A FACILE SYNTHESIS OF MERCAPTOPYRAZOLIDINE USEFUL FOR CONSTRUCTION OF THE PENDANT MOIETY OF 1β-METHYL-CARBAPENEM L-627†

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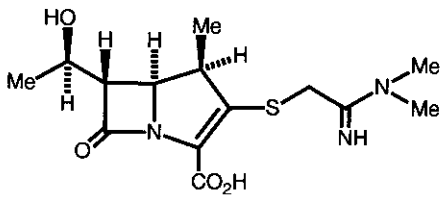
Abstract - A 4-mercaptopyrazolidine derivative (**3**), which is a synthetic intermediate of the pendant moiety of 1β-methylcarbapenem L-627 (**2**), was synthesized by a practical method starting from hydrazine hydrate.

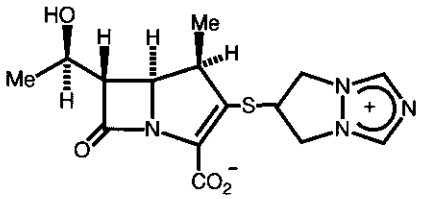
Non-natural 1β-methylcarbapenems (*e.g.*, **1**)[1] have attracted one's attention[2] as a hopeful candidate of new-generation antibiotics because of the excellent feature of their biological activities. Recently, we have disclosed a new 1β-methylcarbapenem (**2**) bearing a σ-symmetric (6,7-dihydro-5*H*-pyrazolo[1,2-a][1,2,4]triazolium-6-yl)thio group at C2 as the important pendant moiety.[3] Compound (**2**) has been submitted to clinical studies on the basis of its excellent antimicrobial activities, chemical stability, and remarkable stability against human renal dehydropeptidase-I.[4] Thus, in order to construct this particular pendant moiety of **2**, we chose 4-mercaptopyrazolidine (**3**) which could be employed for the Michael type addition reaction with (diphenylphosphono)oxy derivative (**4**) to give

† This paper is dedicated to Professor Alan R. Katritzky, University of Florida, on the occasion of his 65th birthday.

thiol adduct (**5**).[3] We now wish to report a few facile synthesis of thiol (**3**) starting from hydrazine hydrate (Schemes 1 and 2).



1



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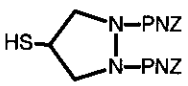

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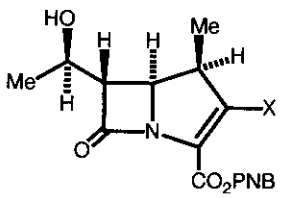
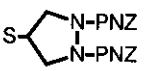
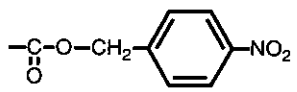


4 X = $OPO(OPh)_2$

5 X =



PNZ =



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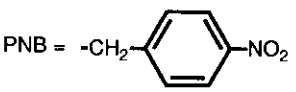
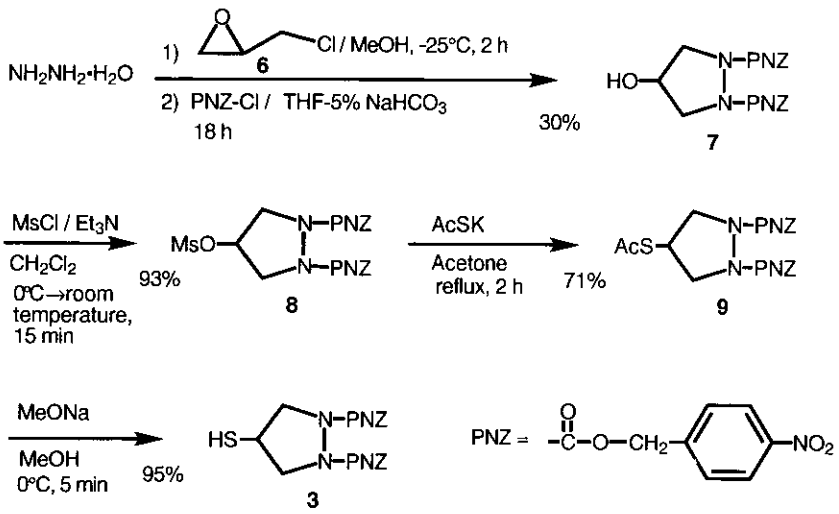


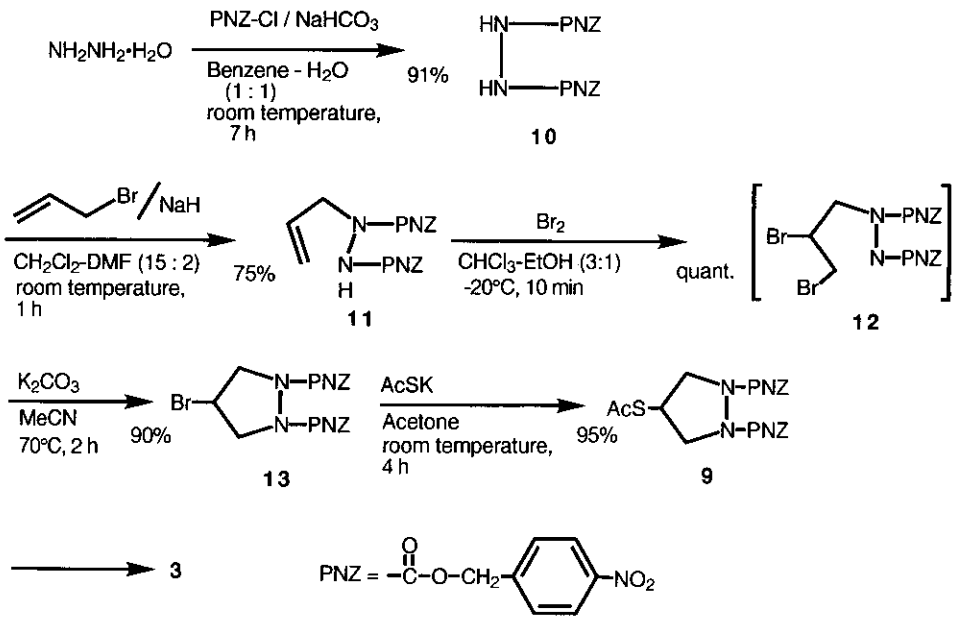
Treatment of hydrazine hydrate with an equimolar amount of *dl*-epichlorohydrin (**6**) in MeOH followed by protection of the resultant cyclic diamine with *p*-nitrobenzyl chloroformate gave compound (**7**) in 30% yield.

Mesylation of **7** with methanesulfonyl chloride and Et_3N in CH_2Cl_2 afforded compound (**8**) in 93% yield. Substitution reaction of mesyloxy group of **8** was performed by its treatment with potassium thioacetate in acetone under the reflux conditions to give acetylthiolate (**9**) (71% yield). This compound was readily converted to the desired thiol (**3**) in 95% yield by methanolysis with sodium methoxide in methanol. All physical and spectroscopic data of the crystalline compound (**3**) should be rationalized for its chemical structure (See experimental part).

Since the chemical yield of **7** from hydrazine hydrate in the synthetic route described above is quite low (30%), we investigated another procedure which is illustrated in Scheme 2. *N,N'*-Bis(*p*-nitrobenzyloxycarbonyl)hydrazine (**10**), obtained in 91% yield by treatment of hydrazine hydrate with



Scheme 1



Scheme 2

p-nitrobenzyl chloroformate, was allowed to react with allyl bromide in the presence of NaH in CH_2Cl_2-DMF (15 : 2) at room temperature to give allylhydrazine bis-PNZ derivative (**11**) in 75% yield. Bromination of **11** followed by cyclization of the resultant dibromide (**12**) with K_2CO_3 in MeCN under heating at 70°C furnished bromopyrazolidine bis-PNZ derivative (**13**) in 90% yield. Compound (**13**) was treated with potassium thioacetate in acetone to give the known acetylthiolate (**9**) in 95% yield. Conversion of **9** to the desired compound (**3**) has been done as described above.

Thus, we achieved a facile and practical synthesis of 4-mercapto-1,2-bis(*p*-nitrobenzyloxycarbonyl)-pyrazolidine (**3**) starting from hydrazine hydrate.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. The ir spectra were recorded on a Hitachi 260-50 spectrophotometer. ^{1}H Nmr spectra were determined on a JEOL JNM-FX 200 (200 MHz) spectrometer in $CDCl_3$ solution and chemical shifts are reported in δ (ppm) relative to tetramethylsilane. Mass spectra were taken on a JEOL JMS-D300 instrument. Elemental analyses were obtained on a Yanaco CHN MT-3 CORDER. Column chromatography was performed on silica gel (Fuji-Davision, BW-127ZH). All reactions were monitored by silica gel F_{254} plates (Merck). All organic extracts were dried over anhydrous sodium sulfate.

4-Hydroxy-1,2-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (7). To a stirred solution of 80% hydrazine hydrate (250.3 mg, 5 mmol) in MeOH (2 ml), a solution of **6** (462.5 mg, 5 mmol) in MeOH (2 ml) was added at -25°C. The mixture was stirred at -25°C for 2 h and the solvent was removed *in vacuo*. To the residue, THF (20 ml), saturated $NaHCO_3$ aqueous solution (20 ml), and *p*-nitrobenzyl chloroformate (2.156 g, 10 mmol) were added. After stirring at room temperature for 18 h, AcOEt (20 ml) was added with vigorous stirring. The organic layer was evaporated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:Me_2CO = 95:5) to give **7** (663 mg, 30%) as colorless needles. mp 150-151°C (CH_2Cl_2-Et_2O). Ir υ_{max} (KBr) cm^{-1}: 3429, 1746, 1693. ^{1}H Nmr δ: 3.20-3.35 (m, 1H), 3.45-3.65 (m, 1H), 3.90-4.05 (m, 1H), 4.05-4.15 (m, 1H), 4.70-4.75 (m, 1H), 5.30 (s, 4H), 7.50 (d, 4H, J = 8.5 Hz), 8.16 (d, 4H, J = 8.5 Hz). High-resolution ms *m/z* Calcd for $C_{19}H_{18}N_4O_9$ (M^+): 446. 1074. Found: 446.1084. *Anal.* Calcd for $C_{19}H_{18}N_4O_9$: C, 51.13; H, 4.06; N, 12.55. Found: C, 50.91; H, 4.00; N, 12.19.

4-Methanesulfonyloxy-1,2-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (8). To a solution of **7** (710 mg, 1.59 mmol) and Et_3N (240.9 mg, 2.39 mmol) in CH_2Cl_2 (15 ml), methanesulfonyl chloride (273.1 mg, 2.39 mmol) was added at 0°C and the mixture was stirred at room temperature for 15 min. The reaction mixture was washed with water and brine and then dried. The solvent was evaporated *in vacuo* to give **8** (775 mg, 93%) as a colorless amorphous powder. Ir υ_{max} (KBr) cm^{-1}: 1719, 1526, 1348. ^1H Nmr δ: 3.00 (s, 3H), 3.40-3.55 (m, 1H), 3.60-3.75 (m, 1H), 4.10-4.25 (m, 1H), 4.50 - 4.65 (m, 1H), 5.30 (s, 4H), 5.35 - 5.40 (m, 1H), 7.52 (d, 4H, J = 8.8 Hz), 8.19 (d, 4H, J = 8.8 Hz). High-resolution ms *m/z* Calcd for $C_{20}H_{20}N_4O_{11}S$ (M^+): 524.0849. Found: 524.0839.

4-Acetylthio-1,2-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (9). From **8**; A suspension of **8** (770 mg, 1.47 mmol) and potassium thioacetate (418.8 mg, 3.67 mmol) in acetone (12 ml) was refluxed for 2 h. The reaction mixture was diluted with water (20 ml) and extracted with AcOEt. The extract was washed with water and brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$) to give **9** (527 mg, 71%) as colorless needles. From **13**; To a solution of **13** (254 mg, 0.5 mmol) in acetone (5 ml), potassium thioacetate (85.5 mg, 0.75 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction mixture was submitted to the same manner mentioned above to give **9** (239.4 mg, 95%). mp 148°C (CH_2Cl_2-Et_2O). Ir υ_{max} (KBr)cm^{-1}: 1703, 1528, 1344. ^1H Nmr δ: 2.30 (s, 3H), 3.20-3.40 (m, 1H),3.60-3.80 (m, 1H), 3.90-4.20 (m, 2H), 4.30-4.50 (m, 1H), 5.30 (s, 4H), 7.50 (d, 4H, J = 8.8 Hz), 8.18 (d, 4H, J = 8.8 Hz). High-resolution ms *m/z* Calcd for $C_{21}H_{20}N_4O_9S$ (M^+): 504.0951. Found: 504.0936. *Anal.* Calcd for $C_{21}H_{20}N_4O_9S$: C, 50.00; H, 4.00; N, 11.11. Found: C, 49.70; H, 3.94; N, 11.00.

***N,N'*-Bis(*p*-nitrobenzyloxycarbonyl)hydrazine (10).** A solution of *p*-nitrobenzyl chloroformate (2.156 g, 10 mmol) in benzene (10 ml) was added to an aqueous solution (water 10 ml) of $NaHCO_3$ (1 g, 12 mmol) and 80% hydrazine hydrate (250 mg, 4 mmol) in water (10 ml) at room temperature. The mixture was stirred at room temperature for 7 h and then precipitated crystals were cropped by filtration, washed with benzene, and dried *in vacuo* at 20-25°C to give **10** (1.42 g, 91%) as colorless needles. mp 172-173°C. Ir υ_{max} (KBr) cm^{-1}: 1700. ^1H Nmr (90 MHz, d_6-DMSO) δ: 5.24 (s, 4H), 7.54 (d, 4H, J = 8.5 Hz), 8.17 (d, 4H, J = 8.5 Hz), 9.15 (br s, 2H).

***N*-Allyl-*N,N'*-bis(*p*-nitrobenzyloxycarbonyl)hydrazine (11).** To a suspension of **10** (390 mg, 1 mmol) and allyl bromide (145.2 mg, 1.2 mmol) in CH_2Cl_2 (3 ml) and DMF (0.4 ml), four 12 mg portions of 60% NaH (1.2 mmol) were added at 20 min intervals at room temperature. The mixture was stirred at room temperature for 1 h, treated with 1N HCl, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$:Me_2CO = 95:5) to give **11** (322.3 mg, 75%) as colorless needles. mp 121-122°C (CH_2Cl_2-Et_2O). Ir υ_{max} (KBr) cm^{-1}: 1757, 1682, 1523. ^1H Nmr δ: 4.20 (d, 2H, J = 7.0 Hz), 5.20-5.40 (m, 2H), 5.26 (s, 4H), 5.80-6.00 (m, 1H), 6.80 (br s, 1H), 7.50 (d, 4H, J = 8.4 Hz), 8.24 (d, 4H, J = 8.4 Hz). High-resolution ms *m/z* Calcd for $C_{19}H_{18}N_4O_8$ (M^+): 430.1125. Found: 430.1145. *Anal.* Calcd for $C_{19}H_{18}N_4O_8$: C, 53.03; H, 4.22; N, 13.02. Found: C, 53.13; H, 4.10; N, 12.90.

4-Bromo-1,2-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (13). Compound (**11**) (292 mg, 0.68 mmol) was dissolved in hot $CHCl_3$ (0.6 ml), and EtOH (0.2 ml) was added to the solution, and then the solution was gradually cooled to -20°C. To the solution, bromine (118.9 mg, 0.74 mmol) was added and the mixture was stirred at -20°C for 10 min. The reaction mixture was treated with saturated aqueous Na_2SO_3 and then extracted with $CHCl_3$. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated *in vacuo* to give **12** (399 mg, 100%) as a yellow amorphous powder. A suspension of **12** (354 mg, 0.6 mmol) and K_2CO_3 (165.6 mg, 1.2 mmol) in MeCN (6 ml) was heated to 70°C for 2 h. After filtration, the filtrate was evaporated *in vacuo*. The residue was dissolved in AcOEt (6 ml) and the solution was washed with brine and dried. The solvent was evaporated *in vacuo* to afford **13** (274.4 mg, 90%) as a colorless amorphous powder. Ir υ_{max} (KBr) cm^{-1}: 1719, 1521, 1343. ^1H Nmr δ: 3.60-3.80 (m, 1H), 3.80-4.00 (m, 1H), 4.30-4.50 (m, 2H), 4.50-4.70 (m, 1H), 5.30 (s, 4H), 7.50 (d, 4H, J = 8.8 Hz), 8.25 (d, 4H, J = 8.8 Hz). High-resolution ms *m/z* Calcd for $C_{19}H_{17}BrN_4O_8$ (M^+): 508.0230. Found: 508.0253. *Anal.* Calcd for $C_{19}H_{17}BrN_4O_8$: C, 44.81; H, 3.36; N, 11.00. Found: C, 44.81; H, 3.36; N, 10.70.

4-Mercapto-1,2-bis(*p*-nitrobenzyloxycarbonyl)pyrazolidine (3). To a solution of **9** (504 mg, 1 mmol) in MeOH (20 ml), 28% MeONa (193 mg, 1 mmol) in MeOH (1 ml) was added at 0°C and then the mixture was stirred at 0°C for 5 min. The reaction mixture was treated with 1N HCl (0.4 ml) and the mixture was concentrated *in vacuo*. To the residue, AcOEt was added and the solution was

washed with water and brine and dried. The solvent was evaporated *in vacuo* to give **3** (439 mg, 95%) as colorless needles. mp 93-94°C (CH_2Cl_2-Et_2O). Ir υ_{max} (KBr) cm^{-1}: 1708, 1522, 1342. ^1H Nmr δ: 1.83 (d, 1H, J = 8.0 Hz), 3.20-3.40 (m, 1H), 3.60-4.00 (m, 3H), 4.10-4.40 (m, 1H), 5.30 (s, 4H), 7.50 (d, 4H, J = 8.5 Hz), 8.17 (d, 4H, J = 8.5 Hz). High-resolution ms *m/z* Calcd for $C_{19}H_{18}N_4O_8S$ (M^+): 462.0845. Found: 462.0835. *Anal.* Calcd for $C_{19}H_{18}N_4O_8S$: C, 49.35; H, 3.92; N, 12.12. Found: C, 49.01; H, 3.81; N, 12.02.

REFERENCE

1. D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles*, **1984**, *21*, 29.
2. (a) R. N. Guthikonda, L. D. Cama, M. Quesada, M. F. Woods, T. N. Salzmann, and B. G. Christensen, *J. Med. Chem.* , **1987**, *30*, 871. (b) C. U. Kim, B. Y. Luh, P. F. Misco, and M. J. Hichicock, *J. Med. Chem.* , **1989**, *32*, 601. (c) M. Sunagawa, H. Matsumura, Y. Inoue, M. Fukasawa, and M. Kato, *J. Antibiotics*, **1990**, *43*, 519. (d) Y. Nagao, T. Kumagai, Y. Nagase, S. Tamai, Y. Inoue, and M. Shiro, *J. Org. Chem.*,**1992**, *57*, 4232 and references cited therein.
3. Y. Nagao, Y. Nagase, T. Kumagai, H. Matsunaga, T. Abe, O. Shimada, T. Hayashi, and Y. Inoue, *J. Org. Chem.*, **1992**, *57*, 4243.
4. (a) K. Ubukata, M. Hikida, M. Yoshida, K. Nishiki, Y. Furukawa, K. Tashiro, M. Konno, and S. Mitsuhashi, *Antimicrob. Agents Chemother.*, **1990**, 994. (b) M. Hikida, K. Kawashima, K. Nishiki, Y. Furukawa, K. Nishizawa, I. Saito, and S. Kuwao, *Antimicrob. Agents Chemother.*, **1992**, 481.

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