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Síntesis de nuevas N-fenil-N-(1-fenilhex-5-en-1-il) acetamidas y su estudio conformacional mediante ^{1}H-RMN

Resumen

Previamente se han evaluado y reportado las propiedades antifúngicas y antiparasitarias para derivados de *N*-acetil procedentes de diferentes *N*-(prop)butenilaminas. En este sentido, la esta investigación presenta un procedimiento de síntesis versátil y eficiente, con la caracterización completa de diferentes *N*-fenil-*N*-(1-fenilhex-5-en-1-yl)acetamidas. Se observaron dos isómeros conformacionales para uno de los compuestos en su espectro ^{1}H/^{13}C-RMN. El análisis conformacional se llevó a cabo usando B3LYP funcional con base en 6-31+G(2d,p) y los datos de espectroscopia RMN. Los valores de ángulo dihedro del sistema alílico —obtenidos por los métodos computacionales citados y el análisis de los datos derivados de ^{1}H-RMN usando la ecuación de Garbisch—, se compararon y se usaron para determinar exitosamente las estructuras conformacionales isoméricas y la interacción intramolecular responsables de la duplicidad de señales y del desplazamiento químico, respectivamente.

Palabras clave: acetamidas, isómeros conformacionales, cálculos computacionales, RMN, ecuación de Garbisch.

Synthesis of new N-phenyl-N-(1-phenylhex-5-en-1-yl)acetamides and their ^{1}H-NMR conformational study

Abstract

Antifungal and antiparasitic activities for N-acetyl derivatives of different N-(prop) butenylamines have been previously evaluated and reported. Consequently, an efficient and versatile synthesis procedure and complete characterization of different N-phenyl-N-(1-phenylhex-5-en-1-yl) acetamides is presented. Two conformational isomers were observed for one of the compounds in their ^{1}H/^{13}C-NMR spectra. The conformational analysis was carried out using the B3LYP functional with the 6-31+G(2d,p) basis and the NMR spectroscopic data. The dihedral angle values of the allylic system obtained by both computational methods and ^{1}H-NMR data analysis (Garbisch's equation) were compared and used to successfully determine the conformational structures and the intramolecular interaction responsible for signal duplicity and chemical shifting respectively.

Keywords: Acetamides, conformational analysis, computational calculation, NMR, Garbisch equation.

Síntese de novas N-fenil-N-(1-fenilhex-5-en-1-il) acetamidas e o seu estudo conformacional por ^{1}H-RMN

Resumo

As atividades antifúngicas e antiparasitárias de N-acetil derivados de diferentes N-(prop) butenilaminas têm sido previamente avaliadas e relatadas. Neste trabalho, apresenta-se uma rota de síntese eficiente e a caracterização completa de diferentes N-fenil-N-(1-fenilhex-5-en-1-il)acetamidas. Nos espectros 1H/13C-RMN foram observados dois isômeros conformacionais para um dos compostos. Foi feita uma análise conformacional usando o funcional B3LYP com bases 6-31+G(2d,p) e os dados de 1H-RMN. Os valores dos ângulos diedros do sistema alílico —obtidos por métodos computacionais e por análise de dados de 1H-RMN (equação de Garbish)— foram comparados e usados para determinar as estruturas dos confôrmeros, o que permitiu determinar as interações intramoleculares responsáveis do diferente deslocamento químico e a conseqüente duplicidade dos sinais no composto que apresentou os dois confôrmeros.

Palavras-chave: acetamidas, isómeros conformacionais, cálculo computacional, RMN, equação de Garbisch.

Introduction

Target oriented synthesis (TOS) is one of the most important methodologies in organic chemistry to access biologically active compounds (1). Molecules, including quinoline and tetrahidroquinoline derivatives, are widely known for their biological and pharmacological activity as well as for their uses in organic electronics (2, 3). Previous reports from our research group have shown both antifungal and antiparasitic activities of *N*-phenyl-α-2-propen-1-yl benzenpropanamines **1a-e** (4, 5). The use of **1a** as synthon for different *N*-heterocycles containing the tetrahydrolepidine and quinoline moiety is well known. These substances are similar to isolated compounds from *Galipea longiflora* and *Galipea officinalis*, which have been studied and used against fever, dysentery, malaria and leishmaniasis treatment, among others (6-13). Literature reports have shown that acetylation of *N*-(prop)butenylamines turns these compounds into biologically active *N*-(prop)butenylacetamides (4, 14-15).

Quantum chemical methods are nowadays-valuable tools in chemistry. Typical applications include calculations of molecular properties, either in order to interpret experimental data or to predict properties of new molecules, and the investigation of reaction mechanisms. Characterization of favoured conformational structures for different biologically active compounds using quantum chemical calculations and NMR (Nuclear Magnetic Resonance) data analysis has also been reported (16-21). Keeping in view the above facts, new *N*-phenyl-*N*-(1-phenylhex-5-en-1-yl)acetamides **2a-f** were prepared by *N*-acetylation of compounds **1a-f**. Their synthesis and characterization data is presented. Quantum chemical calculations were performed in order to interpret the experimental 1H/13C-NMR data and to obtain information about the conformational structure of the synthesized compounds. Biological activity of compounds **2a-f** is currently under study.

Materials and methods (experimental section)

IR spectra were obtained on a FT-IR Bruker Tensor 27™, using KBr windows. IR main signals are condensed in Table 1. GC/MS data were acquired on a HP5890A Series II™ gas chromatography equipped with a HP-5MS™ column (5% methyl phenyl siloxane, 30 m x 0.25 mm x 0.25 μm) and a selective mass detector HP5972™ (EI, 70 eV). NMR spectra were recorded on a Bruker Avance-400™. Coupling constants *J* are reported in Hertz. See Figure 1 for $^{1}H/^{13}C$ assignment.

General procedure for the synthesis of N-phenyl-N-(1-phenylhex-5-en-1yl) acetamides 2a-f

A round bottom flask with a reflux condenser, a thermometer and a magnetic stirrer was filled with 0.35 g (1.24 mmol) of *N*-phenyl-α-2-propen-1-ylbenzenpropanamine (previously prepared) (3) and 3.80 g (37.02 mmol) of acetic anhydride. The reaction mixture was refluxed for 4-6 h and neutralized using $NaHCO_3$. NaOH 0.1 M was used to adjust the mixture to pH 12. Ethyl acetate was used for extraction (20 ml x 3). The organic layer was dried over Na_2SO_4, the solvent removed and the crude product purified by column chromatography on SiO_2 using *n*-heptane and ethyl acetate gradient mixtures. Compounds characterization was carried out using IR, ^{1}H, ^{13}C NMR and GC-MS. Compounds purity was monitored by GC-FID and it was higher than 98%.

Synthesis of* N-*phenyl*-N-*(1-phenylhex-5-en-1-yl)acetamide 2a

From *N*-phenyl-α-2-propen-1-ylbenzen propanamine **1a** (0.33 g, 1.31 mmol) and acetic anhydride (4.32 g, 42.30 mmol). Pure compound **2a** was obtained after column chromatography as a brownish oil. R_f= 0.50 (*n*-heptane:AcOEt, 5:2). MS [EI, 70 eV] (*m/z*, %): 293 (M^+, 2), 252 (38), 210 (100), 117 (13), 91 (47). δ_H ppm ($CDCl_3$, 400 MHz): 1.62 (td, ^3J= 8.0, 7.3, $2H_5$), 1.72 (s, $3H_{4c}$), 2.03-2.19 (m, $\underline{2H_3}$), 2.63 (ddd, ^2J= 14.4; ^3J= 8.3, 7.6, $1H_6$), 2.71 (ddd, ^2J=14.4; ^3J= 8.3, 7.6, $1H_6$), 4.90-5.05 (m, $3H_{1,4}$), 5.76 (dddd, ^3J= 17.7, 9.5, 6.8, 6.4, $1H_2$), 6.94-7.39 (m, $10H_{Arom}$). δ_C ppm ($CDCl_3$, 100 MHz): $23.63_{(4c)}$, $33.13_{(6)}$, $34.57_{(5)}$, $37.75_{(3)}$, $54.07_{(4)}$, $117.11_{(1)}$, $125.86_{(p)}$, $128.25_{(2xm)}$, $128.36_{(2xo)}$, $128.74_{(p')}$, $129.36_{(2xm')}$, $129.86_{(2xo')}$, $135.66_{(2)}$, $139.37_{(i')}$, $141.81_{(i)}$, $171.03_{(4b)}$.

Synthesis of* N-*Phenyl*-N-*(4-methylphenylhex-5-en-1-yl) acetamide 2b

From of *N*-(4-methylphenyl)-α-2-propen-1-ylbenzenpropanamine **1b** (1.07 g, 4.03 mmol) and acetic anhydride (10.79 g, 105.75 mmol). Pure compound was obtained after chromatography column as a brownish oil. R_f= 0.50 (*n*-heptane:AcOEt, 5:2). MS [EI, 70 eV] (*m/z*, %): 307 (M^+, 2), 266 (37), 224 (100), 150 (11), 91 (40). δ_H ppm ($CDCl_3$, 400 MHz): 1.68 (td, ^3J= 8.1, 7.3, $2H_5$), 1.79 (s, $3H_{4c}$), 2.08-2.29 (m, $\underline{2H_3}$), 2.39 (s, $3H_{4d}$), 2.70 (ddd, ^2J= 14.5; ^3J= 8.1, 7.5, $1H_6$), 2.77 (ddd, ^2J= 14.5; ^3J= 8.1, 7.5, $1H_6$), 4.93-5.18 (m, $3H_{1,4}$), 5.83 (dddd, ^3J= 17.5, 9.3, 6.9, 6.5, $1H_2$), 7.06 (d, ^3J= 8.2, $2H_o$), 7.14-7.33 (m, $7H_{Arom}$). δ_C ppm ($CDCl_3$, 100 MHz): $20.98_{(4d)}$, $23.47_{(4c)}$, $33.04_{(6)}$, $34.46_{(5)}$, $37.69_{(3)}$, $53.80_{(4)}$, $116.95_{(1)}$, $125.75_{(p)}$, $128.17_{(2xm)}$, $128.27_{(2xo)}$, $129.51_{(2xo')}$, $129.90_{(2xm')}$, $135.64_{(2)}$, $136.49_{(p')}$, $138.18_{(i')}$, $141.79_{(i)}$, $171.16_{(4b)}$.

Synthesis of* N-*Phenyl*-N-*(4-methoxyphenylhex-5-en-1-yl) acetamide 2c

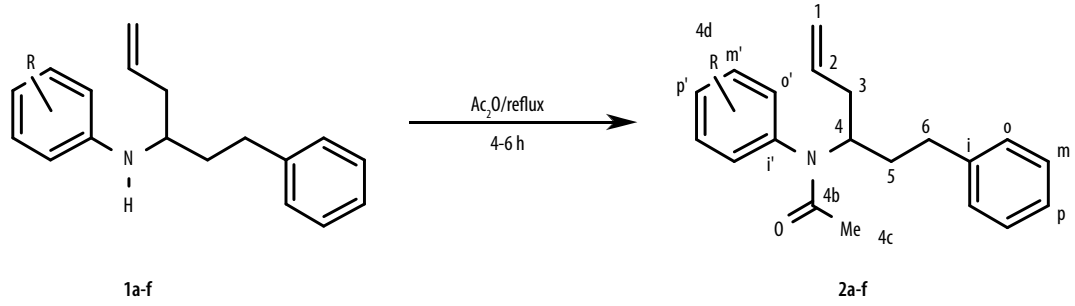
From *N*-(4-methoxyphenyl)-α-2-propen-1-ylbenzenpropanamine **1c** (0.35 g, 1.24 mmol) and acetic anhydride (3.67 g, 35.96 mmol). Pure product was obtained after chromatography column as a brownish oil. R_f= 0.40 (*n*-heptane:AcOEt, 5:2). MS [EI, 70 eV] (*m/z*, %): 323 (M^+, 2), 282 (28), 240 (100), 91 (51). δ_H ppm ($CDCl_3$, 400 MHz): 1.67 (td, ^3J= 8.1, 7.3, $2H_5$), 1.80 (s, $3H_{4c}$), 2.06-2.30 (m, $\underline{2H_3}$), 2.70 (ddd, ^2J= 14.4; ^3J= 8.3, 7.6, $1H_6$), 2.77 (ddd, ^2J=14.4; ^3J= 8.3, 7.6, $1H_6$), 3.83 (s, $3H_{4d}$), 4.98-5.14 (m, $3H_{1,4}$), 5.83 (dddd, ^3J=17.6, 9.5, 6.8, 6.5, $1H_2$), 6.92 (d, ^3J= 9.2, $2H_o$), 7.04-7.35 (m, $7H_{Arom}$). δ_C ppm ($CDCl_3$, 100 MHz): $23.55_{(4c)}$, $33.12_{(6)}$, $34.54_{(5)}$, $37.72_{(3)}$, $53.78_{(4)}$, $55.43_{(4d)}$, $114.43_{(2xm')}$, $117.06_{(1)}$, $125.87_{(p)}$, $128.27_{(2xm)}$, $128.39_{(2xo)}$, $130.87_{(2xo')}$, $131.75_{(i')}$, $135.76_{(2)}$, $141.88_{(i)}$, $159.20_{(p')}$, $171.57_{(4b)}$.

Synthesis of* N-*Phenyl*-N-*(4-bromophenylhex-5-en-1-yl) acetamide 2d

From *N*-(4-bromophenyl)-α-2-propen-1-ylbenzenpropanamine **1d** (0.68 g, 2.06 mmol) and acetic anhydride (7.34 g, 71.91 mmol). Pure product was obtained after column chromatography as a brownish oil. R_f= 0.47 (*n*-heptane:AcOEt, 5:2). MS [EI, 70 eV] (*m/z*, %): 373 (M^+, 2), 330 (33), 290 (95), 288 (100), 91 (82). δ_H ppm ($CDCl_3$, 400 MHz): 1.61-1.73 (m, $2H_5$), 1.79 (s, $3H_{4c}$), 2.17 (ta, ^3J= 7.0, $\underline{2H_3}$), 2.65-2.79 (m, $2H_6$),4.94-5.13 (m, $3H_{4,1}$), 5.81 (dddd, ^3J=17.2, 10.1, 6.6, 6.3, $1H_2$), 7.06 (d, ^3J= 8.8, $2H_o$), 7.14-7.31 (m, $5H_{Arom}$), 7.55 (d, ^3J= 8.8, $2H_{m'}$). δ_C ppm ($CDCl_3$, 100 MHz): $23.63_{(4c)}$, $33.07_{(6)}$, $34.59_{(5)}$, $37.55_{(3)}$, $54.07_{(4)}$, $117.31_{(1)}$, $122.39_{(p')}$, $125.95_{(p)}$, $128.21_{(2xm)}$, $128.41_{(2xo)}$, $131.55_{(2xo')}$, $132.62_{(2xm')}$, $135.44_{(2)}$, $138.42_{(i')}$, $141.53_{(i)}$, $170.67_{(4b)}$.

Synthesis of* N-*Phenyl*-N-*(4-fluorophenylhex-5-en-1-yl) acetamide 2e

From *N*-(4-fluorophenyl)-α-2-propen-1-ylbenzenpropanamine **1e** (0.63 g, 2.34 mmol) and acetic anhydride (6.80 g, 66.62 mmol). Pure product was obtained after column chromatography as a brownish oil. R_f= 0.43 (*n*-heptane:AcOEt, 5:2). MS [EI, 70 eV] (*m/z*, %): 311 (M^+, 2), 270 (36), 228 (100), 117 (15), 91 (51). δ_H ppm ($CDCl_3$, 400 MHz): 1.71-1.82 (m, $2H_5$), 1.87 (s, $3H_{4c}$), 2.22-2.28 (m, $\underline{2H_3}$), 2.79 (ddd, ^2J= 13.8; ^3J= 9.6, 6.9, $1H_6$), 2.84 (ddd, ^2J= 13.8; ^3J= 9.6, 6.9, $1H_6$), 5.06-5.22 (m, $3H_{1,4}$), 5.91 (dddd, ^3J= 17.0, 10.6, 6.6, 6.3, $1H_2$), 7.16-7.40 (m, $9H_{Arom}$).



	R	Yield (%)
2a	H	80
2b	*p*-Me	66
2c	*p*-OMe	92
2d	*p*-Br	82
2e	*p*-F	90
2f	*o*-Me	86

Figure 1. Synthesis of acetamides 2a-f (see labels for $^{1}H/^{13}C$-NMR assignments in experimental section).

δ_C ppm ($CDCl_3$, 100 MHz): $23.55_{(4c)}$, $33.03_{(6)}$, $34.53_{(5)}$, $37.52_{(3)}$, $53.89_{(4)}$, $116.28_{(2xm')}$ (d, ^{2}J= 22.5), $117.21_{(1)}$, $125.91_{(p)}$, $128.18_{(2xm)}$, $128.38_{(2xo)}$, $131.55_{(2xo')}$, $135.19_{(i')}$ (d, ^{4}J= 3.4), $135.49_{(2)}$, $141.57_{(i)}$ $162.07_{(p')}$ (d, ^{1}J=249.1), $171.02_{(4b)}$.

Synthesis of N-*Phenyl*-N-*(2-methylphenylhex-5-en-1-yl) acetamide 2f*

From *N*-(2-methylphenyl)-α-2-propen-1-ylbenzen propanamine **1f** (0.67 g, 2.52 mmol) and acetic anhydride (7.23 g, 70.81 mmol). Pure product was obtained after column chromatography as a brownish oil. R_f = 0.53 (*n*-heptane:AcOEt, 5:2). GC showed a single signal. MS [EI, 70 eV] (*m/z*, %): 307 (M^+, 2), 266 (39), 224 (100), 118 (13), 91 (51). NMR data for α **conformer**: δ_H ppm ($CDCl_3$, 400 MHz): 1.73 (s, $3H_{4c}$), 1.74-1.82 (m, $2H_5$), 2.26 (s, $3H_{4d}$), 2.45-2.51; 2.52-2.59 (m, $\underline{2H}_3$), 2.59-2.67 (m, $2H_6$), 4.75-4.86 (m, $1H_4$), 5.08-5.20 (m, $2H_1$), 5.89 (dddd, ^{3}J= 17.3, 9.9, 6.7, 6.5, $1H_2$), 7.07-7.34 (m, $9H_{Arom}$). δ_C ppm ($CDCl_3$, 100 MHz): $18.44_{(4d)}$, $23.15_{(4c)}$, $33.45_{(6)}$, $33.57_{(5)}$, $38.23_{(3)}$, $55.87_{(4)}$, $117.08_{(1)}$, $125.81_{(p)}$, $126.87_{(m')}$, $128.21_{(p')}$, $128.25_{(2xo)}$, $128.32_{(2xm)}$, $129.64_{(o')}$, $131.54_{(m'')}$, $135.93_{(2)}$, $136.87_{(i')}$, $139.35_{(o'')}$, $141.67_{(i)}$, $171.06_{(4b)}$. NMR data for β **conformer**: δ_H ppm ($CDCl_3$, 400 MHz): 1.49-1.61 (m, $2H_5$), 1.77 (s, $3H_{4c}$), 1.86-2.07; 2.36-2.48 (m, $\underline{2H}_3$), 2.27 (s, $3H_{4d}$), 2.77 (ta, ^{3}J= 8.4, $2H_6$), 4.75-4.86 (m, $1H_4$), 4.95-5.01 (m, $2H_1$), 5.69 (dddd, ^{3}J= 16.6, 10.8, 7.9, 6.0, $1H_2$), 7.07-7.34 (m, $9H_{Arom}$). δ_C ppm ($CDCl_3$, 100 MHz): $18.49_{(4d)}$, $23.06_{(4c)}$, $33.14_{(6)}$, $33.31_{(5)}$, $36.61_{(3)}$, $55.83_{(4)}$, $117.18_{(1)}$, $125.81_{(p)}$, $126.95_{(m')}$, $128.17_{(p')}$, $128.24_{(2xo)}$, $128.34_{(2xm)}$, $129.32_{(o')}$, $131.60_{(m'')}$, $135.42_{(2)}$, $137.02_{(i')}$, $139.22_{(o'')}$, $141.97_{(i)}$, $171.04_{(4b)}$.

Conformational analysis

Ten chemically reasonable structures for compound **2f** were used as the starting point for energy minimization using the Parameterized Model 3 (PM3) semi-empirical method (22). Geometry optimization and vibrational frequency calculations (for verifying that the structures correspond to minima on the potential energy surface) were then carried out using the B3LYP functional with the 6-31+G(2d,p) basis set as implemented in Gaussian 09 (23-31). Seven different possible conformer structures $\mathbf{2f}_1$-$\mathbf{2f}_7$ were found. Energy differences [kcal/mol] for all minima were calculated with and without vibrational zero point energies (VZPE).

Results and discussion

Figure 1 shows the synthesis of new 1-phenylhex-5-en-1-yl-acetamides **2a-f** from *N*-butenylamines **1a-f** using acetic anhydride as both reagent and solvent, under reflux (140°C). Acetamides **2a-f** were easily obtained with yields between 66-92%. Optimal reaction time was established by both TLC and GC in about 4-6 h. Main IR vibration bands of allyl C=C-H and acetamide C=O are listed in Table 1. IR N-H tension and flexion bands in compounds **1a-f** clearly disappeared after acetyl protection.

GC-MS (EI, 70eV) data are condensed in Table 2. Molecular ions corresponding to molecular mass of **2a-f** appeared in all cases with low intensity; base peak Φ_2 results after consecutive allyl [Φ_1] and acetyl [Φ_1-C_2H_3O]$^+$ fragmentation. Benzyl fragment Φ_3 (*m/z* 91) is characteristic in all compounds.

$^{1}H/^{13}C$ and 2D NMR experiments confirmed the structures of compounds **2a-f**. Due to a short relaxation time in ^{13}C- APT NMR spectra for *Co'*, a broad signal appeared; thus, in **2e** it was not possible to assign the correct *C o'-F* coupling constant. Diastereotopic protons H_{3a} and H_{3b} appeared in ^{1}H-NMR as a multiplet from 1.86 ppm to 2.59 ppm in all cases. Correct assignment of allyl-H_2 coupling constants and multiplicity for compounds **2a-f** was completed by comparative simulation con-

Table 1. IR [*v*, cm^{-1}] main signals for compounds 2a-f.

	***v*(C=O**	***v*(C=CH)**	***v*(=C-H) Aromatic *p*-disubstituted**	***v*(=C-H) Aromatic monosubstituted**
2a	1655	915	----	745-701
2b	1655	915	824	749-700
2c	1653	916	837	750-700
2d	1658	917	833	749-700
2e	1658	917	844	750-700
2f	1658	917	763 *	749-700

* *o*- disubstitued.

Table 2. MS (EI, 70eV) [*m/z* (int. %)] main fragments for compounds 2a-f.

	$M^{\cdot+}$	Φ_1, $[M\text{-}C_3H_5]^+$	Φ_2, $[\Phi_1\text{-}C_2H_3O]^+$	Φ_3, $[C_7H_7]^+$
2a	293 (2)	252 (38)	210 (100)	91 (47)
2b	307 (2)	266 (37)	224 (100)	91 (40)
2c	323 (2)	282 (28)	240 (100)	91 (51)
2d	373 (2)	330 (33)	288(100)	91 (82)
2e	311 (2)	270 (33)	228 (100)	91 (51)
2f	307 (2)	266 (39)	224 (100)	91 (51)

sidering a first order spectra ($\Delta\nu/J > 8$) of an AA'MXX' spin system (32); spin simulation was carried out using Mestrenova™ v7.1.1 (test version) (33). Determined experimental values of chemical shifts and coupling constants range for the allyl system were used to simulate the H_2 signal until an identical multiplet was obtained by direct comparison, as shown in Figure 2.

H_2 proton chemical shifts and coupling constants for **2a-f** allyl system are shown in Table 3. Compound **2f** showed a single GC signal but a double group of signals in ^{1}H and ^{13}C-NMR; characteristic coupling constants for the allyl H_2 proton were observed due to the existence of two different conformational isomers (α/β).

^{1}H-NMR integral relation of conformers $\mathbf{2f}_\alpha$ and $\mathbf{2f}_\beta$ was 1:1.15 (Figure 3). ^{1}H-NMR experiments showed that α and β conformational isomers ratio does not change in time at room temperature. Conformers $\mathbf{2f}_\alpha$ and $\mathbf{2f}_\beta$ also showed diastereotopic protons H_{3a} and H_{3b} as separated multiplets.

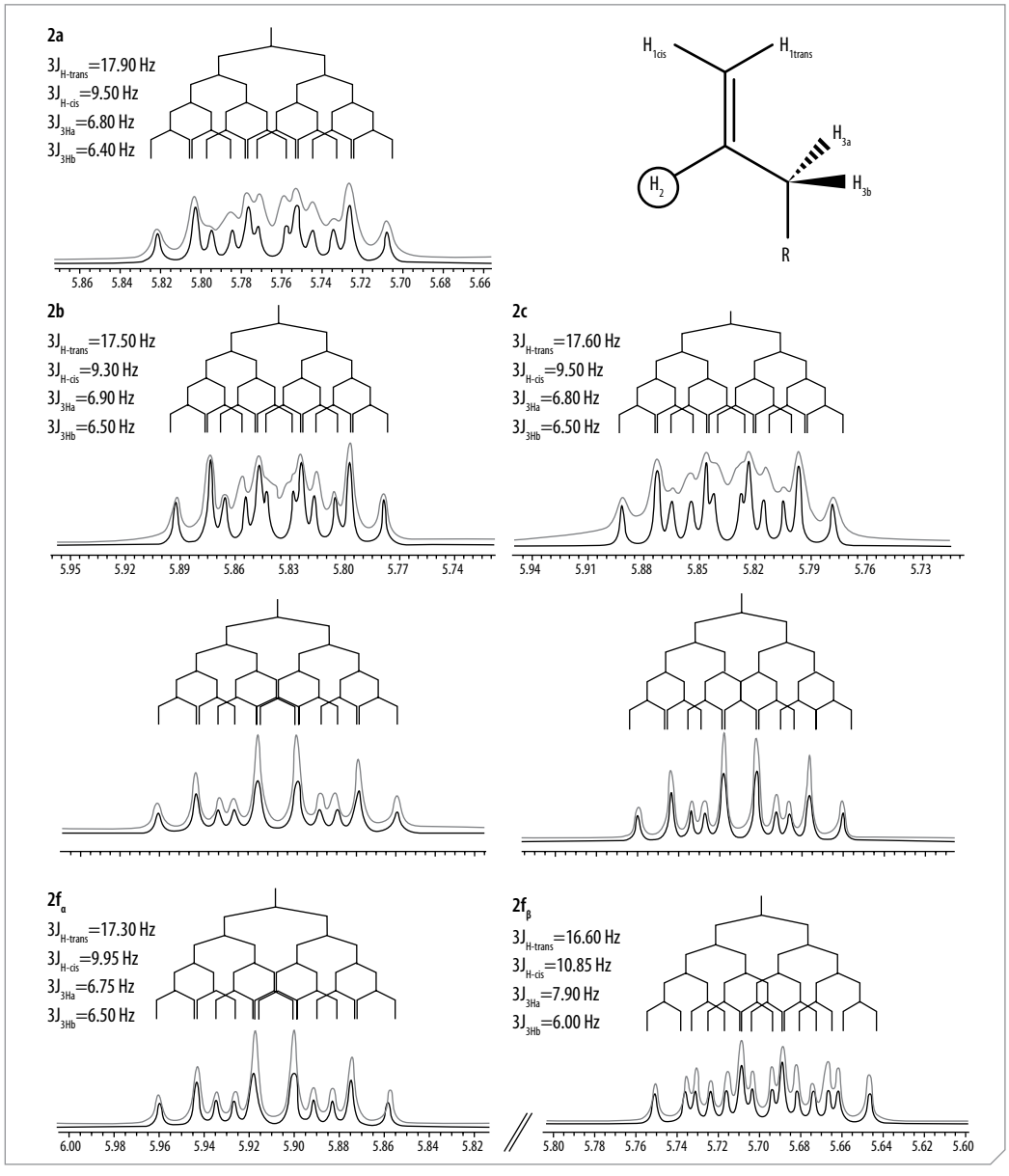


Figure 2. Obtained (black) and simulated (red) spectra for allyl-H2 proton considering an AA'MXX' spin system.

Table 3. ^{1}H-NMR chemical shifts (ppm) and coupling constants ^3J (Hz) for the allyl H_2 nuclei of 2a-f.

Compound	δ [ppm]	^3J(Htrans)	^3J(Hcis)	^3J(H3a)	^3J(H3b)
2a	5.765	17.90	9.50	6.80	6.40
2b	5.834	17.50	9.30	6.90	6.50
2c	5.834	17.60	9.50	6.80	6.50
2d	5.811	17.25	10.10	6.60	6.35
2e	5.907	17.00	10.61	6.60	6.35
2fα	5.898	17.30	9.95	6.75	6.50
2fβ	5.696	16.60	10.85	7.90	6.00

After conformational analysis of **2f**, despite of including both, the electronic energy and the VZPE differences, the optimized structures $\mathbf{2f_1}$-$\mathbf{2f_7}$ showed similar ΔE values, avoiding a direct assignment to explain the duplicity of the signals in ^{1}H-NMR. Molden was used for displaying the molecular structures (34). These structures are qualitatively similar, differing mainly on the allyl group dihedral angles and slightly on rotation of other sigma bonds (Figure 4).

Table 4 shows the energies and the allyl group dihedral angles for each **2f** conformer after optimization, taking $\mathbf{2f_2}$ [lowest electronic energy at the B3LYP(6-31+G(2d,p)) level of theory] as reference for energetic differences.

To correlate the H_2 allyl ^{1}H-NMR signals to a particular conformer, the proposed equation by Garbisch for allyl compounds [Equation 1] was used (35). Garbisch equation is a modified Karplus equation in-

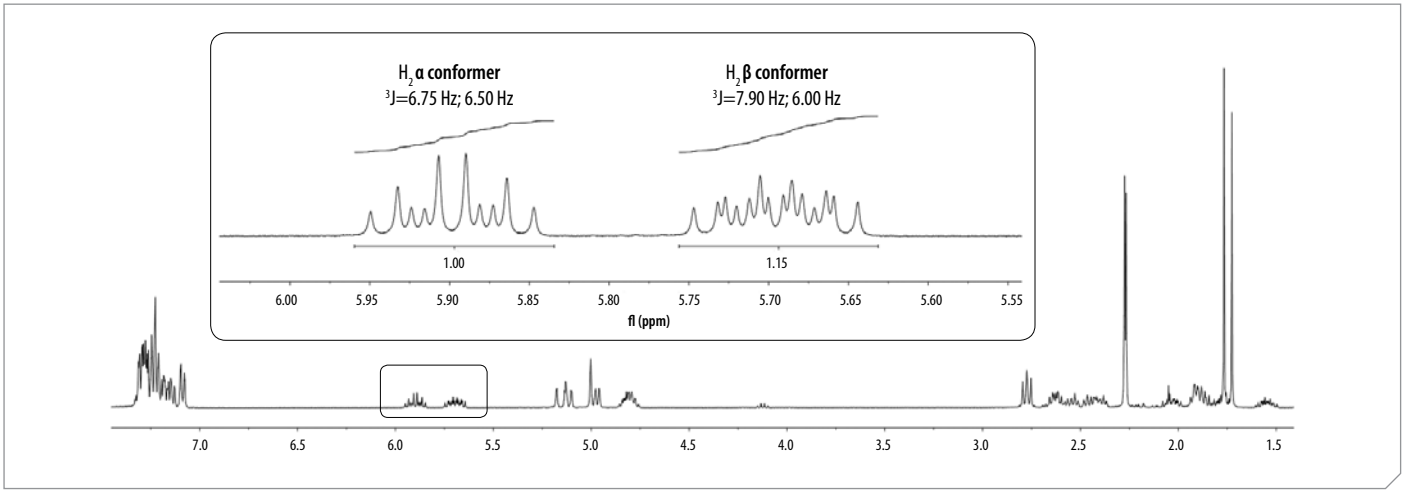


Figure 3. ^{1}H-NMR ($CDCl_3$, 400MHz) spectra of **2f**; the two different allyl-H_2 signals (in expansion) determine the α/β conformers.

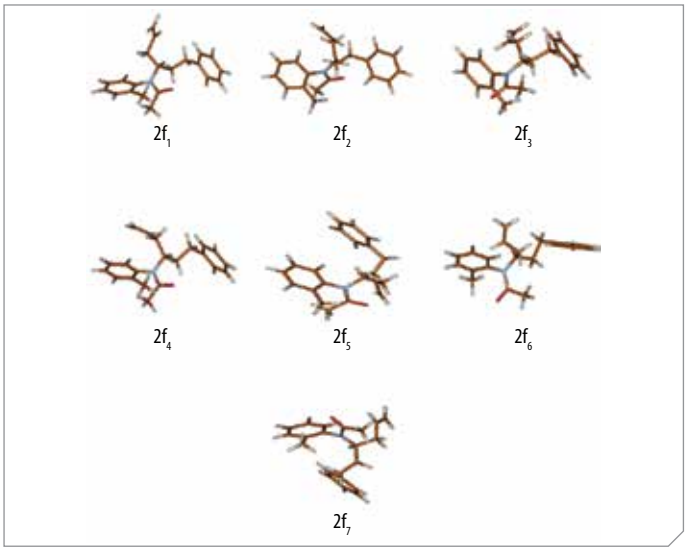


Figure 4. Calculated structures for conformers $2f_{1\text{-}7}$.

Table 4. Calculated energy values and allyl group dihedral angles (degrees) for seven different conformers of 2f.

	ΔE [kcal/mol] (electronic energy)	Total ΔE [kcal/mol] (including VZPE)	Dihedral angles [degrees °]	
			Φ_1	Φ_2
$\mathbf{2f_1}$	0.47	0.46	63	179
$\mathbf{2f_2}$	0	0	170	286
$\mathbf{2f_3}$	1.79	2.02	64	179
$\mathbf{2f_4}$	2.05	2.16	66	181
$\mathbf{2f_5}$	1.08	1.11	173	295
$\mathbf{2f_6}$	5.08	5.25	66	182
$\mathbf{2f_7}$	4.85	5.46	62	178

Table 5. Coupling constants ^3J (Hz) and their corresponding dihedral angles (Φ_1 and Φ_2) from Garbisch equation for allyl protons H_2 and H_{3a}/H_{3b} in compounds **2a-e***.

Compound	$^3JH_{3a}$	$^3JH_{3b}$	Φ_1 [±15°]	Φ_2 [±15°]
2a	6.4	6.8	12.9	133
2b	6.5	6.9	9.1	134
2c	6.5	6.8	9.1	133
2d	6.3	6.6	0.4	130
2e	6.3	6.6	0.4	130

* See also Figure 5.

Table 6. Dihedral angles (Φ_1 y Φ_2) for allyl protons H_2 and H_{3a}/H_{3b} in seven different conformers for **2f**; calculated using the B3LYP[6-31+G(2d,p)] level of theory (left) and from the Garbisch equation (right).

[Equation 1]

	Calculated results								Garbisch's results
	$2f_1$	**$2f_3$**	**$2f_4$**	**$2f_6$**	**$2f_7$**	**$2f_2$**	**$2f_5$**	**α**	**β**
Φ_1	63	64	66	66	62	170	173	9.1	140
Φ_2	179	179	181	182	178	286	295	133	232

volving also σ and π bonds contributions. Some authors suggest that some modifications can be done to make this equation more precise (36-38). With the Garbish equation a relation between observed coupling constants (*J*) and the dihedral angle (Φ) for the allylic proton H_2 and H_3 for each conformer was determined, as shown in Tables 5 and 6.

Dihedral angles for conformers $\mathbf{2f}_{1\text{-}7}$ found in our calculations and conformers $\mathbf{2f}_\alpha$ and $\mathbf{2f}_\beta$ obtained from Garbisch equation are not equivalent, but approximated (Table 6) considering ±15° of uncertainty (32).

A comparison for both models (Figure 5) shows high similarity when a Newman representation of the allyl H_2 and vicinal methylenic protons H_{3a} and H_{3b} are depicted. Considering this fact, it was possible to associate these two different positions for H_{3a} and H_{3b} protons to conformers α and β according to the observed ^{1}H and ^{13}C-NMR spectra, concluding that bulky groups (R and C=C) are located in a pseudo bisecting conformation in Newman's projections (Figure 5).

Thus, possible structures of α/β conformers were established according to their calculated energy, in each case. Allyl group disposition according to Garbisch equation was within the approximation limits with calculated conformers $\mathbf{2f}_1$ and $\mathbf{2f}_2$ (Figure 6).

Analogous calculated structures for **2f** differ basically on the spatial distribution of the allyl group and its dihedral angle; a 2.72 Å dipolar interaction between the allyl proton and the acetyl oxygen atom was observed in conformer $\mathbf{2f}_\beta$ (Figure 7), explaining the chemical shifting to high fields in the ^{1}H-NMR spectrum due to C=O anisotropic protection. Each conformer of **2f** (α and β) was totally elucidated using 2D-NMR experiments (COSY, HSQC and HMBC).

Conclusions

An easy methodology to access new *N*-phenyl-*N*-(1-phenylhex-5-en-1-yl)acetamides **2a-f** using acetic anhydride as reagent and solvent, including green chemistry principles was used. Using quantum chemical calculations and Garbisch's approximation it was possible to determine that compounds **2a-e** prefer a single conformation similar to conformer $\mathbf{2f}_\alpha$. Existence of $\mathbf{2f}_\alpha$ and $\mathbf{2f}_\beta$ conformers explain the double signals observed in both ^{1}H and ^{13}C-NMR spectra for compound **2f**. Coupling constants and chemical shifts values for H_2 allyl proton signals of compounds **2a-f** were described for each conformer and can be used as a comparative base in ^{1}H-NMR allyl-H_2 signal coupling constants assignation.

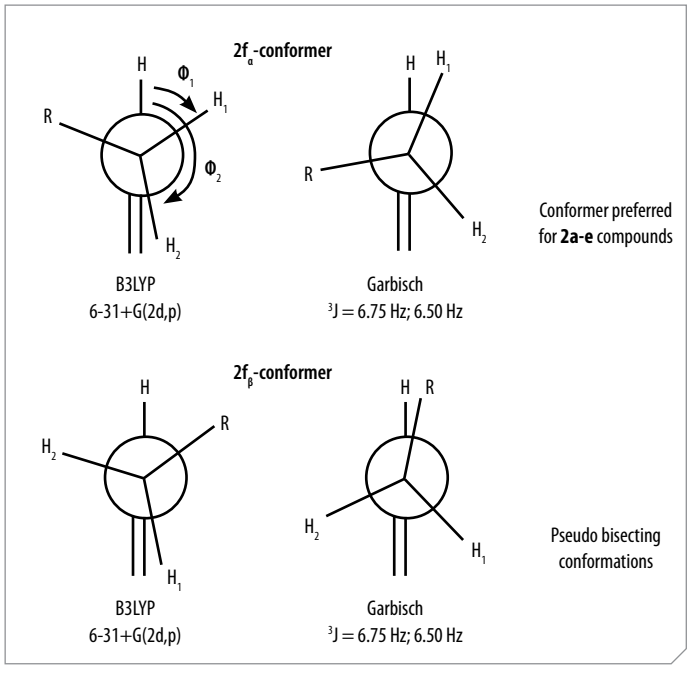


Figure 5. Newman projections for allyl group conformers $\mathbf{2f}_\alpha$ and $\mathbf{2f}_\beta$: left, calculated structures (B3LYP/6-31+G(2d,p); right, according to [Eq. 1].

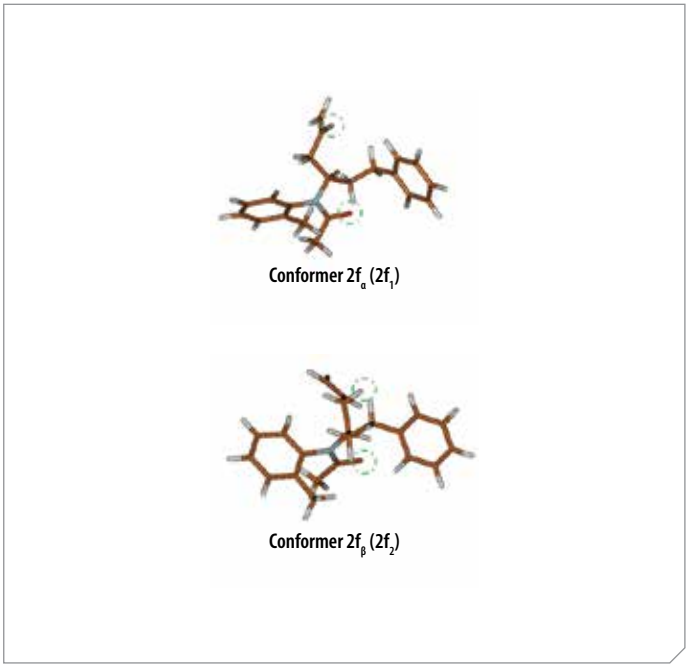


Figure 6. Calculated structures (B3LYP/6-31+G(2d,p) for conformers α and β of 2f.

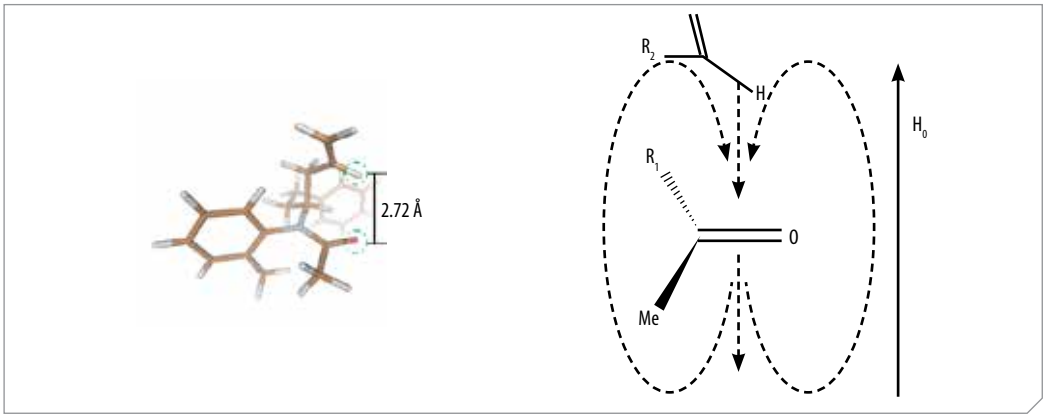


Figure 7. Left: Allyl-H_2 proton interaction at 2.72 Å distance with the carbonyl oxygen in conformer **2f$_\beta$**. Right: The diamagnetic protection zone of double bond C=0.

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