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

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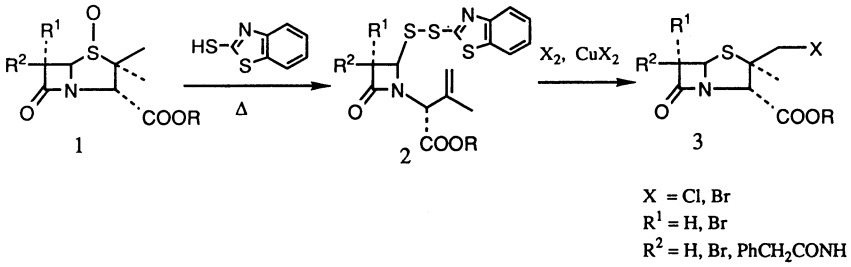
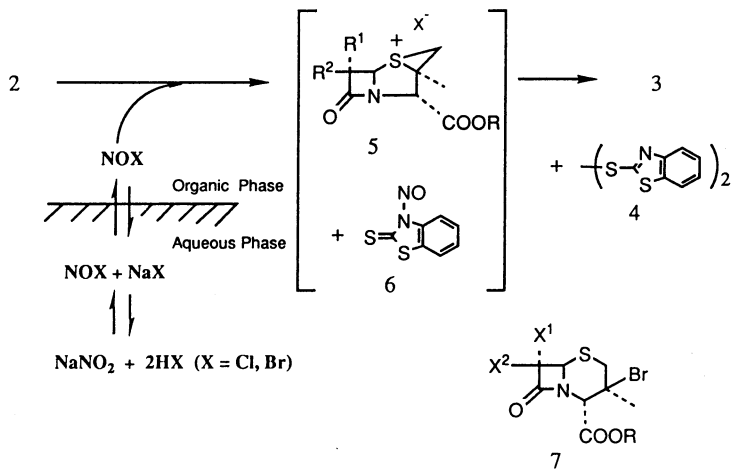
Synopsis. Chlorinative cyclization of 4-(2-benzothiazolyldithio)azetidinones into 2β-(chloromethyl)penams has been successfully performed by treatment with aqueous sodium nitrite in a two-layer solution comprising aqueous hydrochloric acid and dichloromethane layers. Similarly, the corresponding 2β-(bromomethyl)penams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

The nucleophilic substitution of the chlorine atom of 2β-(chloromethyl)penams **3** (X=Cl)[1] is a promising procedure for the synthesis of various 2β-(substituted methyl)penams and 3β-substituted cephams.[1c,2] The 2β-(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** (R^1=R^2=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 2β-(chloromethyl)-penams **3a**—**c** (R^1=R^2=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 2β-(Halomethyl)penams **3**[a]

Entry	4-Dithioazetidinone				Time	Product		Yield[c]
	2	R^1	R^2	R[b]	h	**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	$PhCH_2CONH$	CH_2Ph	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 2β-(bromomethyl)penams **3** (X=Br) by use of hydrobromic acid in place of hydrochloric acid. The 2β-(bromomethyl)penams **3** are very susceptible to isomerization to 3β-bromocepham **7**; indeed, upon the chromatography on a silica gel, **3h** (R^1=R^2=H, X=Br) was partly isomerized to a mixture of **3h** and **7h** (55/44). Fortunately, pure 2β-(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 2β-(halomethyl)penam **3** by the attack of halide ion on the 2β-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. ^{1}H 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 2β-(Chloromethyl)penams (Table 1, Entries 1—7). *p*-Nitrobenzyl 2β-(Chloromethyl)-2α-methylpenam-3α-carboxylate (3a): To a solution of *p*-nitrobenzyl [(*R*)-4-(2-benzothiazol-2-yldithio)-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 (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 again concentrated in vacuo and the residue was crystallized from ether to afford **3a**[1c] (337 mg, 91%); mp 104—105 °C; IR (KBr) 1780, 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.49 (s, 3H, CH_3), 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, CH_2Cl), 5.12 (s, 1H, 3-H), 5.30 (s, 2H, OCH_2), 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 2β-Chloromethyl-2α-methylpenam-3α-carboxylate (3b):** IR (Neat) 1790, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.43 (s, 3H, CH_3), 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, CH_2Cl), 3.81 (s, 3H, OCH_3), 5.01 (s, 1H, 3-H), 5.14 (s, 2H, OCH_2), 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 2β-Chloromethyl-2α-methylpenam-3α-carboxylate (3c):[1c] IR (Neat) 1780, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.33 (s, 3H, CH_3), 3.60 (s, 2H, CH_2Cl), 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, $CHPh_2$), 7.35 (s, 10H, aromatic H).

***p*-Nitrobenzyl 6β-Bromo-2β-chloromethyl-2α-methylpenam-3α-carboxylate (3d):**[1c] Mp 111—113 °C; IR (KBr) 1800, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.49 (s, 3H, CH_3), 3.48, 3.66 (ABq, *J*=12 Hz, 2H, CH_2Cl), 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, OCH_2) 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-2β-chloromethyl-2α-methylpenam-3α-carboxylate (3e):** IR (Neat) 1795, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.40 (s, 3H, CH_3), 3.55 (s, 2H, CH_2Cl), 3.77 (s, 3H, OCH_3), 5.01 (s, 1H, 3-H), 5.12 (s, 2H, OCH_2), 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-2β-chloromethyl-2α-methylpenam-

3α-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 $(M+Na)^+$.

Benzyl 2β-Chloromethyl-2α-methyl-6β-(phenylacetamido-penam-3α-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 2β-Bromomethyl-2α-methylpenam-3α-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 °C. The stirring was continued for 1 h at 0 °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**[1c] (320 mg, 77%); mp 80—82 °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-2β-bromomethyl-2α-methyl-penam-3α-carboxylate (3i):** Mp 111—113 °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 $C_{16}H_{16}Br_3NO_4S$: C, 34.56; H, 2.90; N, 2.52%.

References

1) a) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, **1973**, 3001; b) H. Tanida, T. Tsuji, T. Tsushima, H. Ishitobi, T. Irie, T. Yano, H. Matsumura, and K. Tori, *ibid.*, **1975**, 3303; C) R. G. Micetich, S. N. Maiti, P. Spevak, M. Tanaka, T. Yamazaki, and K. Ogawa, *Synthesis*, **1986**, 292; d) Y. Hamashima, S. Yamamoto, S. Uyeo, M. Yoshioka, M. Murakami, H. Ona, Y. Nishitani, and W. Nagata, *Tetrahedron Lett.*, **1979**, 2595; e) W. J. Gottstein, L. B. Crast, Jr., R. G. Graham, U. J. Hayner, and D. N. McGregor, *J. Med. Chem.*, **24**, 1531 (1981).

2) a) T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, Ger, Offen. 2352199 (1974); *Chem. Abstr.*, **81**, 25687q (1974); b) H. Tanaka, M. Tanaka, A. Nakai, S. Yamada, N. Ishida, T. Ohtani, and S. Torii, *J. Antibiotic.*, **41**, 579 (1988); c) H. Tanaka, M. Tanaka, A. Nakai, S. Yamada, H. Ohbayashi, T. Ohno, and S. Torii, *Chem. Express*, **3**, 618 (1988).

3) H. Tanida and T. Tsuji, Ger. Offen. 2333256 (1974); *Chem. Abstr.*, **80**, 95976m (1974).