The Reaction of 2-Ethoxycarbonyl-3-isothiocyanatopyridine with α-Amino Acids. The Synthesis of 3-Substituted 2-Thiooxo-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-ones

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Received June 19, 1989

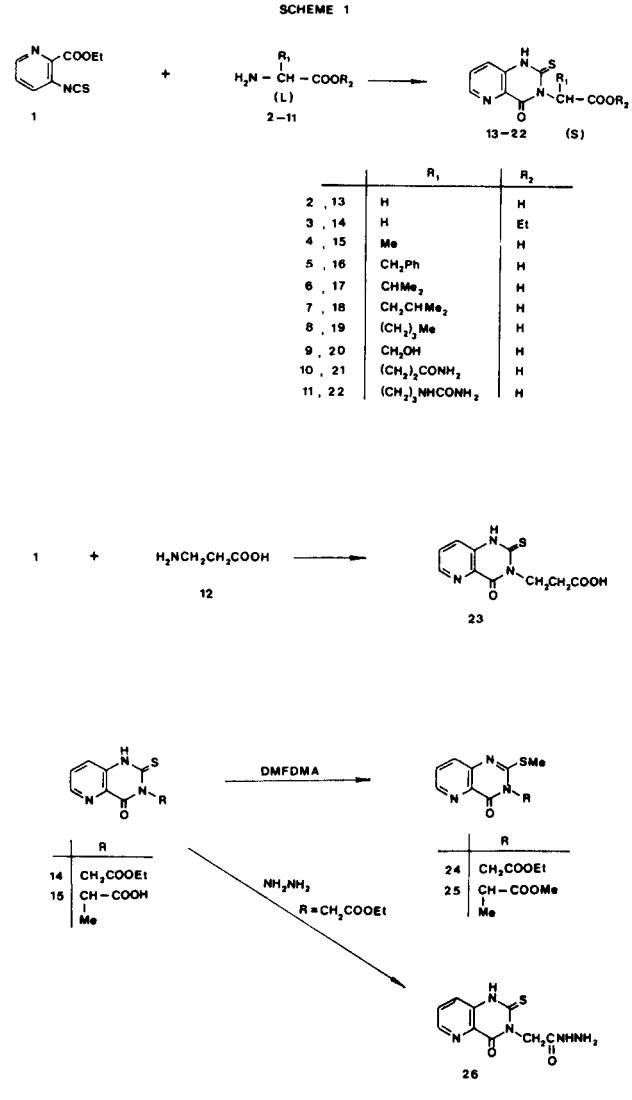
2-Ethoxycarbonyl-3-isothiocyanatopyridine (**1**) reacts with α-amino acids **2-11** and β-alanine (**12**) to give pyrido[3,2-*d*]pyrimidine derivatives **13-23** with the nitrogen of the amino acid component being incorporated into the fused pyrimidine ring at position 3. Methylation of **14** and **15** with DMFDMA produces *S*-methylated products **24** and **25**, while in the reaction of **14** with hydrazine the corresponding hydrazide **26** is formed. The reactions proceed under mild conditions, so that no racemization of chiral substituents was observed.

J. Heterocyclic Chem., **27**, 413 (1990).

Recently, we have reported on some novel methods for preparation of α-heteroaryl substituted α-amino acids from heterocyclic *N*-oxides [1], β-heteroarylamino-α,β-dehydro-α-amino acids from *N'*-heteroaryl-*N,N*-dimethylformamidines or heterocyclic primary and secondary amines [2,4], β-heteroaryl-α,β-dehydro-α-amino acids [5], and some condensed pyranoazoles and pyranoazines from heterocyclic compounds, containing an active methylene or potential methylene group in the ring system, and α-amino acid derivatives [5].

It has been described that phenyl isothiocyanate forms with α-amino acids hydantoins [6-8], while methyl *o*-isothiocyanatobenzoate reacts with α-amino acids to form tetrahydroquinazoline derivatives [9]. In the preceeding paper we have described the synthesis of 2-ethoxycarbonyl-3-isothiocyanatopyridine (**1**) and some of its transformations into pyrido[3,2-*d*]pyrimidine derivatives and other fused systems [10]. In continuation of our research in the field of heterocyclic amino acids we report now the reaction of 2-ethoxycarbonyl-3-isothiocyanatopyridine (**1**) with amino acid derivatives in which pyrido[3,2-*d*]pyrimidine derivatives with the nitrogen of the amino acid component being incorporated into the fused pyrimidine ring at position 3. The following α-amino acids were selected: glycine (**2**) and its ethyl ester (**3**), (L)-alanine (**4**), (L)-phenylalanine (**5**), (L)-valine (**6**), (L)-leucine (**7**), (L)-norleucine (**8**), (L)-serine (**9**), (L)-glutamine (**10**), (L)-citrulline (**11**), and β-alanine **12**. They react with isothiocyanate **1** in a mixture of dioxane and water in slightly alkaline media (*p*H 8-9) under mild conditions either at room temperature or by gentle heating (around 50°) to produce derivatives of pyrido[3,2-*d*]pyrimidines **13-22** and **23** with the amino acid residue attached to nitrogen at position 3 in pyrimidine part of the bicyclic system. The products **14** and **15** were methylated with *N,N*-dimethylformamide dimethyl acetal (DMFDMA), the reagent for which it has been shown previously to methylate mercapto or potential mercapto groups selectively [11], to give the corresponding *S*-methylated products **24** and **25**. When the compound **14** was treated with hydrazine hydrate at room temperature only ester group was transformed into the corresponding hydrazide to give

SCHEME 1



26 in the form of hydrazinium salt.

During cyclizations and other transformations a racemization of chiral centers could occur. However, by addition of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III) as a chiral shift reagent to the chloroform solutions of the bicyclic compounds with a chiral side chains, we observed only one set of peaks in the nmr spectra. On this basis we can conclude, that no racemization took place during these transformations, and therefore, since only (L)-α-amino acids were employed, the chirality of the side chains in bicyclic systems is (*S*).

EXPERIMENTAL

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

2-Ethoxycarbonyl-3-isothiocyanatopyridine (**1**) was prepared according to the procedure described previously [10].

3-Carboxymethyl-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**13**).

To a solution of glycine (**2**, 375 mg) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml) **1** (1.04 g) was added. The mixture was stirred at 50° for 5 hours. The volatile components were evaporated *in vacuo*, water was added to the solid residue and acidified with hydrochloric acid (18%) to *p*H 3. The precipitate was collected by filtration to give **13** (1.05 g, 87%), mp >300° (from DMF); ^{1}H nmr (DMSO-d_6): δ 5.05 (s, CH_2COOH), 7.61 (m, H_7, H_8), 8.45 (dd, H_6).

Anal. Calcd. for $C_9H_7N_3O_3S$·DMF: C, 46.44; H, 4.55; N, 18.05. Found: C, 46.25; H, 4.28; N, 17.80.

3-Ethoxycarbonylmethyl-2-thiooxo-1,2-dihydropyrido[3,2-*d*]-pyrimidine-4(3*H*)-one (**14**).

To a stirred solution of ethyl glycinate hydrochloride (**3**, 715 mg) in a mixture of water (10 ml), dioxane (10 ml) and sodium hydroxide (1 *M*, 5 ml) **1** (1.04 g) was added and the mixture was stirred at 50° for 8 hours, and then at room temperature for 12 hours. The precipitate was collected by filtration and purified by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, and chloroform/methanol, 9:1, as solvent) to give **14** (716 mg, 55%), mp 218-221° (from ethanol); ^{1}H nmr (DMSO-d_6): 120° δ 1.20 (t, OCH$_2$*Me*), 4.13 (q, OCH_2Me), 5.12 (s, NCH_2COOEt), 7.50 (dd, H_7), 7.72 (dd, H_8), 8.49 (dd, H_6), J_{CH_2Me} = 6.8 Hz, J_{H_6,H_7} = 3.8 Hz, J_{H_6,H_8} = 1.7 Hz, J_{H_7,H_8} = 6.0 Hz.

Anal. Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84. Found: C, 50.17; H, 4.20; N, 15.87.

3-[(*S*)-1-Carboxyethyl]-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidine-4(3*H*)-one (**15**).

To a stirred solution of L-alanine (**4**, 445 mg) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml) **1** (1.04 g) in dioxane (3 ml) was added and the mixture was heated at 50° for 24 hours. The volatile components were evaporated *in vacuo*, water (10 ml) was added to the residue and acidified with hydrochloric acid (18%) to *p*H 3. The precipitate was collected by filtration and washed with ethanol to give **15** (900 mg, 72%), mp 284-287°C (from a mixture of water and DMF); ^{1}H nmr (DMSO-d_6): δ 1.53 (d, *Me*CHCOOH), 6.20 (q, MeC*H*COOH), 7.62 (m, H_7, H_8), 8.45 (dd, H_6).

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 48.00; H, 3.22; N, 16.79. Found: C, 47.83; H, 3.43; N, 6.75.

3-[(*S*)-1-Benzyl-1-carboxymethyl]-2-thiooxo-1,2-dihydropyrido-[3,2-*d*]pyrimidine-4(3*H*)-one (**16**).

To a solution of L-phenylalanine (**5**, 826 mg) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml) **1** (1.04 g) in dioxane (3 ml) was added during stirring. The mixture was heated at 50° for 20 hours. The solvent was evaporated *in vacuo*, water (10 ml) was added and the mixture was acidified with hydrochloric acid (18%) to *p*H 3. The precipitate was collected by filtration to give **16** (1.2 g, 73%), mp 194-197° (from water); ms: (M^+-18) = 309; ^{1}H nmr (DMSO-d_6): δ 7.5 (m, Ph), 7.58 (H_7, H_8), 8.45 (H_6).

Anal. Calcd. for $C_{16}H_{13}N_3O_3S$·0.5 H_2O: C, 54.23; H, 4.55; N, 11.86. Found: C, 53.51; H, 4.27; N, 11.70.

3-[(*S*)-2-Methyl-1-carboxypropyl]-2-thiooxo-1,2-dihydropyrido-[3,2-*d*]pyrimidine-4(3*H*)-one (**17**).

To a stirred solution of L-valine (**6**, 586 mg) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml) **1** (1.04 g) was added and the mixture was heated at 50° for 20 hours. The volatile components were evaporated *in vacuo*, water (10 ml) was added to the residue and acidified with hydrochloric acid to *p*H 3. The precipitate was collected by filtration to give **17** (1.0 g, 71%), mp 262-265° (from ethanol); ^{1}H nmr (DMSO-d_6): 105°; δ 0.80 (d) and 1.24 (d) (*Me*$_2$CH) 2.83 (m, Me$_2$C*H*(COOH)CH), 6.11 (d, Me$_2$CHC*H*(COOH)), 7.73 (dd, H_7), 7.86 (dd, H_8), 8.62 (dd, H_6), J_{Me_2CH} = 6.8 Hz, J_{CHCH} = 8.8 Hz, J_{H_6,H_7} = 3.9 Hz, J_{H_6,H_8} = 1.9 Hz, J_{H_7,H_8} = 8.9 Hz.

Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04. Found: C, 51.32; H, 4.69; N, 14.96.

In the same manner the following compounds were prepared:

3-[(*S*)-3-Methyl-1-carboxybutyl]-2-thiooxo-1,2-dihydropyrido-[3,2-*d*]pyrimidin-4(3*H*)-one (**18**).

This compound was prepared from L-leucine (**7**, 660 mg) and **1** at 50°, 4 hours and room temperature, 12 hours, in 97% yield, mp 230-233° (from a mixture of acetic acid and water): ^{1}H nmr (DMSO-d_6): δ 0.95 (d, *Me*$_2$CH), 1.95 (m, Me$_2$C*H*CH_2CH), 6.27 (m, Me$_2$CHCH$_2$C*H*), 8.14 (dd, H_7), 8.43 (dd, H_8), 8.72 (dd, H_6), J_{H_6,H_7} = 4.8 Hz, J_{H_6,H_8} = 1.8 Hz, J_{H_7,H_8} = 8.7 Hz.

Anal. Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.24; H, 5.16; N, 14.33. Found: C, 53.48; H, 5.28; N, 14.18.

3-[(*S*)-1-Carboxypentyl]-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidine-4(3*H*)-one (**19**).

This compound was prepared from L-norleucine (**8**, 50 mg) 50°, 4 hours, in 95% yield, mp 210-213°C (from a mixture of methanol and water); ^{1}H nmr (DMSO-d_6): δ 0.9 (br t, *Me*CH$_2$), 1.4 (m, MeCH$_2$CH$_2$CH$_2$), 2.21 (m, MeCH$_2$CH$_2$CH_2CH), 6.45 [m, Me(CH$_2$)$_3$C*H*], 7.93 (m, H_7, H_8), 8.78 (m, H_6).

Anal. Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32. Found: 53.57; H, 5.12; H, 14.48.

3-[(*S*)-2-Hydroxy-1-carboxyethyl]-2-thiooxo-1,2-dihydropyrido-[3,2-*d*]pyrimidin-4(3*H*)-one (**20**).

This compound was prepared from L-serine (**9**, 105 mg), room temperature, 12 hours, in 55% yield, mp 214-216° (from water);

ms: (M^+ -18) = 249; ^{1}H nmr (DMSO-d_6): δ 4.05 (d, $HOCH_2$), 6.43 (t, $HOCH_2CH$), 6.95 (br s, NH, OH), 7.65 (m, H_7,H_8), 8.47 (m, H_6), 12.86 (br s, COOH).

Anal. Calcd. for $C_{10}H_9N_3O_4S$: C, 44.94; H, 3.39; N, 15.72. Found: C, 44.65; H, 3.26; N, 15.44.

3-[(*S*)-3-Carbamoyl-1-carboxypropyl]-2-thiooxo-1,2-dihydropyrido-[3,2-*d*]pyrimidin-4(3*H*)-one (**21**).

This compound was prepared from L-glutamine (**10**, 160 mg), 50°, 4 hours, in 67% yield, mp 179-181° (from water); ^{1}H nmr (DMSO-d_6): δ 2.25 (m, $COCH_2CH_2CH$), 6.3 (m, $COCH_2CH_2$), 6.55 (br s, NH), 7.06 (br s, CH_2CH), 7.66 (m, H_7,H_8), 8.50 (m, H_6).

Anal. Calcd. for $C_{12}H_{12}N_4O_4S.0.5\ H_2O$: C, 45.42; H, 4.13; N, 17.66. Found: C, 45.28; H, 4.16; N, 17.42.

3-[(*S*)-1-Carboxy-3-ureidopropyl]-2-thiooxo-1,2-dihydropyrido-[3,2-*d*]pyrimidin-4(3*H*)-one (**22**).

This compound was prepared from L-citrulline (**11**, 175 mg), 50°, 8 hours, in 45% yield, mp 235-237° (from water); ^{1}H nmr (DMSO-d_6): δ 1.45 (m) and 2.14 (m) ($NHCH_2CH_2CH_2CH_2$), 2.93 (m, $NHCH_2CH_2CH_2$), 5.22 (br s, NH_2), 5.8 (br s, NH), 6.25 (m, $CH(COOH)CH_2$), 7.65 (m, H_7,H_8), 8.48 (m, H_6), 12.95 (br s, COOH).

Anal. Calcd. for $C_{13}H_{15}N_5O_4S.0.5\ H_2O$: C, 45.08; H, 4.66; N, 20.22. Found: C, 45.25; H, 4.56; N, 20.25.

3-(2-Carboxyethyl)-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**23**).

To a solution of β-alanine (**12**, 445 mg) in water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml) **1** (1.04 g) was added and the mixture was stirred at 50° for 4 hours, and then at room temperature for 4 hours. The volatile components were evaporated *in vacuo*, water (10 ml) was added to the residue and the mixture was acidified with hydrochloric acid (18%) to *p*H 3. The precipitate was collected by filtration to give **23** (610 mg, 49%), mp >300° (from water); ^{1}H nmr (trifluoroacetic acid): δ 3.0 (t, CH_2CH_2COOH), 4.84 (t, CH_2CH_2COOH), 8.19 (dd, H_7), 8.45 (dd, H_8), 8.75 (dd, H_6), $J_{CH_2CH_2}$ = 7.5 Hz, J_{H_6,H_7} = 5.25 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 9.0 Hz.

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.80; H, 3.61; N, 16.72. Found: C, 48.11; H, 3.63; N, 16.60.

3-Ethoxycarbonylmethyl-2-methylthiopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**24**).

The compound **14** (100 mg) and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (2 ml) was heated under reflux for 3 hours. The volatile components were evaporated *in vacuo* and the oily residue was purified by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, chloroform/acetone, 30.1, as solvent) to give **24** (70 mg, 67%), mp 86-87°; ^{1}H nmr (deuteriochloroform): δ 1.28 (t, OCH_2Me), 2.64 (s, SMe), 4.17 (q, OCH_2Me), 4.88 (s, NCH_2COEt), 7.45 (dd, H_7), 7.78 (dd, H_8), 8.60 (dd, H_6), J_{H_6,H_7} = 4.4 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 8.3 Hz, J_{CH_2Me} = 6.8 Hz.

Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.72; H, 4.81; N, 15.21.

3-[(*S*)-1-Methoxycarbonylethyl)-2-methylthiopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**25**).

To a suspension of **15** (100 mg) in anhydrous methanol (3 ml) DMFDMA (2 ml) was added and the mixture was stirred at room temperature for 4 days. The volatile components were evaporated *in vacuo* and diethyl ether (5 ml) was added to the solid residue and the precipitate was collected by filtration to give **25** (45 mg, 40%), mp 149-152° (from ethanol): ^{1}H nmr (deuteriochloroform): δ 1.65 (d, $MeCHCCOH$), 3.53 (s) and 3.65 (s) (SMe and COOMe), 5.60 (q, $MeCHCOOH$), 7.49 (m, H_7,H_8), 8.49 (m, H_6), J_{CHMe} = 6.8 Hz.

Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.66; H, 4.67; N, 14.90.

3-Carbazoylmethyl-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one Hydrazinium Salt (**26**).

A suspension of **14** (400 mg) in hydrazine hydrate (99%, 4 ml) was stirred at room temperature for 8 days. The precipitate was collected by filtration to give **26** (334 mg, 89%), mp >310° (from DMF); ms: M^+ = 251; ^{1}H nmr (DMSO-d_6): δ 5.17 (s, CH_2CO), 5.89 (br s, $NHNH_2$), 7.56 (dd, H_7), 7.73 (dd, H_8), 8.43 (dd, H_6), J_{H_6,H_7} = 3.9 Hz, J_{H_6,H_8} = 2.0 Hz, J_{H_7,H_8} = 6.8 Hz.

Anal. Calcd. for $C_9H_{11}N_5O_2S{\cdot}N_2H_4$: C, 38.16; H, 4.63; N, 34.61. Found: C, 37.88; H, 4.59; N, 34.25.

Acknowledgement.

The authors wish to express their gratitude to the Research Council of Slovenia for partial financial support of this investigation.

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