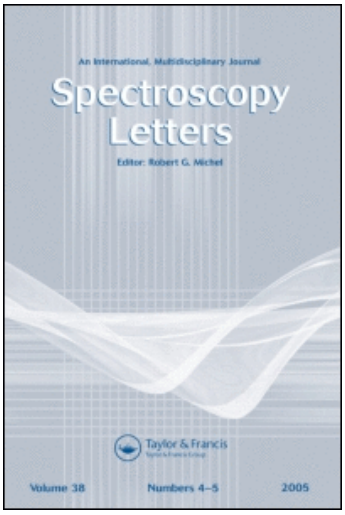

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Studies on Condensed Heterocyclic Compounds Xix. ^{1}H and ^{13}C Nmr Spectroscopy of 6-Aryl-3-(1-*P*-Chlorophenyl-5-Methyl-1,2,3-Triazol-4-Yl)-S-Triazolo[3,4-*B*]-1,3,4-Thiadiazoles

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STUDIES ON CONDENSED HETEROCYCLIC COMPOUNDS XIX. ^{1}H AND ^{13}C NMR SPECTROSCOPY OF 6-ARYL-3-(1-*p*-CHLOROPHENYL-5-METHYL-1,2,3-TRIAZOL-4-YL)-s-TRIAZOLO[3,4-*b*]-1,3,4-THIADIAZOLES

Key words: *^{1}H NMR, ^{13}C NMR, s-triazolo[3,4-b]-1,3,4-thiadiazole, HMBC experiment, SCS effects*

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ABSTRACT

^{1}H and ^{13}C NMR spectra of eight novel 6-aryl-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles were measured and assigned on the basis of the additivity effects induced by the substituents, the signal intensities, data reported earlier for related compounds and two-dimensional HMBC experiment. The SCS effects of the s-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus on the aromatic ring were determined.

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INTRODUCTION

Attention has been increasingly paid to the chemistry of s-triazolo[3,4-*b*]-1,3,4-thiadiazole during recent years on account of its diverse types of biological properties, including antifungal, antiinflammatory, analgesic, hypotensive, hypocholesterolemic and anthelmintic properties.[1-4] Our earlier work on the synthesis of 3,6-disubstituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles revealed antibacterial, herbicidal and plant growth regulative activities for the compounds.[5-7] 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 NMR spectroscopic characterization of some novel 3,6-disubstituted s-triazolo[3,4-*b*]-1,3,4-thiadiazoles, which will be useful in future work in terms of structural elucidation.

Experimental Section

Materials.

4-Amino-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,2,4-triazole (**1**) was prepared by Reid-Heindel's general procedure.[8] Yield: 55%, m.p. 190-192 ℃. Elemental **analysis found**: C, 42.87, H, 3.21, N, 31.69; $C_{11}H_{10}N_7SCl$ requires C, 42.93, H, 3.27, N, 31.86%. ^1H NMR (DMSO-d_6, ppm): δ 14.06 (s, 1H, SH), 7.74 (s, 4H, ArH), 5.89 (br s, 2H, NH_2), 2.46 (s, 3H, CH_3).

General procedure for the preparation of 6-aryl-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-s-triazolo[3,4-*b*]-1,3,4-thiadiazole ($\mathbf{3_{a-h}}$): A mixture of **1** (0.001 mol) and aromatic acid ($\mathbf{2_{a-h}}$) (0.001 mol) in the presence of phosphorus oxychloride (5 ml) was refluxed over oil-bath for 6 hr. After removal of the excess of phosphorus oxychloride under reduced pressure, 50 ml water was added to the residue. The resulting solid was filtered, treated with 10 % aqueous sodium hydroxide, and then washed with water and **recrystallized** from ethanol-DMF.

Methods.

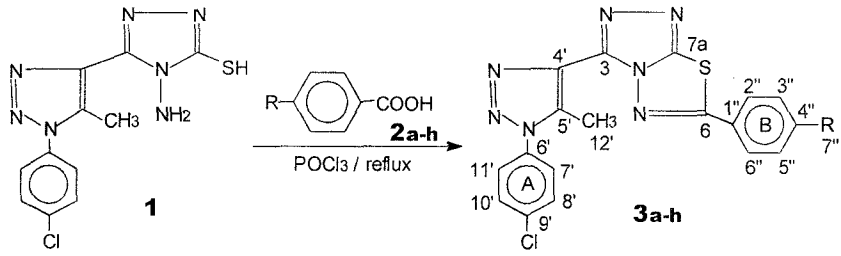
Melting points were determined on a Kofler melting point apparatus and are uncorrected. Elemental analyses were carried out on a 1106 analyzer. ^1H NMR spectra were recorded at 80 MHz on a Bruker FT-AC 80 instrument. ^{13}C NMR spectra were obtained at 100.61 MHz on a Bruker AM 400 spectrometer operating in the CPD mode. Spectra were recorded in DMSO-d_6 solutions and 5 mm NMR tubes were used. All chemical shifts were determined on the δ scale (ppm) relative to internal TMS.

^{1}H NMR spectra were recorded with spectral width 1362.4 Hz, acquisition time 1.5 s, pulse width for a 90° pulse 3.0 μs and relaxation delay 1.0 s. Typical conditions for recording ^{13}C NMR spectra were spectral width 23.8 kHz, aquisition time 0.688 s, pulse width for a 90° pulse 5.0 μs and relaxation delay 2.0 s.

^{1}H detected heteronuclear multiple bond connectivity experiment (HMBC) was performed using the standard pulse sequence. The values of 3.6 ms (Δ_1) and 50 ms (Δ_2) were used for the evolution of long-range $^nJ_{C-H}$ couplings. The spectrum was acquired with spectral widths of F_2 2923.977 Hz (^{1}H) and F_1 18796.992 Hz (^{13}C) employing a data matrix of 1024×160 zero filled to 512 and a relaxation delay of 0.8 s was used.

RESULTS AND DISCUSSIONS

The cyclocondensation of 4-amino-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,2,4-triazole (**1**) with aromatic acids (**2**$_{a-h}$) in the presence of $POCl_3$ afforded the corresponding 6-aryl-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles (**3**$_{a-h}$) (Table 1). The ^{1}H and ^{13}C NMR spectral data for **3**$_{a-h}$ are given in Tables 2 and 3. In the ^{1}H NMR spectra, the triazole methyl group appears as a characteristic singlet at around δ 2.63 ppm and the aromatic protons resonate at δ 7.14-8.46 ppm.



The ^{13}C NMR spectra show the presence of the triazole methyl group in the range δ 9.58-9.62 ppm. The peaks corresponding to the signals of the aromatic ring A were readily identified due to the least variation in chemical shift values, which are in agreement with those previously reported for related compounds.[9]

TABLE 1

Yields, Melting Points and Elemental Analyses for Compounds $\mathbf{3}_{a-h}$

Compd.	Substituent R	Yield (%)	M.p. (℃)	Found (Calculated) (%) C	H	N
$\mathbf{3}_a$	H	49	276-278	54.73 (54.89)	3.19 (3.07)	24.61 (24.89)
$\mathbf{3}_b$	4-F	64	227-228	52.30 (52.50)	2.77 (2.69)	23.62 (23.81)
$\mathbf{3}_c$	4-Cl	63	230-232	50.16 (50.48)	2.70 (2.59)	22.53 (22.89)
$\mathbf{3}_d$	4-Br	60	242-244	45.34 (45.73)	2.71 (2.35)	20.56 (20.74)
$\mathbf{3}_e$	4-I	54	268-270	41.47 (41.60)	2.25 (2.13)	18.65 (18.86)
$\mathbf{3}_f$	4-Me	52	182-183	55.69 (55.95)	3.57 (3.46)	23.82 (24.04)
$\mathbf{3}_g$	4-OMe	50	203-204	53.88 (53.84)	3.33 (3.33)	22.66 (23.13)
$\mathbf{3}_h$	4-NO_2	63	278-280	49.03 (49.26)	2.73 (2.53)	25.23 (25.53)

TABLE 2

^{1}H NMR Spectral Data for Compounds $\mathbf{3}_{a-h}$

Compd.	^{1}H NMR (DMSO-d_6) (δ ppm, J Hz)
$\mathbf{3}_a$	8.08-7.55 (m, 5H, ArH), 7.78 (s, 4H, ArH), 2.63 (s, 3H, CH_3)
$\mathbf{3}_b$	8.10 (dd, J=8.78, 5.22Hz, 2H, ArH), 7.78 (s, 4H, ArH), 7.49 (t, J=8.78Hz, 2H, ArH), 2.63 (s, 3H, CH_3)
$\mathbf{3}_c$	8.05 (d, 2H, J=8.55Hz, ArH), 7.79 (s, 4H, ArH), 7.73 (d, 2H, J=8.55Hz, ArH), 2.64 (s, 3H, CH_3)
$\mathbf{3}_d$	7.99 (d, 2H, J=8.72Hz, ArH), 7.84 (d, 2H, J=8.72Hz, ArH), 7.79 (s, 4H, ArH), 2.63 (s, 3H, CH_3)
$\mathbf{3}_e$	8.01 (d, 2H, J=8.44Hz, ArH), 7.76 (d, 2H, J=8.44Hz, ArH), 7.77 (s, 4H, ArH), 2.63 (s, 3H, CH_3)
$\mathbf{3}_f$	7.88 (d, 2H, J=8.08Hz, ArH), 7.77 (s, 4H, ArH), 7.41 (d, 2H, J=8.08Hz, ArH), 2.63 (s, 3H, CH_3), 2.40 (s, 3H, $ArCH_3$)
$\mathbf{3}_g$	7.93 (d, 2H, J=8.76Hz, ArH), 7.77 (s, 4H, ArH), 7.14 (d, 2H, J=8.76Hz, ArH), 3.87 (s, 3H, OCH_3), 2.63 (s, 3H, CH_3)
$\mathbf{3}_h$	8.46 (d, 2H, J=8.65Hz, ArH), 8.27 (d, 2H, J=8.65Hz, ArH), 7.78 (s, 4H, ArH), 2.64 (s, 3H, CH_3)

TABLE 3

^{13}C NMR Spectra Data for Compounds $\mathbf{3}_{a-h}$

Carbon	$\mathbf{3}_a$	$\mathbf{3}_b$	$\mathbf{3}_c$	$\mathbf{3}_d$	$\mathbf{3}_e$	$\mathbf{3}_f$	$\mathbf{3}_g$	$\mathbf{3}_h$
C-3	140.03	140.04	140.05	140.05	140.05	139.96	139.89	140.23
C-6	166.88	165.76	165.73	165.88	166.22	166.80	166.45	164.93
C-7a	153.99	154.09	154.03	154.04	153.93	153.83	153.83	154.24
C-4'	132.22	132.21	132.15	132.15	132.17	132.24	132.27	132.10
C-5'	135.05	135.04	135.03	135.03	135.05	134.94	134.93	135.14
C-6'	134.69	134.71	134.68	134.68	134.70	134.66	134.66	134.74
C-7'(11')	127.14	127.13	127.11	127.12	127.13	127.09	127.09	127.13
C-8'(10')	129.83	129.84	129.80	129.81	129.83	129.81	129.80	129.85
C-9'	134.27	134.27	134.24	134.25	134.25	134.26	134.27	134.25
C-12'	9.59	9.61	9.59	9.58	9.59	9.60	9.58	9.62
C-1"	129.02	125.64	127.89	128.23	128.43	126.27	121.29	134.60
C-2"(6")	127.24	129.96	128.98	129.06	128.75	127.09	129.03	128.69
C-3"(5")	129.73	116.95	129.80	132.72	138.53	130.19	115.08	124.74
C-4"	132.98	164.62	137.57	126.52	100.75	143.39	162.83	149.66
C-7"						21.13	55.69	

The assignment of the chemical shifts of the aromatic ring B was made by comparison with the calculated values which were obtained by adding the substituent effects[10] of F, Cl, Br, I, CH_3, OCH_3 and NO_2 to the chemical shifts of $\mathbf{3}_a$. Figure 1 shows the correlation between the calculated and measured chemical shifts, which can be expressed as the straight line $y=a+bx$ with a good correlation coefficient 0.99. The calculated and measured chemical shift values differed by an average of *ca.* 0.95 ppm. The ^{13}C, ^{19}F coupling constants of compound $\mathbf{3}_b$ are 251.5 Hz ($^1J_{C\text{-}F}$), 22.1 Hz ($^2J_{C\text{-}F}$) and 9.1 Hz ($^3J_{C\text{-}F}$) for C-4", C-3"(5") and C-2"(6"), respectively, which coincide with the published data.[10]

Compound $\mathbf{3}_a$ was utilized to determine the substituent-induced chemical shift (SCS) effects of the s-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus on the aromatic ring B, which are deshielding at the *ipso*-, *meta*- and *para*-carbons and shielding at the *ortho*-carbon. The results can be represented as follows (taking

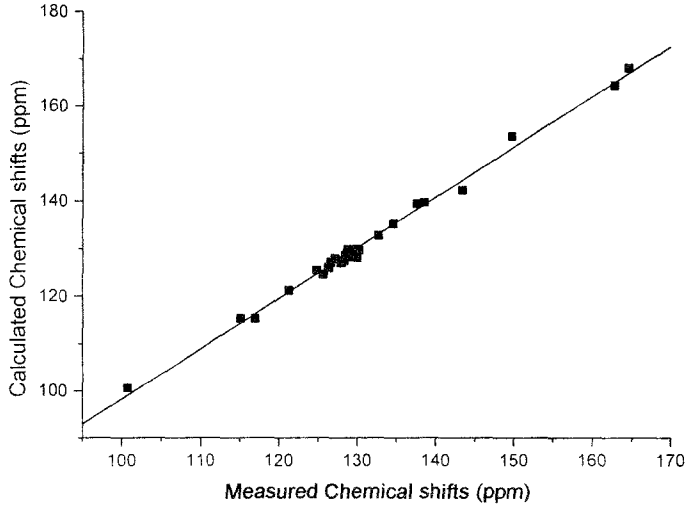


FIG. 1 Correlation between calculated and measured chemical shifts

the δ value for benzene as 128.5 ppm) C-*ipso* +0.52, C-*ortho* −1.26, C-*meta* +1.23 and C-*para* +4.48 ppm, which reflects the electron-withdrawing ability of the s-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus.

With the aid of two-dimensional (2D) HMBC technique, the assignment of C-4', C-5' and C-6 becomes a relatively straightforward task. In compound **3f**, the triazole methyl signal at δ 2.63 ppm shows two correlation peaks with carbons at δ 132.24 and 134.94 ppm, which are assigned to C-4' annd C-5', respectively, on the grounds of peak intensities related to the value of the long-range coupling constant. The highly deshielded carbon at δ 166.80 ppm can be assigned to C-6 based on the $^{3}J_{C\text{-}H}$ correlation with H-2"(6"), which appear at δ 7.88 ppm. Therefore, only C-3 and C-7a remained unassigned, those at δ 139.96 and 153.83 ppm. The large δ value should be identified as C-7a for it is bonded to an additional sulfur atom compared with C-3. These five quaternary carbons of other compounds were

unambiguously assigned by comparison with $\mathbf{3_f}$. Inspection of these five carbons revealed that the variation in chemical shift values was the greatest for C-6 and the least for C-4' and C-5', consistent with the increase in distance from the aromatic ring B.

It appears that the C-6 chemical shifts can not be well correlated with Hammett's constants of the substituents (with a correlation coefficient 0.83). To evaluate the contribution of the field and resonance effects, attempts were made to correlate the C-6 chemical shifts with the F and R constants using the Swain-Lupton equation.[11] However, the multiple linear regression also gave unsatisfactory results (r = 0.84).

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