Revista Iberoamericana de las Ciencias Biológicas y Agropecuarias

Ciba

ISSN: 2007 - 9990

Caracterización espectroscópica del producto de condensación de una dicetona con difenilhidrazina

Spectroscopic characterization of the condensation product of a diketone with diphenylhydrazine

Caracterização espectroscópica do produto de condensação de uma dicetona com difenil-hidrazina

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Revista Iberoamericana de las Ciencias Biológicas y Agropecuarias

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Resumen

A pesar de haber sido sintetizadas desde 1887, las hidracinas e hidrazidas son un conjunto de compuestos del que sorprendentemente no se conocía su destino metabólico hasta años recientes. Actualmente, se sabe que las hidrazonas y sus complejos metálicos presentan innumerables aplicaciones farmacológicas. Los derivados de hidracinas, hidrazonas e hidrazidas se han utilizado como antibióticos, analgésicos, antiinflamatorios y antipiréticos. Asimismo, han tenido papeles importantes como antiplaquetarios, diuréticos, en la insuficiencia cardiaca y funciones antileucemia o en general como agentes antineoplásicos. En la industria funcionan como plastificantes, estabilizadores de polímeros, antioxidantes e iniciadores de la polimerización y las hidrazonas hidroxiladas se utilizan como herbicidas, insecticidas y estimulantes del crecimiento de plantas. Desde esta perspectiva, se puede observar que las hidrazonas tienen actividades farmacológicas promisorias. De ahí que se diseña este trabajo, para sintetizar, purificar y caracterizar compuestos tipo hidrazona con estructuras nuevas para, posteriormente, evaluar su actividad en líneas celulares específicas. El objetivo de este trabajo es la síntesis en condiciones Química Verde, así como la purificación y caracterización de la hidrazona que lleva el nombre de *(E)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona*. La espectroscopia de ultravioleta, infrarrojo, resonancia magnética nuclear y espectrometría de masas, procesos realizados a la hidrazona sintetizada, concuerdan con la estructura propuesta.

Palabras clave: bencilo, hidrazina, producto de condensación, síntesis en condiciones de Química Verde

Abstract

Hydrazines and hydrazides are a group of compounds that were synthetized since 1887, but their metabolic activity was not known until recent years. Nowadays, it is known that hydrazones and their metal complexes have many pharmacological applications. Hydracines derivatives, hydrazones and hydrazides have been used as antibiotics, analgesics, anti–inflammatories, antipyretics, as well as antiplatelet profile, diuretics, for heart failure, anti–leukemia functions or in general terms, as anti–neoplastics. At industrial scale, these compounds function as plasticizers, polymer stabilizers, antioxidants and polymerization initiators. Hydroxilated hydrazones are used

as herbicides, insecticides and plant–growth stimulators. From this perspective, it can be observed that hydrazones have promising pharmacological activities. This is why the aim of the work is to synthetize, purify and characterize hydrazone compounds with new structures in order to evaluate their activity in specific cell lines. Specifically, this research paper deals with synthesis in Green conditions, purification and characterization of hydrazone with the name (*E*)–2–(2,2–diphenylhydrazono)–1,2–diphenilethan–1–one. UV, IR, NMR and MS Spectroscopies have been applied to the compound in order to corroborate the synthetized hydrazone and it was found that the structure agrees with the proposed structure.

Keywords: benzyl, hydrazine, condensation product, synthesis in green conditions.

Resumo

Apesar de terem sido sintetizadas desde 1887, as hidrazinas e hidrazidas são um grupo de compostos cujo destino metabólico era surpreendentemente desconhecido até os últimos anos. Atualmente, sabe-se que as hidrazonas e seus complexos metálicos apresentam inúmeras aplicações farmacológicas. Os derivados de hidrazinas, hidrazonas e hidrazidas têm sido utilizados como antibióticos, analgésicos, antiinflamatórios e antipiréticos. Eles também desempenharam papéis importantes como antiagregantes plaquetários, diuréticos, nas funções de insuficiência cardíaca e antileucemia ou, em geral, como agentes antineoplásicos. Na indústria, eles trabalham como plastificantes, estabilizadores de polímeros, antioxidantes e iniciadores de polimerização e hidrazonas hidroxiladas são usados como herbicidas, inseticidas e estimulantes de crescimento de plantas. Nessa perspectiva, pode-se observar que as hidrazonas apresentam promissoras atividades farmacológicas. Assim, este trabalho é projetado para sintetizar, purificar e caracterizar compostos semelhantes a hidrazona com novas estruturas para posteriormente avaliar sua atividade em linhas celulares específicas. O objetivo deste trabalho é a síntese em condições de Quimica Verde, bem como a purificação e caracterização da hidrazona com o nome de (*E*)-2- (2,2-difenil-hidrazono) -1,2-difeniletan-1-ona. A espectroscopia de ultravioleta, infravermelho, ressonância magnética nuclear e espectrometria de massa, processos realizados na hidrazona sintetizada, concordam com a estrutura proposta.

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ISSN: 2007 - 9990

Palavras-chave: benzila, hidrazina, produto de condensação, síntese em condições de Química Verde.

Fecha recepción: Octubre 2017 **Fecha aceptación:** Febrero 2018

Introduction

Carbonyl group reactions with ammonia derivatives are called condensation reactions because they are released as a by-product of water. These carbonyl group reactions are of nucleophilic addition and are carried out in two stages: addition and elimination, both are accelerated by acid catalysis, through an equilibrium that can be handled by the principle of Le Châtelier. The specific case of benzyl with diphenylhydrazine as reactants gives as a product a hydrazone and a water molecule. This reaction has its importance in the fact that hydrazones are easily identifiable products because they are solid, in many cases they form colored crystals that have characteristic melting points.

Hydrazones have been shown to possess a wide variety of biological activities and are thought to be due to the functional group they contain, NHN = CH, where there is a high electron density and, for this reason, they constitute a vast diversity of compounds for the development of new drugs.

That, on the one hand and on the other, it is known that diseases are an integral part of the lives of human beings. They can be caused by bacteria, parasites, fungi and viruses. And while they can be chronic, acute and sporadic, among others, the variety of types in terms of danger, symptoms and causes is enormous. However, the drugs used to combat them have at the same time undesirable side effects and contraindications. For all the above, researchers have seen the need to perform an exploration to discover drugs with increased biological activities to achieve that the administration of these is performed in low concentrations. At the same time, it is necessary to try

to acquire a drug with high selectivity, sensitivity, specificity and efficacy to achieve the best results.

In order to show the enormous range of biological activities of the hydrazones and, in this way, to expose the importance, transcendence and usefulness of their synthesis, in the following paragraphs we will talk about some serious diseases and the physiological activities of the group of the hydrazones.

Influenza, commonly known as influenza, is an infection of the respiratory tract caused by the RNA virus of the Ortomixoviridae family. The influenza virus causes a variety of symptoms, including fever, runny nose, cough, muscle pain and pneumonia (Thompson et al., 2003, Taubenberger and Morens, 2008). Although it is considered as a disease that heals spontaneously, without a specific treatment, it can become an infection that constitutes a threat of high risk for the life of infants, elderly and immunocompromised patients. Around 3 and 5 million of the world's population is infected annually with influenza, generating between 250,000 and 500,000 deaths worldwide (Shirey et al, 2013). The continuing alarming threat of a potential influenza pandemic, in addition to the recent isolation of resistant strains of neuroaminidase inhibitors, increases the requirements for the development of new anti-influenza drugs. In that sense, many 1,3,4-thiadiazoles, 1,3,4-oxadiazoles and 1,2,4-triazoles have shown a broad spectrum of biological activities (Tawfika, *et al.*, 2018).

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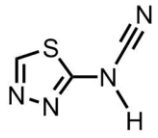
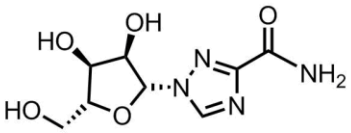
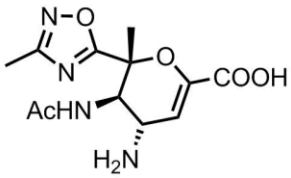
Figura 1. Estructura de 1,3,4–tiadiazoles, 1,3,4–oxadiazoles y 1,2,4–triazoles



(1,3,4-tiadiazol-2-yl)-λ^2-azanocarbonitrilo



1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihidroxi-5-(hidroximetil) tetrahidrofuran-2-il)-1*H*-1,2,4-triazol-3-carboxamida



ácido (2*R*,3*R*,4*S*)-3-acetamido-4-amino-2-metil-2-(3-metil-1,2,4-oxadiazol-5-il)-3,4-dihidro-2*H*-piran-6-carboxílico

Fuente: Tawfika *et al.* (2018)

The hydrazine derivatives, hydrazone and hydrazide derivatives are compounds that contain N-N bond. Such molecules are relatively rare in nature and have been isolated from plants, marine organisms and microorganisms. These compounds exhibit extraordinary structural diversity and relevant biological activities. The enzymes involved in the formation of the N-N bond are still unknown, but many lines of evidence support the participation of activated steps involving N-nitrosation and N-hydroxylation (Le Goff and Ouazzani, 2014).

Natural and synthetic hydrazones have a broad spectrum of biological activities including antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antituberculous and antitumor activities (Padmini et al., 2013; Rollas and Küçükgüzel, 2007). In particular, acylhydrazones with a azomethine proton, NHN = CH, represent relevant candidates for drug discovery (Sharma, Sharma and Dikshit, 2011).

There are two types of trypanosomes that cause disease in humans, African and American. Human African trypanosomiasis (HAT) is caused by the tsetse fly transmitted by protozoan parasites of the species Trypanosoma brucei. HAT is endemic in several areas of sub-Saharan Africa and is subject to epidemic outbreaks (Franco, Simarro, Diarra and Jannin, 2014). It is speculated that the drugs used in the treatment of HAT serve to target biological molecules such as suramin (Wilkinson and Kelly, 2009): a large polyanion that exerts inhibitory activities on several metabolic pathways of protozoa.

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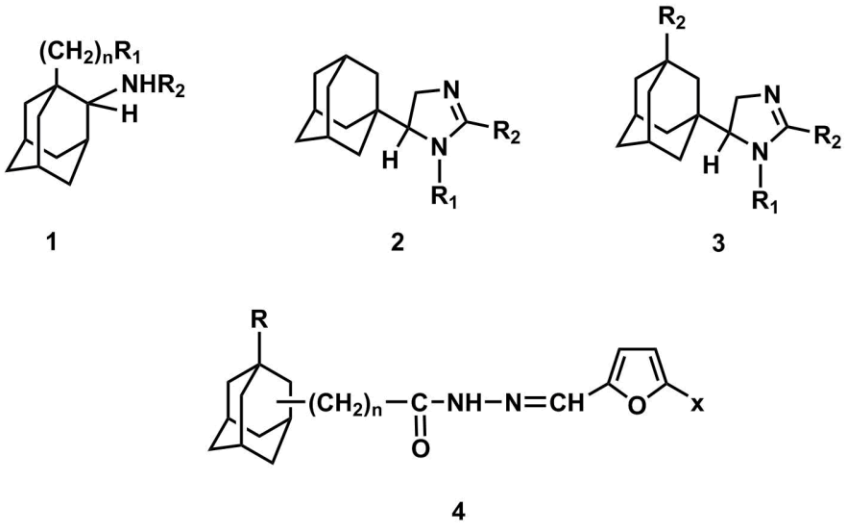
While American human trypanosomiasis or Chagas disease is caused by the protozoan parasite Trypanosoma cruzi, which is transmitted by species of redivid insects (Triatoma infestans, Rhodinius prolixus and Panstrogylus megistus). The disease is endemic in several areas of Latin America. The line of drugs that lead the treatments of American trypanosomiasis are the nitroaromatic compounds, nifurtimox and benznidazole (Bermudez, Davies, Simonazzi, Pablo and Palma, 2016, Patterson and Wyllie, 2014). Its trypanocidal activity is attributed to cytotoxic metabolites produced by the activity of the trypanosome nitroreductase type.

Since nifurtimox has a hydrazone structure of 5-nitro-2-furaldehyde, the adamantane derivatives exhibit a range of trypanocidal activity. Foscolos et al. (2016) designed 5-nitro-2-furaldehyde hydrazones with adamantane alkanohydrazides of the general type shown to evaluate their selective activity against T. cruzi and T. brucei (see figure 2).

Figura 2. 1–alquil–2–adamantanoaminas **1**, 5–(1–adamantil)–2–imidadazolinas **2**, **3** y adamantano carbohidrazonas **4**



Fuente: Foscolos *et al*. (2016)

Figure 3, on the other hand, shows the reactants and the reaction conditions used for the synthesis of the adamantane carbohydrazones.

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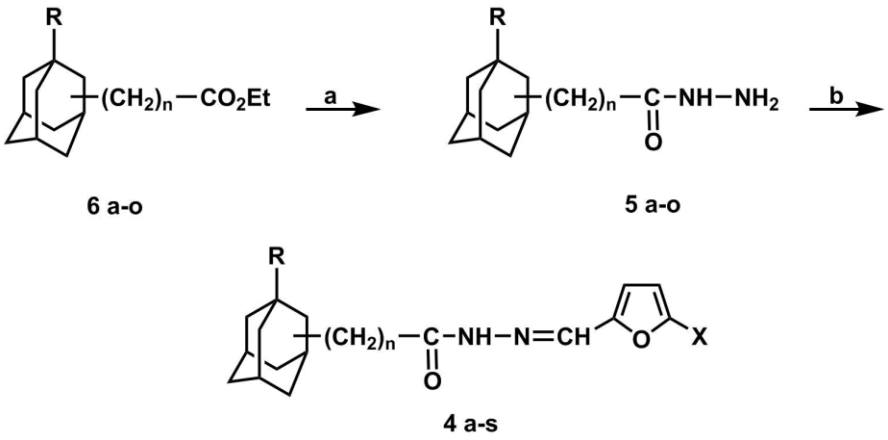
Figura 3. Reactivos y condiciones: *a)* hidrato de hidrazina en DEG a 210–220 ºC, irradiación de microondas por 90 min (*n* = 0.1) o hidrato de hidrazina en EtOH a 150 ºC, irradiación de microondas por 150 min (*n* = 2), *b)* 5–nitro–furaldehído o 2–furaldehído en EtOH a Tº ambiente por 12 h



Fuente: Foscolos *et al*. (2016)

It is clear that, from the results obtained, the hydrazones of 2-furaldehyde with adamantane alkanohydrazides supporting a nitro group in position 5 of the furan ring are active against both T. cruzi and T. brucei.

The most active compounds show a potency 20 times greater than nifurtimox, the most potent against trypanosomes. In order to compare the IC50 of nifurtimox against T. brucei and T. cruzi which is 2.7 μM and 2.1 μM, respectively (Wilkinson, Taylor, Horn, Kelly, Cheeseman, 2008).

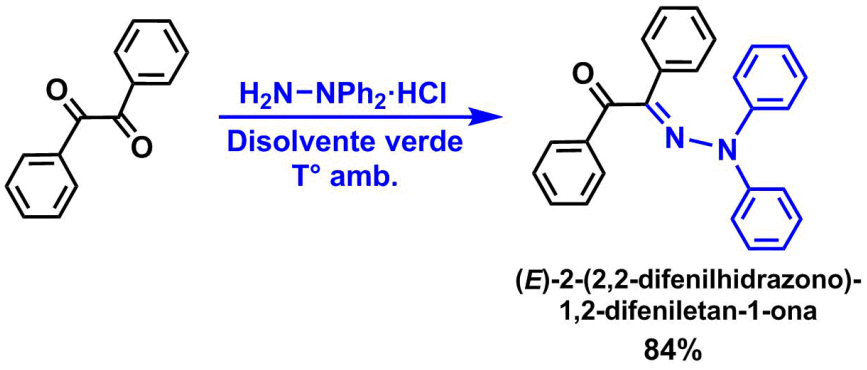
Objective

The main objective of this project is the synthesis in conditions according to the green chemistry of a compound with a new structure of the carbocyclic hydrazone type, for its later separation and purification through standard techniques. Also, perform its characterization using spectroscopic techniques such as ultraviolet-visible (UV-Vis), infrared (IR) and magnetic resonance of hydrogen and carbon thirteen (1H NMR, 13C NMR), Correlated Spectroscopy

(COZY), Heteronuclear Simple Quantum Coherence (HSQC), mass spectrometry (MS) and X-rays.

Next, we present the synthesis scheme under conditions of Green Chemistry of the aromatic hydrazone derived from the condensation reaction of benzyl and (E) -2- (2,2-diphenylhydrazono) -1,2-diphenyletan-1-one (see figure 4).

Figura 4. Esquema de la síntesis de la (*E*)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona.



Fuente: Elaboración propia

Material and methods

The reactants and the deuterated solvents were obtained from the company Aldrich and were used without further purification. The reaction was monitored by CCF with aluminum plates Alugram Sil G / UV254 with a thickness of 0.54 mm.

The IR spectra were determined in KBr pellets and were recorded on a Nicolet FTIR Magna 750. The 1 H NMR and 13 C NMR spectra were obtained on a Varian VX400 (400 MHz) using tetramethylsilane (TMS) as internal reference. The chemical shifts were obtained on a delta scale as parts per million (ppm) and to indicate the multiplicity of the signals in 1H the following abbreviation was used: multiplet (m). The mass spectrum was obtained in a JEOL MStation MS-700 6 keV, and the data are given in units of mass / charge (m / z). The X-ray diffraction data were collected with an Oxford Diffraction Gemini "A" diffractometer.

The methodology was based on chemistry under green chemical conditions with the reagents in equimolar quantities, the use of green solvent (EtOH) and without the use of heating; method that saves time and costs. In addition, it is known that in an organic chemistry laboratory the use of chromatographic columns for the separation and purification of the products is very frequent, however, for the present project, it was not necessary because the hydrazones, being solid products, do not require of this specific method of separation, which reduces the use of large quantities of solvents, waste and byproducts harmful to the environment.

The methodology used for the synthesis of (E) -2- (2,2-diphenylhydrazono) -1,2-diphenyletan-1-one was the following: Diphenylhydrazine (1427 mmol, 262.91 mg) was dissolved in ethanol (green solvent). To this solution was added dropwise (1427 mmol, 300 mg) of benzyl, reagent previously dissolved in the same solvent. The reaction mixture was maintained at room temperature and was monitored by means of the thin layer chromatography (TLC) technique until the disappearance of the raw material, diketone. Then, the reaction mixture was filtered under vacuum. The hydrazone was purified by recrystallization until light yellow crystals were obtained (Toledano et al., 2015). Subsequently, the hydrazone was characterized by melting point (p.f.), and UV-Vis spectroscopy, I.R., 1H-NMR, 13C-NMR, COZY, HSQC and E.M., as well as X-ray diffraction analysis.

Results

The structure of the product obtained with the chosen numbering is found in figure 5. In this figure the modification that suffered the benzyl is marked in blue and it is the way to observe how the reaction made the formation of the bond> C = NN- (hydraziniliden).

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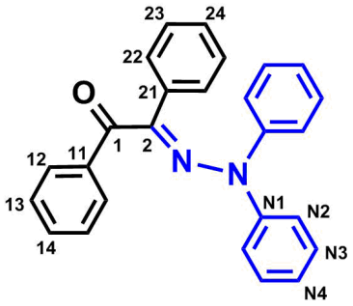
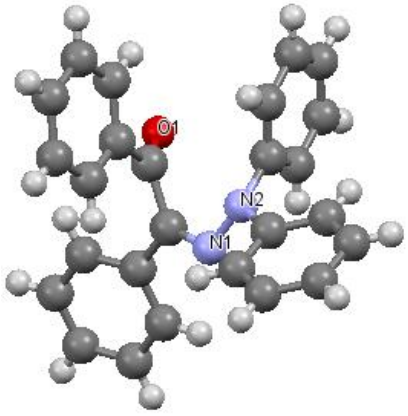
Figura 5. Estructura de la (*E*)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona



Fuente: Elaboración propia

In figure 6, on the other hand, the X-ray structure of the synthesized hydrazone is shown, where it can be confirmed that the new bond exists> C = N-N-, besides that there is a carbonyl group present (red atom)), which shows that the condensation reaction was suffered by a single carbonyl group.

Figura 6. Estructura de rayos–X de la (*E*)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona

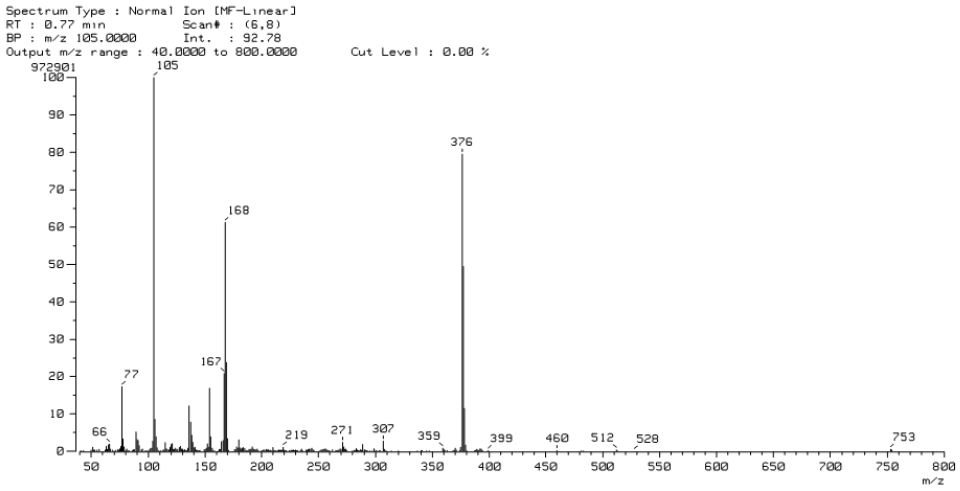


Fuente: Elaboración propia

The physical and spectroscopic data of the synthesized hydrazone (E) -2- (2,2-diphenylhydrazono) -1,2-diphenyletan-1-one are shown below: Yellow crystals, yield: 84% at 25 ° C, m.p. 106-108 ° C. UV-Vis □max = 335 nm. FT IR: (film): (cm-1): 3059□□ (Csp2-H); 1674 □□ (C = C-C = O),

1587.1487 □ (C = N), 1194 (C-N 3rd arom.); 757 □□C-H) out of phenyl plane. In the spectrometry named HRMS (High-Resolution Mass Spectrometry) using the technique (FAB +) was calculated for the structure of formula C26H20N2O [M + H] +, m / z 377.1576; found for [M + H] +, m / z 377.1671. The main fragments are: 376 (79), 168 (62), 105 (100), 77 (18), which correspond to portions of the molecule with the proposed structure.

Figura 7. Espectro de masas de la hidrazona (*E*)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona



Fuente: Elaboración propia

The maximum lambda, λ_{max} = 335nm, it corroborates the fact that in that part of the UV-Vis spectrum the compounds absorb the violet color and, therefore, the yellow color is that observed in the synthesized compound. The FTIR spectra show the most important functional groups of the hydrazone and, compared to the IR spectrum of the raw material, differences are noted.

In the 1 H-NMR spectrum of (E) -2- (2,2-diphenylhydrazono) -1,2-diphenyletan-1-one at 7.65 ppm there is a multiple signal corresponding to 2 hydrogens, which are those that are bound to C12. Centered at 7.56 ppm, another multiple signal that integrates for 3 hydrogens bound to C22 and C14. At 7.38 ppm there is a multiple signal that integrates for 5 hydrogens bound to the C13, C23 and C24 atoms. At 7.18 ppm, another multiplet that integrates for 4 hydrogens bound to the carbons identified with N4

and, finally, at 6.95 ppm is located one more multiplet that integrates for 4 hydrogens bound to the carbons identified with N3.

In the 13 C NMR spectrum, the following signals are located: 205.38 (C1), 197.01 (C2), 149.20 (N1), 146.28 (C11), 135.37 (C21), 133.89 (C14), 129.24 (C23), 128.98(N2), 128.85 (C22) 128.67 (C24), 128.59 (C13), 126.36 (C12), 124.70 (N4), 123.20 (N3).

The 1H NMR spectra completely coincide with the proposed structure, both in the chemical shifts and the multiplicities, and the integration of each peak and 13C NMR, also agree with the chemical shifts and with the different carbon atoms that hydrazone synthesized presents .

Figures 8 and Figure 9 show the two-dimensional COZY and HSQC of the synthesized hydrazone.

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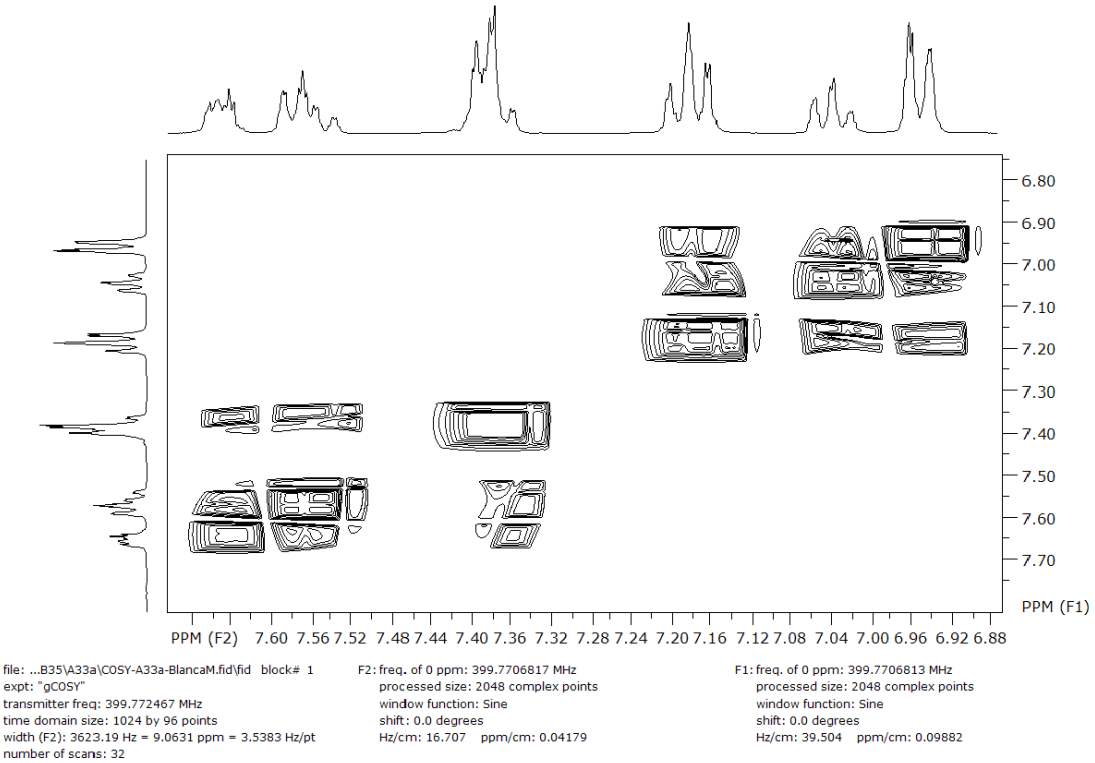
Figura 8. Espectro de RMN en 2D, COSY de la hidrazona sintetizada (*E*)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona



Fuente: Elaboración propia

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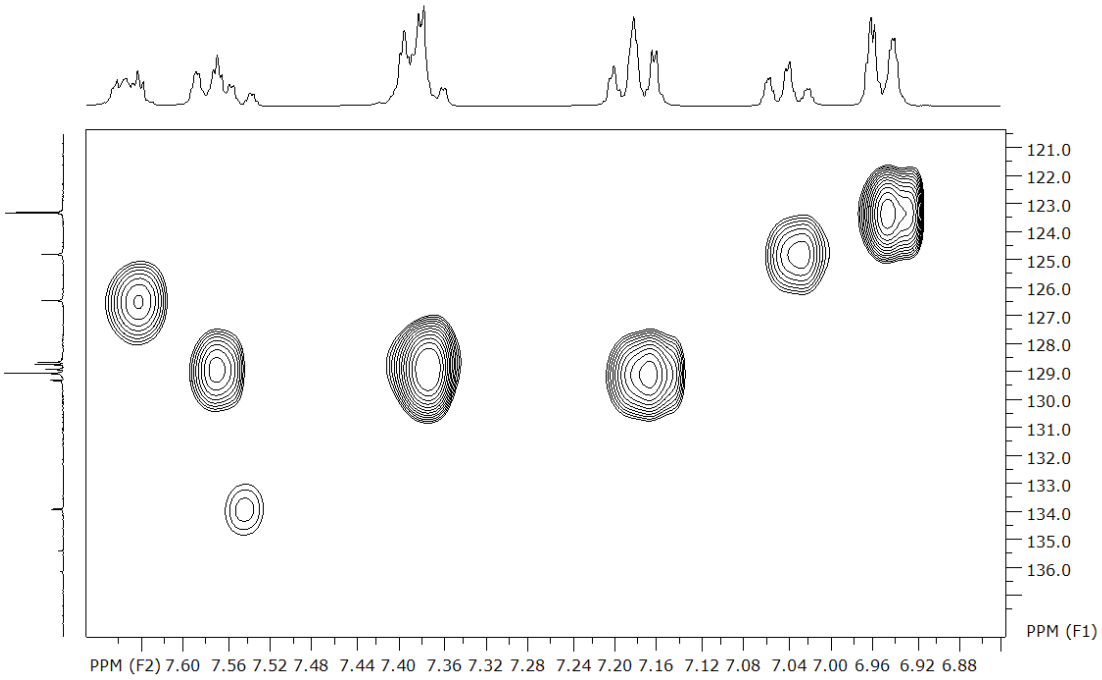
Figura 9. Espectro de RMN en 2D, HSQC de la hidrazona sintetizada (*E*)–2–(2,2–difenilhidrazono)–1,2–difeniletan–1–ona



Fuente: Elaboración propia

Conclusions

The synthesis of hydrazone (E) -2- (2,2-diphenylhydrazono) -1,2-diphenyletan-1-one, which was obtained in the form of light yellow crystals by synthesis under conditions of Green Chemistry with good yield corresponding to the hydrazone of name (E) -2- (2,2-diphenylhydrazono) -1,2-diphenyletan-1-one.

The product obtained was characterized by spectroscopic techniques of UV-Vis, IR, 1H NMR, 13C NMR, two-dimensional spectra of COZY, HSQC, X-rays, and E.M which correspond to the chemical structure that is being proposed.

The hydrazone synthesized has great chemical virtues from the structural point of view, since it can serve as a useful raw material for different subsequent reactions due to the versatility of the remaining carbonyl group, in addition to the existence of the imino group and the phenyls,

reactive sites to perform various chemical reactions with the aim of expanding the range of products that can be obtained and that, once synthesized, could be evaluated in any cell line from which you want to experiment, for example, as anticancer compounds, as bactericides or as amebicides, as We have already experimented with hydrazones from the same group, but with different structures.

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Revista Iberoamericana de las Ciencias Biológicas y Agropecuarias

Ciba

ISSN: 2007 - 9990

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