

An efficient and convenient protocol for the synthesis of optically active [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives containing L-amino acid moieties

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Abstract

New triazolothiadiazoles bearing L-amino acid moieties were synthesized by reaction of 4-amino-5-phenoxy-4*H*-1,2,4-triazole-3-thiol with L-amino acids in the presence of phosphorus oxychloride.

Keywords: carbonothioic dihydrazide; L-amino acid; optical activity; phosphorus oxychloride; 1,2,4-triazole-3-thiol; triazolothiadiazole.

Introduction

Heterocycles bearing a 1,2,4-triazole or 1,3,4-thiadiazole moiety show antibacterial (Farghaly, 2004), antiaggregatory (Czarnocka et al., 1991), antiviral (Küçükgüzel et al., 2008), and anti-inflammatory (Unangst et al., 1992) activities. In addition, *N*-bridged heterocycles derived from 1,2,4-triazoles have found applications in medicine and agriculture (Farghaly et al., 2006). 1,3,4-Thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N-C-S moiety (Omar and Aboulwafa, 1986). They have found applications as antibacterial, antitumor, and anti-inflammatory agents, pesticides, and herbicides (Kurtzer et al., 1965). The [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives, obtained by fusing the 1,2,4-triazole and 1,3,4-thiadiazole rings together, are reported to be antimicrobial and antitubercular agents (Kumar et al., 2010). The preparation of such compounds have been extensively studied in recent years (El-Khawass et al., 1989; Subrahmanya Bhat et al., 2004; Dong et al., 2005; Li and Long, 2005). On the basis of these reports and also as a continuation of our research program on the synthesis of heterocyclic compounds containing 1,2,4-triazole and optically active compounds (Foroughifar et al., 2009a,b,c, 2010a,b,c), we report the synthesis of some

new 3,6-disubstituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles containing L-amino acid moiety, with the hope to improve their biological activities.

Results and discussion

This paper describes a facile synthesis of triazolothiadiazoles **5a–e** (Scheme 1) by the reaction of an aminotriazole **3** with *N*-phthaloyl-L-amino acids **4a–e** (Hoffmann and Schiff-Shenmav, 1962; Zamani et al., 2005; Faghihi, 2007) in the presence of phosphorus oxychloride. A similar synthesis of bis-triazolothiadiazole derivatives **7a–e** by the reaction of an aminotriazole **3** with starting materials **6a–e** (Faghihi and Hajibeygi, 2010; Faghihi and Moghanian, 2010) is shown in Scheme 2. Compound **3** was prepared by heating phenoxyacetic acid **2** with one equivalent of carbonothioic dihydroxyzide **1** at 170°C. All compounds were characterized by IR, ¹H NMR, and ¹³C NMR spectroscopy.

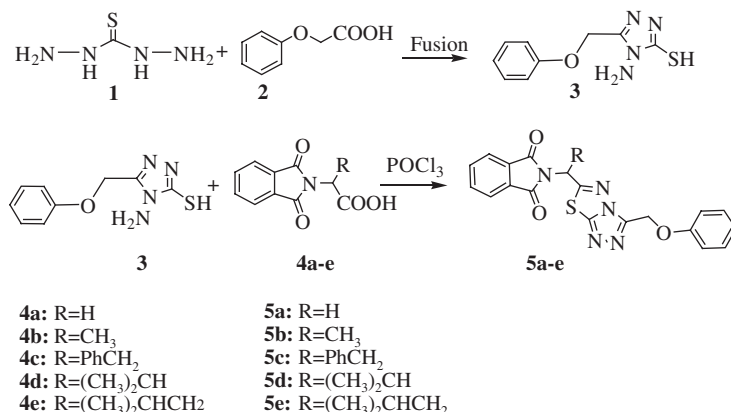
In particular, the IR spectrum of the triazole **3** shows two absorption bands at 2730 cm⁻¹ and 3203–3317 cm⁻¹ due to the presence of SH and NH₂ groups, respectively, which are absent in the IR spectra of the triazolothiadiazoles **5a–e** and **7a–e**. In a similar way, the ¹H NMR spectrum of compound **3** exhibits two characteristics absorptions, a broad singlet at δ 5.68 for the amino group and another absorption at δ 12.95 for the thiol group. These absorptions disappeared upon formation of the triazolothiadiazoles.

Experimental

Purity of the products was checked by thin layer chromatography (TLC) using EtOH/*n*-hexane (1:1) as an eluent. IR spectra were recorded on a Galaxy FT-IR 5000 spectrophotometer using KBr discs. ¹H NMR spectra were recorded on a Bruker spectrometer at 300 MHz in DMSO-*d*₆ using tetramethylsilane (TMS) as an internal standard. ¹³C NMR spectra were recorded at 75 MHz.

4-Amino-5-(phenoxymethyl)-4*H*-1,2,4-triazole-3-thiol (**3**)

An equimolar mixture of thiocarbonylhydrazide (**1**) and 2-phenoxyacetic (**2**) was heated on an oil bath at 170°C for 30 min, then cooled and treated with a sodium bicarbonate solution to remove any unreacted acid **2**. The remaining solid of **3** was filtered, washed with water, dried, and crystallized from ethanol: yield 61%; mp 155–157°C (ref. mp 158°C, Husain and Naseer, 2011); IR: ν 3317, 3203, 3065, 2926, 1587, 1234 cm⁻¹; ¹H NMR: δ 12.95 (s, 1H, exchangeable with D₂O) 7.28–7.34 (m, 2H), 6.92–7.05 (m, 3H), 5.68 (s, 2H, exchangeable with D₂O), 5.11 (s, 2H).



Scheme 1 Synthesis of compounds 5a–e.

General procedure for preparation of compounds 5a–e

A mixture of triazole **3** (1 mmol), *N*-phthaloyl-L-amino acid **4a–e** (1 mmol) in POCl₃ (7 mL) was heated under reflux for 16 h. After cooling, the mixture was slowly poured onto crashed ice with stirring and neutralized with solid potassium carbonate. The mixture was allowed to stand overnight and the resultant solid product **5a–e** was filtered, washed with cold water, and dried under reduced pressure.

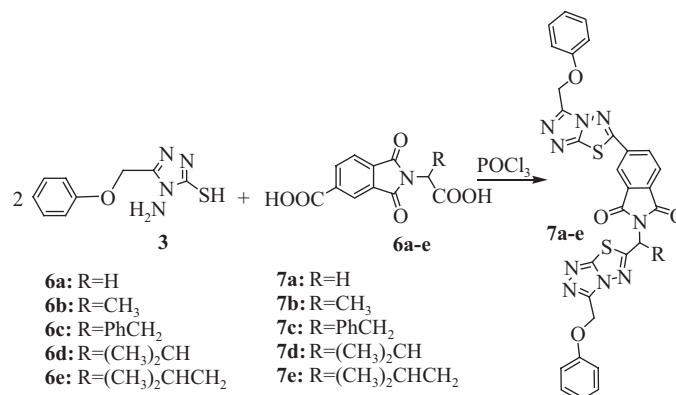
2-[1-(3-(Phenoxyethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)methyl]isoindoline-1,3-dione (5a) Yield 90%; mp 140–142°C; IR: ν 3060, 2960, 1774, 1720, 1597, 1238 cm⁻¹; ¹H NMR: δ 7.91 (br, 2H), 7.95 (br, 2H), 7.23–7.35 (m, 2H), 6.93–7.05 (m, 3H), 5.47 (s, 2H), 5.20 (s, 2H); ¹³C NMR: δ 167.5, 166.6, 158.0, 155.3, 144.0, 135.4, 131.8, 130.1, 124.1, 121.9, 115.3, 59.6, 39.1. Anal. Calcd for C₁₉H₁₃N₅O₃S: C, 58.30; H, 3.35; N, 17.89; S, 8.19. Found: C, 58.04; H, 3.17; N, 17.72; S, 8.08.

2-[1-(3-(Phenoxyethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)ethyl]isoindoline-1,3-dione (5b) Yield 80%; mp 105–107°C; [α]_D²² = -12° (c=0.02, DMSO); IR: ν 3061, 2935, 1778, 1716, 1599, 1238 cm⁻¹; ¹H NMR: δ 7.88–7.96 (m, 4H), 7.25–7.32 (m, 2H), 6.94–7.06 (m, 3H), 5.87 (q, 1H, *J*=7.1 Hz), 5.49 (s, 2H), 1.88 (d, 3H, *J*=7.1 Hz); ¹³C NMR: δ 171.0, 167.4, 158.0, 155.0, 144.1, 135.4, 131.7, 130.0, 124.0, 122.1, 115.5, 59.7, 46.7, 17.0. Anal. Calcd for C₂₀H₁₅N₅O₃S: C, 59.25; H, 3.73; N, 17.27; S, 7.9. Found: C, 59.02; H, 3.65; N, 17.07; S, 7.77.

2-[1-(3-(Phenoxyethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)-2-phenylethyl]isoindoline-1,3-dione (5c) Yield 90%; mp 115–118°C; [α]_D²² = -30° (c=0.02, DMSO); IR: ν 3063, 2920, 1778, 1718, 1599, 1238 cm⁻¹; ¹H NMR: δ 7.85 (br, 4H), 7.19–7.30 (m, 5H), 6.94–7.13 (m, 5H), 6.11 (dd, 1H, *J*=9.0 Hz and 7.7 Hz), 5.49 (s, 2H), 3.70–3.74 (m, 2H); ¹³C NMR: δ 169.3, 167.4, 158.0, 155.4, 144.1, 136.0, 135.6, 130.9, 130.0, 129.4, 129.0, 127.6, 124.1, 122.2, 115.4, 59.6, 52.3, 36.1; Anal. Calcd for C₂₆H₁₉N₅O₃S: C, 64.85; H, 3.98; N, 14.54; S, 6.66. Found: C, 64.61; H, 3.89; N, 14.36; S, 6.49.

2-[2-Methyl-1-(3-(phenoxyethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)propyl]isoindoline-1,3-dione (5d) Yield 90%; mp 101–103°C; [α]_D²² = -28° (c=0.02, DMSO); IR: ν 3065, 2960, 1782, 1714, 1599, 1238 cm⁻¹; ¹H NMR: δ 7.87–7.96 (m, 4H), 7.27–7.33 (m, 2H), 6.96–7.09 (m, 3H), 5.49 (s, 2H), 5.25 (d, 1H, *J*=11.1 Hz), 2.91–2.95 (m, 1H), 1.06 (d, 3H, *J*=6.6 Hz), 0.92 (d, 3H, *J*=6.5 Hz); ¹³C NMR: δ 168.0, 167.8, 157.9, 155.5, 144.0, 135.5, 131.2, 130.0, 124.1, 122.0, 115.4, 59.5, 57.8, 29.6, 20.0, 19.4. Anal. Calcd for C₂₂H₁₉N₅O₃S: C, 60.96; H, 4.42; N, 16.16; S, 7.40. Found: C, 60.78; H, 4.33; N, 16.03; S, 7.21.

2-[3-Methyl-1-(3-(phenoxyethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)butyl]isoindoline-1,3-dione (5e) Yield 85%; mp 98–99°C; [α]_D²² = -30° (c=0.02, DMSO); IR: ν 3068, 2958, 1778, 1716, 1599, 1238 cm⁻¹; ¹H NMR: δ: 7.92–7.94 (m, 4H), 7.25–7.30 (m, 2H), 6.94–7.06 (m, 3H), 5.78 (dd, 1H, *J*=5.0 Hz and 10.0 Hz), 5.48



Scheme 2 Synthesis of compounds 7a–e.

(s, 2H), 2.40–2.43 (m, 1H), 2.02–2.12 (m, 1H), 1.40–1.55 (m, 1H), 0.92 (d, 6H, $J=4.2$ Hz); ^{13}C NMR: δ 170.1, 167.6, 158.0, 155.3, 144.1, 135.6, 131.3, 130.0, 124.2, 122.0, 115.3, 59.6, 49.5, 24.9, 23.1, 21.6. Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_3\text{S}$: C, 61.73; H, 4.73; N, 15.65; S, 7.17. Found: C, 61.59; H, 4.66; N, 15.49; S, 6.94.

General procedure for preparation of compounds (7a–e)

A mixture of triazole **3** (2 mmol) and dicarboxylic acid **6a–e** (1 mmol) in POCl_3 (7 mL) was heated under reflux for 16 h, then slowly poured onto crashed ice with stirring, and neutralized with solid potassium carbonate. After standing overnight the resultant solid product **7a–e** was filtered, washed with cold water, and crystallized from *N,N*-dimethylformamide.

5-[3-(Phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-2-[(3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)methyl]isoindoline-1,3-dione (7a) Yield 73%; mp 247°C (dec); IR: ν 3041, 2893, 1782, 1726, 1599, 1261 cm^{-1} ; ^1H NMR: δ 7.26–7.34 (m, 5H), 7.13–7.17 (m, 3H), 7.01–7.04 (m, 5H), 5.62 (s, 2H), 5.46 (s, 2H), 5.25 (s, 2H); ^{13}C NMR: δ 169.2, 166.4, 166.2, 166.0, 158.1, 158.0, 155.3, 154.6, 144.4, 144.1, 134.8, 134.4, 134.0, 132.5, 130.1, 129.9, 125.1, 122.2, 122.1, 115.5, 115.3, 59.6, 39.1. Anal. Calcd for $\text{C}_{29}\text{H}_{19}\text{N}_9\text{O}_4\text{S}_2$: C, 56.03; H, 3.08; N, 20.28; S, 10.32. Found: C, 55.89; H, 3.02; N, 20.15; S, 10.13.

5-[3-(Phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-2-[1-(3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)ethyl]isoindoline-1,3-dione (7b) Yield 85%; mp 185–186°C; $[\alpha]_D^{22} = -20^\circ$ ($c=0.02$, DMSO); IR: ν 3050, 2882, 1776, 1722, 1599, 1238, 1080 cm^{-1} ; ^1H NMR: δ 7.25–7.34 (m, 5H), 7.13–7.16 (m, 3H), 6.95–7.06 (m, 5H), 5.91 (q, 1H, $J=7.0$ Hz), 5.61 (s, 2H), 5.50 (s, 2H), 1.90 (d, 3H $J=6.9$ Hz); ^{13}C NMR: δ 170.6, 166.4, 166.2, 165.8, 158.0, 157.9, 155.2, 154.6, 144.5, 144.1, 134.8, 134.5, 134.0, 132.8, 130.0, 129.9, 125.1, 122.1, 122.0, 115.4, 115.3, 59.6, 47.1, 17.0. Anal. Calcd for $\text{C}_{30}\text{H}_{21}\text{N}_9\text{O}_4\text{S}_2$: C, 56.68; H, 3.33; N, 19.83; S, 10.09. Found: C, 56.53; H, 3.26; N, 19.70; S, 9.92.

5-[3-(Phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-2-[1-(3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)-2-phenylethyl]isoindoline-1,3-dione (7c) Yield 88%; mp 190–193°C; $[\alpha]_D^{22} = -44^\circ$ ($c=0.02$, DMSO); IR: ν 3065, 2920, 1778, 1724, 1599, 1238 cm^{-1} ; ^1H NMR: δ 7.15–7.21 (m, 5H), 7.25–7.36 (m, 8H), 6.96–7.01 (m, 5H), 6.01 (dd, 1H, $J=8.9$ and 6.8 Hz), 5.60 (s, 2H), 5.50 (s, 2H), 3.71–3.74 (m, 2H); ^{13}C NMR: δ 168.8, 166.4, 166.2, 165.8, 158.1, 158.0, 155.2, 154.8, 144.5, 144.1, 136.0, 135.1, 134.4, 133.7, 132.1, 130.1, 130.0, 129.4, 129.0, 127.7, 125.3, 122.3, 122.1, 115.4, 115.1, 59.6, 52.6, 36.1. Anal. Calcd for $\text{C}_{36}\text{H}_{25}\text{N}_9\text{O}_4\text{S}_2$: C, 60.75; H, 3.54; N, 17.71; S, 9.01. Found: C, 60.52; H, 3.43; N, 17.51; S, 8.82.

2-[2-Methyl-1-(3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)propyl]-5-[3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]isoindoline-1,3-dione (7d) Yield 91%; mp 166–168°C; $[\alpha]_D^{22} = -34^\circ$ ($c=0.02$, DMSO); IR: ν 3040, 2968, 1776, 1720, 1599, 1238, 1078 cm^{-1} ; ^1H NMR: δ 7.28–7.36 (m, 5H), 7.13–7.16 (m, 3H), 6.98–7.10 (m, 5H), 5.61 (s, 2H), 5.50 (s, 2H), 5.29 (d, 1H, $J=11.3$ Hz), 2.91 (m, 1H), 1.02 (d, 3H, $J=6.1$ Hz), 0.97 (d, 3H, $J=5.7$ Hz); ^{13}C NMR: δ 167.8, 166.8, 122.1, 166.7, 166.0, 158.1, 158.0, 155.8, 154.7, 144.5, 144.0, 134.9, 134.2, 134.0, 132.6, 130.1, 129.9, 125.3, 122.3, 115.4, 115.3, 59.5,

58.1, 29.7, 20.0, 19.5. Anal. Calcd for $\text{C}_{32}\text{H}_{25}\text{N}_9\text{O}_4\text{S}_2$: C, 57.91; H, 3.80; N, 18.99; S, 9.66. Found: C, 57.64; H, 3.69; N, 18.72; S, 9.51.

2-[3-Methyl-1-(3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)butyl]-5-[3-(phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]isoindoline-1,3-dione (7e) Yield 90%; mp 152–154°C; $[\alpha]_D^{22} = -30^\circ$ ($c=0.02$, DMSO); IR: ν 3070, 2958, 1776, 1722, 1599, 1238, 1080 cm^{-1} ; ^1H NMR: δ 7.24–7.36 (m, 5H), 7.13–7.16 (m, 3H), 6.93–7.05 (m, 5H), 5.82 (dd, 1H, $J=10.0$ and 4.6 Hz), 5.61 (s, 2H), 5.49 (s, 2H), 2.47 (m, 1H), 2.01 (m, 1H), 1.80 (m, 1H), 0.93 (d, 6H, $J=5.8$ Hz); ^{13}C NMR: δ 169.7, 166.7, 166.5, 165.9, 158.1, 158.0, 155.2, 154.9, 144.5, 144.0, 135.0, 134.2, 133.9, 132.6, 130.1, 130.0, 125.3, 122.1, 122.0, 115.4, 115.3, 59.6, 49.9, 24.9, 23.0, 21.6. Anal. Calcd for $\text{C}_{33}\text{H}_{27}\text{N}_9\text{O}_4\text{S}_2$: C, 58.48; H, 4.02; N, 18.60; S, 9.46. Found: C, 58.26; H, 3.91; N, 18.53; S, 9.31.

Acknowledgments

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