

Simple preparation of new *N*-(6-methyl-2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-ones and their spectroscopic analysis

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Abstract

Objectives. To prepare new *N*-(1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-one molecules and to characterize them by spectroscopic methods. **Materials and methods.** All reagents were purchased from Aldrich, commercial grade. The purity of the products and the composition of the reaction mixtures were monitored by thin layer chromatography over Silufol UV₂₅₄ chromatoplates (0.25 mm). Product isolation and purification were performed by column chromatography (SiO₂) using ethyl acetate. **Results.** Preparation of new *N*-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-ones has been achieved via the one-pot synthesis, based on a BiCl₃-catalyzed imino Diels-Alder cycloaddition reaction of toluidine, *N*-vinylpyrrolidin-2-one and 4-nitro- or 3-nitrobenzaldehydes. The structure of the pyrrolidine derivatives was confirmed by ¹H NMR and ¹³C NMR studies, in addition to inverse-detected 2D NMR experiments and monocrystal X-ray diffraction. **Conclusions.** An efficient, economic, and fast synthetic route (multi-component imino Diels-Alder reaction) was employed in the construction of several new tetrahydroquinoline derivatives, useful and attractive rigid skeleton with well-defined stereochemistry.

Key words: tetrahydroquinoline derivatives, *N*-substituted pyrrolidin-2-ones, three component imino Diels-Alder reaction, one-pot synthesis.

Resumen

Preparación simple de nuevas *N*-(6-metil-2-nitrofenil-1,2,3,4-tetrahydroquinolin-4-il) pirrolidin-2-onas y su análisis espectroscópico.

Objetivos. Preparar nuevas moléculas *N*-(1,2,3,4-tetrahydroquinolin-4-il) 2-oxopirrolidínicas y caracterizarlas por métodos espectroscópicos.

Materiales y métodos. Todos los reactivos usados son de Aldrich, grado comercial. La pureza de los productos y la composición de las mezclas de reacción fueron monitoreadas por cromatografía en capa fina sobre cromatoplasmas de Silufol UV₂₅₄ (0.25 mm). El aislamiento y purificación se realizó usando cromatografía en columna (SiO₂), usando acetato de etilo. **Resultados.** La preparación de las nuevas *N*-(tetrahydroquinolin-4-il) pirrolidin-2-onas 4-nitrofenil (ó 2-nitrofenil) sustituidas en C-2 del anillo tetrahydroquinolínico, se realizó vía síntesis *one-pot* basada en la reacción de cicloadición imino Diels-Alder catalizada por BiCl₃ entre toluidina, *N*-vinilpirrolidin-2-ona y 4-nitrobenzaldehído (3-nitrobenzaldehído). La estructura de los derivados pirrolidínicos fue confirmada por ¹H RMN y ¹³C RMN, además de experimentos 2D RMN y difracción de rayos X de monocristal. **Conclusiones.** Una ruta eficiente, económica y rápida (reacción imino Diels-Alder multi-componente) fue empleada para la construcción de nuevas moléculas *N*-(tetrahydroquinolin-4-il) 2-oxopirrolidínicas, esqueleto muy atractivo y usado con estereoquímica bien definida.

Palabras clave: derivados de la 1,2,3,4-tetrahydroquinolina, pirrolidin-2-onas *N*-sustituidas, reacción imino Diels-Alder de tres componentes, síntesis *one-pot*.

Resumo

Preparação simples de novas N-(6-metil-2-nitrofenil-1,2,3,4-tetrahydroquinoline-4-il) pirrolidin-2-onas e sua análise espectroscópica.

Objetivos. Preparar novas moléculas N-(1,2,3,4-tetrahydroquinoline-4-il) 2-oxopirrolidínicas e sua caracterização por espectroscopia.

Materiais e métodos. Todos os reagentes utilizados são de Aldrich, de grau comercial. A pureza dos produtos e a composição das misturas de reação foram monitoradas por cromatografia em camada fina sobre cromatoplasmas de Silufol UV₂₅₄ (0,25 mm). O isolamento e purificação foi realizado utilizando cromatografia em coluna (SiO₂), utilizando acetato de etila. **Resultados.** Preparação de novas N-(tetrahydroquinoline-4-il) pirrolidin-2-onas 4-nitrofenil (ou 2-nitrofenil) substituídas em C-2 do anel tetrahydroquinoline foi realizada através da síntese “one pot” baseada na reação de cicloadição imino Diels-Alder catalisada por BiCl₃ entre toluidina, N-vinilpirrolidin-2-ona e 4 nitrobenzaldehyde (3 nitrobenzaldehyde). A estrutura dos derivados pirrolidínicos foi confirmada por ¹H RMN y ¹³C RMN, experimentos 2D RMN, assim como difração de raios X e monocristais. **Conclusões.** Uma rota eficiente, econômica e rápida (reação imino Diels-Alder multi-componente) foi utilizada para a construção de novas moléculas N-(tetrahydroquinoline-4-il) 2-oxopirrolidínicas esqueleto muito atraente e usado com estereoquímica bem definida.

Palavras-chave: derivados de 1,2,3,4-tetrahydroquinoline, pirrolidin-2-onas N-substituídas, reação imino Diels-Alder de três componentes, síntese “one-pot”.

Introduction

Quinoline and tetrahydroquinoline structures are an essential feature of many natural products. These heterocycles play a key role in heterocyclic and medicinal chemistry. Their synthesis by various methodologies has been published extensively (1-4). Polyfunctionalized tetrahydroquinolines (THQs) are molecules of great interest in organic synthesis since many natural products present this system in their structure, and because they exhibit diverse biological activities (5-9). Besides their notorious bioactivity, THQs are also important and reliable precursors in quinoline preparation, another group of heterocyclic molecules that has a great number of pharmacological properties (10). An efficient route in the preparation of THQs is the acid-catalyzed Povarov reaction that is classified as imino Diels-Alder cycloaddition (11-13) and permits the condensation of anilines, aldehydes, and electron-rich alkenes using acidic catalysts under mild conditions to achieve the obtainment of new substituted tetrahydroquinolines.

As a part of our research program in the DOS methodology towards the synthesis of bioactive substituted tetrahydroquinolines and quinolines, we are currently conducting research on the synthesis of small drug-like (tetrahydro)quinoline molecules containing a C-2 aryl fragment, whose synthesis could be accomplished via cycloaddition reactions. We want to report here the simple preparation of new N-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-ones using BiCl₃-catalyzed three-component Povarov reaction among 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.

Materials and methods

All reagents were purchased from Aldrich, commercial grade. The purity of the products and the composition of the reaction mixtures were monitored by thin layer chromatography over Silufol UV₂₅₄ 0.25 mm-thick chromatoplates. The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. The IR spectra were recorded on an Infracum FT-02 spectrophotometer in KBr. ¹H NMR spectra were recorded on Bruker AM-400 or AC-300 spectrometers in CDCl₃. Chemical shifts are reported in ppm. (A signal at 7.24 ppm of CHCl₃ in CDCl₃ was used as reference for protons). A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HPMS Chemstation Data System was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 [5%-phenyl-poly(dimethyl-siloxane)]. X ray diffraction single-crystal technique with an AFC7S four circle diffractometer was used. The data acquisition was made to 293 K of temperature with MoKa (λ = 0.71073 Å) radiation and a measurement range between 1 and 25° of theta (θ). The structure elucidation and the refinement were made with the software Shelxs-97 and Shelxl-97, respectively. Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer and were within ± 0.4 of the theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV₂₅₄ TLC aluminum sheet.

Synthesis of new N-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-ones. General procedure

20 mol% BiCl₃ was added to a solution of the toluidine 1 (2.85 mmol) and an appropriate nitrobenzaldehyde **3** or **4** (3.13 mmol) in anhydrous CH₃CN (15 mL) under N₂, and

N-vinylpyrrolidin-2-one **2** (3.42mmol) was added to the resulting mixture. The reaction mixture was stirred at room temperature for 20-24 h and then quenched with a solution of Na₂CO₃. The organic layer was separated and dried with Na₂SO₄. The organic solvent was removed in vacuum to obtain the respective *N*-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-ones **5** or **6**. The reaction mixture was adsorbed under silica gel and separated by chromatography (Hexane / Ethyl acetate).

N-(6-Methyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-one (**5**)

Yellow solid. Mp. 222-223°C. Yield 95%. Anal. calcd for C₂₀H₂₁N₃O₃: C, 68.35; H, 6.00; N, 11.99. M = 351.40. Found: C, 68.46; H, 6.22; N, 12.06. GC-MS: R_t = 44.57 min; *m/z* (EI): 351 (M⁺). IR (KBr): ν 3394, 2916, 1666 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.20 (2H, d, *J* = 8.7 Hz, 3'-H and 5'-H), 7.61 (2H, d, *J* = 8.7 Hz, 2'-H and 6'-H), 6.90 (1H, dd, *J* = 8.0, 1.7 Hz, 7-H), 6.68 (1H, s, 5-H), 6.57 (1H, d, *J* = 8.1 Hz, 8-H), 5.69 (1H, dd, *J* = 11.1, 6.4 Hz, 4-H_{ax}), 4.65 (1H, dd, *J* = 10.7, 3.1 Hz, 2-H_{ax}), 4.03 (1H, br.s, NH), 3.21 (2H, t, *J* = 6.9 Hz, 5''-H), 2.59-2.41 (2H, m, 3''-H), 2.23 (3H, s, 6-CH₃), 2.13-1.99 (4H, m, 4''-H and 3-H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 175.8, 150.6, 147.4, 142.9, 129.0, 128.1, 127.3 (2C), 126.9, 123.9 (2C), 118.8, 115.4, 56.0, 48.1, 42.2, 35.3, 31.3, 20.5, 18.1 ppm.

N-(6-Methyl-2-(3-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-one (**6**)

Yellow solid. Mp. 242-243 °C. Yield 70%. Anal. calcd for C₂₀H₂₁N₃O₃: C, 68.36; H, 6.02; N, 11.96. M = 351.40. Found: C, 68.57; H, 6.28; N, 11.74. GC-MS: R_t = 45.32 min; *m/z* (EI) 264 (M⁺-87). IR (KBr): ν 3326, 2900, 1630 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.41 (1H, t, *J* = 2.0 Hz, 2'-H), 8.20 (1H, ddd, *J* = 8.1, 2.3, 1.0 Hz, 6'-H), 7.77 (1H, br.d, *J* = 7.8 Hz, 4'-H), 7.57 (1H, t, *J* = 7.8 Hz, 5'-H), 6.93 (1H, dd, *J* = 8.1, 2.0 Hz, 7-H), 6.72 (1H, s, 5-H), 6.60 (1H, d, *J* = 8.1 Hz, 8-H), 5.74 (1H, dd, *J* = 11.2, 7.1 Hz, 4-H), 4.71 (1H, dd, *J* = 10.4, 3.5 Hz, 2-H), 4.01 (1H, br.s, NH), 3.30-3.20 (2H, m, 5''-H_{pyrr}), 2.62-2.45 (2H, m, 3''-H_{pyrr}), 2.26 (3H, s, 6-CH₃), 2.16-2.13 (2H, m, 3-H), 2.10-2.02 (2H, m, 4''-H_{pyrr}) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 175.9, 148.7, 145.4, 132.9, 129.9, 128.5, 127.0, 126.7, 122.9, 121.4, 118.9, 115.5, 55.8, 48.2, 43.2, 31.4, 12.2 ppm.

Results and discussion

Based on our experience in the construction of diverse heterocycles containing nitrogen via multi-component Povarov reaction (14-16), the preparation of the selected tetrahydroquinoline compounds **5,6** was achieved using the BiCl₃-catalyzed three-component imino Diels-Alder cycloaddition between toluidine **1**, nitrobenzaldehydes **3,4** and *N*-vinylpyrrolidin-2-one **2** (Figure 1).

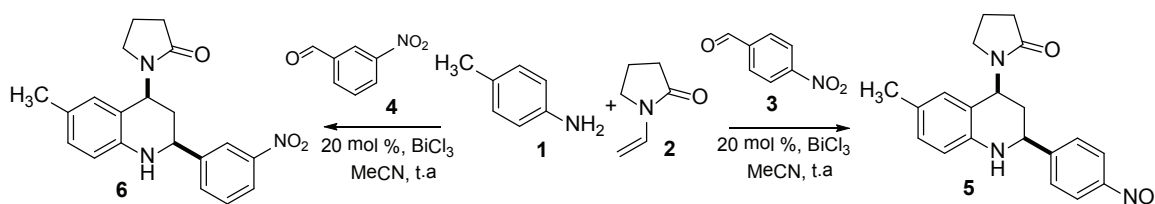


Figure 1. Synthesis of nitrophenyl-tetrahydroquinolines using the multi-component imino Diels-Alder reaction.

1. Physical description, IR data and yields of the 2-nitrophenyl tetrahydroquinolines (5,6).

Comp.	Molecular Formula	Molecular Weight	IR (KBr), ν, cm ⁻¹	mp, °C	Yield (%)
5	C ₂₀ H ₂₁ N ₃ O ₃	351.40	3394, 2947, 2916, 1666, 1620	222-223	95
6	C ₂₀ H ₂₁ N ₃ O ₃	351.40	3271, 2972, 2916, 2854, 1666	242-243	70

These reactions proceeded smoothly in MeCN at room temperature, giving final products that were substances easy to purify and to manipulate. The N-(2-nitrophenyl-1,2,3,4-tetrahydroquinolin-4-yl) pyrrolidin-2-ones **5** and **6** were obtained with good yields: 95% and 70%, respectively (Table 1).

The structures of the C-2 substituted tetrahydroquinolines **5** and **6** were confirmed on the basis of analytical and spectral data and were supported by inverse-detected 2D NMR experiments. IR spectrum characteristic absorption bands of the compound **5** were observed at 3394 and 1666 cm^{-1} , assignable to the amine and amide groups, respectively, and the nitro group signals at 1512 and 1342 cm^{-1} . Their mass spectrum showed a molecular ion m/z : 351 that 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 (Figure 2).

The high value of the coupling constant (10.7-11.1 Hz) of the 4-H and 2-H protons confirmed the axial proton

configurations; therefore, substitutes of the C-2 and C-4 positions of the 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 (Figure 3).

The nitro-isomer **6** has similar chemical behavior in the spectra data. The chemical structures of the obtained N-(tetrahydroquinolinyl) pyrrolidin-2-one molecules were strongly confirmed through IR, ^1H and ^{13}C NMR analyses; however, having a possible mechanism of achieved multi-component condensation, we could anticipate the various diastereomers, *cis* or *trans* configuration. For these reasons, further structural studies were carried out.

X-Ray Diffraction Single Crystal Study

Samples of both compounds **5** and **6** were grown by slow evaporation in ethanol; however, we could obtain suitable crystals only for the compound **5**. The diffraction data of the compound **5** were collected at 273K using a CCD area detector with graphite-monochromatic Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The data were computed using Bruker-AXS software. For the solution and refinement of the structure, Shelxs-97 (17) and Shelxl-97 (18) were used respectively.

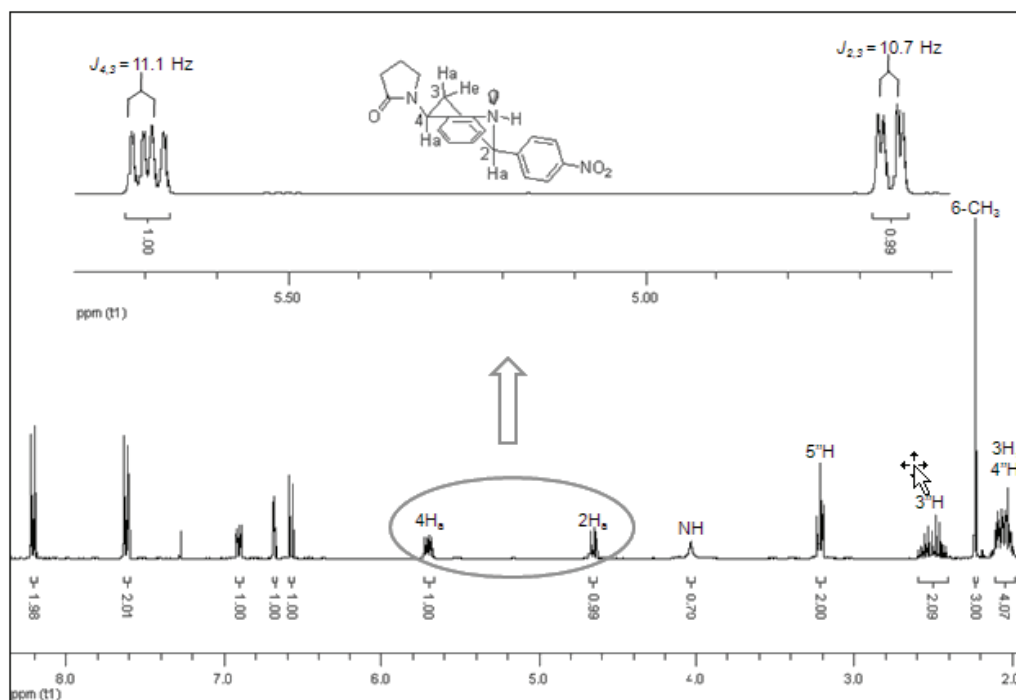


Figure 2. ^1H NMR spectra of N-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl] pyrrolidin-2-one (**5**).

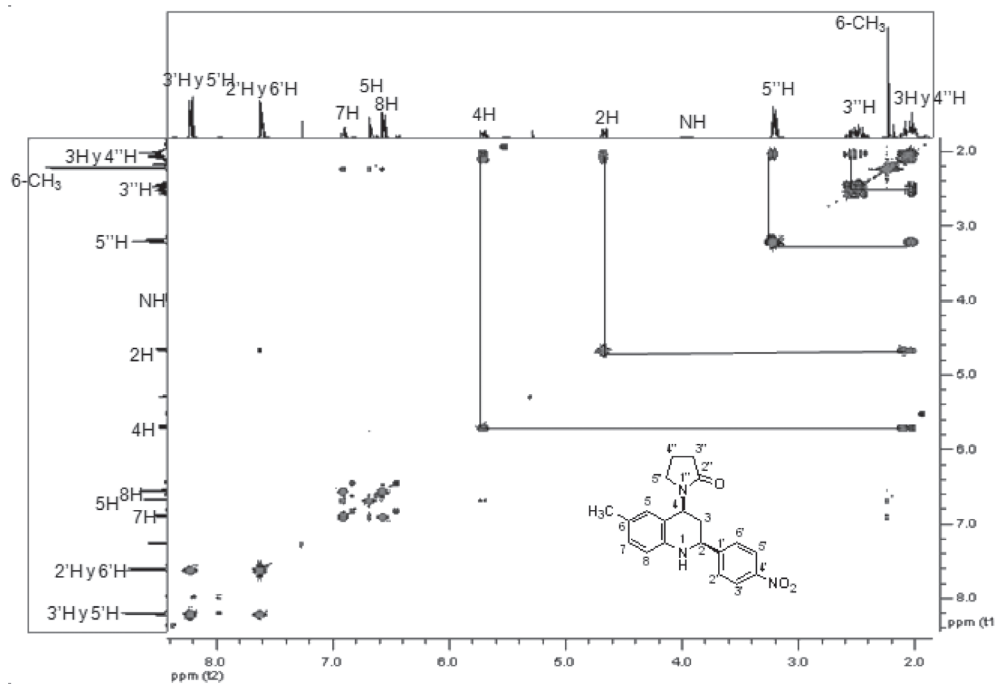


Figure 3. COSY spectrum of *N*-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl] pyrrolidin-2-one (**5**).

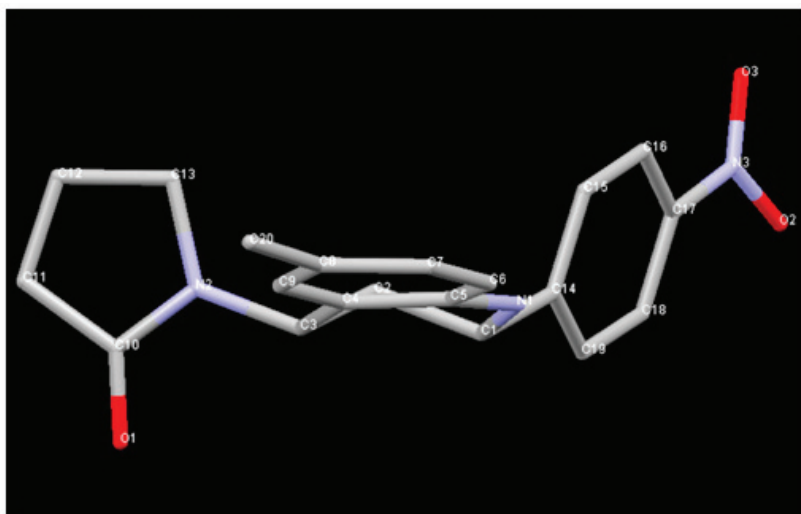


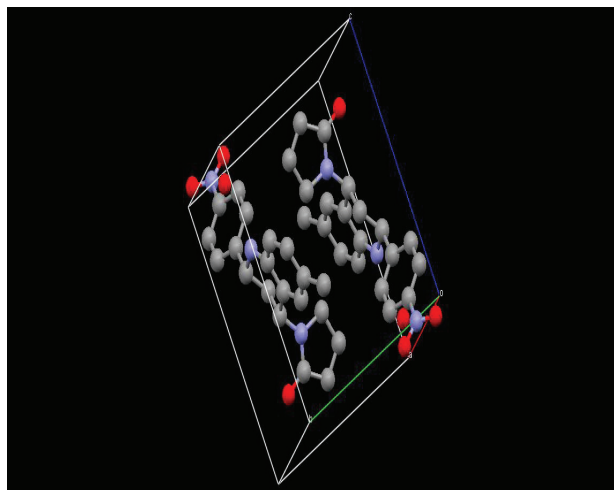
Figure 4. Representation of the unit cell of *N*-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl] pyrrolidin-2-one (**5**).

Molecular and crystal structures were obtained using Mercury software (19). The molecular structure for the compound is presented in the figure 4. A *cis* conformation of the C-2 and C-4 substitutes is evident, as well as a chair configuration adopted by the tetrahydroquinoline system.

Details of cell data and refinement for the compound **5** are summarized in table 2.

Table 2. Crystallographic data obtained by four-circle diffractometry.

Unit cell parameters	$a = 9.109 (2) \text{ \AA}$
	$b = 9.2812 (5) \text{ \AA}$
	$c = 11.011 (3) \text{ \AA}$
	$\alpha = 90.939^\circ (6)$
	$\beta = 100.023^\circ (6)$
	$\gamma = 93.309^\circ (6)$
Volume	913.998 \AA^3
System	Triclinic
Space Group	P-1 (No. 2)
Z	2

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

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

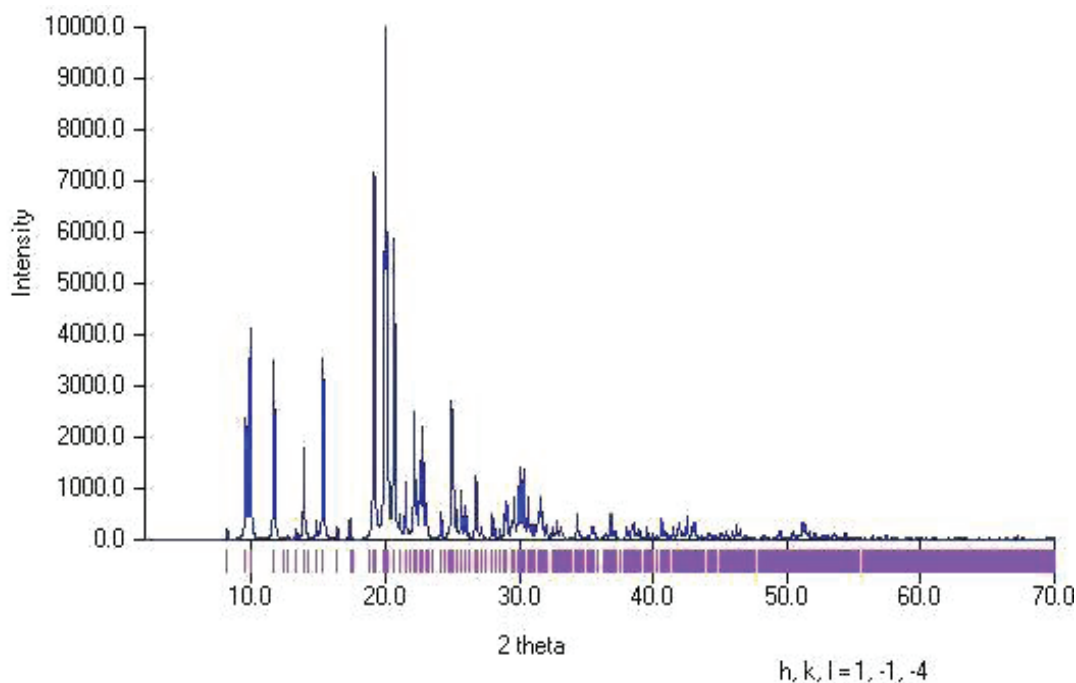


Figure 6. Diffraction profile of *N*-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinolin-4-yl] pyrrolidin-2-one (**5**) simulated in Mercury software.

The packing structure is shown in figure 5 and the powder profile simulated by the single crystal data is shown in figure 6.

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

Table 3 shows the atomic positions. Carbon-bound H atom positions were idealized (C-H=0.93 Å), with H atoms riding on the atoms to which they were attached.

Conclusions

We synthesized two nitro-isomers of *N*-(tetrahydroquinolinyl) pyrrolidin-2-ones using a versatile and simple methodology called the three component imino Diels-Alder cycloaddition. The spectral analysis showed the 2- H_{axial} , 4- H_{axial} configuration; therefore, the di-equatorial disposition of the C-2 and C-4 substitutes confirmed the formation of the endo-adduct during a Diels-Alder cycloaddition process. The

full characterization of the *N*-[6-methyl-2-(4'-nitrophenyl)-1,2,3,4-tetrahydroquinoline-4-yl] pyrrolidin-2-one **5** was possible due to the single crystal X-ray diffraction technique, which provided the following data: compound **5** crystallizes in the triclinic system with $a = 9.109(2)$ Å, $b = 9.281(5)$ Å, $c = 11.011(3)$ Å, $\alpha = 90.939(6)^\circ$, $\beta = 100.023(6)^\circ$, $\gamma = 93.309(6)^\circ$, $Z = 2$, space group P-1 [No. 2], and $V = 1054.0$ Å³.

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Conflicts of interest

The authors declare that no conflicts of interest exist in relation to this work.

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