MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2001; **39**: 411–413

Spectral Assignments and Reference Data

^{1}H and ^{13}C NMR study of 6-aryl-3-cinchopheny-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles

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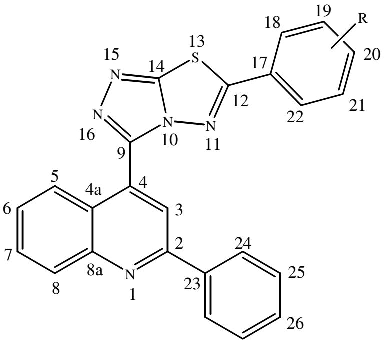
Received 19 September 2000; Revised 2 January 2001; Accepted 22 January 2001

Ten new 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives were synthesized and their NMR spectra were analyzed by 1D and 2D NMR techniques (gCOSY, gHMBC, gHMQC). Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; thiadiazoles

INTRODUCTION

In recent years, 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives have displayed unique properties both in chemical synthesis and in chemical biology,[1–3] as they possess broad-spectrum biological activities such as antibacterial, hypotensive and CNS depressant activities.[4,5] Compounds **1–10** (Scheme 1) have been synthesized utilizing cinchophen as the starting material. These compounds were prepared by the reaction of cincophen **(A)** and ethanol in the presence of sulfuric acid and then reaction with hydrazine hydrate in absolute ethanol to give cincophen hydrazine **(B)**, that yielded 4-amino-5-cinchophenyl-3-thiohydroxy-1,2,4-triazole **(C)** on treatment with CS_2 and KOH. Reaction of **C** with various substituted benzoic acids in the presence of $POCl_3$ gave compounds **1–10** (Scheme 2)



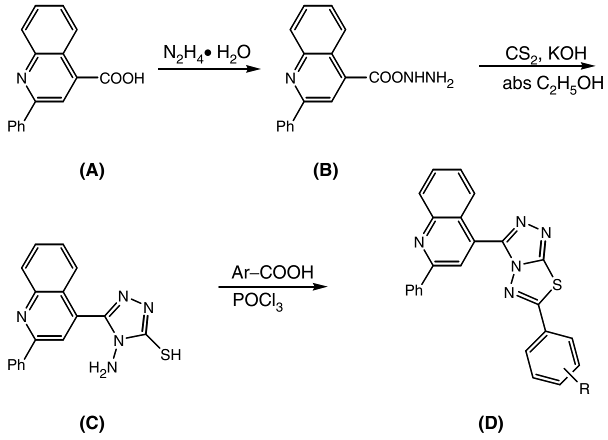
1 R = p-Cl
2 R = p-F
3 R = p-I
4 R = p-CH_3
5 R = m-F
6 R = m-Cl
7 R = m-CH_3
8 R = o-Cl
9 R = p-Br
10 R = m-Br

Scheme 1

^{1}H and ^{13}C NMR data for **1–10**, not previously reported, were of interest to us. We report here the ^{1}H and ^{13}C chemical shifts and part of the $J(^1H, ^1H)$ data. The assignments were based on gCOSY, gHMQC and gHMBC experiments.

EXPERIMENTAL

All the ^{1}H NMR and 2D NMR experiments were recorded at room temperature on a Varian INOVA 500 spectrometer, operating at 499.89 MHz for ^{1}H and 125.71 MHz for ^{13}C. The 90° pulse was 8.6 μs and we used 45° pulses for the experiments. ^{13}C NMR experiments were performed under similar conditions on a Varian VXR-300 spectrometer, operating at 75.43 MHz for ^{13}C. The 90° pulse was 19.6 μs and we used 30° pulses for the measurements. The gradient field strength for gCOSY experiments was 3.6×10^{-4} T cm^{-1}. For the gHMQC and gHMBC experiments we used 11.4×10^{-4}, and 5.7×10^{-4} T cm^{-1}, respectively. The digital resolution for ^{13}C NMR at 75.43 MHz was better than 2.5 Hz, and that for ^{1}H NMR at-500 MHz was better than 0.5 Hz. For the 2D experiments we used digital resolutions between 6 and 19 Hz. The concentration for compound **7** in TFA was 3.58×10^{-2} mol l^{-1}.



Scheme 2

RESULTS AND DISCUSSION

NMR data for **1–10** are presented in Tables 1 and 2.

Assigning ^{1}H NMR data

The ^{1}H NMR spectra chemical shifts of **1–10** range from 7.72 to 9.62 ppm (excluding the methyl group in **4** and **7**). Because of the similarity in structures, assigning the spectra of **7** is described as an example. The single peak at δ 9.63 is H-3. H-8 δ 9.43 appears at a lower field than H-5 owing to the nitrogen atom's electron-attracting ability. H-7 and H-6 can be found with the aid of gCOSY. In each of the 10 compounds, there is a triplet (1H) at δ 8.09 and a doublet (2H) at δ 5.36. This means these three protons are on the unsubstituted benzene ring. We therefore assigned H-26 to δ 8.09, H-25 to δ 7.98 and H-24 to δ 8.33 from their mutual spin–spin couplings. At higher field, a triplet of H-21 at δ 7.72 couples with a doublet of H-20 at δ 7.81 and a multiplet of H-22 at δ 8.00. Finally, H-18 yields a singlet at δ 8.00.

Assigning ^{13}C NMR data

All the tertiary carbons can be distinguished with the help of gHMBC and gHMQC experiments. The assignment of the 10 quaternary carbons depends on gHMBC and analyzing the electron effects in the molecules. We take **7** as an example again. C-8a at δ 141.57 correlates with H-8 at δ 9.43 and C-4a couples with H-5 at δ 8.73 and H-3 at δ 9.63. In addition to coupling of C-23 at δ 131.83 with H-2 and H-24, there are two carbons, δ_a 158.39, δ_b 144.47, that have cross peaks with H-2 on HMBC. Because N-1 was protonated by TFA, the electron density at C-2 is lower than that at C-4. Therefore, C-2 is at δ 158.34. On the substituted benzene ring, C-19 couples with H-20 at δ 7.81 and H-18 at δ 8.00. C-14 and C-17 correlate with H-22 and H-14, H-18, respectively. Concerning the other two carbons, C-12, which has electron-attracting nitrogen and sulfur atoms around it, appears at a lower field than C-9 at δ 139.43. The chemical shifts of other compounds can be assigned in a similar way.

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DOI: 10.1002/mrc.837

Spectral Assignments and Reference Data

Table 1. ^{1}H chemical shifts(ppm) and coupling constants(J,Hz) for compounds **1–10**

^{1}H position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
3	9.58	9.59	9.58	9.58	9.58	9.59	9.63	9.60	9.58	9.61
5	8.79 d $J = 8.0$	8.79 d $J = 8.0$	8.79 d $J = 8.0$	8.73 d $J = 8.0$	8.78 d $J = 9.0$	8.74 d	8.73 d $J = 8.0$	8.73 d $J = 8.0$	8.79 d $J = 8.0$	8.73 d $J = 8.0$
6	8.59 t $J = 8.5$	8.59 t $J = 8.5$	8.58 t $J = 8.5$	8.52 d $J = 8.5$	8.58 t $J = 8.0$	8.54 t $J = 8.5$	8.52 t $J = 8.0$	8.52 t $J = 8.5$	8.57 t $J = 8.5$	8.53 d $J = 8.5$
7	8.40 t $J = 8.5$	8.40 t $J = 8.5$	8.41 t $J = 8.5$	8.37 t $J = 8.5$	8.42 t $J = 8.0$	8.38 d $J = 8.5$	8.36 t $J = 8.0$	8.38 t $J = 8.5$	8.43 t $J = 8.5$	8.36 t $J = 8.0$
8	9.43 d $J = 8.5$	9.43 d $J = 8.5$	9.43 d $J = 8.5$	9.43 d $J = 8.5$	9.43 d $J = 9.0$	9.43 d $J = 8.5$	9.43 d $J = 9.0$	9.43 d $J = 8.5$	9.43 d $J = 7.5$	9.43 d $J = 8.5$
18	8.21 d $J = 7.5$	8.31 q $J = 4.5,6$	8.29 d $J = 8.0$	8.09 d $J = 7.5$	8.00 d $J = 8.5$	8.28	8.00	—	8.13 d $J = 8.5$	8.45 s
19	7.89 d $J = 7.5$	7.59 t $J = 8.5,8.5$	7.95 d $J = 8.0$	7.67 d $J = 7.5$	—	—	—	7.76 t $J = 7.0$	8.06 d $J = 7.0$	—
20	—	—	—	—	7.73 t $J = 8.5$	7.97 d $J = 7.5$	7.81 d $J = 7.5$	7.90 m	—	8.11 m
21	7.89 d $J = 7.5$	7.59 t $J = 8.5, 8.5$	7.95 d $J = 8.0$	7.67 d $J = 7.5$	7.90 q	7.81 t $J = 8.5$	7.72 t $J = 7.5$	7.90 m	8.06 d $J = 7.0$	7.73 t $J = 8.0$
22	8.21d $J = 7.5$	8.31 q $J = 4.5,6$	8.29 d $J = 8.0$	8.09 d $J = 7.5$	8.40 m	8.09 m	8.00 m	8.38 d $J = 6.0$	8.13 d $J = 8.5$	8.12 m
24	8.43 d $J = 7.0$	8.41 d $J = 7.0$	8.39 d $J = 7.0$	8.35 d $J = 7.0$	8.38 d $J = 6.0$	8.36 d $J = 8.0$	8.36 d $J = 8.0$	8.33 d $J = 8.0$	8.04 d $J = 7.0$	8.36 d $J = 7.0$
25	8.05 t $J = 7.0$	8.05 t $J = 7.0$	8.05 t $J = 7.0$	8.00 t $J = 7.0$	8.05 m	8.03 t $J = 7.5$	8.02 m	7.98 t $J = 7.5$	8.06 t $J = 7.0$	8.04 t $J = 7.5$
26	8.15 t $J = 7.0$	8.15 t $J = 7.0$	8.15 t $J = 7.0$	8.10 t $J = 7.0$	8.14 t $J = 7.0$	8.13 m	8.09 $J = 7.5$	8.07 t $J = 7.5$	8.16 m	8.10 m

Table 2. ^{13}C chemical shifts(ppm) for compounds **1–10**

^{13}C position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
2	158.52	158.49	158.34	158.30	158.33	158.56	158.34	158.81	158.47	158.53
3	124.64	124.67	124.63	124.77	124.36	124.63	124.69	124.72	124.65	124.62
4	144.56	144.50	144.51	144.43	144.38	144.61	144.45	144.23	144.54	144.61
4a	126.64	126.64	126.59	126.64	126.36	126.62	126.56	126.56	126.65	126.59
5	123.47	123.47	123.45	123.53	123.22	123.45	123.49	123.48	123.48	123.48
6	139.42	139.39	139.38	139.42	139.21	139.37	139.38	139.37	139.40	139.37
7	134.76	134.73	134.75	134.82	134.51	134.74	134.78	134.81	134.74	134.77
8	129.37	129.34	129.32	129.43	129.12	129.32	129.35	129.35	129.35	129.35
8a	141.52	141.52	141.50	141.58	141.27	141.50	141.53	141.53	141.53	141.53
9	139.71	139.65	139.63	139.58	139.40	139.66	139.50	139.37	139.69	139.56
12	175.74	175.65	176.20	177.26	175.08	175.44	177.34	173.54	175.91	175.25
14	158.14	158.11	158.10	158.17	157.86	158.12	158.06	158.12	158.12	158.09
17	127.24	125.18	128.12	150.87	130.20	124.94	128.71	136.23	127.67	140.74
18	131.14	132.70	130.65	130.13	137.43	134.49	138.44	133.35	131.06	130.59
19	132.98	120.00	142.23	133.30	139.14	167.67	143.85	130.65	136.07	128.68
20	145.39	—[a]	105.03	125.94	129.12	134.62	138.99	134.14	133.50	133.82

Table 2. (*Continued*)

^{13}C position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
21	132.98	120.00	142.23	133.30	133.47	126.16	132.43	138.01	136.07	132.71
22	131.14	132.70	130.65	130.13	127.95	116.47	127.32	127.29	131.06	126.68
23	131.81	131.78	131.76	131.84	131.53	131.76	131.80	131.76	131.79	131.76
24	130.83	130.83	130.78	130.89	130.55	130.78	130.84	130.84	130.81	130.00
25	133.05	133.05	133.03	133.11	133.83	133.03	133.03	133.03	133.06	133.09
26	137.65	137.65	137.63	137.71	137.43	137.63	137.66	137.63	137.63	137.69
$-CH_3$	—	—	—	22.63	—	—	21.99	—	—	—

[a] The peak is overlapped with the peak of CF_3COOD.

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