Synthesis of novel, chiral, water-soluble isothiazole derivatives

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This article describes an easy preparation of some optically active, water soluble N[5],2,3,4-tetrasubstituted isothiazol-5(*2H*)-imine hydrobromides from modified L-α-amino acids. Isothiazole rings are created in two-step reactions by oxidation of chiral 3-amino-2,3-unsaturated thioamides.

Keywords: isothiazoles, chirality, unsaturated thioamides, oxidation, water solubility

Over the last decade a particular interest in the search for more effective and simpler preparation of substituted isothiazoles stemmed from their biological activity.[1] Highly substituted isothiazoles are known as antimicrobial,[2] antitumoral,[3] spasmolytic,[4] herbicidal, insecticidal and fungicidal[5] agents. The application of substituted isothiazole derivatives in pharmacotherapy has been significantly broadened after the discovery of their antiviral properties.[6] Of all the antiviral drugs, isothiazole derivatives are the object of intensive research. Recent investigations have shown that some 3-methylthio-5-aryl-4-isothiazolecarbonitriles possess remarkable antiviral activity against numerous serotypes of rhinoviruses and enteroviruses, and inhibit the replication of HIV-1 and HIV-2 viruses.[7] The diamide of 3-methyl-5-isothiazole-4,5-dicarboxylic acid, known as vratizolin,[8] (ITLC, Denotivir) is a commercially available antiviral drug recommended for the treatment of herpes simplex and varicella zoster viral infections. The pharmacological application of vratizolin and related isothiazoles is however wider then previously expected owing to their antiinflammatory and immunomodulatory properties.[9] The biological activity of the investigated isothiazole derivatives depends however not only on their chemical structures but also on their physical properties such as solubility and stability in aqueous solution.[7a]

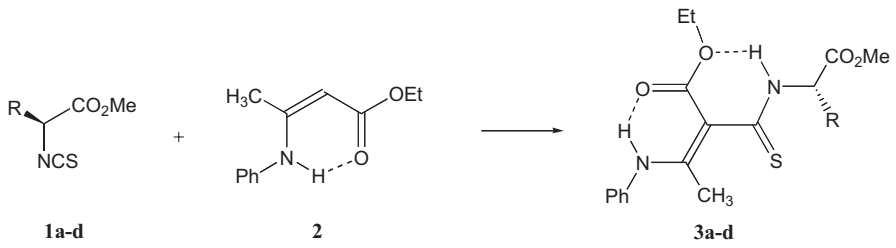
Results

Water solubility is a very desirable feature of organic compounds which are investigated as potential biologically active agents. Although the isothiazole ring is hydrophobic, the introduction of polar groups into this molecule may considerably increase its solubility in water. In our research we have focused on the synthesis of N^5,2,3,4-tetrasubstituted isothiazol-5(*2H*)-imine derivatives bearing a chiral L-α-aminoacid substituent. We wished to determine if the presence of an amino acid group linked to a highly-substituted isothiazole ring would be a sufficient requirement for improvement of its water solubility. The synthesis of N^5,2,3,4-tetrasubstituted isothiazol-5(*2H*)-imines, based on a previously described method,[10] consisting in the oxidation of 3-amino-2,3-unsaturated thioamides. The first step of our investigation involved the preparation of the starting unsaturated thioamides from isothiocyanates and enamines using a standard procedure.[11] As isothiocyanate we used the chiral α-isothiocyanatocarboxylates[12] **1** derived from protected L-α-aminoacids, and as enamine we used ethyl 3-anilinocrotonate **2**.[13] The choice of the 3-anilinocrotonate was predicated by the presence of an ester group which we wished to introduce directly into isothiazole ring to enhance its polarity. The optically active isothiocyanatocarboxylates **1** provided an amino acid group which, after cyclisation, we wished to deprotect to obtain a pure carboxyl substituent. Addition of the chiral isothiocyanatocarboxylates **1** to ethyl 3-anilinocrotonate **2** in a solvent-free system gave novel 3-aminothiocrotonates **3** in good yields (Scheme 1).

The structures of the unsaturated thioamides **3** so obtained were confirmed by NMR, IR and mass spectrometry. Based on NOESY experiments, we found that 3-amino-2,3-unsaturated thioamides **3** existed only as (*E*)-diastereomers; analogously to earlier described 3-anilinothiocrotonate amides,[14] we did not observe any trace of (*Z*)-isomers. The ^{1}H NMR signals of both NH protons were observed at *ca* 10 ppm, indicating strong hydrogen bonding between amino and ester groups.

The second step, the oxidation of the unsaturated thioamides **3** with bromine following the procedure of Goerdeler and Gnad,[15] led to the desired isothiazole hydrobromides **4**. Isolation of the pure diesters of the N^5,2,3,4-tetrasubstituted isothiazol-5(*2H*)-imines **4** was, however, not possible because of their instability. Deesterification of the aminoester groups proceeded spontaneously during isolation and purification, leading to the stable final products, the ethyl 5-(1-carboxyalkylimino)-3-methyl-2-phenyl-2,5-dihydroisothiazole-4-carboxylate hydrobromides **5** (Scheme 2).

Hydrolysis of the 4-ethoxycarbonyl group to form the dicarboxylic acid failed owing to the particular stability of this substituent. All the structures of the isothiazole derivatives **5** synthesised here were confirmed by spectroscopic data. In the ^{1}H NMR spectrum of **5c** (R = CH_2Ph) we observed the



1a-d **2** **3a-d**

a: R = H; **b**: R = CH_3; **c**: R = CH_2Ph; **d**: R = $CH(CH_3)C_2H_5$

Scheme 1

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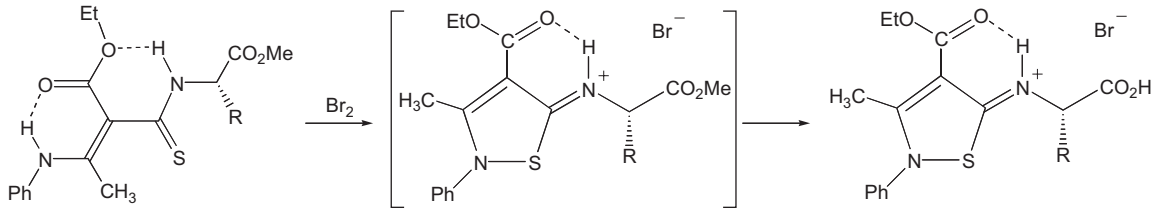

3a-c **4a-c** **5a-c**

Scheme 2

diastereotopic nonequivalence of the benzylic protons: the J_{gem} coupling was 13.8 Hz, and they coupled with the neighbouring proton at C-α with $^3J_{vic}$ values of 4.2 and 9.0 Hz. According to the Karplus-Conroy equation we estimate that the dihedral angles of H–Cα–Cβ–H_a and H–Cα–Cβ–H_b are *ca* 43° and 171°. The obtained *N*[5],2,3,4-tetrasubstituted isothiazol-5(*2H*)-imine hydrobromides **5a–c** were stable as salts and showed good solubility in water. Stoichiometric reaction of the obtained hydrobromides **5** with triethylamine gave rise to cleavage of the isothiazole ring with extrusion of sulfur. This process was particularly rapid in polar protic solvents, while neutralisation of the hydrobromides in methylene chloride led to unstable isothiazol-5(*2H*)-imines which decomposed during separation. Thus, the reaction of the hydrobromide **5c** with triethylamine in methanol led to several decomposition products which were investigated using NMR spectroscopy. We noted that a characteristic feature of these compounds was a presence of the methoxyl group at C-5 carbon atom. This observation is in agreement with earlier reported ring-opening processes of isothiazole rings on reaction with nucleophiles.[16]

Previously we have proved that the oxidative cyclisation of chiral optically active 2,3-unsaturated thioamides with bromine proceeded without racemisation and all prepared isothiazole derivatives were enantiomerically pure.[14] To confirm that our method also gives enantiomerically pure products and proceed without partial racemisation we measured some NMR spectra of the prepared compounds using europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate],$Eu(tfc)_3$, as a chiral NMR shift reagent. However 3-anilinothiocrotonate amides **3** did not interact with $Eu(tfc)_3$, whereas isothiazole derivatives **5** formed very stable complexes with Eu^{3+} ions replacing the chiral ligands. To check on the retention of configuration during the synthesis we synthesised 3-anilinothiocrotonate amide with two chiral centres starting from L-isoleucine. After addition of isothiocyanatocarboxylate **1d** to 3-anilinocrotonate (**2**) we observed only one diastereoisomer **3d**. This observation encouraged us to assume that syntheses of 3-anilinothiocrotonate amides **3** proceeded without racemisation, leading to enantiomerically pure products.

In summary, we have discovered a novel class of chiral *N*[5],2,3,4-tetrasubstituted isothiazol-5(*2H*)-imine hydrobromides. Although the isothiazole rings are considerably hydrophobic owing to the presence of methyl and phenyl substituents, the introduction of one amino acid group into the heterocyclic system results in significant increase in their water solubility. Moreover, the 5-(1-carboxyalkylimino)-3-methyl-2-phenyl-2,5-dihydroisothiazole-4-carboxylic acid ethyl ester hydrobromides (**5**) are very stable, although only as the salts, and they did not further hydrolyse in water, although they decompose easily under basic conditions. The presence of the carboxylic functional group had a strong effect on the chelating properties of these isothiazoles. The products are prepared in enantiomerically pure form in a simple and direct way in two steps from chiral 3-anilinothiocrotonate amides. All reactants used for syntheses of the starting unsaturated thioamides were easy obtained from commercially available L-α-amino acids and ethyl acetoacetate. The synthesised *N*[5],2,3,4-tetrasubstituted isothiazol-5(*2H*)-imine derivatives **5** show a structural similarity with some antiviral isothiazole agents being currently investigated.[7,9]

Experimental

NMR spectra were determined on a Bruker Avance II 300 MHz spectrometer, using TMS as internal standard. IR spectra were measured with a Bruker IFS 48 FT spectrometer in KBr pellets and EI mass spectra were recorded on a Finnigan MAT 95S apparatus. Mass spectrometric analysis of compound **5c** using electrospray (ESI) technique was performed on an Esquire 3000 mass spectrometer. The sample of **5c** was mixed with 30% methanol in water and analysed in the positive-ion mode. Microanalyses were carried out using Euro-EA 3018 analyser. Optical rotations were measured on a Polamat A polarimeter with 0.5 dm tube. Column chromatography was performed using commercial silica gel 60 (70–230 mesh). Melting points were measured on an Electrothermal 9100 apparatus.

Solvent-free synthesis of thiocarbamoyl esters **3a–d**: *general procedure*

Into a 25 ml flask protected against air moisture was added ethyl 3-anilinocrotonate[13] **2** (20 mmol) and methyl isothiocyanato-carboxylate[12] **1a–d** (21 mmol). The mixture was stirred and heated for 90–120 min. at 105°C. After cooling, the residue was purged with petroleum ether/*n*-hexane to remove excess of the methyl isothiocyanatocarboxylate and the crude product was purified by column chromatography using silica gel (cyclohexane:ethyl acetate 10:1) and then crystallised from methanol.

Ethyl (E)-2-[N-(methoxycarbonylmethyl)thiocarbamoyl]-3-phenylamino-but-2-enoate (**3a**): Pale yellow solid (85% yield), m.p. 112°C. IR: ν_{max} 3249, 1740, 1625, 1210 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.17 (t, *J* = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 2.07 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 4.08 (q, *J* = 7.1 Hz, 2H, $O\underline{CH_2}CH_3$), 4.36 (d, *J* = 5.8 Hz, 2H, CH_2), 7.18 (d, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 10.48 (t, *J* = 5.7 Hz, 1H, NH), 10.92 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ 14.3, 17.1, 40.5, 51.7, 59.1, 104.1, 124.5, 125.3, 129.3, 138.0, 156.2, 166.9, 168.5, 198.5 ppm. MS: *m/z* (%) 336 (M^+, 27), 303 (40), 263 (17), 244 (13), 205 (22), 160 (21), 132 (23), 118 (100), 93 (23). Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.18; H, 6.11; N, 8.30%.

Ethyl (S),(E)-2-[N-(1-Methoxycarbonylethyl)thiocarbamoyl]-3-phenylamino-but-2-enoate (**3b**): Pale yellow solid (78% yield), m.p. 110°C. $[\alpha]_D$ -22.8° (c = 0.1, $CHCl_3$). IR: ν_{max} 3274, 1745, 1728, 1635, 1210 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.18 (t, *J* = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 1.40 (d, *J* = 7.3 Hz, 3H, $CH\underline{CH_3}$), 2.04 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.08 (m, 2H, $O\underline{CH_2}CH_3$), 4.92 (m, 1H, $\underline{CH}CH_3$), 7.22 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 2H), 10.44 (d, *J* = 6.8 Hz, 1H, NH), 10.89 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ 14.2, 15.9, 17.1, 51.9, 53.6, 59.0, 104.2, 124.5, 125.3, 129.3, 138.4, 156.1, 166.9, 171.5, 197.2 ppm. MS: *m/z* (%) 350 (M^+, 25), 317 (59), 258 (21), 233 (26), 205 (53), 200 (27), 160 (49), 132 (45), 118 (100), 93 (76). Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.19; H, 6.40; N, 7.94%.

Ethyl (S),(E)-2-[N-[(1-Methoxycarbonyl)-2-phenylethyl]thiocarbamoyl]-3-phenylamino-but-2-enoate (**3c**): Pale yellow solid (95% yield), m.p. 136°C. $[\alpha]_D$ = 74.1° (c = 0.1, $CHCl_3$). IR: ν_{max} 3155, 1755, 1645, 1205 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.06 (t, *J* = 7.1 Hz, 3H,

$OCH_2C\underline{H}_3$), 1.85 (s, 3H, CH_3), 3.13 (dd, J = 9.9 and 14.4 Hz, 2H, $PhC\underline{H}_aH_b$), 3.19 (dd, J = 4.9 and 14.4 Hz, 2H, $PhCH_a\underline{H}_b$), 3.64 (s, 3H, OCH_3), 3.97 (ddq, J = 7.0, 7.1 and 10.8 Hz, 2H, $OC\underline{H}_2CH_3$), 5.20 (ddd, J = 4.9, 7.3 and 9.9 Hz, 1H, CH), 7.14 (d, J = 7.7 Hz, 2H), 7.22 (m, 2H), 7.29 (m, 4H), 7.39 (t, J = 8.0 Hz, 2H), 10.52 (d, J = 7.3 Hz, 1H, NH), 10.88 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): δ 14.1, 16.8, 35.7, 51.9, 58.9, 59.3, 104.2, 124.0, 125.2, 126.6, 128.2, 128.7, 129.3, 137.0, 138.3, 155.9, 166.8, 170.5, 198.1 ppm. Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.77; H, 6.14; N, 6.57. Found: C, 64.76; H, 6.10; N, 6.61%.

Methyl (S,S)-2-[[(E)-2-ethoxycarbonyl-3-(phenylamino)but-2-enethioyl]amino]-3-methylpentanoate (**3d**): Yellow solid (64% yield), m.p. 92°C. $[\alpha]_D$ = 2.4° (c = 0.1, $CHCl_3$). IR: ν_{max} 3260, 1743, 1647, 1202 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, J = 6.9 Hz, 3H, $CHC\underline{H}_3$), 0.99 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.28 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.32 (ddq, J = 5.1, 5.1 and 7.8 Hz, 1H, $CH_3C\underline{H}_aH_b$), 1.58 (ddq, J = 5.1, 5.4 and 7.8 Hz, 1H, $CH_3CH_a\underline{H}_b$), 2.13 (s, 3H, CH_3), 2.15 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 4.20 (q, J = 6.9 Hz, 2H, $OC\underline{H}_2CH_3$), 5.22 (dd, J = 5.1, 5.5 Hz, 1H, CH), 7.11 (d, J = 7.9 Hz, 2H), 7.23 (t, J = 7.9 Hz, 1H), 7.32 (t, J = 5.4 Hz, 2H), 8.44 (br s, 1H, NH), 10.14 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ 11.6, 14.3, 15.5, 25.2, 26.9, 37.4, 52.1, 60.0, 61.8, 105.0, 125.7, 126.2, 129.1, 138.1, 157.1, 167.1, 171.4, 200.6 ppm. Anal. Calcd for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.26; H, 7.22; N, 7.17%.

Iminodihydroisothiazole ester hydrobromides **5a–c**: *general procedure*

A three-necked, 150 ml flask equipped in a stir bar, a condenser and an addition funnel was charged with chloroform (60 ml) and 3-amino-2,3-unsaturated thioamide **3a–c** (10 mmol). The mixture was cooled to 0°C over an ice bath and then bromine (1.76 g, 0.56 ml, 11 mmol) in chloroform (10 ml) was added dropwise over 20 min. The reaction mixture was stirred for 30 min at 0°C and allowed to warm to room temperature over 3 h, then filtered and evaporated under reduced pressure. The crude products were dissolved in acetone/water (8:3, 40 ml) and refluxed for 15 minutes. Then the solvents were removed on a water bath and the residue was purified by chromatography using silica gel (R_f = 0.30–0.41; $CHCl_3$:CH_3OH 7:1).

Ethyl 5-(carboxymethylimino)-3-methyl-2-phenyl-2,5-dihydroisothiazole-4-carboxylate hydrobromide (**5a**): Colourless solid (68% yield), m.p. 103°C. IR: ν_{max} 3400–2400, 1722, 1684 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.63 (s, 3H, CH_3), 4.45 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.48 (d, J = 4.0 Hz, 2H, CH_2), 7.58 (m, 3H), 7.66 (m, 2H), 9.51 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ 14.2, 18.0, 50.6, 62.6, 105.4, 128.1, 130.6, 131.9, 133.7, 162, 4, 167.3, 168.7, 174.2 ppm. Anal. Calcd for $C_{15}H_{17}BrN_2O_4S$: C, 44.90; H, 4.27; N, 6.98. Found: C, 45.01; H 4.33; N, 6.92%.

Ethyl (S)-5-[(1-carboxyethyl)imino]-3-methyl-2-phenyl-2,5-dihydroisothiazole-4-carboxylate hydrobromide (**5b**): Colourless solid (71% yield), m.p. 93°C. $[\alpha]_D$ = 2.0° (c = 0.1, $CHCl_3$). IR: ν_{max} 3500–2450, 1734, 1683 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.64 (d, J = 6.4 Hz, 3H, $CHC\underline{H}_3$), 2.59 (s, 3H, CH_3), 4.34 (q, J = 6.4 Hz, 1H, $C\underline{H}CH_3$), 4.44 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 7.22 (m, 1H), 7.57 (m, 4H), 10.32 (br. s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ 14.1, 16.9, 17.7, 57.3, 62.4, 104.9, 127.8, 130.6, 131.7, 133.7, 163.2, 166.7, 171.3, 173.4 ppm. Anal. Calcd for $C_{16}H_{19}BrN_2O_4S$: C, 46.27; H, 4.61; N, 6.74. Found: C, 46.31; H, 4.80; N, 6.71%.

Ethyl (S)-5-[(1-carboxy-2-phenylethyl)imino]-3-methyl-2-phenyl-2,5-dihydroisothiazole-4-carboxylate hydrobromide (**5c**): Colourless solid (82% yield), m.p. 82°C. $[\alpha]_D$ = 17.3° (c = 0.1, $CHCl_3$). IR: ν_{max} 3580–2350, 1741, 1730, 1683 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J = 6.9 Hz, 3H, $OCH_2C\underline{H}_3$), 2.53 (s, 3H, CH_3), 3.17 (dd, J = 9.0, 13.8 Hz, 1H, $PhC\underline{H}_aH_b$), 3.56 (dd, J = 4.2, 13.8 Hz, 1H, $PhCH_a\underline{H}_b$), 4.38 (q, J = 6.9 Hz, 2H, $OC\underline{H}_2CH_3$), 4.62 (br. s, 1H, CH), 7.28 (m, 4H), 7.36 (m, 3H), 7.57 (m, 3H), 9.55 (br. s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ 14.1, 17.7, 38.2, 62.4, 64.0, 104.8, 127.4, 127.6, 129.0, 129.9, 130.6, 131.6, 133.6, 136.2, 162.9, 166.3, 171.6, 174.5 ppm. ES MS: *m/z* (%) 411 (M^+, 100), 365 (9), 332 (7); EI MS: *m/z* (%) 411 (M^+, 2), 348 (4), 231 (41), 203 (10), 181 (23), 160 (30), 131 (26), 105(100), 91, (40), 85 (49), 77 (45). Anal. Calcd for $C_{22}H_{23}BrN_2O_4S$: C, 53.77; H, 4.72; N, 5.70. Found: C, 53.85; H, 4.79; N, 5.63%.

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