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A NEW METHOD OF CARBON EXTENSION AT C-4 OF AZETIDINONES

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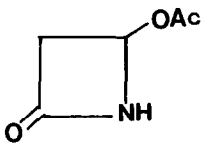
Abstract: Azetidinone carboxylates 7, 9 and 11 were prepared starting from 4-thia azetidinones and carbenes derived from diazoesters.

The availability and the ease with which acetoxy could be exchanged with other groups made 4-acetoxy azetidinone 1 attractive starting material for the construction of biologically interesting bicyclic systems like penems[1], carbapenems[2] and others. Many methods are reported in the literature for the carbon-carbon bond formation at C-4 of these azetidinones through the displacement of the acetoxy or the corresponding sulfonyl group with various carbon nucleophiles[2,3]. The most recent example in this series is the use of tertiary stabilised carbanions[4]. The following report describes a novel method of carbon extension utilising 4-thia azetidinones and the carbenes derived from diazoesters. We have applied this method in the synthesis of some new azetidinone carboxylic acid derivatives.



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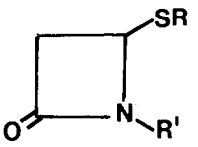
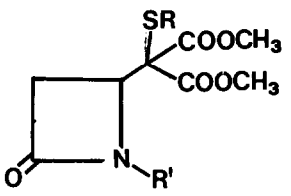
Treatment of azetidinone 2a with 1.2 equivalents of dimethyl diazomalonate at 100° C in the presence of a catalytic amount of Rhodium (II) acetate gave the carbene insertion product 3a [oil, IR (CH_2Cl_2) 1740 cm^{-1} (β-lactam and ester carbonyls), NMR ($CDCl_3$): 0.16, 3H, s, 0.33, 3H, s, 0.95, 9H, s, 3.55, 3H, s, 3.73, 3H, s, 3.37, 2H, d, J = 4.5 Hz, 4.46, 1H, t, J = 4.5 Hz and 7.30-7.60, 5H, m; NMR (C_6D_6) 0.45, 3H, s, 0.64, 3H, s, 1.21, 9H, s, 3.30, 1H, dd, J = 16 and 6 Hz, 3.35, 3H, s, 3.43, 3H, s, 3.68, 1H, dd, J = 16 and 3 Hz, 4.65, 1H, dd, J = 6 and 3 Hz and 7.10-7.80, 5 H, m ppm], in 60 % yield. The proposed structure was in good agreement with the ^{13}C chemical shifts[5]. Treatment of compound 3a with tetrabutylammonium fluoride gave the desilylated product 3a' in quantitative yield.

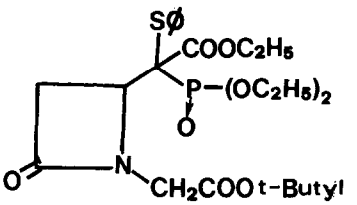
Reaction of compounds 2b, 2c and 2d with dimethyldiazomalonate, under the same conditions, yielded the carbene insertion compounds[6] 3b, 3c and 3d, respectively. Similarly, the reaction of the diazodiethylphosphonoacetic acid ethyl ester[7] with compound 2d afforded azetidinone 4 [oil, IR (CH_2Cl_2) 1760 and 1735 cm^{-1}, NMR ($CDCl_3$): 1.06-1.50, 18H, m, 2.90-4.80, 11H, m and 7.20-7.75, 5H, m ppm] in 58 % yield.



2a R = Phenyl (Ø)	R' = t-Butyldimethylsilyl (tBDMS)
2b R = $CH_2Ø$	R' = tBDMS
2c R = Ø	R' = CH_2COOCH_3
2d R = Ø	R' = CH_2COO t-Butyl



3a R = Ø	R' = tBDMS
3a' R = Ø	R' = H
3b R = $CH_2Ø$	R' = tBDMS
3c R = Ø	R' = CH_2COOCH_3
3d R = Ø	R' = CH_2COO t-Butyl



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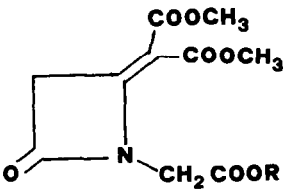
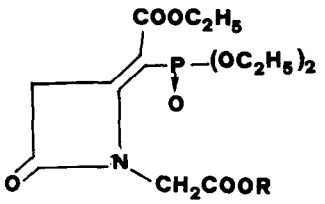
There are several reports in the literature[4,8] describing the synthesis of azetidinones possessing an alkylidene group at C-4. All these coumpounds exhibit the β-lactam carbonyl absorption at about 1840 cm^{-1}, a strong shift to short wave length compared to other β-lactam derivatives. In certain cases the biological activity of the β-lactam antibiotics can be correlated to the chemical reactivity of the β-lactam carbonyl group[9]. Therefore, we carried out the synthesis of some novel 4-alkylidene azetidinone carboxylic acids with the intention of examining their biological activity.

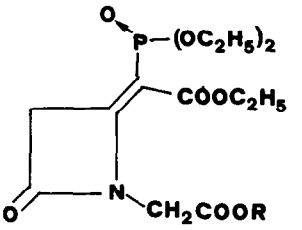
Oxidation of compound 3c with m-chloroperbenzoic acid followed by the thermal elimination of benzenesulphenic acid[4], gave the olefin 5, [oil, IR (CH_2Cl_2) 1820, 1750, 1720 and 1635 cm^{-1}, NMR ($CDCl_3$) 3.76, 6H, s, 3.78, 3H, s, 3.98, 2H, s, and 4.42, 2H, s ppm], in 48 % yield. Our attempts to make the carboxylate 7 from compound 5 under alkaline conditions were unsuccessful and we isolated only the β-lactam free products 12 [IR(KBr): 1735, 1680, 1620 and 1575 cm^{-1}, NMR (D_2O): 3.40, 2H, s, 3.75, 6H, s, 3.83, 3H, s and 4.30, 2H, s ppm) and 13 [IR (KBr): 1560-1700 br, NMR (D_2O): 3.41, 2H, s, 3.74, 6H, s, 3.98, 2H, s ppm]. However, treatment of the t-butylester 6, with trifluoroacetic acid, readily yielded the desired acid, which was subsequently converted to its sodium salt 7 [UV(EtOH) λ max (ε) 267 (16287), IR (KBr) 1810, 1730, 1680 and 1600 cm^{-1}; NMR (D_2O): 3.80, 6H, s; 4.04, 2H, s and 4.14, 2H, s ppm] using aqueous bicarbonate solution.



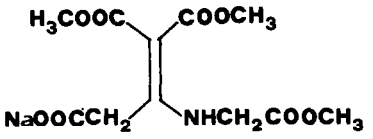
5 R = CH_3
6 R = t-Butyl
7 R = Na



8 R = t-Butyl
9 R = Na



10 R = t-Butyl
11 R = Na



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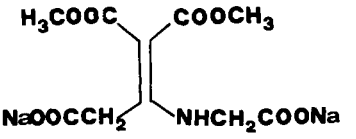

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Similarly, sulfoxidation of azetidinone 4 followed by thermolysis gave the two isomeric olefins 8 [oil, IR (CH_2Cl_2) 1820, 1740, 1705 and 1610 cm^{-1}; NMR ($CDCl_3$) 1.20 - 1.40, 9H, m, 1.48, 9H, s, 3.90 - 4.40, 2H, s ppm] and 10 [oil, IR (CH_2Cl_2) 1820, 1760 sh, 1740, 1705 and 1620 cm^{-1}; NMR ($CDCl_3$) 1.26 - 1.50, 9H, m, 1.44, 9H, s, 3.90 -4.30, 8H, m and 4.42, 2H, s ppm) in 28 and 58 % yield respectively. Treatment of compounds 8 and 10 with trifluoracetic acid, followed by neutralisation afforded the respective sodium salts 9 [UV (EtOH) λmax (ε) 281 (19449); IR (KBr) 1820, 1700 and 1600 cm^{-1}; MNR (D_2O 1.20-1,45, 9H, m and 3.90 -4.40, 10 H, m ppm] and 11 [UV (EtOH) λmax (ε) 275 (12167), IR (KBr) 1820, 1700 and 1620 cm^{-1}; NMR (D_2O) 1.25 -1.45, 9H, m and 3.90 -4.40, 10 H, m ppm] in quantitative yields.

Compounds 7, 9 and 11 did not show any antibacterial activity except against a few highly sensitive organisms.

REFERENCES AND NOTES

1. M. Lang, K. Prasad, J. Gosteli and R.B. Woodward, Helv. Chim. Acta, 63, 1093 (1980).

2. T. Kametani, T. Honda, A. Nakayama and K. Fukumoto, Heterocycles, 14, 1967 (1980).

3. T. Kobayashi, N. Ishida and T. Hiraoka, J.C.S. Chem. Commun. 1980, 736.

4. C.W. Greengrass and D.W.T. Hoople, Tetrahedron Letters, 1981, 1161.

5. ^{13}C NMR chemical shifts of compound 3a are as follows: [4.20 and 4.60 Si($\underline{C}H_3$), 19.7 (Si-$\underline{C}$-), 26.7 (C-($\underline{C}H_3$)$_3$, 44.1 ($\underline{C}H_2$), 53.0 (O$\underline{C}H_3$), 53.2 (O$\underline{C}H_3$), 53.6 ($\underline{C}$H), 67.7 (-$\underline{C}$-), 129.2 (3' and 5' phenyl $\underline{C}$), 129.5 (1' phenyl $\underline{C}$), 129.5 (1' phenyl $\underline{C}$), 130.6 (4' phenyl $\underline{C}$), 137.4 (2' and 6' phenyl $\underline{C}$), 167.1 ($\underline{C}$OO), 167.4 ($\underline{C}$OO) and 173.4 (β-lactam $\underline{C}$O) ppm].

6. Spectral properties:
Compound 3b- [oil, IR (CH_2Cl_2) 1740 cm^{-1}; NMR (C_6D_6) 0.18, 3H, s, 0.34, 3H, s, 0.92, 9H, s, 2.86, 1H, dd, J = 17 and 6 Hz, 3.10, 3H, s, 3.18, 3H, s, 3.26, 1H, dd, J = 17 and 3Hz, 3.74, 2H, s, 4.16, 1H, dd, J = 6 and 3 Hz and 7.06, 5H, s ppm].
Compound 3c - [oil, IR (CH_2Cl_2) 1765, 1745 and 1740 cm^{-1}; NMR ($CDCl_3$) 3.22, 2H, d, J = 4.5 Hz, 3.62, 1H, d, J = 20 Hz, 3.74, 3H, s, 3.76, 6H, s, 4.27, 1H, d, J = 20 Hz, 4.58, 1H, t, J = 4.5 Hz and 7.20 - 7.65, 5H, m ppm].
Compound 3d - [oil, IR (CH_2Cl_2) 1765 and 1740 cm^{-1}; NMR ($CDCl_3$) 1.46, 9H, s, 3.18, 2H, d, J = 4.5 Hz, 3.54, 1H, J = 20 Hz, 3.70, 3H, s, 3.76, 3H, s, 4.22, 1H, d, J = 20 Hz, 4.56, 1H, t, J = 4.5 Hz and 7.20 - 7.60, 5H, m, ppm].

7. Prepared from diethylphosphonoacetic acid ethylester, tosyl azide and diethyl amine in acetonitrile at room temperature in 83 % yield as an oily compound, IR (CH_2Cl_2) 2110, 1700, 1270 and 1020 cm^{-1}.

8. a) M.D. Bachi, O. Goldberg, A. Gross, J. Vaya, J. Org. Chem. 45, 1481 (1980).
b) A. Brandt, L. Bassignani, L. Re, Tetrahedron Letters, 1977, 3159.
c) T.S. Chou, G.A. Koppel, D.E. Dorman, J.W. Paschal, J. Amer. Chem. Soc., 98 7864 (1976).
d) A.C. Kaura, R.J. Stoodley, J.C.S. Chem. Commun. 1979, 344.

9. R.B. Woodward, "Recent advances in the chemistry of β-lactam-antibiotics", J. Elks, London, 1977. The chemical society, special publication No. 28, p. 167.

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