C2-ALKYLAMINOPENEM SYNTHESIS

Takumi Yamasaki, Hiroshi Kadoi, and Isao Nagakura*

Chemical Process Development Laboratory, Drug Substance Manufacturing Plant, Pfizer Pharmaceuticals, 5-Gochi, Taketoyo-cho, Chita-gun, Aichi, Japan

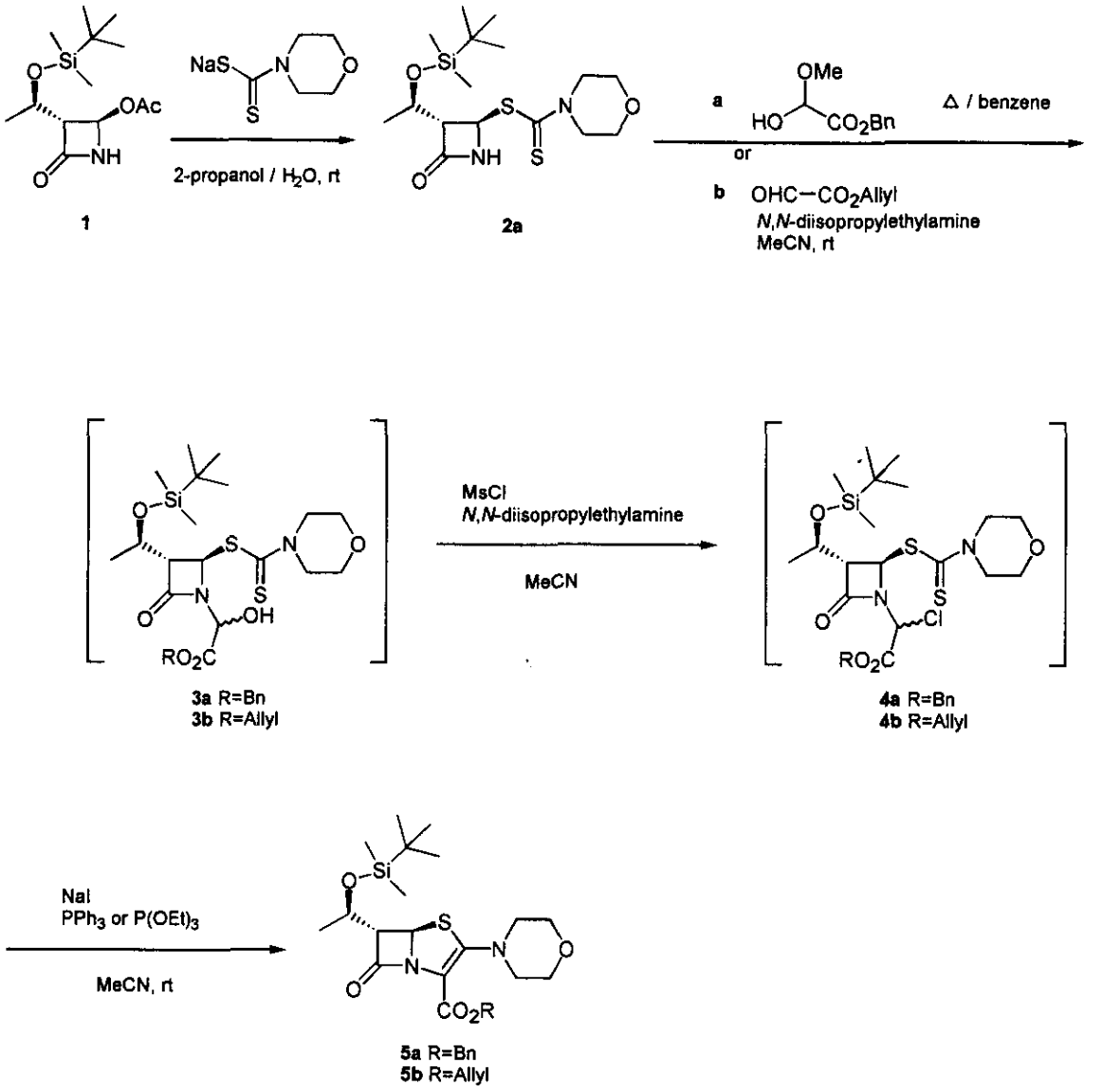
Abstract - A simple synthesis of C2-dialkylaminopenems is described. Azetidinone glyoxylate has been cyclized to C2-aminopenem, *via* an intramolecular sulfide-contraction reaction.

With carbapenem antibiotics, it is known that incorporation of an amino functionality in the C2 position generally leads to dehydropeptidase-1 resistance and strong biological activity against Pseudomonas aeruginosa.[1] These activities are enhanced when the amino group is close to the carbapenem nucleus. This general rule stimulated us to synthesize penem antibiotics bearing alkylamino groups directly connected at the C2 position.

While there are many methodologies for assembling the penem skeleton,[2] synthesis of C2-aminopenems is not straightforward. The classical intramolecular Wittig reaction is limited only to azole derivatives[2] and no intramolecular Wittig cyclization approach has been successfully employed for the preparation of 2-alkylaminopenems.[2-4] For the synthesis of 2-alkylaminopenems, two strategies have been used.[4-5] One[4] involves the intramolecular cyclization of monoalkyliminoazetidinones, and another[5] involves displacement of a leaving group at C2 of the penem framework. The former is limited to monoalkylaminopenems while the latter requires the preparation of C2 activated penems. We describe herein a simple synthetic approach for the synthesis of C2-alkylaminopenems (**Scheme 1**).

We focused our attention on the intramolecular sulfide-contraction approach[6-7] involving **4** taking advantage of the electron donating capability. The thiocarbonate should accelerate nucleophilic displacement of the chloride leaving group in **4**.

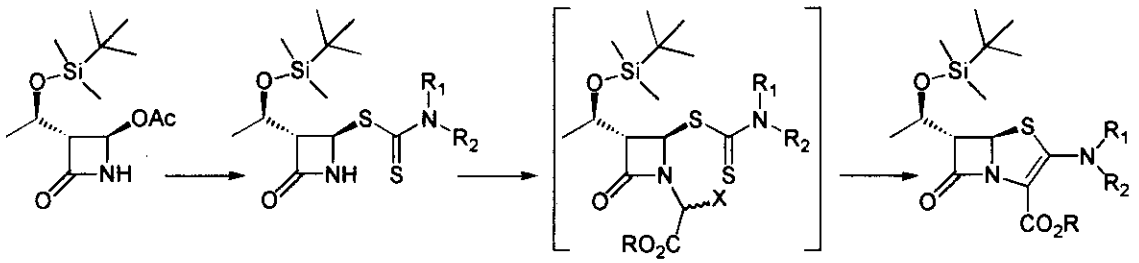
The compound (**2a**), which was obtained from azetidinone (**1**) upon sodium morpholine dithiocarbamate treatment, was allowed to react with benzyl glyoxylate methanol hemiacetal (reflux, 3 days) to give glyoxylate (**3a**) as an oil. Treatment of **3a** with methanesulfonyl chloride and *N,N*-diisopropylethylamine



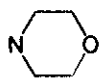
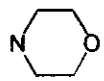
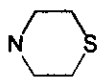
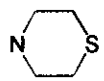
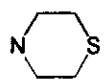
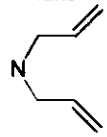
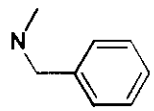
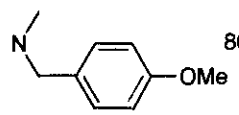
Scheme 1

(DIPEA) in acetonitrile for 3 h at rt provided crude chloride (4a). Addition of triethyl phosphite and sodium iodide to an acetonitrile solution containing chloride provided after 2 h the penem nucleus. Crystals appeared during the concentration of the hexane extract containing crude product. The structure of the colorless crystalline product (**5a**) (16 % yield from **2a**, mp 108℃) was corroborated by IR, NMR, and elemental analysis.[8]

Encouraged by this result, we prepared various C2-amino analogs (**Table 1**).



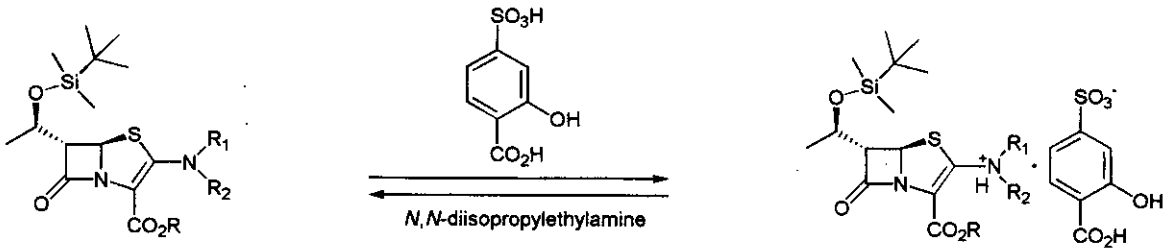
1 **2** **3 X=OH** **4 X=Cl** **5**

	$\begin{matrix}R_1\\N\\R_2\end{matrix}$	Yield (%) **1** to **2**		R	Yield (%) **2** to **5**	mp of **5**
2a		90	**5a**	Bn	16	108−110℃
2a		90	**5b**	Allyl	23	115−117℃
2c		92	**5c**	Bn *	35	95− 97℃
2c		92	**5d** **	*p*-Methoxybenzyl	24	96−100℃
2c		92	**5e**	Allyl *	33	105−107℃
2f		91	**5f** **	Bn	38	−
2g		94	**5g** **	2-Chloroallyl	43	84− 88℃
2g		94	**5h**	2-Trimethylsilylethyl	30	128−130℃
2i		92	**5i** **	Bn	57	60− 63℃
2j		95	**5j** **	*p*-Methoxybenzyl *	43	40− 50℃
2k		91	**5k** **	Bn	42	75− 80℃
2l		86	**5l** **	Bn *	34	−

* : One-pot reaction
** : Sulfosalicylate salt was used for isolation.

Table 1

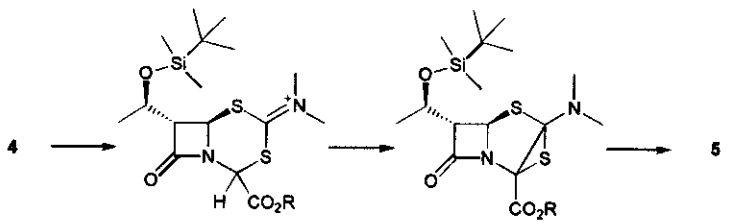
Since the products are unstable and hard to crystallize, several products were isolated as their sulfosalicylate salts for purification, then converted to free base (**5**) by neutralization with DIPEA in ether (**Scheme 2**).



5 **sulfosalicylate salt of 5**

Scheme 2

A one pot conversion of **2**→**5** is possible.[9] Penem (**5c**), (**5e**), (**5j**), and (**5l**) were produced *via* the one pot reaction. The conversion of **4**→**5** proceeds with trialkyl phosphite or triphenylphosphine, and most likely involves an intramolecular cyclization of **4** to yield **A** and transannular cyclization to **B** followed by sulfur exclusion by phosphite gives C2-aminopenem (**5**). Various attempt to remove protecting groups in the esters failed, probably due to instability of the resulting acid.



ACKNOWLEDGMENTS

We gratefully acknowledge discussion with Dr. R. A. Volkmann, Groton Central Research Pfizer.

REFERENCES AND NOTES

1. (a) 'The 23rd International Conference on Antimicrobial Agents and Chemotherapy, Las Vegas', Abstract No. 334.
   (b) Y, Sumita, H. Yamaga, and M. Sunagawa, *J. of Antibiotics*, 1995, 48, 89.
   (c) M. Sunagawa and A. Sasaki, *J.Synthetic Org. Chem. Japan*, 1996, 54, 761.
2. M. Lang, P. Schneider, R.Scartazzini, W. Tosch, E. A. Konopk, and O. Zak, *J. of Antibiotics*,1987, 40, 217 and references cited therein.
3. S. Oida, A. Yoshida, T. Hayashi, N. Takeda, and E. Ohki, *Chem. Pharm. Bull.*, 1980, 28, 3232.
4. M. Cossement, J. M. Brynaert, S. Bogdan, and L. Ghosez, *Tetrahedron Lett.*, 1983, 24, 2563.

5. A. J. Barker, M. R. Teall, and G. Johnson, *Tetrahedron Lett.*, 1987, 28, 2283.

6. J. S. Petersen, G. Fels, and H. Rapoport, *J. Am. Chem. Soc.*, 1984, 106, 4539 and references (6) cited therein.

7. O. Sakurai, T. Ogiku, M. Takahashi, H. Horikawa, and T. Iwasaki, *Tetrahedron Lett.*, 1994, 35, 2187.

8. IR (KBr): 1760, 1680 (cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ ppm: 0 (s, 3H), 0.04 (s, 3H), 0.80 (s, 9H), 1.25 (d, J=6.2 Hz, 3H), 3.34-3.83 (m, 9H), 4.20-4.29 (m, 1H), 5.13 and 5.19 (AB, J=15.4 Hz, 2H), 5.29 (d, J=1.5 Hz, 1H), 7.23-7.43 (m, 5H). Anal. Calcd for $C_{25}H_{36}N_2O_5SSi$; C, 59.49; H, 7.19; N, 5.55. Found: C, 59.32; H, 7.22; N, 5.63.

9. Typical procedure: To a solution of glyoxylic acid allyl ester (0.32 g, 2.0 mmol) and (3*S*, 4*R*)-3-[(1*R*)-1-[(dimethyl-*tert*-butylsilyl)oxy]ethyl]-4-[[(4-thiomorpholinyl)thiocarbonyl]thio]-2-azetidinone (**2c**, 0.75 g, 1.80 mmol) in dry acetonitrile (7.5 mL) was added *N*,*N*-diisopropylethylamine (DIPEA) (0.032 ml, 0.19 mmol) at 3～5℃. After the mixture was stirred at rt for 2 h, DIPEA (1.43 mL, 8.14 mmol) and methanesulfonyl chloride (0.22 mL, 2.78 mmol) were successively added at 3～5℃, and the resulting mixture was stirred for 3.5 h at the same temperature. To the reaction mixture were added triethyl phosphite (0.25 mL, 1.48 mmol) and sodium iodide (0.55 g, 3.70 mmol), then the mixture was stirred further for 2 h. The reaction mixture was diluted with hexane (30 mL), washed with water (three times), 0.1 M citric acid and brine, dried over Na_2SO_4, and the dried hexane solution was concentrated to the crystal slurry. The resulting crystals were filtered, washed with hexane and dried in vacuo to give allyl (5*R*,6*S*)-6-[1(*R*)-[(dimethyl-*tert*-butylsilyl)oxy]ethyl]-2-(4-thiomorpholinyl)-2-penem-3-carboxylate (**5e**, 0.29 g, 33%) as a yellow crystal. Further crop of **5e** was obtained from the mother liquor by the following procedure. To the ether solution of the mother liquor after solvent replacing from hexane to ether was added sulfosalicylic acid (0.13 g, 0.59 mmol) in ether (2 mL), which was prepared by elimination of water from sulfosalicylic acid dihydrate (0.15 g, 0.59 mmol) in ether (15 mL) by means of Dean-Stark trap. The resulting oily precipitate was collected by decantation, washed with ether, dissolved in CH_2Cl_2 (10 mL), neutralized by addition of DIPEA (0.2 mL, 1.15 mmol), washed with water (two times), 0.1 M citric acid (two times) and brine (two times), dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in ether, concentrated to afford an additional **5e** (0.10 g, 11%).

Received, 10th February, 1997