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Synthesis of the new heterocyclic system 7,8-dihydro-6*H*-benzotetrazolothiadiazine and derivatives

Abstract: New *N*,*N*-disubstituted 7,7-dimethyl-7,8-dihydro-6*H*-benzotetrazolothiadiazine-9-amines were synthesized from sodium 1-amino-1*H*-tetrazole-5-thiolate and 2-bromo-5,5-dimethylcyclohexane-1,3-dione in multiple steps. The compounds were characterized by ^{13}C NMR, ^{1}H NMR, IR, MS, and elemental analysis.

Keywords: amines; 2-bromo-5,5-dimethylcyclohexane-1,3-dione; nucleophilic substitution.

DOI 10.1515/hc-2014-0111
Received July 15, 2014; accepted October 20, 2014

Introduction

In recent years, the chemistry of 1,3,4-thiadiazines have received considerable attention owing to their synthetic and biological importance [1]. The fused derivatives including 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine (triazolothiadiazine) exhibit a broad spectrum of pharmacological activities including antifungal [2], antibacterial [3], antiviral [4], anti-Alzheimer [5], anti-HIV [6], antitumor [7], anti-inflammatory [8], antidepressant [9, 10], central nervous system depressant [11], and antioxidant [12] properties. Tetrazole derivatives have also attracted some interest due to their diverse pharmacological potential. For instance, angiotensin II receptor blockers such as losartan [13] and candesartan [14] contain a tetrazole ring in their chemical structures. Therefore, in pursuit of our efforts to develop novel routes to heterocyclic derivatives of thiadiazine with potential biological activities [15, 16] and in view of the possible biological activities of the tetrazole pharmacophore, a synthetic route to the novel tricyclic system of *s*-tetrazolobenzothiadiazine (compounds **6a–f**) was designed. This article reports the successful synthetic approach to this novel heterocyclic system.

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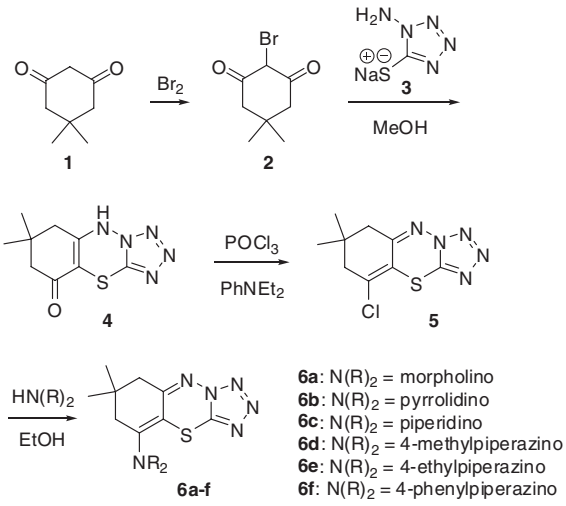
Results and discussion

Strategies for the rapid synthesis and functionalization of new classes of compounds are of considerable interest to both academic and industrial researchers. Although the synthesis of triazolothiadiazine derivatives has been reported, the literature survey revealed that the synthesis of tetrazolothiadiazine derivatives has not been investigated.

Synthesis of 1,3,4-thiadiazines is based on cyclocondensation of heterocyclic amino thiols with an α-halo carbonyl compound. In this research, cyclization of the α-bromodimedone (**2**) with a 1-amino-1*H*-tetrazole-5-thiolate (**3**) [17] in methanol under reflux condition gave the 7,7-dimethyl-7,8-dihydro5*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazin-9(6*H*)-one (**4**), which was subsequently transformed to 9-chloro-7,7-dimethyl-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazine (**5**) by the reaction with phosphorous oxychloride. Reaction of compound **5** with a secondary amine in ethanol in the presence of a catalytic amount of glacial acetic acid led to the replacement of the chlorine atom and gave product **6**. The synthesis of 2-bromo-5,5-dimethylcyclohexane-1,3-dione (**2**) was achieved by bromination of 5,5-dimethylcyclohexane-1,3-dione (**1**) using a reported procedure [18].

The structural assignments of compounds **6a–f** were based on the spectral and microanalytical data. For example, in ^{1}H NMR spectra, the peaks of CH_2 groups of 9-chloro-7,7-dimethyl-7,8-dihydro-6*H*-tetrazolo[1,5-*b*]



Scheme 1 Protocol for synthesis of new heterocyclic system.

[4,1,2]benzothiadiazine and *N*,*N*-disubstituted 7,7-dimethyl-7,8-dihydro-6*H*-benzotetrazolothiadiazine-9-amine appear at δ 2.6 and δ 2.4, respectively. The molecular ion peak is present in the mass spectra of all products.

Conclusion

The synthesis of a family of compounds of the novel tricyclic heterocyclic system, *N*,*N*-disubstituted 7,7-dimethyl-7,8-dihydro-6*H*-benzotetrazolothiadiazine-9-amine, was accomplished.

Experimental

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra (KBr pellets) were obtained on an AVATAR 370FT-IR Thermo Nicolet spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers. The EI mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

Synthesis of 2-bromo-5,5-dimethylcyclohexane-1,3-dione (2)

Bromine (0.51 mL, 10 mmol) was added dropwise to a solution of 5,5-dimethylcyclohexane-l,3-dione (1.4 g, 10 mmol) in acetic acid (20 mL) at room temperature. The mixture was stirred for 2 h. The product was isolated by filtration, washed with ether (2×100 mL), and dried under a reduced pressure: Yield 95%; mp 174–175°C (mp 176°C) [19].

Synthesis of 7,7-dimethyl-7,8-dihydro-5*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazin-9(6*H*)-one (4)

Sodium 1-amino-1*H*-tetrazole-5-thiolate (2.8 g, 20 mmol), prepared by the reported method [17], was added to a solution of compound **2** (4.3 g, 20 mmol) in methanol (50 mL), and the mixture was stirred overnight. The resulting precipitate was filtered off under reduced pressure to give 3.8 g (80%) of the title compound as a white solid; mp: 255°C; ^{1}H NMR (100 MHz): δ 1.10 (s, 6H, $2CH_3$), 2.20 (s, 2H, CH_2), 2.3 (s, 2H, CH_2), 5.12 (br s, 1H, NH); IR: ν 3301 (NH), 2955, 2929 (aliphatic H), 1655 cm^{-1} (C=O); MS: *m/z* 237. Anal. Calcd for $C_9H_{11}N_5OS$: C, 45.56; H, 4.67; N, 29.51; S, 13.51. Found: C, 45.50; H, 4.61; N, 29.41; S, 13.43.

Synthesis of 9-chloro-7,7-dimethyl-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazine (5)

Phosphorous oxychloride (16 mL, 172 mmol) and *N*,*N*-dimethylaniline (1.6 mL, 13.2 mmol) were added successively to compound **4** (2.3 g, 9.7 mmol), and the mixture was heated at 106°C for 3 h, cooled, and poured into ice water. The resultant precipitate was filtered off under reduced pressure to give the title compound as a yellowish solid: mp 245°C; ^{1}H NMR (400 MHz) δ 1.16 (s, 6H, $2CH_3$), 2.64 (s, 2H, CH_2), 2.68 (s, 2H, CH_2). IR: 2868,2956 (aliphatic H), 798 cm^{-1} (Cl); MS: *m/z* 255. Anal. Calcd for $C_9H_{10}ClN_5S$: C, 42.27; H, 3.94; N, 27.39; S, 12.54. Found: C, 42.21; H, 3.85; N, 27.25; S, 12.49.

General procedure for the synthesis of *N*,*N*-disubstituted 7,7-dimethyl-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazin-9-amines 6a–f

A mixture of a secondary amine (2 mmol) and compound **5** (0.5 g, 2 mmol) in ethanol (10 mL), was stirred and heated under reflux for 3–4 h. After completion of the reaction, as monitored by TLC, the mixture was cooled to room temperature and the resulting solid was filtered and washed with ethanol and crystallized from ethyl acetate.

7,7-Dimethyl-9-morpholino-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazine (6a): TLC solvent: acetate/*n*-hexane 2:1, yield 75%, powder, mp 94–96°C; ^{1}H NMR (400 MHz): δ 1.10 (s, 6H, $2CH_3$), 2.37 (s, 2H, CH_2), 2.51 (s, 2H, CH_2), 3.0 (t, *J* = 4.4 Hz, 4H), 3.42 (t, *J* = 4.4 Hz, 4H, $2CH_2O$); IR: ν 2958 (CH_3), 2900 cm^{-1} (CH_2), 1560 cm^{-1} (C=N); MS: *m/z* 306. Anal. Calcd for $C_{13}H_{18}N_6OS$: C, 50.96; H, 5.92; N, 27.43; O, 5.22; S, 10.47. Found: C, 50.89; H, 5.87; N, 27.39; S, 10.41.

7,7-Dimethyl-9-pyrrolidino-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazine (6b): TLC solvent: acetate/*n*-hexane 2:1; yield 70%; powder; mp 170–172°C; ^{1}H NMR (400 MHz): 1.10 (s, 6H, $2CH_3$), 1.9–2.0 (m, 4H, $2CH_2$), 2.40 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 3.54–3.6 (t, *J* = 6.8 Hz, 4H, $2CH_2N$); ^{13}C NMR (100 MHz): 160.7, 154.3, 77.5, 77, 76.5, 64.9, 60.8, 51.3, 45.6, 45.3, 30.3, 27.9, 25.5; IR: ν 2970 (CH_3), 2949 (CH_2), 1543 cm^{-1} (C=N); MS: *m/z* 290. Anal. Calcd for $C_{13}H_{18}N_6S$: C, 53.77; H, 6.25; N, 28.94; S, 11.04. Found: C, 53.71; H, 6.18; N, 28.87; S, 10.98.

7,7-Dimethyl-9-piperidino-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2] benzothiadiazine (6c): TLC solvent: acetate/*n*-hexane 2:1; yield 73%; powder; mp 187–188°C; ^{1}H NMR (100 MHz): 1.10 (s, 6H, $2CH_3$), 1.60–1.80 (m, 6H, $3CH_2$), 2.35 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 2.90–3.10 (m, 4H, $2CH_2N$); IR: ν 2966 (CH_3), 2936 (CH_2), 1552 cm^{-1} (C=N); MS: *m/z* 304. Anal. Calcd for $C_{14}H_{20}N_6S$: C, 55.24; H, 6.62; N, 27.61; S, 10.53. Found: C, 55.19; H, 6.58; N, 27.57; S, 10.47.

7,7-Dimethyl-9-(4-methylpiperazino)-7,8-dihydro-6*H*-tetrazolo-[1,5-*b*][4,1,2] benzothiadiazine (6d): TLC solvent: acetate/*n*-hexane 2:1; yield 68%; powder; mp 117–119°C; ^{1}H NMR (100 MHz): 1.10 (s, 6H, $2CH_3$), 2.40 (s, 5H, N-CH_3, and CH_2), 2.50 (s, 2H, CH_2), 2.50–2.70 (m, 4H, CH_2N), 2.90–3.01 (m, 4H, CH_2N); IR: ν 2960 (CH_3), 2932 (CH_2), 1557 cm^{-1} (C=N); MS: *m/z* 319. Anal. Calcd for $C_{14}H_{21}N_7S$: C, 52.64; H, 6.63; N, 30.69; S, 10.04. Found: C, 52.58; H, 6.58; N, 30.62; S, 9.97.

9-(4-Ethylpiperazino)-7,7-dimethyl-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2] benzothiadiazine (6e): TLC solvent: acetate/*n*-hexane 2:1; yield 70%; mp 145–147°C; ^{1}H NMR (250 MHz): δ 1.22 (s, 6H, $2CH_3$), 1.25 (t, 3H, CH3), 2.5 (s, 2H, CH_2), 2.7 (s, 2H, CH_2), 2.81–3.21 (m, 6H, $3CH_2$), 3.31–3.41 (m, CH_2). ^{13}C NMR (100 MHz): 156.4, 154.7, 141.7, 77.5, 77.2, 77, 76.5, 52.2, 47.7, 45.2, 41.1, 30.4, 27.8, 27.5, 11.3; IR: ν 2957 (CH_3), 2809 (CH_2), 1562 cm^{-1} (C=N); MS: *m/z* 333. Anal. Calcd for $C_{15}H_{23}N_7S$: C, 54.03; H, 6.95; N, 29.40; S, 9.62. Found: C, 53.98; H, 6.91; N, 28.36; S, 9.58.

7,7-Dimethyl-9-(4-phenylpiperazino)-7,8-dihydro-6*H*-tetrazolo[1,5-*b*][4,1,2]benzothiadiazine (6f): TLC solvent: acetate/*n*-hexane 2:1; yield 68%; powder; mp 124–126°C; ^{1}H NMR (250 MHz): 1.04 (s, 6H, $2CH_3$), 2.33 (s, 2H, CH_2), 2.43 (s, 2H, CH_2), 3.00–3.40 (m, 8H, $4CH_2$), 6.75–7.5 (m, 5H, aromatic); IR: ν 3060 (aromatic H), 2958 (CH_3), 2880 (CH_2), 1599 cm^{-1} (C=N); ^{13}C NMR (250 MHz): 156.3, 154.8, 150.7, 129.3, 116.6, 77.52, 77, 76.5, 49.5, 48.4, 45.2, 41.3, 30.5, 27.8; MS: *m/z* 381. Anal. Calcd for $C_{19}H_{23}N_7S$: C, 59.82; H, 6.08; N, 25.70; S, 8.41. Found: C, 59.78; H, 5.97; N, 25.69; S, 8.37.

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