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Synthesis and GIAO NMR Calculations for Some Novel 4-Heteroarylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one Derivatives: Comparison of Theoretical and Experimental ^{1}H- and ^{13}C- Chemical Shifts

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Abstract: 3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) reacted with 5-methylfuran-2-carboxyaldehyde to afford the corresponding 3-alkyl(aryl)-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**). Four newly synthesized compounds have been characterized by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data. In addition, isotropic ^{1}H- and ^{13}C-nuclear magnetic shielding constants of compounds **3** were calculated by employing the direct implementation of the gauge-including-atomic-orbital (GIAO) method at the B3LYP density functional and HF levels of the theory. The geometry of each compound has been optimized using a 6-311G basis set. Nuclear shielding constants were also calculated by using 6-311G basis set. Theoretical values are compared to the experimental data.

Keywords: ^{1}H-NMR, ^{13}C-NMR, GIAO, NMR chemical shifts, 4,5-dihydro-1*H*-1,2,4-triazol-5-ones, Schiff base, syntheses.

Introduction

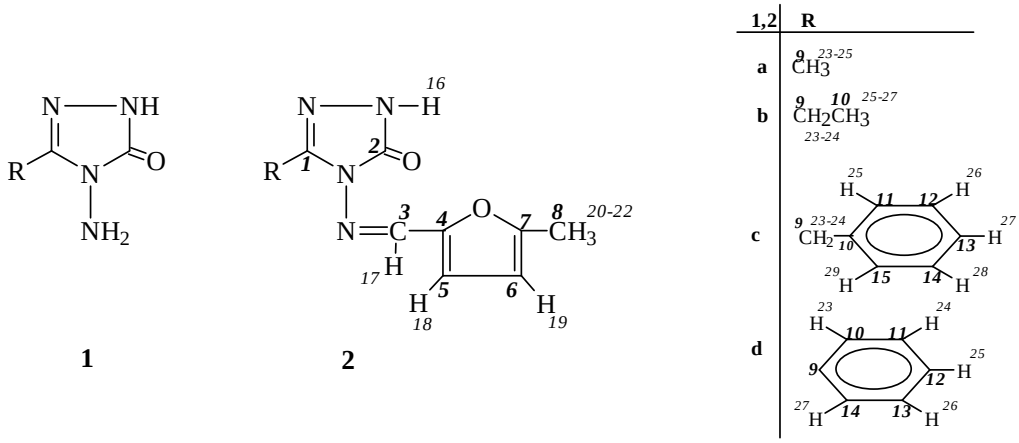
Several articles on the synthesis of some N-arylidenamino-1,2,4-triazole and N-arylidenamino-4,5-dihydro-1H-1,2,4-triazol-5-one derivatives have been published [1-6]. In addition, 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives are reported to show a broad spectrum of biological

activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, anti-inflammatory, antitumor and anti-HIV properties [7-12]. These reports prompted us to synthesize some new potential biological active 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives.

Besides, NMR spectroscopy has proved to be an exceptional tool to elucidate structure and molecular conformation. Ab initio and DFT calculation of NMR shielding at very accurate levels of approximation are available in literature [13]. The widely used methods to calculate chemical shifts are as follows: IGLO (individual gauge localized orbital), LORG (localized or Loacaorbital origin) and GIAO (gauge independent or invariant or including atomic orbital). The GIAO approach [14] is known to give satisfactory chemical shifts for different nuclei [14-16] with larger molecules, yet these quantum chemical calculations often have to be limited to isolated (gas-phase) molecules in some preferred (optimized) structures, while experimental NMR spectra are commonly statically averages affected by dynamic process such as conformational equilibria as well as intra and/or intramolecular interactions.

In the present paper DFT and Ab inito method was used to analyze the experimental ^{1}H and ^{13}C data of four novel 3-alkyl(aryl)-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**), which were synthesized by the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with 5-methylfuran-2-carboxyaldehyde (Scheme 1).

Scheme 1



Experimental

General

IR spectra were recorded using potassium bromide disks on a Perkin-Elmer 1000 FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in deuterated dimethyl sulfoxide with tetramethylsilane as internal standard on a Gemini-Varian spectrometer at 200 MHz and 50 MHz, respectively. UV absorption spectra were measured for ethanol solutions in 10 mm quartz cells between 200 and 400 nm using a Shimadzu-3101 PC UV-VIS-NIR spectrophotometer. Melting points were taken on a Electrothermal 9100 digital melting point apparatus. Chemicals were supplied from Fluka and Merck. The starting compounds **1a-d** were prepared from the reactions of the corresponding ester ethoxy-carbonylhydrazones with hydrazine hydrate according to the literature [17].

*General Method for the Preparation of 3-Alkyl(aryl)-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (**2**)*

3-Alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-one (**1**) (0.01 mol) was dissolved in acetic acid (15 mL) and treated with methyl 5-methylfuran-2-carboxyaldehyde (1.10 mL, 0.01 mol). The mixture was refluxed for 1 h and then evaporated at 50-55 °C in *vacuo*. Several recrystallizations of the residue from an appropriate solvent gave pure compound **2**.

3-Methyl-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**2a**).

White crystals, yield 90 %; m.p. 164 °C (H_2O); Calculated for $C_9H_{10}N_4O_2$ (206.20): 52.42% C, 4.89% H, 27.17% N; found: 52.60% C, 5.05% H, 27.44% N; ^{1}H-NMR: δ 2.23 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 6.34 (d, 1H, Ar-H; *J*=2.44 Hz), 7.06 (d, 1H, Ar-H; *J*=3.22 Hz), 9.50 (s, 1H, N=CH), 11.81 (s, 1H, NH); ^{13}C-NMR: δ 13.02, 15.38 (2CH_3), 110.90, 121.35, 144.78, 158.10 (heteroaromatic carbons), 145.90 (triazole C-3), 148.64 (N=CH), 153.10 (triazole C-5); IR: 3218 (NH), 1697 (C=O), 1593 (C=N) cm^{-1}; UV λ_{max} (ε, $L\cdot mol^{-1}\cdot cm^{-1}$): 312 (23375) nm.

3-Ethyl-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**2b**).

White crystals, yield 80 %; m.p. 179 °C (EtOH-H_2O, 1:3); Calculated for $C_{10}H_{12}N_4O_2$ (220.23): 54.54% C, 5.49% H, 25.44% N; found: 54.38% C, 5.55% H, 25.38% N; ^{1}H-NMR: δ 1.18 (t, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.62 (q, 2H, CH_2), 6.32 (d, 1H, Ar-H), 7.03 (d, 1H, Ar-H), 9.49 (s, 1H, N=CH), 11.82 (s, 1H, NH); ^{13}C-NMR: δ 11.62, 15.33 (2CH_3), 20.26 (CH_2), 110.85, 121.09, 144.77, 158.03 (heteroaromatic carbons), 148.71 (triazole C-3), 149.65 (N=CH), 153.25 (triazole C-5); IR: 3199 (NH), 1701 (C=O), 1593 (C=N) cm^{-1}; UV λ_{max} (ε, $L\cdot mol^{-1}\cdot cm^{-1}$: 312 (24846) nm.

3-Benzyl-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**2c**).

White crystals, yield 85 %; m.p. 166 °C (acetic acid-H_2O, 1:3). Calculated for $C_{15}H_{14}N_4O_2$ (282.30): 63.82% C, 5.00% H, 19.85% N; found: 63.66% C, 4.86% H, 19.72% N; ^{1}H-NMR: δ 2.38 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.33 (d, 1H, Ar-H; *J*=3.30 Hz), 7.05 (d, 1H, Ar-H; *J*=3.30 Hz),7.23-7.33 (m, 5H, Ar-H), 9.49 (s, 1H, N=CH), 11.97 (s, 1H, NH); ^{13}C-NMR: δ 15.37 (CH_3), 32.73 (CH_2), 128.47, 130.14 (2C), 130.77 (2C), 137.41 (aromatic carbons), 110.92, 120.96, 144.72, 158.11 (heteroaromatic carbons), 147.86 (triazole C-3), 148.75 (N=CH), 153.09 (triazole C-5); IR: 3210 (NH), 1682 (C=O), 1574 (C=N), 755, 695 (monosubstituted benzenoid ring) cm^{-1}; UV λ_{max} (ε, $L\cdot mol^{-1}\cdot cm^{-1}$: 311 (28235), 205 (24846) nm.

3-Phenyl-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1H-1,2,4-triazol-5-one (**2d**).

White crystals, yield 65 %; m.p. 217 °C (acetic acid-H_2O, 1:3); Calculated for $C_{14}H_{12}N_4O_2$ (268.28): 62.68% C, 4.51% H, 20.88% N; found: 62.20% C, 5.23% H, 20.77% N; ^{1}H-NMR: δ 2.36 (s, 3H, CH_3), 6.36 (d, 1H, Ar-H; *J*=3.22 Hz), 7.12 (d, 1H, Ar-H; *J*=3.30 Hz),7.50-7.92 (m, 5H, Ar-H), 9.39 (s, 1H, N=CH), 12.37 (s, 1H, NH); ^{13}C-NMR: δ 15.39 (CH_3), 128.52, 129.64 (2C), 130.26 (2C), 131.82

(aromatic carbons), 111.06, 121.64, 146.26, 158.44 (heteroaromatic carbons), 147.63 (triazole C-3), 148.59 (N=CH), 153.26 (triazole C-5); IR: 3160 (NH), 1697 (C=O), 1582 (C=N), 750, 690 (monosubstituted benzenoid ring) cm^{-1}. UV λ_{max} (ε, $L \cdot mol^{-1} \cdot cm^{-1}$: 313 (21712), 228 (12430), 202 (26032) nm.

Computational Methods

The calculations of the new compounds are given in Tables 1-4. The numbering system is shown in Scheme 1. All the structures were fully optimized with the Gaussian 03 program[18]. After the optimization, ^{1}H- and ^{13}C- chemical shifts were calculated with GIAO method [19,20], using corresponding TMS shielding calculated at the same theoretical levels as the reference. All the computations were done using an IBM x225 Xeon computer that has 2048 MB ram. Linear correlation analyses were carried out using SigmaPlot program. The quality of each correlation was judged examining R, the Pearson correlation coefficient [21].

Table 1. Comparision between experimental and calculated chemical shifts (ppm) of **2a**.

Nuclei	Experimental	B3LYP/6-311G	Diff	HF/6-311G	Diff
C-2	153.10	156.22	-3.12	166.13	-13.03
C-1	145.90	157.21	-11.31	163.06	-17.16
C-9	13.02	14.51	-1.49	14.39	-1.37
C-3	148.64	153.12	-4.48	168.01	-19.37
C-5	121.35	131.09	-9.74	135.58	-14.23
C-4	144.78	161.44	-16.66	153.37	-8.59
C-7	158.10	169.97	-11.87	170.68	-12.58
C-6	110.90	118.13	-7.23	115.65	-4.75
C-8	15.38	15.70	-0.32	15.74	-0.36
H-16	11.81	6.98	4.83	6.96	4.85
H-23	2.23	2.10	0.13	2.30	-0.07
H-24	2.23	2.07	0.16	2.04	0.19
H-25	2.23	2.55	-0.32	2.60	-0.37
H-17	9.50	8.50	1.00	9.32	0.18
H-18	7.06	6.65	0.41	7.25	-0.19
H-19	6.34	6.21	0.13	6.37	-0.03
H-20	2.38	2.59	-0.21	2.67	-0.29
H-21	2.38	2.53	-0.15	2.59	-0.21
H-22	2.38	2.19	0.19	2.32	0.06

Table 2. Comparision between experimental and calculated chemical shifts (ppm) of **2b**.

Nuclei	Experimental	B3LYP/6-311G	Diff	HF/6-311G	Diff
C-2	153.25	156.43	-3.18	166.21	-12.96
C-1	148.71	161.11	-12.40	166.41	-17.70
C-9	20.26	24.85	-4.59	20.72	-0.46
C-3	149.65	153.17	-3.52	168.08	-18.43
C-5	121.09	131.05	-9.96	135.42	-14.33
C-4	144.77	161.39	-16.62	153.45	-8.68
C-7	158.03	169.85	-11.82	170.59	-12.56
C-6	110.85	117.91	-7.06	115.63	-4.78
C-8	15.33	15.70	-0.37	15.74	-0.41
C10	11.62	10.00	1.62	9.64	1.98
H-16	11.82	6.99	4.83	6.95	4.87
H-23	2.62	2.43	0.19	2.22	0.40
H-24	2.62	2.99	-0.37	2.84	-0.22
H-17	9.49	8.48	1.01	9.32	0.17
H-18	7.03	6.66	0.37	7.22	-0.19
H-19	6.32	6.21	0.11	6.37	-0.05
H-20	2.37	2.59	-0.22	2.67	-0.30
H-21	2.37	2.54	-0.17	2.58	-0.21
H-22	2.37	2.20	0.17	2.31	0.06
H-25	1.18	1.02	0.16	1.09	0.09
H-26	1.18	1.45	-0.27	1.60	-0.42
H-27	1.18	1.50	-0.32	1.55	-0.37

Table 3. Comparision between experimental and calculated chemical shifts (ppm) of **2c**.

Nuclei	Experimental	B3LYP/6-311G	Diff	HF/6-311G	Diff
C-2	153.09	159.30	-6.21	166.94	-13.85
C-1	147.86	159.77	-11.91	164.70	-16.84
C-9	32.73	37.84	-5.11	32.66	0.07
C-3	148.73	148.40	0.33	157.99	-9.26
C-5	120.96	118.92	2.04	122.18	-1.22
C-4	144.72	164.44	-19.72	158.32	-13.60
C-7	158.11	170.31	-12.20	169.14	-11.03
C-6	110.92	117.05	-6.13	115.29	-4.37
C-8	15.37	15.62	-0.25	15.69	-0.32
C-10	137.41	142.28	-4.87	144.01	-6.60
C-11	130.77	137.36	-6.59	140.57	-9.80
C-12	130.14	134.64	-4.50	138.41	-8.27

Table 3. Cont.

C-16	128.47	133.57	-5.10	137.07	-8.60
C-14	130.14	134.64	-4.50	138.41	-8.27
C-15	130.77	137.36	-6.59	140.57	-9.80
H-16	11.97	6.94	5.03	6.92	5.05
H-23	4.00	3.91	0.09	3.93	0.07
H-24	4.00	3.91	0.09	3.93	0.07
H-17	9.49	10.50	-1.01	10.73	-1.24
H-18	7.05	7.15	-0.10	7.56	-0.51
H-19	6.33	6.20	0.13	6.38	-0.05
H-20	2.38	2.58	-0.20	2.65	-0.27
H-21	2.38	2.58	-0.20	2.65	-0.27
H-22	2.38	2.15	0.23	2.27	0.11
H-25	7.23	7.23	0	7.74	-0.51
H-26	7.33	7.33	0	7.84	-0.51
H-27	7.30	7.27	0.03	7.77	-0.47
H-28	7.33	7.33	0	7.84	-0.51
H-29	7.23	7.23	0	7.74	-0.51

Table 4. Comparison between experimental and calculated chemical shifts (ppm) of **2d**.

Nuclei	**Experimental**	**B3LYP/6-311G**	**Diff**	**HF/6-311G**	**Diff**
C-2	153.26	159.80	-6.54	167.27	-14.01
C-1	147.63	156.02	-8.39	162.39	-14.76
C-9	130.26	134.41	-4.15	134.60	-4.34
C-3	148.59	148.96	-0.37	158.14	-9.55
C-5	121.64	119.29	2.35	122.35	-0.71
C-4	146.26	164.62	-18.36	158.57	-12.31
C-7	158.44	170.46	-12.02	169.08	-10.64
C-6	111.06	117.09	-6.03	115.29	-4.23
C-8	15.39	15.73	-0.34	15.69	-0.30
C-10	129.64	134.89	-5.25	141.15	-11.51
C-11	129.64	134.20	-4.56	136.67	-7.03
C-12	131.82	136.36	-4.54	141.72	-9.90
C-13	128.52	133.61	-5.09	135.51	-6.99
C-14	130.26	135.89	-5.63	142.08	-11.82
H-16	12.37	7.27	5.10	7.27	5.10
H-17	9.39	10.72	-1.33	10.87	-1.48
H-18	7.12	7.16	-0.04	7.48	-0.36
H-19	6.36	6.22	0.14	6.36	0
H-20	2.36	2.59	-0.23	2.65	-0.29

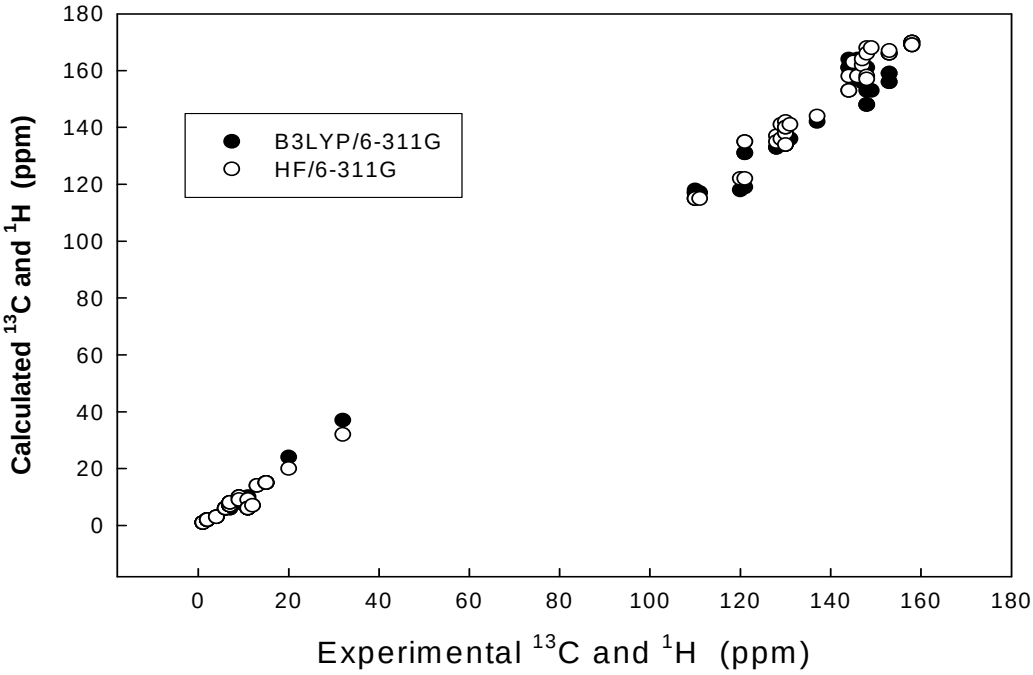
Table 4. Cont.

H-21	2.36	2.59	-0.23	2.65	-0.29
H-22	2.36	2.16	0.20	2.26	0.10
H-23	7.90	8.28	-0.38	8.70	-0.80
H-24	7.54	7.42	0.12	7.92	-0.38
H-25	7.50	7.39	0.11	8.04	-0.54
H-26	7.54	7.41	0.13	7.90	-0.36
H-27	7.92	8.43	-0.51	8.57	-0.65

Results and Discussion

The geometry optimizations were performed at the B3LYP/6-311G and HF/6-311G levels [22] with the Gaussian G03 program package [18]. The ^{1}H- and ^{13}C- chemical shifts were calculated with the B3LYP/6-311G HF/6-311G optimized geometries by GIAO method [19]. In order to obtain the calculated results comparable with the experimental data, we have transformed the absolute shieldings returned by the program in chemical shifts subtracting to the absolute shielding of TMS and the absolute shieldings of the molecule in exam. $\sigma_{rel.} = \sigma_{rel} - \sigma_{abs}$. In particular, each value of the absolute shieldings of the TMS was obtained with the same level of the absolute shieldings of the TMS, which was found with the same level of theory used in the determination of absolute shieldings of the compounds. The experimental and theoretical results, along with the error for each compound, are presented in Tables 1-4. A least squares fit of all data, as shown in Figure 1, shows a strong linear relationship with an R-square value of 0.997 at B3LYP/6-311G and 0.998 at HF/6-311G basis set, respectively.

Figure 1. Plot of overall ^{1}H- and ^{13}C- data



This relationship is also reflected in the results for the individual compounds, in which R-square values are consistently above 0.727. The overall standard error of estimate is 3.43 and 2.78 at B3LYP/6-311G and HF/6-311G basis sets, respectively. The approach of Forsyth and Sebag [23] for emprically scaling theoretical data linear regressions, $\delta_{calc} = a + b\delta_{exp}$ was made and details are summarized in Table 5.

Table 5. Linear regression between experimental chemical shifts and calculated isotropic shielding constants (ppm), $\boldsymbol{\delta_{calc} = a + b\delta_{exp}}$, (r= correlation coefficient, SE=standard error).

Compd. no	Parameter	B3LYP/6-311G ^{13}C	B3LYP /6-311G ^{1}H	HF/6-311G ^{13}C	HF/6-311G ^{1}H
2a	**a**	0.386	1.049	-0.879	1.087
	b	1.062	0.656	1.098	0.691
	r	0.998	0.934	0.998	0.912
	SE	4.408	0.954	4.012	1.179
2b	**a**	0.313	0.847	-2.282	0.875
	b	1.062	0.678	1.107	0.716
	r	0.998	0.944	0.998	0.926
	SE	4.572	0.887	3.595	1.090
2c	**a**	0.124	1.250	-3.353	1.345
	b	1.049	0.750	1.094	0.777
	r	0.993	0.870	0.997	0.853
	SE	5.180	1.251	3.166	1.400
2d	**a**	-2.657	1.280	-3.340	1.345
	b	1.065	0.750	1.093	0.776
	r	0.992	0.870	0.996	0.852
	SE	4.734	1.251	3.348	1.400

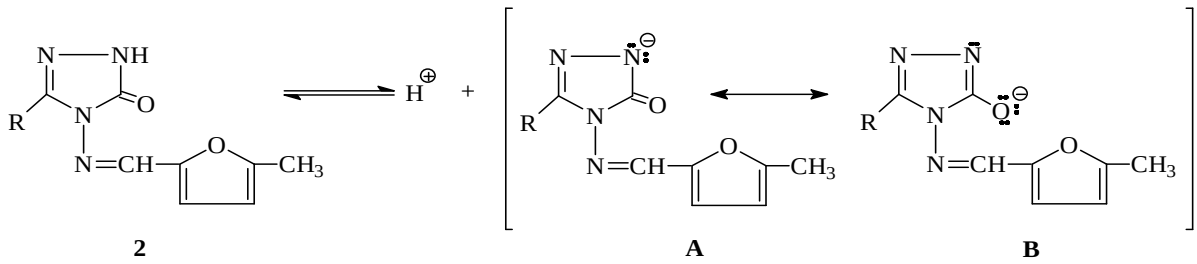
A linear correlation between theoretical and experimental carbon and proton chemical shifts is clearly seen in Tables 1-4. A good quantitative agreement within 1-10 ppm at Tables 3 and 4 is observed for the aromatic carbons of these compounds, which appear to be very satisfactory. It is due to the fact that the experimental chemical shifts in solution are subject to solvent, concentration and temperature effects. Differences are particularly apparent in the aromatic carbons in which chemical shifts are sensitive to substitution. It can also be seen that chemical shifts of the aromatic carbon atoms are not well produced by 6-311G basis set. This is probably due to the sensitivity of the calculations to geometry and rapid rotation of these groups, particularly NMR time scale.

As can be seen at Tables 1-4, the errors range between 3.12-6.21 ppm at B3LYP/6-311G and 12.46-13.85 ppm at HF/6-311G ppm for C-2 atom which belongs to carbonyl group. The carbonyl carbon atom C-2 is more deshielded as a consequence of binding to the oxygen atoms. Similar effect was also observed for C-4 and C-7 atoms connected to the oxygen atom.. All the statistical calculations

were affected by these results. In particular, the large differences calculated for the C-4, C-5, C-6 and C-7 carbons in all compounds were observed between 2 and 19 ppm. This deviation is due to the geometric distortions of furan ring caused by steric hinderance of the methyl substituent. A good quantitative agreement within 4.5-6.0 ppm at B3LYP/6-311G and 6.60-11.82 ppm at HF/6-311G at Tables 3 and 4 were observed for aromatic carbons of **2c** and **2d** compounds, which appeared very satisfactory. This situation derives from the fact that the experimental chemical shifts in solution are subject to solvent, concentration and temperature effects.

The standard errors (SE) and regression coefficients (r) given in Table 5 indicate that HF method provides a some-what better fit for ^{13}C chemical shifts than the DFT(B3LYP) method. In Table 5, the regression coefficient of r=0.99 for B3LYP and HF methods were found for all compounds. From these results, it is understood that the calculated values by both methods are almost close to each other, but some calculated chemical shifts with HF/6-311G show good agreement with experimental data if compared to the B3LYP/6-311G method. SE values are about compunds **2c** and **2d** for HF and B3LYP methods, respectively shown in Table 5. Besides, the best values reached for $\sigma_{calc} = a + b\delta_{exp}$ equation are a=0 and b=1 respectively. As shown in Table 5, b values of 1.06 for B3LYP and 0.99 for HF methods were calculated. The b values were found close to 1 by B3LYP, while chemical shifts which were found by B3LYP method showed much better fitting to that of experimental data if compared to HF method. However, there are no big differences between both methods if compared to each other. With the exception of the N-H protons, both HF and DFT methods are in good agreement with the ^{1}H spectrum of compounds **2a-d**. There has occurred an important difference between experimental and theoretical results more than it is expected. The reason why such a result has come into being is that the N-H hydrogen in 4,5-dihydro-1H-1,2,4-triazol-5-one ring has acidic properties, so that some 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives were titrated potentiometrically with tetrabutylammonium hydroxide in different non-aqueous solvents, and the pK_a values were found between 8.69 and 16.75 [3-6,24-27]. Thus, in the ^{1}H-NMR spectra of the 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives, the signals of N-H protons were observed between δ 11.43 and 12.80 ppm [1-7,11,12,25-30]. This situation can be attributed to the resonance of the negatively formed ions (Scheme 2).

Scheme 2



Conclusions

In this study, the structures of four novel 3-alkyl(aryl)-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**2**) synthesized from the reactions of compounds **1** with 5-methylfuran-2-carboxyaldehyde were identified by using elemental analysis and IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data, and these obtained spectral values were seen as compatible with literature [3-5,25-30]. Correlations between experimental chemical shifts and GIAO-calculated isotropic

shielding constants of protons and carbons as obtained from four new 3-alkyl(aryl)-4-(5-methyl-2-furylmethylenamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were established in order to assess the performance of NMR spectral calculations. DFT-B3LYP and HF levels of the theory 6-311G basis set were considered for geometry optimization and spectral calculations. Depending on computational levels, linear regressions, $\sigma_{calc} = a + b\delta_{exp}$, yield standard deviations of 0.954-5.18 ppm for hydrogen and carbon atoms.

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