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

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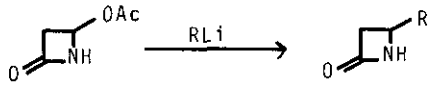
Abstract — Reaction of 4-acetoxy-2-azetidinone (1) with various organolithiums gave the corresponding C-4 substituted compounds (2), (3), and (5). Treatment of 1 with bromoacetaldehyde diethyl acetal in the presence of magnesium afforded 4-ethoxy-2-azetidinone (6) as the only product.

Since carbapenem type antibiotics, such as thienamycin[1] and olivanic acid[2] 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 compounds[3]. 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 described[6]. 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-lactam[7] (1) with 1 eqiv. of n-butyllithium in tetrahydrofuran at -78°C for 15 min afforded the 4-butyl-2-azetidinone (2) in 12 % yield[8]. 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 % yield[8], together with the cleaved compound (4); mp 152°C; ν_{max} ($CHCl_3$) 1740 (C=O) cm^{-1}; δ($CDCl_3$) 2.68 (2H, d, J = 6 Hz, 2 x -C<u>H</u>(CO_2Me)$_2$), 3.33 (1H, m, >C<u>H</u>CH_2-), 3.78 (12H, s, 4 x O<u>C</u>H_3), and 6.03 br (2H, s, N<u>H</u>$_2$); m/e 334 (M^+ + 1). Introduction of an alkoxycarbonyl group to the

Table



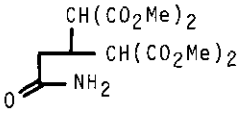
(1)

(2) R=^{n}Bu

(3) R=$CH(CO_2Me)_2$

(5) R=CH_2CO_2Et

(6) R=OEt



(4)

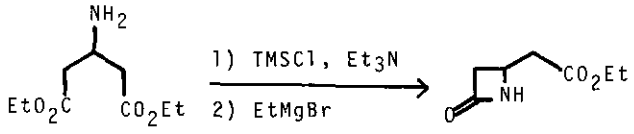
Data / Compd.	IR $\nu_{max}(CHCl_3)$ cm^{-1}	NMR $\delta(CDCl_3)$ ppm	MS
2	3400(NH) 1750(C=O)	3.35-3.80(1H, m, C_4-H) 7.10-7.60(1H, br s, NH)	128(M^++1) 127(M^+)
3	3425(NH) 1740(C=O) 1715(C=O)	2.85(2H, d, J=10Hz, $-CH_2CO$) 3.30(1H, m, C_4-H) 3.55(1H, d, J=6Hz, $-CH(CO_2Me)_2$) 3.83(6H, s, 2 x OCH_3) 8.66(1H, brs, NH)	202(M^++1) 170
5	3425(NH) 1760(C=O) 1730(C=O)	1.31(3H, t, J=7Hz, $-CH_2CH_3$) 2.47-2.87(1H, m, C_3-H) 2.67(2H, d, J=6Hz, $-CH_2CO_2$) 3.20(1H, ddd, J=2, 5 and 15Hz, C_3-H) 3.65-4.10(1H, m, C_4-H) 4.30(2H, q, J=7Hz, $-CH_2CH_3$) 7.67(1H, brs, NH)	158(M^++1) 157(M^+) 129 114 70
6	3425(NH) 1770(C=O)	1.27(3H, t, J=7Hz, $-CH_2CH_3$) 2.83(1H, dd, J=2 and 15 Hz, C_3-H) 3.58(2H, q, J=7Hz, $-CH_2CH_3$) 5.10(1H, dd, J=2 and 3 Hz, C_4-H) 7.40(1H, brs, NH)	116(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 (1) 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 % yield[8]. 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 % yield[8].

In order to confirm its structure, compound (5) was prepared by an alternative route. Silylation of diethyl aminoglutaconate[9] (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



(7) (5)

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.

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8. Yields are not optimized.

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