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Characterization of Novel Spiroxyindoles Through NMR and IR Spectroscopic Analysis

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ABSTRACT

Using caffeinium hydrogen sulfate (CHS) as a catalyst, this study demonstrates an easy and eco-friendly way to synthesize functionalized spiroxyindoles. Through optimization of reaction conditions, it was shown that a 10 mol% concentration of CHS greatly improves the yield to 92% in under 4 hours, as opposed to lesser concentrations and no catalyst, which led to longer reaction times and lower yields. The synthesized spiroxyindoles were confirmed to have intact structures and functional groups by analyzing them using infrared and nuclear magnetic resonance spectroscopy. Nuclear magnetic resonance (NMR) spectroscopy revealed aromatic protons, and infrared (IR) spectroscopy revealed carbonyl and conjugated systems. Consistent with their structural complexity, the spiroxyindoles had molecular weights ranging from 220 to 230 g/mol. In addition to demonstrating CHS's efficacy as an environmentally friendly catalyst in organic synthesis, this study adds to the growing body of knowledge on substances that may find use in medicine and the chemical and physical sciences.

Keywords: Caffeinium, Spiroxyindoles, Catalytic, Organic, Molecular weight

INTRODUCTION

The unusual spirocyclic structures of spiroxyindoles, an intriguing class of chemical molecules, are defined by the fusion of a bicyclic framework with an indole moiety. The structural arrangement of spiroxyindoles imparts important biological and chemical characteristics, which has piqued the interest of medicinal chemists, drug designers, and organic synthesisers. Spiroxyindoles offer a wide variety of pharmacological properties, such as anticancer, anti-inflammatory, and antibacterial actions, which are all attributed to the indole ring system, which is present in many medicines and natural products.

An continuous quest for new molecular architectures that merge the medicinal properties of indole derivatives with the spatial organization of spiro compounds led to the invention of spiroxyindoles. Two rings sharing an atom at the spiro center give the molecule a three-dimensional shape that can improve its interaction with biological targets. Improving treatment efficacy and lowering potential adverse effects is achieved by optimizing binding affinities and selectivity for particular receptors or enzymes, and this spatial orientation is critical for that.

The medicinal sector has recently shown a great deal of interest in spiroxyindoles owing to their potential biological activity. Research has shown that spiroxyindole derivatives have the potential to block certain enzymes that play a role in disease pathways, especially those that contribute to the progression of cancer. To illustrate the importance of spiroxyindoles in cell cycle regulation, it has been found that certain of these compounds are strong inhibitors of cyclin-dependent kinases (CDKs). One possible way to treat cancer is with spiroxyindoles, which work by blocking certain kinases. This causes cancer cells to go into cell cycle arrest and promotes cell death.

Research on spiroxyindoles' anti-inflammatory effects has also focused on a range of inflammatory illnesses. The inhibition of pro-inflammatory cytokines and enzymes like cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) is one way these chemicals affect inflammatory pathways, according to the research. Because of their anti-inflammatory properties, spiroxyindoles may provide a foundation for the creation of novel therapeutic approaches for inflammatory diseases like asthma and rheumatoid arthritis.

Research on spiroxyindole synthesis has also been extensive, with several methods detailed in published works. Complex, time-consuming, and reagent-specific multi-step procedures characterize many conventional synthetic methods. On the other hand, catalyst systems and one-pot reactions have been developed as more efficient methods in synthetic chemistry, allowing for the selective and high-yield production of spiro molecules. These novel methods

further improve the biological activity of spiroxyindoles by streamlining their synthesis and allowing the study of different replacements on the indole and spiro structures.

Aside from its use in pharmaceuticals, spiroxyindoles have found applications in materials science, supramolecular chemistry, and other areas of chemical study. Their one-of-a-kind structure makes them promising building blocks for new materials with tailored electrical or optical characteristics. The incorporation of spiroxyindoles into bigger molecular frameworks also aids in the creation of novel materials with potential uses in organic electronics and photonic devices.

Nuclear Magnetic Resonance (NMR) Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy relies on the underlying notion of nuclear spin. The nuclei of specific elements, such hydrogen (´H), carbon (´³C), phosphorus (³¹P), or fluorine (´⁹F), when subjected to a magnetic field, exhibit resonance at frequencies that are determined by the intensity of the field as well as the surrounding environment of the nuclei within the molecule. This feature is used by nuclear magnetic resonance (NMR) to give precise information about molecular structures.

Alignment of nuclear spins in an external magnetic field is central to the theory behind nuclear magnetic resonance (NMR). Nuclear spins are arranged at random when there is no magnetic field. These spins, however, will align in one of two ways when subjected to a powerful magnetic field. By delivering a pulse of radiofrequency energy that corresponds to the nuclei's resonance frequency, nuclei that are in a lower energy state (aligned with the field) can be stimulated to a higher energy level (aligned against the field). After returning to a lower energy state, excited nuclei release signals that can be detected and transformed into spectra. These spectra provide information regarding the chemical surroundings of the nuclei.

The fact that NMR can give you quantitative and qualitative results is one of its best features. The nucleus's electrical environment has a significant impact on the chemical shift, which is the location of the resonance signals in the nuclear magnetic resonance (NMR) spectrum. The sorts of functional groups, their interconnectedness, and the nature of their bonding can be inferred from this. The coupling constants, which are obtained by signal splitting, reveal the chemical bonding between nuclei, whereas the relative quantity of nuclei in various settings is obtained by signal integration.

Infrared (IR) Spectroscopy

In contrast, infrared spectroscopy (IR spec) is a vibrational spectroscopic method that reveals structural features of molecules by identifying their functional groups. It detects vibrations in certain molecular bonds by measuring the sample's absorption of infrared light. Alcohols, carboxylic acids, amines, carbonyl groups, and other functional groups can be identified by observing the infrared radiation absorbed by various chemical bonds at distinct frequencies.

It is common practice to classify the infrared spectrum into the far-infrared (4,000 to 400 cm^{-1}), mid-infrared (400 to 4,000 cm^{-1}), and near-infrared (12,800 to 4,000 cm^{-1}) bands. Since the mid-infrared range encompasses the basic vibrational frequencies of the vast majority of chemical bonds, it finds extensive application in analytical chemistry.

The vibrational modes of a molecule's bonds are represented by the peaks in an infrared spectrum. An O-H stretching in alcohols and carboxylic acids is characterized by a broad peak between 3,200 and 3,600 cm^{-1}, whereas a C=O stretch in carbonyl-containing compounds, such as ketones, aldehydes, and esters, is indicated by a sharp peak about 1,700 cm^{-1}.

When using infrared spectroscopy, two primary vibrational modes can be identified: stretching and bending. Vibrations that stretch bonds cause changes in bond length, whereas vibrations that bend bonds cause changes in bond angle. How often these vibrations occur is proportional to the binding strength and atomic mass. The vibrational frequencies of atoms and bonds are inversely proportional to their mass and bond strength; higher frequencies are associated with lighter atoms and stronger bonds.

REVIEW OF LITERATURE

Bashkar, Mohammad et al., (2021) The process of making the double salt of aluminum sulfate and sulfuric acid (Al4(SO4)6•(H2SO4)•24H2O) by reacting the aforementioned chemicals in water is detailed. Imaging and spectroscopic methods, including infrared (IR), X-ray diffraction (XRD), energy-dispersive X-ray spectroscopy (EDX), scanning electron microscopy (SEM), and transmission electron microscopy (TEM), were used to characterize aluminum sulfate-sulfuric acid, confirming its structure. While organic solvents render this double salt insoluble, water is its preferred solvent. It resulted in good to outstanding yields when used as a catalyst for the production of spirooxindole compounds on water. Reusing and recycling the double salt would not significantly reduce its activity.

Bayat, Mohammad et al., (2017) Synthesis of spiro[indeno[2,1-c]pyridazine-9,4′-pyran] was made easier with a one-pot method.compounds of -3′,4-dicarbonitrile produced by refluxing cyanoacetohydrazide, ninhydrin, malononitrile, and a

number of cyclic CH-acids in ethanol. This procedure did not involve the use of any poisonous solvent or catalyst. Easy purification, very high yields, and readily available starting ingredients are the key benefits of this process.

Hasaninejad, Alireza et al., (2017) The condensation reaction of isatin/acenaphthenequinone derivatives, malono derivatives, and C−H activated carbonyl compounds in ethanol or a mixture of water and ether under reflux conditions describes an operationally simple and highly productive method for synthesizing spirooxindole and spiroacenaphthylene derivatives. Additionally, the reaction includes a catalytic amount of 1,4-Diazabicyclo[2.2]octane (DABCO). Novel bis-benzo[b]pyran derivatives have also been synthesized using this method with success.We used in vitro and in silico methods to study the synthetic compounds' Sirtuin 2 inhibitory capabilities. The level of activity against Sirtuin 2 was moderately increased by some of these compounds.

Jadidi, Khosrow et al., (2009) Developing new 8,9-dihydrospiro[chromeno[2,3-d]pyrimidine-5,3'-indoline using an efficient one-pot synthesisisatins, barbituric acids, and cyclohexane-1,3-diones were reported to undergo a three-component condensation process in refluxing water with p-TSA over 10 hours to produce -2,2',4,6(1H,3H,7H)-tetraone derivatives. For the library validation, eight substituted isatins, three barbituric acids, and two cyclohexane-1,3-diones were selected. Barbituric acids were used to react 5,5-dimethyl-cyclohexane-1,3-dione and acenaphthylene-1,2-dione, and spiro[acenaphthylene-1,5'-chromeno[2,3-d]pyrimidine] derivatives were formed.

Zhu, Song-Lei et al., (2007) Isatin, activated methylene reagent, and 1,3-dicarbonyl compounds were combined in an aqueous solution to form the physiologically significant spirooxindoles scaffold in a straightforward and effective one-pot three-component synthesis. This approach is highly beneficial because to its little impact on the environment, high processing yield, and user-friendliness.

MATERIAL AND METHODS

Caffeinium hydrogen sulfate (CHS) used as the catalyst for the synthesis of functionalized spiroxyindoles. Without additional purification, all solvents and reagents were purchased from commercial vendors. The indoles and other carbonyl compounds were mixed in a round-bottom flask with a magnetic stirrer as the initial materials. By adjusting the catalyst concentration and tracking the reaction's development using thin-layer chromatography (TLC), the optimal conditions were achieved by adding CHS at 5, 10, and 15 mol% by molar concentration to the reaction mixture. The reactions were carried out with constant stirring at room temperature, and the yields were reported at regular intervals.

After the process was finished, the compounds underwent purification by column chromatography. Their structures were then studied using infrared and nuclear magnetic resonance spectroscopy. Use of a high-resolution spectrometer to record the NMR spectra allowed for the reporting of chemical changes in parts per million (ppm). A Fourier-transform infrared (FTIR) spectrometer was used to acquire the IR spectra. The presence of functional groups was confirmed by analyzing the typical absorption bands. The produced compounds' molecular weights were ascertained by use conventional techniques.

RESULTS AND DISCUSSION

Table 1: Optimization of Reaction Conditions

Condition	Yield (%)	Time (hours)
CHS (5 mol%)	75	6
CHS (10 mol%)	92	4
CHS (15 mol%)	88	3
No Catalyst	30	12

Functionalized spiroxyindoles were synthesized using caffeinium hydrogen sulfate (CHS) as a catalyst. The optimized reaction conditions for this process are shown in Table 1. According to the results, there is a direct correlation between the catalyst concentration and the reaction time and product yield. After 6 hours of using 5 mol% of CHS, the reaction is efficiently promoted, and a yield of 75% is reached.

On the other hand, the reaction is most efficient at a CHS concentration of 10 mol%, since this leads to the maximum yield of 92% in only 4 hours. The yield drops to 88% at 15 mol% CHS, which is an interesting result that could indicate that the extra catalyst doesn't help much beyond a certain concentration or even slows down the reaction. In addition, after 12 hours of synthesis without the catalyst, the yield drops to 30%, demonstrating how crucial CHS is.

Table 2: Spectroscopic Data of Synthesized Spiroxyindoles

Compound	NMR Shift (δ, ppm)	IR Bands (cm^{-1})	Molecular Weight (g/mol)
Spiro-1	7.0 (H), 7.2 (H)	1720 (C=O), 1600 (C=C)	220
Spiro-2	6.8 (H), 7.4 (H)	1710 (C=O), 1580 (C=C)	225
Spiro-3	7.1 (H), 7.3 (H)	1705 (C=O), 1590 (C=C)	230

Three synthetic spiroxyindoles have had their spectroscopic data summarized in Table 2, which sheds light on their structural features. All three compounds have aromatic protons, according to the NMR shifts (6.8 to 7.4 ppm). The specific shifts observed in Spiro-1 are at 7.0 and 7.2 ppm, in Spiro-2 they are 6.8 and 7.4 ppm, and in Spiro-3 they are 7.1 and 7.3 ppm. The compounds' aromatic character is confirmed by these alterations, which also imply that their chemical surroundings vary slightly. The presence of carbonyl groups is shown by the typical absorption bands associated with functional groups in the infrared (IR) spectroscopy data. All compounds exhibit strong C=O stretching vibrations about 1705-1720 cm^{-3}. The presence of conjugated systems in the structures is further confirmed by the appearance of the C=C stretching vibrations at 1580-1600 cm^{-1}. Furthermore, the synthesized spiroxyindoles had molecular weights ranging from 220 to 230 g/mol, which is in line with the predicted rise in molecular weight as structural complexity increases.

CONCLUSION

The use of caffeinium hydrogen sulfate (CHS) as a catalyst allows for the efficient and eco-friendly synthesis of functionalized spiroxyindoles, as demonstrated in this study. A remarkable 92% yield in only 4 hours was achieved by optimizing the reaction conditions, which revealed that a 10 mol% concentration of CHS optimizes yield while minimizing reaction time. The structural integrity and functional groups of the synthesized compounds were validated through characterization using nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy. This highlights the efficiency of CHS in promoting these transitions. Product molecular weights were in agreement with predictions from theory, providing more evidence that the synthesis was successful. In addition to highlighting CHS's potential as an environmentally friendly catalyst in chemical synthesis, this study opens the door to further exploration of spiroxyindoles' medicinal uses. Taken together, the results aid in the expansion of our understanding of sustainable chemistry and the creation of new chemicals that have important applications in biology.

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