

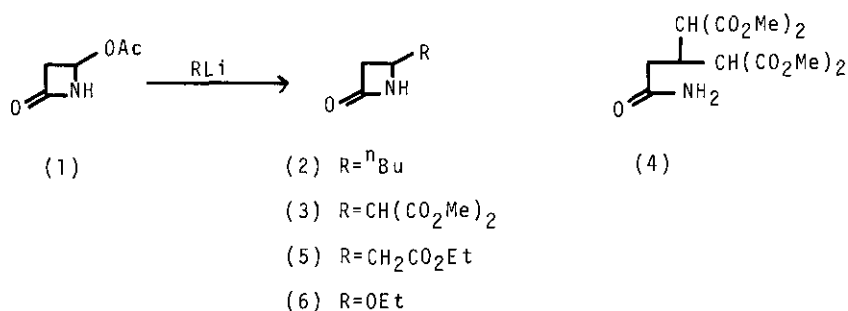
A NEW CARBON-CARBON BOND FORMATION REACTION AT THE C-4 POSITION
OF A β -LACTAM

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Abstract — Reaction of 4-acetoxy-2-azetidinone (**1**) with various organolithiums gave the corresponding C-4 substituted compounds (**2**), (**3**), and (**5**). Treatment of **1** with bromoacetaldehyde diethyl acetal in the presence of magnesium afforded 4-ethoxy-2-azetidinone (**6**) as the only product.

Since carbapenem type antibiotics, such as thienamycin¹ and olivanic acid² are currently very important compounds from the biological point of view, we have been investigating the synthesis of these compounds by the condensation of 4-acetoxy-2-azetidinone with active methylene compounds³. With regard to C-4 substitution of β -lactams, a few papers have been published^{4,5} in which the carbenoid reaction to sulfur was used. Moreover, the reaction of a cuprate reagent with 4-chloro-2-azetidinone derivative has recently been described⁶. We report here a new carbon-carbon bond formation reaction at the C-4 position of a β -lactam which should be very useful in the synthesis of carbapenem and carbacephem type antibiotics. Treatment of the β -lactam⁷ (**1**) with 1 equiv. of *n*-butyllithium in tetrahydrofuran at -78°C for 15 min afforded the 4-butyl-2-azetidinone (**2**) in 12 % yield⁸. The spectroscopic data for all substituted β -lactams prepared are summarized in Table. Reaction of the β -lactam (**1**) with the lithium salt of dimethyl malonate, prepared from *n*-butyllithium and hexamethyldisilazane in tetrahydrofuran, gave the corresponding C-4 substituted product (**3**) in 20 % yield⁸, together with the cleaved compound (**4**); mp 152°C; $\nu_{\max}$ (CHCl₃) 1740 (C=O) cm⁻¹; δ (CDCl₃) 2.68 (2H, d, J = 6 Hz, 2 x -CH(CO₂Me)₂), 3.33 (1H, m, >CHCH₂-), 3.78 (12H, s, 4 x OCH₃), and 6.03 br (2H, s, NH₂); m/e 334 (M⁺ + 1). Introduction of an alkoxycarbonyl group to the

Table



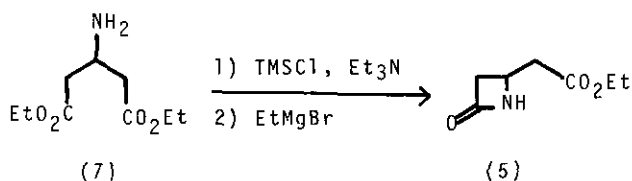
Data Compd.	IR ν_{max} (CHCl_3) cm^{-1}	NMR δ (CDCl_3) ppm	MS
2	3400 (NH) 1750 (C=O)	3.35-3.80 (1H, m, $\text{C}_4\text{-H}$) 7.10-7.60 (1H, br s, NH)	128 ($\text{M}^+ + 1$) 127 (M^+)
3	3425 (NH) 1740 (C=O) 1715 (C=O)	2.85 (2H, d, $J=10\text{Hz}$, $-\text{CH}_2\text{CO}$) 3.30 (1H, m, $\text{C}_4\text{-H}$) 3.55 (1H, d, $J=6\text{Hz}$, $-\text{CH}(\text{CO}_2\text{Me})_2$) 3.83 (6H, s, 2 x OCH_3) 8.66 (1H, brs, NH)	202 ($\text{M}^+ + 1$) 170
5	3425 (NH) 1760 (C=O) 1730 (C=O)	1.31 (3H, t, $J=7\text{Hz}$, $-\text{CH}_2\text{CH}_3$) 2.47-2.87 (1H, m, $\text{C}_3\text{-H}$) 2.67 (2H, d, $J=6\text{Hz}$, $-\text{CH}_2\text{CO}_2$) 3.20 (1H, ddd, $J=2, 5$ and 15Hz , $\text{C}_3\text{-H}$) 3.65-4.10 (1H, m, $\text{C}_4\text{-H}$) 4.30 (2H, q, $J=7\text{Hz}$, $-\text{CH}_2\text{CH}_3$) 7.67 (1H, brs, NH)	158 ($\text{M}^+ + 1$) 157 (M^+) 129 114 70
6	3425 (NH) 1770 (C=O)	1.27 (3H, t, $J=7\text{Hz}$, $-\text{CH}_2\text{CH}_3$) 2.83 (1H, dd, $J=2$ and 15Hz , $\text{C}_3\text{-H}$) 3.58 (2H, q, $J=7\text{Hz}$, $-\text{CH}_2\text{CH}_3$) 5.10 (1H, dd, $J=2$ and 3Hz , $\text{C}_4\text{-H}$) 7.40 (1H, brs, NH)	116 ($\text{M}^+ + 1$) 72

† NMR spectral data are obtained by JNM-PMX 60 in CDCl_3 .

C-4 position was then carried out as follows. The β -lactam (4) was treated with the lithium salt of ethyl acetate in tetrahydrofuran at -78 to -30°C for 3 h to give the desired compound (5) in 15 % yield⁸. However, attempted introduction of an acetaldehyde unit by treatment of bromoacetaldehyde diethyl acetal with magnesium turning afforded none of the desired product, but produced 4-ethoxy-2-azetidinone (6) in 24 % yield⁸.

In order to confirm its structure, compound (5) was prepared by an alternative route. Silylation of diethyl aminoglutaconate⁹ (7) using trimethylchlorosilane and triethylamine and treatment of the product with ethylmagnesium bromide in tetrahydrofuran yielded a compound which was identical to the above product (5).

Scheme



Thus, a new carbon-carbon bond formation reaction at the C-4 position of a β -lactam has been achieved, and its utilization is expected to provide a useful synthetic pathway to carbapenem and carbacephem type antibiotics.

REFERENCES

1. G. Albers-Schönberg, B. H. Arison, O. D. Hensins, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. S. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, J. Amer. Chem. Soc., 1978, **100**, 6491.
2. J. D. Hood, S. J. Box, and M. S. Verrall, J. Antibiotics, 1979, **32**, 295.
3. T. Kametani, S. Hirata, H. Nemoto, M. Ihara, and K. Fukumoto, Heterocycles, 1979, **12**, 523.
4. I. Ernest, Tetrahedron, 1977, **33**, 547.
5. M. D. Bachi, O. Goldberg, and A. Gross, Tetrahedron Letters, 1978, 4167.
6. H. Onoue, M. Narisada, S. Uyeyo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, Tetrahedron Letters, 1979, 3867.

7. K. Clauss, D. Grimm, and G. Prossel, Annalen, 1974, 539.
8. Yields are not optimized.
9. H. Feuer and W. A. Swarts, J. Amer. Chem. Soc., 1955, 77, 5427.

Received, 25th December, 1979