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Note

^{1}H and ^{13}C NMR of bioactive isochromanylacetylarylhydrazone derivatives†

M. R. L. Santos,[1] M. G. de Carvalho,[1] R. Braz-Filho[2]* and E. J. Barreiro[3]

[1] Curso de Pós-Graduação em Química Orgânica, Universidade Federal Rural do Rio de Janeiro, 23851-970 Seropédica, Rio de Janeiro, Brazil
[2] Setor de Química de Produtos Naturais-LCQUI-CCT, Universidade Estadual do Norte Fluminense, 28015-620 Campos, Rio de Janeiro, Brazil
[3] Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, 21910-240 Rio de Janeiro, RJ, Brazil

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ABSTRACT: Careful analysis of the ^{1}H and ^{13}C NMR spectra of a series of isochromanylacetylarylhydrazone derivatives indicated the diastereomeric selective character in the synthetic step used to obtain the derivatives employing acidic conditions during the condensation of the corresponding acylhydrazides with functionalized arylaldehydes. The relative configuration at C=N was characterized by extensive ^{1}H and ^{13}C NMR experiments. Homonuclear $^{1}H \times {}^{1}H$-COSY and heteronuclear $^{13}C \times {}^{1}H$-COSY-$^{n}J_{CH}$ [$n = 1(^{1}J_{CH})$; $n = 2$ ($^{2}J_{CH}$) and 3 ($^{3}J_{CH}$), COLOC] 2D shift-correlated spectra, along with 1D PND and DEPT ^{13}C NMR and NOE difference spectra ($^{1}H\{^{1}H\}$ NOE) were also used in this deduction. © 1998 John Wiley & Sons, Ltd.

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

INTRODUCTION

In a continuing research program aimed at the design, synthesis and pharmacological evaluation of new bioactive compounds, we have previously described the synthesis and analgesic and antiedematogenic profile of a series of isochromanylacetylarylhydrazone derivatives.[1] From this previous work, we were able to identify the pharmacophoric contribution of the acylarylhydrazone framework to *in vivo* analgesic activity.[1] These results led us to synthesize a further series of isochromanylacetylarylhydrazone derivatives (**1–6**) described in a previous paper.[2]

Considering that the key step in the elected synthetic route could lead to a mixture of the *E*-isomers (**1a–6a**) and *Z*-isomers (**1b–6b**),[3] we decided to investigate the spectroscopic properties of this class of derivatives in order to clarify the diastereomeric ratio and the configuration of the N=C double bond. In addition, these studies could allow the elucidation of the diastereoselectivity of the synthetic condensation step and furnish important information about the configurational purity of the pharmacologically active compounds.

Hence the main purpose of this work was the full structural characterization of compounds **1–6**, especially at the C=N configurational level, using mainly one- and two-dimensional ^{1}H and ^{13}C NMR. We describe the assignments of the ^{1}H and ^{13}C chemicals shifts, confirmed by 2D experiments along with ^{1}H NMR, PND and DEPT ^{13}C NMR and $^{1}H\{^{1}H\}$ NOE difference spectra.[4,5]

EXPERIMENTAL

Infrared (IR) spectra were obtained with a Perkin-Elmer 1600-FT spectrometer, using potassium bromide pellets. The mass spectra were recorded on a GC/VG Micromass 12 instrument at 70 eV. One- (1D) and two-dimensional (2D) ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-200 FT spectrometer (^{1}H, 200 MHz; ^{13}C, 50.3 MHz). The samples were prepared in $CDCl_3$ containing TMS as internal standard, and the chemical shifts are expressed as δ (ppm) relative to TMS. The coupling constants are given in hertz. The pulse sequences used in the homonuclear (^{1}H, ^{1}H-COSY) and heteronuclear (^{13}C, ^{1}H shift correlation $^{1}J_{CH}$ and long-range ^{13}C, ^{1}H shift correlation $^{n}J_{CH}$, $n = 2$ and 3) 2D NMR spectra were the Bruker programs COSY-AU and XHCORR-AU [modulated with $^{1}J_{CH} = 140$ Hz (D3 = $0.5/J_{CH}$ and D4 = $0.5/2J_{CH}$) coupling via one-bond and $^{n}J_{CH} = 7$ Hz ($n = 2$ and 3, COLOC:[4] D3 = $0.5/J_{CH}$ and D4 = $0.5/2J_{CH}$,

* *Correspondence to*: R. Braz-Filho, Setor de Química de Produtos Naturais-LCQUI-CCT, Universidade Estadual do Norte Fluminense, 28015-620 Campos, Rio de Janeiro, Brazil.
e-mail: braz@uenf.br
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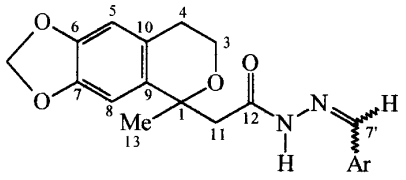
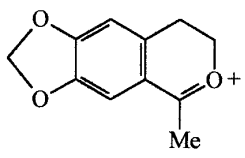
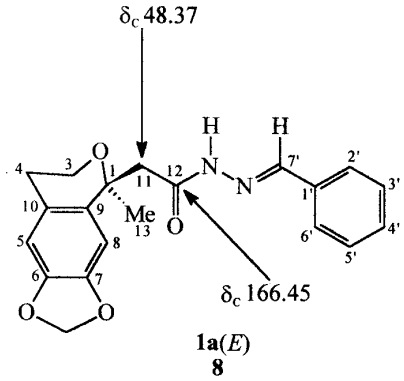


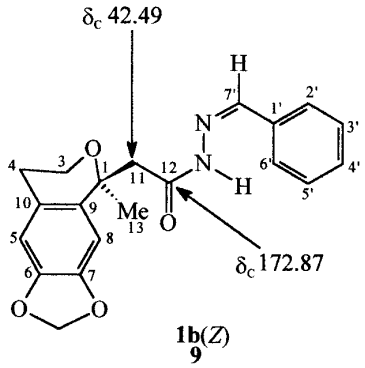
Ar	
1	C_6H_5
2	C_4H_3O
3	4-Me_2N-C_6H_4
4	3-O_2N-C_6H_4
5	4-MeO-C_6H_4
6	4-Br-C_6H_4



7 *m/z* 191 (100 %)



1a(*E*)
8



1b(*Z*)
9

respectively]. The nuclear Overhauser effect (NOE) difference spectra experiments were obtained using the Bruker program NOEDIFF-AU and the DEPT (distortionless enhancement by polarization transfer) spectra by DEPTVAR-AU ($\theta = 90°$ and 135°). The samples for NOE experiments were prepared by bubbling dry nitrogen through the solution for 30 min in order to ensure the removal of oxygen. Splitting patterns of signals in the NMR spectra are as follows: s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br, broad.

RESULTS AND DISCUSSION

The isochromanylacetylarylhydrazones **1–6** were previously synthesized in our laboratory by using classical procedures.[6] The mass spectra of these compounds were used to confirm the molecular formula, which showed the base peak at *m/z* 191 (100%), attributed to the fragment ion **7** as a typical fragmentation pattern in this class of derivatives.

The IR spectra of these compounds exhibited two absorptions at 3400 and 3200 cm^{-1}, resulting from symmetrical and asymmetrical N–H stretching. The presence of a carbonyl group was confirmed by the absorption band at 1665 cm^{-1}.

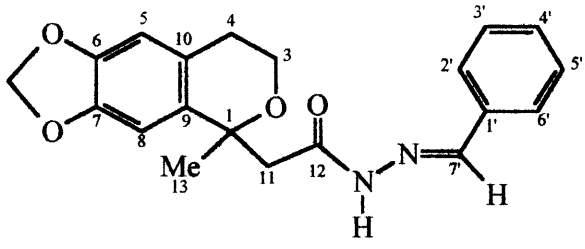
The analysis of the ^1H and ^{13}C NMR spectra revealed, as expected, the presence of both possible isomeric forms: *E*-isomers (**1a–6a**) and *Z*-isomers (**1b–6b**), in a 74–65:26–35 *E*:*Z* ratio. This diasteroselectivity in the condensation step and the N=C bond configuration were also elucidated by analysis of homonuclear ^1H, ^1H-COSY and heteronuclear ^{13}C, ^1H shift correlation $^nJ_{CH}$ [$n = 1$; $n = 2$ and 3 (COLOC)] 2D NMR spectra.[4]

The multiplicities of the carbon signals of all compounds **1–6** were determined by comparative analysis of the PND (proton noise decoupled) and DEPT ^{13}C NMR spectra.

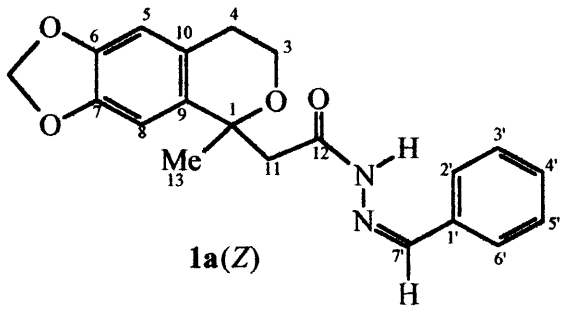
The analysis of ^1H and ^{13}C NMR spectral data for (*E*)-**1a** and (*Z*)-**1b** (Table 1) was used as example. The presence of both *E*- and *Z*-diastereomers in the ^1H and ^{13}C NMR spectra of the mixture of **1a** and **1b** was deduced from the signals at δ_H 8.00 (s, H-7′) and 9.83 (s, HN-12) for **1a** and δ_H 7.70 (s, H-7′) and 9.18 (s, HN-12) for **1b**. The hydrogens H-7′ and HN-12 of the hydrazone moiety appear shielded in **1b** (δ_H 7.70 and 9.18), probably owing to distortion of the coplanar arrangement of the aromatic ring, resulting as a consequence of an attenuation of the deshielding generated by the anisotropic effect of the aromatic ring. Additional significant differences were observed in the chemical shifts of the 2H-11 hydrogens [δ_H 2.90–2.80 (m, **1a**) and 3.46 and 3.10 (d, **1b**)] and carbon CH_2-11 [δ_C 48.37 (**1a**) and 42.49 (**1b**), with a γ-effect of $\Delta\delta_C = -5.88$ ppm (see below) (Table 1).

Unambiguous assignments of the chemical shifts of the hydrogens 2H-11 and 3H-13 and carbons CH_2-11,

Table 1. ^{1}H and ^{13}C NMR spectra data for **1a** and **1b** (200 MHz, $CDCl_3$, TMS as internal standard)[a]



1a(*E*)



1a(*Z*)

	^{13}C × ^{1}H-COSY $^1J_{CH}$		^{13}C × ^{1}H-COSY $^nJ_{CH}$		^{13}C × ^{1}H-COSY $^1J_{CH}$		^{13}C × ^{1}H-COSY $^nJ_{CH}$	
	δ_C	δ_H	$^2J_{CH}$	$^3J_{CH}$	δ_C	δ_H	$^2J_{CH}$	$^3J_{CH}$
C:								
1	75.97	—	3H-13		75.88	—		
6	146.25	—		H-8	145.77	—		H-8
7	146.37	—		H-5	145.89	—		H-5
9	132.34	—		3H-13; H-5	134.58	—		3H-13; H-5
10	126.48	—		H-8	125.79	—		H-8
12	166.45	—	NH; 2H-11		172.87	—	2H-11	
1′	133.48		H-7′		133.85			
CH:								
5	108.25	6.50 (s)			106.25	6.52 (s)		
8	105.39	6.59 (s)			105.51	6.66 (s)		
2′, 6′	127.46	7.70 (m)		H-7; H-4′	126.91	7.61 (m)		H-7′; H-4′
3′, 5′	128.39	7.40 (m)			128.54	7.40 (m)		
4′	130.12	7.40 (m)			129.76	7.40 (m)		
7′	147.10	8.00 (s)		HN-12	143.75	7.70 (s)		
CH_2:								
3	59.72	4.10 (m)			59.86	4.00 (m)		
4	29.18	2.80 (m)		H-5	29.24	2.75 (m)		
11	48.37	2.90 (m)	3H-13		42.49	3.46 (d, J = 14)	3H-13	
						3.10 (d, J = 14)		
OCH_2O	100.80	5.90 (s)			100.60	5.80 (s)		
CH_3:								
13	27.20	1.56 (s)			28.36	1.63 (s)		
HN-12	—	9.83 (s)			—	9.18 (s)		

[a] Chemical shifts (δ, ppm) and coupling constants (J, Hz) of the hydrogen atoms were obtained from the ^{1}H NMR spectrum. The homonuclear ^{1}H, ^{1}H-COSY 2D NMR spectrum was also used for these assignments. Multiplicity of signals of carbon atoms deduced by comparative analysis of PND and DEPT ^{13}C NMR spectra.

C-12 and CH_3-13 of both stereoisomers (**1a** and **1b**) were deduced from 2D ^{1}H, ^{1}H-COSY and 2D ^{13}C, ^{1}H shift correlation $^nJ_{CH}$ ($n = 1$; $n = 2$ and 3) spectra through cross peaks which revealed the following connectivities: (a) CH_2-11 of **1a** (δ_C 48.37) and 2H-11 hydrogens (δ_H 2.90–2.80, $^1J_{CH}$); (b) CH_2-11 of **1b** (δ_C 42.49) and 2H-11 hydrogens [δ_H 3.46 (d, J = 14 Hz) and δ_H 3.10 (d, J = 14 Hz, $^1J_{CH}$)]; (c) CH_2-11 of **1a** (δ_C 48.37) and 3H-13 (δ_H 1.56, $^3J_{CH}$); (d) CH_2-11 of **1b** (δ_C 42.49) and 3H-13 (δ_H 1.63, $^3J_{CH}$); (e) carbonyl carbon C-12 (δ_C 166.45) of **1a** and HN-12 (δ_H 9.83, $^2J_{CH}$) and 2H-11 (δ_H 2.90–2.80, $^2J_{CH}$); (f) C-12 of **1b** (δ_C 172.87) and 2H-11 (δ_H 3.46 and 3.10, $^2J_{CH}$). Steric hindrance in **1b** may be used to account for the presence of a conformation with distortion in the coplanar arrangement. As a consequence, the chemical shift of the carbonyl carbon is increased (δ_C 172.87), which is consistent with the inhibition of an additional mesomeric effect involving this carbonyl group (deshielded). All these observations are entirely in accordance with the structures shown for **1a** and **1b**, supporting the modification of the chemical shifts.

A difference in the chemical shifts of the aromatic hydrogens (H-5 and H-8) in the pair of the diastereomers was also observed. The ambiguity in this assignment was eliminated by using NOE experiments, which revealed the spatial proximity of H-8 and 3H-13 (dipolar coupling). Irradiation at δ_H 1.56 (3H-13) of **1a** and δ_H 1.63 (3H-13) of **1b** revealed 3% NOEs at δ_H 6.59 (H-8) of **1a** and δ_H 6.66 (H-8) of **1b**. The presence of a cross peak revealing the connectivity of carbon C-4 (δ_C 29.18) and hydrogen H-5 (δ_H 6.50, $^3J_{CH}$), observed in the 2D ^{13}C, ^{1}H shift correlation $^nJ_{CH}$ ($n = 2$ and 3) spectrum (**1a**, Table 1) was also used to confirm these assignments. As expected, the chemical shifts of C-8 at δ_C 105.39 for **1a** and 105.51 for **1b** are different from C-5, at δ_C 108.25 for **1a** and 106.25 for **1b** as a consequence of

Table 2. ^{1}H NMR spectral data for **1–6** (200 MHz, $CDCl_3$, TMS as internal standard)[a]

H	**1a** (*E*)	**1b** (*Z*)	**2a** (*E*)	**2b** (*Z*)	**3a** (*E*)	**3b** (*Z*)	**4a** (*E*)	**4b** (*Z*)	**5a** (*E*)	**5b** (*Z*)	**6a** (*E*)	**6b** (*Z*)
3	4.10 (m)	4.00 (m)	3.80 (m)	4.00 (m)	4.10 (m)	4.10 (m)	3.98 (m)	4.06 (m)	3.95 (m)	4.02 (m)	4.03 (m)	3.84 (m)
4	2.80 (m)	2.75 (m)	2.65 (m)	2.65 (m)	2.80 (m)	2.90 (m)	2.84 (m)	2.58 (m)	2.57 (m)	2.75 (m)	2.67 (m)	2.67 (m)
5	6.50 (s)	6.52 (s)	6.49 (s)	6.44 (s)	6.49 (s)	6.52 (s)	6.49 (s)	6.57 (s)	6.48 (s)	6.49 (s)	6.49 (s)	6.51 (s)
8	6.59 (s)	6.66 (s)	6.57 (s)	6.64 (s)	6.59 (s)	6.61 (s)	6.58 (s)	6.64 (s)	6.58 (s)	6.65 (s)	6.58 (s)	6.63 (s)
11	2.90 (m)	3.46 (d, $J = 14$) 3.10; (d, $J = 14$)	2.87 (d, $J = 14$) 2.83 (d, $J = 14$)	3.45 (d, $J = 14$) 3.03; (d, $J = 14$)	2.90 (d, $J = 12$) 2.80 (d, $J = 12$)	3.50 (d, $J = 12$) 3.06 (d, $J = 12$)	2.8–2.9 (m)	3.41 (d, $J = 12$) 3.18 (d, $J = 12$)	2.76 (m) 2.94 (m)	3.45 (d, $J = 13$) 3.07 (d, $J = 13$)	2.85 (d, $J = 15$) 2.82 (d, $J = 15$)	3.48 (d, $J = 13$) 3.11 (d, $J = 13$)
13	1.56 (s)	1.63 (s)	1.54 (s)	1.60 (s)	1.55 (s)	1.62 (s)	1.55 (s)	1.52 (s)	1.55 (s)	1.62 (s)	1.62 (s)	1.55 (s)
2′	7.70 (m)	7.61 (m)	7.24 (s)	7.20 (s)	7.57 (d, $J = 9.2$)	7.47 (d, $J = 9.0$)	8.20 (m)	8.16 (m)	7.61 (m)	7.54 (m)	7.44 (m)	7.48 (m)
3′	7.40 (m)	7.40 (m)	6.67 (m)	6.67 (m)	6.62 (d, $J = 9.2$)	6.66 (d, $J = 9.0$)	—	—	6.86 (m)	6.86 (m) m	7.53 (m)	7.57 (m)
4′	7.40 (m)	7.40 (m)	7.46 (m)	7.46 (m)	—	—	8.11 (m)	8.07 (m)	—	—	—	—
5′	7.40 (m)	7.40 (m)	8.21 (s)	7.60 (s)	6.62 (d, $J = 9.2$)	6.66 (d, $J = 9.0$)	7.54 (m)	7.54 (m)	6.86 (m)	6.86 (m)	7.53 (m)	7.57 (m)
6′	7.70 (m)	7.61 (m)	—	—	7.57 (d, $J = 9.2$)	7.47; (d, $J = 9.0$)	7.92 (m)	7.81 (m)	7.61 (m)	7.54 (m)	7.44 (m)	7.48 (m)
7′	8.00 (s)	7.70 (s)	—	—	7.83 (s)	7.58 (s)	8.43 (s)	8.21 (s)	7.92 (s)	7.65 (s)	7.99 (s)	7.67 (s)
OCH_2	5.90 (s)	5.80 (s)	5.88 (s)	5.88 (s)	5.90 (s)	5.89 (s)	5.87 (s)	5.82 (s)	5.87 (s)	5.90 (s)	5.89 (s)	5.83 (s)
HN-12	9.83 (s)	9.18 (s)	9.79 (s)	9.40 (s)	9.64 (s)	8.90 (s)	10.02 (s)	9.96 (s)	9.75 (s)	9.34 (s)	9.85 (s)	9.67 (s)

[a] Chemical shifts (δ) in ppm and coupling constants (J) in Hz. Homonuclear ^{1}H, ^{1}H-COSY and heteronuclear ^{13}C, ^{1}H shift correlation [$^{1}J_{CH}$; $^{n}J_{CH}$ ($n = 2$ and 3, COLOC)] 2D NMR spectra were also used for these assignments.

Table 3. ^{13}C NMR spectral data for **1–6** (50.3 MHz, $CDCl_3$, TMS as internal standard)[a]

C	**1a** (*E*)	**1b** (*Z*)	**2a** (*E*)	**2b** (*Z*)	**3a** (*E*)	**3b** (*Z*)	**4a** (*E*)	**4b** (*Z*)	**5a** (*E*)	**5b** (*E*)	**6a** (*E*)	**6b** (*Z*)
1	75.97	75.88	75.79	75.79	75.82	75.82	76.10	76.10	75.94	75.94	75.99	75.90
3	59.72	59.86	59.57	59.71	59.56	59.72	59.97	59.97	59.72	59.86	59.78	59.91
4	29.18	29.24	29.03	28.75	29.09	29.15	29.37	29.37	29.22	29.22	29.22	29.22
5	108.25	106.25	108.04	111.63	108.14	108.14	108.43	108.43	108.26	108.26	108.30	108.30
6	146.25	145.77	146.10	145.70	146.19	146.00	146.67	146.04	146.49	145.78	146.35	145.80
7	146.37	145.89	146.19	145.77	146.17	146.00	146.67	146.04	146.42	145.92	146.46	145.88
8	105.39	105.51	105.29	111.63	105.46	105.32	105.53	105.39	105.26	105.42	105.50	105.38
9	132.34	134.58	132.36	134.54	132.52	134.76	132.39	132.39	132.55	134.77	132.85	134.50
10	126.48	125.79	125.82	126.10	125.76	126.33	125.87	125.87	125.85	126.30	125.78	126.52
11	48.37	42.49	48.54	42.31	48.07	42.29	48.98	43.14	48.43	42.60	48.51	42.61
12	166.45	172.87	166.60	172.78	165.84	171.97	166.91	172.97	166.20	172.39	166.53	172.89
13	27.20	28.36	27.15	28.23	27.09	28.50	27.36	28.52	27.20	28.40	27.21	28.41
1′	133.48	133.85	149.06	149.19	120.96	121.54	135.76	134.28	126.67	126.52	132.22	132.52
2′	127.46	126.91	—	—	128.89	128.16	122.25	121.58	129.05	128.42	128.82	128.30
3′	128.39	128.54	144.17	144.00	111.32	111.55	148.35	148.40	113.90	114.05	131.67	131.80
4′	130.12	129.76	112.87	112.37	151.44	151.20	124.38	124.11	161.23	160.94	124.38	123.93
5′	128.39	128.54	133.38	129.82	111.32	111.55	129.56	129.73	113.90	114.04	131.67	131.80
6′	127.46	126.91			128.89	128.16	132.58	132.33	129.05	128.42	128.82	128.30
7′	147.10	143.75	137.31	137.39	147.90	144.48	144.88	140.78	147.06	143.32	142.44	134.50
OCH_2O	100.80	100.60	100.68	100.50	100.65	100.49	100.96	100.75	100.79	100.59	100.87	100.68

[a] Chemical shifts (δ) in ppm. The multiplicity of the signal was deduced by comparative analysis of the PND and DEPT spectra. Homonuclear ^{1}H, ^{1}H-COSY and heteronuclear ^{13}C, ^{1}H shift correlation [$^1J_{CH}$; $^nJ_{CH}$ (n = 2 and 3, COLOC)] 2D NMR spectra were also used for these assignments.

the γ-effect of the CH_2-11 methylene and CH_3-13 methyl groups. Analogous modification was observed in the chemical shifts of carbon CH_2-11 in **1a** (δ_C 48.37) and **1b** (δ_C 42.49). This is consistent with a γ-effect [$\Delta\delta_C = 42.49$ (**1b**) $- 48.37$ (**1a**) $= -5.88$ ppm], attributed to the nitrogen atom of the hydrazone moiety, as shown for **1a** and **1b** including the relative configuration of the chiral carbon C-1 (**8** and **9**).

The ^{1}H (Table 2) and ^{13}C (Table 3) chemical shifts assignments for the bicyclic moiety of **2–6** were subsequently made by comparative analysis with data obtained for **1** (after attribution of the chemical shifts of the remaining hydrogen and carbon atoms, Table 1) and aryl groups by application of the usual shift parameters, observed multiplicities of the signals of carbon atoms, comparison with models and 2D shift-correlated spectra when necessary (Tables 2 and 3).

The ^{1}H and ^{13}C NMR spectra of **1–6** revealed the presence of only the hydrazone tautomeric form. These results (Table 2) are in agreement with other ^{1}H NMR studies of phenylhydrazones,[7] including the minor chemical shifts for hydrogen H-7′ of the *Z*-stereoisomers **1b–6b** when compared with the *E*-stereoisomers **1b–6b** (Table 2).

The hydrogen chemical shift dependence of **1a** and **1b** on solvent was also investigated (Table 4). Specific solvent effects on the resonance positions of the nuclei of dissolved compounds consist mainly of hydrogen-bonding effects and aromatic solvent-induced shifts (ASIS effects).[8] DMSO-d_6 showed major shifts for HN-12 (δ_H 11.21) of **1b** when compared with **1a** (δ_H 11.11). A reverse of the order of appearance of these signals is observed in $CDCl_3$ [δ_H 9.82 (**1a**) and 9.03 (**1b**)] and is maintained in benzene-d_6 [δ_H 9.93 (**1a**) and 9.53 (**1b**)] (Table 4). These results suggest the presence of a more effective intermolecular hydrogen bonding (solvent–solute) in DMSO-d_6. Table 4 also summarizes the difference in the chemical shifts of hydrogen H-7′ in **1b** and **1a**. A positive value of $\Delta\delta$(ASIS) indicates a deshielding, as can be observed by comparison involv-

Table 4. ^{1}H NMR chemical shifts (δ, ppm) of the hydrogen HN-12 and CH-7′ in $CDCl_3$, DMSO-d_6, benzene-d_6 and $\Delta\delta$(ASIS) $= \delta(C_6D_6) - \delta(CDCl_3)$ for **1**[a]

Compound	H	$CDCl_3$	DMSO-d_6	Benzene-d_6	$\Delta\delta$(ASIS) (ppm)
1a	HN-12 (*E*)	9.82	11.11	9.93	0.11
1b	HN-12 (*Z*)	9.03	11.21	9.53	0.53
1a	CH-7′ (*E*)	8.00	8.16	7.66	− 0.34
1b	CH-7′ (*Z*)	7.72	7.94	8.43	0.71

[a] A positive value of $\Delta\delta$(ASIS) indicates a downfield shift relative to the signal in $CDCl_3$ as solvent.

ing the aliphatic solvent $CDCl_3$.[9] The exact geometry of these transient complexes involving the specific interaction of solvent–solute molecules with regional dependence is not known. The induced magnetic field of the π electrons of benzene (anisotropic effect) deshields $(+\Delta\delta_H)$ the hydrogens located in the peripheral region and shields $(-\Delta\delta_H)$ those above and below the molecular plane.

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