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# SULFENIC ACID TRIMETHYLSILYL ESTERS. A CONVENIENT PROTECTION FOR A REACTIVE FUNCTIONALITY.

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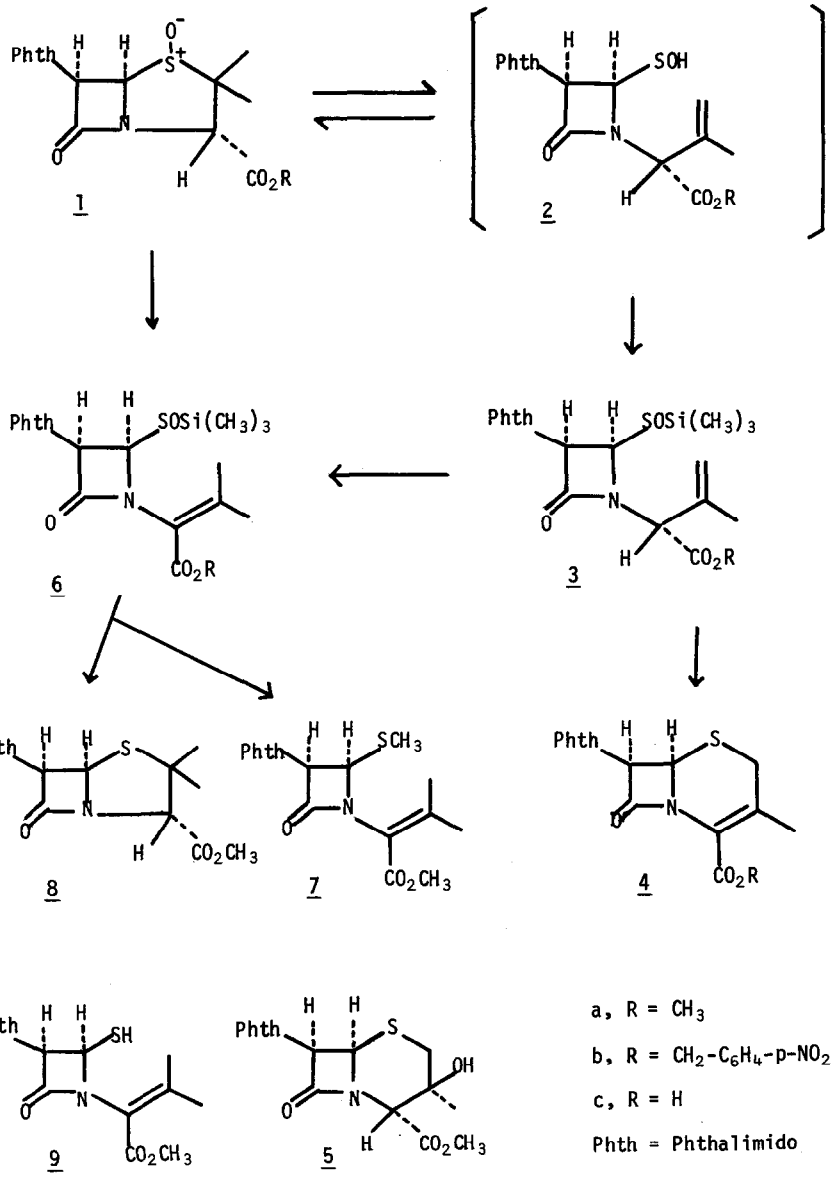
In general, the isolation of free aliphatic sulfenic acids has been unsuccessful,[1] and except for the mono- and disulfenic acids from anthraquinone[2] and the silver salt of 1-methyluracil-4-sulfenic acid,[3] this reactive functionality has only been known as a transient species. Since the important thermal rearrangement of penicillin sulfoxide 1 to deacetoxycephalosporin 4 has been proposed via a sulfenic acid 2,[4] it is desirable to develop a protecting group for this function which would allow its isolation in a stable condition and yet allow its intrinsic reactivity to be realized either in the protected state or else by way of a facile hydrolysis of the protecting group. I report here the successful utilization of the trimethylsilyl ester group for this purpose.

When the penicillin sulfoxide ester 1a was refluxed in benzene (nitrogen purged, 2 hrs.) with 100% excess silylating agent[5,6] and then the solvent and excess reagent removed in vacuum, the trimethylsilyl ester 3a was obtained as a gum $[\alpha]_D^{27}$ -164° (c 1.10, benzene), in nearly quantitative yield. The structure 3a was supported by nmr ($CDCl_3$, δ): 0.05 (9H, s, $-Si(CH_3)_3$), 2.04 (3H, br.s, $CH_3$), 3.84 (3H, s, $-CO_2CH_3$), 5.07 (1H, s, -CHCOO-), 5.20 (2H, br.s, $C=CH_2$), 5.84 (2H, s, β-lactam protons) and 7.85 (4H, m, $-C_6H_4$); $\nu_{CO}$ ($CHCl_3$) 1770 $cm^{-1}$ (β-lactam); and high resolution mass spectrum, m/e 448 ($M^+$, $C_{20}H_{24}N_2O_6SSi$) along with m/e 389 ($M^+ - COOCH_3$), 359 ($M^+ - OSiMe_3$), 327 ($M^+ - SOSiMe_3$), 262 ($M^+ - C_8H_4O_2-N=C=C=O$), the latter fragmentation being characteristic of a β-lactam.

In the same fashion the p-nitrobenzyl ester 1b gave the trimethylsilyl ester 3b and free acid 1c yielded a bis trimethylsilyl ester[7] (3c, R = $-Si(CH_3)_3$, nmr ($CDCl_3$, δ): 0.37), $[\alpha]_D^{27}$ -45.5° (c 1.10, benzene); $\nu_{CO}$ ($CHCl_3$) 1795 $cm^{-1}$. When ester 3a was treated with methane




a, R = $CH_3$

b, R = $CH_2$-$C_6H_4$-p-$NO_2$

c, R = H

Phth = Phthalimido

sulfonic acid in benzene-dimethylacetamide,[8] it was converted into the cephem derivative 4a (70%).[9] The sulfenic acid 2a can be regenerated in situ by stirring the ester 3a in chloroform under moist air, whereupon recyclization occurred under these conditions to yield sulfoxide 1a (50%, crystallized) and small amounts of 4a and the 3β-hydroxycephem 5, identical to a sample prepared by the described procedure.[8]

The sulfenic acid silyl ester functionality permits certain base catalyzed reactions to be performed on other parts of the molecule, e.g. upon treatment of 3a with a trace of triethylamine in anhydrous benzene there was obtained the α,β-isomer 6a, m.p. 95°, nmr ($CDCl_3$, δ): 0.05 (9H, s, $-Si(CH_3)_3$), 2.27 and 2.37 (6H, 2s, isopropylidene methyls), 3.84 (3H, s, $-COOCH_3$), 5.74 and 5.95 (2H, two d, J = 4.5 Hz, β-lactam protons) and 7.87 (4H, m, $-C_6H_4$). The α,β-isomers 6a, 6b and 6c (R = $Si(CH_3)_3$)[7] can be obtained in one step by refluxing the respective sulfoxides 1a, 1b and 1c in benzene (nitrogen purged, 4 hrs.) with 100% excess silylating agent[5,6] plus a trace of triethylamine. Reductive reactions on the sulfenic ester function are also possible without removal of the protecting group. Thus reaction of 6a with excess trimethylphosphite in benzene (25°) gave the methyl sulfide 7,[10] nmr ($CDCl_3$, δ): 2.24 (6H, s, isopropylidene methyls), 2.02 (3H, s, $SCH_3$), and the penicillin 8. The latter compound presumably is the result of Michael type cyclization of the azetidinone mercaptan 9 formed by the deoxygenation reaction.[10]

The sulfenyltrimethylsilyl esters are stable as solids under anhydrous conditions and are reasonably stable during room temperature storage. I believe that this protective function may be of great utility in exploring the chemistry of the reactive sulfenic acid functionality.[11]

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5. The silylating agent consisted of 2:1 molar ratio of trimethylsilyl chloride and hexamethyldisilazane. Use of trimethylsilylacetamide gave identical results.

6. Belgian patent 763104 (1971) stated that penicillin sulfoxides upon heating in the presence of at least 5 moles excess of a nitrogenous organic base and of a compound of silicon-halide can be converted into deacetoxycephalosporin derivatives. Neither isolation of the intermediate sulfenic acid silyl ester or the reaction mechanism was described.

7. All new compounds have given satisfactory spectral, analytical and mass spectral data.

8. G. E. Gutowski, B. J. Foster, C. J. Daniels, L. D. Hatfield, and J. W. Fisher, Tetrahedron Letters, 3433 (1971).

9. Compound 4a [m.p. 176-177°, $[\alpha]_D^{26}$ -4.7 (c 1.0, $CHCl_3$) and compound 4b [m.p. 186-188°, $[\alpha]_D^{26}$ -7.2 (c 1.0, $CHCl_3$)] were identical to samples prepared as described in ref. 8, using methane sulfonic acid as catalyst.

10. The sulfide 7 is produced from the Arbusov Transformation of an unstable phosphonium salt formed as an intermediate in the reaction of the trimethylsilyl ester 6a with trimethylphosphite. It is identical with a sample prepared by Dr. R. D. G. Cooper of the Lilly Research Laboratories and I thank him for a sample. Cf. R. D. G. Cooper, F. L. José, J. Amer. Chem. Soc., 92, 2575 (1970).

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