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A simple and efficient procedure for the synthesis of optically active s-triazolothiadiazole derivatives

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Abstract

A series of novel s-triazolothiadiazoles **3a–h** were prepared by condensation reaction of substituted amino triazoles **1a–b** with *N*-phethaloyl-L-amino acids **2a–d** in the presence of the phosphoroxy chloride ($POCl_3$) as an anhydrous reagent. The structure of all synthesized compounds was confirmed by IR, ^1H NMR, and ^{13}C NMR spectroscopy.

Keywords: s-Triazolothiadiazole; L-Amino acid; 1,2,4-Triazole-3-thiol; Optical activity; Phosphorus oxychloride

In the last few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. *N*-Bridged heterocyclic compounds derived from 1,2,4-triazoles have found several applications in the field of medicine, agriculture and industry [1]. 1,3,4-Thiadiazoles display a wide range of biological activities, possibly due to the presence of the toxophoric N–C–S linkage [2]. They are also known to have applications as pesticides, herbicides, dyes, antibacterial, fungicidal, antitumor activity and electrochemical properties [3–7]. [1,2,4]-Triazolo-[3,4-b]-[1,3,4]-thiadiazole derivatives, produced by fusion of the biolibale [1,2,4]-triazole and [1,3,4]-thiadiazole rings, are reported to possess antibacterial, antifungal, CNS depressant, anticonvulsant and analgesic effects [8]. Preparation of these compounds have been extensively studied during the past few years and the most convenient and general method for the synthesis of [1,2,4]-triazolo[3,4-b]-[1,3,4]thiadiazole derivatives involves the reaction of 5-substituted 4-amino-(4*H*)-1,2,4-triazole-3-thioles with carboxylic acids [9]. On the basis of these reports and also in continuation of our research program on the synthesis of heterocyclic compounds containing 1,2,4-triazole and optically active compounds [10–17], we wish to 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, because chirality is a main factor of the bioactive molecules and recognition phenomena associated with these molecules.

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1. Experimental

Purity of the compound was checked by thin layer chromatography (TLC) using EtOH/*n*-hexane (1:1, v/v) as an eluent. IR spectra were prepared on a galaxy series FT-IR 5000 spectrophotometer using KBr discs. NMR spectra were recorded on Brucker spectrophotometer (300 MHz) in DMSO-d_6 using TMS as an internal standard. C, H, N and S analyses were performed on a Vario EL III elemental analyzer.

A mixture of amino triazole **1a–b** (2 mmol), *N*-phethaloyl-L-amino acid **2a–d** (2 mmol) in $POCl_3$ (10 mL) was refluxed for 16 h. The reaction mixture slowly was poured into crashed ice with stirring and neutralized with solid potassium carbonate. The mixture was allowed to stand overnight and the solid separated out was filtered and washed with cold water. The compound so obtained was dried and giving the pure products **3a–h**.

*2-(1-(3-(4-Nitrobenzyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)ethyl)isoindoline-1,3-dione (**3a**):* mp: 176–178 °C; Yield 80%, $[\alpha]_D^{22}$ −15 (*c* 0.02, DMSO); IR (KBr, cm^{-1}): 3061 (aromatic CH stretch.), 2935 (aliphatic CH stretch.), 1778, 1716 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, 2H, $H_{arom.}$ J = 8.0 Hz) 7.97 (br, 4H, $H_{arom.}$), 7.56 (d, 2H, $H_{arom.}$ J = 8.3 Hz), 5.82 (q, 1H, N–CH, J = 6.9 Hz), 4.57 (s, 2H, $PhCH_2$), 1.86 (d, 3H, CH_3, J = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 167.3, 154.2, 147.0, 145.7, 143.7, 135.4, 131.6, 130.7, 124.0, 123.9, 46.7, 30.5, 17.0.; Calcd. for: $C_{20}H_{14}N_6O_4S$: C, 55.29; H, 3.25; N, 19.35; S, 7.38; Found: C, 55.02; H, 3.16; N, 19.22; S, 7.24.

*2-(1-(3-(4-Nitrobenzyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2-phenylethyl)isoindoline-1,3-dione (**3b**):* mp: 201–203 °C; Yield 90%, $[\alpha]_D^{22}$ −27 (*c* 0.02, DMSO); IR (KBr, cm^{-1}): 3063 (aromatic CH stretch.), 2920 (aliphatic CH stretch.), 1778, 1718 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11 (d, 2H, J = 7.1 Hz, $H_{arom.}$), 7.90 (br, 4H, $H_{arom.}$), 7.56 (d, 2H, J = 7.0 Hz, $H_{arom.}$), 7.18–7.33 (m, 3H, $H_{arom.}$), 6.98–7.14 (m, 2H, $H_{arom.}$), 6.07 (dd, 1H, J = 9.9, 7.7 Hz, N–CH), 4.56 (s, 2H, $PhCH_2$), 3.72–3.75 (m, 2H, $PhCH_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 167.4, 154.5, 146.9, 145.4, 143.7, 136.1, 135.4, 131.5, 130.6, 129.5, 129.1, 127.3, 124.1, 123.8, 46.8, 36.6, 30.6; Calcd. for: $C_{26}H_{18}N_6O_4S$: C, 61.17; H, 3.55; N, 16.46; S, 6.28; Found: C, 61.02; H, 3.49; N, 16.32; S, 6.19.

*2-(2-Methyl-1-(3-(4-nitrobenzyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)propyl)isoindoline-1,3-dione (**3c**):* mp: 156–158 °C; Yield 90%, $[\alpha]_D^{22}$ −35 (*c* 0.02, DMSO); IR (KBr, cm^{-1}): 3065 (aromatic CH stretch.), 2960 (aliphatic CH stretch.), 1782, 1714 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10 (d, 2H, J = 7.0 Hz, $H_{arom.}$), 7.83–7.91 (m, 4H, $H_{arom.}$), 7.56 (d, 2H J = 6.9 Hz, $H_{arom.}$,), 5.21 (d, 1H, J = 9.9 Hz, N–CH), 4.58 (s, 2H, $PhCH_2$), 2.88–2.94 (m, 1H, $CH(Me)_2$), 1.06 (d, 3H, J = 6.1 Hz, CH_3), 0.92 (d, 3H, J = 6.0 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 167.4, 154.3, 146.9, 145.6, 143.7, 135.5, 131.0, 130.7, 124.1, 123.6, 46.8, 30.5, 29.6, 20.0, 19.1; Calcd. for: $C_{22}H_{18}N_6O_4S$: C, 57.13; H, 3.92; N, 18.17; S, 6.93; Found: C, 56.98; H, 3.86; N, 18.02; S, 6.83.

*2-(3-Methyl-1-(3-(4-nitrobenzyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)butyl)isoindoline-1,3-dione (**3d**):* mp: 130–131 °C; Yield 85%, $[\alpha]_D^{22}$ −28 (*c* 0.02, DMSO); IR (KBr, cm^{-1}): 3068 (aromatic CH stretch.), 2958 (aliphatic CH stretch.), 1778, 1716 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.09 (d, 2H, J = 6.7 Hz, $H_{arom.}$), 7.91 (br, 4H, $H_{arom.}$), 7.56 (d, 2H, J = 7.0 Hz, $H_{arom.}$), 5.72 (dd, 1H, J = 4.8, 10.1 Hz, N–CH), 4.57 (s, 2H, $PhCH_2$), 2.41 (br, 1H, CH), 2.05 (m, 1H, CH_2), 1.55 (m, 1H, CH_2), 0.90 (d, 6H J = 7.1 Hz, 2 CH_3,); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 167.5, 154.7, 146.9, 145.5, 143.6, 135.5, 131.3, 130.7, 124.1, 123.9, 49.5, 30.7, 24.9, 23.0, 21.5; Calcd. for: $C_{23}H_{20}N_6O_4S$: C, 57.97; H, 4.23; N, 17.64; S, 6.73; Found: C, 57.73; H, 4.16; N, 17.45; S, 6.61.

*2-(1-(3-((4-Chlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)ethyl)isoindoline-1,3-dione (**3e**):* mp: 135–137 °C; Yield 80%, $[\alpha]_D^{22}$ −10 (*c* 0.02, DMSO); IR (KBr, cm^{-1}): 3061 (aromatic CH stretch.), 2935 (aliphatic CH stretch.), 1778, 1716 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74–7.91 (m, 4H, $H_{arom.}$), 7.30 (d, 2H, J = 8.3 Hz, $H_{arom.}$), 7.03 (d, 2H, J = 8.3 Hz, $H_{arom.}$), 5.87 (q, 1H, J = 6.9 Hz, N–CH), 5.50 (s, 2H, OCH_2), 1.88 (d, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.0, 167.4, 156.9, 155.1, 144.0, 135.2, 131.7, 129.7, 124.9, 123.5, 117.1, 60.1, 46.7, 17.0; $C_{20}H_{14}ClN_5O_3S$: C, 54.61; H, 3.21; N, 15.92; S, 7.29; Found: C, 54.33; H, 3.09; N, 15.72; S, 7.14.

*2-(1-(3-((4-Chlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2-phenylethyl)isoindoline-1,3-dione (**3f**):* mp: 177–180 °C; Yield 90%, $[\alpha]_D^{22}$ −30 (*c* 0.02, DMSO); IR(KBr, cm^{-1}): 3063 (aromatic CH stretch.), 2920 (aliphatic CH stretch.), 1778, 1718 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75–7.90 (m, 4H, $H_{arom.}$), 7.19–7.32 (m, 4H, $H_{arom.}$), 6.94–7.13 (m, 5H, $H_{arom.}$), 6.14 (dd, 1H, J = 10.0, 6.8 Hz, N–CH), 5.54 (s, 2H, OCH_2), 3.74–3.78 (m, 2H, $PhCH_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.0, 167.5, 156.6, 155.5, 143.6, 136.1, 135.4, 131.7, 129.7, 129.5, 129.0, 127.5, 124.1, 123.5, 117.3, 59.8, 36.0; $C_{26}H_{18}ClN_5O_3S$: C, 60.52; H, 3.52; N, 13.57; S, 6.21; Found: C, 60.31; H, 3.44; N, 13.41; S, 6.38.

*2-(1-(3-((4-Chlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-3-methylbutyl)isoindoline-1,3-dione (**3g**):* mp: 98–100 °C; Yield 90%, $[\alpha]_D^{22}$ −33 (*c* 0.02, DMSO); IR (KBr, cm^{-1}): 3065 (aromatic CH stretch.), 2960 (aliphatic CH stretch.), 1782, 1714 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75–7.88 (m, 4H, $H_{arom.}$), 7.26 (d, 2H, J = 7.1 Hz, $H_{arom.}$), 7.05 (d, 2H, J = 7.8 Hz, $H_{arom.}$), 5.47 (s, 2H, OCH_2), 5.25 (d, 1H, J = 11.0 Hz, N–CH), 2.91–2.95 (m, 1H, $CH(Me)_2$), 1.04 (d, 3H, J = 6.7 Hz, CH_3), 0.93 (d, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 167.3, 156.5, 154.9, 143.5, 135.4, 131.5, 129.6, 125.7, 124.0, 117.1, 60.0, 46.7, 29.7, 20.1, 19.3; $C_{22}H_{18}ClN_5O_3S$: C, 56.47; H, 3.88; N, 14.97; S, 6.85; Found: C, 56.28; H, 3.81; N, 14.79; S, 6.69.

*2-(1-(3-((4-Chlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-4-methylpentyl)isoindoline-1,3-dione (**3h**):* mp: 90–92 °C; Yield 85%, $[\alpha]_D^{22}$ −24 (*c* 0.02, DMSO); IR(KBr, cm^{-1}): 3068 (aromatic CH stretch.), 2958 (aliphatic CH stretch.), 1778, 1716 (C=O), 1599 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.90 (br, 4H, $H_{arom.}$), 7.28 (d, 2H, J = 8.1 Hz, $H_{arom.}$), 7.06 (d, 2H, J = 8.1 Hz, $H_{arom.}$), 5.77 (dd, 1H, J = 4.9, 9.4 Hz, N–CH), 5.50 (s, 2H, OCH_2), 2.47 (br, 1H, CH), 2.05 (br, 1H, CH_2), 1.41–1.50 (m, 1H, CH_2), 0.90 (d, 6H, 2 CH_3, J = 6.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.1, 167.6, 156.8, 155.1, 143.8, 135.5, 131.3, 129.7, 125.8, 124.1, 117.2, 60.0, 49.5, 24.9, 23.1, 21.5; $C_{23}H_{20}ClN_5O_3S$: C, 57.32; H, 4.18; N, 14.53; S, 6.65; Found: C, 57.08; H, 4.08; N, 14.40; S, 6.49.

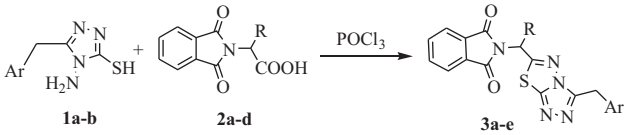
2. Results and discussion

In this present work, a series of **8** new compounds were synthesized. Scheme 1 illustrates the way used for the preparation of target compounds. Starting materials **1a–b** were prepared by the condensation of carbonothiohydrazide with corresponding substituted acetic acid by employing well known method available in the literature [18]. The desired *N*-phethaloyl-L-amino acids **2a–d** was prepared according to the literature [19,20].

The resultant 5-substituted 4-amino-(4H)-1,2,4-triazole-3-thioles **1a–b** was further converted to 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **3a–h** through one pot reaction by condensation with *N*-phethaloyl-L-amino acids **2a–d** in the presence of $POCl_3$. Phosphorus oxychloride was necessary for this condensation, which activates the carboxyl group of amino acids and increases its electrophilicity to enhance the addition of amino triazoles **1a–b** to it. This procedure afforded various triazolothiadiazoles in 80–90% yields.

The structure of newly synthesized compounds was confirmed by recording the IR, ^{1}H NMR and ^{13}C NMR data. The structure of **3a** was confirmed by IR, ^{1}H NMR and ^{13}C NMR. The IR spectrum of **3a** exhibited absorption bands at 3041 cm^{-1} due to aromatic CH, 1782 and 1726 cm^{-1} due to C=O for imide's carbonyl groups. Additional support for the structure of **3a** was obtained by recording its ^{1}H NMR spectrum, which exhibited a singlet at δ 5.82 due to NCH proton, three singlets at δ 8.17, 7.97 and 7.56, integrating for eight aromatic protons.

The infrared spectra of the triazole **3** showed two absorption bands, at 2730 cm^{-1} and 3203–3317 cm^{-1} due to SH and NH_2 groups which were absent in the IR spectra of the triazolo thiadiazoles **3a–h**. Similarly the ^{1}H NMR spectra of the compounds **3** showed two characteristics absorption (broad singlet at δ 5.68) that was attributed to the NH_2 group, and another at δ 12.95, was assigned to the SH, which were disappeared by the formation of the triazolothiadiazoles. The absence of these absorptions due to the SH and NH_2 groups of triazoles **3** established that all the triazole had converted to s-triazolothiadiazoles by reacting with the COOH groups of the various *N*-phethaloyl-L-amino acids **2a–d**.



1a-b **2a-d** **3a-e**

3a: R= CH_3, Ar= 4-NO_2Ph
3b: R= $PhCH_2$, Ar= 4-NO_2Ph
3d: R= $(CH_3)_2CH$, Ar= 4-NO_2Ph
3d: R= $(CH_3)_2CHCH_2$, Ar= 4-NO_2Ph
3e: R= CH_3, Ar= 4-ClPhO
3f: R= $PhCH_2$, Ar= 4-ClPhO
3g: R= $(CH_3)_2CH$, Ar= 4-ClPhO
3h: R= $(CH_3)_2CHCH_2$, Ar= 4-ClPhO

Scheme 1. Synthesis of s-triazolothiadiazoles **3a–h**.

3. Conclusion

We have been able to synthesize some novel s-triazolothiadiazoles having L-amino acid moiety. This reaction may be useful for combinational synthesis of type **3** compounds having various R and Ar substitutions with a view to test for biological activities.

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