromethyl- and 6α-methoxypenicillin sulfoxides also undergo this reaction. The reaction contrasts with the well-known Cooper reaction which usually gives thiazolinoazetidinones.

Recently our research group discovered a clinically useful β-lactam antibiotic[1] (code-number: 6059-S; moxalactam in U.S.A.) having a unique 7α-methoxy-1-oxacephem nucleus and established an industrially feasible route[2] to the nucleus employing epi-oxazolinoazetidinones A[3] as key intermediates. Our continuing efforts have been focused on finding out an alternative synthesis in particular via the 7α-unsubstituted 1-oxacephem nucleus which itself can lead to usuful antibiotics. Potential intermediates in such a synthesis are normal oxazolinoazetidinones 2 having the but-3-enoate side chain at the azetidinone nitrogen. In this paper we describe a successful one-step synthesis of oxazolines 2 from penicillin sulfoxides 1.

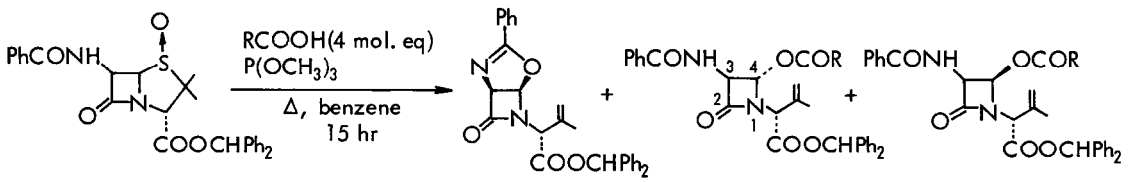


This work stems from our earlier finding that small amounts of oxazolines 2[4] (a: R^1 = Ph; R^2 = $CHPh_2$; R^3 = H; R^4 = H; 5%, c: R^1 = CH_2Ph; R^2 = $CHPh_2$; R^3 = H; R^4 = H; 2%) were formed as by-products besides thiazolines 3 (a: 66%. c: 70%) when penicillin S-oxides 1a and 1c underwent the Cooper reaction.[5] We had rationalized the formation of the oxazolines 2 by assuming carbonium ion intermediate B. In 1978 Suarato et al.[6] reported that 4α-acyloxyazetidinones analogous to 4 were obtained in reaction of penicillin sulfoxides with trimethyl phosphite and carboxylic acids. This report led us to anticipate that formation of the carbonium ion B is facilitated in the presence of an acid and that oxazolines 2 would be effectively formed under acid conditions.



1 3 2 B

Thus, penicillin β-sulfoxide 1a was heated in refluxing benzene with an equimolar amount of trimethyl phosphite in the presence of four molar equivalents of pivalic acid, benzoic acid, or picolinic acid. As expected, no thiazoline was formed in this reaction and, instead, the



1a 2a 4 5

oxazoline 2a was isolated in 34, 46, and 55% yields besides varied amounts of 4-acyloxy compounds, 4 and 5.[7] Clearly the acid acts not only as a nucleophile but also as a proton donor. With lowering the pKa value and the nucleophilicity of the acid, the oxazoline yield increases. This observation led us to use a catalytic amount of squaric acid () with a low pK_1 value (0.54-1.0)[8] and little nucleophilicity for the oxazoline formation. Triphenyl phosphine was used in preference to trimethyl phosphite on the basis of mechanistic consideration (see below). N,N-Dimethylacetamide (DMA) was found essential as a co-solvent and an optimal amount of DMA was 5-10% of the solvent. A larger amount of DMA caused double-bond isomerization at the butenoate side chain.

In a typical procedure triphenylphosphine (0.68 g, 2.59 mmol), squaric acid (11 mg, 0.096 mmol), and DMA (1 ml) were added to a solution of penicillin sulfoxide 1a (1.0 g, 1.99 mmole) in toluene (20 ml). The solution was refluxed for 1.5 hours with azeotropic removal of water by using a Dean-Stark apparatus containing molecular sieves 4A. The reaction mixture was washed with water, dried, and evaporated. Triphenylphosphine sulfide was removed by crystallization of the residue from acetonitrile. The desired oxazoline 2a (760 mg, 1.68 mmol) was obtained from the filtrate by evaporation followed by crystallization from methanol.

In Table were summarized data on the reaction of various penicillin sulfoxides. The results indicate that the conversion proceeded smoothly on 6α-unsubstituted compounds including 2β-chloromethyl derivatives[9] (runs 1-9), and that the reaction was applicable also to 6α-methoxy substrates[9] (runs 10-13) though the product yields were generally low.

Table. Transformation of Penicillin Sulfoxides 1 to Oxazolines 2

Run	1[i]	R^1	R^2	R^3	R^4	PR_3-H^+[ii]	Solvent[iii]	Time (hr)	2 (%)	Mp (°C)
1	a	Ph	$CHPh_2$	H	H	Ph_3P-SA	DCE-Tol (2:1)	9	73	134-135
2	a	Ph	$CHPh_2$	H	H	Ph_3P-SA	Tol	1.5	84	
3[iv]	a	Ph	$CHPh_2$	H	H	Ph_3P-PA	Tol	1.17	75	
4	b	Ph	t-Bu	H	H	Ph_3P-SA	DCE-Tol (1:4)	1.67	83	116-117
5	c	$PhCH_2$	$CHPh_2$	H	H	Ph_3P-SA	DCE-Tol (1:2)	7.5	61	102-103
6	d	$PhCH_2$	CH_2Ph	H	H	Ph_3P-SA	DCE-Tol (3:2)	6.0	58	foam
7	e	$PhOCH_2$	CH_2CCl_3	H	H	Ph_3P-SA	DCE-Tol (1:1)	5.5	56	foam
8	f	Ph	$CHPh_2$	Cl	H	Ph_3P-SA	C_6H_6	0.33	80	138-140
9	g	$PhOCH_2$	$CHPh_2$	Cl	H	Ph_3P-SA	C_6H_6	0.25	73	foam
10	h	Ph	$CHPh_2$	H	OCH_3	Ph_3P-SA	C_6H_6	0.42	45	foam
11	i	$PhCH_2$	$CHPh_2$	H	OCH_3	Ph_3P-SA	C_6H_6	0.50	27	foam
12	j	Ph	$CHPh_2$	Cl	OCH_3	Ph_3P-SA	C_6H_6	0.17	26	foam
13	k	$PhCH_2$	$CHPh_2$	Cl	OCH_3	Ph_3P-SA	C_6H_6	0.17	59	foam

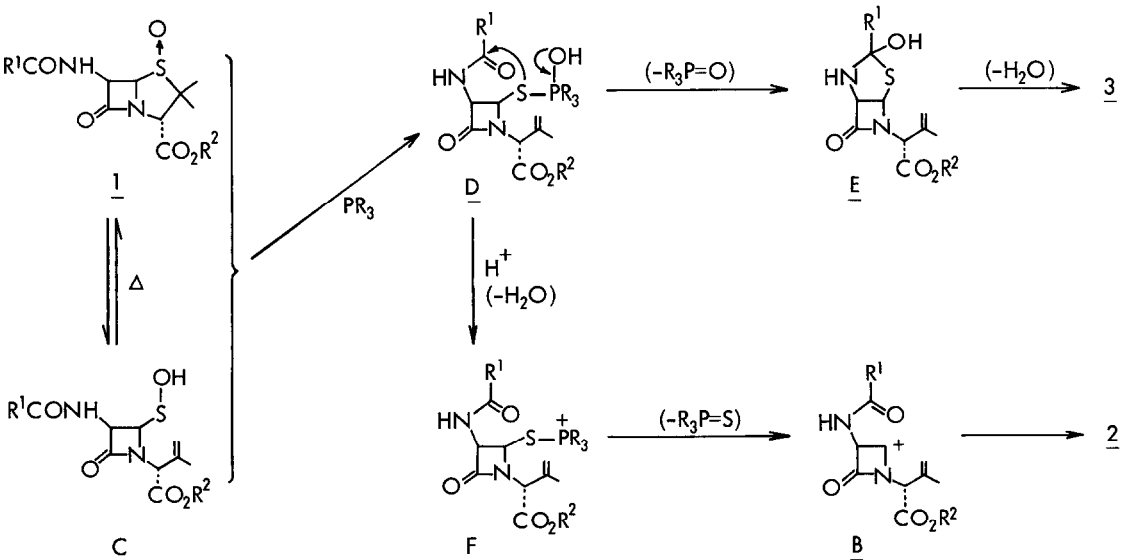
i) The stereochemistry of the sulfoxides is β in 1a-e and α in 1f-k

ii) SA: squaric acid; PA: picolinic acid.

iii) DCE: 1,2-dichloroethane; Tol: toluene. In all experiments were used a 5-10% amount of DMA (N,N-dimethylacetamide) as a co-solvent except for run 3.

iv) In this experiment, DMA was not used and an equimolar amount of picolinic acid was used as the acid catalyst.

In the following we suggest a probable mechanism for the formation of the oxazolines 2 in comparison with that for the thiazoline formation in the well-known Cooper reaction. Reasonably a common intermediate is hydroxyphosphorane D whose formation via sulfenic acid C has been



proposed by Hatfield et al.[10] In the absence of proton, the S-P bond cleavage with formation of phosphine oxide would occur to effect formation of thiazolidine E leading to thazoline 3. On the other hand, proton-catalyzed dehydration of D would dominate in the presence of an acid to give phosphonium ion F, which, with facile elimination of phosphine sulfide, could be converted into carbonium ion B leading to oxazoline 2. Clealy the triphenyl phosphonium ion (R = Ph) F is more stable than the trimethoxy counterpart (R = OCH_3) to afford a basis for the selection of triphenylphosphine as the reagent.

References and Notes

† This work was applied for Japanese patent on July 10, 1979.

1) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani and W. Nagata, J. Med. Chem. 22, 757 (1979).

2) M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi and W. Nagata, Tetrahedron Lett. 351 (1980).

3) Y. Hamashima, S. Yamamoto, S. Uyeo, M. Yoshioka, M. Murakami, H. Ona, Y. Nishitani and W. Nagata, Tetrahedron Lett. 2595 (1979).

4) 2a: NMR ($CDCl_3$) δ 1.75 s 3 H, 4.94 s 1 H, 5.06 bs 2 H, 5.29 d 1 H (4.0 Hz), 6.30 d 1 H (4.0 Hz), 6.97 s 1 H, 7.2-7.9 m 15 H; IR ($CHCl_3$) 1780, 1743, 1633 cm^{-1}. 2c: NMR ($CDCl_3$) δ 1.47 bs 3 H, 3.60 s 2 H, 4.78 s 1 H, 4.90 s 2 H, 5.07 d 1 H (4.0 Hz), 6.11 d 1 H (4.0 Hz), 6.89 s 1 H, 7.3 m 15 H; IR ($CHCl_3$) 1775, 1741, 1643 cm^{-1}.

5) R. D. G. Cooper and F. L. José, J. Am. Chem. Soc. 92, 2575 (1970).

6) A. Suarato, P. Lombardi, C. Galliani and G. Franceshi, Tetrahedron Lett. 4059 (1978).

7) Yields of 4 and 5 varied considerably depending upon the acid used. Thus, 41% of a 1:2 mixture of 4 and 5, 34% of 4 accompanied by a trace amount of 5, and a trace amount of 4 were obtained respectively, when pivalic acid (pKa = 5.05), benzoic acid (pKa = 4.21), and picolinic acid (pKa = 3.40) were used. 4 (R' = $(CH_3)_3C$-): foam; NMR ($CDCl_3$) δ 1.15 s 9 H, 1.88 s 3 H, 4.93 s 1 H, 4.80-5.2 m 3 H, 6.10 d 1 H (2 Hz), 6.90 bs 1 H, 7.1-7.8 m 16 H; IR ($CHCl_3$) 1780, 1740, 1666 cm^{-1}. 5 (R' = $(CH_3)_3C$-): foam; NMR ($CDCl_3$) δ 1.07 s 9 H, 1.88 s 3 H, 4.88 s 1 H, 4.9-5.1 m 2 H, 5.60 dd 1 H (4 Hz, 8 Hz), 6.02 d 1 H (4 Hz), 6.95 s 1 H, 7.2-7.9 m 16 H, IR ($CHCl_3$) 1772, 1740, 1674 cm^{-1}.

8) A. H. Schmidt, Synthesis, 961 (1980).

9) The 2β-chloromethyl penicillin α-sulfoxides were prepared according to the known procedures: see K. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nagaguchi and T. Oku, Tetrahedron Lett. 3001 (1973) and S. Uyeo, T. Aoki and W. Nagata, Heterocycles, 11, 305 (1978). 6α-Methoxylation was carried out by the conventional method; G. A. Koppel and R. E. Koehler, J. Am. Chem. Soc. 95, 2403 (1973).

10) L. D. Hatfield, J. Fisher, F. L. José and R. D. G. Cooper, Tetrahedron Lett. 4897 (1970).

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