TRANSFORMATION OF AMINES AND N-HETEROARYLFORMAMIDINES INTO ESTERS OF SUBSTITUTED β-AMINO-α,β-DEHYDRO-α-AMINO ACIDS

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Abstract - Esters of substituted β-amino-α,β-dehydro-α-amino acids 5 were prepared either by transformation of N-heteroaryl-N,N-dimethylformamidines 2 with 3 into 4, followed by ring opening, or by treatment of primary or secondary amines 1 with 9.

Recently, the synthesis of novel α-amino acids and dipeptides became of considerable interest, since some of these compounds exhibit ACE inhibition and antihypertensive activity.[1,2] On the other hand, many nonproteinogenic amino acids, such as β-amino acids, aromatic and heterocyclic amino acids have been isolated as secondary metabolites from various natural sources[3] and α,β-dehydroamino acids as components of microbial metabolites.[4] General methods for the preparation for majority of these compounds have not been described in the literature.[5]

N'-Heteroaryl-N,N-dimethylformamidines are important class of compounds, since they undergo a variety of reactions in which the dimethylamino group is substituted with nucleophiles to give intermediates in the formation of various heterocyclic systems.[6]

In this communication we report on two methods, according to which esters of substituted β-amino-α,β-dehydro-α-amino acids can be obtained:

Method A: In the reaction of N'-heteroaryl-N,N-dimethylformamidines 2, prepared from heterocyclic amines 1 (R^1=heteroaryl, R^2=H) and N,N-dimethylformamide dimethyl acetal (DMFDMA), with 5-oxo-2-phenyl-1,3-oxazole (3) in the presence of acetic anhydride the corresponding heteroarylaminomethyleneoxazoles 4 are formed. They exist in tautomeric form 4b as shown on the basis of ^{1}H nmr data supported by methylation with DMFDMA to give 4b (R^1=heteroaryl, R^2=Me).[7] The compounds 4b (R^1=heteroaryl,

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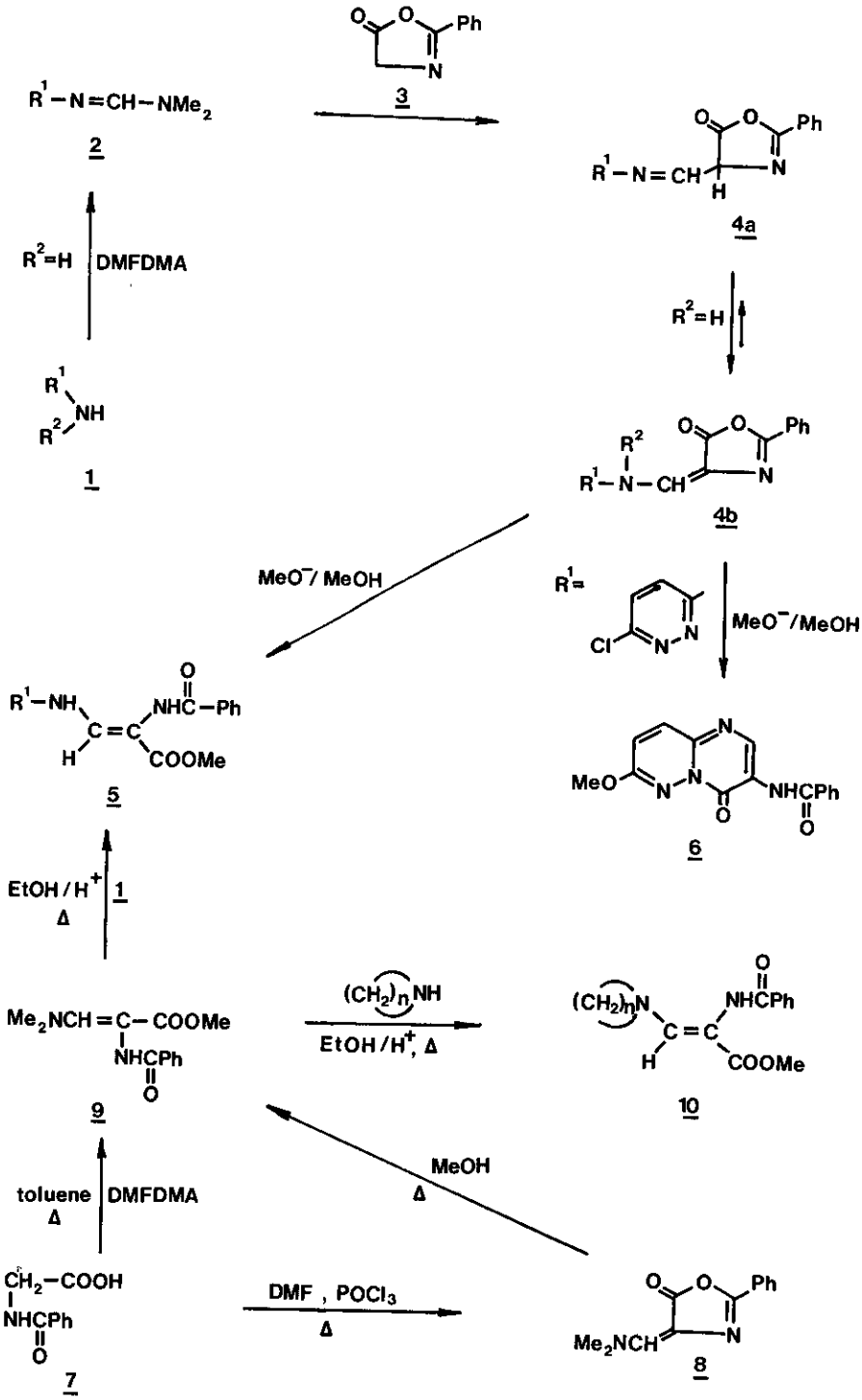
+Dedicated to Professor W.Pfleiderer on the occasion of his 60th birthday



SCHEME 1

R^2=H) can be further transformed with sodium methoxide in methanol into methyl esters of β-heteroarylamino-α,β-dehydro-α-amino acid derivatives 5, which exist in (Z)-form as shown by X-ray analysis.[8] However, in some instances, cyclization into fused pyrimidines occurs in this transformation. For example, when 4b (R^1= 6-chloropyridazinyl-3, R^2=H) was treated with sodium methoxide in methanol, pyrimido/1,2-b/pyridazine derivative 6 was produced. Furthermore, the method is limited to the primary, mostly heterocyclic, amines from which the corresponding formamidines 2 can be obtained.

In order to avoid the limitations, mentioned above, another method was developed in which the primary and secondary amines can be used.

Method B: Methyl 2-benzoylamino-3-dimethylaminopropenoate (9), prepared previously in a two-step reaction from hyppuric acid (7) by treatment with DMF and $POCl_3$ to give 8, followed by methanolysis,[9] can be obtained in a one-step reaction from 7 by treatment with DMFDMA. This, when treated with primary or secondary heterocyclic, aromatic or aliphatic (saturated heterocyclic) amines, produced the compounds 5 or 10. (Scheme 1).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^{1}H nmr spectra were obtained on a JEOL C 60 HL or 90Q FT spectrometers with TMS as internal standard and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 240 C.

2-Phenyl-4-heteroarylaminomethylene-5(4H)-oxazolones 4b (R^1=heteroaryl, R^2=H). - To a stirred solution of 2 (R^1=heteroaryl, R^2=H)(0.001 mole) in acetic anhydride (4 ml) 3 (0.001 mole) was added and the mixture was heated at 70°C (2 h). The volatile components were evaporated in vacuo to give 4b. The following compounds were prepared in this manner:

2-Phenyl-4-(2-pyridylamino)methylene-5(4H)-oxazolone (4b; R^1=pyridyl-2, R^2=H): 57 %, mp 145-148°C (from a mixture of ethanol and water), nmr ($CDCl_3$) δ: 6.62 (m, 3'H), 7.05-7.50 (m), 7.55-8.00 (m) (Ph, 4'-H, 5'-H), 8.10 (s, CHNH), 8.30 (s, CHNH), 9.00 (m, 6'-H). Anal.Calcd.for $C_{15}H_{11}N_3O_2$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.98; N, 4.11; H, 16.03.

2-Phenyl-4-(5-methyl-2-pyridylamino)methylene-5(4H)-oxazolone (4b; R^1=5-methylpyridyl-2, R^2=H): 37 %, mp 166-169°C (from a mixture of ethanol and water), nmr ($CDCl_3$)δ: 2.47 (s, 5'-Me), 7.00-7.70 (m, Ph, 3'-H), 8.10 (s, CHNH), 8.30 (m, 6'-H). Anal.Calcd.

for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.94; H, 4.70, N, 15,34.

2-Phenyl-4-(2-pyrimidinylamino)methylene-5(4H)-oxazolone (4b; R^1=pyrimidinyl-2, R^2=H): 58 %, mp 250-251°C (from a mixture of DMF and ethyl acetate), nmr ($CDCl_3$) δ:6.88 (t, 5'-H), 7.20-7.50 (m), 7.75-8.00 (m) (Ph), 8.42 (d, 4'-H, 6'-H), 8.48 (d, CHNH), 9.50 (br d, CHNH), J(4'-H, 5'-H)=5.0 Hz, J(CHNH)=12.0 Hz. Anal.Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.19; H, 3.83; N, 21.01.

2-Phenyl-4-(4-chloro-6-methyl-2-pyrimidinylamino)methylene-5(4H)oxazolone (4b; R^1=4-chloro-6-methylpyrimidinyl-2, R^2=H): 71 %, mp 177-179°C (from ethanol), nmr (DMSO-d_6) δ: 2.37 (s, 6'-Me), 6.93 (s, 5'-H), 7.25-7.42 (m), 7.65-7.96 (m) (Ph, CHNH). Anal.Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.46; H, 3.72; N, 17.74.

2-Phenyl-4-(6-chloro-3-pyridazinylamino)methylene-5(4H)-oxazolone (4b, R^1=6-chloropyridazinyl-3, R^2=H): 46 %, mp 209-211°C (from ethanol), nmr ($CDCl_3$) δ: 7.30-7.56 (m), 7.70-7.96 (m) (Ph, 4'-H, 5'-H), 8.18 (s, CHNH), 8.30 (s, CHNH). Anal.Calcd. for $C_{14}H_9ClN_4O_2$: C, 55.92; H, 3.02; N, 18.63. Found: C, 55.94; H, 3.01; N,18.58.

2-Phenyl-4-(2-pyrazinylamino)methylene-5(4H)-oxazolone (4b; R^1=pyrazinyl-2, R^2=H): 46 %, mp 216-218°C (from a mixture of ethanol and water), nmr ($CDCl_3$) δ: 7.35-7.60 (m), 7.75-8.12 (m) (Ph), 8.12 (s, CHNH), 8.20 (s, 3'-H, 5'-H), 8.55 (s, 6'-H), 11.25 (br s, CHNH). Anal.Calcd. for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.86; H, 3.82; N, 20.97.

2-Phenyl-4-[N-methyl-(2-pyrimidinyl)amino]methylene-5(4H)-oxazolone (4b; R^1=pyrimidinyl-2, R^2=Me): A mixture of 4b (R^1=pyrimidinyl-2, R^2=H) (0.001 mole) and DMFDMA (0.15 ml) in toluene (2 ml) was heated under reflux (2 h). The precipitate was, after cooling, collected by filtration to give 4b (R^1=pyrimidinyl-2, R^2=Me), 58 %, mp 250-251°C (from a mixture of DMF and ethyl acetate), nmr (DMSO-d_6) δ: 5.96 (s, N-Me), 6.89 (t, 5'-H), 7.22-7.49 (m), 7.76-8.01 (m) (Ph), 8.41 (d, 4'-H, 6'-H), 8.46 (s, CH-N), J(4'-H, 5'-H)=5.0 Hz. Anal.Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4,32; N, 19.99. Found: C, 64.59; H, 4.41; N, 20.20.

Methyl (Z)-2-Benzoylamino-3-heteroarylaminopropenoates. General procedures. - Method A: A mixture of 4b (R^1=heteroaryl, R^2=H) (0.001 mole) and sodium methoxide prepared from sodium (50 mg) in methanol (5 ml) was stirred at room temperature (2 h). The precipitate was collected by filtration to give 5 (R^1=heteroaryl, R^2=H).

Method B: A mixture of a primary or secondary amine 1 (0.001 mole) and 9 (0.001 mole) in ethanol (3 ml) and hydrochloric acid (36 %, 0.1 ml) was heated under reflux

(2-3 h). The volatile components were evaporated in vacuo and the solid residue was recrystallized from an appropriate solvent to give 5 or 10.

The following compounds were prepared in this manner:

Methyl (Z)-2-Benzoylamino-3-(2-pyrimidinyl)aminopropenoate (5; R^1=pyrimidinyl-2): method A 48 %, method B 76 %, mp 182°C (from ethanol), nmr ($CDCl_3$) δ: 3.78 (s, OMe), 6.73 (t, 5'-H), 7.32-7.90 (m, Ph), 8.21 (d, CHNH), 8.34 (d, 4'-H, 6'-H), 9.63 (d, CHNH), J(4'-H, 5'-H)=5.0 Hz, J(CHNH)=11.3 Hz. Anal.Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.24; H, 4.82; N, 18.83.

Methyl (Z)-2-Benzoylamino-3-(4-methyl-2-pyrimidinyl)aminopropenoate (5; R^1=4-methylpyrimidinyl-2): method A 80 %, method B 92 %, mp 228-230°C (from a mixture of toluene and ethanol), nmr ($CDCl_3$) δ: 2.39 (s, 4'-Me), 3.78 (s, OMe), 6.59 (d, 5'-H), 7.28-7.90 (m, Ph), 8.16 (d, 6'-H), 8.21 (d, CHNH), J(5'-H, 6'-H)=5.3 Hz, J(CHNH)= 11.0 Hz. Anal.Calcd. for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61,42; H, 5.35; N, 17.85.

Methyl (Z)-2-Benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)aminopropenoate (5; R^1=4-chloro-6-methylpyrimidinyl-2): method A 67 %, method B 78 %, mp 207-209°C (from a mixture of ethanol and water), nmr ($CDCl_3$)δ: 2.31 (s, 6'-Me), 3.73 (s, OMe), 6.58 (s, 5'-H), 7.28-7.84 (m, Ph), 8.09 (d, CHNH), 8.18 (s, NHCO), 9.56 (d, CHNH), J(CHNH)=10.7 Hz. Anal.Calcd. for $C_{16}H_{15}ClN_4O_3$: C, 55.42; H, 4.36; N, 16.16. Found: C, 55.27; H, 4.49; N, 16.36.

Methyl (Z)-2-Benzoylamino-3-(3-pyridazinyl)aminopropenoate (5; R^1=pyridazinyl-3): method B 87 %, mp 208-210°C (from ethanol), nmr (90 MHz, $CDCl_3$) δ: 3.70 (s, OMe), 7.31 (dd, 4'-H), 7.76 (dd, 5'-H), 7.44-7.70 (m), 7.95-8.14 (m) (Ph), 8.68 (d, CHNH), 8.84 (dd, 6'-H), 9.35 (s, NHCO), 9.54 (d, CHNH), J(4'-H, 5'-H)=8.5 Hz, J(5'-H, 6'-H)= 4.2 Hz, J(4'-H, 6'-H)=1.5 Hz, J(CHNH)=11.9 Hz. Anal.Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.78. Found: C, 60.17; H, 4.55; N, 18.91.

Methyl (Z)-2-Benzoylamino-3-(6-chloro-3-pyridazinyl)aminopropenoate (5; R^1=6-chloropyridazinyl-3): method B 73 %, mp 238-240°C (from ethanol), nmr (90 MHz, DMSO-d_6) δ: 3.70 (s, OMe), 7.43 (d, 4'-H), 7.76 (d, 5'-H), 7.44-7.69 (m), 7.95-8.14 (m) (Ph), 8.62 (d, CHNH), 9.40 (s, NHCO), 9.67 (br d, CHNH), J(4'-H, 5'-H)=8.5 Hz, J(CHNH)= 11.4 Hz. Anal.Calcd. for $C_{15}H_{13}N_4O_3$: C, 54.14; H, 3.94; N, 16.84. Found: C, 54.24; H, 3.86; N, 16.94.

Methyl (Z)-2-Benzoylamino-3-(2-pyrazinyl)aminopropenoate (5; R^1-pyrazinyl-2): method A 81 %, method B 89 %, mp 178-182°C (from a mixture of methanol and water) nmr (90

MHz, $CDCl_3$) δ: 3.88 (s, OMe), 7.44-7.72 (m), 7.72-8.04 (m) (Ph), 8.11-8.39 (m, 3'-H, 5'-H, 6'-H), 8.42 (s, NHCO), 8.72 (d, CHNH), 10.06 (d, CHNH), J(CHNH)=12.7 Hz. Anal. Calcd.for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73:, N, 18.78. Found: C, 60.60; H, 4.55; N, 19.01.

Methyl (Z)-2-Benzoylamino-3-anilinopropenoate (5; R^1=phenyl): method B 71 %, mp 172-175°C (from ethanol), nmr (90 MHz, DMSO-d_6) δ: 3.63 (s, OMe), 6.84-8.11 (m, PhN, (PhCO), 7.89 (d, CHNH), 8.84 (d, CHNH), 9.13 (s, NHCO), J(CHNH)=12.8 Hz. Anal.Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.15; H, 5.38; N, 9.49.

Methyl (Z)-2-Benzoylamino-3-(1-pyrrolidinyl)aminopropenoate (10; n=4): method B 83 %, mp 185-187°C (from toluene), nmr (90 MHz, DMSO-d_6) δ: 1.74 (m,$(CH_2)_2$), 3.40 (m, CH_2-N-CH_2), 3.54 (s, OMe), 7.31-7.64 (m), 7.83-8.04 (m) (PhCO), 7.53 (s, CH=), 9.07 (s, NH). Anal.Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6,61; N, 10.21. Found: C, 65.90; H, 6.93; N, 10.32.

Methyl (Z)-2-Benzoylamino-3-piperidinopropenoate (10; n=5): method B 59 %, mp 162°C (from toluene), nmr (90 MHz, DMSO-d_6) δ: 1.74 (m, $(CH_2)_3$), 3.11 (m, CH_2-N-CH_2), 3.53 (s, OMe), 7.32-7.63 (m), 7.82-8.04 (m) (PhCO), 7.54 (s, CH=), 9.05 (s, NH). Anal.Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.48; H, 7.08; N, 10.01.

3-Benzoylamino-7-methoxypyrimido[1,2-b]pyridazin-4-one (6). - A mixture of 4b (R^1=6-chloropyridazinyl-3, R^2=H) (0.001 mole) and sodium methoxide prepared form sodium (50 mg) in methanol (5 ml), was stirred at room temperature (3 h). The precipitate was collected by filtration and recrystallized from ethanol to give 6, 34 %, mp 213-214°C, nmr ($CDCl_3$) δ: 4.08 (s, OMe), 6.90 (d, 8'-H), 7.36-7.92 (m, Ph), 7.62 (d, 9'-H), 8.89 (s, NH), 9.42 (s, 2-H), J(8'-H, 9'-H)=9.0 Hz. Anal.Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.98; H, 4.07; N, 19.07.

Methyl 2-Benzoylamino-3-dimethylaminopropenoate (9). - To a suspension of 7 (0.01 mole) in toluene (7 ml) DMFDMA (0.04 mole) was added and the mixture was heated under reflux (3-4 h). The precipitate was, after cooling, collected by filtration to give 9, 72 %, mp 171°C, identical with the compound prepared previously[9].

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