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SYNTHESIS OF β-(*N*-1,2,3-TRIAZOLYL)- SUBSTITUTED α,β-UNSATURATED α-AMINO ACID DERIVATIVES. A NEW EXAMPLE OF 1*H*- TO 2*H*-1,2,3-TRIAZOLE ISOMERISATION

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ABSTRACT : Synthesis of β-1*H*-1,2,3-triazol-1-yl and β-2*H*-1,2,3-triazol-2-yl α,β-unsaturated α-amino acid derivatives is reported. 1*H*-1,2,3-Triazole **4** was found to isomerise to the corresponding 2*H*-1,2,3-triazole **7**.

Non-proteinogenic amino acids and their derivatives represent an important class of compounds.[1] Of particular interest are heterocyclic amino acids having side chain with an amino acid moiety attached to a ring nitrogen. For example, a well-known naturally occurring compound of this type with increasing synthetic interest is quisqualic acid, an agonist at multiple excitatory amino acid receptor subtypes in the central nervous system.[2] On the other hand, several synthetic nucleo amino acids having adenine, guanine, thymine, cytosine, and uracil were utilised in the preparation of biologically active somatostatin analogues[3] and peptidic nucleic acids.[4] In our research program on the development of new

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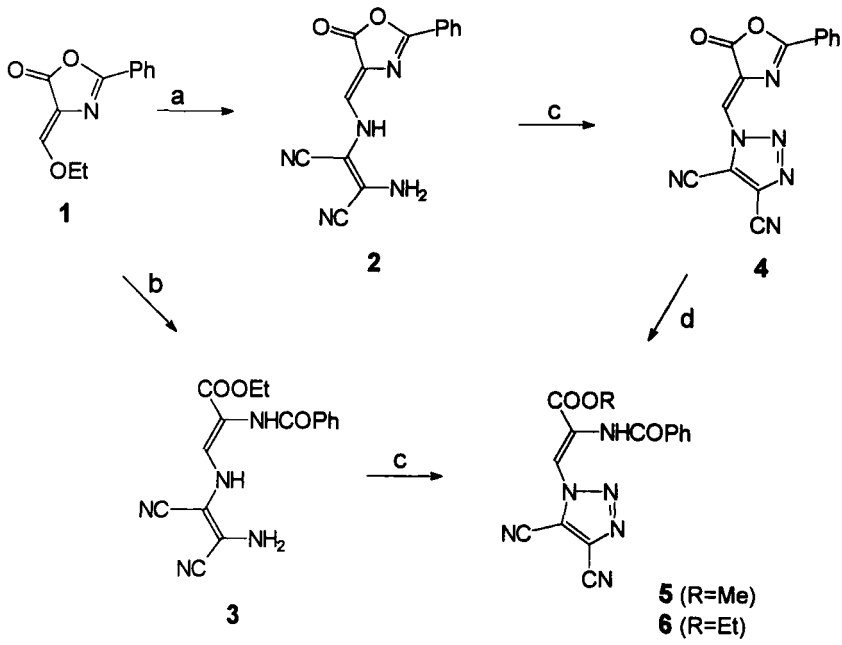
approaches to various heterocyclic amino acid derivatives[5] we became interested in *N*-(1*H*-1,2,3-triazolyl)alanine derivatives bearing additional functional groups on ring carbons capable of subsequent functionalisation of the triazole ring. As far as we know, there are no relevant data concerning the synthesis of β-(1,2,3-triazolyl)alanine derivatives except for the work of Sheehan and Robinson reporting the preparation of α-amino-1,2,3-triazole-4-propionic acid in the study of the histamine analogues.[6] Here we disclose preliminary results of the first approach to *N*-1,2,3-triazolyl substituted amino acid derivatives.

Our approach to β-1*H*-1,2,3-triazol-1-yl substituted α-amino acid derivatives is based on the use of 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone **1**[7] as a source of the α-amino acid residue, and diaminomaleonitrile as a synthon for the 1,2,3-triazole system.[8] Thus, treatment of **1** with diaminomaleonitrile in ethanol resulted in the formation of **2**, which was subsequently transformed with isopentyl nitrite in acetic acid into the triazole **4**. In order to avoid any other possible conversion of the triazole **4**, oxazolone ring opening was performed under very mild conditions by treatment with methanol or ethanol at room temperature without any catalyst giving rise to the corresponding esters **5** and **6** in 44% and 31% overall yields, respectively. A shorter, but less successful alternative route was also designed consisting of the diazotation of **3**, originated by heating of the oxazolone **1** with diaminomaleonitrile in ethanol, to yield the ethyl ester **6** in 6.5% overall yield (Scheme 1).

On treatment with hot 1,4-dioxane or upon melting the 1*H*-1,2,3-triazole **4** readily isomerised to the corresponding 2*H*-1,2,3-triazole **7**. This is a new clear example of 1*H*- to 2*H*-1,2,3-triazole isomerisation.[9] Subsequent treatment of **7** with water resulted in the formation of the corresponding acid **8** in 23% overall yield,

Scheme 1

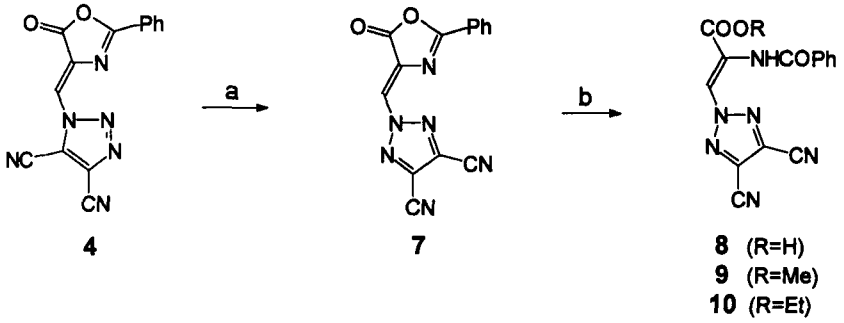


a) diaminomaleonitrile, ethanol, rt; b) diaminomaleonitrile, ethanol, reflux; c) isopentyl nitrite, acetic acid, rt; d) R=Me: methanol, rt; R=Et: ethanol, rt.

whereas reactions with methanol and ethanol afforded the esters **9** and **10** in 37% and 30% overall yields, respectively (Scheme 2). All attempts to prepare the 1,2,3-triazoles **3-10** from **1** and 1*H*-1,2,3-triazole-4,5-dicarbonitrile[10] in different solvents failed. It is of interest to note that the syntheses of related benzotriazole derivatives were described in literature.[5b,11]

Both series of triazoles have (*Z*) configuration on the carbon-carbon double bond, established by ^{13}C NMR spectroscopy on the basis of magnitude of ^{3}J coupling constant between carbonyl carbon and β hydrogen.[12] Differentiation between

Scheme 2



a) 1,4-dioxane, reflux; b) R=H: water, reflux; R=Me: methanol, rt; R=Et: ethanol, rt.

isomeric 1*H*- and 2*H*-1,2,3 triazoles was done by mass spectrometry on the basis of [M^+-28] ion corresponding to loss of N_2 from 1*H*-triazoles.[13] Further support came from ^{13}C NMR spectra confirming the symmetrical structure of the 2-substituted 2*H*-triazole system.

In conclusion, we presented the first approach to some β-(*N*-1,2,3-triazolyl) substituted α,β-unsaturated α-amino acid derivatives. The method is attractive from the practical standpoint because it is mild, selective and uses only one common key compound **4** for the synthesis of the amino acid derivatives having the 1*H*-1,2,3-triazole or 2*H*-1,2,3-triazole system.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are uncorrected. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (300 MHz for ^1H and 75.4 MHz for ^{13}C) with TMS as internal standard. Elemental

analysis for C, H, N were obtained on a Perkin-Elmer CHN Analyzer 2400. IR spectra were recorded on a Perkin-Elmer 1310 or 727 B spectrometer. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. 4-Ethoxymethylene-2-phenyl-5(*4H*)-oxazolone **1**[7] was prepared as described in the literature. All other compounds were used without purification as obtained from commercial sources.

Compound 2: A mixture of 4.932 g (46 mmol) of diaminomaleonitrile, 9.911 g (46 mmol) of **1**, and 75 mL of ethanol was stirred at room temperature for 3 h. After 24 h standing at rt, the reaction mixture was cooled, and the solid was collected by filtration to give 12.37 g (97%) of **2**; mp 224-226°C (ethanol). IR (KBr) ν_{max}(cm^{-1}): 3400 and 3180 (NH), 2220 and 2200 (CN), 1750 and 1720 (CO). ^{1}H-NMR (DMSO-d_6) δ: 7.33 (s, 1H, CH), 7.53 (s, 2H, NH_2), 7.57 (m, 3H, Ph), 7.94 (m, 2H, Ph), 9.96 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 95.2, 112.1, 114.4, 115.7, 121.0, 126.2, 126.6, 129.2, 131.7, 136.6, 155.6, 166.9. *Anal.* Calcd for $C_{14}H_9N_5O_2$: C, 60.22; H 3.25; N 25.08. Found: C, 59.94; H 2.94; N, 24.83.

Compound 3: A mixture of 216 mg (2 mmol) of diaminomaleonitrile, 434 mg (2 mmol) of **1**, and 15 mL of ethanol was refluxed for 9 h. After cooling, the solid was collected by filtration to give 475 mg (73%) of **3**; mp 212.5-214.5°C (ethanol). IR (KBr) ν_{max} (cm^{-1}): 3360 and 3334 (NH), 2210 and 2190 (CN), 1660-1610 (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.19 (t, 3H, *J*=7.0Hz, CH_3), 4.12 (q, 2H, *J*=7.0Hz, CH_2), 7.00 (bs, 2H, NH_2), 7.47 (m, 4H, CH, three H of Ph), 7.95 (m, 3H, NH, two H of Ph), 9.23 (s, 1H, NH). *Anal.* Calcd for $C_{16}H_{15}N_5O_3$: C, 59.07; H 4.65; N 21.53. Found: C, 58.72; H 4.58; N, 21.51.

Compound 4: To a suspension of 5.594 g (20 mmol) of **2** in 40 mL of acetic acid, 6 mL (45 mmol) of isopentyl nitrite was added dropwise at rt. The reaction

mixture was then stirred for 1 h at rt. After cooling, the solid was collected by filtration to give 3.782 g (65%) of **4**; mp 187-188°C dec. IR (KBr) ν_{max} (cm^{-1}): 2250 (CN), 1810 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.64 (m, 2H, Ph), 7.75 (m, 1H, Ph), 7.94 (s, 1H, CH), 8.24 (m, 2H, Ph). MS (EI, m/z, %): 290 (M^+, 12), 262 (M^+-N_2, 20), 105 (100), 77 (48). *Anal.* Calcd for $C_{14}H_6N_6O_2$: C, 57.92; H 2.08; N 28.97. Found: C, 57.89; H 2.02; N, 29.10.

Compound 5: A mixture of 291 mg (1 mmol) of **4** and 2.5 mL of methanol was allowed to stand at rt for 7 days. After cooling, the solid was collected by filtration to give 225 mg (70%) of **5**; mp 164-166°C; IR (KBr) ν_{max} (cm^{-1}): 3340 (NH), 2240 (CN), 1730 and 1675 (CO). ^{1}H NMR (DMSO-d_6) δ: 3.85 (s, 3H, CH_3), 7.54 (m, 2H, Ph), 7.64 (m, 1H, Ph), 7.84 (m, 2H, Ph), 7.85 (s, 1H, CH), 10.51 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 53.2, 105.7, 109.1, 117.9, 118.5, 124.9, 127.8, 128.6, 129.8, 132.0, 132.7, 162.7, 165.7. MS (EI, m/z, %): 322 (M^+, 3), 294 (M^+-N_2, 8), 105 (100), 77 (48). *Anal.* Calcd for $C_{15}H_{10}N_6O_3$: C, 55.89; H 3.13; N 26.09. Found: C, 55.71; H 2.97; N, 26.20.

Compound 6: a) A mixture of 412 mg (1.4 mmol) of **4** and 2.5 mL of ethanol was allowed to stand at rt for 6 days. After cooling, the solid was collected by filtration to give 235 mg (49%) of **6**; mp 143-144°C (ethanol); IR (KBr) ν_{max} (cm^{-1}): 3350 (NH), 2240 (CN), 1730 and 1680 (CO). ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, 3H, *J*=7.1Hz, CH_3), 4.31 (q, 2H, *J*=7.1Hz, CH_2), 7.53 (m, 2H, Ph), 7.62 (m, 1H, Ph), 7.83 (m, 2H, Ph), 7.84 (s, 1H, CH), 10.47 (s, 1H, NH). MS (EI, m/z, %): 336 (M^+, 1), 308 (M^+-N_2, 3), 291 (3), 217 (15), 105 (100), 77 (58). *Anal.* Calcd for $C_{16}H_{12}N_6O_3$: C, 57.14; H 3.60; N 24.99. Found: C, 57.05; H 3.30; N, 25.06.

b) To a suspension of 333 mg (1.02 mmol) of **3** in 2 mL of acetic acid, 0.3 mL (2.25 mmol) of isopentyl nitrite was added dropwise at rt. The reaction mixture

was then stirred for 1 h. The solid was collected by filtration to give 13 mg (4%) of **3**. The filtrate was cooled to 0°C and the solid was filtered to give 29 mg (9%) of **6**.

Compound 7: A mixture of 512 mg (1.8 mmol) of **4** and 2 mL of 1,4-dioxane was refluxed for 3 h. After cooling, the solid was collected by filtration to give 283 mg (55%) of **7**; mp 208-210°C (1,4-dioxane). IR (KBr) ν_{max} (cm^{-1}): 2260 (CN), 1810 (CO).^{1}H NMR ($CDCl_3$) δ: 7.60 (m, 2H, Ph), 7.74 (m, 1H, Ph), 7.86 (s, 1H, CH), 8.26 (m, 2H, Ph). ^{13}C NMR (DMSO-d_6) δ: 109.1, 122.7, 124.3, 128.0, 128.8, 129.6, 130.6, 134.9, 165.9, 166.6. MS (EI, m/z, %): 290 (M^+, 40), 105 (100), 77 (57). *Anal.* Calcd for $C_{14}H_6N_6O_2$: C, 57.92; H 2.08; N 28.97. Found: C, 57.48; H 1.82; N, 29.00.

Compound 8: A mixture of 50 mg (0.17 mmol) of **7** and 5 mL of water was refluxed for 4 h. After cooling, the solid was collected by filtration to give 22 mg (41%) of **8**; mp 170-172°C (water). IR (KBr) ν_{max} (cm^{-1}): 3280 (NH), 2250 (CN), 1710 and 1655 (CO). ^{1}H NMR (DMSO-d_6) δ: 7.55 (m, 2H, Ph), 7.63 (m, 1H, Ph), 7.91 (m, 2H, Ph), 8.06 (s, 1H, CH), 10.25 (s, 1H, NH). *Anal.* Calcd for $C_{14}H_8N_6O_3$: C, 54.55; H 2.62; N 27.26. Found: C, 54.14; H 2.34; N, 27.34.

Compound 9: A mixture of 122 mg (0.4 mmol) of **7** and 3 mL of methanol was allowed to stand at rt for 7 days. After cooling, the solid was collected by filtration to give 95 mg (68%) of **9**; mp 186-188°C (methanol). IR (KBr) ν_{max} (cm^{-1}): 3340 (NH), 2250 (CN), 1730 and 1670 (CO). ^{1}H NMR (DMSO-d_6) δ: 3.83 (s, 3H, CH_3), 7.57 (m, 2H, Ph), 7.66 (m, 1H, Ph), 7.92 (m, 2H, Ph), 8.09 (s, 1H, CH), 10.41 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 53.2, 109.0, 123.5, 125.5, 126.3, 127.8, 128.8, 132.4, 132.7, 163.3, 165.4. MS (EI, m/z, %): 322 (M^+, 5), 291 (4),

203 (12), 105 (100), 77 (44). *Anal.* Calcd for $C_{15}H_{10}N_6O_3$: C, 55.89; H 3.13; N 26.09. Found: C, 55.83; H 2.93; N, 26.33.

Compound 10: A mixture of 122 mg (0.4 mmol) of **7** and 3 mL of ethanol was allowed to stand at rt for 10 days. After cooling, the solid was collected by filtration to give 72 mg (54%) of **10**; mp 161-163°C (ethanol). IR (KBr) ν_{max} (cm^{-1}): 3320 (NH), 2250 (CN), 1725 and 1675 (CO). ^1H NMR (DMSO-d_6) δ: 1.28 (t, 3H, *J*=7.1Hz, CH_3), 4.29 (q, 2H, *J*=7.1Hz, CH_2), 7.57 (m, 2H, Ph), 7.66 (m, 1H, Ph), 7.92 (m, 2H, Ph), 8.08 (s, 1H, CH), 10.39 (s, 1H, NH). MS (EI, m/z, %): 336 (M^+, 3), 291 (5), 217 (35), 105 (100), 77 (50). *Anal.* Calcd for $C_{16}H_{12}N_6O_3$: C, 57.14; H 3.60; N 24.99. Found: C, 57.06; H 3.42; N, 25.11.

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