Alkylation of 4-Acetoxy-2-azetidinone Derivative with Lithium Enolates of α-*N*-(Diphenylmethylene)amino Acid Esters

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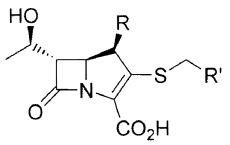
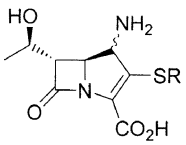
Since the discovery of thienamycin (**1**),[1] extensive efforts have been devoted to the development of new carbapenem antibiotics. Shih *et al.* at Merck developed 1β-methylcarbapenem (**2**) which possesses fairly strong stability against renal dehydropeptidase-I and chemical stability.[2] In addition, they reported the synthesis of 1-heteroatom-substituted carbapenems, including 1-aminocarbapenems (**3**), which are effective against Gram-positive and Gram-negative bacteria.[3] Their approach to the synthesis of 1-aminocarbapenems (**3**) involves introduction of the amino group at the C-4 side chain of (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-methoxycarbonylmethyl-2-azetidinone by bromination, substitution with azide, and reduction in sequence and cyclization *via* the Merck carbene insertion reaction.

We have been interested in a short route to the synthesis of **3** by alkylation at the C-4 position of 4-acetoxy-2-azetidinone derivative (**4**) with lithium enolate of *N*-protected glycine ester followed by cyclization. However, it was observed that treatment of 4-acetoxy-2-azetidinones with lithium or sodium enolates did not give good yields of alkylation products.[4] Several special methods were developed for the alkylation of 4-acetoxy-2-azetidinones by reaction with silyl enolates in the presence of Lewis acid,[5] or boron enolates,[6] tin (II) enolates,[7] zinc enolates[8] or zirconium enolates.[4e,9] From these results Nagao *et al.*[7c] rationalized that cyclic *N*-acylimines readily obtained from 4-acetoxy-2-azetidinones by removal of acetic acid behave as soft electrophile, so that they react easily with soft anions such as silyl, boron, tin (II), zinc or zirconium enolates. Nagao *et al.*[10] reported a highly diastereocontrolled alkylation at the C-4 position of 4-acetoxy-2-azetidinone employing chiral tin (II) enolate of *N*-cbz protected glycine derivative (52% yield).

We assumed that the lithium enolate of benzophenone imine of glycine ester would react easily with 4-acetoxy-2-azetidinone derivative (**4**), because it should have a soft basicity due to the delocalization of negative charge by diphenylmethylideneamino group resonance.[11] Here we report the alkylation at the C-4 position of **4** with the lithium enolates of benzophenone imines of glycine esters and other α-amino acid esters.



1. R = H, R' = CH_2NH_2
2. R = CH_3, R' = $C(=NH_2)N(CH_3)_2$



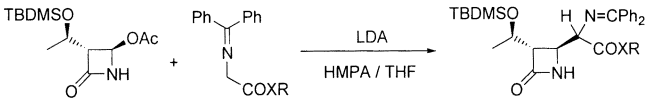
3. R = Alkyl, Aryl

α-*N*-(Diphenylmethylene)amino acid esters and thioesters[12] were prepared as described by O'Donnell.[13] The lithium enolates of *N*-(diphenylmethylene)glycine esters (**5**), generated with 1.2 equiv. of LDA in THF at -78 °C, were reacted with **4** in THF containing a small amount of HMPA at room temperature to give a diastereomeric mixture of C-4 alkylated 2-azetidinones (**6**) in 71-95% yields.[14] The two diastereomers were isolated by silica gel column chromatography with chloroform-ethyl acetate. The enhanced diastereoselectivity was observed with the increase of the bulk of alkyl substituents in *N*-(diphenylmethylene)glycine esters (**5**) as shown in Table 1. The stereochemistry of the newly formed chiral center at the side chain of the two diastereomers was tentatively assigned by their 2D NOESY spectra on the basis of conformational preference due to hydrogen bonding of the amide NH with the ester carbonyl group.[15]

Treatment of **4** with lithium enolates of **7** in reaction conditions similar to those described for the reactions of **4** with lithium enolates of **5** gave the corresponding alkylation products (**8**) in good yields (Table 2). In each alkylation reaction, two diastereomers formed were isolated by silica gel chromatography. The stereochemistry of the newly formed chiral center at the side chain of the two diastereomers was tentatively assigned by their 2D NOESY spectra in a similar manner to that for the case of **6a**.[16]

In summary, we have shown that the alkylation of 4-acetoxy-2-azetidinone derivative (**4**) with the lithium enolates of benzophenone imines of glycine esters and other α-amino acid esters gave good yields of alkylation products, which can be utilized for the synthesis of 1-aminocarbapenems and

Table 1. Alkylation of **4** with lithium enolates of various *N*-(diphenylmethylene)glycine esters (**5**)

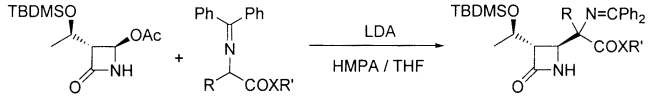


4 **5** **6**

Product[a]	XR	Diastereoselectivity (*R* : *S*)[b]	Yield (%)[c]
6a	OMe	71 : 29	95
6b	OEt	76 : 24	91
6c	OAllyl	78 : 22	71
6d	OBn	82 : 18	85
6e	OPNB	85 : 15	81
6f	OPh	93 : 7	81
6g	SEt	77 : 23	84

[a]All products were confirmed by ^1H and ^{13}C NMR, IR and other characterization. [b]Determined by ^1H NMR for the purified products. [c]Isolated yields.

Table 2. Alkylation of **4** with lithium enolates of some α-*N*-(diphenylmethylene)amino acid esters (**7**)



4 **7** **8**

Product[a]	R	XR'	Ratio of isomers[b] (*R*) : (*S*)	Yield (%)[d]
8a	Me	OMe	1 : 1	87
8b	"	OEt	1 : 1	85
8c	"	OPh	1 : 0.8	81
8d	"	SEt	1 : 1.1	86
8e	Ph	OMe	1 : 2.5	78
8f	$PhCH_2$	OMe	1 : 1	79
8g	$(CH_3)_2CH$	SEt	1 : 0.8[c]	91
8h	$(CH_3)_2CHCH_2$	SEt	1 : 0.9[c]	45
8i	$CH_3SCH_2CH_2$	SEt	1 : 1.2[c]	95
8j	$BnOCH_2$	SEt	1 : 1.5	67
8k	$BnOCOCH_2$	SEt	1 : 1[c]	28

[a]All products were confirmed by ^1H and ^{13}C NMR, IR and other characterization. [b]Determined by ^1H NMR for the purified products. [c]Determined by HPLC for purified products. [d]Isolated yields.

other 1-substituted carbapenems.

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14. A representative procedure: To a solution of *N*-(diphenylmethylene)glycine methyl ester (760 mg, 3.00 mmol) in THF (15 mL) at -78 °C was added an 1.5 *M* solution of LDA in THF (2.4 mL, 3.60 mmol) with stirring under nitrogen atmosphere. The mixture was stirred at -78 °C for 1h. After addition of HMPA (0.8 mL) and a solution of **4** (862 mg, 3.00 mmol) in THF (10 mL), the mixture was stirred at -78 °C for 30 min and at room temperature for 1h. The reaction was then quenched with 25% aqueous NH_4Cl (20 mL) and the mixture was transferred to a separatory funnel containing 20 mL of Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with water and saturated NaCl solution, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the product as an oily residue which was purified by chromatography over silica gel with hexane-ethyl acetate (4 : 1). The two diastereomers were separated by silica gel column chromatoraphy with chloroform-ethyl acetate (35 : 1). **(*R*)-6a** (0.98 g, 68%): $[\alpha]^{19}_D$ -121.3°(c 2.0, $CHCl_3$); **(*S*)-6a** (0.40 g, 27%): $[\alpha]^{18}_D$ +96.6°(c 2.0, $CHCl_3$).
15. The NOESY spectrum of **(*R*)-6a** showed that a NOE was observed between the α-hydrogen (δ 4.17 ppm) at the side chain and C-4 hydrogen (δ 4.13 ppm) of β-lactam moiety, whereas that of **(*S*)-6a** showed that a NOE was observed between the α-hydrogen (δ 4.23 ppm) at the side chain and C-3 hydrogen (δ 2.90 ppm) of β-lactam moiety.
16. In the case of **8a**, the NOESY spectrum of **(*R*)-8a** showed that a NOE was observed between the α-methyl hydrogen (δ 1.44 ppm) at the side chain and C-4 hydrogen (δ 3.71 ppm) of β-lactam moiety, whereas that of **(*S*)-8a** showed that a NOE was observed between the α-methyl hydrogen (δ 1.45 ppm) at the side chain and C-3 hydrogen (δ 1.22 ppm) of β-lactam moiety.