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Simple Preparation of New Potential Bioactive Nitrogen-Containing Molecules and Their Spectroscopy Analysis

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1. Introduction

The impact of research on the small molecules chemistry is difficult to quantify and currently, it is still one of the most active areas of organic chemistry, medicinal chemistry and lately chemical biology. In recent years, a lot of interest has been shown in the preparation of nitrogen-containing compounds due to their numerous biologically significant activities. But it is the separation and purification process of the new synthetized organic molecules, the ones that take a key role in drug design and development.

Many texts about the simple and optimal preparation of bioactive compounds have been published, and in this chapter the multicomponent reactions and efficient linear process, which allow the synthesis of this kind of structures, will be discussed. However, the purpose of this chapter is to reveal those important aspects that finally determined why a molecule can be used and distributed as a drug: their preparation, purification, and characterization.

In almost all organic synthetic methodologies the purification process use simple column chromatography techniques (gravity or external pressure) using different support materials (solid adsorbents) as the stationary phase. Column chromatography is advantageous over most of the other chromatographic techniques because it can be used in both analytical and preparative applications. After the preparation and purification of a new compound has been realized, it becomes the characterization step. New purified molecules must be strongly characterized to determine its structural configuration. Among different analysis techniques, NMR experiments and X-Ray crystallography are the most efficient ways to determine the relative stereochemistry and, in suitable cases, also the absolute configuration of the obtained products.

In the development of our medicinal program directed to small molecules for drug delivery, the strategies for the preparation of nitrogen-containing molecules such as substituted indoles, tetrahydroquinolines, and N-substituted amides of carboxylic acids are illustrated in this chapter as well as their synthetic applications and analytic characterization. The discussion is complemented with a deep explanation of the analytical techniques employed

for their isolation and purification including the spectroscopic and spectrometric techniques using for the elucidation structure for every new compound.

2. Simple preparation of new N-aryl-N-(3-indolmethyl) acetamides and their spectroscopic analysis

The vital importance of derivatives like indole-3-acetic acid, as a hormone responsible for the plant growth, and tryptophan, as a constituent of proteins and indispensible precursor of indole alkaloids, enhances the current interest for the design of simple and efficient synthetic routes for the preparation of molecules with the indole skeleton.

The research of the indol chemistry has been and it is still one of the most active areas of heterocyclic chemistry. In the past decades, a lot of interest has been shown in the preparation of substituted indoles due to their numerous biologically significant activities (Gribble, 2003). The derivatives of 3-indolylmethanamine **1** are the important intermediates of natural and natural-like products, such as hydro-γ-carboline and pyrido[4,3-*b*]indole derivatives (Wynne & Stalick, 2002; Molina et al., 1996). This 3-indolyl methanamine motif is also embedded in numerous indole alkaloids from the simple alkaloid gramine **2** to complex aspidospermine alkaloid **3** (Baxter et al., 1999; Saxton, 1998) (Fig. 1).

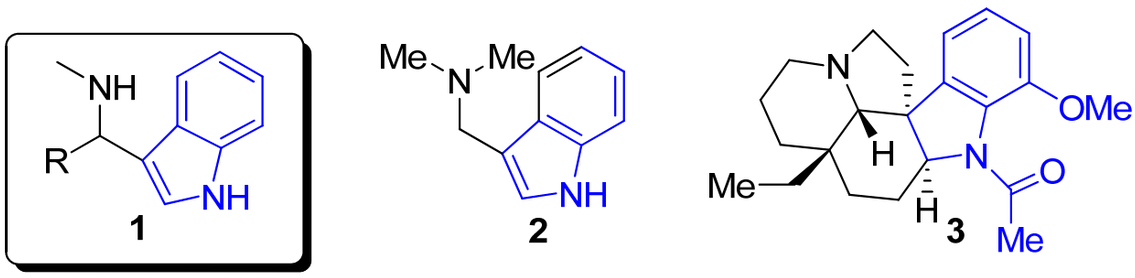

Fig. 1. Relevant natural alkaloids derived from the 3-indolylmethanamine system.

As a result of their biological and synthetic importance, a variety of methods have been reported for the preparation of 3-substituted indoles, using indol or 3-indolcarboxyaldehyde as starting materials. Generally, the Mannich reaction (Dai et al., 2006) and the catalyzed Friedel-Crafts alkylation reactions of indoles (Ke et al., 2005; Zhao et al., 2006; Jiang et al., 2005; Shirakawa & Kobayashi, 2006) are considered as a powerful carbon-carbon bond process to afford the 3-indolylmethanamine derivatives **1**. However, another synthetic route to access to these compounds by using 3-indolcarboxyaldehyde, via its imino derivatives, is valid. This route has been used by our laboratory, which recently started an own medicinal program directed to small molecules for drug delivery. The particular interest in 3-indolylmethanamine derivatives molecules, that could serve as useful precursors to many drug-like indolic or quinolinic compounds, is based on the evaluated antiparasitic properties of some analogues (Kouznetsov et al., 2004a, Kouznetsov et al., 2004b; Vargas et al., 2003). In this novel direction, the simple preparation of new (3-indolmethyl)acetamide and (1-acetylindolmethyl-3)acetamide, regulating only the solvent nature, is the relevant fact that has not been described and it gives the opportunity to prepare more of this kind of compounds.

2.1 Synthesis and purification of the new the (3-indolmethyl)acetamide and (1-acetylindolmethyl-3)acetamide

Aldimines are valuable starting materials not only for different N-containing heterocycles but also to diverse secondary heteroaromatic amines (Hutchins & Hutchins, 1991), which represent good candidates for bio-screening with diverse types of activities (Kleemann & Engel, 2005; Evers et al., 2005). Thus, the N-aryl imine **6**, the main and value starting, can be prepared from commercially available 3-indolaldehyde **4** and 2-cyanoaniline **5**, according to published methods (Colyer et al., 2006). This aldimine is obtained as a white and stable solid after purification by recrystallization in 95 % yield (Fig. 2). The method employed to obtain the precursor **7**, is one of the most known procedures to reduce an aldimines with an excess of $NaBH_4$ in methanol, protocol that is still the reaction of choice to produce secondary amines in reasonably good yield. Thus, *N*-(2-cyanophenyl)-*N*-(3-indolylmethyl)amine **7** is prepared as was described and was obtained as white solid in 70 % yield after purification through recrystallization (Bello et al., 2010). This example, in which the main precursor is prepared in a linear process and purified by recrystallization, represents an excellent technique that avoids the loss of value material and it will be increase the global yields of the final product.

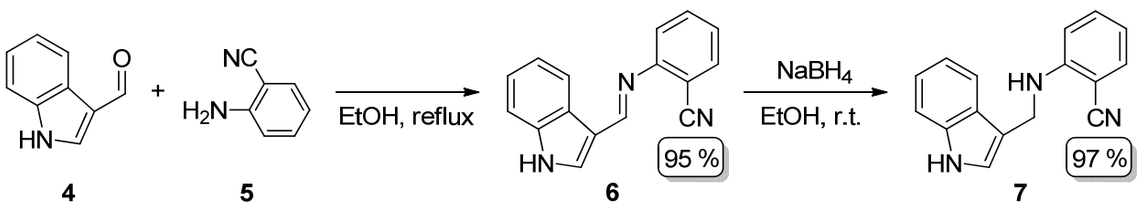

Fig. 2. Synthesis and reduction of the aldimine **6** to give the desired secondary amine **7** in excellent overall yields.

Besides the efficient preparation and easily purification of compound **7**, this amine has interesting structural elements to use in the synthesis of different indolic heterocycles. In this case, the study of its acetylation by acetic anhydride is showed.

First, to a stirred solution of amine **7**, using in toluene as solvent due to the insolubility of compound **7** in polar common solvents (CH_3CN, CH_2Cl_2, AcOEt and DMF), it is added Et_3N and acetic anhydride, the mixture is refluxed for appropriate time to obtain the *N*-(2-cyanophenyl)-*N*-(3-indolmethyl)acetamide **8** in acceptable yield (50 %) after purification using silica gel 60 Mesh and using a mixture of hexane: ethyl acetate (2:1) as an eluent.

Then, the acetylating reaction described above was performed between the amine and an excess acetic anhydride in the presence of Et_3N at 100 ˚C, without the organic solvent (toluene). After the usual workup, the diacetylated indole **9** is obtained in good yield (85 %) using the same parameters employed to the purification of compound **8**. This simple change in the reaction conditions could afford different acetamides based on the 3-indolyl methanamine motif (Fig. 3). This finding reveals a selective process to protect different amino groups and represents a good protocol to the synthetic organic chemistry, especially within those processes that require a particular position protection.

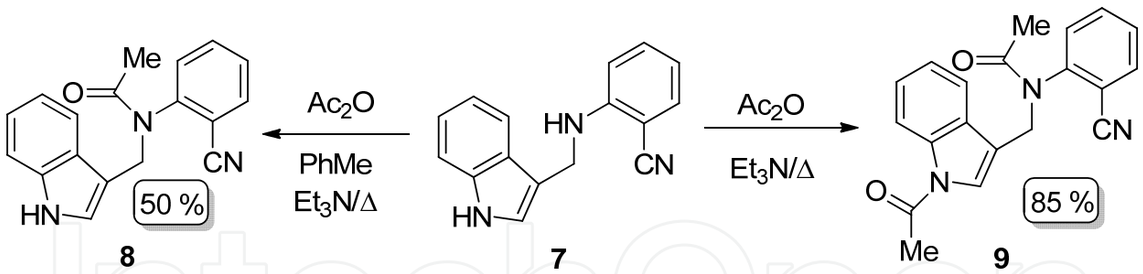

Fig. 3. Synthesis and purification of the *N*-aryl-*N*-(3-indolmethyl)acetamides **8** and **9**.

2.2 Characterization of the *N*-aryl-*N*-(3-indolmethyl)acetamides 8 and 9 by spectroscopy and spectrometric techniques

The structures of the C-3 substituted indoles **7-9** were confirmed on the basis of recorded analytical and spectral data and are supported by inverse-detected 2D NMR experiments. The IR spectrum of compound **7** illustrates the characteristic absorption bands at 3402 and 3352 cm^{-1} assignable to tension vibrations of CH_2-N-H and N-H_{indol}, respectively. Its ^1H NMR spectrum displays a duplet at δ 4.56 ppm (J = 4.9 Hz) ppm corresponding to two protons coupling with the neighbor N-H proton (br. s, 4.84 ppm), which suggest the presence of the methylenic unit linked to the N-H function. The peaks find at δ 7.17-7.3, 7.36-7.40 and 7.63 ppm reveals the presence of aromatic protons of the indole moiety. The ^{13}C NMR spectra, also showed all expected characteristic peaks at δ 39.4 (CH_2), 117 (CN), and 95.6-150.2 (aromatic carbons).

The mass spectrometric analysis of compound **8** gives a molecular ion peak $M^{+\cdot}$, at m/z 289, suggesting the molecular formula $C_{18}H_{15}N_3O$, and indicating that the acetyl group is coupling with **7**. The acetamide **8** displayed characteristic infrared absorption bands with a single amine absorption band at 3342 cm^{-1} and with a carbonyl sign at 1701 cm^{-1} suggesting the acetylation reaction involvement of the CH_2-N; this is the band appearing at high wave number of the corresponding N-H_{indol} vibration tension in the IR spectrum. Its ^1H NMR spectra analysis showed a singlet at 2.58 ppm corresponding to three protons which belong to the acetyl group and another singlet at 4.55 ppm due to the presence of the methylenic 3-CH_2-N indolic protons. This signal's multiplicity is explained by assuming the proton N-H next to it, substituted now for the acetyl group, which leaves no possibility to H,H coupling, while it does happen with the amine **7**.

The ^{13}C NMR spectrum of the acetamide **8** displayed characteristic carbonyl signal at 168 ppm, this is strong evidence to the new acetyl group bonded to the molecule; in addition to a signal at 39.3 and 23.9 ppm, showing the presence of CH_2 and CH_3 in the molecule. Introduction of an acetyl group into the molecule affects the chemical shift of the hydrogen bonded to the aromatic carbon close to the acetylatin nitrogen; this appears at 116 ppm for the compound **7** and at 123 ppm for the acetamide **8**. The signal at 39.3 ppm for CH_2-N has been distinguished on the basis of the DEPT-135 experiment. On the basis of these spectral studies, compound **8** was characterized as the *N*-(2-cyanophenyl)-*N*-(1*H*-indol-3-ylmethyl)acetamide.

The new compound **9** gave a molecular ion peak at m/z 331 in the mass spectrometric analysis, corresponding to the molecular formula $C_{20}H_{17}N_3O_2$ as indicated by its EI-MS. The

loss of 43 units (one acetyl group) generates the same mass spectrum as the acetamide **8**. The IR spectrum of this molecule shows bands at 1704 and 1654 cm^{-1}, assignable to two carbonyl groups while the N-H absorption bands are not observed in the region of 3300-3400 cm^{-1}. The ^{1}H NMR spectrum showed, as expected, two singlets at δ 22.4 and 23.9 ppm, which integrated for three protons each. In the case of the methylenic protons, they appeared to be diasterotopic resonating at the high field frequencies δ 4.75 and 5.46 ppm with a coupling constant *J* = 15 Hz, usual constant value to a germinal coupling. Of course, the aromatic protons were also assigned.

The ^{13}C NMR spectrum showed all expected characteristic peaks at δ 169.4 (ArN-CO-), 168.5 ($Ar_{indol}N$-CO-) ppm, in addition to a signal at δ 117.3 ppm showing the presence of C≡N in the molecule. Besides, methyl carbons at 23.9 ($Ar_{indol}NCO$-CH_3) and 22.4 (ArNCO-CH_3) ppm and the methylene carbon at δ 42.8 ppm were also displayed in the ^{13}C NMR.

With respect to the characterization of the diacetamide **9**, through X-ray diffraction, the monoclinic system was determined with the compound crystallized at 25ºC from heptane-ethyl acetate (2:1) (Fig. 4).

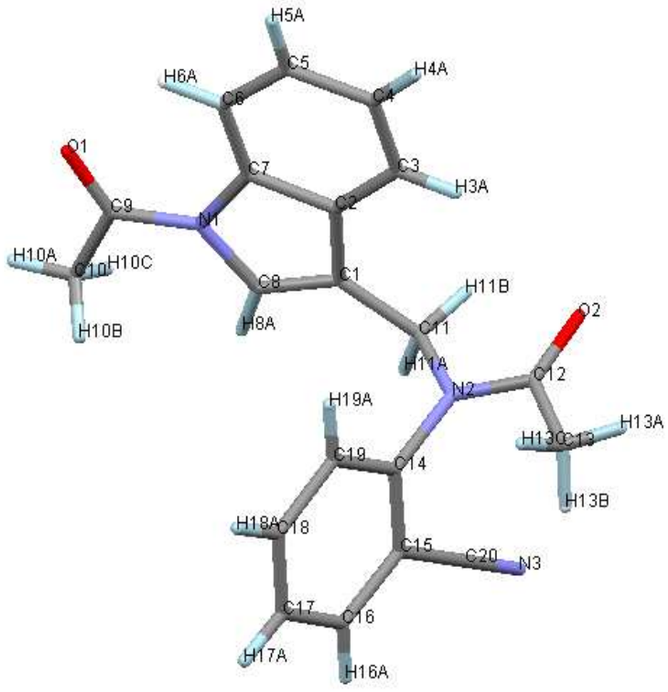

Fig. 4. X-Ray structure of the diacetamide **9**.

The crystallized material has the following cell constants: a = 11.1184(19) Å, b = 8.0048(13) Å, c = 20.534(4) Å and space group P $2_1/n$ (Table 1), possessing the different bond lengths of the molecule constituent atoms was also extracted with this technique (Table 1).

From this data, the different bond lengths of the two amide bonds present within the structure were as expected. Even knowing the double bond character of the amide bonds, in this case, the amide bond distance between the aliphatic nitrogen N2 and C12 is 1.364 Å, while the distance between the aromatic nitrogen N1 and C9 is 1.388 Å.

Crystal morphology	White parallelepipede
Chemical formula	$C_{20}H_{17}N_3O_2$
Molecular weight	331.13
Crystal system	Monoclinic
Space group	$P2_1/n$
Cells constants	a = 11.1184(19) Å, b = 8.0048(13) Å and c = 20.534(4) Å, α = 90°, β = 94.281(4), γ = 90°
Volume	1822.4(5) $Å^3$
Absorption coefficient	0.82 mm^{-1}
Temperature	293(2) K
Range for data collection	1.99-28.09
Index range	h = -13 → 28, k = -9 → 7, l = -23 →23
R	0.0567
R_w	0.0582
Threshold expression	>2sigma(l)
Diffraction radiation	$M_0K\alpha$
λ	0.71070 Å

Table 1. Crystal data and structure refinement parameters of diacetamide **9**.

From this data, the different bond lengths of the two amide bonds present within the structure were as expected. Even knowing the double bond character of the amide bonds, in this case, the amide bond distance between the aliphatic nitrogen N2 and C12 is 1.364 Å, while the distance between the aromatic nitrogen N1 and C9 is 1.388 Å.

These data correspond with the thought that the amide bond N2-C12 is shorter because of the electron withdrawing inductive effect from the α-cyanophenyl substituent and the possibility of the nitrogen non-shared electrons to be delocalized on the amide bond through a mesomeric effect giving this bond a stronger double bond character.

On the other hand, the amide bond N1-C9 is longer because the nitrogen non-shared electrons are compromised with the aromatic system and they are not as available to be delocalized on the amide bond giving it less double bond character (Table 2).

2.3 Conclusions

An efficient, economic, and fast synthetic route was designed and its illustrated in this section showing the possible construction of the *N*-aryl-*N*-(3-indolmethyl)acetamides with the incorporation of the indolic core as a structural analogues of some alkaloids.

The acylation method is worth as a regioselective process because the conditions variations lead to the mono- or di-acetamide. The characterization of the obtained compounds through different techniques gives evidence enough and strong support with regard to the success of the proposed scheme.

Number	Atom 1	Atom 2	Length (Å)
1	O1	C9	1.220
2	O2	C12	1.221
3	N1	C7	1.415
4	N1	C8	1.405
5	N1	C9	1.388
6	N2	C11	1.473
7	N2	C12	1.364
8	N2	C14	1.430
9	N3	C20	1.143
10	C1	C2	1.449
11	C1	C8	1.338
12	C1	C11	1.489
13	C2	C3	1.385
14	C2	C7	1.404
15	C3	H3A	0.931
16	C3	C4	1.371
17	C4	H4A	0.929
18	C4	C5	1.378
19	C5	H5A	0.931
20	C5	C6	1.377
21	C6	H6A	0.930
22	C6	C7	1.384
23	C8	H8A	0.930
24	C9	C10	1.481
25	C10	H10A	0.960
26	C10	H10B	0.961
27	C10	H10C	0.961
28	C11	H11A	0.971
29	C11	H11B	0.971
30	C12	C13	1.497
31	C13	H13A	0.961
32	C13	H13B	0.960
33	C13	H13C	0.960
34	C14	C15	1.387
35	C14	C19	1.364
36	C15	C16	1.388
37	C15	C20	1.427
38	C16	H16A	0.930
39	C16	C17	1.363
40	C17	H17A	0.929
41	C17	C18	1.360
42	C18	C18A	0.929
43	C18	C19	1.397
44	C19	H19A	0.931

Table 2. Bond lengths between the molecule atoms of diamide **9**.

3. A convenient procedure for the synthesis of new quinoline derivatives and their spectroscopic analysis

Quinoline and tetrahydroquinoline structures are essential feature of many natural products. These heterocycles play a key role in heterocyclic and medicinal chemistry. Their syntheses by various methodologies have been published extensively (Kouznetsov et al, 2005; Kouznetsov et al., 1998; Katrizky et al., 1996; Jones, 1984).

Polyfunctionalized tetrahydroquinolines (THQs) are molecules of great interest in organic synthesis due to the fact that many natural products present this system in their structure, and these compounds exhibit diverse biological activities (Glushenko et al., 2008; Broch et al., 2008; Ichikawa et al., 2004; Morsali, et al., 2004; Chen et al., 2000).

Apart from their marked bioactivities, THQs are also important and reliable precursors in quinoline preparation, another group of heterocyclic molecules that has a great number of pharmacological properties (Trpkovska et al., 2003). An efficient route for the preparation of THQs is the acid-catalyzed Povarov reaction that is classified as imino Diels-Alder cycloaddition (Kouznetsov, 2009; Paazderski et al., 2007; Kouznetsov & Mora, 2006; Youssed et al., 2003) that permits the condensation of anilines, aldehydes, and electron-rich alkenes using acidic catalysts under mild conditions to afford new substituted tetrahydroquinolines.

For any Direct Oriented Synthesis (DOS) methodology towards the synthesis of bioactive substituted tetrahydroquinolines and quinolones, this route represents an easily and scalable approach for the investigations on the synthesis of small drug-like (tetrahydro)quinoline molecules containing C-2 aryl fragment, those synthesis could be accomplished via cycloaddition reactions. In this order, this section explain the simple preparation of new *N-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl)* pyrrolidin-2-ones using $BiCl_3$-catalyzed three component Povarov reaction between nitrobenzaldehydes, toluidine and N-vinylpyrrolidin-2-one, and their transformations into potentially bioactive 2-aryl-tetrahydroquinoline derivatives, *N-amidyl* substituted at the C-4 position.

3.1 Synthesis of new *N-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl)* pyrrolidin-2-ones

Having an experience in the construction of diverse heterocycles containing nitrogen via multi-component Povarov reaction, (Kouznetsov et al., 2010; Kouznetsov et al., 2007; Kouznetsov et al., 2006). The preparation of the selected tetrahydroquinoline compounds **14** and **15** was achieved using $BiCl_3$ as a catalyst for the three-component imino Diels-Alder cycloaddition between toluidine **10**, nitrobenzaldehydes **12** and **13** and *N*-vinylpyrrolidin-2-one **11** (NVP) (Bermudez et al., 2011) (Fig. 5).

These reactions proceeded smoothly in MeCN and at room temperature giving final products, substances easy to purify by column chromatography using silica gel as a support and a mixture of petroleum ether and ethyl acetate (2:1) as an isocratic eluent. The *N-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl)* pyrrolidin-2-ones **14** and **15** can be obtained with good respective yields 95% and 70% (Table 3) as a easily handle solids.

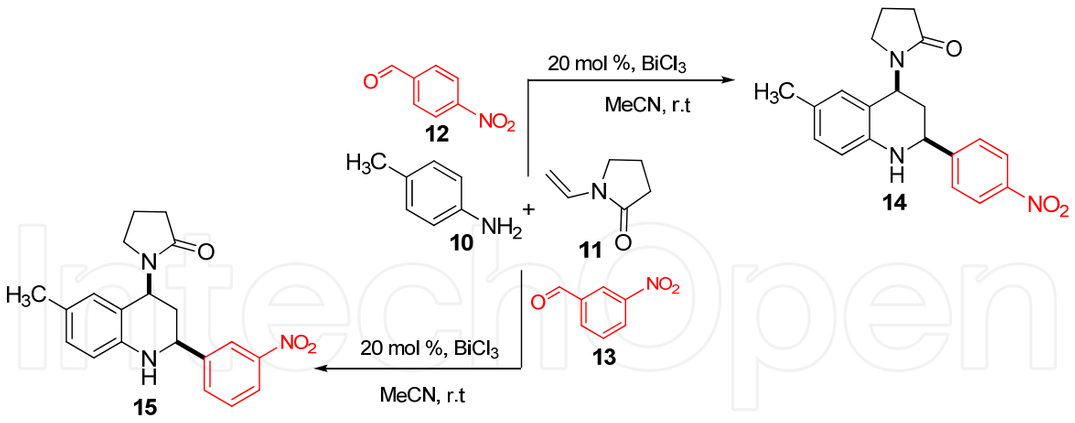

Fig. 5. Synthesis of nitrophenyl-tetrahydroquinolines using the multi-component imino Diels-Alder reaction.

Comp.	Molecular Formula	Molecular Weight	IR (KBr), ν, cm^{-1}	mp, °C	Yield (%)
14	$C_{20}H_{21}N_3O_3$	351.40	3394, 2947, 2916, 1666, 1620	222-223	95
15	$C_{20}H_{21}N_3O_3$	351.40	3271, 2972, 2916, 2854, 1666	242-243	70

Table 3. Physical description, IR data and yields of the 2-nitrophenyl tetrahydroquinolines **14,15**.

3.2 Characterization of the *N-[6-methyl-2-(4´-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one 14 by spectroscopy and spectrometric techniques

The structures of the C-2 substituted tetrahydroquinolines **14** and **15** were confirmed on the basis of analytical and spectral data and were supported by inverse-detected 2D NMR experiments. The IR spectrum show the characteristic absorption bands of the compound **14** at 3394 and 1666 cm^{-1}, assignable to the amine and amide group, respectively, and the nitro group signals at 1512 and 1342 cm^{-1}. Their mass spectrum showed a molecular ion m/z: 351, it coincided with the molecular weight (351 g/mol). The ^1H NMR spectrum of this compound presented the 4-H proton signal at 5.69 ppm, observed as a double doublet with the coupling constants 6.4 Hz and 11.1 Hz.

This fact suggested axial-axial and axial-equatorial interactions between 4-H and 3-H protons. On the other hand, the 2-H proton signal was observed at 4.65 ppm with the coupling constants 3.1 Hz and 10.7 Hz that indicated at vicinal axial-axial and axial-equatorial interactions (Fig. 6).

The high value of the coupling constant (10.7-11.1Hz) of the 4-H and 2-H protons confirmed the axial proton configurations; therefore, substituents of the C-2 and C-4 positions of tetrahydroquinoline ring have the equatorial disposition, respectively.

On the other hand, it was found by the COSY experiment that the signal at 2.13-1.99 ppm belongs to the 3-H proton, observing the 3-H (4"-H) (2.13–1.99 ppm) and 4.65 ppm (2-H) and 5.69 ppm (4-H) cross peaks interactions (Fig. 7).

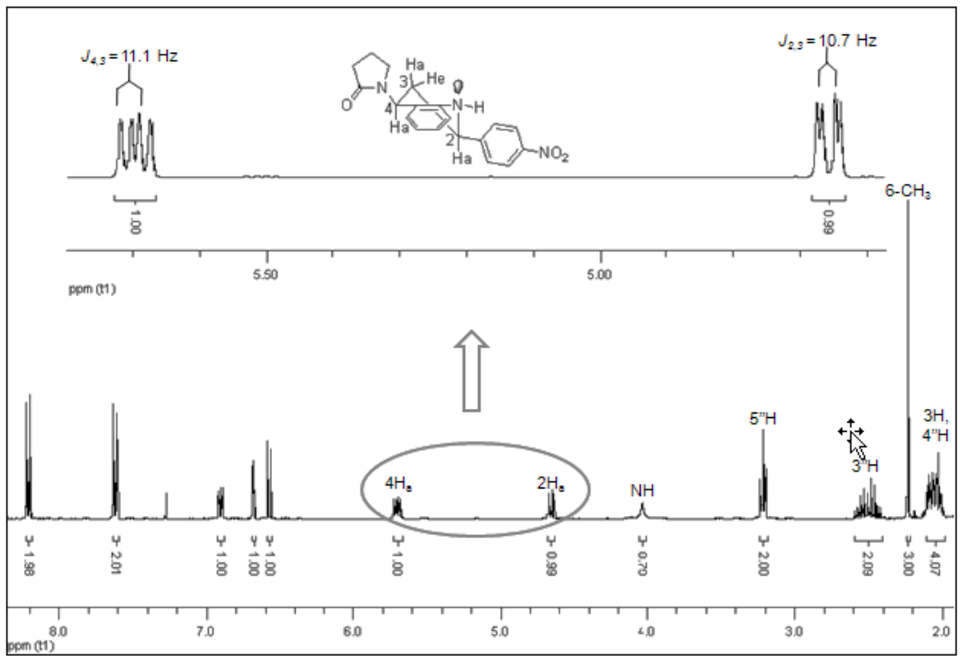

Fig. 6. ^{1}H NMR spectra of *N-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one **14**.

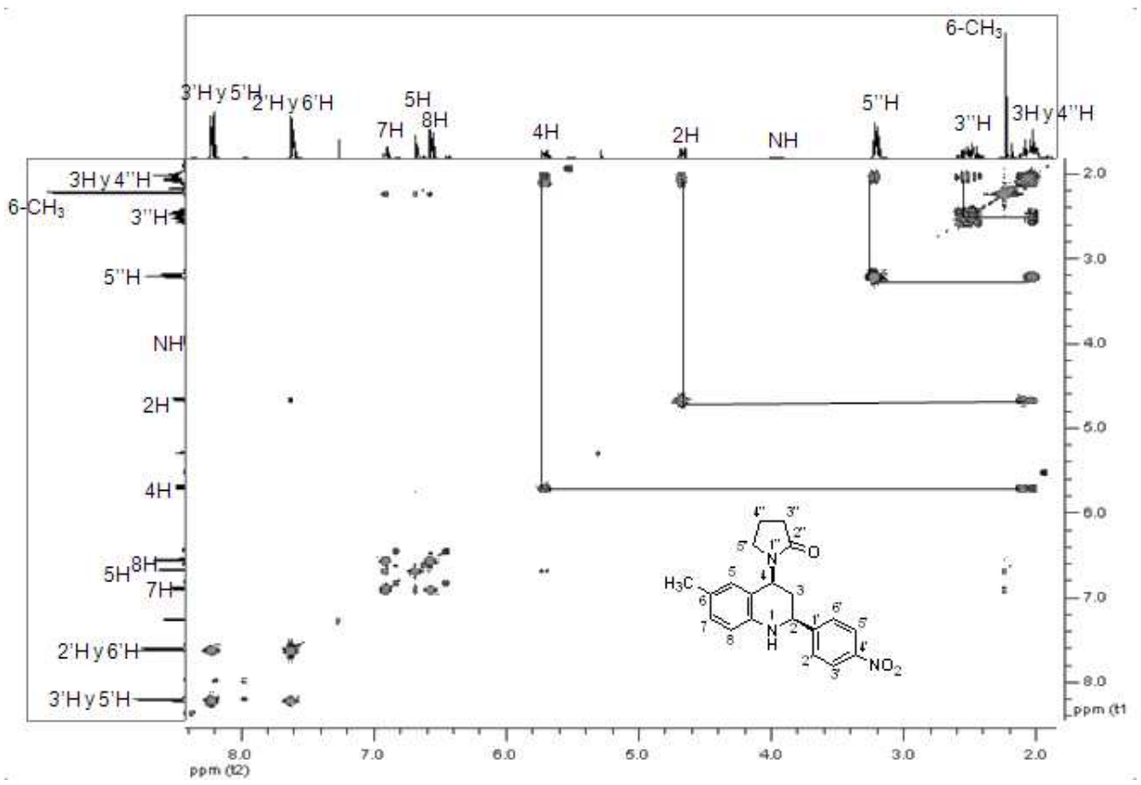

Fig. 7. COSY spectrum of *N-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one **14**.

The nitro-isomer **15** has similar chemical behavior in the spectra data. The chemical structures of the obtained *N-(1,2,3,4-tetrahydroquinolin-4-yl)* pyrrolodin-2-one molecules were strongly confirmed through IR, ^{1}H and ^{13}C NMR analyses.

However, having a possible mechanism of realized multi-component condensation, we could anticipate the various diastereomers the *cis* or *trans* configuration. For these reasons, further structural studies were realized.

3.3 X-Ray diffraction single crystal study

Samples crystals of both compounds of interest were growth by slow evaporation in ethanol. However, the difficulty to obtain suitable crystals from compound **15** only allows performing the study for the compound **14**. The diffraction data of the compound **14** were collected at 273K using a CCD area detector with graphite-monochromatic Mo K_{α} radiation (λ = 0.71073 Å).

This data were computed using Bruker-AXS software. For solution and refinement of the structure Shelxs-97 and Shelxl-97 (Sherldrick, 1997a; Sheldrick, 1997b) were used respectively. Molecular and crystal structures were obtained using Mercury software (Allen, 2002).

The molecular structure for the compound is presented in the Figure 8, where a *cis* conformation of the C-2 and C-4 substituents is evident, as well as a chair configuration that adopts tetrahydroquinoline system.

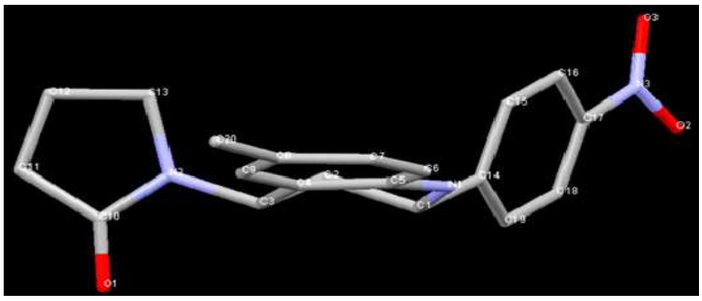

Fig. 8. Representation of the unit cell of *N-[6-methyl-2-(4´-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one **14**.

The details of cell data and refinement for the compound **14** are summarized in Table 4.

Unit cell parameters	a = 9.109 (2) Å b = 9.2812 (5) Å c = 11.011 (3) Å α = 90.939° (6) β = 100.023° (6) γ = 93.309° (6)
Volumen	913.998 Å^3
System	Triclinic
Space Group	P-1 (No. 2)
Z	2

Table 4. Crystallographic data obtained by four-circle diffractometry.

The structure packing is showed in the Figure 9 and finally, the powder profile simulated by the single crystal data is shown in Figure 10.

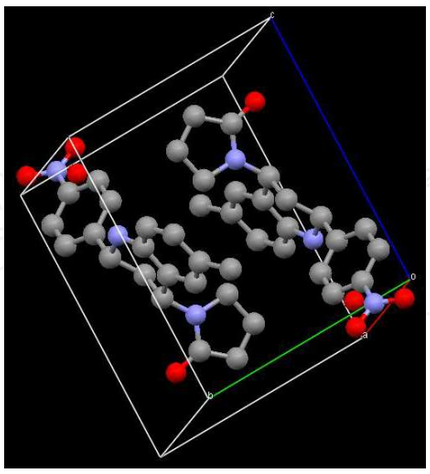

Fig. 9. Molecular packing of the unit cell of *N-[6-methyl-2-(4´-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one **14**.

By means of single crystal study of the compound *N*-[6-methyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl] pyrrolidin-2-one 1**5** was determined that crystals obtained from ethanol crystallizes in the triclinic system with space group P-1 (No 2).

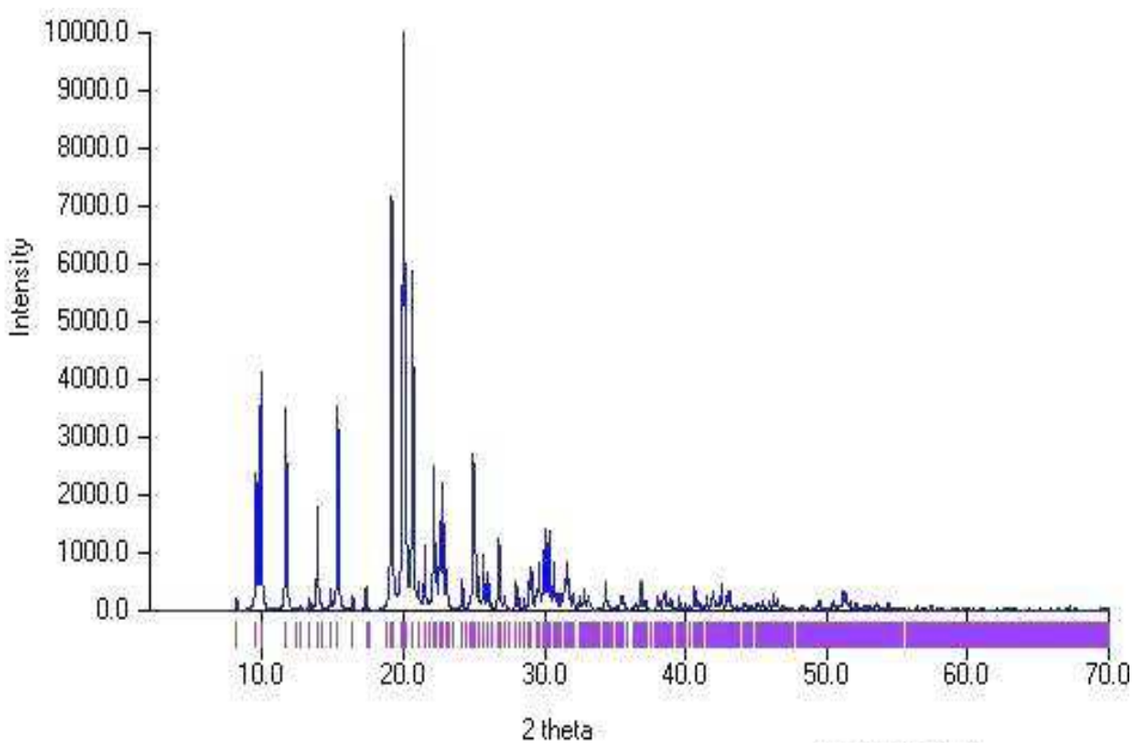

Fig. 10. Diffraction profile of *N-[6-methyl-2-(4´-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one **14** simulated in Mercury software.

Table 5 shows the atomic positions. Carbon-bound H-atoms positions were idealized (C-H=0.93 Å), with H atoms riding on the atoms to which they were attached.

Number	Label	Xfrac	Yfrac	Zfrac
1	O1	0.3653	0.1204	0.8134
2	O2	-0.2751	0.1442	-0.069
3	O3	-0.2013	0.3615	-0.0633
4	N1	0.4385	0.1546	0.3218
5	N2	0.3999	0.2993	0.6826
6	N3	-0.1902	0.242	-0.0246
7	C1	0.2924	0.1252	0.3587
8	C2	0.281	0.2232	0.4685
9	C3	0.4102	0.2053	0.576
10	C4	0.5578	0.2277	0.5329
11	C5	0.5642	0.1906	0.4089
12	C6	0.7043	0.1999	0.3716
13	C7	0.8288	0.2495	0.4491
14	C8	0.8236	0.2933	0.5723
15	C9	0.6885	0.2777	0.6119
16	C10	0.3777	0.2485	0.7914
17	C11	0.3736	0.3751	0.8765
18	C12	0.3898	0.5036	0.8068
19	C13	0.4078	0.4576	0.6777
20	C14	0.1688	0.1496	0.2534
21	C15	0.1696	0.2758	0.1861
22	C16	0.0548	0.3036	0.0958
23	C17	-0.0664	0.2057	0.0701
24	C18	-0.0721	0.0818	0.135
25	C19	0.0456	0.0548	0.2264
26	C20	0.9644	0.3544	0.6587

Table 5. Atomic positions in the unit cell of *N-[6-methyl-2-(4´-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl]* pyrrolidin-2-one (**14**).

3.4 Conclusions

The synthesis of two new nitro-isomers of *N-(tetrahydroquinolinyl)* pyrrolidin-2-ones using a versatile and simple methodology called the three component imino Diels-Alder cycloaddition is illustrated as an excellent route for the preparation of novel kind of structures, the spectral analysis showed the 2-H_{axial}, 4-H_{axial} configuration; therefore the di-equatorial disposition of the C-2 and C-4 substituent that confirmed the formation of the endo-adduct during a Diels-Alder cycloaddition process.

The full characterization of *N*-[6-methyl-2-(4´-nitrophenyl)-1,2,3,4-tetrahydroquinoline-4-yl] pyrrolidin-2-one **14** was possible due to the single crystal X-ray diffraction studies, given the following data: the compound **14** crystallizes in the triclinic system with *a* = 9.109(2) Å, *b* = 9.281(5) Å, *c* = 11.011(3) Å, α = 90.939 (6)°, β = 100.023 (6)°, γ = 93.309 (6)°, Z = 2, space group P-1 [No. 2], and V = 1054.0 A^3.

4. Convenient and scaleable three-step synthesis of new N-benzyl (pyridyl) cinnamamides from substituted (hetero)aromatic aldehydes

The relatively stable amide bond is not only common in natural-occurring materials like peptides and vitamins, it is also found in many synthetic substances. Among these important and interesting class of organic molecules: *N-benzylcinnamides* and *N-phenylcinnamides* have been always the focus of attention of organic, bioorganic and medicinal chemists due to their many useful synthetic applications (Takasu et al., 2003; Bernini et al., 2006; Nair et al., 2007) as well as their diverse (bio)chemical properties (Curtis et al., 2003; Tamiz et al., 1999; Lewis et al., 1991). Moreover, *N-amide* cinnamic acid derivatives are frequently presented in the nature (Mbaze et al., 2009; Vasques et al., 2002).

Both types of amides could be prepared generally via acylation reactions of the corresponding benzylamines or anilines and cinnamic acid derivatives (anhydrides or acyl halides) that are frequently used in the preparation of drug candidate molecules (Carey et al., 2006). However, the known acylation reactions for *N-benzylcinnamides* preparation employ hazardous and corrosive reagents (e.g., $SOCl_2$, PCl_3, $(COCl)_2$, NEt_3) besides the starting functionalized benzylamines are not commercially available products, and almost any of their functional groups needs to be protected to ensure chemoselective amide formation (Nesterenko et al., 2003).

Considering the reported biological properties of certain *N-arylcinnamides* and *N-benzylcinnamides* that have showed *in vitro* antimycotic activity (Leslie et al., 2010) and the inhibition of the transcription of carcinogenic genes in infected cells (Sienkiewicz et al., 2007). The need of an easy, rapid and "green" protocol for the synthesis of these kind of compounds is necessary to explore new pharmacological targets, and in this order the challenge of the organic chemistry is currently focused on the design of novel methodologies that suppress the use of acyl chloride (including any dangerous reagent required for their synthesis) and promoting the direct condensation between carboxylic acids and amines, coupling that currently is performed using efficient promoters such as *N,N'*-dicyclohexylcarbodiimide (DCC) (Amma & Mallouk, 2004), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (ByPOB) (McCalmont, 2004; Baures et al; 2002), triethylamine (Walpole, et al., 1993) and boron-based catalysts like BH_3·THF (Huang et al., 2007).

The search of bioactive not only requires a good synthetic route, all the reagents must be stable and inexpensive to improve the structural complexity as in the biological properties. In this case, the integrity of most of the benzylamines is compromised when they are exposed to air moisture or even stored at low temperatures for a long period of time (Nazih & Heissler, 2002). A way to prevent this effects is based on choosing an appropriate strategy that enables the preparation of the desired amount benzylamines at lower cost than those acquired commercially, which could be possible by reduction of nitriles (Haddenham et al., 2009) and oximes (Gannett et al., 1988).

The "green" protocol described in this section is directed to enhance the disadvantages already described for the existing methodologies. Considering first the excellent chemical reactivity of aldehyde group against hydroxylamine's nucleophilicity to give oximes, this part was based on the existing methodologies which were improved according to the green

chemistry principles with the use of less hazardous Na_2CO_3 as a base to release the nucleophile (Dallinger & Kappe, 2007; Roberts & Strauss, 2005; Yadav & Meshram, 2001; Varma, 1999). The posterior reduction of the prepared oximes give the functionalized benzylamines (pyridylmethylamines) in quantitative yield, this allows the coupuling of the corresponding amines, without further purification, with cinnamic acid in the presence of boric acid to afford the final products in agreement to our previous experience synthesizing this type of compounds (Hernandez et al., 2008).

4.1 Synthesis of new *N-benzyl* (pyridyl) cinnamamides from substituted (hetero)aromatic aldehydes

The choice of diverse (hetero)aromatic aldehydes **16a-k** was motived by the interest in quest for N-hetarylmethyl cinnamamides with antioxidant and anticancer properties. The direct condensation of **16a-k** and hydroxylamine in the presence of Na_2CO_3 is realize in an ethanol/water medium. Thus, a mixture of aldehydes **16a-k**, Na_2CO_3 and hydroxylamine hydrochloride was mixed in deionized water for 5 min. at room temperature, and then a small amount of the respective aldehyde was added for a period of another 5 minutes. The reaction mixture was stirring for 15 min. and after traditional work-up, the pure products, the substituted aldoximes **17a-k** were obtained in quantitative yield (Fig. 11).

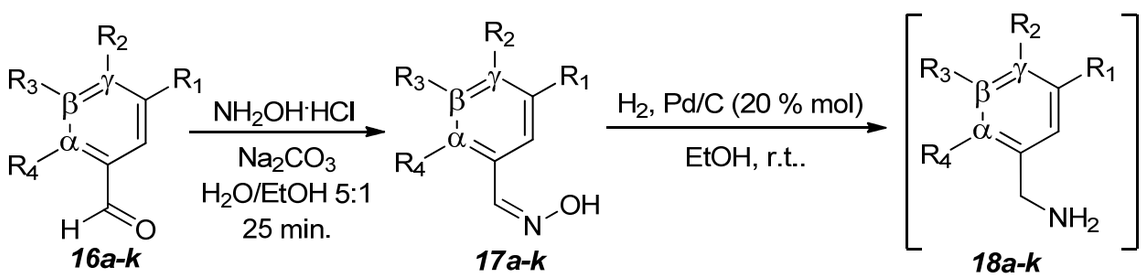

Fig. 11. Preparation of the respective (hetero)benzylamines from the aldehydes **16a-k** in a scalable methodology.

Taking into consideration that one of the most "atom-economical" procedures for the preparation of an amine is hydrogenation of an oxime in which the only by-product is water, we addressed also to this approach (Trost, 1995; Trost, 1991). Having in our hands the eleven solid and stable aldoximes **17a-k** obtained in first step, each of them was hydrogenated at room temperature overnight under H_2 atmosphere using 10 % palladium on charcoal in ethanol (Fig. 11).

The hydrogenation mixture obtained in the second step is filtered through celite and the filtrate was concentrated to dryness allowing the crude amine **18a-k**, which was quickly added, without any further purification, to an anhydrous toluene solution of *trans*-cinnamic acid **19** in the presence of $B(OH)_3$ (10 % mol) at 110 ^oC for 6-10 h (Fig. 12).

The required workup at the end of the reaction can be perform in two ways: one consist in the precipitation of the product of interest with a solution of $NaHCO_3$ and their subsequent washing with water or that can be purified with column chromatography depending on the complexity of the final crude. For the second choice, the recommended support is neutral or basic alumina (Al_2O_3) due to the acidity of the *trans*-cinnamic acid that will remain from the

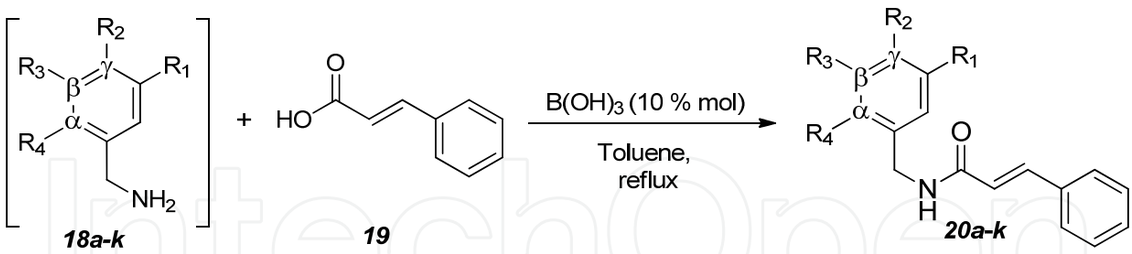

Fig. 12. Rational design of the three-step synthesis of the corresponding *N-benzyl cinnamides* from substituted (hetero) aromatic aldehydes.

reaction. An acid support like common silica gel (SiO_2) will retain both substances (the amide of interest and the residual cinnamic acid). After the method of preference for the purification of the amides has applied, the final products the N-benzylcinamides **20a-k** were obtained in excellent yields and with a high purity level (Table 6).

Comp. **20**	R_1	R_2	R_3	R_4	Yield (%)
a	H	Cl	H	H	80
b	H	OCH_3	H	H	87
c	H	OCH_3	OCH_3	H	91
d	H	OH	OCH_3	H	67
e	H	OCH_3	OH	H	72
f	OCH_3	OCH_3	OCH_3	H	95
g	-OCH_2O-		H	H	94
h	H	H	-C_4H_4-		92
i	H	H	H	α=N	84
j	H	H	β=N	H	89
k	H	γ=N	H	H	90

Table 6. Synthesized *N-benzyl cinnamides* **20a-k**.

The ^1H NMR spectra of the compounds **20** display a general group of characteristic signals for this series. For example, in the cinnamide **20g** spectrum the methylene protons at 4.47 ppm (2H, d, *J* = 5.7 Hz, -CH_2) is the signal that is observed in high fields, signal that is coupling with the N-H signal, observed as a triplet at 5.99 ppm (1H, *J* = 5.7 Hz, NH). The analysis of olefinic protons indicate the *trans* configuration of the final products when the high value of the coupling constant observed is compared with the typical value for the *cis* configuration: in the case of compound **20g**, and for the entire 11 synthetized molecules, the assignment of the proton at 6.41 ppm (1H, d, *J* = 15.7 Hz, =CHCO) and the coupling in trans form with the other olefinic proton, the one that appears at lower fields, at 7.66 ppm (1H, *J* = 15.7 Hz, =CHPh) confirmed the configuration of all the products (Fig. 13).

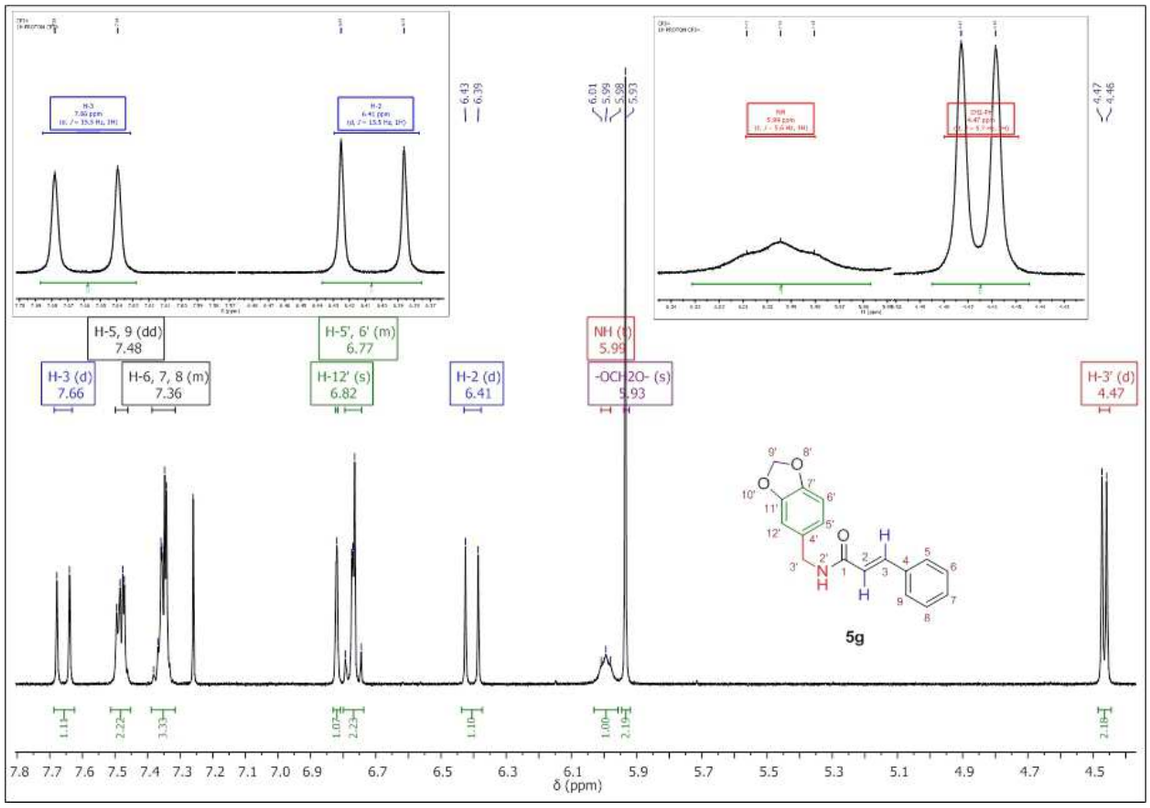

Fig. 13. ^{1}H-NMR spectrum of the *N-(3,4-methylenedioxybenzyl) cinnamamide* **5g**.

4.2 Conclusions

The improvement of the existing methodologies for the preparation of benzylamines, is described as protocol that enhances the efficiently, easily, rapidly and safety way in which the oximes can be obtained, leading to explore their synthetic use in the preparation of more complex systems or evaluate their pharmacological properties as a potential reactivators of the acetylcholinesterase enzyme (Sinko et al., 2010) or their allergenic activity (Bergström et al., 2008).

Taking into account that boronic compounds have showed catalytic activity in peptide synthesis, it is demonstrated also that boric acid is a practical and useful catalyst for amidation between cinnamic acid and the prepared benzylamines due to its remarkable catalytic potential. The notable features of this procedure are mild and green reaction conditions, good reaction rates, cleaner reaction profiles and excellent global yields for a linear synthesis of three steps. The recollected spectral data described for *N-benzyl cinnamides* should be reliable in the structural analysis of natural cinnamides and these substances could serve as a model for small-molecule screening towards new bioactive compounds.

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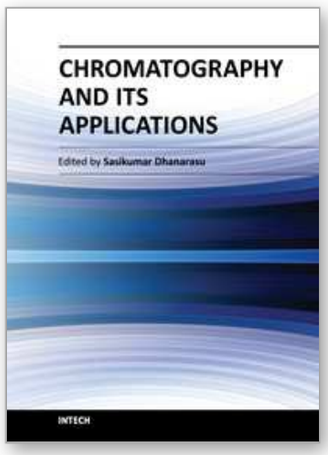

Chromatography and Its Applications

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Chromatography is a powerful separation tool that is used in all branches of science, and is often the only means of separating components from complex mixtures. The Russian botanist Mikhail Tswett coined the term chromatography in 1906. The first analytical use of chromatography was described by James and Martin in 1952, for the use of gas chromatography for the analysis of fatty acid mixtures. A wide range of chromatographic procedures makes use of differences in size, binding affinities, charge, and other properties. Many types of chromatography have been developed. These include Column chromatography, High performance liquid chromatography (HPLC), Gas chromatography, Size exclusion chromatography, Ion exchange chromatography etc. In this book contains more details about the applications of chromatography by various research findings. Each and every topics of this book have included lists of references at the end to provide students and researchers with starting points for independent chromatography explorations. I welcome comments, criticisms, and suggestions from students, faculty and researchers.

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