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Spectral Assignments and Reference Data

^{1}H and ^{13}C NMR spectral characterization of some novel 7*H*-1,2,4-triazolo[3, 4-*b*] [1,3,4] thiadiazine derivatives

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Some novel 1, 2, 4-triazolo[3,4-*b*][1,3,4]thiadiazines derivatives were synthesized. The complete ^{1}H and ^{13}C NMR chemical shift assignments were analyzed on one- and two-dimensional NMR techniques, including DEPT, NOE-DIF, COSY, HMBC, and HSQC. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; 1,2,4-triazolo[3,4-*b*][1,3,4]; thiadiazines; synthesis

INTRODUCTION

1,2,4-Triazoles and *N*-bridged heterocycles are found to be associated with diverse pharmacological properties.[1–3] Broad biological and pharmacological properties of various thiadiazines fused with a triazole ring have been extensively studied.[4–9] In particular, various substituted 7*H*-1,2,4–triazolo-[3,4-*b*][1,3,4] thiadiazines have been shown to possess diverse pharmacological properties, such as antimicrobial, bactericidal, anti-inflammatory, antiviral, antihypertensive, antifungal, antihelminthic, and analgesic effects.[10–13] Prompted by the biological properties of 1,2,4-triazole derivatives and 1,3,4-thiadiazines, and in continuation of our studies on *N*-bridged heterocycles,[14–15] we report here the synthesis and spectral characterization of some 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4] thiadiazine derivatives (Scheme 1), of which compounds **1a, 1b, 1d, 1e, 1f, 1o**, and **1q** were known.[12,13]

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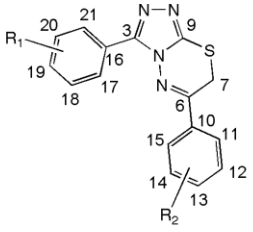

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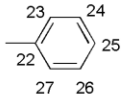
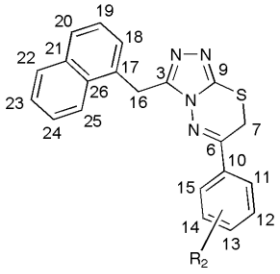
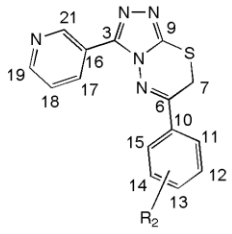


1a-1r

1a, R_1 = 4-C_2H_5O ; R_2 = 4-Br
1b, R_1 = 4-C_2H_5O ; R_2 = 4-Cl
1c, R_1 = 4-C_2H_5O ; R_2 = 2,4-diCl
1d, R_1 = 4-C_2H_5O ; R_2 = 4-CH_3
1e, R_1 = 4-C_2H_5O ; R_2 = 4-CH_3O
1f, R_1 = 4-C_2H_5O ; R_2 = 4-NO_2
1g, R_1 = 4-C_2H_5O ; R_2 = 4-phenyl
1h, R_1 = 2-C_2H_5O ; R_2 = 4-CH_3
1i, R_1 = 2-C_2H_5O ; R_2 = 4-NO_2
1j, R_1 = 2-C_2H_5O ; R_2 = 4-phenyl
1k, R_1 = 2-C_2H_5O ; R_2 = 4-Cl
1l, R_1 = 2-OH ; R_2 = 4-NO_2
1m, R_1 = 2-OH ; R_2 = 4-CH_3
1n, R_1 = 2-OH ; R_2 = 4-H
1o, R_1 = 2-OH ; R_2 = 4-Br
1p, R_1 = 2-OH ; R_2 = 2,4-diCl
1q, R_1 = 4-Cl ; R_2 = 4-NO_2
1r, R_1 = 4-CH_3O ;R_2 = 4-phenyl



2a-2e



3a-3d

2a, R_2 = 4-H
2b, R_2 = 4-NO_2
2c, R_2 = 4-CH_3O
2d, R_2 = 4-Br
2e, R_2 = 4-CH_3

3a, R_2 = 4-CH_3
3b, R_2 = 4-Br
3c, R_2 = 4-CH_3O
3d, R_2 = 2,4-diCl

Scheme 1. Structure of various 3,6-disubstituted-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines.

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EXPERIMENTAL

Materials

Various 5-substituted-4-amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones[13] were prepared by methods given in the literature.[16–18] All other chemicals and solvents used were of analytical reagent grade.

Preparation of various 3,6-disubstituted-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines

The mixture of 5-substituted-4-amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (40 mmol), *ω*-bromoacetophenones (42 mmol), ethanol (70 ml), and water (30 ml) was stirred and refluxed for 3 h. The solution was cooled and then filtered. The precipitate was washed with ether and dried. The crude material was recrystallized from 70% ethanol solution to obtain the pure products (**1a**–**1r**, **2a**–**2e**, and **3a**–**3d**) at a yield of 63–86%.

NMR spectra

All NMR experiments were performed at 293 K using a solution of 20 mg of the compound dissolved in 0.5 ml of dimethyl sulfoxide (DMSO)-d_6 on a Bruker AVANCE-300 instrument with a 5 mm BBFO probe head equipped with shielded Z-gradient coil. The gradient field was 50×10^{-4} T cm^{-1}. ^{1}H NMR spectra were recorded at a proton frequency of 300.13 MHz with a spectral width of 4.5 kHz and 11 μs (90°) pulse. The ^{13}C NMR spectra were obtained using a spectral width of 20 kHz, a 3.9 μs (30°) pulse, and a 1.8 s acquisition time; 1024 scans with 32 768 data points each were used. Exponential multiplication was applied before Fourier transformation in both cases. The chemical shifts were referenced to tetramethylsilane (TMS). The long-range ^{1}H–^{13}C correlation (HMBC) spectra were obtained using the hmbcgpndqf program in the Bruker software. The spectra resulted from a 256 × 1024 data matrix size with 16 scans per t_1 increment, 200 μs delay for homospoil/gradient recovery (D_{16}), 1 ms for homospoil/gradient pulse (P_{16}), and 5 : 3 : 4 gradient combination using a pulse sequence optimized for 8 Hz. Spectral widths of 3.5 kHz in f_2 and 15.5 kHz in f_1 were used. The acquisition time was 0.57 s, the delay was set to 3.45 ms, the recycle time was 1.50 s, and the Fourier transformation was done on a 2k × 1k data matrix. The one-bond heteronuclear correlation (HSQC) spectra were obtained using the hsqcetgp program in the Bruker software. The spectra were measured with the same D_{16} (200 μs) and P_{16} (1 ms) and a different 4 : 1 gradient combination. The acquisition time was 0.14 s, the delay was set to 3.45 ms, and an average ^{1}J(C, H) of 145 Hz was used; the recycle time was 1.55 s. The Fourier transformation was done on a 2k × 1k data matrix.

RESULTS AND DISCUSSION

In order to unequivocally assign all NMR signals, we used 1D and 2D techniques such as DQF-COSY, HSQC, and HMBC.

In Scheme 1, the structures and numbering of the title compounds are presented. Their ^{1}H and ^{13}C NMR chemical shifts are given in Tables 1 and 2, respectively. For example, assigning the spectra of **1k** is described as follows. H-7 (*δ* 4.41), H-11, H-15 (*δ* 7.90), H-12, H-14 (*δ* 7.61), methylene proton (*δ* 3.98), and methyl (*δ* 1.05) proton were assigned directly, and the ^{1}H signals of H-18∼H-21 were determined by the combination of COSY, HSQC, and HMBC experiments. Seven quaternary carbons were observed by DEPT technique and assigned by HMBC experiments, the assignments were C-3 at

Table 1. ^{1}H NMR data for compounds **1a**–**2r**, **2a**–**2e**, and **3a**–**3d**(Solvent: DMSO-d_6)

Compound	7	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	R_1	R_2
1a	4.42	7.95	7.80		7.80	7.95		7.92	7.12		7.12	7.92							4.12, 1.36	
1b	4.42	8.01	7.66		7.66	8.01		7.93	7.12		7.12	7.93							4.12, 1.36	
1c	4.30		7.89		7.64	7.72		7.92	7.12		7.12	7.92							4.12, 1.35	
1d	4.40	7.96	7.39		7.39	7.96		7.91	7.12		7.12	7.91							4.12, 1.36	2.40
1e	4.38	7.95	7.30		7.30	7.95		7.92	7.12		7.12	7.92							4.12, 1.36	3.67
1f	4.50	8.25	8.40		8.40	8.25		7.94	7.13		7.13	7.94							4.13, 1.37	
1g	4.47	8.10	7.90		7.90	8.10		7.97	7.13		7.13	7.97		7.78	7.53	7.43	7.53	7.78	4.13, 1.37	
1h	4.37	7.77	7.34		7.34	7.77			7.18	7.08	7.54	7.52							3.98, 1.03	2.36
1i	4.50	8.11	8.37		8.37	8.11			7.19	7.11	7.56	7.53							4.01, 1.05	
1j	4.45	7.98	7.85		7.85	7.98			7.20	7.12	7.51	7.48		7.75	7.55	7.43	7.55	7.75	4.02, 1.08	
1k	4.41	7.90	7.61		7.61	7.90			7.18	7.10	7.55	7.52							3.98, 1.05	
1l	4.52	8.21	8.37		8.37	8.21			6.98	7.42	7.02	7.83							10.30	
1m	4.44	7.95	7.38		7.38	7.95			6.98	7.39	7.05	7.99							10.20	2.40
1n	4.46	8.07	7.58	7.58	7.58	8.07			6.98	7.41	7.04	7.91							10.20	
1o	4.44	7.99	7.80		7.80	7.99			6.96	7.42	7.05	7.92							10.20	
1p	4.32		7.90		7.65	7.73			6.95	7.41	7.06	7.88							10.30	
1q	4.52	8.25	8.39		8.39	8.25		8.01	7.67		7.67	8.01								
1r	4.47	8.10	7.89		7.89	8.10		8.00	7.17		7.14	8.00		7.77	7.51	7.40	7.51	7.77	3.85	
2a	4.39	7.97	7.47	7.52	7.47	7.97	4.74		7.53	7.50	7.85		7.95	7.57	7.60	8.29				
2b	4.46	8.21	8.38		8.38	8.21	4.76		7.50	7.47	7.85		7.95	7.57	7.59	8.29				
2c	4.41	7.97	7.14		7.14	7.97	4.75		7.47	7.44	7.79		7.96	7.54	7.56	8.27				3.85
2d	4.38	7.91	7.77		7.77	7.91	4.74		7.48	7.45	7.84		7.94	7.55	7.58	8.28				
2e	4.37	7.88	7.36		7.36	7.88	4.75		7.48	7.44	7.85		7.94	7.55	7.59	8.28				2.38
3a	4.46	7.94	7.40		7.40	7.94		8.73	7.94	8.90		9.32								2.40
3b	4.89	7.98	7.80		7.80	7.98		8.79	7.98	8.96		9.35								
3c	4.45	8.02	7.13		7.13	8.02		8.74	7.95	8.90		9.33								3.86
3d	4.48		7.91		7.67	7.74		8.74	7.94	8.91		9.34								

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Table 2. ^{13}C NMR data for compounds **1a–2r**, **2a–2e**, and **3a–3d** (Solvent: DMSO-d_6)

Compound	3	6	7	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	R_1	R_2
1a	151.65	155.03	22.73	141.95	132.92	132.23	129.57	125.79	129.57	132.23	118.26	129.60	114.79	160.17	114.79	129.60							63.45, 14.70	
1b	151.75	154.99	22.84	142.05	130.60	129.40	129.51	136.94	129.51	129.40	118.30	129.70	114.86	160.25	114.86	129.70							63.53, 14.75	
1c	151.60	156.10	22.80	141.98	132.81	129.92	127.85	136.48	132.47	133.43	118.36	129.75	114.78	160.11	114.78	129.75							63.46, 14.72	
1d	151.54	155.80	22.76	142.06	130.87	127.60	129.54	142.27	129.54	127.60	118.43	129.82	117.77	160.13	114.77	129.82							63.45, 14.71	21.16
1e	151.44	155.44	22.66	142.06	125.76	129.53	114.72	162.40	114.72	129.53	118.50	129.78	114.77	160.10	114.77	129.78							63.46, 14.72	55.71
1f	151.83	154.23	22.97	141.89	139.60	129.03	124.41	149.24	124.41	129.03	118.06	129.69	114.83	160.25	114.83	129.69							63.47, 14.68	
1g	151.62	155.52	22.80	142.07	132.55	128.30	127.36	143.43	127.36	128.30	118.39	129.59	114.79	160.15	114.79	129.59	138.93	126.99	129.23	128.44	129.23	126.99	63.45, 14.70	
1h	151.35	154.54	23.18	141.93	130.71	127.34	129.76	142.12	129.76	127.34	115.51	156.87	112.67	120.45	132.32	131.23							63.69, 14.43	21.11
1i	151.60	152.99	23.33	141.85	139.52	128.78	124.29	149.24	124.29	128.78	115.54	156.85	112.78	120.53	132.55	131.31							63.73, 14.49	
1j	151.34	154.46	23.25	142.07	139.39	128.08	127.34	143.36	127.34	128.08	115.29	156.94	112.76	120.52	132.50	131.33	138.87	126.97	129.22	128.45	129.22	126.97	63.80, 14.52	
1k	151.32	153.78	23.16	141.95	132.23	129.17	129.32	136.82	129.32	129.17	115.13	156.85	112.74	120.49	132.50	131.29							63.73, 14.40	
1l	151.30	154.15	23.13	142.22	139.50	129.10	124.28	149.34	124.28	129.10	111.66	156.77	116.78	132.18	119.35	129.50								
1m	150.73	156.22	22.86	142.71	130.66	127.74	129.89	142.71	129.89	127.74	111.31	156.87	116.80	132.18	119.30	129.20								21.20
1n	151.03	156.23	23.08	142.50	132.08	127.76	129.32	132.20	129.32	127.76	111.64	156.84	116.80	132.20	119.32	129.24								
1o	151.08	156.22	22.84	142.32	132.80	129.67	130.60	125.99	130.60	129.67	111.70	156.79	116.78	132.05	119.31	129.29								
1p	151.23	156.23	22.89	142.34	132.75	129.98	127.82	136.51	132.48	133.51	111.72	156.71	116.77	132.14	119.23	129.25								
1q	151.12	154.70	23.08	142.86	139.44	129.16	124.26	149.35	124.26	129.16	124.70	129.86	129.20	135.35	129.20	129.86								
1r	151.60	155.49	22.78	142.09	132.53	128.28	127.35	143.43	127.35	128.28	118.56	129.59	114.38	160.87	114.38	129.59	138.92	126.98	129.21	128.43	129.21	126.98	55.48	
2a	152.49	154.89	22.93	140.59	132.05	127.60	129.17	131.98	129.17	127.60	27.90	133.58	127.64	125.66	127.72	131.65	128.17	125.96	126.38	124.23	131.65			
2b	152.72	153.15	23.00	140.48	139.51	128.98	124.16	149.28	124.16	128.98	27.93	133.59	127.77	125.70	127.79	131.92	128.65	125.98	126.42	124.22	131.65			
2c	152.60	155.21	22.70	140.56	125.56	129.65	114.78	162.55	114.78	129.65	27.92	133.53	127.70	125.68	127.75	131.80	128.60	125.96	126.41	124.21	131.65			55.73
2d	152.52	153.98	22.75	140.52	132.79	132.20	129.55	125.88	129.55	132.20	27.90	133.58	127.69	125.67	127.74	132.03	128.64	125.97	126.40	124.22	131.65			
2e	152.42	155.09	22.82	140.91	130.65	127.62	129.76	142.43	129.76	127.62	27.87	133.58	127.72	125.66	127.77	131.90	128.64	125.97	126.40	124.20	131.65			21.18
3a	148.62	156.81	23.06	143.75	130.51	127.86	129.92	142.77	129.92	127.86	123.76	138.99	125.66	147.77		145.25								21.24
3b	148.41	156.15	23.15	143.81	132.53	129.89	132.35	126.30	132.35	129.89	124.02	140.17	126.18	146.85		144.34								
3c	148.47	156.41	22.92	143.72	125.34	129.83	114.78	162.70	114.78	129.83	123.85	139.00	125.68	147.65		145.17								55.79
3d	148.43	156.08	23.18	143.70	132.38	129.58	127.92	135.94	132.60	133.32	123.85	139.32	125.84	146.69		145.12								

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δ 151.32, C-6 at δ 153.78, C-9 at δ 141.95, C-10 at δ 132.23, C-13 at δ 136.82, C-16 at δ 115.13, and C-17 at δ 156.85. All the other ^{1}H and ^{13}C NMR chemical shifts were determined completely by the same methods. Distinguishing H-18 from H-19 and H-22 from H-25 for compounds **2a**–**2e** was not easy and NOE difference spectra were applied. Because of the similarity in structures, we take **2e** as an example. The signals at δ 7.48 and δ 8.28 were increased by 5.5% and 9.6%, respectively, by radiating at δ 4.75 (H-16, methylene proton), and thus the signals of H-18 (δ 7.48) and H-25 (δ 8.28) were assigned.

From Table 1 it may be concluded that substitution on the aromatic ring moiety has little effect on the heterocyclic system H-7 proton. Thus, the H-7 proton resonates in the narrow range of 4.30–4.52 ppm, with the exception of compound **3b**. Generally, the electron-accepting group on the aromatic ring shifts the signal downfield, whereas the electron-donating substituents shift the signal upfield.

The ^{13}C NMR spectra exhibit characteristic signals for C-3, C-6, C-7, and C-9 of the fused ring at δ 148.41–152.72, 153.15–156.81, 22.66–23.33, and 140.48–143.81, respectively. As shown in Table 2, the signals corresponding to the heterocyclic system are relatively insensitive to the nature of the substituent on the aryl ring. C-3 in these systems resonates in the narrow range of 151–152 ppm, with the exception of compounds **3a–3d**.

Acknowledgements

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