Transformations of *N*-Heteroarylformamidines into Derivatives of β-Heteroarylamino-α,β-dehydro-α-amino Acids, β-Heteroarylamino-α-amino Acids, and Dipeptides

Branko Stanovnik*, Jurij Svete and Miha Tišler

Department of Chemistry, Edvard Kardelj University,
61000 Ljubljana, Yugoslavia

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Transformations of *N'*-heteroaryl-*N,N*-dimethylformamidines **1** as a general method for the preparation of β-heteroarylamino-α,β-dehydro-α-amino acids, β-heteroarylamino-α-amino acid derivatives **5-9**, and dipeptides **10**, are described.

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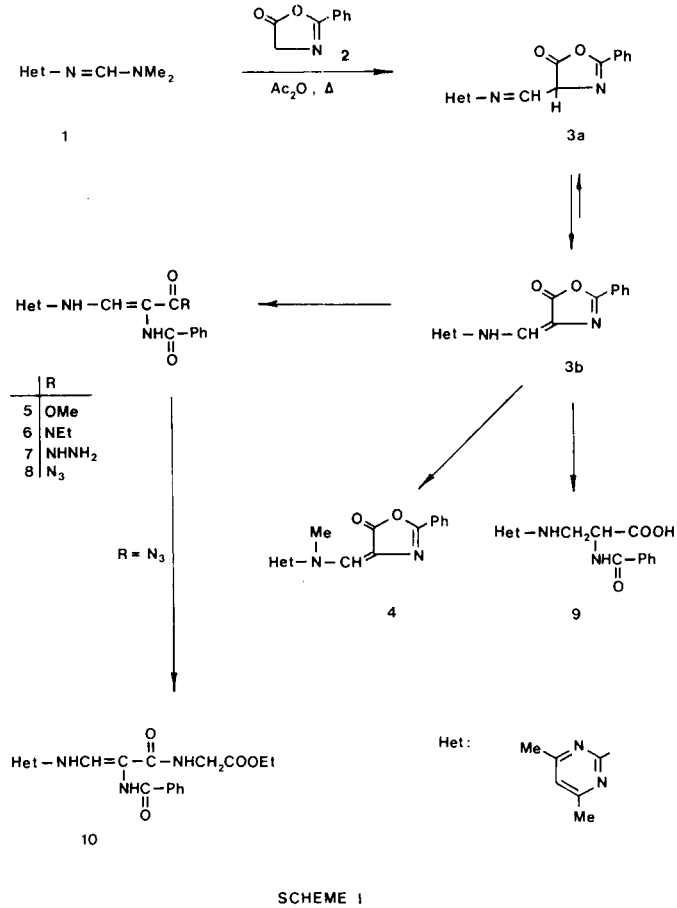
Recently, the synthesis of novel α-amino acids are dipeptides became of considerable interest, since some of these compounds exhibit ACE inhibition and antihypertensive activity [1,2]. On the other hand, many nonproteinogenic amino acids, such as β-amino acids, aromatic and heterocyclic amino acids,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

N'-Heteroaryl-*N,N*-dimethylformamidines are an 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 the transformation of *N'*-heteroaryl-*N,N*-dimethylformamidines into β-heteroarylamino-α,β-dehydro-α-amino acids and β-heteroarylamino-α-amino acids as a general synthetic method for the preparation of this class of compounds.

In the reaction of *N'*-heteroaryl-*N,N*-dimethylformamidines **1** with 5-oxo-4,5-dihydro-5-phenyl-1,3-oxazole (**2**) in the presence of acetic anhydride the corresponding heteroarylaminomethyleneoxazoles **3**, the key intermediates in further transformations into α-amino acids, are formed. Methylation [7] of **3b** with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) is taking place at the former heterocyclic amino group to give **4**. Compounds **3b** can be further transformed with sodium methylate in methanol to produce methyl esters **5**, with diethylamine to give amides **6** and with hydrazine into hydrazides **7**. By treatment of hydrazides **7** with nitrous acid the acyl azides **8** are formed. The reduction of the C=C double bond with sodium borohydride, followed by opening of the oxazole ring, gives *N*-benzoylated amino acid derivatives **9**. The acyl azides **8** can be transformed with esters of amino acids, usually in the form of their hydrochlorides, into dipeptides **10** (Scheme 1). A great variety of heterocyclic formamidines can be used in these transformations.



SCHEME 1

EXPERIMENTAL

The experimental conditions are demonstrated with the following examples (Het = 4,6-dimethylpyrimidinyl-2) [8].

Compound **3b**.

To a stirred solution of **1** [9] (178 mg, 0.001 mole) in acetic anhydride (4 ml) **2** [10,11] (161 mg, 0.001 mole) was added and the mixture was heated at 70° (2 hours). The volatile components were evaporated *in vacuo* to give **3b** (197 mg, 68%), mp 188-190°; nmr (deuteriochloroform/TMS): δ 2,3 (s, 4-Me, 6-Me), 6.5 (s, H_5), 7.19-7.38 (m), 7.65-7.95 (m) (2-Ph), 8.30 (s, C*H*NH), 8.64 (br s, CHN*H*).

Anal. Calcd. for $C_{16}H_{14}H_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.41; H, 4.86; N, 19.12.

Compound **4**.

A mixture of **3** (294 mg, 0.001 mole) and DMFDMA (0.15 ml) in toluene (2 ml) was heated under reflux (2 hours). The precipitate was, after cooling, separated by filtration to give **4**, (256 mg, 89%), mp 238-240° (from a mixture of 1-propanol and toluene); nmr (deuteriochloroform/TMS): δ 2.40 (s, 4'-Me), 4.01 (s, N-Me), 6.60 (s, H_5), 7.20-7.40 (m), 7.75-7.95 (m), (2-Ph), 8.82 (s, N = CH).

Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.10; H, 5.35; N, 18.00.

Compound **5**.

A mixture of **3** (294 mg, 0.001 mole) and sodium methylate, prepared from sodium (50 mg) in methanol (5 ml) was stirred at room temperature (2 hours). The precipitate was filtered to give **5** (316 mg, 97%), mp 208-210° (from a mixture of methanol and ethanol); nmr (deuteriochloroform/TMS): δ 2.32 (s, 4'-Me), 3.78 (s, OMe), 6.46 (s, H_5), 7.3-7.45 (m), 7.65-7.90 (m) (PhCO), 8.17 (br s, NHCO), 8.27 (d, NHC*H*), 9.07 (br d, N*H*CH), 9.07 (br d, N*H*CH), J_{NHCH} = 10.5 Hz.

Anal. Calcd. for $C_{17}H_{18}N_4O_3$: C, 62.56; H, 5.56; N, 17.17. Found: C, 62.73; H, 5.72; N, 17.25.

Compound **6**.

A mixture of **3** (294 mg, 0.001 mole) and diethylamine (2 ml) was heated under reflux (7 hours). The excess of diethylamine was evaporated *in vacuo* and a mixture of ethanol and water (1:1, 3 ml) was added to the oily residue. The precipitate was filtered to give **6** (233 mg, 67%) mp 154-156° (from a mixture of ethanol and water), nmr (deuteriochloroform/TMS): δ 1.26 (t, CH_2*Me*), 2.25 (s, 4'-Me, 6'-Me), 3.48 (q, C*H*$_2$Me), 6.35 (s, H_5), 7.15-7.40 (m), 7.65-7.90 (m) (PhCO), 7.43 (d, NHC*H*), 8.20 (br d, N*H*CH), 8.85 (br s, NHCO), J_{CH_2Me} = 7.0 Hz, J_{NHCH} = 10.0 Hz.

Anal. Calcd. for $C_{20}H_{25}N_5O_2$: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.15; H, 7.17; N, 18.87.

Compound **7**.

A mixture of **3** (294 mg, 0.001 mole) and hydrazine hydrate (98%, 0.1 ml) in methanol (5 ml) was stirred at room temperature (2 hours). The precipitate was filtered and washed with diethyl ether to give **7** (303 mg, 93%), mp 175-180° dec (from ethanol); nmr (DMSO-d_6/TMS): δ 2.26 (s, 4'-Me, 6'-Me), 4.19 (br s, NH), 6.62 (s, H_5), 7.25-7.50 (m), 7.75-8.0 (m) (PhCO), 8.0 (d, NHC*H*), 8.72 (br s, NH), 9.05 (br d, N*H*CH), J_{NHCH} = 10.5 Hz.

Anal. Calcd. for $C_{16}H_{18}N_6O_2$: C, 58.88; H, 5.56; N, 25.75. Found: C, 58.84; H, 5.59; N, 25.50.

Compound **8**.

To a mixture of **7** (326 mg, 0.001 mole), water (10 ml) and hydrochloric acid (concentrated, 0.5 ml) a solution of sodium nitrite (105 mg) in water (3 ml) was added dropwise at 0°. The mixture was stirred at room temperature (1 hour) and the precipitate filtered to give **8** (310 mg, 92%), mp 145-150° dec; ir (potassium bromide): δ 2150 (cm^{-1}; (N_3); nmr (DMSO-d_6/TMS): δ 2.32 (s, 4'-Me, 6'-Me), 6.75 (s, H_5), 7.25-7.50 (m), 7.70-8.0 (m) (PhCO), 8.49 (d, NHC*H*), 9.13 (br s, NHCO), 10.19 (br d, N*H*CH), J_{NHCH} = 12.7 Hz.

Anal. Calcd. for $C_{16}H_{15}N_7O_2$: N, 29.07. Found: N, 29.15.

Compound **9**.

To a solution of **3** (294 mg, 0.001 mole) in anhydrous ethanol (2.5 ml) sodium borohydride (50 mg) was added and the mixture was heated under reflux (1 hour). Water (1 ml) was added and the mixture was extracted with chloroform (3 times, 10 ml each time). The combined extracts were dried over anhydrous sodium sulphate, the solvent was evaporated *in vacuo*, petroleum ether (5 ml) was added to the residue. The precipitate formed after standing in refrigerator overnight was filtered to give **9** (279 mg, 89%), mp 83-85° (from chloroform/petroleum ether); nmr (deuteriochloroform/TMS): δ 2.25 (s, 4'-Me), 3.64 (dd, NHC*H*$_2$), 4.0 (Br t, N*H*CH$_2$), 6.0 (t, CH$_2$C*H*), 6.20 (br s, N*H*CC), 7.0-7.35 (m), 7.45-7.70 (m) (COPh), J_{NHCH_2} = 4.5 Hz, J_{CH_2CH} = 6.0 Hz.

Anal. Calcd. for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83. Found: C, 60.92; H, 5.60; N, 17.55.

Compound **10**.

To a suspension of **8** (674 mg, 0.002 mole) in chloroform (40 ml) a solution of ethyl glycinate (257 mg, 0.0025 mole) in ethanol (5 ml) was added and the mixture was left at room temperature (20 days). The solvent was evaporated *in vacuo* and the crude residue recrystallized from water to give **10** (177 mg, 22%), mp 165-170°; nmr (deuteriochloroform/TMS): δ 1.20 (t, CH_2*Me*), 2.20 (s, 4'-Me, 6'-Me), 3.99 (d, C*H*$_2$NH), 4.04 (q, C*H*$_2$Me), 6.31 (s, H_5), 7.1-7.4 (m), 7.65-7.90 (m) (PhCO), 7.24 (d, NHC*H*), 8.15 (NHCO), 8.37 (br d, N*H*CH), 8.58 (br t, CH_2C*H*), J_{CH_2Me} = 6.9 Hz, J_{NHCH} = 10.5 Hz.

Anal. Calcd. for $C_{20}H_{23}N_5O_4 \cdot 1/2\ H_2O$: C, 59.10; H, 5.95; N, 17.23. Found: C, 59.03; H, 5.86; N, 17.03.

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