Synthesis of 3-(R-Phenyl)-6-phenyl-7-(1*H*-1,2,4-triazol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

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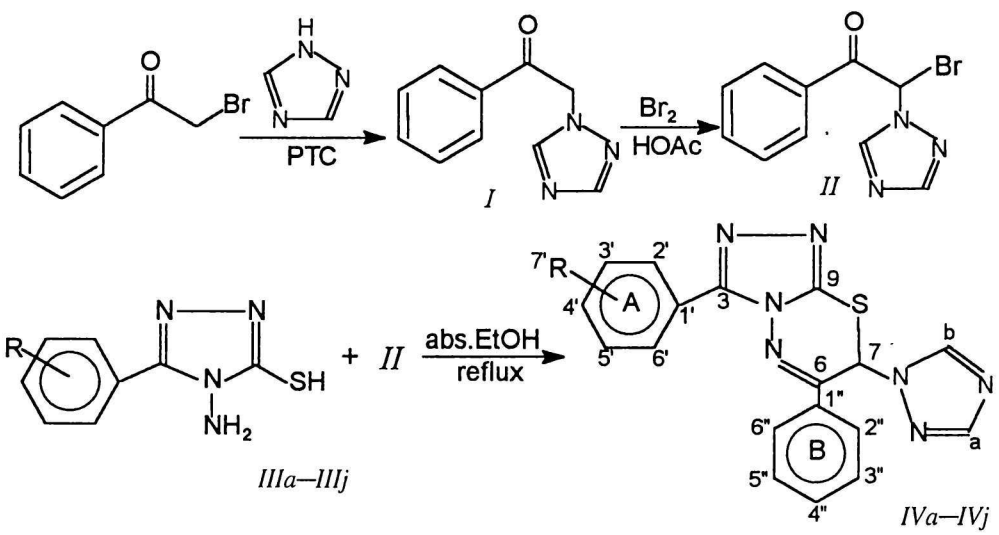
Ten novel 3-substituted phenyl-6-phenyl-7-(1*H*-1,2,4-triazol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines were synthesized by the condensation of 4-amino-3-substituted phenyl-5-sulfanyl-1,2,4-triazoles with ω-bromo-ω-(1*H*-1,2,4-triazol-1-yl)acetophenone in refluxing absolute ethanol. All the compounds synthesized were confirmed by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data.

[1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazine is a very attractive fused heterocyclic system mainly due to its multiple pharmacological applications including antiparasitic, analgesic, antibacterial, and anti-inflammatory effects [1—4]. Further, a considerable number of compounds bearing 1*H*-1,2,4-triazole ring have been reported to possess broad-spectrum biological activities [5—9], among which some commercially antifungal agents have been developed such as triadimefon, triadimenol, and diniconazole. An understanding of their biological effects requires a chemical and physicochemical knowledge of these compounds. To our knowledge, this class of heterocycles have not been previously subjected to a detailed ^{13}C NMR study. Prompted by these observations, we report now the synthesis and ^{13}C NMR spectroscopic characterization of a system in which 1*H*-1,2,4-triazole moiety has been firstly incorporated into [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine ring system.

The cyclization of 3-substituted 4-amino-5-sulfanyl-1,2,4-triazoles with α-halogenocarbonyl compounds has been the most useful method for the formation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine ring system. However, this cyclization has afforded different products under various reaction conditions [10]. As anticipated, the treatment of 4-amino-3-(R-phenyl)-



Scheme 1

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Table 1. Characterization of Compounds *IV*

Compound	R	Formula	w_i(found)/% (w_i(calc.)/%)			Yield	M.p.
			C	H	N	%	°C
IVa	H	$C_{18}H_{13}N_7S$	59.90 (60.15)	3.84 (3.65)	27.22 (27.28)	68	219—222
IVb	4-Cl	$C_{18}H_{12}N_7SCl$	54.66 (54.89)	3.04 (3.07)	24.78 (24.89)	71	232—233
IVc	3-Cl	$C_{18}H_{12}N_7SCl$	54.63 (54.89)	3.34 (3.07)	24.69 (24.89)	74	210—212
IVd	4-Br	$C_{18}H_{12}N_7SBr$	49.27 (49.33)	2.89 (2.76)	22.37 (22.37)	66	240—243
IVe	4-CH_3	$C_{19}H_{15}N_7S$	60.97 (61.11)	4.13 (4.05)	25.95 (26.26)	72	223—225
IVf	2-Cl	$C_{18}H_{12}N_7SCl$	55.11 (54.89)	3.12 (3.07)	25.06 (24.89)	70	229—232
IVg	4-I	$C_{18}H_{12}N_7SI$	44.88 (44.55)	2.58 (2.49)	20.17 (20.20)	59	237—239
IVh	4-OCH_3	$C_{19}H_{15}N_7OS$	58.27 (58.60)	4.25 (3.88)	24.83 (25.18)	75	205—207
IVi	3-CH_3	$C_{19}H_{15}N_7S$	60.97 (61.11)	4.09 (4.05)	25.98 (26.26)	62	206—208
IVj	3-OCH_3	$C_{19}H_{15}N_7OS$	58.47 (58.60)	3.95 (3.88)	24.82 (25.18)	67	188—190

Table 2. IR and ^{1}H NMR Spectral Data for Compounds *IV*

Compound	IR $\tilde{\nu}_i$/cm^{-1}	^{1}H NMR (DMSO-d_6) δ
IVa	3066 (ArH), 1593 (C=N), 1268 (N—N=C), 679 (C—S—C)	9.00 (s, 1H, TrH), 7.57—8.16 (m, 12H, ArH, SCH and TrH)
IVb	3046 (ArH), 1598 (C=N), 1273 (N—N=C), 681 (C—S—C)	8.99 (s, 1H, TrH), 7.55—8.17 (m, 11H, ArH, SCH and TrH)
IVc	3058 (ArH), 1596 (C=N), 1269 (N—N=C), 680 (C—S—C)	9.00 (s, 1H, TrH), 7.36—8.14 (m, 11H, ArH, SCH and TrH)
IVd	3040 (ArH), 1594 (C=N), 1272 (N—N=C), 681 (C—S—C)	8.97 (s, 1H, TrH), 7.49—8.11 (m, 11H, ArH, SCH and TrH)
IVe	3034 (ArH), 1613 (C=N), 1273 (N—N=C), 680 (C—S—C)	8.99 (s, 1H, TrH), 7.37—8.07 (m, 11H, ArH, SCH and TrH), 2.40 (s, 3H, CH_3)
IVf	3063 (ArH), 1592 (C=N), 1267 (N—N=C), 680 (C—S—C)	8.95 (s, 1H, TrH), 7.39—8.17 (m, 11H, ArH, SCH and TrH)
IVg	3038 (ArH), 1592 (C=N), 1271 (N—N=C), 680 (C—S—C)	8.98 (s, 1H, TrH), 7.49—8.08 (m, 11H, ArH, SCH and TrH)
IVh	3057 (ArH), 1611 (C=N), 1255 (N—N=C), 678 (C—S—C)	8.98 (s, 1H, TrH), 7.12—8.11 (m, 11H, ArH, SCH and TrH), 3.85 (s, 3H, OCH_3)
IVi	3064 (ArH), 1591 (C=N), 1265 (N—N=C), 677 (C—S—C)	9.00 (s, 1H, TrH), 7.42—8.03 (m, 11H, ArH, SCH and TrH), 2.41 (s, 3H, CH_3)
IVj	3058 (ArH), 1600 (C=N), 1274 (N—N=C), 682 (C—S—C)	8.99 (s, 1H, TrH), 7.11—8.02 (m, 11H, ArH, SCH and TrH), 3.83 (s, 3H, OCH_3)

5-sulfanyl-1,2,4-triazoles *IIIa—IIIj* with ω-bromo-ω-(1*H*-1,2,4-triazol-1-yl)acetophenone *II* refluxing absolute ethanol resulted in cyclocondensation to give the corresponding 3-(R-phenyl)-6-phenyl-7-(1*H*-1,2,4-triazol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines *IVa—IVj* (Scheme 1, Table 1).

The IR spectra of *IVa—IVj* (Table 2) displayed three characteristic absorption bands: at 1591—1613 cm^{-1} for ν(C=N), 1255—1274 cm^{-1} for ν(N—N=C), and 677—682 cm^{-1} for ν(C—S—C), respectively. The ^{1}H NMR spectra exhibited a singlet for one 1*H*-1,2,4-triazole proton at δ = 8.95—9.00. The other 1*H*-1,2,4-triazole proton, SCH proton, and aromatic protons resonated as a multiplet at δ = 7.11—8.17. The mass spectra (Table 3) showed the expected molecular ion in high abundance. The fragmentation of *IVa—IVj* in-

Table 3. Mass Spectral Data for Compounds *IV*

Compound	m/z (I_r/%)
IVa	359 (M^+, 81), 291 (5), 212 (2), 198 (12), 184 (7), 171 (4), 161 (12), 147 (25), 125 (10), 116 (23), 103 (100), 77 (25)
IVb	393 (M^+, 79), 325 (5), 246 (2), 232 (13), 195 (6), 184 (11), 147 (25), 137 (100), 125 (12), 116 (35), 102 (83), 77 (28)
IVc	393 (M^+, 98), 325 (7), 232 (17), 195 (12), 184 (16), 147 (69), 137 (100), 125 (16), 116 (43), 111 (12), 102 (86), 77 (28)
IVd	437 (M^+, 43), 369 (3), 276 (7), 239 (3), 195 (5), 181 (43), 147 (23), 125 (11), 116 (32), 102 (100), 89 (19), 77 (27)
IVe	373 (M^+, 100), 305 (6), 226 (6), 212 (17), 184 (8), 175 (5), 147 (12), 131 (10), 125 (14), 117 (91), 103 (40), 77 (19)
IVf	393 (M^+, 15), 325 (2), 255 (4), 232 (3), 184 (3), 147 (40), 137 (55), 125 (7), 116 (25), 103 (59), 77 (21), 69 (100)
IVg	485 (M^+, 45), 417 (2), 386 (2), 324 (8), 254 (5), 229 (54), 184 (6), 147 (14), 125 (8), 116 (22), 102 (100), 77 (21)
IVh	389 (M^+, 100), 321 (7), 242 (3), 228 (16), 201 (10), 184 (5), 147 (14), 133 (86), 125 (14), 116 (21), 103 (42), 77 (13)
IVi	373 (M^+, 100), 305 (5), 226 (6), 212 (13), 184 (8), 175 (7), 147 (18), 117 (71), 116 (51), 103 (36), 89 (26), 77 (18)
IVj	389 (M^+, 100), 321 (5), 242 (10), 228 (9), 184 (6), 174 (4), 147 (18), 133 (66), 125 (9), 116 (27), 103 (57), 77 (19)

Table 4. ^{13}C NMR Spectral Data for Compounds *IV*

Carbon	δ							
	IVa	*IVb*	*IVd*	*IVe*	*IVg*	*IVh*	*IVi*	*IVj*
C-3	137.78	138.08	138.12	137.50	138.10	137.19	137.67	137.87
C-6	151.09	150.20	150.30	151.20	150.50	150.96	151.12	150.78
C-7	49.11	49.09	49.07	49.08	49.04	49.12	49.05	49.12
C-9	148.79	148.95	148.95	148.62	148.90	148.59	148.64	148.78
C-a	153.36	153.39	153.39	153.36	153.38	153.36	153.38	153.38
C-b	144.27	144.28	144.29	144.26	144.28	144.26	144.27	144.28
C-1″	131.78	131.64	131.63	131.81	131.62	131.89	131.78	131.81
C-2″(6″)	127.39	127.47	127.48	127.36	127.47	127.38	127.33	127.34
C-3″(5″)	129.51	129.52	129.52	129.51	129.53	129.54	129.51	129.53
C-4″	132.47	132.55	132.56	132.45	132.55	132.44	132.45	132.52
C-1′	125.58	124.38	124.21	122.80	125.00	117.94	125.53	126.78
C-2′	128.03	129.16	129.86	127.98	129.70	129.61	128.45	113.03
C-3′	128.94	129.68	132.08	129.51	137.89	114.46	138.19	159.32
C-4′	130.54	135.38	124.73	140.43	97.85	160.98	131.15	116.42
C-5′	128.94	129.68	132.08	129.51	137.89	114.46	128.80	130.19
C-6′	128.03	129.16	129.86	127.98	129.70	129.61	125.24	120.31
C-7′				21.03		55.40	21.04	55.27

volved the fission of triazole and thiadiazine ring systems to afford $RC_6H_4CN]^{+\cdot}$ and $C_6H_5CN]^{+\cdot}$ ions. The ion peak formed by the direct loss of the 1*H*-1,2,4-triazole group from the molecular ion could be observed in each case.

In their ^{13}C NMR spectra (Table 4), the signals at δ = 153.36—153.39 and δ = 144.26—144.29 were attributable to C-a and C-b of the 1*H*-1,2,4-triazole ring, respectively, by comparison with the chemical shifts of the model compound [11]. The C-7 signal of the SCH carbon appeared at δ = 49.04—49.12. The peaks corresponding to the signals of the aromatic ring B were readily identified due to the least variation in chemical shift values. The assignment of the chemical shifts of the aromatic ring A was made by comparison with the calculated values which were obtained by adding the substituent effects [12] of Cl, Br, I, CH_3, and OCH_3 to the chemical shifts of *IVa*. The remaining C-3, C-6, and C-9, which were at around δ = 137.66, 150.70, and 148.77, were successively assigned on the basis of their chemical surroundings and data reported earlier for related compounds [13].

EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus. Elemental analyses were carried out on an Elementar vario EL analyzer. IR spectra were obtained in KBr disc with a Nicolet FT-IR 170SX spectrometer. MS were taken with an HP-5988A instrument (EI at 70 eV). ^{1}H NMR spectra were recorded at 80 MHz on a Bruker FT-AC 80 instrument. ^{13}C NMR spectra were obtained at 100.61 MHz on a Bruker AM 400 spectrometer. Spectra were recorded in DMSO-d_6 solutions and all chemical shifts were determined on the δ scale relative to internal TMS.

ω-Bromoacetophenone and 4-amino-3-(R-phenyl)-5-sulfanyl-1,2,4-triazoles *IIIa*—*IIIj* were prepared following methods in the literature [14, 15], respectively.

ω-(1*H*-1,2,4-Triazol-1-yl)acetophenone (*I*)

A mixture of ω-bromoacetophenone (10 mmol), 1*H*-1,2,4-triazole (10 mmol), potassium carbonate (22

mmol), and PEG-600 (0.5 mmol) in dry ethyl acetate (20 cm^3) was refluxed for 3—5 h. The inorganic salt was filtered off and the filtrate was washed with water to neutral reaction. The separated aqueous layer was extracted with ethyl acetate. The acetate portion was dried with sodium sulfate and the solvent was removed. Yield 36 %, m.p. = 114—116 °C [16].

ω-Bromo-ω-(1*H*-1,2,4-triazol-1-yl)-acetophenone (*II*)

Bromine (1.5 mmol) was added to a solution of *I* (1.5 mmol) in acetic acid (10 cm^3). The mixture was stirred at room temperature for 2 h and water (20 cm^3) was added to it. The mixture was extracted with chloroform. The chloroform solution was washed with sodium carbonate and water to neutral reaction. The chloroform layer was dried with sodium sulfate, the solvent was removed and the residue was used in the next step without further purification.

3-(R-Phenyl)-6-phenyl-7-(1*H*-1,2,4-triazol-1-yl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (*IVa—IVj*)

A mixture of *IIIa—IIIj* (1.5 mmol) and *II* (1.5 mmol) in absolute ethanol (25 cm^3) was heated under reflux for 12 h. The reaction mixture was concentrated and cooled. The resulting solid was collected by filtration, treated with aqueous potassium carbonate solution, washed with water, and recrystallized from ethanol.

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