Tetrahedron Letters,Vol.24,No.21,pp 2193-2194,1983 0040-4039/83/212193-02$03.00/0
Printed in Great Britain 

# A SYNTHESIS OF GEMINALLY FUNCTIONALIZED HETEROCYCLIC AMINOCARBOXYLIC ACIDS BY CYCLOADDITION OF ETHYL N-ACETYL-α,β-DEHYDROALANINATE WITH 1,3-DIPOLES

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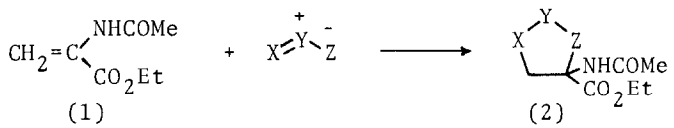
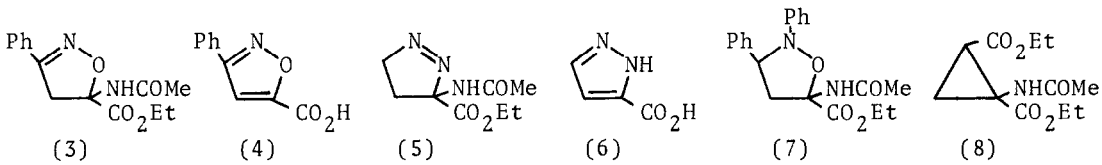
ABSTRACT 1,3-Dipolar cycloaddition of α,β-dehydroalaninate with dipoles proceeded with high regioselectivity to afford the title compounds in good yields.

α,β-Dehydroalaninates are recognized to be intermediates of extensive value in both organic synthesis[1] and biological transformations.[2] The vast majority of the literature dealing with the chemistry of α,β-dehydroalaninates involves nucleophilic and electrophilic addition reactions to give β and α substituted amino acids, respectively. Relatively few applications of the cycloaddition using α,β-dehydroalaninates to a synthesis of geminally functionalized cyclic aminocarboxylic acids have been described to date; some of these functionalized amino acids have been known[3] to have the noticeable biological activities. We have recently reported[4] that α,β-dehydroamino acids serve as a dienophile to afford the cycloaliphatic amino acids having an interesting carbon-skeleton. We now report that 1,3-dipolar cycloaddition of ethyl N-acetyl-α,β-dehydroalaninate (1) generally proceeds with remarkably high regioselectivity, thus providing a viable method for the synthesis of geminally funtionalized heterocyclic aminocarboxylic acids (2).



(1) (2)

Ethyl N-acetyl-α,β-dehydroalaninate (1) was allowed to react with benzonitrile oxide in THF (r.t., 2hr) to give a single regioisomer, isoxazoline (3) (mp 136-137°C), in 85% yield: NMR ($d_6$-DMSO) δ 1.21 (t, 3H), 1.90 (s, 3H), 3.77 (d, 2H), 4.18 (q, 2H), 7.2-7.8 (m, 5H), 9.23 (s, 1H). Support for the regiochemistry was obtained by treatment of (3) with hot dil.HCl which produced the known isoxazole (4) (mp 174-175°C; lit.,[5] mp 176-178°C) in 95% yield. (1) also underwent regiospecific 1,3-dipolar cycloaddition with diazomethane to afford pyrazoline (5) in 95% yield: NMR ($CDCl_3$) δ 1.27 (t, 3H), 2.07 (s, 3H), 1.9-2.3 (m, 2H), 4.25 (q, 2H), 4.6-5.9 (m, 2H), 7.38 (brs, 1H). In NMR spectra of (5), two methylene signals on the pyrazoline ring were observed separately as multiplets at the region of δ 2.0 and δ 5.0, indicating that (5) is the 3-disubsti-



(3) (4) (5) (6) (7) (8)

tuted pyrazoline. The pyrazoline (5) was saponified, followed by acid treatment, to be converted into the known pyrazole (6) (mp 207-209°C; lit.,[6] mp 216°C). The 1,3-dipolar cycloaddition was also carried out using C,N-diphenylnitrone as a dipole. Treatment of (1) with C,N-diphenylnitrone (50-60°C, 26hr, THF) provided a mixture of the stereoisomers[7] of isoxazolidine (7) (mp 123-129°C) in 75% yield: NMR ($CDCl_3$) δ 1.22+1.28 (t+t, 3H), 1.81+1.99 (s+s, 3H), 2.6-3.0 (m, 2H), 4.58+4.95 (t+t, 1H), 4.18+4.24 (q+q, 2H), 6.7-7.2 (m, 5H), 7.2-7.6 (m, 5H), 7.97+8.20 (brs+brs, 1H). This cycloaddition has proved to proceed regiospecifically on the basis of the NMR spectra in which two methine triplets corresponding to the proton on C-3 were observed at δ 4.58 and δ 4.95. Thus, regardless of the presence of acetamido group[8], the regiochemistry and the rate of reaction in the cycloaddition using the α,β-dehydroalaninate show striking similarities to those in the case of ethyl acrylate.[9] This is further confirmed by the less reactivity of (1) with ethyl diazoacetate which easily reacts with electron rich dipolarophiles such as enamines[10]; the reaction of (1) with ethyl diazoacetate was much slower than that with diazomethane, yielding the cyclopropane derivative (8),[11] a single stereoisomer (mp 72-73°C), only in 12.5% yield (55°C, 24hr): NMR ($CDCl_3$) δ 1.27 (t, 6H), 1.5-2.0 (m, 2H), 1.99 (s, 3H), 2.72 (t, 1H), 4.13 (q, 2H), 4.16 (q, 2H), 6.53 (s, 1H).

The application of the 1,3-dipolar cycloaddition with high regioselectivity to a preparation of biologically interesting functionalized amino acids is now under investigation.

## References and Footnotes

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(Received in Japan 26 February 1983)