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VERSATILE CHEMICAL MODIFICATION OF THE C-2 SIDE CHAIN OF CARBAPENEM ANTIBIOTICS

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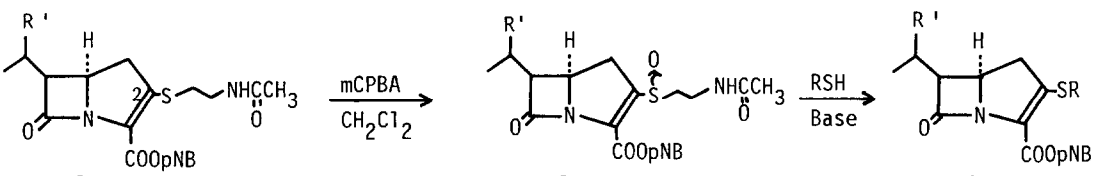
ABSTRACT: Substitution of the C-2 side chain of carbapenem antibiotics with various types of sulfenyl groups was effected *via* carbapenem S-oxides by two ways.

Novel beta-lactam antibiotics which possess a common structure of 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system(conventionally called carbapenem) have been isolated from fermentation broths of several species of *Streptomyces*.[1-3] These carbapenem compounds display potent antimicrobial activity against Gram-positive and Gram-negative bacteria including beta-lactamase-producing organisms. Recent chemical and biological studies have indicated that the C-2 side chain of the carbapenem compounds plays an important role in antimicrobial activity.[4,5] The method for the displacement of the C-2 side chain recently reported by Corbett[6] is limited to carbapenem compounds having a double bond in the C-2 side chain such as MM 13902 and epithienamycins B and D. Thus a more versatile method is required for the carbapenem antibiotics with the saturated C-2 side chains which are more commonly encountered in nature.

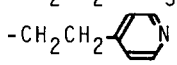
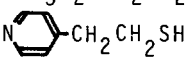
This communication describes two new methods which are conveniently and practically employable for the modification of the C-2 side chain of carbapenem compounds under mild reaction conditions.



1 a R'=H b R'=OH 2 3 pNB=p-nitrobenzyl

The first method consists of the initial S-oxidation of carbapenem compounds followed by displacement of the sulfinyl group in carbapenem S-oxides by different sulfenyl groups under mild basic conditions. For instance, PS-5 ester(1a) was treated with m-chloroperbenzoic acid in methylene chloride at -35°C for 45 minutes to afford PS-5 S-oxide(2a).[7] The reaction of 2a(1.0 equiv.) with n-butyl mercaptan(1.1 equiv.) in dried N,N-dimethylformamide(DMF) in the presence of triethylamine(TEA) at -35°C for 10 minutes provided compound 3a(R=n-butyl) in an isolated yield of 67 %. Table 1 summarizes the results of reaction of carbapenem S-oxides with several mercaptans.

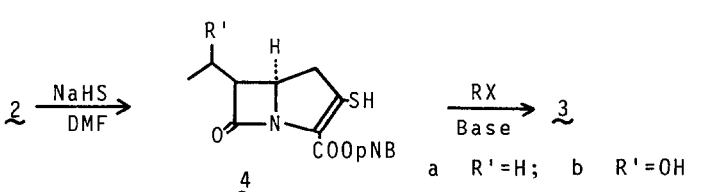
Table 1. Synthesis of 3

Product[8] R'	R	Mercaptan	Isolated yield(%)
H	$-CH_2CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2SH$	67.0
H			61.0
H	$-CH_2CH_2N(CH_3)_2$	$(CH_3)_2NCH_2CH_2SH$	64.8
H			83.7
H	$-CH_2CH_2COOpNB$	$pNBOOCCH_2CH_2SH$	81.9
H	$-CH_2\underset{NH_2}{C}HCOOpNB$	$pNBOOC\underset{NH_2}{C}HCH_2SH$	67.2
H	$-CH_2CH_2OH$	$HOCH_2CH_2SH$	70.0
H			77.5
OH*			53.6
H	-H	NaHS	25.8[9]

* Epithienamycin C was used as the starting material.

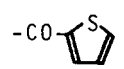
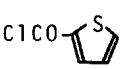
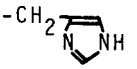
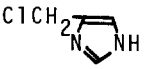
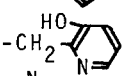
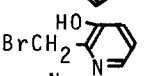
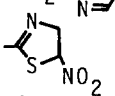
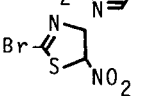
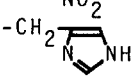
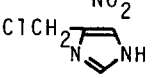
Although most of products were obtained in reasonable yields by this method, 2-mercaptocarbapenem, the simplest product, showed an unsatisfactory yield because of its chemical instability during isolation and purification.

The alternative method consists of alkylation or acylation of 2-mercaptocarbapenem prepared by the aforementioned modification method, giving compound 3. In practice it is more advantageous to carry out the reaction in one pot without isolation of 2-mercaptocarbapenem, starting from carbapenem S-oxides. This method finds practical utility when the former method is not applicable or gives a low reaction yield.



For example, PS-5 S-oxide(2a; 1.0 equiv.) was treated with sodium hydrosulfide (1.0 equiv.) in dried DMF at -45°C for 30 minutes, and then with TEA(2.0 equiv.) and thenoyl chloride(1.5 equiv.) at -40°C for 30 minutes, yielding compound 3a (R=thenoyl). Table 2 shows the results of alkylation or acylation of 2-mercapto-carbapenem(4).

Table 2. Synthesis of 3 via 2-mercaptocarbapenem

Product[10] R'	R	Reagent used	Isolated yield from 2 (%)
H	$-CH_3$	N_2CH_2	58.2
H	$-COCH_3$	$O(COCH_3)_2$	56.1
H			63.9
H			67.2
H			53.0
H			87.3
OH*			63.2

* N-Acetylthienamycin was used as the starting material.

New carbapenem derivatives prepared by the two modification methods, after removal of the p-nitrobenzyl group by hydrogenolysis(H_2, PtO_2, 50 % aqueous dioxane), exhibited excellent antimicrobial activity superior or comparable to the parent carbapenem compounds.

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5. Y. Fukagawa, K. Okamura, N. Shibamoto and T. Ishikura, In "Beta-Lactam Antibiotics" edited by S. Mitsuhashi, Japan Scientific Societies Press, Tokyo, pp.158(1981).
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7. PS-5 S-oxide(2a) was obtained as a mixture of alpha and beta oxides in a yield of 90 %. UV$\lambda_{max}^{CHCl_3}$ nm(ε) 267(13000), 310(7800); IR($CHCl_3$, cm^{-1}) 1785(beta-lactam), 1720(ester), 1680(amide); FD-MS(m/z) 449(M^+).
8. For all the carbapenem compounds listed in this table, satisfactory spectroscopic data were obtained. For example, compound 3a(R=n-butyl) gave the following data: UVλ_{max}^{THF} nm(ε) 270(9900), 322.5(11300); IR($CHCl_3$, cm^{-1}) 1765(beta-lactam), 1695(ester); NMR($CDCl_3$)δ 0.92(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.06(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.60(4H, m, $C\underline{H}_2$), 1.88(2H, m, $C\underline{H}_2CH_3$), 2.84(2H, t, J=7.0 Hz, $SC\underline{H}_2$), 2.96(1H, dd, J=8.0, 18.0 Hz, C-1$\underline{H}$), 3.12(1H, dt, J=2.5, 7.0 Hz, C-6$\underline{H}$), 3.29(1H, dd, J=9.0, 18.0 Hz, C-1$\underline{H}$), 3.94(1H, m, C-5$\underline{H}$), 5.19(1H, d, J=14.0 Hz, ArC$\underline{H}$H), 5.49(1H, d, J=14.0 Hz, ArCH$\underline{H}$), 7.62(2H, d, J=9.0 Hz, Ar$\underline{H}$), 8.18(2H, d, J=9.0 Hz, Ar$\underline{H}$); MS(m/z) 404(M^+), 334(M^+-EtCH=C=O).
9. Although Corbett[6] obtained 2-mercaptocarbapenem as the equilibrium mixture with 2-thioxocarbapenam, our preparation of 2-mercaptocarbapenem (4a) was found to be the sole isolable product without 2-thioxocarbapenam. UVλ_{max}^{THF} nm 310(sh.), 269.5; IR($CHCl_3$, cm^{-1}) 1778(beta-lactam), 1690(ester); NMR($CDCl_3$)δ 1.06(3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.59(1H, s, S$\underline{H}$), 1.80(2H, m, $C\underline{H}_2CH_3$), 3.00(2H, d, J=9.0 Hz, C-1$\underline{H}$), 3.20(1H, m, C-6$\underline{H}$), 3.92(1H, dt, J=3.0, 9.0 Hz, C-5$\underline{H}$), 5.22(1H, d, J=14.0 Hz, ArC$\underline{H}$H), 5.53(1H, d, J=14.0 Hz, ArCH$\underline{H}$), 7.65(2H, d, J=9.0 Hz, Ar$\underline{H}$), 8.22(2H, d, J=9.0 Hz, Ar$\underline{H}$).
10. For all the carbapenem compounds listed in this table, satisfactory spectroscopic data were obtained. For example, compound 3a(R=thenoyl) gave the following data: UVλ_{max}^{THF} nm(ε) 315(sh.)(14300), 266(20100); IR($CHCl_3$, cm^{-1}) 1773(beta-lactam), 1717(ester); NMR($CDCl_3$)δ 1.02(3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.90(2H, m, $C\underline{H}_2CH_3$), 2.80-4.00(3H, m, C-1$\underline{H}$, C-6$\underline{H}$), 4.12(1H, dt, J=3.0, 9.0 Hz, C-5$\underline{H}$), 5.30(1H, d, J=14.0 Hz, ArC$\underline{H}$H), 5.55(1H, d, J=14.0 Hz, ArCH$\underline{H}$), 7.21(1H, t, J=4.5 Hz, C-4'$\underline{H}$), 7.79(1H, d, J=4.5 Hz, C-5'$\underline{H}$), 7.93(1H, d, J=4.5 Hz, C-3'H), 7.72(2H, d, J=9.0 Hz, Ar$\underline{H}$), 8.30(2H, d, J=9.0 Hz, Ar$\underline{H}$); MS(m/z) 458(M^+), 388(M^+-EtCH=C=O).

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