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Synthesis and tautomerism of spiro-pyrazolines

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ABSTRACT

An experimental study on the synthesis, tautomerism, and acid promoted structural changes of spiro-pyrazolines is described. The target was achieved through a [3+2]-dipolar cycloaddition of an alkene with nitrile imines generated in situ and was isolated in high yield. The synthesized cycloadduct displayed a tendency to exhibit an imine–enamine type of tautomerism as evidenced by X-ray crystal and NMR studies. Furthermore, addition of an acid resulted in the transformation of an imine tautomer to an enamine. The current report constitutes a first formal observation of this kind of tautomerism observed in spiro-indoline pyrazolines.

Introduction

Spiro-isoxazolines[1–3] and spiro-pyrazolines[4,5] are of recurring interest to the chemists engaged in the drug-discovery areas of natural product synthesis and heterocyclic methodology development. These compounds incorporate useful isoxazole[6] or pyrazole[7] based motifs in their core structures and are junctioned to another carbocyclic/heterocyclic ring at one carbon atom. When compared to spiro-isoxazolines, spiro-pyrazolines, isosterically equivalent to spiro-isoxazolines where the nitrogen replaces the oxygen, are structurally rigid and present the flexibility for possible synthetic and biological property exploration.[5] In addition to the synthesis of pyrazoles and pyrazoline derivatives, tautomerism is another area of equal interest due to their high application potential in biological systems, chemical reactivity, and molecular recognition.[8–10] Although, the importance of tautomerism (imine–enamine) has been described very well for pyrazole related ring systems,[9–11] it is rarely observed in analogous spiro-pyrazolines. As of today, only three reports exist on the structural changes observed in spiro-pyrazolines.[12]

Our long standing interest in this area resulted in the establishment of efficient strategies for the construction of architecturally complex natural product analogues and bioactive heterocycles of synthetic and biological interest.[5,6d,7g,13,14] In addition to methodology development, we are also equally interested in assessing structural and biological applications for spiro-pyrazolines. Recently, we demonstrated the construction of 1,3,5-trisubstituted pyrazoles on the basis of the 1,3-dipolar cycloaddition protocol, which was then followed by an unforeseen ring fragmentation/elimination.[14] We observed that the placement of an electron-rich or electron-deficient substituent of the aromatic ring at *ortho*-, *meta*-, and *para*-positions is crucial for the identity of the final product (pyrazole or spiro-pyrazoline). Additionally, we also postulated a mechanism based on the occurrence of an imine–enamine type of tautomerism and the factors leading to pyrazole formation rather than the anticipated spiro-pyrazoline (Scheme 1). Based on these observations, we decided to extend the investigation of this protocol for the preparation of a spiro-pyrazoline with an electron rich *para*-methoxy group on the aromatic ring. Herein, we present results from our ongoing research highlighting the first imine–enamine type of tautomerism observed in spiroindoline-pyrazolines.

Results and discussion

During our studies toward synthesizing spiro-pyrazolines, we discovered that when 1,3,3-trimethy-2-methylenelindoline (**1**) was used as the dipolarophile, spiro-pyrazoline **6** was the only product isolated. The cycloaddition process[7g,14–16] leading to the desired spiro-pyrazoline **6**[17] formation occurred with complete regiochemical integrity and in good isolated yield (Scheme 2). While assessing the NMR spectrum of the synthesized spiro-pyrazoline **6**, we observed an inconsistency with respect to the

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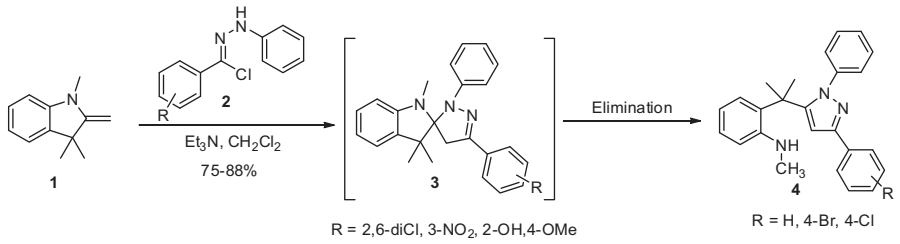
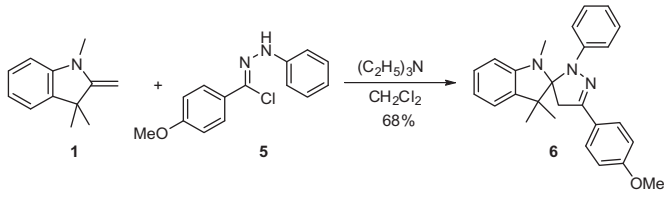


Scheme 1. Pyrazole synthesis from the spiro-pyrazoline intermediate **3**.



Scheme 2. Spiro-pyrazoline isolated from 1,3-dipolar cycloaddition.

diastereotopic methylene protons. The inconsistency with the methylene protons suggested the need for a detailed NMR study in selected solvents and data comparison of the reported spiro-pyrazolines. The spiro-pyrazoline **6** was subjected to NMR studies in chloroform-*d* and benzene-d_6 solvents.[18] The ^{1}H NMR spectra clearly evidenced the spiro-pyrazoline to exist as imine **6** and enamine tautomer **7** in benzene-d_6 and chloroform-*d* solvents, respectively. The enamine tautomer **7** ($CDCl_3$) displayed the enamine (CH═C—NH) proton (multiplet) peak at δ 4.15–4.17 ppm, and the imine tautomer (C_6D_6) **6** displayed the desired diastereotopic proton (C═N—CH_2—) doublets at δ 3.00 and 3.4 ppm (Scheme 3).

Additional DEPT-135 studies in benzene-d_6 solvent concluded the methylene peak at δ 39.8 ppm facing downward demonstrating the occurrence of spiro-pyrazoline as the imine **6**. Furthermore, the observed methylene peak was absent when the study was repeated in chloroform-*d*. This type of observed tautomerism is the first of its kind and to our knowledge, only Toth's research group has documented similar results exhibited by spirochromone-pyrazolines.[12] The existence of a spiro-pyrazoline as imine **6** and enamine **7** tautomers in chloroform and benzene solvents is depicted in Figure 1 where the imine tautomer is slightly yellow in C_6D_6. However, the enamine tautomer exists as a reddish-pink colored compound in $CDCl_3$.

Gratifyingly, the existence of spiropyrazoline **6** as a crystalline solid enabled us to perform X-ray studies to reveal compound's regio-structural features.[19–21] Compound **6** ($C_{26}H_{27}N_3O$) was unambiguously confirmed by the X-ray structural analysis and revealed the presence of a –CH_2– group at C15 carbon position, which provided the necessary evidence to show that the compound exists in the form of an imine (CH_2–C═N) tautomer as a major conformer in the solid state. The ORTEP rendition of the crystal structure of **6** is as shown in Figure 2.

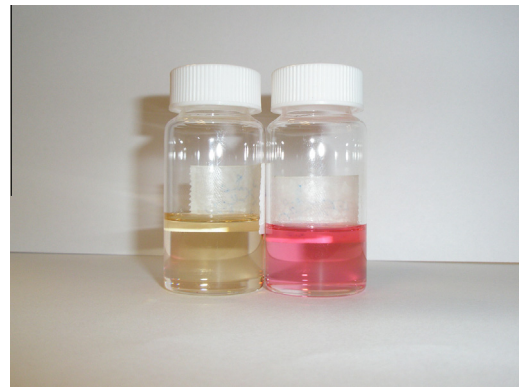


Figure 1. Spiro-pyrazoline existence as imine (left: benzene) and enamine (right: chloroform) tautomer.

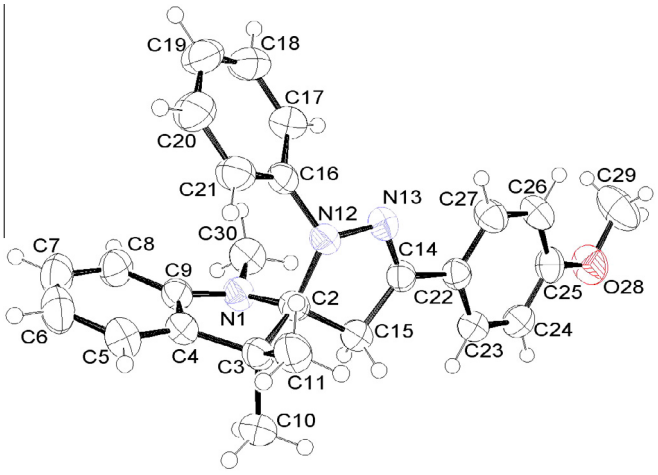
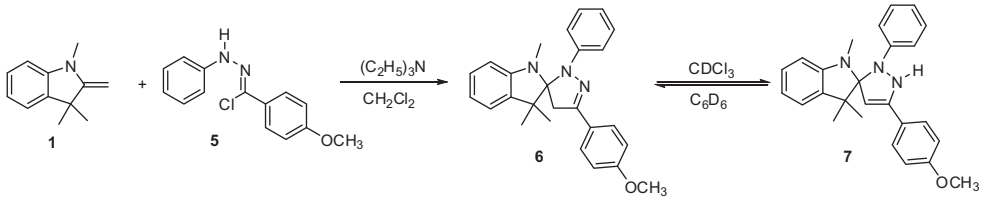


Figure 2. Thermal ellipsoid plot of spiro-pyrazoline **6**.

Our next idea was to spectroscopically observe any structural changes that the spiro-pyrazoline would undergo from imine to enamine, or enamine to imine, in the presence of a proton source. We hypothesized that an acidic environment would provide a



Scheme 3. Enamine-imine tautomerism exhibited by spiro-pyrazoline in chloroform-*d* and benzene-d_6 solvents.