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N-ACYLIMINES AS INTERMEDIATES IN REACTIONS OF α-SUBSTITUTED α-AMINO ACIDS AND DEHYROAMINO ACIDS

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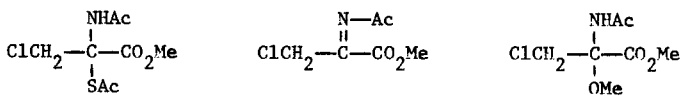
N-Acylimines are of current interest and have been isolated or proposed as intermediates in various reactions[1,2]; elimination reactions of α-substituted amides to form N-acylimines have been reported[2]. During the course of studies on α-substituted α-amino acids, we have observed reactions that are consistent with the formation of N-acylimines as intermediates in both displacement reactions on α-substituted N-acylalanines and in addition reactions to dehydroalanine derivatives. In contrast, limited studies of analogous addition reactions to N-methyldehydroalanine derivatives indicate that N-acylimmonium ions are not formed as intermediates in these reactions.

Treatment of N-acetyl-2-acetylthio-3-chloro-D,L-alanine methyl ester[3] (1) [mp 118.5 - 120.0° from ether-pet ether (bp 60-90°); prepared (51%) by sequentual treatment of N-acetyldehydroalanine methyl ester[4] (9) with chlorine and thioacetic acid; nmr ($CDCl_3$) δ 2.10 (s, 3H, N-acetyl), 2.30 (s, 3H, S-acetyl), 3.86 (s, 3H, methyl ester), 3.90 and 4.85 (AB doublets, J = 11 Hz, 2H, methylene), 7.27 (m, 1H, NH)] with NaOMe in anhydrous methanol at ambient temperature for 7 minutes gave the 2-methoxyalanine 3[5]. The formation of 3 can be rationalized as proceeding from 1 by an elimination reaction to give an intermediate N-acylimine 2 with subsequent

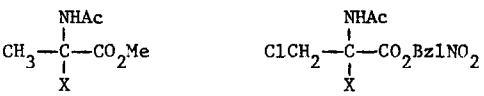


1 2 3

addition of methanol. An authentic sample of 3[3] [mp 112 - 112.5° from EtOAc - pet ether (bp 60-90°); nmr ($CDCl_3$) δ 2.12 (s, 3H, N-acetyl), 3.27 (s, 3H, OMe), 3.88 (s, 3H, methyl ester), 3.84 and 4.60 (AB doublets, J = 11 Hz, 2H, methylene), 6.9 (brd s, 1H, NH)] was pre-

pared from the dehyroalanine 9 by reaction with chlorine in CCl_4 followed by addition of MeOH[6].

The α-substituted alanines 4[3] and 7[3] undergo similar reactions with NaOMe in anhydrous methanol to yield the corresponding α-methoxyalanines 5 and 8, respectively. The α-acetylthioalanine 4 [mp 166.5 - 167.5° from ethyl acetate; nmr ($CDCl_3$ plus 2 drops of trifluoroacetic acid) δ 2.00 (s, 3H, β-protons), 2.15 (s, 3H, N-acetyl), 2.36 (s, 3H, S-acetyl), 3.90 (s, 3H, methyl ester), 8.10 (m, 1H, NH)] was prepared (55-89%) by treatment of acrylate 9 with HCl in thioacetic acid, while treatment of p-nitrobenzyl 2-acetamidoacrylate[3] with N-chlorosuccinimide/HCl/LiOAc[7] in acetic acid gave (71%) the α-acetoxy derivative 7 [mp 125-126.5° from acetone-pet ether (bp 60-90°); nmr (DMSO-d_6) δ 1.90 (s, 3H, N-acetyl), 2.06 (s, 3H, O-acetyl), 4.26 and 4.50 (AB doublets, J = 6 Hz, 2H, β-protons), 5.34 (s, 2H, benzyl), 7.66 and 8.25 (A_2B_2 pattern, 4H, aromatic), 9.16 (s, 1H, NH)]. The α-methoxyalanine 5 is a known compound[8], while 8 was characterized by its analytical[3] and spectral data [mp 151.5-152° from ethyl acetate; nmr ($CDCl_3$ plus 3 drops of trifluoroacetic acid) δ 2.30 (s, 3H, N-acetyl), 3.34 (s, 3H, OMe), 3.95 and 4.48 (AB doublet, J = 6 Hz, 2H, β-protons), 5.46 (s, 2H, benzyl), 7.42 (m, 1H, NH), 7.63 and 8.33 (A_2B_2 pattern, 4H, aromatic)].



4, X = SAc

5, X = OMe

6, X = H

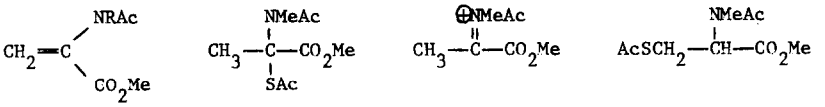
7, X = OAc

8, X = OMe

Treatment of 4 with $NaBH_4$ in methanol gave a mixture of products, from which N-acetyl-DL-alanine methyl ester (6) was shown to be one of the main components[9]; 6 is likely formed by reduction of an intermediate acylimine. It is of interest that the apparent formation of acylimines in the above reactions is favored over the normally facile methanolysis and reductive hydrolysis of a thiol ester[10].

It was of interest to study the N-methyl-α-acetylthioalanine 11, as elimination to an N-acylimine is not possible for 11 and processes analogous to the above reactions would occur through an N-acylimmonium ion 12. However, attempts to prepare 11 by the addition of HCl or HBr to N-acetyl-N-methyldehydroalanine methyl ester (10)[3,11] in thioacetic acid gave, via Michael addition, the β-acetylthioalanine 13 rather than the desired α-acetylthio derivative

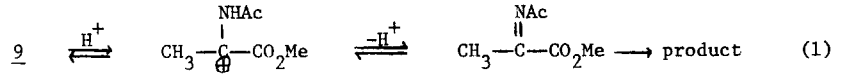
11. Compound 13 also was obtained by the known[12] radical-initiated conjugate addition of thioacetic acid to 10. The addition of HBr to 10, as followed by nmr, showed the main reaction pathway again to be a slow Michael addition to furnish β-substituted products rather than α-substituted products as is known[13] to be the case for the des-N-methyl analog 9.



9 R = H 11 12 13

10 R = Me

The above results indicate that different reaction pathways are occurring in the addition reactions involving 9 and 10. N-Acylimines are proposed as intermediates in electrophilic addition reactions involving 9 in which the initially-formed carbonium ion can lose a proton



(1)

to form the N-acylimine (equation 1). Likewise, the known[14] facile nucleophilic displacement of α-haloalanines likely occur via N-acylimine intermediates. The N-methyl analog 10 cannot lose a proton to form an acylimine; therefore, Michael addition to give β-substituted products is more favorable than formation of an N-acylimmonium ion intermediate 12. The unfavorable nature of N-acylimmonium ions is reasonably due to the electrophilic nature of the N-acyl group, which effect would be expected to destabilize a positively-charged immonium ion. These results provide evidence that in the N-acyldehydroalanine system, the formation of N-acylimines is favored over reaction pathways involving conjugate addition or N-acylimmonium ions, respectively

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