Pergamon

Tetrahedron Letters, Vol. 38, No. 32, pp. 5687-5690, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01239-2

Side Chain Substitution Reaction of 2-Arylsulfinyl and 2-Arylsulfonyl Intermediates for 1β-Methylcarbapenems.

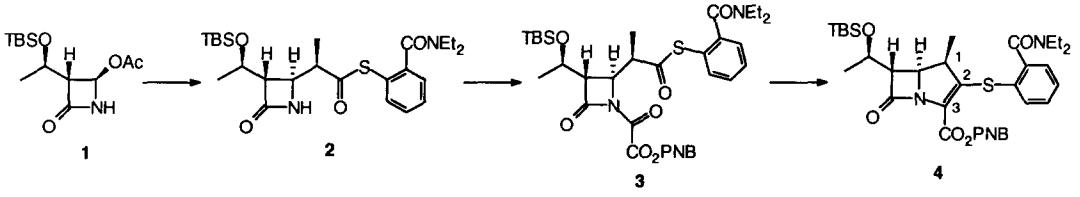
Kozo Oda* and Akira Yoshida

Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd.,
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan

Abstract : Sulfoxide **5** and sulfone **6** derived from 1β-Methylcarbapenem **4** yielded the precursors of 1β-methylcarbapenems by $MgBr_2{\cdot}Et_2O$ mediated C-2 side chain substitution reaction with functionalized mercaptans. © 1997 Elsevier Science Ltd.

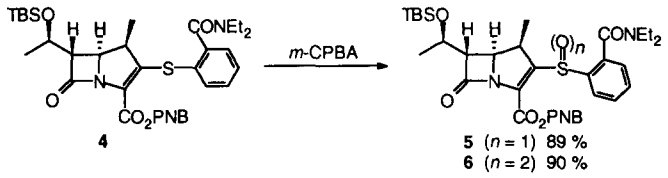
1β–Methylcarbapenems comprise a potent and broad spectrum of antibiotics.[1] They are more beneficial than 1-unsubstituted carbapenems such as thienamicin,[2] because of their enhanced chemical stability and resistance to renal dehydropeptidase-1.

In the previous paper, we presented our plan for a general and convergent route to 1β-methylcarbapenems involving the side chain substitution reactions of 2-sulfinyl and 2-sulfonyl intermediates with mercaptans, and reported the successful preparation of precursor **4** from 4-acetoxyazetidinone **1**.[3]



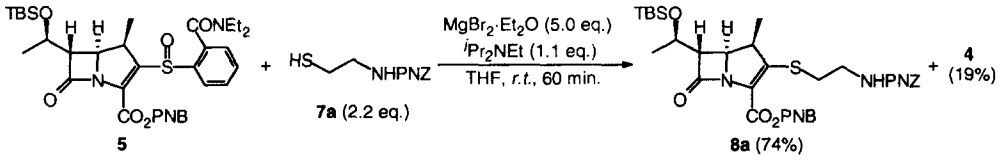
It was reported that the substitution reaction of the 2-sulfinyl group of 1-unsubstituted carbapenems was performed utilizing organic base, resulting in moderate yield.[4a,b] In contrast, the corresponding reaction of a 1β-methylcarbapenem derivative afforded a substituted product in rather poor yield, around 30%.[4c] It was also observed in our preliminary attempt that the analogous substitution reaction of sulfoxide **5** with mercaptan **7a** (2.0 equiv) in the presence of $^{i}Pr_2NEt$ resulted in only 4% yield of the 1β-methylcarbapenem **8a**, the precursor of 1β-methylthienamycin,[5] accompanied by some unidentified polar products. In this paper, the extent to which addition of $MgBr_2{\cdot}Et_2O$ greatly improved the efficiency of the substitution reaction of sulfoxide **5** and sulfone **6** is described.

The substrates, sulfoxide **5** and sulfone **6**, were prepared by oxidation of 1β-methylcarbapenem **4** with *m*-chloroperbenzoic acid (*m*-CPBA) as shown in Scheme 1.



Scheme 1

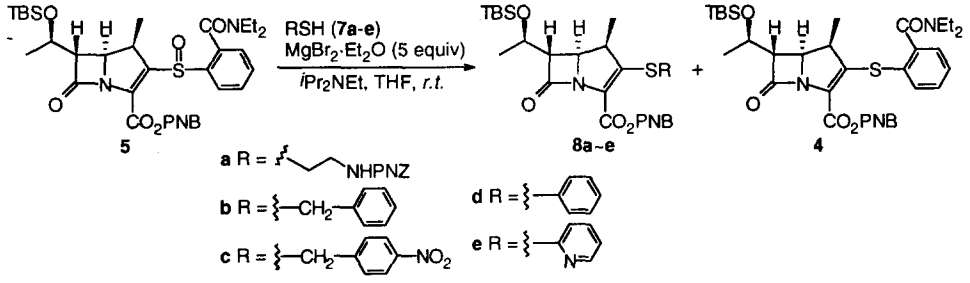
When $MgBr_2 \cdot Et_2O$ (5 equiv) was added to the previously mentioned conventional conditions, for the purpose of promoting the addition step of mercaptan, the yield of **8a** increased to 74%. In this reaction, compound **4** (19%) was formed as the sole by-product.[6]



Scheme 2

Other examples using various mercaptans are summarized in Table 1.[7] In some cases, an equivalent result was obtained even in the absence of $^iPr_2NEt$, although the rate of reaction was generally decelerated in the absence of the base.

Table 1 Side Chain Substitution of Sulfoxide **5**



Entry	Mercaptan (equiv)	$^iPr_2NEt$ (equiv)	Reaction time	Product	Yield (%)	**4** (%)
1	**7a** (1.1)	1.0	120 min	**8a**	55*	trace
2	**7a** (2.2)	1.1	60 min	**8a**	74	19
3	**7a** (2.2)	-	22 hr	**8a**	68	14
4	**7b** (2.0)	1.1	60 min	**8b**	79	trace
5	**7c** (2.0)	-	45 min	**8c**	88	trace
6	**7d** (2.2)	-	40 min	**8d**	65	28
7	**7e** (2.2)	2.0	90 min	**8e**	70	trace

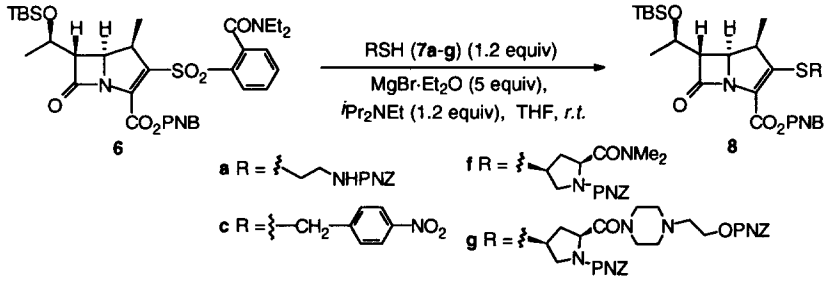
* 37% of sulfoxide **5** was recovered.

As shown in Table 1, substituted products **8** were obtained in reasonable yields. Although sulfide **4** was also formed to a certain extent depending on the nature of the mercaptan used (entries 2, 3, 6), it should be

noted that no product with a cleaved β-lactam ring was detected.

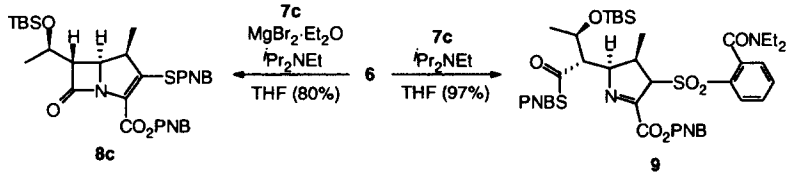
As theoretically determined, two equivalents of mercaptan were employed for complete consumption of sulfoxide **5** in the substitution reaction, due to the competing disulfide formation which was caused by the high reactivity of liberated sulfenic acid.[6] In order to avoid this problem, a substitution reaction employing sulfone **6** as the substrate was attempted. Reactions with sulfone **6** proceeded similarly in the presence of $MgBr_2 \cdot Et_2O$ (5 equiv), but the addition of base (1.2 equiv) was necessary in all cases. The reactions were slower than those of corresponding sulfoxides and it took from several hours to one day to complete the reactions. However, satisfactory yields were achieved by use of only a slight excess of mercaptan (1.2 equiv), which was an economical advantage when expensive mercaptan was used. The results using various mercaptans are listed in Table 2.

Table 2 Side Chain Substitution of Sulfone **6**



Entry	Mercaptan	Reaction time	Product	Yield (%)
1	**7a**	19 hr	**8a**	87
2	**7c**	16 hr	**8c**	56
3	**7f**	19 hr	**8f**	73
4	**7g**	22 hr	**8g**	60

The effect of the addition of $MgBr_2 \cdot Et_2O$ was quite remarkable as shown below. When the reaction between 2-sulfonyl derivative **6** and mercaptan **7c** was carried out in the absence of $MgBr_2 \cdot Et_2O$, compound **9**, with a cleaved β-lactam ring, was obtained as the sole product. Similar ring cleavage was also observed in the conventional base-promoted reaction between a sulfoxide and a mercaptan.[4c]



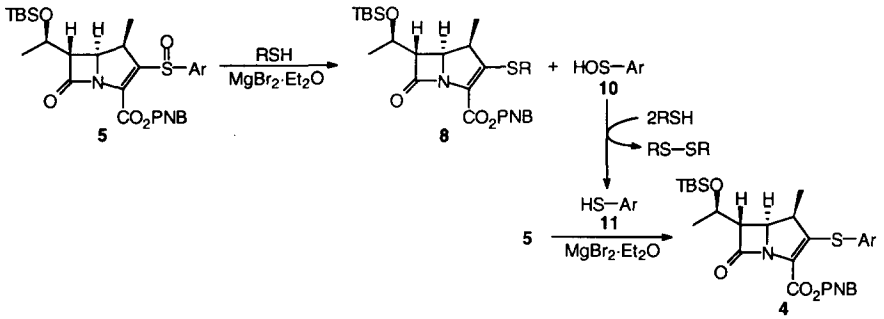
Scheme 3

Desilylation of **8a** and **8f** according to the procedure developed by Seki,[8] afforded the reported derivatives of 1β-methylthienamycin[5] and meropenem[9] in 84% and 69% yield, respectively.

In conclusion, it was found that $MgBr_2 \cdot Et_2O$ effectively promotes the side chain substitution reaction of sulfoxide **5** and sulfone **6** with a variety of mercaptans in the synthesis of various 1β-methylcarbapenem derivatives.

References and Notes

1. Shih, D. H.; Baker, F.; Cama, L,; Christensen, B. G. *Heterocycles* **1984**, *21*, 29-40.
2. a) Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A. Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B. Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491-6499.
   b) Kahan, J. S.; Kahan, F. M.; Goegelman, G.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W. Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiotics* **1979**, *32*, 1-12.
3. Oda, K.; Yoshida, A. being submitted
4. a) Sakamoto, M.; Yamamoto, K; Isshiki, K.; Ishikura, T.; Fukagawa, Y.; Yoshioka, T. *J. Antibiotics* **1990**, *43*, 1254-1270 and references cited therein.
   b) Takemura, M.; Higashi, K.; Fujiwara, H.; Sato, M.; Furukawa, M. *Chem. Pharm. Bull.* **1986**, *34*, 1089-1093.
   c) Rao, V. S.; Remillard, R.; Menard, M. *Heteroatom Chemistry* **1992**, *3*, 25-31.
5. Shih, D. H.; Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1985**, *26*, 587-590.
6. Theoretically, compound **4** can be produced by the $MgBr_2{\cdot}Et_2O$ promoted reaction between sulfoxide **5** and 2-(diethylaminocarbonyl)benzenethiol **11** which would arise from sulfenic acid **10** via reduction by the substrate mercaptan.



7. Typical procedure: To a solution of sulfoxide **5** (341 mg, 0.499 mmol) and mercaptan **7c** (294 mg, 1.11 mol) in tetrahydrofuran (10 ml) was added $MgBr_2{\cdot}Et_2O$ (657 mg, 2.54 mmol) and $^iPr_2NEt$ (97 µl, 0.56 mmol), and the reaction mixture was stirred for 60 min at room temperature. After being diluted with EtOAc, the solution was washed with water and brine in turn, dried over anhydrous $MgSO_4$, then concentrated. The oily residue was purified by silica gel flush column chromatography to give **4** (63 mg, 19 %) as a colorless crystalline solid from the less polar fraction (EtOAc/hexane = 1/1) and **8a** (264 mg, 74 %) as a pale yellow foam from the more polar fraction (EtOAc/hexane = 3/2).
8. Seki, M.; Kondo, K.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *Synlett* **1995**, 609-611.
9. Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *43*, 519-532.

(*Received in Japan* 26 *May* 1997; *revised* 16 *June* 1997; *accepted* 18 *June* 1997)