Heterocycl. Commun., Vol. 17(5-6), pp. 211–214, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/HC.2011.048

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

Naesr Foroughifar[1,*], Sattar Ebrahimi[2], Akbar Mobinikhaledi[3] and Reza Mozafari[3]

[1] Faculty of Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran
[2] Department of Chemistry, Malayer Branch, Islamic Azad University, Malayer, Iran
[3] Department of Chemistry, Faculty of Sciences, Arak University, Arak 38156-879, Iran

*Corresponding author
e-mail: n_forougifar@yahoo.com

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 dihydraoxyzide **1** at 170°C. All compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

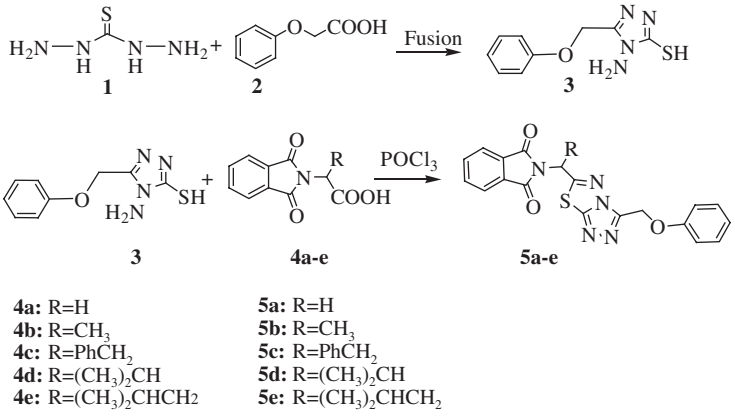
In particular, the IR spectrum of the triazole **3** shows two absorption bands at 2730 cm^{-1} and 3203–3317 cm^{-1} due to the presence of SH and NH_2 groups, respectively, which are absent in the IR spectra of the triazolothiadiazoles **5a–e** and **7a–e**. In a similar way, the ^{1}H NMR spectrum 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. ^{1}H NMR spectra were recorded on a Brucker spectrometer at 300 MHz in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz.

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

An equimolar mixture of thiocarbohydrazide (**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}; ^{1}H NMR: δ 12.95 (s, 1H, exchangeable with D_2O) 7.28–7.34 (m, 2H), 6.92–7.05 (m, 3H), 5.68 (s, 2H, exchangeable with D_2O), 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 $POCl_3$ (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.

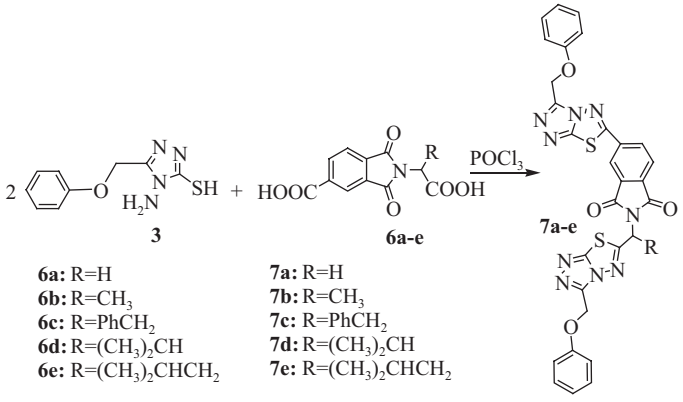
2-[(3-(Phenoxymethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)methyl]isoindoline-1,3-dione (5a) Yield 90%; mp 140–142°C; IR: ν 3060, 2960, 1774, 1720, 1597, 1238 cm^{-1}; ^1H NMR: δ 7.91 (br, 2H) 7.95 (br, 2H), 7.23–7.35 (m, 2H), 6.93–7.05 (m, 3H), 5.47 (s, 2H), 5.20 (s, 2H); ^{13}C NMR: δ 167.5, 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 $C_{19}H_{13}N_5O_3S$: 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-(Phenoxymethyl)-[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; $[\alpha]_D^{22}$=-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); ^{13}C 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 $C_{20}H_{15}N_5O_3S$: 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-(Phenoxymethyl)-[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; $[\alpha]_D^{22}$ =-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); ^{13}C 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 $C_{26}H_{19}N_5O_3S$: 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-(phenoxymethyl)-[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; $[\alpha]_D^{22}$ =-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); ^{13}C 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 $C_{22}H_{19}N_5O_3S$: 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-(phenoxymethyl)-[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; $[\alpha]_D^{22}$ =-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 $C_{23}H_{21}N_5O_3S$: 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}; ^{1}H 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 $C_{29}H_{19}N_9O_4S_2$: 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° (c=0.02, DMSO); IR: ν 3050, 2882, 1776, 1722, 1599, 1238, 1080 cm^{-1}; ^{1}H 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 $C_{30}H_{21}N_9O_4S_2$: 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° (c=0.02, DMSO); IR: ν 3065, 2920, 1778, 1724, 1599, 1238 cm^{-1}; ^{1}H 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 $C_{36}H_{25}N_9O_4S_2$: 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° (c=0.02, DMSO); IR: ν 3040, 2968, 1776, 1720, 1599, 1238, 1078 cm^{-1}; ^{1}H 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 $C_{32}H_{25}N_9O_4S_2$: 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; $[\alpha]^{22}{}_D$ =-30° (c=0.02, DMSO); IR: ν 3070, 2958, 1776, 1722, 1599, 1238, 1080 cm^{-1}; ^{1}H 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 $C_{33}H_{27}N_9O_4S_2$: 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

We are thankful to North Tehran Branch, Islamic Azad University for their financial support.

References

Czarnocka, J. A.; Foks, H.; Nasal, A.; Petrusewicz, J.; Damasiewicz, B.; Radwanska, A.; Kaliszan, R. Synthesis and pharmacological activity of 5-substituted-s-triazole-3-thiols. *Pharmazie* **1991**, *46*, 109–112.

Dong, H. -S.; Wang, B. Synthesis of some novel 3,6-bis(1,2,3-triazolyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole derivatives. *J. Chin. Chem. Soc*. **2005**, *52*, 103–108.

El-Khawass, S. M.; Habib, N. S.; Fu, H. Synthesis of 1,2,4-triazole, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole and 1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazine derivatives of benzotriazole. *J. Heterocycl. Chem.* **1989**, *26*, 177–181.

Faghihi, Kh. Facile and rapid synthesis of some optically active imide-acid derivatives using microwave irradiation. *J. Sci. I.A.U (JSIAU)* **2007**, *17*, 2–6.

Faghihi, Kh.; Hajibeygi, M. New flame retardant and optically active poly (amide-imide)s based on N-trimellitylimido-L-amino acid and phosphine oxide moiety in the main chain: synthesis and characterization. *Mater. Sci. Poland* **2010**, *28*, 545–556.

Faghihi, Kh.; Moghanian, H. Synthesis and charactrization of optically active poly(amide-imide)s containing phosphosensitive chalcone units in the main chain. *Chin. J. Polymer Sci*. **2010**, *28*, 695–704.

Farghaly, A. -A. H. Synthesis, reactions and antimicrobial activity of some new indolyl-1,3,4-oxadiazole, triazole and pyrazole derivatives. *J. Chin. Chem. Soc*. **2004**, *51*, 147–151.

Farghaly, A. -R.; De Clercq, E. D.; El-Kashef, H. Synthesis and antiviral activity of novel[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles, [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-*b*]-[1,3,4] thiadiazepines. *Arkivoc* **2006**, *10*, 137–151.

Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S. Synthesis of a novel class of Aza crown macrocycles and lariat crown ethers containing two 1,2,4-triazole rings as subunits. *Synthesis* **2009a**, *15*, 2557–2560.

Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S.; Moghanian, H.; Bodaghi Fard, M. A.; Kalhor, M. Synthesis of a new class of azathia crown macrocycles containing two 1,2,4-triazole or two 1,3,4-thiadiazole rings as subunits. *Tetrahedron Lett.* **2009b**, *50*, 836–839.

Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S.; Moghanian, H.; Bodaghi Fard, M. A. A simple and efficient procedure for synthesis of optically active 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole derivatives containing L-amino acid moieties. *J. Chin. Chem. Soc.* **2009c**, *56*, 1043–1047.

Foroughifar, N.; Khanpour, M.; Ebrahimi, S. A simple and efficient procedure for synthesis of optically active 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole derivatives containing L-amino acid moieties. *Eur. J. Chem.* **2010a**, *1*, 33–36.

Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S. A simple and efficient procedure for synthesis of optically active 1,3,4-oxadiazole derivatives containing L-amino acid moieties. *Turk. J. Chem.* **2010b**, *34*, 603–611.

Foroughifar, N.; Mobinikhaledi, A.; Ebrahimi, S. An efficient and convenient protocol for the synthesis of novel 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines. *Synthet. Commun.* **2010c**, *40*, 2421–2428.

Hoffmann, E.; Schiff-Shenmav, H. Some observations on the synthesis of phthaloylamino acids. *J. Org. Chem*. **1962**, *27*, 4686–4688.

Husain, A.; Naseer, M. A. Studies on fused heterocyclic 3,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazoles: synthesis and biological evaluation. *Med. Chem. Res.* **2011**, *20*, 47–54.

Küçükgüzel, İ.; Tatar, E.; Küçükgüzel Ş. G.; Rollas, S.; De Clercq, E. Synthesis of some novel thiourea derivatives obtained from 5-[(4-aminophenoxy)methyl]-4-alkyl/aryl-2,4-dihydro-3*H*-1-,2,4-triazole-3-thiones and evaluation as antiviral/anti-HIV and anti-tuberculosis agents. *Eur. J. Med. Chem.* **2008**, *43*, 381–392.

Kumar, S. G. V.; Prasad, R. Y.; Mallikarjuna, B. P.; Chandrashekar, S. M. Synthesis and pharmacological evaluation of clubbed isopropylthiazole derived triazolothiadiazoles, triazolothiadiazines and mannich bases as potential antimicrobial and antitubercular agents. *Eur. J. Med. Chem.* **2010**, *45*, 5120–5129.

Kurtzer, F.; Katritzky, A. R.; Boulton, A. J. Advances in Heterocyclic Chemistry; Academic Press: New York, 1965, Vol. 5, pp. 165.

Li, D.; Long, D. Synthesis of 1,4-bis[(3-aryl)-s-triazolo(3,4-*b*)-(1,3,4)thiadiazole-6-yl]benzenes. *Synthet. Commun.* **2005**, *35*, 2495–2500.

Omar, A. -M. M. E.; Aboulwafa, O. M. Synthesis and *in vitro* antimicrobial and antifungal properties of some novel 1,3,4-thiadiazole and *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. *J. Heterocycl. Chem*. **1986**, *23*, 1339–1345.

Subrahmanya Bhat, K.; Jagadeesh Prasad, D.; Poojary, B.; Shivarama Holla, B. Synthesis of some new 1,2,4-triazolo[3,4,-*b*]thiadiazole derivatives as possible anticancer agents. *Phosph. Sulfur Silicon* **2004**, *179*, 1595–1603.

Unangst, P. C.; Shrum, G. P.; Connor, D. T.; Dyer, R. D.; Schrier, D. J. Novel 1,2,4-oxadiazoles and 1,2,4-thiadiazoles as dual 5-lipoxygenase and cyclooxygenase inhibitors. *J. Med. Chem*. **1992**, *35*, 3691–3698.

Zamani, Kh.; Faghihi, Kh.; Ebrahimi, S. Synthesis of some novel optically active isocoumarin and 3,4-dihydroisocoumarin containing L-valine and L-leucine moieties. *Turk. J. Chem.* **2005**, *29*, 171–175.

Received July 28, 2011; accepted November 25, 2011