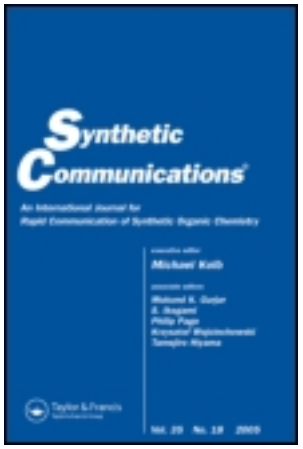

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Efficient Conversion of N-Terminal of L-Tyrosine, DL-Phenyl Alanine, and Glycine to Substituted 2-Thioxo-thiazolidine-4-ones: A Stereospecific Synthesis

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EFFICIENT CONVERSION OF *N*-TERMINAL OF L-TYROSINE, DL-PHENYL ALANINE, AND GLYCINE TO SUBSTITUTED 2-THIOXO-THIAZOLIDINE-4-ONES: A STEREOSPECIFIC SYNTHESIS

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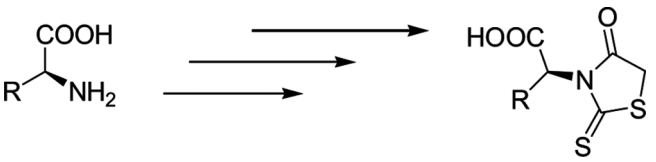
GRAPHICAL ABSTRACT



Abstract *We report facile and efficient conversion of the amino functional group of amino acids such a s L-tyrosine, DL-phenylalanine, and glycine to the corresponding (±)-2-thioxo-thiazolidine-4-ones (rhodanines). Stereospecific synthesis of amino acid–incorporated rhodanine is achieved in the case of L-tyrosine. Knoevenagel condensation over the active methylene group at the fifth position of the corresponding rhodanines is also described. The substituted rhodanine incorporated with tyrosine in the form of a dimer connected via two-carbon linker possesses significant anticancer activity against A549 cells (human lung cancer cells).*

Keywords A549 cells; anticancer activity; Knoevenagel condensation; rhodanine; stereospecific synthesis; 2-thioxo-thiazolidine-4-one

INTRODUCTION

Thiazolidine heterocycles are of considerable interest from both synthetic and biological points of view.[1] Thiazolidinone derivatives are reported to have anticonvulsant,[2] antibacterial,[3] and antiviral[4] properties. A thiazolidine-2,4-dione derivative, LY213829, used for the treatment of inflammatory bowel disease,[5] and rosiglitazone,[6] used for non-insulin-dependant diabetes mellitus, contain the thiazolidine-2,4-dione motif. The 2-thioxo-4-thiazolidinone (rhodanine) moiety, being a bioisostere of thiazolidine-2,4-dione, is also known to have diverse pharmacological properties.[7,8] Rhodanine has been synthesized by various methods such as

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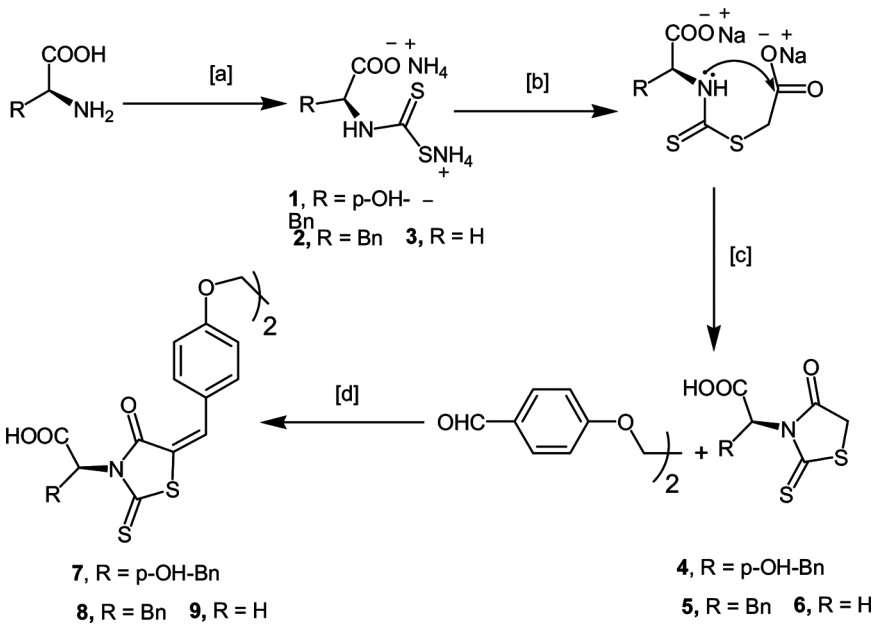
the addition of isothiocyanate to mercaptoacetic acid followed by acid cyclization or the reaction of ammonia or primary amines with carbon disulfide and chloro-acetic acid in the presence of a base.[9] Recently, Alizadeh et al. have reported three-component coupling of carbon disulfide, primary amine, and acetylenic esters to get rhodanine derivatives.[10] Rhodanines possess active CH_2 groups and hence condense with aldehydes, especially in the presence of basic catalysts. This Knoevenagel condensation has been accomplished using piperidinium benzoate in refluxing toluene using a Dean–Stark apparatus,[11] sodium acetate in refluxing glacial acetic acid,[9] or piperidine and glacial acetic acid in refluxing toluene.[12] In continuation of our recent report on glitazones, we proposed to synthesize the biologically active molecules by varying the existing protocols, which could allow us access to amino acid–substituted rhodanines.[13] There are very few reports using amino acids.[8] We, therefore, started the synthesis of the title compounds with amino acids such as L-tyrosine, DL-phenylalanine, and glycine.

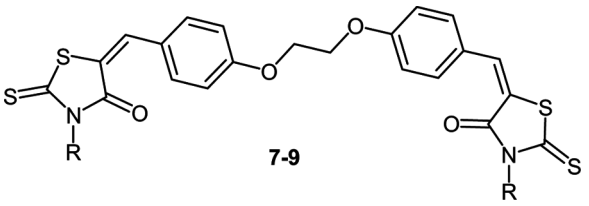
RESULTS AND DISCUSSION

The synthesis of the title compounds with amino acids such as L-tyrosine, DL-phenylalanine, and glycine is shown in Scheme 1. Stereospecific synthesis is demonstrated in the case of L-tyrosine by retaining the original configuration. In this protocol, each amino acid was converted to the corresponding ammonium salt and

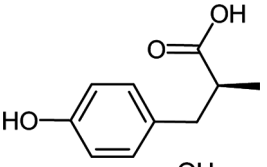
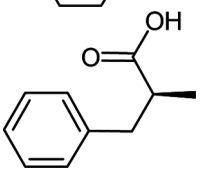
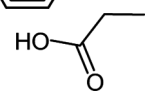


Scheme 1. Synthesis of 2-thioxo-thiazolidine-4-one derivatives incorporated with tyrosine, phenyl alanine, and glycine residues: (a) H_2O, 0–5 °C, aqueous ammonia solution 25–30%, CS_2, stir for 10 h; (b) 5–10 °C, sodium chloroacetate solution; (c) 6 N HCl, two drops $POCl_3$, 50–60 °C for 3 h; (d) toluene, dimeric *p*-hydroxy benzaldehyde, *N*-methyl piperazine, ammonium acetate, molecular sieves, reflux for 15 h.

Table 1. L-Tyrosine, DL-phenylalanine, and glycine incorporated 2-thioxo-thiazolidine-4-ones



7-9

Entry	R	CTC_{50}[a] (μg)
7		3.6
8		>200
9		>200

[a]CTC_{50}: Concentration that inhibited 50% growth of A549 cells.

then reacted with carbon disulfide using water as solvent to yield the corresponding dithiocarbomates (**1**, **2**, and **3**). The reaction proceeded spontaneously and was completed in 10 h. The dithiocarbamates formed were then reacted with sodium chloroacetate and later cyclized under acidic conditions in the presence of phosphorous oxychloride to yield products in which the *N*-terminal of amino acid is converted to the corresponding 2-thioxo-thiazolidine-4-ones **4, 5,** and **6** (77–86%). Compound **4** was found to be enantiomerically pure with the retention of original configuration. Further, they were subjected to the Knoevenagel condensation with dimeric *p*-hydroxy benzaldehyde (linked via two-carbon linker), using *N*-methyl piperazine and ammonium acetate in refluxing toluene to yield **7, 8,** and **9** (76–89%, Table 1).[14] Knoevenagel condensation was performed on **4, 5,** and **6** without the aid of a Dean–Stark apparatus. Table 1 lists the substituted 2-thioxo-thiazolidine-4-ones synthesized. Despite the heating in the Knoevenagel condensation, compound **7** was found to be enantiomerically pure with retention of the original configuration.

Apart from good yields, the advantages of the present protocol when compared to the reported ones lie in the relative ease with which the ammonium salt of dithiocarbamate is prepared rather than the sodium salt and completion of the reaction at room temperature without the necessity for heating.[8] We also observed that the dithiocarbamates are relatively more stable under cold conditions (<5 °C). The use of phosphorous oxychloride along with HCl was found to be useful in the

cyclization step for enhancing the yields. Apart from these advantages, another advantage in using this protocol is the stereospecific synthesis. The rate of Knoevenagel condensation with aldehydes over the active methylene group has been shown to increase when *N*-methyl piperazine and ammonium acetate are used rather than a piperidine and acetic acid mixture under similar conditions.[12]

The structures of the synthesized compounds were confirmed from infrared (IR), mass, and NMR analysis. The cross peaks in heteronuclear correction (HETCOR) spectrum for compound **7** helped us to identify protons attached to carbons (or vice versa) as shown in Fig. 1. Cross peaks for hydrogens at 3.43 δ ppm in ^{1}H NMR spectrum show that they are bonded to the carbon at 36.0 δ ppm in ^{13}C NMR spectrum (β hydrogens attached to the β carbon of tyrosine structural part). Cross peaks for hydrogens at 4.43 δ ppm in ^{1}H NMR spectrum are bonded to the carbons at 67.08 δ ppm in ^{13}C NMR spectrum (methylene protons attached to the methylene carbon atoms of two-carbon linker). Cross peaks for hydrogen at 5.62 δ ppm in ^{1}H NMR spectrum show that they are bonded to the carbon at 60.38 δ ppm in ^{13}C NMR spectrum (α hydrogen attached to the α carbon of tyrosine structural part). This indicates that the α-hydrogen becomes highly acidic after the amino group is converted to the polar 2-thioxo-thiazolidine-4-one motif. Cross peaks for hydrogen at 7.68 δ ppm in ^{1}H NMR spectrum show that they are bonded to the carbon at 132.94 δ ppm in ^{13}C NMR spectrum (=CH, at the fifth position of thiazolidinedione ring system). The reason for this deshielding is attributed to the

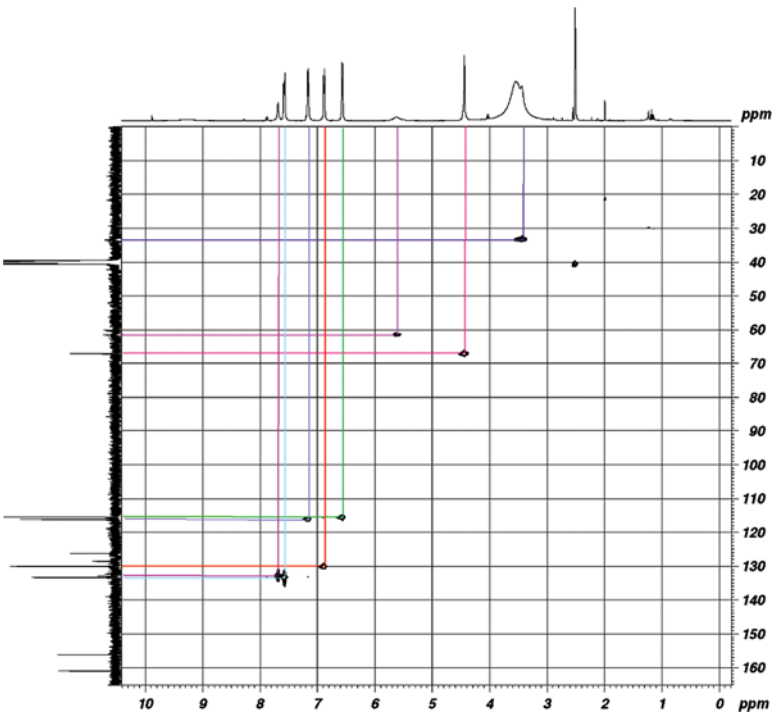


Figure 1. ^{1}H-^{13}C HETCOR spectrum for compound **7** cross peaks are shown in different lines. (Figure is provided in color online.)

cis-position of the exocyclic carbonyl function of 2-thioxo-thiazolidine-4-one ring to the =CH and hence the *Z* configuration.[12–14] Similarly, other hydrogens and carbon atoms are cross-correlated via cross peaks as shown in Fig. 1.

Compounds **7, 8,** and **9** were subjected to in vitro cytotoxicity assay against A549 cells (human lung cancer cells). The assay was performed by the sulforhodamine B (SRB) method.[15] The results are given in Table 1. Surprisingly, compound **7** exhibits cytotoxicity with CTC_{50} of 3.6 μg (Table 1).

In summary, we report here a simple, efficient stereospecific method to synthesize some novel rhodanines of biological interest incorporated with amino acids such a s L-tyrosine, DL-phenyl alanine, and glycine. Conditions for Knoevenagel condensation reaction were also optimized. The results are encouraging us to extend this protocol to the other amino acids.

EXPERIMENTAL

The infrared(IR) spectra of the compounds were recorded on Shimadzu and Perkin-Elmer Fourior transform (FT)–IR spectrophotometer, using KBr pellet or neat technique, and are expressed in centimeters $^{-1}$. NMR spectra were recorded on AV-400-and 500-MHz spectrometers using tetramethylsilane (TMS) as internal standard and dimethylsulfoxide (DMSO-d_6) as a solvent. The chemical shifts are expressed in δ ppm, and the following abbreviations are used: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartlet; and m, multiplet. The high-resolution mass spectrometric (HRMS) analysis was done on a Perkin-Elmer Sciex API-150-EX by electrospray (ESI) ionization and turnover frequency (TOF) detection techniques. All the reactions were monitored using thin-layer chromatography. (TLC) performed using 4% methanol in chloroform as mobile phase on aluminum plates that were are precoated with silica gel GF. A Merck Microlab 200 autoanalyzer was used for the estimation of glucose and triglycerides.

Preparation of Title Compounds

Water (10 ml) and ammonia solution (30 ml, 25–30%) were transferred into a conical flask. The conical flask was placed in an ice bath, and the temperature was maintained at 0–5 °C. Carbon disulfide (0.0031 M) was then added. L-Tyrosine or (±)-phenyl alanine or glycine (0.003 M) was added slowly to this solution for a period of 30 min with continuous stirring. A cotton plug was put to the flask, and the reaction mixture was stirred for 10 h and allowed to stand for 2 h in a refrigerator to yield dithiocarbamate of the corresponding amino acids (**1, 2,** and **3**). Sodium chloroacetate solution was prepared by dissolving chloroacetic acid (0.003 M) and NaOH (0.003 M) each in 3 ml of water, separately. Then both were mixed and stirred for 30 min. Solid sodium carbonate was then added slowly until the reaction mixture became basic to litmus. Sodium chloroacetate solution was added into a flask containing dithiocarbamate solution slowly at 5–10 °C under stirring. The reaction mixture was allowed to stir for 1 h. The uncyclized *N*-substituted rhodanine formed was cyclized by adding 10 ml of 6 N HCl and two or three drops of phosphorous oxychloride and heating at 60–70 °C for about 3 h. All the reactions were monitored with TLC using 20% methanol in chloroform as the mobile phase. The spots on TLC were

detected using alcoholic *dodeca*-phosphomolybdinum staining and heating, apart from using ninhydrin reagent. The reaction mixture was allowed to cool. The solid formed was filtered and recrystallized with diethyl ether to obtain **4, 5,** and **6** (77–86%). Compounds **7, 8,** and **9** were prepared by subjecting **4, 5,** and **6** to the Knoevenagel condensation reaction with substituted aldehyde (76–89%).

Knoevenagel Condensation Reaction

Equimolar amounts of the substrate, **4** or **5** or **6** (0.002 M), and 20–30 ml of dry toluene were transferred to a flat-bottomed flask. *N*-Methyl piperazine (0.0001 M), ammonium acetate (0.0001 M), and molecular sieves (0.5 g) were then added. The reaction mixture was stirred for 5 min and then heated under reflux at 110 °C with occasional stirring for about 15 h. After the completion of the reaction, the reaction mixture was allowed to cool, and the precipitated solid was filtered and recrystallized using methanol to obtain the pure compound.

Physical, Analytical, and Spectral Data of Compounds 7, 8, and 9

(−)-2-{5-[1-[4-(2-{4-[3-[(−)-1-Carboxy-2-(4-hydroxy-phenyl)-ethyl]-thiazolidin-(5)-ylidenemethyl]-phenoxy}-ethoxy)-phenyl]-meth-(*Z*)-ylidene]-thiazolidin-3-yl}-3-(4-hydroxy-phenyl)-propionic acid (7). Yellow crystals, mp 210–216 °C, yield 65%. FTIR (KBr, cm^{-1}): 3500–2500 (O-H & N-H), 3000 (Ar-H), 2935 (AliC-H), 1697 (C=O), 1508 (ArC=C), 1242 (C=S), 1172 (C-O), 1039 (C-N). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 3.43 (bs, 4H, 2 × CH_2), 4.43 (s, 4H, 2 × CH_2), 5.62 (bs, 2H, 2 × CH), 6.55 (d, $J = 8.5$ Hz, 4H, ArH), 6.87 (d, $J = 8.5$ Hz, 4H, ArH), 7.15 (d, $J = 8.5$ Hz, 4H, ArH), 7.56 (d, $J = 8.5$ Hz, 4H, ArH), 7.68 (s, 2H, 2 × = CH), 9.30 (bs, 2H, OH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 36.0 (2 × CH_2), 60.38 (2 × CH), 67.08 (2 × CH_2), 115.51 (2 × = C), 115.51 (6ArC), 116.15 (4ArC), 126.28 (2ArC), 128.57 (2ArC), 130.06 (4ArC), 132.94 (2 × = CH), 133.35 (6ArC), 156.14 (2 × C=O), 160.90 (2 × C=O). HRMS (ES-TOF) m/z found 851.4293 (M + Na), calculated 851.0 (M + Na).

(±)-2-{5-[1-[4-(2-{4-[3-((−)-1-Carboxy-2-phenyl)-ethyl]-thiazolidin-(5)-ylidenemethyl]-phenoxy}-ethoxy)-phenyl]-meth-(*Z*)-ylidene]-thiazolidin-3-yl}-3-phenyl propionic acid (8). Yellow crystals, mp 178–181 °C, yield 71%. FTIR (KBr, cm^{-1}): 3500–2500 (O-H & N-H), 3012 (Ar-H), 2958 (AliC-H), 1692 (C=O), 1503 (ArC=C), 1221 (C=S), 1143 (C-O), 1007 (C-N). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): 3.39 (bs, 4H, 2 × CH_2), 4.40 (s, 4H, 2 × CH_2), 5.63 (bs, 2H, 2 × CH), 6.82–7.38 (m, 10H, ArH), 7.21 (d, $J = 8.5$ Hz, 4H, ArH), 7.58 (d, $J = 8.5$ Hz, Hz, 4H, ArH), 7.70 (s, 2H, 2 × = CH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 36.11 (2 × CH_2), 60.40 (2 × CH), 67.11 (2 × CH_2), 115.62 (2 × = C), 115.74 (6ArC), 116.23 (4ArC), 126.36 (2ArC), 128.69 (2ArC), 130.28 (4ArC), 132.45 (2 x = CH), 133.71 (6ArC), 156.30 (2 × C=O), 160.70 (2 x C=O). HRMS (ES-TOF) m/z found 819.2173 (M + Na), calculated 819.0 (M + Na).

5-[3-(1-Carboxymethyl)-thiazolidin-(5)-ylidenemethyl]-phenoxy]-ethoxy)-phenyl]-meth-(*Z*)-ylidene]-thiazolidin-3-yl-ethanoic acid (9). Cream-colored crystals, mp 242–247 °C, yield 78%. FTIR (KBr, cm^{-1}): 3500–2500 (O-H & N-H),

3027 (Ar-H), 2971 (AliC-H), 1679 (C=O), 1492 (ArC=C), 1235(C=S), 1149 (C-O), 1026 (C-N). ^{13}C NMR (500 MHz, DMSO-d_6, δ ppm): 36.07 ($2 \times CH_2$), 71.43 ($2 \times CH_2$), 115.67 ($2 \times =C$), 115.81 (6ArC), 116.19 (4ArC), 126.30 (2ArC), 128.65 (2ArC), 130.14 (4ArC), 132.40 ($2 \times =CH$), 133.61 (6ArC), 156.30 ($2 \times C=O$), 162.70 ($2 \times C=O$), 197.30 (C=S). HRMS (ES-TOF) m/z found 639.0819 (M + Na),), calculated 639.0 (M + Na).

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