

A Facile Halogenative Cyclization of 4-(2-Benzothiazolyldithio)azetidinones (Kamiya's Disulfide) into 2 β -(Halomethyl)penams in a Two Layer System

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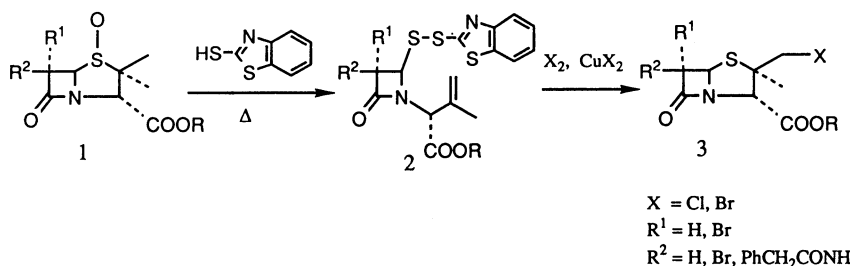
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Synopsis. Chlorinative cyclization of 4-(2-benzothiazolyldithio)azetidinones into 2 β -(chloromethyl)penams has been successfully performed by treatment with aqueous sodium nitrite in a two-layer solution comprising aqueous hydrochloric acid and dichloromethane layers. Similarly, the corresponding 2 β -(bromomethyl)penams can be obtained by use of aqueous hydrobromic acid in place of aqueous hydrochloric acid.

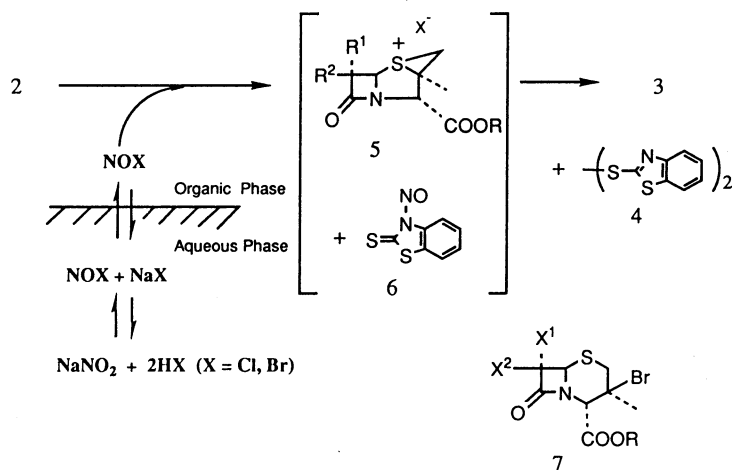
The nucleophilic substitution of the chlorine atom of 2 β -(chloromethyl)penams **3** (X=Cl)¹⁾ is a promising procedure for the synthesis of various 2 β -(substituted methyl)penams and 3 β -substituted cepham.^{1c,2)} The 2 β -(chloromethyl)penams **3** (X=Cl) has been prepared by a two-step operation involving thermolysis of penicillanate 1-oxides **1** with 2-mercaptobenzothiazole leading to Kamiya's disulfide **2**^{1a)} and subsequent chlorinative cyclization with chlorine and copper(II) chloride (Scheme 1).^{1a-c)} In a practical sense, however, the hitherto known methods for the latter step (**2**—**3**) suffer from inevitable disadvantages due to the contamination of overchlorination products and/or

difficulties in removing copper complexes generated in the reaction. Therefore, we needed a new device for the chlorinative cyclization of 4-(2-benzothiazolyldithio)azetidinones **2** in high product selectivities without the tedious workup process. For this purpose, we have elaborated a unique two-layer system, comprising aqueous sodium nitrite-hydrochloric acid and dichloromethane as illustrated in Scheme 2 in which the chlorinative cyclization of **2** can be performed smoothly to afford **3** (X=Cl) in satisfactory yields.

The present method is characterized by the simple operation and the high yield of the product **3** (X=Cl). Into the two-layer solution comprising a dichloromethane solution of 4-dithioazetidinones **2** (R¹=R²=H) and aqueous 22% hydrochloric acid was added portionwise aqueous 8% sodium nitrite. After being stirred for a few hours, the organic layer was separated and worked up in a conventional manner to afford 2 β -(chloromethyl)penams **3a—c** (R¹=R²=H, X=Cl) together with bis(2-benzothiazoyl) disulfide **4** in good yields, (Table 1, Entries 1—3). Undesired side products, e.g. overchlorina-



Scheme 1.



Scheme 2.

Table 1. A Facile Synthesis of 2 β -(Halomethyl)penams 3^{a)}

Entry	4-Dithioazetidinone				Time h	Product		Yield ^{c)} %
	2	R ¹	R ²	R ^{b)}		3	X	
1	2a	H	H	PNB	2	3a	Cl	91
2	2b	H	H	PMB	2	3b	Cl	92
3	2c	H	H	CHPh ₂	2	3c	Cl	92
4	2d	Br	H	PNB	3	3d	Cl	91
5	2e	Br	Br	PMB	5	3e	Cl	93
6	2f	Br	Br	CHPh ₂	5	3f	Cl	95
7	2g	H	PhCH ₂ CONH	CH ₂ Ph	2	3g	Cl	91
8	2a	H	H	PNB	1	3h	Br	77(99) ^{d)}
9	2e	Br	Br	PMB	5	3i	Br	95

a) Carried out with 8% aqueous sodium nitrite (1.1–2 equiv) in 22% hydrochloric acid (or 10% hydrobromic acid) and dichloromethane. b) PNB: *p*-nitrobenzyl; PMB: *p*-methoxybenzyl. c) Isolated yields. d) A mixture of 3h and 7h (56/44) was obtained after column chromatography.

tion products or β -lactam ring-opened products were not detected in the crude products. The isolation of the product 3 from the disulfide 4 can be easily performed by a fractional recrystallization from acetone and/or methanol.

The chlorinative cyclization of various 4-dithioazetidinones derivatives 2 was similarly performed in the two layer system (Entries 4–9). 3-Bromo-, 3,3-dibromo-, and 3-(phenylacetamido)azetidinones 2d–g were transformed to the corresponding penicillanates 3d–g in good yields.

In addition, the two-layer system can be applied successfully to the preparation of the corresponding 2 β -(bromomethyl)penams 3 (X=Br) by use of hydrobromic acid in place of hydrochloric acid. The 2 β -(bromomethyl)penams 3 are very susceptible to isomerization to 3 β -bromocepham 7; indeed, upon the chromatography on a silica gel, 3h (R¹=R²=H, X=Br) was partly isomerized to a mixture of 3h and 7h (55/44). Fortunately, pure 2 β -(bromomethyl)penams 3 were obtained by fractional recrystallization from acetone and/or ether immediately after the reaction.

Although the reaction mechanism has not yet been clarified, nitrosyl halide (NOX) generated in the aqueous phase seems to play a significant role; thus, in an aqueous phase, sodium nitrite would react with hydrogen halide to generate nitrosyl halide, which moves to the organic phase and reacts with 4-dithioazetidinones 2, generating tricyclo sulfonium ion 5 and nitroso intermediate 6. In turn, the former would produce 2 β -(halomethyl)penam 3 by the attack of halide ion on the 2 β -methylene carbon of 5, while the latter would undergo disproportionation and/or further reaction with 4-dithioazetidinones 2 to give dimer 4.

Experimental

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-1 grating spectrophotometer. ¹H NMR spectra were taken on a Hitachi R-24 (60 MHz) and a JEOL MX-100 spectrometers (100 MHz) using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-DX303 spectrometer. Microanalyses were performed in our laboratory.

General Procedure for Synthesis of 2 β -(Chloromethyl)penams (Table 1, Entries 1–7). *p*-Nitrobenzyl 2 β -(Chloromethyl)-2 α -methylpenam-3 α -carboxylate (3a): To a solution of *p*-nitrobenzyl [(*R*)-4-(2-benzothiazol-2-ylidithio)-2-oxo-1-azetidinyl]isopropenylacetate (2a) (501 mg, 1 mmol) in dichloromethane (4 ml) and 22% hydrochloric acid (4 ml) was added sodium nitrite (76 mg, 1.1 mmol) in water (1 ml) portionwise at 0 °C. The stirring was continued for 2 h at 0 °C. The precipitates bis(2-benzothiazolyl) disulfide (4) were filtered and washed with a small amount of dichloromethane. The filtrates and washing were combined, washed with water, aqueous sodium hydrogencarbonate, and brine, and dried (Na₂SO₄). After concentration in vacuo, the residue was taken up with a small amount of acetone and insoluble materials were filtered off. The filtrate was again concentrated in vacuo and the residue was crystallized from ether to afford 3a^{1a)} (337 mg, 91%); mp 104–105 °C; IR (KBr) 1780, 1775 cm⁻¹; ¹H NMR (CDCl₃) δ =1.49 (s, 3H, CH₃), 3.15 (dd, *J*=2 and 16 Hz, 1H, 6-H), 3.63 (dd, *J*=4 and 16 Hz, 1H, 6-H), 3.60 (s, 2H, CH₂Cl), 5.12 (s, 1H, 3-H), 5.30 (s, 2H, OCH₂), 5.40 (dd, *J*=2 and 4 Hz, 5-H), 7.57 (d, *J*=8 Hz, 2H, aromatic H), 8.26 (d, *J*=8 Hz, 2H, aromatic H).

p-Methoxybenzyl 2 β -Chloromethyl-2 α -methylpenam-3 α -carboxylate (3b): IR (Neat) 1790, 1750 cm⁻¹; ¹H NMR (CDCl₃) δ =1.43 (s, 3H, CH₃), 3.09 (dd, *J*=2 and 16 Hz, 1H, 6-H), 3.60 (dd, *J*=4 and 16 Hz, 1H, 6-H), 3.59 (s, 2H, CH₂Cl), 3.81 (s, 3H, OCH₃), 5.01 (s, 1H, 3-H), 5.14 (s, 2H, OCH₂), 5.37 (dd, *J*=2 and 4 Hz, 1H, 5-H), 6.89 (d, *J*=9 Hz, 2H, aromatic H), 7.32 (d, *J*=9 Hz, 2H, aromatic H); FAB-MS *m/z* 378 (M–Na)⁺.

Benzhydryl 2 β -Chloromethyl-2 α -methylpenam-3 α -carboxylate (3c):^{1a)} IR (Neat) 1780, 1745 cm⁻¹; ¹H NMR (CDCl₃) δ =1.33 (s, 3H, CH₃), 3.60 (s, 2H, CH₂Cl), 3.11 (dd, *J*=2 and 16 Hz, 1H, 6-H), 3.76 (dd, *J*=4 and 16 Hz, 1H, 6-H), 5.13 (s, 1H, 3-H), 5.40 (dd, *J*=2 and 4 Hz, 5-H), 6.94 (s, 1H, CHPh₂), 7.35 (s, 10H, aromatic H).

p-Nitrobenzyl 6 β -Bromo-2 β -chloromethyl-2 α -methylpenam-3 α -carboxylate (3d):^{1a)} Mp 111–113 °C; IR (KBr) 1800, 1750 cm⁻¹; ¹H NMR (CDCl₃) δ =1.49 (s, 3H, CH₃), 3.48, 3.66 (ABq, *J*=12 Hz, 2H, CH₂Cl), 4.83 (d, *J*=1.3 Hz, 1H, 6-H), 5.15 (s, 1H, 3-H), 5.27, 5.38 (ABq, *J*=9 Hz, 2H, OCH₂), 5.47 (d, *J*=1.3 Hz, 1H, 5-H), 7.57 (d, *J*=9 Hz, 2H, aromatic H), 8.27 (d, *J*=9 Hz, 2H, aromatic H).

p-Methoxybenzyl 6,6-Dibromo-2 β -chloromethyl-2 α -methylpenam-3 α -carboxylate (3e): IR (Neat) 1795, 1735 cm⁻¹; ¹H NMR (CDCl₃) δ =1.40 (s, 3H, CH₃), 3.55 (s, 2H, CH₂Cl), 3.77 (s, 3H, OCH₃), 5.01 (s, 1H, 3-H), 5.12 (s, 2H, OCH₂), 5.75 (s, 1H, 5-H), 6.82 (d, *J*=9 Hz, 2H, aromatic H), 7.24 (d, *J*=9 Hz, 2H, aromatic H); FAB-MS *m/z* 536 (M+Na)⁺.

Benzhydryl 6,6-Dibromo-2 β -chloromethyl-2 α -methylpenam-

3 α -carboxylate (3f): IR (Neat) 1810, 1760 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.31 (s, 3H, CH_3), 3.52, 3.68 (ABq, J =12 Hz, 2H, CH_2Cl), 5.16 (s, 3H, 3-H), 5.85 (s, 1H, 5-H), 6.94 (s, 1H, CHPh_2), 7.35 (s, 10H, aromatic H); FAB-MS m/z 582 ($\text{M}+\text{Na}$) $^+$.

Benzyl 2 β -Chloromethyl-2 α -methyl-6 β -(phenylacetamido)-penam-3 α -carboxylate (3g):³⁾ IR (CHCl_3) 3410, 1780, 1775, 1680 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.62 (s, 3H, CH_3), 3.37 (s, 2H, PhCH_2CO), 3.59 (s, 2H, CH_2Cl), 5.02 (s, 1H, 3-H), 5.14 (s, 2H, OCH_2), 5.45–5.70 (m, 2H, 5-H and 6-H), 6.38 (d, J =8 Hz, 1H, NH), 7.27 (s, 5H, aromatic H), 7.32 (s, 5H, aromatic H).

***p*-Nitrobenzyl 2 β -Bromomethyl-2 α -methylpenam-3 α -carboxylate (3h):** To a solution of **2a** (501 mg, 1 mmol) in dichloromethane (10 ml) and 10% hydrobromic acid (4 ml) was added sodium nitrite (76 mg, 1.1 mmol) in water (1 ml) portionwise at 0 $^\circ\text{C}$. The stirring was continued for 1 h at 0 $^\circ\text{C}$. The precipitates bis(2-benzothiazolyl) disulfide (**4**) were filtered and washed with a small amount of dichloromethane. The filtrate and washings were combined, washed with water, aqueous sodium hydrogencarbonate, and brine, and dried (Na_2SO_4). After concentration in vacuo, the residue was taken up with a small amount of acetone, and insoluble materials were filtered off. The filtrate was concentrated and crystallized from ether to afford **3f**¹⁰⁾ (320 mg, 77%); mp 80–82 $^\circ\text{C}$; IR (KBr) 1790, 1760 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.53 (s, 3H, CH_3), 3.15 (dd, J =2 and 16 Hz, 1H, 6-H), 3.57 (s, 2H, CH_2Br), 3.65 (dd, J =4 and 16 Hz, 1H, 6-H), 5.18 (s, 1H, 3-H), 5.31 (s, 2H, OCH_2), 5.43 (dd, J =2 and 4 Hz, 1H, 5-H), 7.57 (d, J =9 Hz, 2H, aromatic H), 8.26 (d, J =9 Hz, 2H, aromatic H).

In a similar manner, **3i** was obtained.

***p*-Methoxybenzyl 6,6-Dibromo-2 β -bromomethyl-2 α -methylpenam-3 α -carboxylate (3i):** Mp 111–113 $^\circ\text{C}$; IR (KBr) 1800, 1750 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.44 (s, 3H, CH_3), 3.54 (s, 2H, CH_2Br), 3.80 (s, 3H, OCH_3), 5.11 (s, 1H, 3-H), 5.16 (s, 2H, OCH_2), 5.85 (s, 1H, 5-H), 6.69 (d, J =9 Hz, 2H, aromatic H), 7.32 (d, J =9 Hz, 2H, aromatic H). Found: C, 34.42; H, 2.83; N, 2.53%. Calcd for $\text{C}_{16}\text{H}_{16}\text{Br}_3\text{NO}_4\text{S}$: C, 34.56; H, 2.90; N, 2.52%.

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