Amino Acid Derivatives in Organic Synthesis, Part 4 [1]:
Facile Synthesis of Heterocycles Containing a Glycine Residue

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Z. Naturforsch. 55b, 104–108 (2000); received August 20, 1999

N-Cyanoacetylglutamates, Thiazolo[2,3-a] pyridines, Pyridin-1-acetic Acid, Pyrazolo[4,5-b] pyrans

Pyridines, thiazolopyridines and pyrazolopyrans containing glycine residue were prepared by reacting N-cyanoacetylglutamate ylidenes with active methylene compounds via a Michael addition - intracyclization synthetic pathway.

Simple routes for the synthesis of heterocycles with an amino acid residue were previously reported [1–3] as the incorporation of these residues improves the pharmacokinetics and toxicity of active compounds [4,5]. However, trials to deesterify these residues for coupling purposes were unsuccessful. So, we tried herein new approaches for synthesizing heterocycles carrying one or two glycine moieties with free carboxylic acid group to facilitate further peptide linkage [6] on one hand and on the other one could be able to form metal chelates, a property having a significant output on the toxicological behaviour [7].

Results and Discussion

The reported N-cyanoacetylglutline (2a) [8] could be prepared in good yield by reacting ethyl cyanoacetate with potassium glycinate. It condensed readily with benzaldehyde and its 4-chloro derivative to give the corresponding benzylidene compounds 3a,b showing in their 1H NMR spectra the methine singlet at $\delta = 8.2$ ppm [9] instead of the cyanoethylidene one. These were then treated with active methylene compounds to prepare the target compounds .

Thus, compounds 3a,b reacted with 3-methylpyrazolin-5-one in ethanol/triethylamine to form the pyrazolopyrans 4a,b which showed absence of the IR CN absorption and revealed the pyrazolopyran H-4 at $\delta = 4.7$ ppm [10] in their 1HNMR spectra. The mass spectral data of 4b showed the base peak at $m/z = 98$ corresponding to the methylpyrazolone moiety and another fragment at $m/z = 220$ corresponding to the 3-methyl-4-(4-chlorobenzylidene)pyrazolin-5-one moiety which is also in accord with the proposed structure.

Then, compound 3b was reacted with the thiazolone derivative 5 and a product was obtained having a molecular ion peak at $m/z = 451$ and for which the thiazolopyridine structure 6 was given based on analytical and spectral data as well as on analogy [11]. The formation of 6 can be explained via a Michael addition involving the ethoxymethylene nucleophile followed by cyclization to form the pyridine nucleus.

Following a similar synthetic route (Michael addition-cyclization), another pyridine derivative 7 could be obtained successfully by reacting 3a with malononitrile; this assignment was confirmed by the mass spectral data showing the molecular ion peak at $m/z = 296$ along with elemental and spectral data (cf. Experimental).

$\text{[Benzothiazol-2-(y)acetyl] glycine (2b)}$ could be also prepared similar to the cyano derivative 2a starting with ethyl benzothiazol-2-acetate (1b) instead of ethyl cyanoacetate. Its chemical behaviour also confirmed the given structure. Thus, it was nitrated and diazotized at the methylene group adjacent to the heterocyclic ring to afford the corresponding oximino and diazo derivatives 8,9, respectively. The structural assignment is based on analytical and spectral data (cf. Experimental).

Also, compound 2b condensed readily with 2-furaldehyde and thiophene-2-aldehyde to give the corresponding arylidene derivatives 11a,b. The latter were then treated with malononitrile affording new products showing spectral similarities to com-

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pound 7 along with the benzothiazolyl and furyl or thiényl residues. Accordingly, structure 12 was assigned to these products.

Compound 2b was then treated with 3a in an attempt to prepare a heterocycle with two glycine residues. The isolated product gave a molecular ion peak at m/z = 480, it lacked the IR CN absorption while two glycinate methylene signals were detected at δ 3.7 and δ 4.3 ppm in the 1H NMR spectrum in addition to a pyridine 4-H at δ 4.9 ppm [9]. Among several assumptions, structure 10 fitted more to the analytical and spectral data obtained and so given to this product, probably formed through the previously described pathway.

**Experimental**

Melting points are uncorrected and were taken on Electrothermal 9100 apparatus. IR spectra were recorded with a Carl Zeiss spectrophotometer model “UR 10” in KBr pellets. 1H NMR spectra were determined with a Jeol 270 MHz instrument (internal TMS). Mass spectra were recorded with a Finigan SSQ 7000 mass spectrometer. IR spectra were determined with a Jeol 270 MHz instrument “UR 10” in KBr pellets.

N-(1-Arylacetyl) glycines (2a,b)

Potassium glycinate (10 mmol) and ethyl cyanoacetate or ethyl benzothiazol-2-acetate (10 mmol) in ethanol / DMF mixture (30 ml; 1:1 v/v) were stirred at room temperature for 24 h. The solution was neutralized with acetic acid and the product was extracted with ethyl acetate. The organic layer was dried over anhydrous Na2SO4, concentrated and the crude product was crystallized.

N-Cyanoacetylglycine (2a)

Yield 60%; m.p. 141–143 °C (EtOH). 1H NMR: δ = 12.70 (brs, 1H, OH), 8.60 (s, 1H, NH), 3.85 (s, 2H, CH2CN), 3.72 (s, 2H, CH2glycinate). IR: 3300–3200 (OH, NH), 2220 (CO). MS: m/z = 250 [M+].

**C20H18N2O3 (294.33)**

Calcd C 52.8 H 4.0 N 11.2 S 12.8%.

Found C 52.6 H 3.8 N 10.9 S 12.7%.

N-(1-(4-Chlorophenyl)-2-cyanoacryloyl)glycine (3a):

Yield 80%; m.p. 165–166 °C (EtOH). 1H NMR: δ = 12.73 (brs, 1H, OH), 8.68 (brs, 1H, NH), 8.20 (s, 1H, ylidene H), 7.60–7.74 (m, 5H, C6H5), 3.76 (s, 2H, CH2). IR: 3350–3200 (OH, NH), 2220 (CN), 1685 (CO), 1650 (CO).

**C21H16ClN2O3 (352.87)**

Calcd C 52.6 H 3.8 N 11.9%.

Found C 52.6 H 3.8 N 11.9%.

N-(1-Phenyl-2-cyanoacryloyl)glycine (3a):

Yield 80%; m.p. 165–166 °C (EtOH). 1H NMR: δ = 12.73 (brs, 1H, OH), 8.68 (brs, 1H, NH), 8.20 (s, 1H, ylidene H), 7.60–7.74 (m, 5H, C6H5), 3.76 (s, 2H, CH2). IR: 3350–3200 (OH, NH), 2220 (CN), 1685 (CO), 1650 (CO).

**C21H16N2O3 (328.33)**

Calcd C 52.6 H 3.8 N 11.9%.

Found C 52.6 H 3.8 N 11.9%.

N-[1-(4-Chlorophenyl)-2-cyanoacryloyl]glycine (3b):

Yield 75%; m.p. 230–232 °C (EtOH). 1H NMR: δ = 12.70 (brs, 1H, OH), 8.68 (brs, 1H, NH), 8.20 (s, 1H, ylidene H), 7.62 and 7.96 (2 m, 4H, C6H4), 3.88 (s, 2H, CH2). IR: 3350–3200 (OH, NH), 2220 (CN), 1680 (CO), 1650 (CO).

**C20H15ClN2O3 (344.83)**

Calcd C 54.5 H 3.4 Cl 13.4 N 10.56%.

Found C 54.3 H 3.1 Cl 13.1 N 10.2 %.

Reaction of 3 with 3-methylpyrazolin-5-one or malononitrile or 2b and reaction of 11 with malononitrile.

A mixture of each of 3a,b (10 mmol) with 3-methylpyrazolin-5-one (10 mmol) or 3a (10 mmol) with malononitrile (10 mmol) or 3a (10 mmol) with 2b (10 mmol) or 11a,b (10 mmol) with malononitrile (10 mmol) was refluxed in ethanol (30 ml) in presence of triethylamine (20 mmol) for 6 h. The reaction mixture was partially concentrated, the solid obtained was collected by filtration and recrystallized.

6-Amino-5-carboxyglicino-3-methyl-4-phenyl-1H-pyrazolo[4,5-b]pyran (4a): Yield 50%; m.p. 239 °C (dioxane). 1H NMR: δ = 12.54 (brs, 1H, CO2H), 12.20. (brs, 1H, NH), 8.68 (s, 1H, NH),
7.15-7.42 (m, 7H, C₆H₅ and NH₂), 4.70 (s, 1H, pyrazolopyran 4-H), 3.60 (s, 2H, glycinate CH₂), 2.14 (s, 3H, CH₃). IR: 3800-2900 (OH, NH, NH₂), 1680 (CO), 1620 (CO). C₁₆H₁₈N₄O₄ (328.32)

Calcd C 58.5 H 4.9 N 17.1%,
Found C 58.4 H 4.6 N 16.8%.

6-Amino-5-carboxyglycino-4-(4-chlorophenyl)-3-methyl-1H-pyrazolo[4,5-b] pyran (4b): Yield 40%; m.p. > 300 °C (dioxane). ¹H NMR : δ =12.80 (s, 1H, C₀H₂), 12.16 (brs, 1H, NH), 7.20–7.43 (m, 6H, C₆H₅ and NH₂), 4.80 (s, 1H, pyran 4-H), 2.12 (s, 3H, CH₃). IR: 3380-3200 (OH, NH and NH₂), 1670 (CO carboxyl), 1650 (CO).

C₁₆H₁₅ClN₄O₄ (362.76)

Calcd C 53.0 H 4.2 Cl 9.8 N 15.5%,
Found C 52.7 H 4.0 Cl 9.5 N 15.1%.

6-Amino-3,5-dicyano-2-hydroxy-4-phenyl-4//-pyridin-l-acetic acid (7): Yield 40%; m.p. 205 °C (dioxane). ¹H NMR: δ = 12.70 (brs, 1H, OH), 12.24 (s, 1H, NH), 11.45 (brs, 1H, OH), 9.00 (brs, 1H, NH), 7.72 (brs, 2H, NH₂). 7.10–7.50 (m, 9H, C₆H₅ and benzothiazole H), 5.05 (s, 1H, pyridine 4-H), 4.35 (s, 2H, acetate CH₂), 3.66 (s, 2H, glycinate CH₂).

C₁₅H₁₂N₄O₄S (296.28)

Calcd C 60.8 H 4.1 N 18.9%,
Found C 60.5 H 3.8 N 18.5%.

2-Amino-5-(benzothiazol-2-yl)-3-carboxyglycino-6-hydroxy-4-phenyl-4//-pyridin-1-acetic acid (10): Yield 35%; m.p. 185 °C (acetic acid).

¹H NMR: δ = 12.70 (brs, 1H, OH); 12.24 (s, 1H, NH), 11.45 (brs, 1H, OH), 9.00 (brs, 1H, NH), 7.72 (brs, 2H, NH₂). 7.10–7.50 (m, 9H, C₆H₅ and benzothiazole H), 5.05 (s, 1H, pyridine 4-H), 4.35 (s, 2H, acetate CH₂), 3.66 (s, 2H, glycinate CH₂).

IR: 3350–3150 (OH, NH, NH₂), 1690 (CO), 1650 (CO).

2-Amino-5-(benzothiazol-2-yl)-3-cyano-4-(2-furyl)-6-hydroxy-4//-pyridin-1-acetic acid (12a): Yield 30%; m.p. 208 °C (EtOH). ¹H NMR: δ = 11.30 (brs, 1H, carboxylic OH), 10.45 (s, 1H, OH), 7.90–8.00 (m, 3H, benzothiazole 4-H, 7-H and furan 5-H), 7.45–7.60 (m, 2H, benzothiazole 5-H and 6-H), 6.25–6.30 (m, 2H, furan 3-H, 4-H), 4.30 (s, 1H, pyridine 4-H), 4.10 (s, 2H, CH₂).

C₁₉H₁₄N₄O₄S (394.31)

Calcd C 57.9 H 3.6 N 14.2 S 8.1%,
Found C 57.7 H 3.4 N 13.9 S 7.8%.

2-Amino-5-(benzothiazol-2-yl)-3-cyano-6-hydroxy-4-(2-thienyl) pyridin-1-acetic acid (12b): Yield 20%; m.p. 210–12 °C (EtOH). ¹H NMR: δ =
11.50 (brs, 1H, carboxylic OH)), 10.35 (s, 1H, OH), 7.95–8.05 (m, 3H, benzothiazole 4-H, 7-H and thiophene 5-H), 7.40–7.60 (m, 3H, benzothiazole 5-H, 6-H and thiophene 4-H), 7.10 (q, J=7 Hz, 1H, thiophene 4-H), 4.35 (s, 1H, pyridine 4-H), 4.10 (s, 2H, CH2). IR: 3300–3200 (OH, NH), 2200 (CN), 1660 (CO).

C19H14CIN403S2 (410.48)
Calcd C 55.6 H 3.4 N 13.7 S 15.6%,
Found C 55.4 H 3.3 N 13.3 S 15.4%.

4-Amino-6-(4-chlorophenyl)-5-carboxyglycin-7-ethoxycarbonyl-3-hydroxy-6H-thiazolo[2,3-a]pyridine (6):

Compound 3b (10 mmol) was refluxed with an equimolar amount of 5 in ethanol (30 ml) in presence of triethylamine (20 mmol) for 1h. A precipitate was formed on hot, filtered off and recrystallized to give 6: Yield 60%; m.p. 234–236 °C (acetic acid). 1H NMR: δ = 13.60 (brs, 1H, NH), 9.00 (brs, 1H, NH), 8.05 (m, 2H, benzothiazole 4-H, 7-H), 7.52 (m, 2H, benzothiazole 5-H, 6-H), 4.00 (s, 2H, CH2). IR: 3400 (OH carbonyl), 3100–2500 (NH, OH oximino, ring stretching), 1710 (CO carbonyl), 1660 (CO).

C19H18CIN5O6S (451.87)
Calcd C 50.5 H 4.0 Cl 3.9 N 9.3 S 7.1%,
Found C 50.2 H 3.8 Cl 7.6 N 9.0 S 6.7%.

The nitrosation reaction of 2b:

To a solution of compound 2b (10 mmol) in dioxane (20 ml) in presence of hydrochloric acid (1 ml), an aqueous solution of sodium nitrite (10 mmol in 2 ml water) was added dropwise with stirring over 30 minutes at 5–10 °C. Stirring was kept for further 2h, water added till precipitation occured and the solid formed was collected, washed with water and crystallized to give 8: Yield 60%; m.p. 234–236 °C (acetic acid). 1H NMR: δ = 13.60 (brs, 1H, NH), 9.00 (brs, 1H, NH), 8.05 (m, 2H, benzothiazole 4-H, 7-H), 7.52 (m, 2H, benzothiazole 5-H, 6-H), 4.00 (s, 2H, CH2). IR: 3400 (OH carbonyl), 3100–2500 (NH, OH oximino, ring stretching), 1710 (CO carbonyl), 1660 (CO).

C11H13N3O5S (279.27)
Calcd C 47.3 H 3.3 N 15.1 S 11.5%,
Found C 47.1 H 3.0 N 14.6 S 11.0%.

The diazotization reaction of 2b:

Phenyl diazonium chloride [12] was added to a cooled mixture of 2b (10 mmol, 2.5 g) and sodium acetate trihydrate (5 g) in DMF (30 ml) with stir-
ring for 30 minutes; water was then added and the precipitate formed was filtered off and recrystallized to give 9: Yield 40%; m.p. 242 °C (acetic acid). \(^1\)H NMR: \(\delta = 14.56 (s, 1\text{H}, \text{OH})\), 10.10 (brs, 1\text{H}, NH), 8.52 (s, 1\text{H}, NH), 8.10 (m, 2\text{H}, benzothiazole 4-H, 7-H), 7.62 (m, 2\text{H}, benzothiazole 5-H, 6-H), 7.25–7.50 (m, 5\text{H}, \text{C}_6\text{H}_5), 3.90 (s, 2\text{H}, \text{CH}_2). \[\text{IR: 3400 (OH), 3100-2900 (NH and ring stretching), 1715 (CO), 1640 (CO).}\]

\[\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3\text{S} (354.37) \]
\[\text{Calcd C 57.6 H 4.0 N 15.8 S 9.1\%}, \]
\[\text{Found C 47.4 H 3.7 N 15.7 S 8.7\%}.\]

\[\text{N-[2-(Benzothiazol-2-yl)-1-heteroarylacryloyl]-glycines 11 a,b}\]

Compound 2b (10 mmol) was refluxed with an equimolar amount of 2-furaldehyde or thiophene-2-aldehyde in ethanol (30 ml) in presence of triethylamine (20 mmol) for 1 h. After partial concentration, the solid product formed was filtered off and recrystallized.

\[\text{N-[2-(Benzothiazol-2-yl)-1-(2-furyl)acryloyl]-glycine (11a): Yield 25%; m.p. 198 °C (acetic acid).} \]
\[\text{\(^1\)H NMR: } \delta = 12.75 (\text{brs, 1H, OH}), 9.05 (\text{brs, 1H, NH}), 7.90-8.00 (\text{m, 3H, benzothiazole 4-H, 7-H and furan 5-H}), 7.50-7.65 (\text{m, 2H, benzothiazole 5-H, 6-H and thiophene 3-H}), 7.22 (q, 1H, thiophene 4-H), 4.40 (s, 2H, \text{CH}_2). \text{IR: 3400, 3300 (OH, NH), 1740 (CO), 1680 (CO).}\]

\[\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4\text{S} (344.41) \]
\[\text{Calcd C 58.5 H 3.7 N 8.5 S 9.8\%}, \]
\[\text{Found C 58.3 H 3.4 N 8.2 S 9.4\%}.\]

\[\text{N-[2-(Benzothiazol-2-yl)-1-(2-thienyl)acryloyl]-glycine (11b): Yield 20%; m.p. 200 °C (acetic acid).} \]
\[\text{\(^1\)H NMR: } \delta = 12.60 (\text{brs, 1H, OH}), 9.35 (\text{s, 1H, OH}), 9.35 (\text{s, 1H, NH}), 8.15-8.05 (\text{m, 3H, benzothiazole 4-H, 7-H and thiophene 5-H}), 7.50-7.65 (\text{m, 2H, benzothiazole 5-H, 6-H and thiophene 3-H}), 7.22 (q, 1H, thiophene 4-H), 4.40 (s, 2H, \text{CH}_2). \text{IR: 3400, 3300 (OH, NH), 1705 (CO), 1690 (CO).}\]

\[\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4\text{S} (344.41) \]
\[\text{Calcd C 58.5 H 3.7 N 8.5 S 9.8\%}, \]
\[\text{Found C 58.3 H 3.4 N 8.2 S 9.4\%}.\]

**Acknowledgements**

The support of the Third World Academy of Science (TWAS) is gratefully acknowledged.

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